Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Inhaled Antimuscarinics
AHFS Class 120808
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I. Overview

The inhaled antimuscarinics are approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-5] Tiotropium is also approved to reduce exacerbations in patients with COPD.[5] These agents antagonize the action of acetylcholine at its receptor site and produce bronchodilation by inhibiting cholinergic receptors in bronchial smooth muscle. The effect is site-specific and leads to dilation of both large and small airways.

The inhaled antimuscarinics have been shown to alleviate dyspnea, improve exercise tolerance, decrease hyperinflation associated with COPD, and reduce the frequency of disease exacerbations. Tiotropium has a longer duration of action than ipratropium and can be dosed once daily.

The inhaled antimuscarinics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ipratropium inhalation solution is the only product that is available in a generic formulation. This class was last reviewed in December 2008.

Table 1. Inhaled Antimuscarinics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ipratropium	aerosol inhaler, inhalation solution*	Atrovent HFA®	ipratropium, Atrovent HFA®
Tiotropium	dry powder inhaler	Spiriva®	Spiriva®

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the inhaled antimuscarinics are summarized in Table 2. For a comprehensive overview of the treatment of asthma and COPD, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Inhaled Antimuscarinics

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): **British Guideline on the Management of Asthma[27] (2009)**	• The addition of short-acting anticholinergics is generally of no value. • The anticholinergics do not give protection against exercise-induced asthma at normal doses.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention[24] (2009)**	• Inhaled ipratropium bromide is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. • The benefits of ipratropium bromide in the long-term management of asthma have not been established, although it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from rapid-acting β_2-agonists. • Inhaled anticholinergics are not recommended for the long-term management of asthma in children.
Global Initiative for Asthma (GINA): **Global Strategy for**	• Inhaled ipratropium is not recommended for the daily management of asthma in children ≤5 years of age.

Clinical Guideline	Recommendation(s)
the Diagnosis and Management of Asthma in Children 5 years and Younger[45] (2009)	
National Heart, Lung, and Blood Institute (NHLBI): **Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[38] (2007)**	• Tiotropium and ipratropium have not demonstrated effectiveness in the long-term management of asthma. • Ipratropium bromide, administered in multiple doses along with SABA in moderate or severe asthma exacerbations in the Emergency Department, provides additive benefit.
International Primary Care Respiratory Group (IPCRG): **Management of Asthma[28] (2006)**	• Inhaled anticholinergics are not recommended as first-line therapy in asthma.

National Institute for Clinical Excellence (NICE): **Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care[20] (2010)**	Treatment Considerations
	• As needed short-acting bronchodilators should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
	• A once-daily, long-acting muscarinic antagonist (LAMA) is preferred to a four-times-daily, short-acting muscarinic antagonist (SAMA) in patients with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, as well as in those who begin regular maintenance bronchodilator therapy with a muscarinic antagonist.
	• The following treatments are recommended as maintenance therapy in patients with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed:
	  o If FEV_1 ≥50% predicted: either long-acting β_2-agonist (LABA) or LAMA
	  o If FEV_1 <50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler or LAMA
	• The following treatments are recommended as maintenance therapy in patients with stable COPD and an FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
	  o Consider LABA+ICS in a combination inhaler
	  o Consider LAMA in addition to LABA where ICS is declined or not tolerated
	• Offer LAMA in addition to LABA+ICS to patients with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1.
	• Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA, irrespective of their FEV_1.
	Delivery Systems
	• In most cases, bronchodilator therapy is best administered using a hand-held inhaler device (including a spacer device if appropriate).
	• Patients with distressing or disabling breathlessness despite maximal therapy using inhalers should be considered for nebulizer therapy.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[18]**	Treatment Considerations • Most studies have indicated that the existing medications for COPD do not modify the long-term decline in lung function. Therefore, pharmacotherapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance.

Clinical Guideline	Recommendation(s)
(2009)	• Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis or on a regular basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. • The principal bronchodilator treatments are β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. • Regular treatment with long-acting bronchodilators, including nebulized formulations, are more effective than treatment with short-acting bronchodilators. • Regular use of a long-acting β_2-agonist or a short-or long-acting anticholinergic improves health status. • Treatment with a long-acting inhaled anticholinergic drug reduces the rate of COPD exacerbations and improves the effectiveness of pulmonary rehabilitation. • Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. Delivery Systems • COPD patients may have more problems in effective coordination and find it harder to use a metered-dose inhaler (MDI) than do healthy volunteers or younger asthmatics. • Dry powder inhalers (DPIs) may possibly provide improved drug deposition; however, this has not been established in COPD. • Nebulizers are not recommended for regular treatment because they require appropriate maintenance.
American College of Physicians (ACP): **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease**[46] **(2007)**	• Clinicians should prescribe one of the following maintenance monotherapies for symptomatic patients with COPD and FEV_1 <60% predicted: long-acting inhaled β_2-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. • Monotherapy with a long-acting inhaled β_2-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. • Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness, but differ in adverse effects, reductions in deaths, and hospitalizations. • Evidence is insufficient to recommend one agent over another. • Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV_1 <60% predicted. • When to use combination therapy instead of monotherapy has not been clearly established. Studies do not consistently demonstrate benefits of combination therapy over monotherapy.
International Primary Care Respiratory Group (IPCRG): **Management of Chronic Obstructive Pulmonary Disease** [21] **(2006)**	• None of the current pharmacologic treatments for COPD have been shown to modify the long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Bronchodilators (anticholinergics and β_2-agonists) are central to symptom management in COPD. • For regular treatment, long-acting bronchodilators are more effective than short-acting bronchodilators.
American Thoracic Society (ATS)/European Respiratory Society (ERS): **Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary**	• Medications for COPD can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present, no treatment has been shown to modify the rate of decline in lung function. • A short-acting bronchodilator as needed is recommended for symptom control in patients with intermittent symptoms.

Clinical Guideline	Recommendation(s)
Disease[19] (2004)	• For patients with persistent symptoms, a long- or short-acting bronchodilator is recommended. If symptoms are not controlled, consider using alternate classes or combine classes. • Three types of bronchodilators are in common clinical use: β-agonists, anticholinergic drugs and methylxanthines. • Short-acting bronchodilators can increase exercise tolerance acutely in COPD. Combining short-acting agents produces a greater change in spirometry over 3 months than either agent alone. • Long-acting inhaled β_2-agonists improve health status, possibly to a greater degree than using regular ipratropium. Additionally, these drugs reduce symptoms, rescue medication use and increase the time between exacerbations compared with placebo. • Combining long-acting inhaled β-agonists and ipratropium leads to fewer exacerbations than either drug alone. • Tiotropium improves health status and reduces exacerbations and hospitalizations compared with both placebo and regular ipratropium.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the inhaled antimuscarinics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Inhaled Antimuscarinics[1-5]

Indication	Ipratropium	Tiotropium
Long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema		✔
Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	✔	
To reduce exacerbations in COPD patients		✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the inhaled antimuscarinics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Inhaled Antimuscarinics[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ipratropium	7	Not reported	Liver	Renal (3) Feces (48)	2 to 3.8
Tiotropium	20	72	Liver (25)	Renal (14) Feces	120-144

V. Drug Interactions

There are no significant drug interactions reported with the inhaled antimuscarinics.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the inhaled antimuscarinics are listed in Table 5. In January 2010, the FDA issued a follow-up to the previous early communication (October 2008), which described a potential increase in the risk of stroke, heart attack, or death from a cardiovascular cause related to the use of tiotropium.[39] The FDA completed its review and believes the available data do not support an association between the use of tiotropium and an increased risk for these serious adverse events.[47]

Table 5. Adverse Drug Events (%) Reported with the Inhaled Antimuscarinics[1-5]

Adverse Events	Ipratropium	Tiotropium
Cardiovascular		
Arrhythmia	<1	<1
Chest pain	3	1-7
Edema	-	5
Hypotension	<1	-
Palpitation	✔	<1
Tachycardia	<1	<1
Central Nervous System		
Depression	-	1-4
Dizziness	1-3	<1
Headache	5-9	6
Insomnia	<1	4
Nervousness	<1	-
Paresthesia	-	1-3
Tremor	<1	-
Dermatological		
Dry skin	-	<1
Rash	<1	4
Pruritus	<1	<1
Skin infection	-	<1
Skin ulcer	-	<1
Urticaria	<1	<1
Endocrine and Metabolic		
Edema	-	3-5
Hypercholesterolemia	-	1-3
Hyperglycemia	-	1-3
Gastrointestinal		
Abdominal pain	-	5
Bitter taste	<1	-
Constipation	<1	1-5
Diarrhea	<1	-
Dyspepsia	1-5	1-6
Dysphagia	-	<1
Gastrointestinal pain	-	3-6
Gastrointestinal reflux	-	1-3
Gingivitis	-	<1
Intestinal obstruction	-	<1
Nausea	1-4	-
Stomatitis	-	1-3
Throat irritation	-	<1
Vomiting	-	1-4
Xerostomia	2-4	5-16
Genitourinary		
Urinary retention	<1	<1
Urinary tract infection	2-10	4-7

Adverse Events	Ipratropium	Tiotropium
Musculoskeletal		
Arthralgia	-	4
Arthritis	<1	≥3
Back pain	2-7	-
Joint swelling	-	<1
Leg cramps	-	1-3
Myalgia	-	3-4
Skeletal pain	-	1-3
Respiratory		
Bronchitis	10-23	-
Bronchospasm	2	✔
COPD exacerbation	8-23	-
Cough	3-6	3
Dyspnea	7-10	-
Epistaxis	-	1-4
Laryngitis	-	1-3
Laryngospasm	<1	-
Pharyngitis	4	7-13
Rhinitis	2-6	3-6
Sinusitis	1-11	3-11
Sputum increased	1	-
Upper respiratory tract infection	9-34	41-43
Ocular		
Blurred vision	-	<1
Cataract	-	1-3
Eye pain	<1	-
Glaucoma	<1	<1
Intraocular pressure increased	-	<1
Mydriasis	<1	-
Narrow-angle glaucoma, worsening	-	✔
Pupil dilation	-	<1
Other		
Accidents	-	5-13
Allergic skin reactions	✔	2-4
Anaphylactic reactions	<1	-
Angioedema	<1	<1
Candidiasis	-	<1
Dehydration	-	<1
Dysphonia	-	1-3
Herpes zoster	-	1-3
Hypersensitivity reaction	<1	1-3
Infection	-	1-4
Influenza-like symptoms	2-8	3
Moniliasis	-	3-4

✔ Percent not specified
\- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the inhaled antimuscarinics are listed in Table 6.

Table 6. Usual Dosing Regimens for the Inhaled Antimuscarinics[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ipratropium	COPD: Aerosol inhaler: two inhalations four times a day; patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours Inhalation solution: 500 mcg administered three to four times a day by oral nebulization, with doses 6 to 8 hours apart	Safety and efficacy in children have not been established.	Aerosol inhaler: 17 mcg Inhalation solution: 0.2 mg/ml
Tiotropium	COPD: Two inhalations of the powder contents of a single capsule once daily	Safety and efficacy in children have not been established.	Dry powder inhaler: 18 mcg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the inhaled antimuscarinics are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Inhaled Antimuscarinics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Peters et al.[22] (2010) Tiotropium 18 mcg QD and beclomethasone 80 mcg BID vs beclomethasone 160 mcg BID vs beclomethasone 80 mcg and salmeterol 50 mcg BID	DB, XO, RCT Patients ≥18 years of age with asthma, FEV_1 >40% predicted, and non-smoking status (<10 pack-years)	N=210 52 weeks	Primary: Morning peak expiratory flow Secondary: FEV_1 before bronchodilation, number of asthma-control days, asthma symptoms, rescue-therapy use, asthma exacerbations, use of health services, biomarkers of airway inflammation, and results of validated questionnaires	Primary: Patients receiving tiotropium had a morning peak expiratory flow that was 25.8 L/min higher than that of patients receiving beclomethasone 160 mcg twice daily (95% CI, 14.4 to 37.1; P=0.001). There were no significant differences between tiotropium treatment and salmeterol treatment with respect to the morning PEF, which was 6.4 L/min higher among patients receiving tiotropium (95% CI, −4.8 to 17.5; P=0.26). Secondary: Compared to the administration of beclomethasone 160 mcg twice daily, the addition of tiotropium to beclomethasone improved most secondary outcomes, including evening peak expiratory flow (P=0.001), proportion of asthma control days (P=0.01), FEV_1 before bronchodilation (P=0.004), and daily symptom scores (P=0.001). The addition of tiotropium to beclomethasone increased the prebronchodilator FEV_1 more than the addition of salmeterol (P=0.003).
COPD				
Matera et al.[30] (1996) Ipratropium 40 mcg QID and salmeterol 50 mcg BID vs ipratropium	SB, XO, RCT Male patients ≥40 years of age with COPD and FEV_1 between 16% - 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 and changes in the area under the FEV_1 response-time curve (AUC)	Primary: The peak response for salmeterol (28.8%) was greater than that for ipratropium (26.0%). Equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium (28.0%). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes when compared to placebo (P=0.05). Only salmeterol and salmeterol plus ipratropium induced a significant spirometric increase over the 12 hour monitoring period (P=0.05). All of the AUC values for active treatments were significantly greater than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mcg QID vs salmeterol 50 mcg BID vs placebo				for placebo (P=0.05). The AUC values for salmeterol and salmeterol plus ipratropium were significantly greater than for ipratropium alone (P=0.05). There was no significant difference between the salmeterol and salmeterol plus ipratropium AUC (P>0.05).
Van Noord et al.[31] (2000) Ipratropium 40 mcg QID and salmeterol 50 mcg BID vs salmeterol 50 mcg BID vs placebo	RCT, DB, PG, MC Patients 40-75 years of age with COPD and FEV_1 ≤75% predicted	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication used, PEF, clinic lung function, adverse events, exacerbations	Primary: Treatment with salmeterol led to a mean peak increase in FEV_1 of 7% predicted after 2 hours, followed by a plateau. After 12 hours, the improvement was 2% of predicted. Salmeterol plus ipratropium produced a peak increase in FEV_1 of 11% predicted after 2 hours. After 12 hours, the improvement was 3% predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. Secondary: Throughout the treatment period there was a mean decrease in the daytime symptom score from 1.9 to 1.7 in the placebo group (P=NS), 2.0 to 1.4 (P=0.001) in the salmeterol group and 2.0 to 1.3 (P=0.001) in the salmeterol plus ipratropium group. Compared with placebo, treatment with salmeterol and salmeterol plus ipratropium was associated with a higher percentage of days and nights without the use of additional albuterol (P=0.01). No difference was observed between the two active treatment groups (P=0.35). Improvements in morning PEF were significantly better in both active treatment groups than in the placebo group (P=0.001), whereas no difference was observed between the salmeterol and the salmeterol plus ipratropium groups. The changes in evening PEF were in favor of both active treatment arms compared with placebo (P=0.001), whereas the improvement was better in the salmeterol plus ipratropium group vs the salmeterol group (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean increase in FEV_1 was 1% predicted for placebo, 5% predicted for salmeterol, and 8% for the salmeterol plus ipratropium group (all, P=0.01). The change in FVC was 4% predicted with placebo, 7% predicted with salmeterol, and 12% predicted with salmeterol plus ipratropium. The differences between salmeterol plus ipratropium vs salmeterol alone and between salmeterol plus ipratropium vs placebo were both significant (P=0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (P=0.055). The reported incidence and nature of possible and probably drug-related side effects were similar among the three groups. A total of 35 patients experienced a COPD exacerbation, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group, and six (13%) in the salmeterol plus ipratropium group. The only significant difference was between the salmeterol plus ipratropium group and the placebo group (P=0.01).
Ogale et al.[23] (2010) Ipratropium exposure vs no ipratropium exposure	Cohort Veterans with a new diagnosis of COPD	N=82,717 6 years	Primary: Death or hospitalization from cardiovascular events (CVEs) during the period of interest (acute coronary syndrome, heart failure, or cardiac dysrhythmia)	Primary: Forty percent of the cohort received no COPD medication during the study. More than 44% were exposed to anticholinergics at some time during the study period. A total of 329,255 prescriptions were dispensed for anticholinergic agents. Only 78 were for tiotropium, while the remaining prescriptions were for ipratropium alone by metered-dose inhaler (55%) or nebulization (7%), or ipratropium in a fixed-dose combination with albuterol (38%). During the total follow-up period of 274,025 patient-years, there were 6,234 CVEs, for a rate of 2.2 CVEs per 100 patient-years. Nearly 75% of the patients followed had at least one cardiovascular risk factor at study entry. There were 6,234 CVEs (44% heart failure, 28% acute coronary syndrome, 28% dysrhythmia). Compared with subjects not exposed to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ipratropium within the past year, any exposure to ipratropium within the past 6 months was associated with an increased risk of CVE: ≤4 and ≥4 30-day equivalents (HR 1.40; 95% CI, 1.30-1.51 and HR 1.23; 95% CI, 1.13 – 1.36, respectively). Overall, exposure to anticholinergics was associated with a 29% higher risk of CVEs relative to no exposure in the past year. Among subjects who received anticholinergics more than 6 months prior, there did not appear to be an elevated risk of a CVE. Effect modification by the presence of CVD at baseline was statistically significant (P=0.01).
McCrory et al.[33] (2002) Ipratropium vs β-agonists, combination of β-agonists and ipratropium, or placebo	MA Adult patients with COPD and symptoms consistent with an acute exacerbation	N=525 (9 trials) 1 hour to 14 days	Primary: Short-term changes in FEV_1, weighted mean difference (WMD) of long-term effects on FEV_1	Primary: There was no significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to the use of a β-agonist. The change in FEV_1 was not significant when ipratropium was added to a β-agonist (WMD: 0.02 L; 95% CI, 0.08 to 0.12). These results were similar 24 hours post-dose (long-term) between the ipratropium and β-agonist groups (WMD: 0.05 L; 95% CI, -0.14 to 0.05).
Casaburi et al.[29] (2005) Tiotropium 18 mcg QD vs placebo	RCT, DB, PC, MC Patients ≥40 years of age with COPD, FEV_1 ≤60% and FEV_1/FVC ≤70% predicted	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: Transitional dyspnea index (TDI), St. George's respiratory questionnaire (SGRQ), rescue albuterol use	Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time than patients receiving placebo. The difference between the treatments was 1.65 minutes (P=0.183). Patients receiving tiotropium showed significantly longer exercise endurance times compared to placebo both after 13 weeks of treatment (including 8 weeks of PR) and following the termination of the PR program after 25 weeks of treatment. The mean differences were 5.35 minutes (P=0.025) and 6.6 minutes (P=0.018), respectively. The mean increase in endurance time from day 29 before PR to day 92 after PR was 80% in the tiotropium group and 57% in the placebo group. Secondary: On day 92, the mean TDI focal score for tiotropium was 1.75 and 0.91 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo. On day 176, the placebo group showed a decline in the TDI focal score to 0.08 while the improvement in the tiotropium group was maintained at 1.75. At 12 weeks following PR, the difference between treatment groups was 1.67 units (P=0.03). The SGRQ total score in the tiotropium group was lower (i.e., improved) on each test day compared to the placebo group. After PR, the SGRQ scores improved by 7.27 units in the tiotropium group compared with 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant. On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication per day when compared to patients receiving placebo over 25 weeks of treatment (P=0.05).
Tashkin et al.[40] (2008) UPLIFT Tiotropium 18 mcg QD vs placebo	RCT, DB, PC, PG Patients ≥40 years of age with COPD, smoking history of ≥10 pack-years, postbronchodilator FEV_1 ≤70% predicted and FEV_1 ≤70% of the FVC	N=5,993 4 years	Primary: Yearly rate of decline in mean FEV_1 prebronchodilator and postbronchodilator Secondary: Rate of decline in mean FVC and SVC; health-related quality of life (using SGRQ); exacerbations of COPD and related hospitalizations; rate of death from any cause and lower respiratory conditions	Primary: There were no significant differences in the rate of decline in the mean values for FEV_1 and FVC either before or after bronchodilation from day 30 to the end of study drug treatment among the treatment groups. In the tiotropium group, the mean values for FEV_1 and FVC before and after bronchodilation showed significant improvements that were maintained at all time points. Mean improvements in FEV_1 in the tiotropium group ranged from 87 to 103 ml before bronchodilation and from 47 to 65 ml after bronchodilation compared to placebo (P<0.001). In a post hoc analysis, between-group differences in the rate of decline in postbronchodilator FEV_1 were observed in favor of tiotropium compared to placebo in the subgroup of patients who were not receiving either inhaled corticosteroids or long-acting β-agonists at baseline (40 ml in the tiotropium group and 47 in the placebo group; P=0.046). Secondary: The mean change in the SGRQ total score favored tiotropium vs placebo (P=0.001), but was not considered clinically significant. The between-group difference in SGRQ total score favored tiotropium at any time point assessed (P=0.001). Tiotropium significantly delayed the time to first exacerbation, with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mean of 16.7 months compared to 12.5 months in the placebo group. Tiotropium was associated with a reduction in the mean number of exacerbations of 14% (P=0.001). Tiotropium delayed the time to first hospitalization for an exacerbation compared to placebo [HR 0.86 (95% CI, 0.81 – 0.91). There was no difference in the mean number of exacerbations leading to hospitalization between the two groups. In the intent-to-treat analysis, 941 patients died: 14.9% in the tiotropium group and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 – 1.02).
Celli et al.[58] (2009) UPLIFT Tiotropium 18 mcg QD vs placebo	RCT, DB, PC, PG (post-hoc analysis) Patients ≥40 years of age with COPD, smoking history of ≥10 pack-years, postbronchodilator FEV_1 ≤70% predicted and FEV_1 ≤70% of the FVC	N=5,993 4 years	Primary: Mortality Secondary: Mortality rates adjusted by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications	Primary: The total number of deaths from any cause (on-treatment) was 411 (13.6%) in the placebo group and 381 (12.8%) in the tiotropium group (HR 0.84; 95% CI, 0.73–0.97; P=0.016). For the full 4-year, protocol-defined treatment period (1,440 days), there were 921 deaths. Mortality was significantly lower in patients randomized to tiotropium compared with placebo (HR, 0.87; 95% CI, 0.76–0.99; P=0.034). For the period of 4 years + 30 days (1,470 days), there were 941 deaths, with a lower risk of death in the tiotropium group (HR 0.89; 95% CI, 0.79–1.02; P=0.086). Between Days 1,440 and 1,470, there were four deaths in the placebo group and 16 deaths in the tiotropium group. Secondary: Adjustment by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications subgroups did not alter the results of the analysis. The most common causes of death were lower respiratory events, cancer, general disorders, and cardiac disorders. The hazard ratios for lower respiratory and cardiac mortality during treatment were 0.86 (95% CI, 0.68–1.09) and 0.86 (95% CI, 0.75–0.99), respectively.
Decramer et al.[50] (2009) UPLIFT	DB, PC, MC, RCT (Subgroup analysis) Patients ≥40 years	N=2,739 4 years	Primary: Yearly rate of decline in mean FEV_1	Primary: Rate of decline of mean FEV_1 was less in the tiotropium group than in the control group (43 mL/year vs 49 mL/year; P=0.024).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tiotropium 18 mcg QD vs placebo	of age with GOLD stage II COPD		prebronchodilator and postbronchodilator Secondary: Health status measured by SGQR, time to first exacerbation, and time to exacerbation resulting in hospital admission	The rate of decline of mean prebronchodilator FEV_1 did not differ between the treatment groups (35 mL/year vs 37 mL/year; P=0.38). The rate of decline of mean postbronchodilator FEV_1 was lower in the tiotropium group than in the control group (43 mL/year vs 49 mL/year; P=0.024). Secondary: Health status, measured by SGQR, was better at all time points in tiotropium group vs control (P≤0.06 at all time points). Time to first exacerbation (HR 0.82; 95% CI, 0.75–0.90) and time to exacerbation resulting in hospital admission (HR 0.74, 0.62–0.88, respectively) were both longer in the tiotropium group than the control group.
Halpin et al.[51] (2009) Tiotropium 18 mcg QD vs placebo	RCT (pooled analysis) Patients ≥40 years of age with stable COPD, FEV_1 ≤65% predicted, FEV_1/FVC ≤70%, and smoking history ≥10 pack-years	N=6,171 (9 trials) ≥24 weeks	Primary: Proportion of patients with COPD exacerbation, proportion of patients with hospitalization due to COPD exacerbation, time to first COPD exacerbation, time to first hospitalization for exacerbation	Primary: Tiotropium reduced the risk of COPD exacerbation by 21% compared to placebo (95% CI, 0.729 to 0.862, P<0.0001). Tiotropium reduced the risk of hospitalization associated with COPD exacerbation by 21% compared to placebo (95% CI, 0.65 to 0.96; P=0.015). The cumulative incidence rate of COPD exacerbation at 46 weeks was 42.1% for tiotropium compared with 50.8% for placebo (P<0.001). The cumulative incidence rate of hospitalizations associated with COPD exacerbation at 46 weeks was 8.5% for tiotropium compared with 10.8% for placebo (P=0.015). The protective effect of tiotropium was consistent regardless of age, gender, ICS use, and disease severity.
Van Noord et al.[17] (2000) Tiotropium 18 mcg QD	MC, DB, DD, PG Patients with stable COPD, mean age of 65 years and	N=288 15 weeks	Primary: Changes in FEV_1 and FVC Secondary:	Primary: The FEV_1 response, at all time points on days 8, 50, and 92, was significantly greater after tiotropium than after ipratropium (differences of 0.09 l, 0.11 l, 0.081; P=0.05). The results for FVC closely reflect those obtained for FEV_1. Tiotropium performed consistently better than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ipratropium 40 mcg QID	average FEV_1 of 41% of predicted values		Daily records of peak expiratory flow (PEF), use of albuterol	ipratropium. The differences in trough FEV_1 values were most pronounced (P=0.001), whereas differences in peak FEV_1 increase did not reach statistical significance (P>0.05). Secondary: The improvement in both morning and evening PEF was greater in the tiotropium group than in the ipratropium group. The difference in morning PEF between the groups was statistically significant up through week 10 (P=0.05). For evening PEF, the difference reached statistical significance during the first seven weeks of the treatment period (P=0.05). In both groups, there was a drop in the use of rescue albuterol, the reduction being greater in the tiotropium group than in the ipratropium group (P=0.05).
Vincken et al.[14] (2002) Tiotropium 18 mcg QD vs ipratropium 40 mcg QID	RCT, DB, PG, MC Patients ≥40 years of age with COPD, FEV_1 of ≤65% predicted and FVC ≤70%	N=535 12 months	Primary: Changes in spirometry Secondary: Peak Expiratory Flow Rate (PEFR), rescue albuterol use, Baseline Dyspnea Index (BDI), TDI, SGRQ, quality of life (QOL)	Primary: By the end of day 8, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12%) compared with 20 mL for the ipratropium group. Tiotropium was more effective than ipratropium at all time points on all test days, except for the first 2 hours following the first dose and up to 1 hour after the dose, 1 week later (P=0.05). At the end of one year, trough FEV_1 was 120 mL above the day 1 baseline for patients receiving tiotropium, and had declined by 30 mL for those receiving ipratropium (difference of 150 mL between groups, P=0.001 at all time points). The FVC results paralleled the FEV_1 results. At the end of one year, the trough FVC was 320 mL above the day 1 baseline for patients receiving tiotropium and 110 mL for those receiving ipratropium (mean difference of 210 mL between groups). Secondary: Throughout the 1-year treatment period, morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group (P=0.01 at all weekly intervals).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				On average, patients receiving tiotropium self-administered approximately 4 fewer inhalations of albuterol per week compared to patients receiving ipratropium (P=0.05 for 40 of the 52 weeks). The BDI focal scores for the two groups were comparable. Tiotropium significantly improved all components of the TDI on all test days compared to ipratropium (P=0.05). The proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at 1 year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%, P=0.004). During the 1-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30±1.13 on day 364, P=0.05). QOL, as assessed by the SF-36 questionnaire, suggested that tiotropium was more effective than ipratropium in all physical domains. The differences between treatment groups were only significant in physical health summary on the last 2 test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and not significant.
Niewoehner et al.[53] (2009) Tiotropium 18 mcg QD vs ipratropium-albuterol MDI QID	DD, DB, PG, RCT (pooled analysis) Patients ≥40 years of age with COPD, current or former cigarette smoker with lifetime consumption of ≥10 pack-years, postbronchodilator FEV_1 ≤70% of	N=676 (2 trials) 12 weeks	Primary: Trough FEV_1, FEV_1 $AUC_{0–6}$, and FVC Secondary: PEF, albuterol rescue therapy, total albuterol use, and patient global evaluations	Primary: Mean change in trough FEV_1 was significantly larger in the tiotropium group compared to the ipratropium/albuterol group (difference, 86 ml; 95% CI, 49 to 133 ml; P<0.0001). Mean FEV_1 $AUC_{0–6}$ in the tiotropium arm was statistically non-inferior to the ipratropium/albuterol arm (difference, 17 ml; 95% CI, -21 to 56 ml, P=0.0003), but not statistically superior (P=0.37). Mean peak FEV_1 responses were larger in the ipratropium/albuterol arm compared with the tiotropium arm, with differences ranging from 120 to 134 ml (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Concomitant medications allowed throughout the trial included inhaled corticosteroids, theophylline, and stable doses of prednisone (not to exceed 10 mg daily or its equivalent)	predicted, prebronchodilator FEV_1 ≤65% of predicted, and FEV1/FVC ≤70% who were receiving ipratropium-albuterol (18/103 mcg) MDI for ≥1 month			Differences in FVC responses were similar to those observed with the FEV_1. Mean FVC trough for the tiotropium group was significantly larger on study days 42 and 84 (P<0.01) compared with the ipratropium/albuterol group, but the $AUC_{0–6}$ was not (P>0.5). Secondary: Weekly mean morning peak expiratory flow and FEV_1 were both significantly larger in the tiotropium arm compared with the ipratropium/albuterol arm for morning measurements (P<0.05), but not for evening measurements. No significant treatment-related differences were detected in albuterol rescue therapy, physician global evaluations, or patient reported shortness of breath. Total albuterol use was significantly lower in the tiotropium group compared to the ipratropium/albuterol group (5.3 vs 6.8 puffs per day based on weekly means, P<0.001). Mean patient global evaluations were statistically significantly better (P<0.05) for the tiotropium group on study day 42, but not on study day 84.
Tashkin et al.[56] (2009) Tiotropium 18 mcg QD vs arformoterol 15 mcg BID vs arformoterol 15	MB, PG, MC, RCT Patients ≥45 years of age with COPD, smoking history ≥15 pack-years, breathless severity ≥2 on Medical Council Dyspnea Score, prebronchodilator FEV_1 >0.7, FEV_1/FVC ≤70%, FEV_1 ≤65%	N=234 2 weeks	Primary: Difference in mean FEV_1 AUC_{0-24} Secondary: Differences in rescue therapy use and occurrence of adverse events	Primary: Mean FEV_1 AUC_{0-24} improved to a similar degree with arformoterol (0.10 L) and tiotropium (0.08 L), and was greater with combination therapy (0.22 L; all P<0.005). Peak FEV_1, peak FVC, 24-h trough FEV_1, and inspiratory capacity also improved to a similar degree with arformoterol and tiotropium, and were greatest with combination therapy. Dyspnea (mean transition dyspnea index) improved to a similar degree with arformoterol (+2.3) and tiotropium (+1.8), and was greatest with combination therapy (+3.1; all P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg BID and tiotropium 18 mcg QD	predicted			Levalbuterol use decreased for all treatment groups (range -1.8 to -2.5 actuations per day). All treatments had similar overall frequencies of adverse events: arformoterol (25.0%), tiotropium (27.5%) and combination (30.8%).
Van Noord et al.[61] (2005) Tiotropium 18 mcg QD for 6 weeks vs formoterol 12 mcg BID for 6 weeks vs tiotropium 18 mcg QD and formoterol 12 mcg BID for 6 weeks	RCT, DB, XO Patients with COPD	N=71 18 weeks	Primary: FEV_1, FVC, rescue medication use	Primary: Tiotropium produced a significantly greater improvement in average daytime FEV_1 (0–12 h) than formoterol (127 ml versus 86 ml). The average nighttime FEV_1 (12–24 h) was not different among the treatment groups (tiotropium 43 ml and formoterol 38 ml). Combination therapy had significantly greater improvements in both endpoints compared to monotherapy (daytime 234 ml and nighttime 86 ml). Changes in FVC were similar to the changes in FEV_1 results. Daytime salbutamol use was significantly lower with combination therapy compared to monotherapy (tiotropium plus formoterol 1.81 puffs/day, tiotropium 2.41 puffs/day, formoterol 2.37 puffs/day).
Rabe et al.[35] (2008) Tiotropium 18 mcg QD and formoterol 12 mcg BID vs salmeterol 50mcg BID and fluticasone 500 mcg BID	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <80% and FEV_1/FVC ≤70% predicted at visit 1, and prebronchodilator FEV_1 ≤65% predicted at visit 2	N=605 6 weeks	Primary: FEV_1 AUC 0–12h and peak FEV_1 Secondary: Peak FVC and FVC AUC 0–12; morning predose FEV1 and FVC	Primary: The FEV_1 $AUC_{0–12}$ mean difference was 78 mL higher in patients receiving tiotropium + formoterol compared to those receiving salmeterol + fluticasone (P=0.0006). The difference in peak FEV_1 was 103 mL in favor of tiotropium + formoterol (P=0.0001). Secondary: The 12-h FVC profile and peak FVC were significantly higher with tiotropium + formoterol compared to salmeterol + fluticasone (P=0.0001). There was no significant difference in predose FEV_1, however the difference in predose FVC favored tiotropium + formoterol (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brusasco et al.[11] (2003) Tiotropium 18 mcg QD vs salmeterol 50 mcg BID vs placebo	RCT, PC, DB, DD Patients with ≥40 years of age with COPD, FEV_1 ≤65% and FVC ≤70% predicted	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity Secondary: Quality of life (SGRQ), dyspnea (TDI focal score), spirometry, adverse events	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo (P=0.01). There was no significant difference with salmeterol compared to placebo. The proportion of patients with at least one exacerbation was 32%, 35%, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (P>0.05). Fewer COPD exacerbations/patient year occurred in the tiotropium group (1.07) than in the placebo group (1.49, P<0.05). The salmeterol group did not differ from placebo (1.23 events/year). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant. The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared with 11.1 days in the salmeterol group and 10.9 days in the placebo group (P<0.05). Secondary: The SGRQ total score improved by 4.2, 2.8, and 1.5 units during the 6 month trial for the tiotropium, salmeterol, and placebo groups, respectively. A significant difference was observed for tiotropium vs placebo (P=0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared with placebo (P=0.001 and P=0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (P=0.17).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Tiotropium was statistically better than salmeterol in peak FEV_1 and area under the curve from 0 to 3 hours. For trough FEV_1 values, tiotropium exhibited a similar trend. Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%).
Donohue et al.[13] (2002) Tiotropium 18 mcg QD vs salmeterol 50 mcg BID vs placebo	RCT, PC, DB, MC Patients ≥40 years of age with stable COPD, FEV_1 ≤60% and FEV_1/FVC ≤70% predicted	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 had improved by 137 mL with tiotropium compared to placebo and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL, P=0.01). As with FEV_1, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (P=0.01). Secondary: PEFR improved by 27.3 L/minute, 21.4 L/minute, and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (P=0.001) and tiotropium was better than salmeterol in improving evening PEFR (P=0.05). At 6 months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (P=0.01), and 0.24 units for salmeterol (P=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference 0.78 units, P=0.05). At 6 months, the mean improvement in SGRQ was -5.14 units for tiotropium (P=0.05 vs placebo), -3.54 units for salmeterol (P=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance.
Briggs et al.[62] (2005) Tiotropium 10	RCT, DB, PG Patients with COPD	N=653 12 weeks	Primary: Lung function	Primary: After 12 weeks, the average post-dose FEV_1 over 12 hours was significantly higher with tiotropium compared with salmeterol (167 vs. 130 ml, respectively, P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg QD vs salmeterol 50 mcg BID				Peak FEV_1 was significantly higher with tiotropium compared with salmeterol (262 vs. 216 ml, respectively, P=0.01). The average FEV_1 responses from 0-6 h and 6-12 h were higher in the tiotropium group compared with salmeterol (P<0.05). Peak and average FVC were significantly higher with tiotropium compared with salmeterol (P<0.01). Morning pre-dose FEV_1 responses were not significantly different among the treatment groups. Tiotropium demonstrated a significantly higher pre-dose FVC than salmeterol (P<0.05).
van Noord et al.[60] (2010) Tiotropium 18 mcg QD vs salmeterol 50 mcg BID vs tiotropium 18 mcg QD and salmeterol 50 mcg QD vs tiotropium 18 mcg QD and salmeterol 50 mcg BID	RCT, DB, XO Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤60% predicted and FEV_1/FVC ≤70%	N=95 24 weeks	Primary: FEV_1, FVC, effects on dyspnea (TDI focal score), rescue albuterol use	Primary: FEV_1 increased by 72 mL with tiotropium plus salmeterol QD compared to 97 mL with either monotherapy agent (P<0.0001). Treatment with tiotropium plus salmeterol BID provided comparable daytime bronchodilator effects (0-12h: 12mL, P=0.38) as tiotropium plus salmeterol QD, but significantly more bronchodilation during the night-time (12-24h: 73mL, P<0.0001). Clinically relevant improvements in TDI focal score were achieved with bronchodilator combinations including salmeterol QD or BID (2.56 and 2.71; P<0.005 vs. monotherapy). Symptom benefit of combination therapies was also reflected in less need for reliever medication. All treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aaron et al.[34] (2007) Tiotropium 18 mcg QD vs tiotropium 18 mcg QD and salmeterol 50 mcg BID vs tiotropium 18 mcg QD and fluticasone-salmeterol 500/50 mcg BID	DB, MC, PC, RCT Patients ≥35 years of age with ≥1 COPD exacerbation in last 12 months requiring systemic steroids or antibiotics; history of ≥10 pack-years of cigarette smoking; documented chronic airflow obstruction with FEV_1/FVC <0.70 and a postbronchodilator FEV_1 ≤65% of the predicted value	N=449 1 year	Primary: Proportion of patients who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics Secondary: Number of COPD exacerbations per patient-year; number of hospitalizations for COPD and all causes; changes in health-related quality of life, dyspnea, and lung function	Primary: The proportion of patients who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics in the tiotropium + placebo group (62.8%) did not differ from the tiotropium + salmeterol group (64.8%; [95% CI, -12.8 to 8.8%) or from the tiotropium + fluticasone/salmeterol group (60.0%; 95% CI, -8.2 to 13.8%). Secondary: COPD exacerbations did not significantly differ between the tiotropium + placebo and the other 2 treatment groups. Patients treated with tiotropium + fluticasone/salmeterol had lower rates of severe exacerbations of COPD requiring hospitalization than did patients treated with tiotropium +placebo (P=0.01). Tiotropium + salmeterol did not statistically affect hospitalization rates compared with tiotropium + placebo. All-cause hospitalizations were reduced in patients treated with tiotropium + fluticasone/salmeterol compared with patients treated with tiotropium + placebo (P=0.04). Treatment with tiotropium + salmeterol or tiotropium + fluticasone/salmeterol improved health-related quality of life significantly more than did therapy with tiotropium + placebo. Dyspnea scores did not significantly differ among the treatment groups. Tiotropium + fluticasone-salmeterol improved lung function compared with tiotropium + placebo (P=0.049). Tiotropium + salmeterol did not statistically improve lung function compared with tiotropium + placebo.
Welte et al.[57] (2009) Tiotropium 18 mcg QD and budesonide-formoterol (320/9 mcg) BID	DB, PG, MC RCT Patients ≥40 years of age with COPD symptoms for ≥2 years, ≥1 COPD exacerbation in the previous 12 months requiring systemic	N=660 12 weeks	Primary: Change in pre-dose FEV_1 Secondary: Mean predose FVC and IC, mean postdose FEV_1, mean FVC at 5 and	Primary: Treatment with budesonide/formoterol plus tiotropium significantly increased mean predose FEV_1 by 6% (65 mL) and mean postdose FEV_1 by 11% (123 and 131 mL at 5 and 60 min postdose, respectively) versus tiotropium monotherapy (all, P=0.001). Secondary: Mean change in predose FVC was +53 mL (P=0.021), 5 min postdose FVC was 157 mL (P=0.001), and 60 min postdose FVC was 160 mL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tiotropium 18 mcg QD	steroids and/or antibiotics, smoking history of ≥10 pack-years, FEV_1 ≤50% predicted and FEV_1/FVC <70% predose		60 minutes, IC at 60 minutes plus SGRQ	(P=0.001). Mean change in predose IC was 64 mL (P=0.020) and 110 mL at 60 min postdose Over the study period, SGRQ improved +3.8 with budesonide/formoterol added to tiotropium compared to +1.5 with tiotropium alone (mean difference, –2.3; 95% CI, –4.23 to –0.32; P=0.023). Improvements in SGRQ of +4 were seen in 49.5% and 40.0% of patients in the budesonide/formoterol added to tiotropium and tiotropium alone, respectively (P=0.016). A similar proportion of patients in each arm had a deterioration in SGRQ more than -4 (27.6 and 29.7%, respectively). The number of severe exacerbations decreased by 62% (95% CI, 0.25 to 0.57; P=0.001).
Lee et al.[52] (2009) Tiotropium-containing regimens vs non-tiotropium combination regimens	Cohort Veterans ≥45 years of age with COPD who were switched to regimens containing tiotropium	N=42,090 Death, no prescription refill for 180 days, or 547 days from index date, whichever occurred first	Primary: Difference in all-cause mortality, COPD exacerbations, and COPD hospitalizations	Primary: Treatment with tiotropium + ICS + LABA was associated with a 40% reduction in death compared with ICS + LABA (95% CI, 0.45-0.79). Treatment with tiotropium + ICS + LABA was associated with a 16% reduction of COPD exacerbations compared with other regimens (95% CI, 0.73-0.97). There was no significant difference in exacerbations with tiotropium + ICS + LABA compared with ICS + LABA (HR 1.03; 95% CI, 0.88-1.21). Treatment with tiotropium + ICS + LABA was associated with a 22% reduction of COPD hospitalizations compared with other regimens (95% CI 0.62-0.98). There was no significant difference in hospitalizations with tiotropium + ICS + LABA compared with ICS + LABA (HR 1.15; 95% CI, 0.90-1.46). Other 3-drug combination regimens that included tiotropium and the 4-drug combination regimens that included tiotropium + ICS + LABA + ipratropium were associated with increased mortality risk (HR=1.38, 95% CI 1.06 – 1.81 and HR=1.36, 95% CI 1.05 – 1.76, respectively).
Barr et al.[32] (2005)	MA	N=6,584 (9 trials)	Primary: Exacerbations,	Primary: Reduced exacerbations seen in the tiotropium group compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tiotropium vs placebo, ipratropium, LABA	Patients with COPD	≥1 month	hospitalizations, mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use, adverse events	(OR 0.75; 95% CI 0.66 to 0.85) and compared to ipratropium (OR 0.64; 95% CI 0.44 to 0.92). Hospitalizations for COPD exacerbations were reduced in the tiotropium group compared to placebo (OR 0.65; 95% CI 0.50 to 0.85) and compared to ipratropium and salmeterol but these differences were not statistically significant (OR 0.59; 95% CI 0.32 to 1.09; OR 0.59; 95% CI 0.29 to 1.23). Cumulative all-cause mortality was 1.5% in the control groups and there were no statistically significant differences between any of the treatment groups over the duration of the trials. Secondary: In the tiotropium group, there was a greater mean change in trough FEV_1 from baseline that was statistically significant compared to placebo (140 ml; 95% CI 118 to 162 ml), ipratropium (150 ml; 95% CI 106 to 193ml) and salmeterol (40 ml; 95% CI 12-68 ml). In the tiotropium group, there was a greater mean change in trough FVC from baseline that was statistically significant compared to placebo (278 ml; 95% CI 208 to 348 ml) ipratropium (210 ml; 95% CI 112 to 308 ml) and salmeterol (90 ml; 95% CI 35-145 ml). In the tiotropium group, there was a greater mean change in morning peak flow from baseline that was statistically significant compared to the placebo (21 ml; 95% CI 15 to 28 ml) and ipratropium (16 ml; 95% CI 7 to 25 ml). There was no difference between the tiotropium and salmeterol groups (0 ml; 95% CI -8 to 9 ml). In the tiotropium group, dry mouth was significantly increased compared to placebo (OR 5.4; 95% CI 3.3 to 8.8), ipratropium (OR 2.1; 95% CI, 1.05 to 4.2), and salmeterol (OR 5.1; 95% CI 2.2 to 12).
Baker et al.[49] (2009) Tiotropium vs	MA Patients with COPD	N=31,020 (43 trials) 4 to 60 weeks	Primary: COPD exacerbations and all-cause mortality Secondary:	Primary: Long-acting β_2-agonists, tiotropium, inhaled corticosteroids, and combination inhaled corticosteroid with long-acting β_2-agonists therapy each decreased the odds of having an exacerbation by 16%, 31%, 15%, and 24%, respectively, compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhaled corticosteroids vs long-acting β_2-agonists vs combination therapy			Withdrawal from trial based on drug class	Tiotropium reduced the odds of having at least one exacerbation by 18% compared with long-acting β_2-agonists and by 19% compared with inhaled corticosteroids alone. Compared with combination therapy, tiotropium reduced exacerbations by 9%. Only combination therapy was associated with a mortality benefit, showing a 29% reduction compared with placebo and a 25% reduction compared with long-acting β_2-agonists alone. Compared with combination therapy, tiotropium use non-significantly increased mortality by 4%. Secondary: Each of the four drug classes was associated with a significant reduction in withdrawals (26–41%) compared with placebo. Both tiotropium and combination therapy significantly reduced patient withdrawals compared with long-acting β_2-agonists or ICS alone.
Puhan et al.[54] (2009) Tiotropium vs LABA monotherapy vs ICS monotherapy vs ICS + LABA combination therapy	MA Patients with stable COPD	N=26,786 (35 trials) ≥4 weeks	Primary: Comparison of treatments by reported COPD exacerbations Secondary: Comparison of treatments by reported COPD exacerbations in patients with FEV_1 ≤40% or FEV_1 >40% predicted	Primary: All regimens significantly reduced exacerbations compared to placebo: tiotropium (OR 0.41; 95% CI, 0.64 – 0.80), ICS (OR 0.78; 95% CI, 0.70 to 0.86), LABA (OR 0.77; 95% CI, 0.64 – 0.84), and ICS + LABA (OR 0.72; 95% CI, 0.64 – 0.80). Neither tiotropium nor combination therapy reduced exacerbations more than LABA monotherapy (OR 1.02; 95% CI, 0.90 – 1.16 and OR 0.93; 95% CI, 0.84 – 1.04, respectively). Combined treatment was not more effective than LABA or tiotropium monotherapy (OR 0.93; 95% CI, 0.84 – 1.04 and OR 1.02; 95% CI, 0.90 to 1.16, respectively) Secondary: In patients with FEV_1 ≤40% predicted, tiotropium, ICS, and ICS + LABA significantly reduced exacerbations compared to LABA monotherapy (OR 0.83; 95% CI, 0.71 – 0.98; OR 0.75; 95% CI, 0.57 – 1.00, and OR 0.79; 95% CI, 0.67 – 0.93, respectively). In patients with FEV_1 >40% predicted, there was no difference in COPD exacerbations between treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rodrigo et al.[55] (2009) Tiotropium vs placebo, LABA, or ICS + LABA	MA Patients >35 years of age with stable COPD	N=18,111 (19 trials) ≥4weeks	Primary: Major CV events (composite of nonfatal MI, stroke, and CV death), CV mortality (includes sudden death), nonfatal MI, and nonfatal stroke (includes TIA) Secondary: All cause mortality	Primary: There was no difference in the incidence of major CV events among the treatment groups (RR 0.96; 95% CI, 0.82 – 1.12). There was no difference in CV deaths among the treatment groups (RR 0.93; 95% CI, 0.73 – 1.20). There was no difference in nonfatal MI among the treatment groups (RR 0.84; 95% CI, 0.6 – 1.09). There was no difference in nonfatal stroke among the treatment groups (RR 1.04; 95% CI, 0.78 – 1.39). Secondary: Tiotropium did not significantly increase the risk of all-cause mortality (RR 0.97; 95% CI, 0.86 - 1.09).
Celli et al.[59] (2010) Tiotropium 18 mcg QD vs placebo	MA Patients ≥40 years of age with COPD and smoking history of ≥10 pack-years, and spirometric confirmation of airflow limitation including an FEV_1 ≤70% of FVC	N=19,545 (30 trials) ≥4 weeks	Primary: All-cause mortality and selected CV events, including a composite CV endpoint including CV deaths, nonfatal MI, nonfatal stroke, and the terms sudden death, sudden cardiac death, and cardiac death	Primary: For all-cause mortality, the incidence rate was 3.44 (tiotropium) and 4.10 (placebo) per 100 patient-years (RR 0.88; 95% CI, 0.77–0.999). The incidence rate for the CV endpoint was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years (RR 0.83; 95% CI 0.71–0.98). The incidence rate for CV mortality (excluding nonfatal MI and stroke) was 0.91 (tiotropium) and 1.24 (placebo) per 100 patient-years (RR 0.77; 95% CI 0.60–0.98). The relative risk of total MI, cardiac failure, and stroke were 0.78 (95% CI, 0.59-1.02), 0.82 (95% CI, 0.69-0.98), and 1.03 (95% CI, 0.79-1.35), respectively.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, COPD=chronic obstructive pulmonary disease, ED=emergency department, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, LOS=length of stay, PEF=peak expiratory flow, PEFR=peak expiratory flow rate

Additional Evidence

Dose Simplification
Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. Evidence-based guidelines for the selection of the appropriate inhalation delivery device have been published. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[41] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[41] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[41] Incorrect technique can result in decreased drug delivery and potentially decreased efficacy. The ability of a patient to use a particular inhalation device correctly may be affected by a number of factors. These factors include age, cognitive status, coordination, manual dexterity/strength, severity of respiratory disease, and visual acuity.[43] Adherence to inhaled therapy is often poor, with rates of 40% to 72% being reported.[43] Patient preference should be considered when selecting an inhalation delivery device. Barta et al. mailed a survey to 82 patients (most with COPD) using a home nebulizer treatment.[44] It consisted of 29 questions covering topics of well-being, symptom control, self-confidence, dependency, time, and technical issues, side effects, and compliance. In the questionnaire, 98% of patients reported the benefits of using a nebulizer outweighed the disadvantages. The perceived advantages were the ability to control symptoms and be less dependent on health care providers, hospitals and care givers. When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.[41]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Inhaled Antimuscarinics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ipratropium	aerosol inhaler, inhalation solution*	Atrovent HFA®	$$$$	$
Tiotropium	dry powder inhaler	Spiriva®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The inhaled antimuscarinics are approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[1-5] Tiotropium is also approved to reduce exacerbations in patients with COPD.[5] Tiotropium has a longer duration of action than ipratropium, which distinguishes tiotropium and ipratropium as long- and short-acting antimuscarinics, respectively. Ipratropium inhalation solution is the only product that is available in a generic formulation.

Most studies have indicated that the existing medications to treat COPD do not modify the long-term decline in lung function.[18] Therefore, the goal of treatment is to decrease symptoms and complications. Bronchodilators are central to the symptomatic management of COPD. The principal bronchodilators are β_2-agonists, antimuscarinics and xanthines. For the treatment of mild airflow obstruction, guidelines recommend the use of a short-acting bronchodilator as needed for the relief of breathlessness and exercise limitation.[18-21] For patients who require daily maintenance therapy to control symptoms, an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic).[18,20-21] Treatment guidelines do not indicate a preference as there is insufficient evidence to favor one long-acting bronchodilator over another.[18,46] When selecting an inhaled antimuscarinic, a long-acting agent is preferred over a short-acting agent due to differences in efficacy.[18,20]

Clinical trials have demonstrated that the regular use of a short- or long-acting antimuscarinic improves health status.[11,13-14,17,27,29-31,34-35,40,50-53,56-58] Tiotropium has been shown to significantly reduce COPD exacerbations, improve spirometric indices, and lead to improvements in health-related quality of life and symptom scales compared to treatment with ipratropium.[14,17] In addition, tiotropium may provide a greater clinical benefit than long-acting β_2-agonists.[11,13,61-63]

Several meta-analyses and observational studies have been conducted by independent investigators to assess the link between the use of inhaled antimuscarinics and cardiovascular events.[23,36-37,55,59] In 2008, the FDA released several communications describing a potential increased risk of stroke, myocardial infarction, or death from cardiovascular causes with tiotropium.[39] However, the results of the UPLIFT trial did not support these findings.[40,58] In January 2010, the FDA completed its review and informed health care providers that the data do not support an association between the use of tiotropium and an increased risk for these serious adverse events.[47]

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. According to the ACCP/ACAAI guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[41] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[41] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability, clinical setting, patient age and the ability to use the selected device correctly, device use with multiple medications, drug administration time, convenience in both outpatient and inpatient settings, as well as physician and patient preference.[41]

Therefore, all brand short-acting inhaled antimuscarinics within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Tiotropium offers significant clinical advantages in general use over short-acting inhaled antimuscarinics.

XI. Recommendations

No brand short-acting inhaled antimuscarinic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Tiotropium (Spiriva®) is recommended for preferred status.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
4. Atrovent HFA® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; July 2010.
5. Spiriva HandiHaler® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; June 2010.
6. Rennard SI, Serby CW, Ghafouri M, et al. Extended therapy with ipratropium is associated with improved lung function in patients with COPD: a retrospective analysis of data from seven clinical trials. Chest. 1996;110(1):62-70.
7. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. Ann Intern Med. 2005;143(5):317-26.
8. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8-hours with once-daily tiotropium in patients with COPD. Chest. 2005;128(3):1168-78.
9. O'Donnell DE, Fluge T, Gerken F. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. Eur Respir J. 2004;23(6):832-40.
10. Celli B, ZuWallack R, Wang S, et al. Improvements in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest. 2003;124(5):1743-8.
11. Brusasco V, Hodder R, Miravitlles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax. 2003;58(5):399-404.
12. Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. Chest. 2003;123(5):1441-9.
13. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest. 2002;122(1):47-55.
14. Vincken W, van Noord JA, Greefhorst APM, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J. 2002;19(2):209-16.
15. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19(2):217-24.
16. Casaburi R, Briggs D Jr., Donohue JF, et al. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD. Chest. 2000;118(5):1294-1302.
17. Van Noord JA, Bantje TA, Eland ME, et al. A randomized controlled comparison of tiotropium and ipratropium in the treatment of COPD. Thorax. 2000;55(4):289-94.
18. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009. 93 p. Available at: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed October 2010.
19. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
20. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 June. 61 p. Available at: http://guidance.nice.org.uk/CG101. Accessed October 2010.
21. Bellamy D, Bouchard J, Henrichsen S, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J 2006;15:48-57.
22. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010;363:1715-1726.
23. Ogale SS, Lee TA, Au DH, et al. Cardiovascular events with ipratropium bromide in COPD. Chest 2010;137(1):13-19.
24. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.

25. Boulet LP, Becker A, Berube D, et al. Summary of recommendations from the Canadian Asthma Consensus Report, 1999. CMAJ. 1999;161(suppl 11):S1-S12.
26. The American Thoracic Society Workshop on Refractory Asthma. Proceeding of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. Am J Respir Crit Care Med. 2000;162(6):2341-51.
27. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
28. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
29. Casaburi R, Kukafka D, Cooper CB, et al. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 2005;127(3):809-17.
30. Matera MG, Caputi M, Cazzola M, et al. A combination with clinical recommended dosages of salmeterol and ipratropium is not more effective than salmeterol alone in patients with chronic obstructive pulmonary disease. Respir Med. 1996;90(8):497-9.
31. Van Noord JA, de Munck DRAJ, Bantje ThA, et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J. 2000;15(5):878-85.
32. Barr RG, Bourbeau J, Camargo CA et al. Tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.:CD002876.
33. McCrory DC, Brown CD. Anticholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2002, Issue 4. Art. No.:CD003900.
34. Aaron SD, Vandemheen KL, Fergusson D et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007;146:545-55.
35. Rabe K, Timmer W, Sagkriotis A et al. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. Chest 2008; 134:255-62.
36. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2008;300:1439-1450.
37. Lee TA, Pickard S, et al. Risk of death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med 2008;149:380-390.
38. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
39. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070651.htm. Accessed November 2010.
40. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.
41. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. American College of Chest Physicians /American College of Asthma, Allergy, and Immunology. Chest 2005;127:335-371.
42. Filuk R. Delivery system selection: clinical considerations. AHDB 2008;1(8S):13-17.
43. Rand CS. Patient adherence with COPD therapy. Eur Respir Rev 2005;14:97-101.
44. Barta SK, Crawford A, Roberts CM. Survey of patients' views of domiciliary nebuliser treatment for chronic lung disease. Respir Med 2002;96:375-381.
45. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.
46. Qaseem A, Snow V, Shekelle P, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians (ACP). Ann Intern Med 2007;147:633-8.
47. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva

HandiHaler). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm197429.htm. Accessed November 2010.

48. Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of airways obstruction in the elderly: recommendations for prescribing. Drugs Aging 2008;25(5):415-442.
49. Baker WL, Baker EL, Coleman CI. Pharmacologic treatments for chronic obstructive pulmonary disease: a mixed-treatment comparison meta-analysis. Pharmacotherapy 2009;29(8):891-905.
50. Decramer M, Celli B, Kesten S, et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomized controlled trial. Lancet 2009;374:1171-1178.
51. Halpin D, Menjoge S, Viel K. Patient-level pooled analysis of the effect of tiotropium on COPD exacerbations and related hospitalizations. Prim Care Resp J 2009;18(2):106-113.
52. Lee TA, Wilke C, Joo M, et al. Outcomes associated with tiotropium use in patients with chronic obstructive pulmonary disease. Ann Intern Med 2009;169(15):1403-1410.
53. Niewoehner DR, Lapidus R, Cote C, et al. Therapeutic conversion of the combination of ipratropium and albuterol in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2009;22(6):587-592.
54. Puhan MA, Bachmann LM, Kleijnen J, et al. Inhaled drugs to reduced exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. BMC Med 2009. Available at: http://www.biomedcentral.com. Accessed October 2010.
55. Rodrigo J, Castro-Rodriguez JA, Nannini LJ, et al. Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. Respir Med 2009;103 (10):1421-1429.
56. Tashkin DP, Donohue JF, Mahler DA, et al. Effects of arformoterol twice daily, tiotropium once daily, and their combination in patients with COPD. Respir Med 2009;103:516-524.
57. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-750.
58. Celli B, Decramer M, Kesten S, et al. Mortality in 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:984-955.
59. Celli B, Decramer M, Leimer I, et al. Cardiovascular safety of tiotropium in patients with COPD. Chest 2010;137(1):20-30.
60. van Noord JA, Aumann JL, Janssens E et al. Combining tiotropium and salmeterol in COPD: Effects on airflow obstruction and symptoms. Respir Med 2010;104:995-1004.
61. Van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Resp J 2005;26:214-22.
62. Briggs DD Jr, Covelli H, Lapidus R, et al. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther 2005;18:397-404.
63. Chen AM, Bollmeier SG, Finnegan PM. Long-acting bronchodilator therapy for the treatment of chronic obstructive pulmonary disease. Ann Pharmacother 2008;42:1832-42.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Respiratory Beta-Adrenergic Agonists
AHFS Class 121208
February 9, 2011

I. Overview

The respiratory beta-adrenergic agonists (β_2-agonists) are approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and exercise-induced bronchospasm.[1-16] They stimulate β_2-receptors and relax airway smooth muscle, which leads to bronchodilation.

All of the β_2-agonists elicit a similar biologic response; however, they differ in their dosing requirements, pharmacokinetic parameters and adverse events. Short-acting β_2-agonists include albuterol, ipratropium/albuterol, levalbuterol, metaproterenol, pirbuterol and terbutaline. These agents increase airflow within 30 minutes and the effects may last up to 4-5 hours. Short-acting β_2-agonists are the treatment of choice for relieving acute asthma symptoms; however, they are not recommended for scheduled daily use. Long-acting β_2-agonists (LABAs) include albuterol (extended-release tablets), arformoterol, formoterol and salmeterol. They are administered twice daily for the maintenance treatment of bronchospasm associated with asthma and COPD.

The respiratory beta-adrenergic agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Albuterol (immediate-release tablets, inhalation solution, sustained-release tablets and syrup), ipratropium/albuterol (inhalation solution), levalbuterol (inhalation solution), metaproterenol (syrup and tablets) and terbutaline (tablets) are available in a generic formulation. There are currently no aerosol or dry powder inhalers available generically. This class was last reviewed in December 2008.

Table 1. Respiratory Beta-Adrenergic Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Albuterol	aerosol inhaler, inhalation solution, sustained-release tablet, syrup, tablet	AccuNeb®*, ProAir HFA®, Proventil HFA®, Ventolin HFA®	albuterol, ProAir HFA®, Proventil HFA®, Ventolin HFA®
Arformoterol	inhalation solution	Brovana®	none
Formoterol	inhalation solution, dry powder inhaler	Foradil®, Perforomist®	Foradil®
Ipratropium and albuterol	aerosol inhaler, inhalation solution	Combivent®, DuoNeb®*	albuterol and ipratropium, Combivent®
Levalbuterol	aerosol inhaler, inhalation solution	Xopenex®*, Xopenex HFA®	levalbuterol, Xopenex HFA®
Metaproterenol	syrup, tablet	N/A	metaproterenol
Pirbuterol	aerosol inhaler	Maxair Autohaler®	Maxair Autohaler®
Salmeterol	dry powder inhaler	Serevent Diskus®	Serevent Diskus®
Terbutaline	tablet	N/A	terbutaline

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the respiratory beta-adrenergic agonists are summarized in Table 2. For a comprehensive overview of the treatment of asthma and chronic obstructive pulmonary disease, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Respiratory Beta-Adrenergic Agonists

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): **British Guideline on the Management of Asthma[20] (2009)**	General Treatment Considerations • Inhaled corticosteroids are the recommended preventer drug for adults and children for achieving overall treatment goals. • The first choice as add-on therapy to inhaled corticosteroids in adults and children (5-12 years of age) is an inhaled long-acting β_2-agonist. In children <5 years of age, the first choice as add-on therapy to inhaled corticosteroids is leukotriene receptor antagonists. • Long-acting β_2-agonists (LABAs) should not be used without inhaled corticosteroids. • There is no difference in efficacy in giving inhaled corticosteroid and long-acting β_2-agonist in combination or in separate inhalers. Once a patient is stable, the combination inhalers might be advantageous as they may prevent the accidental use of the long-acting β_2-agonist without the inhaled corticosteroid. • An inhaled short-acting β_2-agonist should be prescribed as short-term reliever therapy for all patients with symptomatic asthma. Exercise-induced Asthma • The following treatments provide protection against exercise-induced asthma: inhaled corticosteroids, short-acting β_2-agonists, LABAs, theophyllines, leukotriene receptor antagonists, chromones, and β_2-agonist tablets. • LABAs and leukotriene antagonists provide more prolonged protection than short-acting β_2-agonists, but some tolerance may develop with LABAs. No tolerance has been demonstrated with leukotriene receptor antagonists. • If exercise is a specific problem in patients who are well controlled on inhaled corticosteroids, consider the following therapies: leukotriene receptor antagonists, LABAs, chromones, oral β_2-agonists, or theophyllines. • Inhaled short-acting β_2-agonists are the drug of choice immediately prior to exercise. Delivery Systems • For acute asthma, the use of a pressurized metered dose inhaler (pMDI) + spacer is at least as good as a nebulizer at treating mild and moderate exacerbations of asthma in children and adults. • For stable asthma in children aged 0-5, there is no evidence comparing nebulizer and other inhalers, and there is insufficient evidence to draw conclusions regarding pMDI compared to a dry powder inhaler (DPI). A pMDI + spacer are the preferred method of delivery of β_2-agonists. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. Where this is ineffective, a nebulizer may be required. • For stable asthma in children aged 5-12, there is no significant difference between pMDI + spacer and DPI. • For stable asthma in adults, there is no significant difference between pMDI ± spacer and DPI. Patients have been shown to prefer Turbohaler to pMDI. • The choice of a reliever inhaler for stable asthma should be based on

Clinical Guideline	Recommendation(s)
	patient preference and the assessment of correct use. Many patients will not be prepared to carry a spacer.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention[19] (2009)**	Controller Medications – Adults • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. To achieve control, add-on therapy with another type of controller medication is preferred over increasing the dose of the inhaled glucocorticosteroid. • Long-acting β_2-agonists (LABAs) should not be used as monotherapy in asthma as they do not affect airway inflammation. They are most effective when combined with inhaled glucocorticosteroids. This combination is preferred when a medium dose of an inhaled glucocorticosteroid alone fails to achieve control of asthma. • Studies have shown that delivering an inhaled glucocorticosteroid and a LABA in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers may increase compliance and ensure that the LABA is always accompanied by a glucocorticosteroid. • LABAs, when used in combination with an inhaled glucocorticosteroid, can be used to prevent exercise-induced bronchospasm. They may also provide longer protection than rapid-acting inhaled β_2-agonists. Controller Medications - Children • Inhaled glucocorticosteroids are the most effective controller therapy and are the recommended treatment for children of all ages. • Inhaled LABAs should not be used as monotherapy in children with asthma. They are primarily used as add-on therapy in children >5 years of age whose asthma is insufficiently controlled by inhaled glucocorticosteroids, or as single-dose therapy for exercise-induced bronchoconstriction. Inhaled LABAs have not been adequately studied in children ≤5 years of age. • Combination products containing an inhaled glucocorticosteroid and a LABA are preferred to the coadministration of each component as separate inhalers. Fixed combination inhalers ensure that the LABA is always accompanied by a glucocorticosteroid. The combination of budesonide and formoterol has been shown to reduce asthma exacerbations in children ≥4 years of age with moderate to serve asthma. • If a combination inhaler containing formoterol and budesonide is selected, it may be used for both rescue and maintenance. Whether this approach can be employed with other combinations of controller and reliever requires further study. • The use of oral LABAs is not recommended due to potential adverse events. Reliever Medications – Adults • Rapid-acting inhaled β_2-agonists are the mediations of choice for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction, in both adults and children of all ages. They should be used only on an as needed basis at the lowest dose and frequency required. • Short-acting oral β_2-agonists are appropriate for use in patients who are unable to use inhaled medications. Reliever Medications - Children • Rapid-acting inhaled β_2-agonists are the most effective bronchodilators and are the preferred treatment for acute asthma in children of all ages. Oral therapy is rarely needed and should be reserved for young

Clinical Guideline	Recommendation(s)

	children who cannot use inhaled therapy.
	Exacerbations of Asthma
	• The repeated administration of rapid-acting inhaled β_2-agonists (2 to 4 puffs every 20 minutes for the first hour) achieves rapid reversal of airflow limitation for patients with mild to moderate exacerbations. Additional treatment should be titrated depending upon the patient's response.
	• Bronchodilator therapy delivered via a MDI (ideally with a spacer) produces at least an equivalent improvement in lung function at the same dose delivered via nebulizer.
	• No additional medication is necessary if the rapid-acting inhaled β_2-agonist produces a complete response (PEF returns to >80% of predicted or personal best) and the response lasts for 3 to 4 hours.
	Device Selection – Children
	• Children <4 years of age
	  o Preferred: pressurized MDI plus spacer with face mask
	  o Alternate: nebulizer with face mask
	• Children 4 – 6 years of age
	  o Preferred: pressurized MDI plus spacer with mouthpiece
	  o Alternate: nebulizer with mouthpiece
	• Children >6 years of age
	  o Preferred: DPI, or breath-actuated MDI, or pressurized MDI plus spacer with mouthpiece
	  o Alternate: nebulizer with mouthpiece

Global Initiative for Asthma (GINA): **Global Strategy for the Diagnosis and Management of Asthma in Children 5 years and Younger[18] (2009)**	Controller Medications
	• A low-dose inhaled glucocorticosteroid is the recommended initial treatment option in children ≤5 years of age.
	• The effect of long-acting inhaled β_2-agonists (LABAs) or combination products (LABA plus glucocorticosteroid) has not been adequately studied in children ≤5 years of age. Therefore, LABAs cannot be recommended in this age group.
	Reliever Medications
	• Rapid-acting inhaled β_2-agonists are the most effective bronchodilators and are the preferred reliever treatment for asthma in children ≤5 years of age.
	• An MDI with spacer is an effective way for delivering reliever therapy. Nebulizer therapy is also an option when delivery is not optimal because of lack of cooperation or distress, or when the child is hypoxic.
	• Oral therapy is not recommended due to its slower onset of action and adverse events.
	Exacerbations of Asthma
	• Initial home management includes 2 puffs of a rapid-acting β_2-agonist administered via a mask or spacer device.
	Device Selection
	• Children <4 years of age
	  o Preferred: pressurized MDI plus spacer with face mask
	  o Alternate: nebulizer with face mask
	• Children 4 – 5 years of age
	  o Preferred: pressurized MDI plus spacer with mouthpiece
	  o Alternate: pressurized MDI plus spacer with face mask or nebulizer with mouthpiece or face mask

National Heart, Lung, and Blood Institute (NHLBI): **Expert Panel Report 3: Guidelines for**	Long-Term Control Medications • Inhaled corticosteroids (ICSs) are the most effective long-term therapy for mild, moderate, or severe persistent asthma.

Clinical Guideline	Recommendation(s)

the Diagnosis and Management of Asthma[17] (2007)	• LABAs are not recommended for use as monotherapy for long-term control of persistent asthma or to treat acute symptoms or exacerbations of asthma; however, they are used as an adjunct to ICS therapy.
	• LABAs are the preferred treatment to combine with ICS in children ≥12 years of age and adults. For children ≥5 years of age, LABAs should be considered an adjunctive therapy in those who have asthma that requires more than low-dose ICS.
	• Use of long-acting bronchodilators is not currently recommended to treat acute symptoms or exacerbations of asthma.
	• LABAs may be used before exercise to prevent EIB, but frequent and chronic use of LABAs for EIB may indicate poorly controlled asthma.
	Quick-Relief Medications
	• Short-acting bronchodilators (SABAs) are the preferred treatment for the relief of acute symptoms and prevention of exercise-induced bronchospasm (EIB).
	• Scheduled daily use of short-acting bronchodilators is not recommended.
	Exercise-Induced Bronchospasm (EIB):
	• Pretreatment before exercise with inhaled β_2-agonists will prevent EIB in >80% of patients.
	• SABAs used shortly before exercise (or as close to exercise as possible) may be helpful for 2–3 hours. LABAs can be protective up to 12 hours.
	Device Selection
	• Metered-dose inhaler (MDI):
	  o ≥5 years of age
	  o <5 years of age with a spacer or valved holding chamber (VHC) with face mask
	• Breath-actuated MDI:
	  o ≥5 years of age
	• Dry powder inhaler (DPI):
	  o ≥4 years of age
	• Spacer or VHC
	  o ≥4 years of age
	  o <4 years of age with VHC with face mask
	• Nebulizer:
	  o Patients of any age who cannot use MDI with VHC and face mask

International Primary Care Respiratory Group (IPCRG): **Management of Asthma[21] (2006)**	• When patients present with infrequent symptoms, prescribe rapid-acting β_2-agonists. • Prescribe a rapid-acting β_2-agonist for patients with exercise-induced asthma. • For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting β_2-agonist.
National Institute for Clinical Excellence (NICE): **Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care[26] (2010)**	General Treatment Considerations • Inhaled agents are preferred over oral treatments because of the reduction in systemic side effects. • As needed short-acting bronchodilators should be the initial empirical treatment for the relief of breathlessness and exercise limitation. • In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the following treatments are recommended as maintenance therapy: o If FEV_1 ≥50% predicted: either long-acting β_2-agonist

Clinical Guideline	Recommendation(s)
	(LABA) or long-acting antimuscarinic agent (LAMA) o If FEV_1 <50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler or LAMA • In people with stable COPD and an FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA: o Consider LABA+ICS in a combination inhaler o Consider LAMA in addition to LABA where ICS is declined or not tolerated • Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1. • Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA, irrespective of their FEV_1. Delivery Systems • In most cases, bronchodilator therapy is best administered using a hand-held inhaler device (including a spacer device if appropriate). • Patients with distressing or disabling breathlessness despite maximal therapy using inhalers should be considered for nebulizer therapy.
Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[24] (2009)**	General Treatment Considerations • Most studies have indicated that the existing medications for COPD do not modify the long-term decline in lung function. Therefore, pharmacotherapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. • Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis or on a regular basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. • The principal bronchodilator treatments are β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. • Regular treatment with long-acting bronchodilators is more effective than treatment with short-acting bronchodilators. • There is insufficient evidence to favor one long-acting bronchodilator over others. • Regular use of a long-acting β_2-agonist or a short-or long-acting anticholinergic improves health status. • Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. • An inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status. Device Systems • COPD patients may have more problems in effective coordination and find it harder to use a metered-dose inhaler (MDI) than do healthy volunteers or younger asthmatics. • Alternative breath-activated or spacer devices are available. • Dry powder inhalers (DPIs) may possibly provide improved drug deposition; however, this has not been established in COPD. • Nebulizers are not recommended for regular treatment because they require appropriate maintenance.
American College of Physicians	• Clinicians should prescribe one of the following maintenance

Clinical Guideline	Recommendation(s)
(ACP): **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease[22] (2007)**	monotherapies for symptomatic patients with COPD and FEV_1 <60% predicted: long-acting inhaled β_2-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. • Monotherapy with a long-acting inhaled β_2-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. • Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness, but differ in adverse effects, reductions in deaths, and hospitalizations. • Evidence is insufficient to recommend one monotherapy agent over another. • Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV_1 <60% predicted. • When to use combination therapy instead of monotherapy has not been clearly established. • Studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy.
International Primary Care Respiratory Group (IPCRG): **Management of Chronic Obstructive Pulmonary Disease[23] (2006)**	• None of the current pharmacologic treatments for COPD have been shown to modify the long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Bronchodilators (anticholinergics and β_2-agonists) are central to symptom management in COPD. • For regular treatment, long-acting bronchodilators are more effective than short-acting bronchodilators.
American Thoracic Society (ATS)/European Respiratory Society (ERS): **Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease[25] (2004)**	• Medications for COPD can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present, no treatment has been shown to modify the rate of decline in lung function. • A short-acting bronchodilator as needed is recommended for symptom control in patients with intermittent symptoms. • For patients with persistent symptoms, a long- or short-acting bronchodilator is recommended. If symptoms are not controlled, consider using alternate classes or combine classes. • The inhaled route is preferred when both inhaled and oral formulations are available. • Three types of bronchodilators are in common clinical use: β-agonists, anticholinergic drugs and methylxanthines. • Short-acting bronchodilators can increase exercise tolerance acutely in COPD. Combining short-acting agents produces a greater change in spirometry over 3 months than either agent alone. • Long-acting inhaled β_2-agonists improve health status, possibly to a greater degree than using regular ipratropium. Additionally, these drugs reduce symptoms, rescue medication use and increase the time between exacerbations compared with placebo. • Combining long-acting inhaled β_2-agonists and ipratropium leads to fewer exacerbations than either drug alone. • No good comparative data between different long-acting inhaled β-agonists are presently available although it is likely that their effects will be similar. • Combining long-acting β_2-agonists and theophylline appears to produce a greater spirometric change than either drug alone.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory beta-adrenergic agonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Respiratory Beta-Adrenergic Agonists[1-16]

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

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

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory beta-adrenergic agonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Respiratory Beta-Adrenergic Agonists[1-16]

Generic Name(s)	Onset (minutes)	Duration (hours)	Bio-availability (%)	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Albuterol	HFA: 5-15 Neb: 5 Tab: 30 Syrup: 30	IR: 3-6 ER: 12	INH: <20 IR/ER: 100	10	Renal (64-98)	ER: 9.3 HFA: 4.6-6 Neb: 5 Tab: 5-7.2 Syrup: 5-7.2
Arformoterol	6.7	12	Not reported	52-65	Renal (67)	26
Formoterol	3-5	12	Not reported	31-64	DPI: Renal (59-62) Neb: Renal (1-2)	DPI: 10 Neb: 7
Ipratropium and albuterol	0.25-1	3-6	I: 2-7	A: 10 I: 0-9	A: Renal (64-98) I: Renal (3.7-5.6)	A: 5-7.5 I: 1.6
Levalbuterol	5-17	3-6	Not reported	Not reported	Renal (80-100)	4
Metaproterenol	1-30	1-5	<10	Not reported	Not reported	Not reported
Pirbuterol	5-30	3-4	Not reported	Not reported	Renal (51)	2-3
Salmeterol	10-20	12	Not reported	96	Renal (25)	5.5
Terbutaline	5-45	1.5-8	100	Not reported	Renal (30-50)	3.4

A=albuterol, I=ipratropium, IR=immediate-release oral formulation, ER=extended-release oral formulation, INH=inhalation

V. Drug Interactions

Significant drug interactions with the respiratory beta-adrenergic agonists are listed in Table 5.

Table 5. Significant Drug Interactions with the Respiratory Beta-Adrenergic Agonists[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Albuterol	1	Monoamine oxidase Inhibitors	Monoamine oxidase inhibitors may increase the pharmacologic effects of albuterol. Headache, hyperpyrexia and hypertension (possibly hypertensive crisis and intracranial hemorrhage) may occur.
Albuterol, arformoterol, formoterol, ipratropium/albuterol, levalbuterol, salmeterol	1	β-adrenergic blocking agents	Pharmacologic effects of beta-adrenergic agonists may be decreased by beta-adrenergic blockers. Untoward physiologic effects, characterized by bronchospasm, may occur.
Salmeterol	1	HIV Protease Inhibitors	Pharmacologic effects of salmeterol may be increased by HIV protease inhibitors. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations,

Generic Name(s)	Significance Level	Interaction	Mechanism
			and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of the swallowed portion of a salmeterol dose.
Salmeterol	1	Imidazoles	Pharmacologic effects of salmeterol may be increased by imidazoles. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by imidazoles may decrease the metabolic elimination of the swallowed portion of the salmeterol dose.
Salmeterol	1	Macrolides & Ketolides	Pharmacologic effects of salmeterol may be increased by macrolides and ketolides. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by macrolides and ketolides may decrease the metabolic elimination of the swallowed portion of a salmeterol dose.
Salmeterol	1	Nefazodone	Pharmacologic effects of salmeterol may be increased by nefazodone. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by nefazodone may decrease the metabolic elimination of the swallowed portion of a salmeterol dose.
Terbutaline	1	Linezolid	Pharmacologic effects of terbutaline may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur. Mechanism depends on the specific sympathomimetic involved.
Albuterol, arformoterol, formoterol, ipratropium/albuterol, levalbuterol,	2	Linezolid	Coadministration of linezolid and beta-adrenergic agonists may result in adverse cardiovascular effects

Generic Name(s)	Significance Level	Interaction	Mechanism
metaproterenol, pirbuterol, salmeterol			characterized by hypertension. Inhibition of monoamine oxidase by linezolid may result in reversible enhancement of the pressor response with concomitant administration of beta-adrenergic agonists.
Albuterol, arformoterol, formoterol, ipratropium/albuterol, levalbuterol	2	Tricyclic Antidepressants	Alpha-adrenergic (vascular) effects of direct-acting sympathomimetics may be increased. Effects of indirect-acting sympathomimetics may be decreased. Tricyclic antidepressants interfere with neuronal uptake of sympathomimetic amines.
Metaproterenol, pirbuterol, salmeterol	2	COMT Inhibitor	The combination of select beta-adrenergic agonists with COMT inhibitors may result in inhibition of the pathway responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the respiratory beta-adrenergic agonists are listed in Tables 6 – 7. The boxed warnings for the long-acting respiratory beta-adrenergic agonists are listed in Tables 8 – 9. A meta-analysis of all clinical trial data for the LABAs was presented at an FDA Advisory Committee meeting in December 2008.[75] The meta-analysis included data from 110 trials, which included 60,954 patients. Three major outcomes were evaluated, including asthma-related death, death or intubation, and hospitalization. There was a significant difference in asthma-related deaths with LABAs compared to non-LABA therapy. There was also a significant difference in the composite outcome (death, intubation, hospitalization) between LABA and non-LABA therapy. In a subgroup analysis, the risk was 3.63 (95% CI, 1.51-5.75) per 1000 subjects with the LABAs compared to non-LABA therapy in patients who were not receiving an inhaled corticosteroid. In contrast, patients who received an inhaled corticosteroid did not have an increased risk with LABAs (0.25; 95% CI, -1.69 to 2.18). Based on the findings of this meta-analysis, the Advisory Committee voted unanimously that the benefits of salmeterol and formoterol did not outweigh the risks and recommended that the labeling requirements with the LABAs be enhanced.

Table 6. Adverse Drug Events (%) Reported with the Respiratory Beta-Adrenergic Agonists (Drugs A – I)[1-16]

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Ipratropium/ Albuterol‡	Ipratropium/ Albuterol§
Cardiovascular								
Angina	✔	✔	<3	7	✔	✔	-	<2
Arrhythmias	✔	✔	✔	<2	✔	✔	-	<2
Chest pain/discomfort	<1	0.9-1.7	✔	7	1.9	-	2.6	0.3
Congestive heart failure	-	-	-	<2	-	-	-	-
ECG abnormal	-	-	-	✔	-	-	-	-
Heart block	-	-	-	<2	-	-	-	-
Hypertension	✔	✔	✔	✔	✔	✔	-	<2
Hypotension	✔	✔	✔	✔	✔	✔	-	-
Myocardial ischemia/infarction	✔	✔	✔	<2	-	-	-	-
Palpitations	5	-	-	✔	✔	✔	✔	<2
Syncope	-	-	-	-	-	-	-	-
Tachycardia	5	✔	3	✔	✔	✔	✔	<2
Central Nervous System								
Anxiety	✔	✔	✔	-	-	-	-	-
Agitation	-	-	-	<2	-	-	-	-
Cerebral infarct	-	-	-	<2	-	-	-	-
Circumoral paresthesia	-	-	-	<2	-	-	-	-
CNS stimulation	✔	✔	✔	✔	-	-	-	-
Coordination difficulty	-	-	-	-	-	-	-	-
Dizziness	2	✔	3	<2	1.6	2.4	-	<2
Drowsiness	<1	-	-	-	-	-	✔	-
Excitement	20	-	-	-	-	-	-	-
Fatigue	-	-	-	<2	✔	✔	-	<2

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Ipratropium/ Albuterol‡	Ipratropium/ Albuterol§
Headache	7	0.9-1.7	7	✔	✔	✔	-	5.6
Hypokinesia	-	-	-	<2	-	-	-	-
Insomnia	2	-	-	<2	1.5	2.4	-	<2
Irritable behavior	✔	✔	✔	-	-	-	-	-
Nervousness	20	-	7	<2	✔	✔	-	<2
Nightmares	✔	✔	✔	-	-	-	-	-
Paresthesia	-	-	-	<2	-	-	-	,2
Restlessness	<1	✔	<1	-	-	-	-	-
Somnolence	2	-	-	<2	-	-	-	-
Sweating	-	-	-	-	-	-	-	-
Seizure	✔	✔	✔	-	-	-	-	-
Tremor	20	✔	✔	<2	1.9	✔	-	<2
Vertigo	-	-	✔	-	-	-	-	-
Weakness	2	-	-	-	-	-	-	-
Dermatological								
Angioedema	✔	-	✔	-	-	-	-	<2
Dry skin	-	-	-	<2	-	-	-	-
Flushing	<1	-	-	-	-	-	✔	-
Herpes simplex/zoster	-	-	-	<2	-	-	-	-
Photodermatitis	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	1.5	-	<1	-
Rash	✔	✔	✔	4	1.1	-	<1	-
Skin discoloration	-	-	-	<2	-	-	-	✔ -
Skin hypertrophy	-	-	-	<2	-	-	-	-
Urticaria	✔	0.9-1.7	✔	✔	-	-	<1	<2
Endocrine and Metabolic								
Hyperglycemia	✔	-	-	✔	✔	✔	-	-
Hypokalemia	✔	✔	✔	<2	✔	✔	-	-
Lactic acidosis	✔	✔	✔	-	✔	✔	-	-
Gastrointestinal								
Constipation	-	-	-	<2	-	-	✔	-
Diarrhea	✔	✔	✔	6	-	4.9	1.8	<2
Dry mouth	✔	✔	✔	-	1.2	1.3-3.3	-	<2
Dyspepsia	✔	✔	✔	-	-	3.3	1.3	<2
Gastrointestinal distress	-	-	-	-	-	-	-	-
Gastroenteritis	✔	0.9-3.4	✔	<2	-	-	-	-
Heartburn	-	-	-	-	-	-	-	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Ipratropium/ Albuterol‡	Ipratropium/ Albuterol§
Nausea	2	0.9-1.7	-	-	-	4.9	1.4	2
Oral candidiasis	-	-	-	<2	-	-	-	-
Oral moniliasis	-	-	-	<2	-	-	-	-
Periodontal abscess	-	-	-	<2	-	-	-	-
Rectal hemorrhage/melena	-	-	-	<2	-	-	-	-
Sore throat	-	-	-	-	-	-	✔	-
Taste changes	✔	✔	✔	-	-	-	✔	<2
Vomiting	-	-	7	-	-	2.4	-	<2
Genitourinary								
Breast neoplasm	-	-	-	<2	-	-	-	-
Calcium crystalluria	-	-	-	<2	-	-	-	-
Cystitis	-	-	-	<2	-	-	-	-
Glycosuria	-	-	-	<2	-	-	-	-
Hematuria	-	-	-	<2	-	-	-	-
Kidney calculus	-	-	-	<2	-	-	-	-
Nocturia	-	-	-	<2	-	-	-	-
PSA increase	-	-	-	<2	-	-	-	-
Pyuria	-	-	-	<2	-	-	-	-
Urinary tract disorder	-	-	-	<2	-	-	-	-
Urine abnormality	-	-	-	<2	-	-	-	-
Urinary difficulty	<1	✔	<1	-	-	-	-	-
Urinary tract infection	-	-	✔	-	-	-	1.6	<2
Hematologic								
Liver enzyme elevation	-	-	-	-	-	-	-	-
Musculoskeletal								
Arthralgia	✔	✔	✔	<2	-	-	✔	<2
Arthritis	-	-	-	<2	-	-	-	-
Back pain	-	-	-	-	4.2	-	✔	-
Bone disorder	-	-	-	<2	-	-	-	-
Leg cramps	-	-	-	4	1.7	-	1.4	-
Muscle cramps	✔	✔	✔	<2	1.7	✔	-	-
Pain	<1	-	3-5	8	-	-	1.3	2.5
Rheumatoid arthritis	-	-	-	<2	-	-	-	-
Tendinous contracture	-	-	-	<2	-	-	-	-
Respiratory								
Asthma exacerbation	✔	11-13	✔	-	✔	✔	-	-
Bronchitis	-	0.9-1.7	-	✔	4.6	-	1.7	12.3

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Ipratropium/ Albuterol‡	Ipratropium/ Albuterol§
Bronchospasm	✔	✔	✔	-	-	-	✔	0.3
Chest infection	-	-	-	-	2.7	-	-	-
COPD exacerbation	-	-	-	-	-	4.1	✔	-
Cough	✔	✔	5	-	-	-	-	4.2
Cold symptoms	-	3.4	-	-	-	-	-	-
Drying of oropharynx	✔	✔	✔	-	-	-	-	-
Drying of secretions	-	-	-	-	-	-	-	-
Dysphonia	-	-	-	<2	1	-	-	<2
Dyspnea	-	-	✔	4	2.1	-	-	4.5
Epistaxis	✔	✔	✔	-	-	-	-	-
Hoarseness	✔	✔	✔	-	-	-	-	-
Increased sputum	-	-	-	-	1.5	-	-	<2
Irritation	-	-	-	-	-	-	-	-
Laryngospasm	-	-	-	-	-	-	-	<2
Lung disease	-	-	-	-	-	-	6.4	-
Lung carcinoma	-	-	-	<2	-	-	-	-
Lymphadenopathy	-	0.9-2.6	-	-	-	-	-	-
Nasal congestion	-	1	-	-	-	-	-	-
Oral mucosal abnormality	-	-	-	<2	-	-	-	-
Pharyngitis	✔	<1	14	-	3.5	3.3	4.4	2.2
Pneumonia	-	-	-	-	-	-	1.3	1.4
Pulmonary edema	✔	✔	✔	-	-	-	-	-
Respiratory disorder	-	-	-	2	-	-	-	2.5
Rhinitis	✔	✔	5-16	-	-	-	-	1.1
Sinusitis	-	-	-	5	2.7	-	✔	2.3
Skin/appendage infection	-	0-1.7	-	-	-	-	-	-
Throat irritation	✔	✔	1	-	-	-	-	-
Upper respiratory tract infection	-	-	21	-	7.4	-	✔	10.9
Viral respiratory infection	✔	2.6	7	-	-	-	-	-
Voice alterations	-	-	-	<2	-	-	✔	-
Wheezing	-	-	-	-	-	-	✔	-
Other								
Acute eye pain	-	-	-	-	-	-	✔	-
Alopecia	-	-	-	-	-	-	-	-
Anaphylactic reaction	✔	0.9-3.4	6	✔	-	-	-	<2
Back pain	-	-	-	6	-	-	-	-
Blurred vision	-	-	-	<2	-	-	✔	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Ipratropium/ Albuterol‡	Ipratropium/ Albuterol§
Edema	-	-	✔	3	-	-	-	<2
Fever	-	-	6	-	2.2	-	-	-
Glossitis	✔	✔	✔	-	-	-	-	-
Glaucoma	-	-	-	<2	-	-	-	-
Influenza	-	-	3	-	-	-	-	1.4
Otitis media	✔	0.9-4.3	✔	-	-	-	-	-
Tonsillitis	-	-	-	-	1.2	-	-	-
Tongue ulceration	✔	✔	✔	-	-	-	-	-
Trauma	-	-	-	-	-	-	-	-
Viral infection	-	-	-	-	17.2	-	-	-
Worsening glaucoma	-	-	-	-	-	-	✔	-

✔ Percent not specified
- Event not reported
*Oral formulations.
‡Inhalation solution formulation.
§Aerosol formulation.

Table 7. Adverse Drug Events (%) Reported with the Respiratory Beta-Adrenergic Agonists (Drugs L – T)[1-16]

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Pirbuterol	Salmeterol	Terbutaline*
Cardiovascular						
Angina	-	-	✔	-	-	-
Arrhythmias	-	✔	✔	-	1-3	1.5
Chest pain	<2	-	<1	✔	-	-
ECG abnormal	<2	-	-	-	-	-
Hypertension	<2	<2	0.4	-	-	-
Hypotension	<2	-	-	✔	-	-
Palpitations	-	-	3.8	1.7-1.9	✔	5
Syncope	<2	-	<1	-	✔	-
Tachycardia	2.7	✔	17.1	1.2- 2.9	✔	3.5
Vasodilations	-	-	-	-	-	1
Central Nervous System						
Anxiety	2.7	-	-	✔	1-3	1
Asthenia	3	-	-	-	-	-
Confusion	-	-	-	✔	-	-
Depression	-	-	-	✔	-	-
Dizziness	1.4-2.7	2.7	2.4	0.6-1.2	4	3.5
Fatigue	-	-	<1	✔	-	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Pirbuterol	Salmeterol	Terbutaline*
Hallucinations	-	-	-	-	-	<1
Headache	-	-	7	1.3-2	13-17	7.5
Hyperkinesia	-	-	-	✔	-	-
Hypertonia	-	-	-	-	-	<1
Hypesthesia of the hand	<2	-	-	-	-	-
Insomnia	<2	-	1.8	✔	-	1.5
Migraine	2.7	-	-	-	-	-
Nervousness	2.8-9.6	✔	20.2	4.5-6.9	✔	35
Paresthesia	<2	-	-	-	1-3	<1
Sensory disturbances	-	-	<1	-	1-3	-
Somnolence	-	-	-	-	-	5.5
Sweating	<2	-	-	-	-	1
Tremor	6.8	✔	1-17	1.3-9.4	✔	15
Weakness	-	-	<1	✔	-	-
Dermatological						
Angioedema	-	✔	-	-	✔	-
Bruising	-	-	-	✔	-	-
Contact dermatitis	-	-	-	-	1-3	-
Diaphoresis	-	-	<1	-	-	-
Eczema	-	-	-	-	1-3	-
Flushing	-	-	-	-	-	-
Hives	-	-	<1	-	-	-
Photodermatitis	-	-	-	-	1-2	-
Pruritus	-	-	2	✔	-	-
Rash	7.5	✔	-	✔	1-3	<1
Skin reaction	-	-	-	-	4	-
Urticaria	3	✔	-	-	3	-
Endocrine and Metabolic						
Hyperglycemia	-	-	-	-	1-3	-
Gastrointestinal						
Abdominal pain	-	-	-	✔	-	-
Anorexia	-	-	-	✔	-	-
Constipation	-	<2	-	-	-	-
Dental discomfort	-	-	-	-	1-3	-
Diarrhea	1.5-6	-	1.2	1.3	-	-
Dry mouth	<2	-	<1	1.3-2.1	-	1.5
Dyspepsia	1.4-2.7	-	-	-	-	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Pirbuterol	Salmeterol	Terbutaline*
Dyspeptic symptoms	-	-	-	-	1-3	-
Gastroenteritis	<2	<2	-	-	-	-
Gastrointestinal infections	-	-	-	-	1-3	-
Gastrointestinal distress	-	-	-	-	1-3	-
Glossitis	-	-	-	✔	-	-
Hyposalivation	-	-	-	-	1-3	-
Nausea	<2	-	3.6	1.3-1.7	1-3	3
Oral candidiasis	-	-	-	-	1-3	-
Stomatitis	-	-	-	✔	-	-
Taste changes	-	-	<1	✔	-	-
Vomiting	<2	10.5	<1	✔	3	<1
Genitourinary						
Vaginal moniliasis	-	<2	-	-	-	-
Hematuria	-	<2	-	-	-	-
Musculoskeletal						
Arthralgia	-	-	-	-	1-2	-
Articular rheumatism	-	-	-	-	1-2	-
Leg cramps	2.7	-	-	-	-	-
Muscle cramps	-	-	-	-	3	-
Muscle spasm	-	-	-	-	3	<1
Muscle stiffness	-	-	-	-	1-3	-
Muscle tightness	-	-	-	-	1-3	-
Muscle rigidity	-	-	-	-	1-3	-
Musculoskeletal inflammation	-	-	-	-	1-3	-
Myalgia	1.5	<2	-	-	12	-
Pain	1.4-3.0	4	<1	-	1-3	-
Respiratory						
Asthma	9-9.1	9.4	2	-	3-4	-
Bronchitis	-	2.6	-	-	7	-
Bronchospasm	-	-	-	-	✔	-
Cough	1.4-4.1	-	<1	1.2	4	-
Dyspnea	-	✔	-	-	-	-
Epistaxis	-	<2	-	-	-	-
Influenza	-	-	-	-	5	-
Laryngeal irritation/swelling	-	-	<1	-	1-3	-
Laryngeal spasm	-	-	-	-	1-3	-
Lung Disorder	-	<2	-	-	-	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Pirbuterol	Salmeterol	Terbutaline*
Nasal congestion	-	-	-	-	-	-
Oral mucosal abnormality	-	-	-	-	1-3	-
Pharyngitis	3-10.4	6.6-7.9	-	-	6	-
Rhinitis	2.7-11.1	7.4	-	-	2	-
Sinus headache	-	-	-	-	1-3	-
Sinusitis	1.4-4.2	-	-	-	-	-
Throat irritation	-	-	-	✔	-	-
Viral respiratory infection	-	-	-	-	4	-
Wheezing	<2	-	-	-	-	-
Other						
Accidental injury	4.5-6.1	9.2	-	-	-	-
Acne	-	<2	-	-	-	-
Alopecia	-	-	-	✔	-	-
Anaphylaxis	-	-	-	-	1-3	-
Conjunctivitis	-	<2	-	-	1-3	-
Cyst	-	<2	-	-	-	-
Chills	<2	-	<1	-	-	-
Chatty	-	-	<1	-	-	-
Clonus on flexed foot	-	-	<1	-	-	-
Dysmenorrhea	-	<2	-	-	-	-
Ear pain	-	<2	-	-	-	-
Ear signs	-	-	-	-	4	-
Edema	-	-	<1	✔	1-3	-
Eye itch	<2	-	-	-	-	-
Fever	3-9.1	-	<1	-	1-3	-
Flu syndrome	-	<2	<1	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	<1
Herpes Simplex	-	<2	-	-	-	-
Lymphadenopathy	3	-	-	-	-	-
Liver enzyme elevation	-	-	-	-	-	<1
Turbinate edema	1.4-2.8	-	-	-	-	-
Viral infection	6.9-12.3	<2	-	-	-	-

✔ Percent not specified
- Event not reported
*Oral formulations.
‡Inhalation solution formulation.
§Aerosol formulation.

Table 8. Boxed Warning for the Long-Acting Beta-Adrenergic Agonists Approved for Asthma[1]

WARNING
Asthma-related death: Long-acting beta$_2$-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABAs. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Because of this risk, use of LABAs for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use LABAs only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue the LABA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use LABAs for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. **Pediatric and adolescent patients:** Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require the addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be considered to ensure adherence with both drugs. In cases in which use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be ensured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

Table 9. Boxed Warning for the Long-Acting Beta-Adrenergic Agonists Approved for COPD[1]

WARNING
Asthma-related death: Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of long-acting beta$_2$-agonists. The safety and efficacy of arformoterol and formoterol inhalation solution in patients with asthma have not been established. All long-acting beta$_2$-agonists are contraindicated in patients with asthma without use of a long-term asthma control medication.

VII. Dosing and Administration

The usual dosing regimens for the respiratory beta-adrenergic agonists are listed in Table 10.

Table 10. Usual Dosing Regimens for the Respiratory Beta-Adrenergic Agonists[1-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Albuterol	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Aerosol inhaler: 1-2 inhalations every 4-6 hours; maximum, 12 inhalations daily Inhalation solution: 2.5 mg 3-4 times daily	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Aerosol inhaler: ≥4 years of age: 1-2 inhalations every 4-6 hours; maximum, 12 inhalations daily Inhalation solution: 2-12 years of age: 0.63-1.25	Aerosol inhaler: 90 mcg Inhalation solution: 0.63 mg/3 ml 1.25 mg.3 ml 2.5 mg/0.5 ml 2.5 mg/3 ml 5 mg/ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Syrup: 2-4 mg 3-4 times daily; maximum, 8 mg 4 times daily Tablet (IR): 2-4 mg 3-4 times daily Tablet (SR): 4-8 mg every 12 hours; maximum, 32 mg daily Exercise-Induced Bronchospasm: Aerosol inhaler: 2 inhalations 15-30 minutes before exercise	mg 3-4 times daily; maximum, 2.5 mg 3-4 times daily Syrup: 2-5 years of age: 0.1 mg/kg of body weight 3 times daily; maximum, 4 mg 3 times daily; 6-14 years of age: 2 mg 3-4 times daily; maximum, 24 mg daily Tablet (IR): 6-12 years of age: 2 mg 3-4 times daily Tablet (SR): 6-12 years of age: 4 mg every 12 hours; maximum, 24 mg daily in divided doses Exercise-Induced Bronchospasm: Aerosol inhaler: ≥4 years of age: 2 inhalations 15-30 minutes before exercise	Syrup: 2 mg /5 ml Tablet (IR): 2 mg 4 mg Tablet (SR): 4 mg 8 mg
Arformoterol	COPD: 15 mcg every 12 hours; maximum 2 doses per 24 hours	Safety and efficacy in children has not been established.	Inhalation solution: 15 mcg/2 ml
Formoterol	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 mcg) inhaled every 12 hours COPD: Inhalation solution: 20 mcg every 12 hours Dry powder inhaler: the contents of 1 capsule (12 mcg) inhaled every 12 hours Exercise-Induced Bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 mcg) inhaled at least 15 minutes before exercise	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 mcg) inhaled every 12 hours Exercise-Induced Bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 mcg) inhaled at least 15 minutes before exercise	Inhalation solution: 20 mcg/2 ml Dry powder inhaler: 12 mcg
Ipratropium and albuterol	COPD: Aerosol inhaler: 2 inhalations 4 times a daily; maximum, 12 inhalations daily Inhalation solution: 1 vial four times daily; maximum, 6 vials daily	Safety and efficacy in children has not been established.	Aerosol inhaler: 18-103 mcg Inhalation solution: 0.5-3 mg/3 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Levalbuterol	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Aerosol inhaler: 1-2 inhalations every 4-6 hours; maximum, 12 inhalations daily Inhalation solution: 0.63 mg 3 times daily every 6-8 hours; maximum, 1.25 mg 3 times daily	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Aerosol inhaler: ≥4 years of age: 1-2 inhalations every 4-6 hours; maximum, 12 inhalations daily Inhalation solution: 6-11 years of age: 0.31 mg 3 times daily; maximum:0.63 mg 3 times daily	Aerosol inhaler: 45 mcg Inhalation solution: 0.31 mg/3 ml 0.63 mg/3 ml 1.25 mg/3 ml 1.25 mg/0.5 ml
Metaproterenol	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Syrup: 2 teaspoonfuls 3-4 times daily; maximum, titrated to patient's response Tablet: 20 mg 3-4 times daily; maximum, titrated to patient's response	Asthma, Nocturnal Asthma, Reversible Bronchospasm: Syrup: 6-9 years of age (<60 lb): 1 teaspoonful 3-4 times daily >9 years of age (>60 lb): 2 teaspoonfuls 3-4 times daily; maximum, titrated to patient's response Tablet: 6-9 years of age (<60 lb): 10 mg 3-4 times daily >9 years of age (>60 lb): 20 mg 3-4 times daily; maximum, titrated to patient's response	Syrup: 10 mg/5 ml Tablet: 10 mg 20 mg
Pirbuterol	Asthma, Nocturnal Asthma, Reversible Bronchospasm: 1-2 inhalations repeated every 4-6 hours; maximum, 12 inhalations daily	Asthma, Nocturnal Asthma, Reversible Bronchospasm: ≥12 years of age: 1-2 inhalations repeated every 4-6 hours; maximum, 12 inhalations daily	Aerosol inhaler: 200 mcg
Salmeterol	Asthma, Nocturnal Asthma, Reversible Bronchospasm: 1 inhalation (50 mcg) 2 times daily COPD: 1 inhalation (50 mcg) 2 times daily Exercise-Induced Bronchospasm: 1 inhalation (50 mcg) at least 30 minutes before exercise	Asthma, Nocturnal Asthma, Reversible Bronchospasm: ≥4 years of age: 1 inhalation (50 mcg) 2 times daily Exercise-Induced Bronchospasm: ≥4 years of age: 1 inhalation (50 mcg) at least 30 minutes before exercise	Dry powder inhaler: 50 mcg
Terbutaline	Asthma, Nocturnal Asthma, Reversible Bronchospasm: 2.5-5 mg repeated every 6 hours 3 times daily; maximum, 15 mg daily	Asthma, Nocturnal Asthma, Reversible Bronchospasm: 12-15 years of age: 2.5 mg repeated every 6 hours 3 times daily; maximum, 7.5 mg daily	Tablet: 2.5 mg

IR=immediate-release, SR=extended-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory beta-adrenergic agonists are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Respiratory Beta-Adrenergic Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Casaburi et al.[31] (1991) Albuterol 5 mg via compressed air vs isoproterenol 5 mg via compressed air	RCT Individuals presenting for routine pulmonary function testing	N=180 Clinic visit	Primary: Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)	Primary: There was no statistical difference in FEV_1 or FVC at 5 and 10 minutes post-administration between the two groups.
Carl et al.[32] (2003) 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)	RCT, DB, PRO Patients 1 to 18 years of age with asthma presenting to the emergency department	N=482 Variable duration	Primary: Hospital admission rate Secondary: Length of stay (LOS), emergency department (ED) LOS, intensification, number of aerosols, requirement for oxygen, and adverse effects	Primary: Compared with the albuterol group (45%), the levalbuterol group (36%) had a significantly lower hospitalization rate (P=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse effects (P=0.26 to P=0.94).
Schreck et al.[33] (2005) Albuterol 2.5 mg via nebulization (plus standard	RETRO, OS, CR Patients >1 year of age with acute asthma presenting to the ED requiring	N=736 9 months	Primary: Patient disposition, ED LOS, and objective measures of patient upon arrival	Primary: In the levalbuterol group, there was a significantly lower hospitalization rate compared with albuterol (4.7% and 15.1%; P=0.0016). The rate of 15.1% is comparable to the hospitals average admission rate of 16.4%. There was no significant difference between the two treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment) vs levalbuterol 1.25 mg via nebulization (plus standard treatment)	nebulization with a short-acting beta-adrenergic agonist			concerning ED LOS and other objective measures upon patient presentation (P=0.762).
Qureshi et al.[34] (2005) Albuterol 2.5-5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25-2.5 mg via nebulization (plus standard treatment)	PRO, DB, RCT Children 2-14 years of age with a known history of asthma presenting to a pediatric ED with an acute moderate or severe asthma exacerbation	N=129 Study was complete after patient received 5 doses, was admitted, or discharged	Primary: Changes from baseline in clinical asthma score and FEV_1 after the 1st, 3rd, and 5th treatment Secondary: Number of treatments, length of ED care, rate of hospitalizations, and changes in pulse rate, respiratory rate and oxygen saturation	Primary: There were no differences between the treatment groups after the first, third, and fifth nebulizer treatments in the primary outcome of improvement in asthma score or percentage of predicted FEV_1. Secondary: There were no differences between albuterol and levalbuterol with regards to number of treatments (3 vs 3), length of care (125 minutes vs 121 minutes, rate of hospitalization (8 patients vs 7 patients), or changes in pulse rate, respiratory rate, and pulse oximetry readings. There was no difference between the groups in the number of children who received ipratropium after the third nebulizer treatment (46% in the levalbuterol and 38% in the racemic albuterol group). There were no differences in adverse events between the treatment groups.
Nowak et al.[35] (2006) Albuterol 2.5 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg vs levalbuterol 1.25	RCT, DB, PRO, MC, PG Patients ≥18 years of age presenting to the ED or clinic with an acute asthma exacerbation	N=627 1 month	Primary: Time to meet ED discharge criteria Secondary: Comparisons of FEV_1 change from baseline, the proportion of patients hospitalized, and the effect of	Primary: The median time to discharge was similar with levalbuterol (76.0) and albuterol (78.5 minutes; P=0.74). Secondary: There was no significant difference in the admission rate between the albuterol (9.3%) and the levalbuterol (7.0%) groups (P=0.28). After dose 1 and cumulative doses over time, there was a greater FEV_1 improvement following levalbuterol compared with albuterol (P=0.021). For individuals not taking corticosteroids chronically before the trial, there

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg			plasma concentration of (S)-albuterol at presentation on FEV_1 response and on hospitalization	were significantly fewer hospitalizations in the levalbuterol group compared to albuterol (3.8% vs 9.3%; P=0.03). There was no significant difference in the overall frequency of adverse effects in the two treatment groups.
Nelson et al.[36] (1998) Albuterol 1.25 mg via nebulization TID vs albuterol 2.5 mg via nebulization TID vs levalbuterol 0.63 mg via nebulization TID vs levalbuterol 1.25 mg via nebulization TID vs placebo	RCT, DB, PG, PC Patients ≥12 years of age, non-smokers, ≥6 month history of chronic and stable asthma, and ≥15% improvement in FEV_1 after a single dose of albuterol 2.5 mg via nebulization	N=362 4 weeks	Primary: Peak change in FEV_1 after 4 weeks Secondary: Area under the curve (AUC), use of rescue racemic albuterol meter dose inhaler	Primary: Change in peak FEV_1 in the combined levalbuterol group was not significantly greater than combined albuterol (0.84 and 0.74 L). 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 4, 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). 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=.003) compared to the high dose groups.
Gawchik et al.[37] (1999)	RCT, DB, XO, PC Patients 3-11 years	N=43 4 treatment	Primary: Differences in peak change in FEV_1,	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC was significantly improved in all treatment arms (with the exception

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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)	of age with a history of asthma for at least 6 months and reversibility of 12% or more 30 minutes after 2.5 mg of albuterol administered by nebulization	visits (2-8 days apart)	peak percent change in FEV_1 and AUC	of albuterol 1.25 mg in AUC) compared with 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo (1 dose)				
Milgrom et al.[38] (2001) 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	MC, RCT, DB, PG, PC Patients 4-11 years of age with asthma and reversibility of at least 15% to albuterol	N=338 3 weeks	Primary: Peak percent change in FEV_1 from baseline Secondary: Change in pulmonary function, percent of responders within 30 minutes after dose, time to peak improvement in FEV_1, use of rescue medications, symptoms, symptom-free days, asthma control days, and adverse effects	Primary: A significant improvement was seen in peak percent change in FEV_1 from baseline in all active treatment arms compared with placebo on day 21 (P<0.019). Secondary: Immediately after nebulization on days 0 and 21, there were clinically significant changes for all groups except placebo (P<0.02). 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 0, significantly more patients responded to levalbuterol 0.31 mg (62.9%) than to albuterol 1.25 mg (41.8%), immediately after nebulization; however, this was not statistically significant (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).
Nowak et al.[39] (2004) Albuterol 2.5 mg via nebulization (3 doses)	PRO, OL Adult asthmatics presenting to the ED with an acute asthma exacerbation	N=93 2 hours	Primary: Percent change in FEV_1 from baseline following the 3rd nebulization	Primary: The median percent change in FEV_1 was greater for 1.25 mg levalbuterol (74%), compared with 2.5 mg albuterol, (39%), 0.63 mg levalbuterol (37%), and 3.75 mg levalbuterol (26%) after three doses. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs albuterol 5 mg via nebulization (3 doses) vs levalbuterol 0.63 mg via 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			Secondary: Change and percent change from baseline FEV_1 at each time point, the percent of responders, and the time to achieve a 15% and 50% increase from baseline	Compared to baseline at 60 minutes post treatment, levalbuterol 1.25 mg, 2.5 mg, and 5.0 mg improved the median percent predicted FEV_1 by 33%-38% compared to 12%-24% with 2.5 mg and 5.0 mg doses of albuterol and 0.63 and 3.75 mg doses of levalbuterol. The (S) albuterol levels were found to be significantly inversely correlated with baseline FEV_1 (P=0.004), and percent change in FEV_1 60 minutes post dose (P=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levalbuterol 5 mg via nebulization (3 doses)				
Skoner et al.[104] (2005) Albuterol 1.25 to 5 mg TID via nebulizer vs levalbuterol 0.31 mg to 0.63 mg TID via nebulizer vs placebo	RCT, DB, MC Children 2-5 years of age with asthma	N=211 21 days	Primary: Adverse events, safety parameters, PEF, Pediatric Asthma Questionnaire (PAQ), and the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ)	Primary: After treatment, the PAQ decreased in all groups (P=NS). In the subset of subjects able to perform PEF (51.7%), all active treatments improved PEF after the first dose compared to placebo (placebo: 1.4; levalbuterol 0.31 mg: 12.4; levalbuterol 0.63 mg: 16.7; albuterol: 18.0 L/min; P<0.01). PACQLQ measurements improved more than the minimally important difference only in the levalbuterol-treated groups, and were significant in children <33 pounds (P<0.05). Asthma exacerbations occurred primarily in children ≥33 pounds, and one serious asthma exacerbation occurred in the albuterol group. Albuterol and levalbuterol 0.63 mg, but not levalbuterol 0.31 mg or placebo, led to significant increases in ventricular heart rate.
Berger et al.[76] (2006) Albuterol HFA 180 mcg QID vs levalbuterol HFA 90 mcg QID vs placebo	MC, RCT, DB Patients 4-11 years of age with asthma	N=150 28 days	Primary: Peak percent change in FEV_1 Secondary: Area under the FEV_1 percent change from predose curve and peak % predicted FEV_1, adverse events	Primary: Levalbuterol significantly improved the peak percent change in FEV_1 compared to placebo (25.6% vs 16.8%, respectively; P<0.001). There was no significant difference with albuterol compared to placebo (21.8% vs 16.8%, respectively; P=NS). Secondary: Results for levalbuterol were similar for the other spirometry endpoints (P<0.05 vs placebo). No levalbuterol-treated patients had a peak percent change in FEV_1 <10% compared to 15.8% of albuterol-treated patients and 30.3% of placebo-treated patients. The incidence of adverse events was 43.4% for levalbuterol, 56.4% for albuterol, and 51.4% for placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The rate of discontinuation was 1.3% for levalbuterol, 2.6% for albuterol, and 8.6% for placebo. The rate of asthma attacks was similar among treatments (levalbuterol 10.5%, albuterol 12.8%, and placebo 14.3%). The use of rescue medications (days/week) decreased with both active treatments (levalbuterol compared with placebo, P<0.001; albuterol compared with placebo, P<0.01; and levalbuterol compared with albuterol, P>0.05).
Hamilos et al.[88] (2007) Albuterol HFA 180 mcg QID vs levalbuterol HFA 90 mcg QID	MC, PG, OL Patients ≥12 years of age with mild to moderate asthma (mean FEV_1 68.3W% predicted)	N=745 6 months to 1 year	Primary: Adverse events, Secondary: asthma attacks (requiring hospitalization, a visit to the emergency department or clinic, or a burst of corticosteroids), rescue medication use, quality of life (Adult Asthma Quality of Life Questionnaire)	Primary: Rates of adverse events were similar with levalbuterol (72%) and albuterol (76.8%; P=0.12). Rates of β-mediated adverse events, serious adverse events, and discontinuations because of adverse events were low (<15%) and were comparable between groups. Rates of asthma adverse events for levalbuterol and racemic albuterol were 18.3% and 19.6%, respectively. Secondary: Rates of asthma attacks were similar between groups. Rates of rescue medication use and daytime asthma control days were similar between groups. Quality of life improved to a similar extent in both groups.
Tripp et al.[100] (2008) Albuterol HFA 90 mcg per dose (1x, 2x, 4x, 8x, and 16x) administered over a 2-hour period	RCT, AC, MC, XO Patients with asthma	N=49 Single-day	Primary: Safety and efficacy	Primary: Heart rate and (R)-albuterol exposure increased for both racemic albuterol HFA and levalbuterol HFA. For cumulative doses of 8x or greater, racemic albuterol HFA treatment had greater increases in mean heart rate than levalbuterol HFA (2.8 beats/min; 95% CI, 0.3-5.3). For cumulative doses of 16x, racemic albuterol HFA treatment had greater increases in mean heart rate than levalbuterol HFA (3.5 beats/min; 95% CI, 0.6-6.4). (R)-albuterol plasma levels ranged from 10% to 18% higher after racemic

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levalbuterol HFA 45 mcg per dose (1x, 2x, 4x, 8x, and 16x) administered over a 2-hour period				albuterol HFA dosing versus after levalbuterol HFA. FEV_1 improvements were similar for both treatments. The relative potencies of the 2 therapies (based on FEV_1) were similar (ratio, 1.1; 90% CI, 0.9-1.2).
Wolfe et al.[40] (1991) Albuterol syrup 2 mg TID vs metaproterenol syrup 10 mg TID	MC, IB, PG, RCT Patients 6-9 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, adverse effects	Primary: There was a greater degree of bronchodilation with albuterol compared to metaproterenol from 2 to 8 hours post dose (P<0.05). The peak percent improvement in $FEV_1$from baseline was significantly greater for albuterol compared to metaproterenol (29.3% vs 20.6%, P<0.05). There were no significant differences in the mean change from baseline in systolic blood pressure in either group, however with metaproterenol the chronotropic effect was significantly greater (P<0.05) at 1 hour on day 1 and 28 and 1.5 hour on day 28 compared to albuterol. There was no significant difference in the frequency of adverse effects between the two groups.
Habib et al.[103] (1987) Albuterol 5 mg via nebulizer vs metaproterenol 15 mg via nebulizer	RCT, DB Patients reversible airway obstruction utilizing intermittent positive pressure ventilation	N=20 7 days	Primary: Lung function and adverse events	Primary: There were no significant differences observed between the spirometric responses or the adverse effects of the two groups to either agent.
Papi et al.[69] (2007)	MC, DB, DD, PG, RCT	N=455 6 months	Primary: Mean rate of morning PEFR	Primary: The morning peak expiratory flow rate at 6 months was significantly higher among patients receiving as-needed combination therapy and in for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albuterol 100 mcg as needed (as needed albuterol) vs beclomethasone-albuterol 250/100 mcg in a single inhaler as needed (as needed combination) vs beclomethasone 250 mcg BID and albuterol 100 mcg as needed (regular beclomethasone) vs beclomethasone-albuterol 250/100 mcg BID in a single inhaler and albuterol 100 mcg as needed (regular combination)	Patients 18-65 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 ≥75% of predicted value, associated with either an increase in FEV_1 ≥12% of predicted value after inhalation of 200 mcg of albuterol or a positive methacholine challenge		Secondary: Lung function, symptom scores, and number/severity of exacerbations	patients receiving regular beclomethasone therapy compared to the use of as-needed albuterol therapy. The morning peak expiratory flow rate did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy. Secondary: The evening peak expiratory flow rate was significantly higher in the group receiving regular beclomethasone therapy, but not in the group receiving as-needed combination therapy compared to as-needed albuterol therapy. The prebronchodilator FEV_1 and forced vital capacity (FVC) were significantly higher after as-needed combination therapy, but not after regular beclomethasone therapy compared with as-needed albuterol therapy. These values did not differ significantly between patients receiving as-needed combination therapy and those receiving regular beclomethasone therapy or regular combination therapy. The FEV_1 and FVC increased significantly in the as-needed combination group and in the regular combination group, and evening peak expiratory flow rate increased significantly in the regular combination group. The evening peak expiratory flow rate and FEV_1 (percentage of the predicted value) increased significantly in the regular beclomethasone group. The group receiving as-needed combination therapy had fewer nocturnal awakenings, and the group receiving regular beclomethasone had less daily use of rescue medication compared to as-needed albuterol therapy. The percentage of symptom-free days was significantly higher in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy. The percentage of symptom-free days increased significantly in all groups, except the group receiving as-needed albuterol therapy, in which the number of nocturnal awakenings increased significantly. The regular beclomethasone group had fewer daytime asthma symptoms at 6 months than at baseline. A total of 237 exacerbations occurred during the study, 38 in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				receiving as-needed combination therapy, 83 in those receiving as-needed albuterol therapy, 33 in those receiving regular beclomethasone therapy, and 83 in those receiving regular combination therapy. The mean number of exacerbations per patient per year was lower in the as-needed combination group (0.74) and in the regular beclomethasone group (0.71) than in the as-needed albuterol group (1.63, P<0.001) and in the regular combination group (1.76, P<0.001). The percentage of patients with at least one exacerbation was not significantly different in the group receiving as-needed combination therapy (4.92%) and the group receiving regular beclomethasone therapy (5.66%, P=0.802) or the group receiving regular combination therapy (10.09%, P=0.133). The percentage of patients with at least one exacerbation was significantly lower both in the group receiving as-needed combination therapy and in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy (17.80%) (P=0.002 and P=0.005, respectively). The time to first exacerbation differed significantly between groups, with the shortest time to first exacerbation in the as-needed albuterol group (P=0.003 by the log-rank test).
Rabe et al.[70] (2006) Budesonide-formoterol 160/4.5 mcg BID and terbutaline MDI 0.4 mg as needed vs budesonide-formoterol 160/4.5 mcg BID and formoterol	DB, PG, RCT, MC Patients >12 years of age with asthma who had >1 severe asthma exacerbation in the 12 months before entry, use of inhaled corticosteroids for >3 months and at a constant dose for ≥4 weeks immediately before entry, FEV_1 50–100% of predicted normal	N=3,394 12 months	Primary: Time to first severe exacerbation Secondary: Total number of severe exacerbations, time to first and total number of emergency treatment or hospitalizations, asthma symptom scores—asthma control	Primary: The time to first severe exacerbation was longer with as needed budesonide-formoterol vs formoterol (P=0.0048) or terbutaline (P<0.0001). As-needed formoterol prolonged the time to first severe exacerbation versus terbutaline (P=0.0051). Secondary: As-needed budesonide-formoterol reduced the risk of a severe exacerbation by 27% (95% CI, 10–41%) versus formoterol and by 45% (95% CI, 32–55%) versus terbutaline. The risk reduction with as-needed formoterol versus terbutaline was 24% (95% CI, 8–37%). The yearly rate of severe exacerbations per patient was reduced with as-needed budesonide-formoterol by 33% versus formoterol (P<0.0001), by 48% versus terbutaline (P<0.0001), and by 22% with as-needed formoterol versus terbutaline (P=0.012; table 2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MDI 4.5 mcg as needed vs budesonide-formoterol 160/4.5 mcg BID and budesonide-formoterol 160/4.5 mcg as needed	(prebronchodilator) with 12% reversibility or more after inhalation of terbutaline 1 mg		questionnaire score; mild exacerbations; FEV1; morning and evening peak expiratory flow (PEF); and reliever medication use	Rates of exacerbations needing emergency room treatment or hospitalization were reduced with as-needed budesonide-formoterol by 27% (P=0.046) versus formoterol and by 39% (P=0.0010) versus terbutaline, respectively. There was no significant difference between formoterol and terbutaline. The proportion of patients with more than one exacerbation was lowest in the as-needed budesonide-formoterol group (3%, 7%, and 7% of patients in the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively). Mild exacerbation days were reduced by 10–18% with as-needed budesonide-formoterol compared with both formoterol P=0.043) and terbutaline (P<0.0001). The time to first mild exacerbation was longer with as-needed budesonide-formoterol versus terbutaline (P=0.0080), but the difference between as-needed budesonide-formoterol and formoterol was not significant (P=0.059). Mean asthma symptom scores decreased for all groups, with a greater reduction in the budesonide-formoterol for maintenance and reliever therapy group versus maintenance therapy plus formoterol (P=0.0002) or terbutaline (P=0.0007). Night-time awakenings were reduced by 2% (7 nights per year) with as-needed budesonide-formoterol versus formoterol (P=0.018) and by 3% versus terbutaline (P=0.0025). No between-group differences were seen with as-needed formoterol compared with terbutaline for asthma symptom scores or night-time awakenings. Asthma-control days increased in all groups with no between-group differences. Overall ACQ-5 scores improved to a greater extent with as-needed budesonide-formoterol than with formoterol (P=0.0009) and terbutaline (P<0.0001). No difference in overall ACQ-5 scores was seen with formoterol versus terbutaline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean FEV_1 improved in each of the treatment groups when all patients used maintenance budesonide-formoterol plus as-needed terbutaline (run-in). Additional increases in FEV_1 of 0.05 L and 0.08 L were seen with as-needed budesonide-formoterol versus formoterol (P=0.0001) and terbutaline (P<0.0001). Mean morning PEF increased from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol versus both formoterol (4.8 L per min; P=0.004) and terbutaline (7.5 L per min; P<0.0001). Similar improvements were noted with as-needed budesonide-formoterol for mean evening PEF compared with formoterol (5.4 L per min; P=0.0011) and terbutaline (6.3 L per min; P=0.0001). There was no significant difference in morning or evening PEF between as-needed formoterol and terbutaline. The mean reliever use decreased to 1.02 inhalations per day in the budesonide-formoterol group and to 1.23 and 1.26 inhalations per day in the formoterol and terbutaline groups, respectively. Patients receiving budesonide-formoterol used fewer as-needed inhalations per day than those receiving formoterol or terbutaline (P<0.0001 for both) and on 52% of treatment days patients in the budesonide-formoterol group did not use any as-needed medication compared with 48% in both comparator groups. There was no significant difference in reliever use between the formoterol and terbutaline groups.
Pohunek et al.[71] (2006) Budesonide-formoterol 80/4.5mcg BID (fixed-dose inhaler) vs budesonide 100	RCT, DB, PG, AC, MC Patients 4-11 years of age with PEF >50% of predicted normal who had received stable treatment with an inhaled corticosteroid, and history of an	N=630 12 weeks	Primary: Change in morning PEFR Secondary: Change from baseline in: evening PEF; total asthma-symptom score; night-time awakenings due to asthma symptoms;	Primary: The change in morning PEFR was significantly greater with budesonide/formoterol compared with budesonide (mean difference 10.9 L/min; P<0.001). There was no significant difference in morning PEF between patients treated with budesonide/formoterol and those who received budesonide + formoterol in separate inhalers (P=0.14). Significantly greater changes in evening PEF were seen in patients treated with budesonide/formoterol compared to budesonide (mean difference 9.1 L/min; P<0.001). There was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg 2 puffs BID vs budesonide 100 mcg 2 puffs BID and formoterol 4.5 mcg 2 puffs BID (separate inhalers)	average of ≥1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study		use of reliever medication; reliever-free days; symptom-free days; change in FEV_1, change in health-related quality of life (Pediatric Asthma Quality of Life Questionnaire [PAQLQ])	Patients treated with budesonide/formoterol had significantly greater changes in FEV_1 compared with budesonide (mean difference 0.078 L; P<0.001). There was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers. Asthma symptoms improved from baseline with all treatments, with no significant between-group differences. Overall PAQLQ(S) scores improved in all treatment groups, with adjusted mean changes of 0.437, 0.494 and 0.501 for the budesonide/ formoterol, budesonide + formoterol in separate inhalers and budesonide treatment groups, respectively. No significant between-group differences were observed. Scores were also improved for the individual domains, indicating improvements with regard to symptoms, emotional function and activity limitation; there were no differences between the treatment groups.
Peters et al.[73] (2007) LOCSS Fluticasone 100mcg BID vs montelukast 5-10 mg QD vs fluticasone-salmeterol 100mcg/50mcg QHS	DB, MC, RCT Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-bronchodilator, reversibility of airway obstruction by ≥12% with the use of a β-agonist or provocative concentration of methacholine producing a 20% decrease in FEV_1 of ≤8 mg/ml within the previous 2 years. Patients were stable on fluticasone 100 mcg BID and step-	N=500 16 weeks	Primary: Time to treatment failure Secondary: Measures of pulmonary function, measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients	Primary: The rates of treatment failure were 20.2% in the fluticasone group, 20.4% in the fluticasone/salmeterol group, and 30.3% in the montelukast group (HR, 1.6; 95% CI, 1.1 to 2.6; P=0.03 for both comparisons). Secondary: Mean prebronchodilator FEV_1 values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone/salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value; P=0.002 and P<0.001, respectively). Asthma control, as measured with the use of the Asthma Control Questionnaire, was better in the fluticasone group and in the fluticasone/salmeterol group than in the montelukast group. The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone/salmeterol group (22.9% vs. 17.1%, P=0.06) and in the fluticasone group (22.9% vs. 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	down therapy was being attempted.			fluticasone group than in the montelukast group (16.7% vs. 25.4%; P=0.04), with a similar trend in the fluticasone/salmeterol group (17.3%, vs. 25.4% in the montelukast group; P=0.06). The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6% to 85.8%.
Boonsawat et al.[41] (2003) Formoterol 18 mcg administered at 0, 30, and 60 minutes vs albuterol 100 mcg administered at 0, 30, and 60 minutes	RCT, DB, DD, PG Patients 18-67 years of age with asthma presenting to the emergency department with acute bronchoconstriction	N=88 1 day	Primary: FEV_1, asthma symptoms	Primary: A non-significant increase in FEV_1 at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group, P=0.18). There was a significant increase in the maximum FEV_1 between 75-240 and 15-45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51% vs 36%, P<0.05). Subjective symptom score assessments decreased during the course of the study.
Lee-Wong et al.[95] (2008) Formoterol 12 mcg every 30 minutes, up to 2 treatments vs albuterol 2.5 mcg via nebulization every 30 minutes, up to 2 treatments	RCT Patients 18 to 65 years of age who presented to the emergency department with mild to moderate asthma exacerbation (PEFR 40% to 60% of predicted)	N=34 1 treatment period	Primary: Symptom scores and PEFR	Primary: At 30 and 60 minutes, the mean PEFR of the albuterol group increased from 43.7% of predicted to 51.9% of predicted and 54.6% of predicted, respectively. The formoterol group had changes in the mean PEFR from 49.3% of predicted to 55.5% of predicted and 57.3% of predicted, respectively. The mean change in the 2 groups was not significantly different at 30 and 60 minutes (P=0.64 and P=0.57, respectively). Symptom scores improved in the albuterol group by 3.7 and 5.5 from 0 minutes to 30 and 60 minutes, respectively. In the formoterol group, these values were 3.1 and 4.9 at 30 and 60 minutes, respectively. The mean change in the 2 groups was not significantly different at 30 and 60 minutes (P=0.61 and 0.76, respectively).
Pauwels et al.[42] (2003) Formoterol 4.5 mcg as needed	RCT, OL, MC Patients ≥6 years of age with asthma requiring the use of beta-adrenergic	N=18,124 6 month	Primary: Asthma-related and non-asthma-related serious adverse events (SAE),	Primary: The number of adverse effects was not statistically significant between the two groups. There was a significantly higher number of asthma-related DAE with formoterol compared to albuterol (1% vs 0.5%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs albuterol 200 mcg administered as needed	agonists as reliever medication		discontinuation due to adverse effects (DAE), and time to first exacerbation Secondary: Rescue reliever mediation	Compared with albuterol, there was a significantly longer time to first asthma exacerbation than with formoterol (P<0.001). Secondary: Rescue inhaler use decreased in both groups over the course of the study, with a significantly greater decrease seen in the formoterol group (P<0.001).
Molimard et al.[43] (2001) Formoterol 12 mcg and albuterol aerosol inhaler to use as needed vs albuterol 100 mcg per inhalation to be used throughout the day on demand (ODS)	MC, RCT, OL, PG Patients ≥18 years of age with moderate persistent asthma	N=259 3 months	Primary: The mean change in morning predose PEF Secondary: Mean increase in evening predose PEF for the entire treatment period, and day and night use of albuterol and scores on the St. George's Hospital Respiratory Questionnaire (SGRQ)	Primary: There was a higher mean increase in the morning PEF in the formoterol group than in the ODS group (+25.7 L/min and 4.5 L/min (P<0.0001). Secondary: At visits 3 and 5 there was a significantly greater improvement in predose FEV_1 with formoterol compared to ODS (P<0.01, P<0.05). At the conclusion of three months, the mean changes from baseline in the number of puffs of albuterol during the day and night were: -0.8 and -0.4 with formoterol and +0.1 and +0.1 for ODS (P<0.0001). There was a significantly higher increase in symptom-free days and nights in the formoterol group when compared to ODS (+20%, +30%, P<0.0001, P<0.003). A significantly higher decrease was seen in the SGRQ score with formoterol (-6.4) compared to ODS (-3.5) (P=0.05).
Pleskow et al.[44] (2003) Formoterol 12 mcg BID vs formoterol 24 mcg BID	MC, RCT, DB, PC, DD, PG Patients 12-75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: FEV_1 at the 12-hour evaluation time point Secondary: AUC of FEV_1, and percent of predicted FEV_1	Primary: At the 12-hour mark, both formoterol groups showed significant improvements in FEV_1compared to placebo and albuterol (P<0.001 and P<0.002) with no statistical difference between albuterol and placebo at this time. Secondary: Both formoterol groups showed significant improvements at all time points vs placebo (P<0.001) with the exception of formoterol 12 mcg at time 0. Both groups also showed significant improvement compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs albuterol 180 mcg QID vs placebo				albuterol at time 0, 2-6 hours, and 10-12 hours (P<0.001 and P<0.002). In the albuterol group, there was a significant difference at all time points compared to placebo, except 0, 4-6 and 10-12 hours (P<0.013). The AUC of FEV_1 was significantly different in favor of both formoterol groups compared to placebo (P<0.001), formoterol 24 mcg compared to albuterol (P<0.001) and albuterol compared to placebo (P<0.008) at all visits. Both medications were well tolerated with no significant difference between them.
Wolfe et al.[72] (2006) Formoterol 24 mcg BID vs formoterol 12 mcg BID, with up to 2 additional 12 mcg daily doses of formoterol as needed for worsening symptoms (12 mcg bid plus on demand) vs formoterol 12 mcg BID vs	MC, RCT, DB, PC Patients ≥12 years of age with persistent asthma, FEV_1 ≥40% of predicted normal, and FEV_1 reversibility ≥12% after treatment with albuterol	N=2,085 16 weeks	Primary: Serious asthma exacerbations (SAE)	Primary: Nine patients had SAEs requiring hospitalization: two patients (0.4%) in the 24 mcg BID group; one patient (0.2%) in the 12 mcg BID plus on demand group; five patients (0.9%) in the 12 mcg BID group; one patient (0.2%) in the placebo group. All events were asthma-related, except for two SAE in the 12 mcg BID group that were later considered not to be asthma-related by independent reviewers who were not associated with the conduct of the study. Proportions of patients with SAE (requiring systemic corticosteroids) were similar in the 24 mcg BID group (6.3%), 12 mcg BID group (5.9%) and placebo group (8.8%) and lower in the 12 mcg BID plus on demand group (4.4%; P=0.0057 vs placebo). All formoterol treatment regimens had a significant effect on FEV_1 measured 2 hours after dose during the study (P<0.0001 vs placebo); and on predose trough FEV_1 measured at all visits after baseline (P<0.002 vs placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Bouros et al.[55] (1999) Formoterol 12 mcg BID and beclomethasone 500 mcg daily vs beclomethasone 1,000 mcg daily	OL, MC, RCT, PG Patients ≥18 years of age with asthma who were symptomatic on 500 mcg daily of inhaled beclomethasone	N=132 12 weeks	Primary: Mean PEF during final 7 days of treatment Secondary: Overall PEF, asthma symptoms, rescue medication, and safety	Primary: There was a treatment effect of 20.36 L/min in the combination group over the patients receiving the double dose of steroid (P=0.021). Secondary: For the entire treatment period, the combination group had an overall evening premedication PEF that was significantly higher compared to the double dose of steroid (P<0.05). There was a decrease in day and night symptom scores in both groups but there was a significant difference in favor of the combination treatment arm (night P=0.001, day P<0.001). In both groups the number of puffs of rescue medication taken decreased during the study, with a significant improvement seen with the combination compared to the double dose of the steroid (night P=0.003, day P<0.001) There was no significant difference in adverse events in either group.
Ralston et al.[85] (2005) Levalbuterol 1.25 mg via nebulization (≤6 doses) vs albuterol 5 mg and ipratropium 0.25 mg via nebulization (≤3 doses) followed by albuterol 5 mg via	RCT, PRO, DB Patients 6-18 years of age with a history of asthma (any severity), ability to use a peak flow meter, and peak expiratory flow (PEF) <80% predicted upon presentation to the ED	N=154 1 day	Primary: Emergency department (ED) length of stay (LOS) Secondary: Percent change in PEF, percent change in heart rate, number of nebulized treatments until disposition, frequency of adjunctive treatment in ED,	Primary: The ED LOS was not significantly different among the treatment groups (P=0.130). Secondary: Significantly more patients in the albuterol/ipratropium group were given systemic steroids (P=0.014). No other secondary endpoints were statistically significant between groups (P=0.257 to P=1.00).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nebulization (≤3 doses)			frequency of unplanned return to medical facility within 72 hours of discharge	
Tinkelman et al.[45] (1990) Metaproterenol via inhalation vs pirbuterol via inhalation	MC, DB, PG Asthmatic patients	N=133 12 weeks	Primary: Onset of action, peak effect, side effects, and tolerance	Primary: There was no clinical difference between the two treatment groups in the outcomes.
Von Berg et al.[30] (1998) Salmeterol 50 mcg BID vs placebo	RCT, DB, PG, PC Patients 6-15 years of age with a documented history of reversible airway obstruction requiring β-adrenergic agonist treatment for symptomatic control	N=426 12 months	Primary: Change from baseline in mean morning peak expiratory flow (PEF) Secondary: Percent of symptom-free nights and days, percent of nights and days with no rescue inhaler, and incidence of asthma exacerbations	Primary: Over the first 6 months of the study, the adjusted mean change above baseline in mean morning PEF was 341 minutes in patients treated with salmeterol compared with 171 minutes for placebo. (P<0.001). This significant improvement was maintained throughout the second 6 months of the study (P=0.03). Over the first 6 months of the study, the adjusted mean change above baseline in mean evening PEF was 251 minutes in patients treated with salmeterol compared with 121 minutes for placebo. (P<0.001). This significant improvement was maintained throughout the second 6 months of the study (P=0.05). Secondary: Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the treatment groups. There was a higher frequency distribution of the percentage of nights with no rescue inhaler use in patients receiving salmeterol compared to placebo that was significant throughout the 12-month treatment period (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During the 12-month treatment period there was no statistically significant difference between the treatment groups in the number of patients with asthma exacerbations (P=0.20).
Nelson et al.[28] (2006) SMART Salmeterol 42 mcg BID vs placebo	MC, RCT, DB, PG, PC, OS Patients >12 years of age with a diagnosis of asthma and currently using asthma medications	N=26,355 28 weeks	Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations	Primary: There were 3 asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol (P<0.05). Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary endpoints. For the primary and two of the secondary endpoints there were a statistically significant difference in African Americans receiving salmeterol compared to placebo (P<0.05). Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%; P=0.022).
Boulet et al.[48] (1997) Salmeterol 50 mcg BID vs albuterol 200 mcg QID	MC, RCT, DB, PG Patients ≥12 years of age with mild to moderate asthma requiring daily pharmacotherapy for at least 6 months	N=228 15 weeks	Primary: FEV_1 Secondary: PEF, symptoms, use of rescue medication, adverse events	Primary: Salmeterol treatment resulted in a significantly greater mean improvement in FEV_1 compared with albuterol treatment from hours 3-6 (P<0.001) and 10-12 (P<0.012). This effect was maintained throughout the study. Secondary: A significant improvement in evening PEF was seen for salmeterol-treated patients compared to albuterol (34 L/min vs 6 L/min; P<0.001). The average percent increase of symptom free days in the salmeterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group was significantly greater than albuterol (29% vs 15%; P=0.012). There was no significant difference in rescue medication use between the two groups and both treatments were well tolerated.
Faurschou et al.[49] (1996) Salmeterol 100 mcg BID and on-demand albuterol vs albuterol 400 mcg and on demand albuterol	MC, DB, DD, RCT, PG Patients ≥18 years of age with asthma currently receiving inhaled corticosteroids	N=190 6 weeks	Primary: PEFR Secondary: Symptom scores, use of rescue inhaler, FEV_1, and patient and physician assessment of efficacy	Primary: The mean morning PEFR improved by 33 L/min in the salmeterol group compared to 4 L/min in the albuterol group at the conclusion of the study (P<0.001). There was a significant reduction in diurnal variation in the salmeterol group (39 L/min to 22 L/min) compared to the albuterol group (34 L/min to 37 L/min; P<0.001). Secondary: Salmeterol increased FEV_1 after 3 and 6 weeks compared to baseline significantly more than albuterol (P<0.05 for both weeks). There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group (P<0.001); however, there was no significant difference in symptom-free days. There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol-treated group (P<0.04).
Martin et al.[52] (1999) Salmeterol 84 mcg BID vs albuterol extended-release tablets 4 mg in the morning and 8 mg in the evening	MC, DB, DD, RCT, XO Patients 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, safety analysis	Primary: PEF and FEV_1 were significantly improved in both treatment groups (P<0.001), but there was no significant differences among the treatment groups. Secondary: There was a significant improvement in the percentage of nights without awakenings 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. A significant decrease in baseline puffs per day of a rescue inhaler was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				observed in both the salmeterol (4.57 to 1.85; P<0.001) and the extended release albuterol tablets (4.57 to 2.66; P<0.001). The decrease with salmeterol was significantly greater (P<0.001). A total of 78% of the patients treated with extended release albuterol tablets and 75.9% of patients treated with salmeterol listed adverse effects during the study. A difference that was not statistically significant.
Campbell et al.[93] (1999) Salmeterol Accuhaler (SM DPI) or pressurized MDI (SM MDI) 50 mcg BID for 8 weeks, then cross-over to eformoterol* for 4 weeks vs eformoterol* Turbohaler (eFM) 12 mcg BID for 8 weeks, then cross-over to salmeterol for 4 weeks	RCT, XO, OL Patients ≥12 years of age with mild to moderate persistent asthma who were not adequately controlled on inhaled corticosteroids	N=469 12 weeks	Primary: Asthma symptoms, nocturnal awakenings, exacerbations, hospital admissions	Primary: There was no significant difference in asthma symptoms between the treatment groups (% of days symptom-free and using no rescue medicine to relieve symptoms: eFM, 32.8 vs SM DPI, 24.1 vs SM MDI, 28; P=NS). There was no significant difference in nocturnal awakenings between the treatment groups. Patients in all treatment groups gained an additional 1 to 1.5 nights undisturbed by asthma per week; P=NS). There was no significant difference in exacerbations between the treatment groups. The mean number of episodes of worsening of asthma per patient were 0.12 (eFM), 0.13 (SM DPI), and 0.12 (SM MDI; P=0.9144 for eFM vs SM DPI, P=0.9041 for eFM vs SM MDI). There was no significant difference in the percent of patients with worsening asthma between the treatment groups: 11 (eFM), 12 (SM DPI), and 12 (SM MDI; P values not reported). There was no significant difference in the number of episodes of worsening asthma resulting in short course of oral or nebulized steroids: 13 (eFM), 5 (SM DPI), and 11 (SM MDI; P values not reported). There was no significant difference between the treatment groups in hospital admissions or visits to the emergency department (P values not reported). There was no significant difference between the treatment groups in the number of admissions/visits: 1 (eFM), 1 (SM DPI), and 2 (SM MDI). The Turbohaler was preferred by patients given both Turbohaler and a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				pressurized MDI (P=0.0168) and was considered to be more convenient to carry around than the Accuhaler (P<0.0001). No other differences were found between the three devices.
Everden et al.[94] (2004) Salmeterol DPI (SM DPI) 50 mcg BID vs eformoterol* Turbohaler (eFM) 12 mcg BID	RCT, OL, PG Patients 6-17 years of age with moderate persistent asthma who were not adequately controlled on inhaled corticosteroids	N=156 12 weeks	Primary: Changes in daytime reliever β_2-agonist therapy, total 24-h reliever use, symptom scores, patient and care giver health-related quality of life (HRQL)	Primary: Daytime reliever use decreased significantly from baseline by 65% in the eformoterol group and by 52% in the salmeterol groups (P<0.001). Compared with salmeterol, eformoterol produced a greater decrease in daytime (-0.46 inhalations/day; P=0.081) and 24 hour (-0.70 inhalations/day; P=0.043) reliever use. The percentage of patients who did not require any reliever medication during the study was significantly higher in the eformoterol group (P<0.05 vs. salmeterol at weeks 8 and 12). There was no significant difference in asthma symptoms between the treatment groups. The overall daytime symptom scores were -0.70 (eFM) compared to -0.53 (SM DPI; 95% CI, -0.36 to 0.02; P=0.052). There was no significant difference in the overall night-time symptom scores between the treatment groups: -0.50 (eFM) compared to -0.47 (SM DPI; 95% CI, -0.22 to 0.17; P=0.687). There was no significant difference in poorly controlled days per patient per 12 weeks: 12.4 (eFM) vs 17.0 (SM DPI; P=0.107). There was no significant difference in the median days time to achieve pre-defined criteria for asthma control: 12 (eFM) vs 26 (SM DPI; P=0.175). There was no significant difference in nocturnal awakenings (nights per week): -1.03 (eFM) vs -1.31 (SM DPI; 95% CI, -0.36 to 0.92); P=0.632). There was no significant difference in the percent of patients experiencing a severe exacerbation: 17 (eFM) vs 17 (SM DPI; P=NS). There was no significant difference in the frequency of mild exacerbations

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				per patient per 12 weeks: 7.8 (eFM) vs 12.2 (SM DPI; P=0.051). There was no significant difference in quality of life between the treatment groups (P=NS). There was no significant difference in the amount of missed work among the treatment groups. The proportion of days in which parents were unable to attend work or participate in leisure activities because of child's asthma was 0.76% with eFM compared to 3.52% with SM DPI (P=0.071). There was no significant difference in the amount of missed school (1% to 2% of days in both groups; P=NS). There was no significant difference in compliance rates among the treatment groups (90% vs. 88% P=NS).
Vervloet et al.[46] (1998) Salmeterol 50 mcg BID vs formoterol 12 mcg BID	RCT, PG, OL, MC Patients ≥18 years of age with moderate to severe asthma and currently using regular inhaled corticosteroids	N=482 6 months	Primary: Asthma symptoms, rescue medication use, quality of life, missed days of work, emergency room visits, and inpatient hospitalization days	Primary: There was no significant difference in asthma symptoms. The number of episode-free days per patient per 6 months was 97 (formoterol) compared with 95 (salmeterol; P=NS). There was no significant difference in rescue medication use. The mean number of puffs per patient per 6 months was 199 (formoterol) compared with 203 (salmeterol); P=0.406). There was no significant difference in quality of life. The percentage of patients reaching a clinically relevant improvement in quality of life after 6 months of treatment was 64 (formoterol) compared with 62 (salmeterol; P=NS). There was no significant difference in the number of missed days of work. The mean number of days of absence from paid work per patient per 6 months was 3.19 (formoterol) compared with 2.64 (salmeterol; P=0.144). There was no significant difference in emergency room visits (mean per patient per 6 months): 0.027 (formoterol) compared with 0.095 (salmeterol; P=0.188).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the number of inpatient hospitalization days (mean number of days per patient per 6 months): 0.58 (formoterol) compared with 0.43 (salmeterol); P=0.996).
Condemi et al.[47] (2001) Salmeterol 50 mcg BID vs formoterol 12 mcg BID	MC, OL, PG Patients 18-75 years of age with moderate to moderately severe asthma and currently on inhaled corticosteroids	N=528 6 months	Primary: Mean morning PEF measured 5 minutes after dosing Secondary: Mean morning and evening predose PEF, number of episode-free days, use and time of rescue medications, symptom score, overall mean morning predose PEF, and safety	Primary: There was a significant increase in mean PEF values measured 5 minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 L/min vs 371.7 L/min; P<0.001). Secondary: Individuals receiving formoterol reported using significantly fewer actuations of rescue medication per week within 30 minutes of dosing (1.4 vs 2.1; P<0.005), significantly fewer actuations between morning and evening doses (5.6 vs 7.7; P<0.03) and significantly fewer actuations between evening and morning doses (2.8 vs 4.2; P<0.03) compared to salmeterol. Patients experienced significantly more episode free days in the formoterol group compared to salmeterol (9.5 vs 7.8; P<0.04). Mean morning predose PEF, mean evening predose PEF and nighttime or daytime symptom scores did not differ significantly between treatments.
Schermer et al.[98] (2004) Salmeterol 50 mcg BID vs formoterol 12 mcg BID vs placebo	RCT, MC, DB, PC, XO Patients with moderate persistent asthma	N=35 2 weeks	Primary: FEV_1 and Visual Analogue Scale (VAS) scores, PEFR, and use of rescue medications	Primary: Formoterol and salmeterol both caused a significant increase in FEV_1 (0.45 L [95% CI, 0.01 to 0.80] and 0.27 L [95% CI, 0.08 to 0.62] respectively). At 3 minutes post-dose, more patients demonstrated an onset of action ($\geq$15% increase in FEV_1) with formoterol than salmeterol (36% vs. 13%; P=0.063), as well as at 6 hours post-dose (42% vs. 27%; P=0.063). VAS scores were similar for formoterol and salmeterol at the pre-treatment assessment, but tended to be higher with formoterol after 2 weeks treatment. There was no difference between formoterol and salmeterol with regards to PEFR values or the use of rescue medication.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fifty percent of patients preferred formoterol compared to 29% of patients receiving salmeterol (P<0.001). Significant associations between FEV_1 and VAS ratings existed only at 10, 15 and 30 min post-dose time points not before or after these time points.
Nightingale et al.[101] (2002) Salmeterol 50 mcg BID vs formoterol 12 mcg BID vs placebo	RCT, PC, XO Patients with severe asthma whose symptoms were not being controlled by high doses of inhaled corticosteroids (≥1,500 mcg/day) or with regular oral corticosteroid	N=42 4 weeks	Primary: Morning pre-treatment PEF, FEV_1, FVC, evening PEF, symptom scores, and use of rescue medications	Primary: The mean morning PEF was greater in patients receiving formoterol (mean increase, 14.4 L/min) or salmeterol (mean increase, 14.8 L/min) compared with those receiving placebo, but there was no difference between these treatments. There were no significant treatment effects for any other outcome measures.
Brambilla et al.[51] (2003) Salmeterol 50 mcg BID and on-demand albuterol vs formoterol 12 mcg BID and on-demand albuterol vs on-demand albuterol	MC, RCT, OL, PG Patients ≥18 years of age with moderate to severe persistent asthma suboptimally controlled on inhaled corticosteroids and on-demand albuterol (with or without salmeterol)	N=6,239 4 weeks	Primary: Difference in evening predose PEF between patients continued on salmeterol and those switched to formoterol Secondary: Morning predose PEF, asthma symptom score, use of rescue inhaler	Primary: A significant increase in mean evening predose PEF was seen in patients switched to formoterol from salmeterol or albuterol as needed compared to patients staying on salmeterol (402.9 vs 385.5 L/min; P<0.001) and albuterol as needed (409.3 vs 385 L/min; P<0.001). Secondary: In patients switched to formoterol compared to individuals who continued to receive salmeterol or on-demand albuterol there was a significant increase in morning predose PEF, a significantly reduction in both daytime and nighttime asthma symptom score, a significant higher percent of symptom free days, a significant reduction in rescue medication use (all P<0.001). There was no significant difference in the incidence of adverse effects between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brambilla et al.[50] (1994) Salmeterol 50 mcg BID vs terbutaline 5 mg SR tablets BID	MC, RC, DB, DD, PG Patients 18-67 years of age with asthma and >15% reversibility after inhaled albuterol	N=159 2 weeks	Primary: Number of awakening-free nights over the last week of treatment Secondary: Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake	Primary: In the salmeterol group, the mean number of awakening-free nights over the last week of treatment was significantly higher than with the terbutaline SR (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 SR on morning PEF (P=0.04) and PEF daily variations (P=0.01). A significantly greater percent of individuals in the salmeterol group (30%) compared to the terbutaline group (9%) stopped using rescue albuterol during the day (P=0.004), but there was no significant difference at night. Significantly fewer patients in the albuterol group reported adverse events (16% vs 29%; P=0.04).
Estelle et al.[56] (1997) Salmeterol 50 mcg BID vs beclomethasone 200 mcg BID vs placebo	RCT, DB, PC, PG Patients 6-14 years of age with stable asthma	N=241 56 weeks	Primary: Airway hyper-responsiveness Secondary: PEF, rescue inhaler use, and adverse effects	Primary: During months 1-2 of the study, there was significantly less airway hyperresponsiveness with beclomethasone compared to salmeterol (P=0.003) or placebo (P<0.001); however, this difference was lost 2 weeks after discontinuation of treatment. Secondary: In the beclomethasone group, the PEF varied significantly less when compared to the salmeterol and placebo groups (P=0.002 and P=0.02, respectively) with the similar effects seen with beclomethasone and salmeterol. Compared to the placebo group, individuals receiving beclomethasone required significantly less rescue medication and had fewer withdrawals due to exacerbations (P<0.001, P=0.03); however, the difference between salmeterol and placebo was not significant. Height in the beclomethasone-treated children increased by 3.96 cm during months 1-12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; P=0.018) and the salmeterol-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated children (5.40 cm, P=0.004).
Lemanske et al.[89] (2010) BADGER Salmeterol 50 mcg BID + fluticasone 100 mcg BID (LABA step-up therapy) vs fluticasone 250mcg BID (ICS step-up therapy) vs fluticasone 100 mcg BID + montelukast 5 to 10 mg QD (LTRA step-up therapy)	RCT, DB, XO Patients 6 to 17 years of age with uncontrolled asthma (diary-reported symptoms, rescue use of an inhaled bronchodilator with ≥2 puffs/day, or peak flows <80% of the predetermined reference value) while receiving fluticasone 100 mcg BID	N=165 48 weeks	Primary: Differential response to each of the three step-up therapies on the basis of fixed threshold criteria for the following three asthma-control measures: need for treatment with oral prednisone for acute exacerbations, number of asthma control days, FEV_1 (One treatment period was ranked as better than another if the total amount of prednisone received during the period was ≤180 mg, if the number of annualized asthma-control days during the final 12 weeks of the period was increased by at least 31 days, or if the FEV_1 at the end of the period was at least 5% higher)	Primary: A differential response occurred in 161 of 165 patients (98%; P<0.001). The proportion of patients who had a better response to LABA step-up was higher than the proportion with a better response to LTRA step-up (52% vs. 34%, P=0.02), and the proportion with a better response to LABA step-up was higher than the proportion with a better response to ICS step-up (54% vs. 32%, P=0.004), whereas the responses to LTRA and ICS step-up therapies were similar. The response to LABA step-up therapy was significantly more likely to be the best response, as compared with the response to LTRA step-up (relative probability, 1.6; 95% CI, 1.1 to 2.3; P=0.004) and the response to ICS step-up (relative probability, 1.7; 95% CI, 1.2 to 2.4; P=0.002). Higher scores on the Asthma Control Test before randomization (indicating better control at baseline) predicted a better response to LABA step-up (P=0.009). White race predicted a better response to LABA step-up, whereas black patients were least likely to have a best response to LTRA step-up (P=0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gappa et al.[109] (2009) Salmeterol-fluticasone 50/100 mcg BID (SFC) vs fluticasone 200 mcg BID	RCT, DB, MC, PG Patients 6-14 years of age with persistent asthma uncontrolled by standard ICS doses	N=283 8 weeks	Primary: Change in mean morning PEF, asthma symptom scores, number of days without asthma symptoms, use of rescue albuterol, asthma control, and exacerbations	Primary: Mean increase in morning PEF was 30.4 L/min in SFC group and 16.7 L/min in fluticasone group. The mean improvement from baseline in morning PEF was significantly larger after SFC (+8.6 L/min, 95% CI, 1.3 to infinity). Patients in the SFC group experienced more days without asthma symptoms (8.7%; 95% CI, 1.2 to 16.3) and more days without albuterol use (8.0%; 95% CI, 0.6-15.3) than patients receiving fluticasone. Good asthma control was achieved for a longer period in SFC group (3.4 weeks) than in the fluticasone group (2.7; P=0.02). Asthma exacerbations were recorded in 3 and 6 patients receiving SFC and fluticasone, respectively. Both treatments were generally well tolerated. Serious adverse events were reported in 2 and 1 patients in the SFC and fluticasone groups, respectively.
Lazarus et al.[57] (2001) Salmeterol 42 mcg BID vs triamcinolone 400 mcg BID vs placebo	RCT, DB, PC, PG, MC Patients 12-65 years of age with persistent asthma	N=164 28 weeks	Primary: Change in AM PEF from the final week of the run in period to the final week of treatment Secondary: FEV_1, asthma symptom scores, rescue albuterol use, quality of life scores, and number of exacerbations	Primary: No significant difference in AM PEF measures was seen between the treatment groups; however, they were both more effective compared to placebo. Secondary: There was no significant difference between the salmeterol and triamcinolone groups in terms of asthma symptom scores, rescue inhaler use, or quality of life; both treatment arms were more effective compared to placebo in these categories. There were significantly more group treatment failures in the salmeterol group than the triamcinolone (25% vs 6%; P=0.004) as well as more exacerbations (20% vs 7%; P=0.04).
Tattersfield et al.[53] (2001) Terbutaline 0.5 mg	DB, RCT, PG Patients ≥18 years of age with asthma	N=362 12 weeks	Primary: Time to first severe exacerbation	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhaled as needed vs formoterol 4.5 mcg inhaled as needed	for at least six months who were treated with a constant dose of inhaled corticosteroid for at least 4 weeks		Secondary: Morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of relief medication, and safety data	compared with terbutaline group of 0.55. Secondary: No significant difference was seen between the treatment groups concerning daytime or nighttime symptoms. It was documented that prebronchodilator FEV_1 was greater in the formoterol group than terbutaline. Both treatment groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40). Both treatments were well tolerated.
Hermansson et al.[54] (1995) Terbutaline 500 mcg QID vs salmeterol 50 mcg BID	MC, OL, RCT, PG 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, FEV_1	Primary: Salmeterol produced greater improvements than terbutaline in morning and evening PEF and diurnal variation (P<0.001, P=0.045, P<0.001, respectively). After 4 weeks, there was a significant difference in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (P<0.001, P=0.008, P=0.002, P=0.007) with salmeterol compared to terbutaline. After 4 weeks, there were no significant differences in FEV_1 or FVC between the two groups (P=0.598 and P=0.916, respectively).
Hancox et al.[58] (1999) Terbutaline 1,000 mcg QID vs budesonide 400 mcg BID vs	RCT, XO, PC Individuals aged 9-64 years of age with mild to moderate asthma with documented hyper-responsiveness	N=61 24 weeks	Primary: Construct a rank order of treatment from worst [1] to best [4], period of asthma control for each subject Secondary: PEF, nocturnal and daytime symptoms, use of rescue	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 then either placebo or terbutaline (P<0.01). Mean evening peak flow was higher with all treatments (P<0.0003) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
terbutaline 1,000 mcg QID and budesonide 400 mcg BID vs placebo			medication, and compliance	was higher with the combined treatment than either active medication alone (P<0.0002), but no significant difference was seen between the two active medications alone. Nocturnal awakenings and percent of days during which wheeze was reported were reduced significantly in all treatment groups compared with placebo (P<0.0001, P<0.001), but did not differ significantly between the treatment groups. Rescue inhaler use significantly decreased (P<0.001) in all treatment groups compared with placebo, but did not differ significantly between the treatment groups. The self reported compliance was above 90% for all groups and did not differ significantly.
Salpeter et al.[29] (2006) Long-acting beta-adrenergic agonists vs placebo	MA Patients diagnosed with asthma	N=33,826 (19 trials) ≥3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma exacerbations, asthma-related deaths	Primary: Long-acting beta-adrenergic agonists (formoterol and salmeterol) resulted in an increase in severe exacerbations that required hospitalization (OR 2.6; 95% CI, 1.6 to 4.3), life-threatening exacerbations (OR 1.8; 95% CI, 1.1 to 2.9), and asthma-related deaths (OR 3.5; 95% CI, 1.3 to 9.3) when compared with placebo, with similar risks seen in adults and children.
Chronic Obstructive Pulmonary Disease (COPD)				
Combivent Study Group[82] (1994) Albuterol 100 mcg QID vs ipratropium 21 mcg QID	PRO, RCT, DB, PG, MC Patients ≥40 years of age with stable COPD	N=534 12 weeks	Primary: FEV_1, area under the curve (AUC), symptom score, and safety	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (P<0.001 to P=0.015). There was no difference in symptom score between the groups. Compared with either agent alone, the overall FVC response was significantly greater in the combination group (P<0.01 to P=0.04). There were no significant differences between any of the treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs albuterol 100 mcg and ipratropium 21 mcg QID (fixed-dose combination MDI)				in terms of adverse effects or safety.
Dorinsky et al.[83] (1999) Albuterol 180 mcg QID vs ipratropium bromide 36 mcg QID vs albuterol-ipratropium 180/36 mcg QID	RETRO, RCT, DB, PG, MC Patients ≥40 years of age with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during the 3 months prior to the trials, FEV_1 ≤65% predicted value, and FEV_1 ≤70% of FVC	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as increase in FEV_1 of 12% and 15% from baseline)	Primary: The percentage of patients demonstrating a 15 % increase in FEV_1 at 15 and 30 minutes after medication administration was significantly higher in the albuterol/ipratropium group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day 1 and 2 (of 4) ($P<0.05$). Overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from 2-8%. Significantly greater percentage of patients demonstrated a 12% or 15% increase in FEV_1 on 3 or more test days in albuterol/ipratropium group compared to the individual treatment groups ($P<0.05$).
Friedman et al.[84] (1999) Albuterol 180 mcg QID vs ipratropium bromide 36 mcg QID	RETRO, RCT, DB, PG, MC Patients ≥40 years of age with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during the 3 months	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC from time 0-4 hours, total health care expenditures	Primary: There was a significant improvement in FEV_1 in albuterol/ipratropium group compared to other treatment groups on all test days ($P<0.01$). There was a significantly higher FEV_1 AUC_{0-4} in albuterol/ipratropium group compared to other treatment groups on all test days ($P\leq0.008$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs albuterol-ipratropium 180/36 mcg QID	prior to the trials, FEV_1 ≤65% predicted value, FEV_1 ≤70% of FVC			
Tashkin et al.[86] (2007) Albuterol and ipratropium QID via nebulizer vs albuterol and ipratropium QID via inhaler vs albuterol and ipratropium nebulizer (morning and night)and MDI inhaler (afternoon and evening)	SB, PG, MC Patients >50 years of age with COPD, history of >10 pack-years of cigarette smoking, FEV_1 >30% and <65% of predicted and a FEV_1 <70% of FVC	N=140 12 weeks	Primary: Quality of life and symptom sub-scores at 6 weeks and 12 weeks Secondary: Patient symptoms score, peak flow, and pre- and post-dose FEV_1	Primary: At 6 weeks, the total quality of life score was improved in the concomitant treatment group only (P=0.0196). Improvements in the symptoms sub-scores were seen in the nebulizer-only and concomitant treatment groups (P<0.019 and P<0.004, respectively). Improvement in the impacts sub-score was seen in the MDI inhaler-only group (P=0.0283). At 12 weeks, improvement in the symptoms sub-score was seen in the concomitant treatment group only (P=0.0186). Secondary: Changes in peak flow and pre-or post-bronchodilator FEV_1 were not significantly different between the treatment groups at 6 weeks or 12 weeks. Patient symptom scores improved from baseline to week 6 and week 12 in the concomitant group (P<0.05), and at week 12 in the nebulizer-only group (P<0.05). There were no significant differences between the treatment groups.
Baumgartner et al.[74] (2007) Arformoterol 15 mcg BID via nebulizer vs arformoterol 25	DB, DD, MC, PC RCT Patients ≥35 years of age with COPD	N=717 12 weeks	Primary: Pulmonary function Secondary: Dyspnea (Traditional Dyspnea Index); health status (St. George's Respiratory	Primary: Mean improvement in trough FEV_1 over 12 weeks was significantly greater with all 3 arformoterol doses (15 mcg BID, +16.9%; 25 mcg BID, +18.9%; 50 mcg QD, +14.9%) and for salmeterol (+17.4%) relative to placebo (+6.0%; P<0.001). There were significantly greater improvements in the mean percentage change in FEV_1 $AUC_{0\text{-}12h}$ from the predose value over 12 weeks (15 mcg BID, 12.7%; 25 mcg BID, 13.9%; 50 mcg QD, 18.9%; salmeterol, 9.8%) versus placebo (2.7%; P≤0.001). All doses of arformoterol were statistically different from salmeterol (P<0.024).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg BID via nebulizer vs arformoterol 50 mcg QD via nebulizer vs salmeterol 42mcg BID vs placebo			Questionnaire); adverse events; COPD exacerbations	Secondary: At week 12, TDI focal scores were significantly greater with all arformoterol doses compared with placebo (mean [95% CI]: 15 mcg BID, 0.97 [0.25 to 1.69]; 25 mcg BID, 1.08 [0.3 to 1.86]; 50 mcg QD, 1.04 [0.32 to 1.771]), suggesting treatment-associated improvement in dyspnea; however, the difference between salmeterol and placebo was not statistically significant (0.36 [-0.40 to 1.12]). Improvements in health status, as measured using SGRQ total scores, were -2.6 to -3.6 U in the arformoterol groups, -4.4 U for salmeterol, and -1.2 U for placebo. The 95% CI of differences vs placebo suggested significant improvement for the arformoterol 25 mcg BID and salmeterol groups. There was a similar frequency of AEs and COPD exacerbations across all groups.
Hanrahan et al.[105] (2008) Arformoterol 15 mcg BID via nebulizer vs arformoterol 25 mcg BID via nebulizer vs arformoterol 50 mcg QD via nebulizer vs	RCT, DB (pooled analysis of 2 trials) Patients ≥35 years of age with COPD	N=1,456 12 weeks	Primary: Percent change in trough FEV_1, percent change in FEV_1 average $AUC_{(0 - 12 hrs)}$ and peak percent change FEV_1 from pre-dose	Primary: Improvement in trough FEV_1 averaged over 12 weeks was greater for arformoterol and salmeterol compared to placebo (mean differences from placebo, arformoterol 15 mcg BID: 11.4%; 25 mcg BID: 15.4%; 50 mcg daily: 10.9%; salmeterol: 11.6%). Greater improvements occurred after the first dose compared to placebo (mean differences between arformoterol and placebo for trough FEV_1: 13% to 19%; FEV_1 $AUC_{(0 - 12 hrs)}$: 19-24%; peak percent change: 20-25%) and at week 12 (trough FEV_1 : 10-13%; FEV_1 $AUC_{(0 - 12 hrs)}$: 6-13%; peak percent change: 7-14%). Increases in FEV_1 $AUC_{(0 - 12 hrs)}$ and peak percent change were greater for arformoterol than for salmeterol (95% CI excluded zero). After 12 weeks, 78-87% of arformoterol subjects had ≥10% increases in FEV_1 from pre-dose (56% salmeterol, 44% placebo); the median time to response was 3-13 minutes (142 minutes salmeterol).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 42 mcg BID vs placebo				
Donohue et al.[119] (2008) Arformoterol 50 mcg QD vs salmeterol 42 mcg BID	RCT, MC, OL Patients with COPD	N=793 12 months	Primary: Adverse events, COPD exacerbations, use of short-acting bronchodilators, and pulmonary function	Primary: The frequency of adverse events was similar for those taking arformoterol (90.5%) and salmeterol (88.3%). Tremor was more frequent among patients treated with arformoterol (13.4%) than those treated with salmeterol (1.1%). The frequency of COPD exacerbations did not increase over 12 months for arformoterol and salmeterol (weeks 0-13: 15.7% and 11.7%, respectively; weeks 39-52: 10.0% and 9.4%, respectively). Supplemental ipratropium bromide and albuterol use decreased for both groups by 0.8-1.5 actuations/day. Mean predose FEV_1 improved for arformoterol and salmeterol at week 13 (7.1% and 7.6%, respectively), and the improvement continued at week 52 (5.9% and 6.2%, respectively). Mean peak percent predicted postdose FEV_1 declined by about 2% for both treatments over the course of the 52-week study, but was higher for arformoterol than for salmeterol.
Tashkin et al.[112] (2009) Arformoterol 15 mcg BID vs tiotropium 18 mcg QD	MB, PG, MC, RCT Patients ≥45 years of age with COPD, smoking history ≥15 pack-years, breathless severity ≥2 on Medical Council Dyspnea Score,	N=234 2 weeks	Primary: Difference in mean FEV_1 AUC_{0-24} Secondary: Differences in rescue therapy use and occurrence of adverse events	Primary: Mean FEV_1 AUC_{0-24} improved to a similar degree with arformoterol (0.10 L) and tiotropium (0.08 L), and was greater with combination therapy (0.22 L; all P<0.005). Peak FEV_1, peak FVC, 24-h trough FEV_1, and inspiratory capacity also improved to a similar degree with arformoterol and tiotropium, and were greatest with combination therapy. Dyspnea (mean transition dyspnea index) improved to a similar degree

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs arformoterol 15 mcg BID and tiotropium 18 mcg QD	prebronchodilator FEV_1 >0.7, FEV_1/FVC ≤70%, FEV_1 ≤65% predicted			with arformoterol (+2.3) and tiotropium (+1.8), and was greatest with combination therapy (+3.1; all P<0.05). Secondary: Levalbuterol use decreased for all treatment groups (range -1.8 to -2.5 actuations per day). All treatments had similar overall frequencies of adverse events: arformoterol (25.0%), tiotropium (27.5%) and combination (30.8%).
Benhamou et al.[64] (2001) Formoterol 24 mcg inhaled via dry powder inhaler (1 dose) vs albuterol 400 mcg inhaled via dry powder inhaler (1 dose) vs placebo	RCT, PC, DB, XO Patients 40-75 years of age with stable, reversible COPD	N=25 1 dose	Primary: AUC (0-30 min) of FEV_1 in 1minute Secondary: AUC (0-1 hour) of FEV_1 in 1minute, AUC (0-3 hours) of FEV_1 in 1 minute, maximal change in FEV_1 a percent of predicted value	Primary: There were no significant differences between formoterol (5.89) and salmeterol (6.06) in the primary endpoint, but both were statistically higher than placebo (-0.32; P<0.0001). Secondary: There were no statistical differences between the two active medication groups in secondary endpoints, and each had a similar onset (5 minutes). No serious adverse effects or clinically relevant changes in vital sign were observed in any of the groups.
Cazzola et al.[65] (2002) Formoterol 12 mcg, 12 mcg, and 24 mcg vs albuterol metered	RCT, SB, XO Patients 51-77 years of age with COPD who had an acute exacerbation (defined as sustained worsening of the patient's condition from	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary: Spirometric data (inspiratory capacity and FVC),	Primary: There was a significant increase in FEV_1, inspiratory capacity (IC), and FVC in both the albuterol and formoterol groups compared to baseline after 48 mcg of formoterol and 800 mcg of albuterol (P<0.05). There was no significant difference between FEV_1, IC, and FVC values in the formoterol group compared to the albuterol group after 48 mcg of formoterol and 800 mcg of albuterol. There was a significant increase in change in FEV_1 values after 24 mcg of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose inhaler (MDI) 200 mcg, 200 mcg, and 400 mcg Doses were administered on two consecutive days	stable and beyond normal day-to-day variations, FEV_1 <70% of personal best that is acute in onset and necessitating a change in the medication regimen)		pulse rate, SpO_2 values	formoterol compared to 48 mcg of formoterol (P=0.022). There was no significant difference in pulse rate or SpO_2 values compared to baseline after 48 mcg of formoterol or 800 mcg of albuterol (P>0.05). SpO_2 values decreased below 90% in 2 patients after the highest dose of formoterol and in 1 patient after the highest dose of albuterol. The clinical significance of was not reported.
Donohue et al.[106] (2008) Formoterol 20 mcg BID via nebulizer (FFIS) vs formoterol 12 mcg BID via dry powder inhaler (FA) vs placebo	OL, AC, ES Patients ≥40 years of age with COPD who were current or former smokers	N=569 12 months	Primary: Safety	Primary: A total of 73% of FFIS-treated patients and 78% of FA-treated patients experienced an adverse event over the course of the study. The majority of were mild to moderate and considered unrelated to treatment. COPD exacerbation occurred in 15.8% of FFIS-treated and 17.9% of FA-treated patients. Deaths, serious adverse events, and discontinuations for adverse events occurred in 1.3%, 16.2%, and 5.4% of the nebulized group vs 1.9%, 17.9%, and 7.5% of the inhaled group, respectively. There were no clinically significant changes from baseline in any laboratory parameters.
Bouros et al.[97] (2004) Formoterol 12 to 24 mcg vs salmeterol 50 to 100 mcg	RCT, MC, PC, XO Patients with stage II and III COPD who demonstrated an increase in FEV_1 of ≤12% from the patient's predicted normal value after salbutamol	N=47 Single dose	Primary: Inspiratory capacity (IC) measured before dosing and at 5, 10, 15 and 30 min and 1, 2, 3 and 4 hr post-dose	Primary: Both formoterol and salmeterol increase IC in patients with COPD. Formoterol 12 mcg was significantly more effective than salmeterol 50 mcg during the first hour post-dose as indicated by notable differences at all times during the first hour post-dose.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	inhalation			
Cote et al.[107] (2009) Formoterol 12 mcg BID vs salmeterol 50 mcg BID	RCT, OL, MC, PG Patients ≥40 years of age with COPD who were current or former smokers	N=270 28 days	Primary: Pulmonary function, changes in baseline in the 6 minute walk test (MWT), rescue medication use, and safety assessments	Primary: Change from baseline in FEV_1 at 5 minutes postdose on day 28 was 0.13 L in the formoterol group compared with 0.07 L in the salmeterol group (P=0.022). At 30 minutes postdose on day 28, the change from baseline in FEV_1 was 0.17 L in the formoterol group compared with 0.07 L in the salmeterol group (P<0.001). Similar changes were reported at 60 min post-dose. There was no significant difference in walking distance or use of rescue medication between the treatment groups. Treatment-emergent adverse events were generally mild-to-moderate in both groups, with 25.5% reported in the formoterol group and 17.3% reported in the salmeterol group (P=0.105).Treatment-associated adverse events were observed in 5.8% of patients in the formoterol group and 1.5% of patients in the salmeterol group (P=0.103).
Berton et al.[110] (2010) Formoterol 12 mcg BID plus tiotropium 18 mcg QD (FOR-TIO) vs formoterol 12 mcg BID plus placebo (FOR-PLA)	XO, DB Patients with moderate to severe COPD	N=33 2 weeks	Primary: Change in inspiratory capacity (IC), obtained on constant-speed treadmill tests to the limit of tolerance (Tlim)	Primary: FOR-TIO was more effective than FOR-PLA in increasing post-treatment FEV_1 and Tlim (1.34 L vs. 1.25 L and 124 vs. 68, respectively; P<0.05). FOR-TIO slowed the rate of decline in exercise IC compared to FOR-PLA (Δ isotime-rest=-0.27 L vs. -0.45 L, P<0.05). End-expiratory lung volume (% total lung capacity) was further reduced with FOR-TIO (P<0.05). Improvement in Tlim with FOR-TIO was also related to larger increases in FEV_1 (P<0.05).
Van Noord et al.[120]	RCT, DB, XO	N=71	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) Formoterol 12 mcg BID for 6 weeks vs tiotropium 18 mcg QD for 6 weeks vs tiotropium 18 mcg QD and formoterol 12 mcg BID for 6 weeks	Patients with COPD	18 weeks	FEV_1, FVC, rescue medication use	Tiotropium produced a significantly greater improvement in average daytime FEV_1 (0–12 h) than formoterol (127 ml versus 86 ml). The average nighttime FEV_1 (12–24 h) was not different among the treatment groups (tiotropium 43 ml and formoterol 38 ml). Combination therapy had significantly greater improvements in both endpoints compared to monotherapy (daytime 234 ml and nighttime 86 ml). Changes in FVC were similar to the changes in FEV_1 results. Daytime salbutamol use was significantly lower with combination therapy compared to monotherapy (tiotropium plus formoterol 1.81 puffs/day, tiotropium 2.41 puffs/day, formoterol 2.37 puffs/day).
Ikeda et al.[81] (1995) Ipratropium 40 mcg plus albuterol 200 mcg vs ipratropium 80 mcg plus albuterol 400 mcg vs ipratropium 40 mcg vs ipratropium 80	DB, RCT, PC, XO Adult male patients with stable COPD	N=26 1 month	Primary: FEV_1, FVC, and adverse reactions	Primary: All treatments led to a significant improvement in FEV_1 and FVC compared to placebo ($P<0.01$). Treatment with ipratropium/albuterol 80/400 mcg led to significantly greater improvements in FEV_1 compared to other treatment groups ($P<0.05$). Low-dose ipratropium/albuterol led to significant improvements in FVC compared to low-dose ipratropium ($P<0.01$), but not high-dose ipratropium (P=NS). No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and averse effects.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg vs placebo				
Datta et al.[67] (2003) Levalbuterol 1.25 mg via nebulizer vs albuterol 2.5 mg via nebulizer vs albuterol 2.5 mg combined with ipratropium 0.5 mg via nebulizer vs placebo	RCT, DB, XO Patients with COPD (mean age of 69 years), FEV_1 45%-75% of predicted value, FEV_1/FVC ratio of <0.70, stable disease (absence of clinical exacerbation and no change in COPD medications in previous month)	N=30 4 days	Primary: FEV_1 Secondary: FVC, pulse rate, oxygen saturation (measured by pulse oximetry), hand tremor (rating scale 0-7, rated by same blinded investigator for all patients)	Primary: Mean change in FEV_1 from baseline increased significantly in all 3 active treatment groups compared to placebo at 0.5 hours and persisted at 1 hour (P<0.05). At 2 hours, only the combined albuterol and ipratropium group had a mean change in FEV_1 that was significantly better than placebo (P=0.04). This effect persisted at 3 hours for the combined albuterol and ipratropium group (P<0.05). There were no significant differences between active treatment groups at any time during the study. The percentage of patients in exhibiting a positive bronchodilator response (defined as both a >12% increase and a 0.20 liter increase in FEV_1) was significantly increased in all 3 active treatment groups compared to placebo at 0.5 hours ($P \leq 0.03$) and this persisted at 1 hour ($P \leq 0.03$). The percentage of patients in exhibiting a positive bronchodilator response at 2 and 3 hours was only significant compared to placebo in the combined albuterol and ipratropium group (P=0.03 at 2 hours and P=0.003 at 3 hours). Between-group comparisons were not reported. Secondary: All 3 active treatment groups led to significant improvements in FVC compared to placebo at 0.5 hours (P<0.05) and remained significant at 1 hour only for the combined albuterol and ipratropium group (P<0.05). No significant differences between active treatment groups and placebo were noted from 2 hours on. Differences in FVC between active treatment groups were similar. Significant increases in pulse rate compared to placebo were noted at 0.5 hours in the albuterol and levalbuterol groups (P<0.01) but no differences were noted at 1 hour and beyond.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant changes in oxygen saturation were noted in any group compared to placebo. No significant differences in hand tremor noted between groups.
Donohue et al.[102] (2006) Levalbuterol (LEV) 0.63 mg or 1.25 mg TID via nebulizer vs albuterol (RAC) 2.5 mg TID via nebulizer vs placebo	RCT, MC, DB, PG Adults with COPD	N=209 6 weeks	Primary: Average FEV_1 $AUC_{(0\text{-}8\ hrs)}$ over weeks 0, 2 and 6, rescue medication use, safety parameters, COPD exacerbations, and global evaluations	Primary: All active treatments demonstrated improvements in the percent change in FEV_1 $AUC_{(0\text{-}8\ hrs)}$ during the double-blind period and at each visit compared to placebo (P<0.05). Rescue medication use vs. baseline (doses/day) changed over time: placebo +0.38; LEV 0.63 mg +0.07; LEV 1.25 mg -0.84 (P=0.02 vs. RAC); RAC +0.97. The overall rate of adverse events was 56.4% for placebo, 56.6% for LEV 0.63 mg, 67.3% for LEV 1.25 mg, and 65.4% for RAC. COPD exacerbations occurred in all groups (placebo 12.7%, LEV 0.63 mg 11.3%; LEV 1.25 mg 18.4%; RAC 21.2%). Withdrawals due to COPD exacerbations were significantly higher in the RAC group compared with placebo (PBO 0%; LEV 0.63 mg 1.9%; LEV 1.25 mg 4.1%; RAC 9.6% (P=0.01 vs. placebo).
Hanania et al.[68] (2003) Salmeterol 50 mcg BID vs fluticasone 250 mcg BID vs fluticasone-	RCT, DB, PC, MC Patients 40-87 years of age with COPD, current or former smokers with ≥20 pack-year history, FEV_1/FVC ratio of ≤70%, baseline, FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and 2-hour post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, chronic respiratory disease questionnaire (CRDQ), chronic bronchitis	Primary: There was a significant increase in pre-dose FEV_1 in the fluticasone/salmeterol group compared to the salmeterol group (P=0.012) and placebo (P<0.001). There was no significant difference between the fluticasone/salmeterol group and the fluticasone group. There was a significant increase in 2-hour post-dose FEV_1 in the fluticasone/salmeterol group compared to the salmeterol group (P<0.001), placebo (P<0.001), and fluticasone group (P≤0.048). Secondary: There was a significant increase in the morning PEF values in the fluticasone/salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (P≤0.034), though improvements were also

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 250/50 mcg BID vs placebo			symptom questionnaire (CBSQ), exacerbations, and supplemental albuterol use	seen from baseline in salmeterol and fluticasone monotherapy groups (P<0.001). There was a significant improvement in the dyspnea index observed in fluticasone/salmeterol group (P=0.023) compared to placebo, in addition to improvements in fluticasone (P=0.057) and salmeterol (P=0.043) monotherapy groups compared to placebo (NOTE: difference in fluticasone monotherapy group not significant). There was a significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (P=0.036) and placebo (P=0.002). There was a numerical reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to salmeterol monotherapy group. There was a significant increase in CRDQ scores in the fluticasone/salmeterol group compared to placebo (P=0.006). There was a significant increase in CRDQ scores in fluticasone monotherapy group compared to placebo (P=0.002). There was a significant increase in CBSQ scores in fluticasone/salmeterol group and fluticasone monotherapy group compared to placebo (P≤0.017).
Matera et al.[111] (1996) Salmeterol 50 mcg BID and ipratropium 40 mcg QID vs ipratropium 40 mcg QID vs	SB, XO, RCT Male patients ≥40 years of age with COPD and FEV_1 between 16% - 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 and changes in the area under the FEV_1 response-time curve (AUC)	Primary: The peak response for salmeterol (28.8%) was greater than that for ipratropium (26.0%). Equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium (28.0%). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes when compared to placebo (P=0.05). Only salmeterol and salmeterol plus ipratropium induced a significant spirometric increase over the 12 hour monitoring period (P=0.05). All of the AUC values for active treatments were significantly greater than for placebo (P=0.05). The AUC values for salmeterol and salmeterol plus ipratropium were significantly greater than for ipratropium alone (P=0.05). There was no significant difference between the salmeterol and salmeterol plus ipratropium AUC (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 mcg BID vs placebo				
Van Noord et al.[113] (2000) Salmeterol 50 mcg BID and ipratropium 40 mcg QID vs salmeterol 50 mcg BID vs placebo	RCT, DB, PG, MC Patients 40-75 years of age with COPD and FEV_1 ≤75% predicted	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication used, PEF, clinic lung function, adverse events, exacerbations	Primary: Treatment with salmeterol led to a mean peak increase in FEV_1 of 7% predicted after 2 hours, followed by a plateau. After 12 hours, the improvement was 2% of predicted. Salmeterol plus ipratropium produced a peak increase in FEV_1 of 11% predicted after 2 hours. After 12 hours, the improvement was 3% predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. Secondary: Throughout the treatment period there was a mean decrease in the daytime symptom score from 1.9 to 1.7 in the placebo group (P=NS), 2.0 to 1.4 (P=0.001) in the salmeterol group and 2.0 to 1.3 (P=0.001) in the salmeterol plus ipratropium group. Compared with placebo, treatment with salmeterol and salmeterol plus ipratropium was associated with a higher percentage of days and nights without the use of additional albuterol (P=0.01). No difference was observed between the two active treatment groups (P=0.35). Improvements in morning PEF were significantly better in both active treatment groups than in the placebo group (P=0.001), whereas no difference was observed between the salmeterol and the salmeterol plus ipratropium groups. The changes in evening PEF were in favor of both active treatment arms compared with placebo (P=0.001), whereas the improvement was better in the salmeterol plus ipratropium group vs the salmeterol group (P=0.01). The mean increase in FEV_1 was 1% predicted for placebo, 5% predicted for salmeterol, and 8% for the salmeterol plus ipratropium group (all, P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The change in FVC was 4% predicted with placebo, 7% predicted with salmeterol, and 12% predicted with salmeterol plus ipratropium. The differences between salmeterol plus ipratropium vs salmeterol alone and between salmeterol plus ipratropium vs placebo were both significant (P=0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (P=0.055). The reported incidence and nature of possible and probably drug-related side effects were similar among the three groups. A total of 35 patients experienced a COPD exacerbation, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group, and six (13%) in the salmeterol plus ipratropium group. The only significant difference was between the salmeterol plus ipratropium group and the placebo group (P=0.01).
van Noord et al.[108] (2010) Salmeterol 50 mcg BID vs tiotropium 18 mcg QD vs tiotropium 18 mcg QD and salmeterol 50 mcg QD vs tiotropium 18 mcg QD and salmeterol	RCT, DB, XO Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤60% predicted and FEV_1/FVC ≤70%	N=95 24 weeks	Primary: FEV_1, FVC, effects on dyspnea (TDI focal score), rescue albuterol use	Primary: FEV_1 increased by 72 mL with tiotropium plus salmeterol QD compared to 97 mL with either monotherapy agent (P<0.0001). Treatment with tiotropium plus salmeterol BID provided comparable daytime bronchodilator effects (0-12h: 12mL, P=0.38) as tiotropium plus salmeterol QD, but significantly more bronchodilation during the night-time (12-24h: 73mL, P<0.0001). Clinically relevant improvements in TDI focal score were achieved with bronchodilator combinations including salmeterol QD or BID (2.56 and 2.71; P<0.005 vs. monotherapy). Symptom benefit of combination therapies was also reflected in less need for reliever medication. All treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 mcg BID				
Donohue et al.[116] (2002) Salmeterol 50 mcg BID vs tiotropium 18 mcg QD vs placebo	RCT, PC, DB, MC Patients ≥40 years of age with stable COPD, FEV_1 ≤60% and FEV_1/FVC ≤70% predicted	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 had improved by 137 mL with tiotropium compared to placebo and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL, P=0.01). As with FEV_1, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (P=0.01). Secondary: PEFR improved by 27.3 L/minute, 21.4 L/minute, and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (P=0.001) and tiotropium was better than salmeterol in improving evening PEFR (P=0.05). At 6 months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (P=0.01), and 0.24 units for salmeterol (P=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference 0.78 units, P=0.05). At 6 months, the mean improvement in SGRQ was -5.14 units for tiotropium (P=0.05 vs placebo), -3.54 units for salmeterol (P=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance.
Brusasco et al.[115] (2003) Salmeterol 50 mcg BID vs tiotropium 18 mcg	RCT, PC, DB, DD Patients with ≥40 years of age with COPD, FEV_1 ≤65% and FVC ≤70% predicted	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity Secondary: Quality of life (SGRQ), dyspnea	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo (P=0.01). There was no significant difference with salmeterol compared to placebo. The proportion of patients with at least one exacerbation was 32%, 35%, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs placebo			(TDI focal score), spirometry, adverse events	Fewer COPD exacerbations/patient year occurred in the tiotropium group (1.07) than in the placebo group (1.49, P<0.05). The salmeterol group did not differ from placebo (1.23 events/year). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant. The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared with 11.1 days in the salmeterol group and 10.9 days in the placebo group (P<0.05). Secondary: The SGRQ total score improved by 4.2, 2.8, and 1.5 units during the 6 month trial for the tiotropium, salmeterol, and placebo groups, respectively. A significant difference was observed for tiotropium vs placebo (P=0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared with placebo (P=0.001 and P=0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (P=0.17). Tiotropium was statistically better than salmeterol in peak FEV_1 and area under the curve from 0 to 3 hours. For trough FEV_1 values, tiotropium exhibited a similar trend. Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%).
Briggs et al.[117] (2005)	RCT, DB, PG Patients with COPD	N=653 12 weeks	Primary: Lung function	Primary: After 12 weeks, the average post-dose FEV_1 over 12 hours was significantly higher with tiotropium compared with salmeterol (167 vs.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Salmeterol 50 mcg BID vs tiotropium 10 mcg QD				130 ml, respectively, P=0.03). Peak FEV_1 was significantly higher with tiotropium compared with salmeterol (262 vs. 216 ml, respectively, P=0.01). The average FEV_1 responses from 0-6 h and 6-12 h were higher in the tiotropium group compared with salmeterol (P<0.05). Peak and average FVC were significantly higher with tiotropium compared with salmeterol (P<0.01). Morning pre-dose FEV_1 responses were not significantly different among the treatment groups. Tiotropium demonstrated a significantly higher pre-dose FVC than salmeterol (P<0.05).
Rabe et al.[114] (2008) Salmeterol 50mcg BID and fluticasone 500 mcg BID vs tiotropium 18 mcg QD and formoterol 12 mcg BID	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <80% and FEV_1/FVC ≤70% predicted at visit 1, and prebronchodilator FEV_1 ≤65% predicted at visit 2	N=605 6 weeks	Primary: FEV_1 AUC 0–12h and peak FEV_1 Secondary: Peak FVC and FVC AUC 0–12; morning predose FEV1 and FVC	Primary: The FEV_1 $AUC_{0–12}$ mean difference was 78 mL higher in patients receiving tiotropium + formoterol compared to those receiving salmeterol + fluticasone (P=0.0006). The difference in peak FEV_1 was 103 mL in favor of tiotropium + formoterol (P=0.0001). Secondary: The 12-h FVC profile and peak FVC were significantly higher with tiotropium + formoterol compared to salmeterol + fluticasone (P=0.0001). There was no significant difference in predose FEV_1, however the difference in predose FVC favored tiotropium + formoterol (P=0.05).
Exercise-Induced Bronchospasm				
Berkowitz et al.[59] (1986) Albuterol MDI 0.18 mg 15 minutes prior to	SB, RCT, XO Patients 12-17 years of age with asthma and exercised-induced	N=18 4 days	Primary: Mean percent increase in FEV_1 five minutes after medication, mean workload for	Primary: The mean increase in percentage of predicted FEV_1 was significantly higher five minutes post administration of albuterol or metaproterenol than with placebo (P<0.0005). A significantly greater increase was also seen five minutes after the administration of metaproterenol when compared with albuterol (P<0.01). On the days when the subjects received the active

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
exercise vs metaproterenol MDI 1.3 mg 15 minutes prior to exercise vs placebo	bronchospasm (FEV_1 >20% of pre-exercise level) following a treadmill exercise test		exercise challenges, mean decrease in FEV_1 from baseline, and the number of patients in whom broncho-constriction was blocked over time	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 did (P<0.05).
Shapiro et al.[60] (2002) Albuterol 180 mcg prior to exercise challenge vs formoterol 12 mcg prior to exercise challenge vs formoterol 24 mcg prior to exercise challenge	DD, XO Patients 12-50 years of age with a baseline FEV_1 >70% and ≥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). In addition, both formoterol doses produced significantly greater inhibition of FEV_1 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. 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: For length of coverage, 89%-94% of patients given formoterol and 79% of patients receiving albuterol were protected within 15 minutes of administration. Seventy-one percent of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving albuterol and 29% receiving placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Nineteen percent of patients treated with albuterol required a rescue inhaler at least once compared to 0% of patients receiving formoterol. There was no statistical difference in the percent of patients experiencing adverse effects in all of the groups.
Pearlman et al.[96] (2006) Formoterol 12 to 24 mcg vs albuterol 180 mcg vs placebo	RCT, DB, XO Patients 4-11 years of age with exercise-induced bronchoconstriction	N=23 4 treatment periods	Primary: Maximum % decrease in FEV_1 from the pre-exercise value after exercise challenge tests (6 minute treadmill) conducted 15 minutes and 4, 8, and 12 hours after give the dose	Primary: The maximum percentage decrease in FEV_1 after the 4 hour exercise test was significantly less for formoterol, 12 and 24 mcg, vs. placebo (P<0.001 for both) or albuterol (P=0.016 and P=0.010, respectively). Albuterol was not significantly different from placebo. Formoterol, 12 and 24 mcg, differed from placebo at 8 hours (P=0.002 and P=0.001, respectively), with a smaller difference between albuterol and placebo (P=0.045). Protection against EIB (<20% maximum decrease in FEV_1) across all time points was observed for 77% and 74% of children with formoterol, 12 and 24 mcg, respectively, compared with 35% with albuterol and 27% with placebo.
Richter et al.[61] (2002) Formoterol 12 mcg prior to exercise challenge vs salmeterol 50 mcg prior to exercise challenge vs terbutaline 500 mcg prior to	DB, DD, PC, RCT, XO Patients 25-48 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 (5, 30, or 60 minutes), area under the curve of percent change in FEV_1 from end of exercise to 90 minutes	Primary: At 5 minutes, there was a significantly greater response with terbutaline than salmeterol (P<0.001). At 5, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol (P<0.05). There was no significant difference between terbutaline and formoterol at any of the time points. Mean pre-exercise FEV_1 was significantly larger in all active medication groups compared with placebo at 30 and 60 minute intervals (P<0.01) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the 5-minute interval (P<0.05). A significant decrease was seen in AUC with increasing time between inhalation and exercise with terbutaline, formoterol, and salmeterol (P<0.01); however, there was no difference between treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
exercise challenge vs placebo				
Edelman et al.[62] (2000) Salmeterol 100 mcg BID vs montelukast 10 mg QD	RCT, PG, DB Patients 15-45 years of age with asthma, nonsmokers for ≥1 year, smoking history ≤15 pack-years, decrease in FEV_1 of ≥20% after a standardized exercise challenge	N=191 8 weeks	Primary: Change from baseline in the maximal percentage decrease in FEV_1 at the end of 8 weeks of treatment Secondary: Change from baseline for maximal percent decrease in FEV_1 at days 1-3 and week 4, the time required after maximal decrease to return to within 5% of pre-challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of exercise test, and the number and percent of patients whose decrease in	Primary: By day 3, similar reductions in maximal percentage decrease in FEV_1 were seen with both therapies. Sustained improvement occurred in the montelukast group at weeks 4 and 8; however, at these time points, the bronchoprotective effect of salmeterol decreased significantly. At week 8, the percentage inhibition in the maximal percentage decrease in FEV_1 was 57.2% in the montelukast group and 33.0% in the salmeterol group (P=0.002). By week 8, 67% of patients receiving montelukast and 46% of patients receiving salmeterol had a maximal percentage decrease in FEV_1 of <20%. Secondary: Improvement in maximal percent decrease in FEV_1 was similar in both groups between days 1-3, and was maintained at week 4 in the montelukast group but not in the salmeterol group (P=0.015). A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre-challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (P<0.001, P<0.001, P=0.010, P<0.001). Approximately 26% of patients in the montelukast group required rescue doses of medication after exercise challenge at any post treatment visit compared to 40% in the salmeterol group (P=0.044). After 8 weeks, 66.7% of patients in the montelukast group achieved a decrease in FEV_1 of <20% after exercise challenging compared to 45.6% of patients receiving salmeterol (P=0.028). Both medications were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			FEV_1 from pre-exercise levels was <10%, 10-20%, 20-40% and >40%	
Storms et al.[63] (2004) Salmeterol 50 mcg QD vs montelukast 10 mg QD vs placebo	MC, RCT, PG, DB Patients 15-45 years of age with asthma, documentation of exercise-induced bronchospasm, and uncontrolled on inhaled corticosteroids for at least 2 months	N=122 4 weeks	Primary: Effect on the maximum FEV_1 Secondary: Effects of treatment on pre-exercise FEV_1, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise FEV_1 level and average clinic exercise-assessment questionnaire (CEAQ)	Primary: After 4 week, the maximum post-rescue medication FEV_1 improved in the montelukast and placebo group, but not in the salmeterol group (+1.5%, +1.2% and -3.9%, respectively). The maximum FEV_1 was significantly less in the salmeterol group compared to the montelukast (P<0.001) and placebo group (P<0.001). The difference between the montelukast and placebo groups was not significant. Secondary: There was a significant improvement in the mean change from baseline in pre-exercise FEV_1 in the salmeterol group compared to the placebo (at week 1, P<0.001) and montelukast group (at weeks 1 and 4, P=0.010). In addition, there was no difference between the montelukast and placebo groups. Montelukast significantly decreased exercise-induced bronchospasm (EIB) at week 4 compared to placebo (P=0.008), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups. Compared to both placebo and salmeterol, after 4 weeks of treatment montelukast permitted significantly faster rescue with beta-adrenergic agonists (P=0.036, P=0.005). After 4 weeks, there was a significant difference in the CEAQ score immediately and 10 minutes after exercise with montelukast compared to placebo (P<0.020).

*Eformoterol=formoterol (formerly known as eformoterol in the UK)
Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: CI=confidence interval, CR=case review, DB=double-blind, DD=double-dummy, IB=investigational blinded, MC=multicenter, Meta=meta-analysis, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blinded, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, COPD=chronic obstructive pulmonary disease, ED=emergency department, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, LOS=length of stay, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, SAE=serious asthma exacerbations

Additional Evidence

Dose Simplification
Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. Evidence-based guidelines for the selection of the appropriate inhalation delivery device have been published. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[77] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[77] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[77] Incorrect technique can result in decreased drug delivery and potentially decreased efficacy. The ability of a patient to use a particular inhalation device correctly may be affected by a number of factors. These factors include age, cognitive status, coordination, manual dexterity/strength, severity of respiratory disease, and visual acuity.[78] Adherence to inhaled therapy is often poor, with rates of 40% to 72% being reported.[79] Patient preference should be considered when selecting an inhalation delivery device.[81] Bunnag et al. evaluated albuterol in the form of a dry powder inhaler, a metered dose inhaler with a chlorofluorocarbon (CFC) propellant, and a metered dose inhaler with a hydrofluoroalkane (HFA) propellant in patients with asthma and COPD.[80] After receiving all 3 forms of albuterol, patients completed an evaluation questionnaire indicating their preferences. The dry powder inhaler was preferred by 47.5% of patients, followed by the HFA metered dose inhaler (32.5%) and the CFC metered dose inhaler (20%). There was no difference noted in the ease of use among the 3 devices in 59.9% of subjects. Barta et al. mailed a survey to 82 patients (most with COPD) using a home nebulizer treatment.[87] It consisted of 29 questions covering topics of well-being, symptom control, self-confidence, dependency, time, and technical issues, side effects, and compliance. In the questionnaire, 98% of patients reported the benefits of using a nebulizer outweighed the disadvantages. The perceived advantages were the ability to control symptoms and be less dependent on health care providers, hospitals and care givers. When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.[77]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Respiratory Beta-Adrenergic Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Albuterol	aerosol inhaler, inhalation solution, sustained-release tablet, syrup, tablet	AccuNeb®*, ProAir HFA®, Proventil HFA®, Ventolin HFA®	$$-$$$	$-$$$$
Arformoterol	inhalation solution	Brovana®	$$$$$	N/A
Formoterol	inhalation solution, dry powder inhaler	Foradil®, Perforomist®	$$$$-$$$$$	N/A
Ipratropium and albuterol	aerosol inhaler, inhalation solution	Combivent®, DuoNeb®*	$$-$$$$	$$$
Levalbuterol	aerosol inhaler, inhalation solution	Xopenex®*, Xopenex HFA®	$$$-$$$$$	$$$$$
Metaproterenol	syrup, tablet	N/A	N/A	$-$$
Pirbuterol	aerosol inhaler	Maxair Autohaler®	$$$$	N/A
Salmeterol	dry powder inhaler	Serevent Diskus®	$$$$	N/A
Terbutaline	tablet	N/A	N/A	$-$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The respiratory beta-adrenergic agonists (β_2-agonists) are approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and exercise-induced bronchospasm.[1-16] They are often classified as short- or long-acting agents based on differences in their pharmacokinetic properties. Short-acting β_2-agonists include albuterol, ipratropium/albuterol, levalbuterol, metaproterenol, pirbuterol and terbutaline. They are the treatment of choice for relieving acute asthma symptoms; however, they are not recommended for scheduled daily use. Long-acting β_2-agonists (LABAs) include albuterol (extended-release tablets), arformoterol, formoterol and salmeterol. They are administered twice daily for the maintenance treatment of bronchospasm associated with asthma and COPD. The respiratory β_2-agonists are available in a variety of dosage forms, including aerosol inhaler, dry powder inhaler, immediate-release tablets, inhalation solution, sustained-release tablets and syrup. Albuterol (immediate-release tablets, inhalation solution, sustained-release tablets and syrup), ipratropium/albuterol (inhalation solution), levalbuterol (inhalation solution), metaproterenol (syrup and tablets) and terbutaline (tablets) are available in a generic formulation. There are currently no aerosol or dry powder inhalers available generically.

For the treatment of asthma, guidelines recommend the use of a short-acting inhaled β_2-agonist for all stages of the disease.[17-21] They should be used on an as needed basis for symptom control and for the pre-treatment of exercise-induced bronchospasm. Short-acting oral β_2-agonists are appropriate for use in patients who are unable to use inhaled medications.[19] For the long-term maintenance treatment of asthma, the inhaled corticosteroids are recommended as first-line therapy.[17-21] When additional therapy is needed, guidelines recommend the addition of an inhaled LABA in children 5-12 years of age and adults. The use of an oral LABA is not recommended due to potential adverse events.[19] LABAs should not be used as monotherapy since they do not affect airway inflammation. Guidelines do not give preference to one short- or long-acting β_2-agonist over another for the treatment of asthma.

An increased risk of asthma-related death has been reported with the use of the inhaled LABAs.[9,16] The data are insufficient to determine whether concurrent use of inhaled corticosteroids mitigates the increased risk of asthma-related death. According to the prescribing information, the use of an inhaled LABA should only be considered as additional therapy for patients who are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.[9,16] Once asthma control is achieved and maintained, the patient should be assessed at regular intervals and therapy should be stepped down (e.g., discontinue the LABA) if possible. Patients should then be maintained on a long-term asthma control medication, such as an inhaled corticosteroid. The inhaled LABAs should not be used for patients whose asthma is adequately controlled on a low or medium dose of an inhaled corticosteroid.[9,16] The available data also suggest that the inhaled LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.[9,16,99] For pediatric and adolescent patients with asthma who require the addition of an inhaled LABA to an inhaled corticosteroid, a fixed-dose combination product

should be considered to ensure adherence with both drugs. If the use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and an inhaled LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatments. If adherence cannot be ensured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.[9,16,99]

For the treatment of asthma, several comparative studies have demonstrated similar improvements in respiratory endpoints with the use of short-acting β_2-agonists; however, a few studies have demonstrated greater efficacy with one agent over another.[31-40, 45,76,85,88,100] The LABAs have been shown to be more effective than the routine use of short-acting β_2-agonists for the maintenance treatment of asthma.[41-44,48-50,54] Clinical studies directly comparing the LABAs have also demonstrated similar outcomes for the majority of the endpoints assessed, including their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on inhaled corticosteroids alone.[46-47,93-94,98] There does not appear to be a difference in adverse events with the LABAs.[90-92]

For the treatment of COPD, most studies have indicated that respiratory medications do not modify the long-term decline in lung function; therefore, the goal of treatment is to decrease symptoms and complications.[24] Bronchodilators are central to the symptomatic management of COPD. The principal bronchodilators are β_2-agonists, antimuscarinics and xanthines. For the treatment of mild airflow obstruction, guidelines recommend the use of a short-acting bronchodilator as needed to relieve breathlessness and exercise limitation.[23-26] For patients who require daily maintenance therapy to control symptoms, the use of an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic). Treatment guidelines do not indicate a preference as there is insufficient evidence to favor one long-acting bronchodilator over another.[22,24] Regular treatment with long-acting bronchodilators are more effective than treatment with short-acting bronchodilators.[24] Studies directly comparing the LABAs have demonstrated similar improvements in some, but not all, respiratory endpoints.[74,97,105,107,118-119] Some studies suggest that formoterol may have a faster onset of action than salmeterol.[97,107] Tiotropium may provide a greater clinical benefit than LABAs with regards to spirometric endpoints, dyspnea, exacerbations, quality of life, and health care resource utilization.[115-118,120] Combining an inhaled antimuscarinic with a β_2-agonist has also been shown to be more effective than monotherapy.[81-84,108,110-112,120] Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.[1-3]

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. According to the ACCP/ACAAI guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[77] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[77] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability, clinical setting, patient age and the ability to use the selected device correctly, device use with multiple medications, drug administration time, convenience in both outpatient and inpatient settings, as well as physician and patient preference.[77]

Therefore, all brand short-acting respiratory beta-adrenergic agonists within the class reviewed are comparable to each other and to the generics and OTC products (if available) and offer no significant clinical advantage over other alternatives in general use. The brand long-acting respiratory beta-adrenergic agonists offer significant clinical advantages over the short-acting respiratory beta-adrenergic agonists, generics and OTC products (if available) and are comparable to each other. However, for patients with asthma, the long-acting respiratory beta-adrenergic agonists are not recommended as first-line therapy. For patients with COPD, the long-acting respiratory beta-adrenergic agonists do not offer significant clinical advantages over other long-acting inhaled bronchodilators (e.g., inhaled antimuscarinics). Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

XI. Recommendation

No brand respiratory beta-adrenergic agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
4. AccuNeb® [package insert]. Nappa, CA: DEY; January 2007.
5. ProAir HFA® [package insert]. Horsham, PA: Teva Respiratory, LLC; July 2010.
6. Proventil HFA® [package insert]. Kenilworth, NJ: Schering Corporation; February 2009.
7. Ventolin HFA® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2009.
8. Brovana® [package insert]. Marlborough, MA: Sepracor, Inc.; June 2010.
9. Foradil® [package insert]. Kenilworth, NJ: Schering Corporation; May 2010.
10. Perforomist® [package insert]. Napa, CA: Dey Pharma; May 2010.
11. Combivent® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; November 2008.
12. DuoNeb® [package insert]. Napa, CA: DEY; January 2006.
13. Xopenex® [package insert]. Marlborough, MA: Sepracor Inc.; February 2009.
14. Xopenex HFA® [package insert]. Marlborough, MA: Sepracor Inc.; June 2009.
15. Maxair Autohaler® [package insert]. Northridge, CA: 3M Drug Delivery Systems; January 2008.
16. Serevent Diskus® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2010.
17. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
18. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.
19. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.
20. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
21. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
22. Qaseem A, Snow V, Shekelle P, et al., Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians (ACP). Ann Intern Med 2007;147:633-8.
23. Bellamy D, Bouchard J, Henrichsen S, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J 2006;15:48-57.
24. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009. 93 p. Available at: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed October 2010.
25. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
26. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 June. 61 p. Available at: http://guidance.nice.org.uk/CG101. Accessed October 2010.
27. Sears MR. Safety of long acting beta-agonists: Are new data really required? Chest 2009;136;604-607.
28. Nelson HS, Weiss ST, Bleeker ER et al. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129:15-26.
29. Salpeter SR et al. Meta-Analysis: Effect of Long-Acting B-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths, Annals of Internal Medicine. 2006, 144: 904-913.

30. Von Berg A, De Blic J, La Rosa M et al. A comparison of regular salmeterol vs as required salbutamol therapy in asthmatic children. Respir Med. 1998;92:292-299.
31. Casaburi R, Adame D, Hong CK. Comparison of albuterol to isoproterenol as a bronchodilator for use in pulmonary function testing. Chest. 1991;100:1597-1600.
32. Carl JC, Myers TR, Kirchner HL et al. Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. J Pediatr. 2003;143:731-736.
33. Schreck DM, Babin S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED. Am J Emerg Med. 2005;23:842-847.
34. Qureshi F, Zaritsky A, Welch C eta l. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. Ann Emerg Med. 2005;46:29-36.
35. Nowak R, Emerman C, Hanrahan et al. A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. Am J Emerg Med. 2006;24:259-267.
36. Nelson HS, Bensch G, Pleskow WW et al. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. J Allergy Clin Immunol. 1998;102(6):943-952.
37. Gawchik SM, Saccar CL, Noonan M et al. The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients. J Allergy Clin Immunol. 1999;103:615-621.
38. Milgrom H, Skoner DP, Bensch G et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol. 2001;108:938-945.
39. Nowak RM, Emerman CL, Schaefer K et al. Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study. Am J Emerg Med. 2004;22:29-36.
40. Wolfe JD, Shapiro GG, Ratner PH. Comparison of albuterol and metaproterenol syrup in the treatment of childhood asthma. Pediatrics.1991;88(2):312-319.
41. Boonsawat W, Charoenratanakul S, Pothirat C et al. Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. Respir Med. 2003;97:1067-1074.
42. Pauwels RA, Sears MR, Cambell M et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J. 2003;22:787-794.
43. Molimard M, Bourcereau J, Le Gros V et al. Comparison between formoterol 12 mcg b.i.d. and on-demand salbutamol in moderate persistent asthma. Respir Med. 2001;94:64-70.
44. Pleskow W, LaForce CF, Yegen U, et al. Formoterol delivered via the dry powder Aerolizer inhaler versus albuterol MDI and placebo in mild-to-moderate asthma: a randomized, double-blind, double-dummy trial. Journal of Asthma. 2003;40(5):505-514.
45. Tinkelman DG, Brandon ML, Grieco M et al. Comparison of safety and efficacy of inhaled pirbuterol with metaproterenol. Annals of Allergy. 1990;64:202-206.
46. Vervloet D, Ekstrom T, Pela R et al. A 6-month comparison between formoterol and salmeterol in patients with reversible obstructive airway disease. Respir Med. 1998;92:836-842.
47. Condemi JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a Multicenter, randomized, open-label trial. Clin Ther. 2001;23:1529-1541.
48. Boulet LP, Laviolette M, Boucher S et al. A twelve-week comparison of salmeterol and salbutamol in the treatment of mild-to-moderate asthma: a Canadian Multicenter study. J Allergy Clin Immunol. 1997;99(1):13-21.
49. Faurschou P, Steffensen I, Jacques L. Effect of addition of inhaled salmeterol to the treatment of moderate-to-severe asthmatics uncontrolled on high-dose inhaled steroids. Eur Respir J. 1996;9:1885-1890.
50. Brambilla C, Chastang C, Georges D et al. Salmeterol compared with slow release terbutaline in nocturnal asthma. Allergy. 1994;49:421-426.
51. Brambilla C, Le Gros V, Bourdeix I. Formoterol 12 mcg bid administered via single-dose dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on demand salbutamol: a multicenter, randomized, open label, parallel-group study. Clin Ther. 2003;25(7);2022-2036.
52. Martin JM, Kraft M, Beaucher WN et al. Comparative study of extended release albuterol sulfate and long-acting inhaled salmeterol xinafoate in the treatment of nocturnal asthma. Ann Allergy Asthma Immunol. 1999;83:121-126.
53. Tattersfield AE, Lofdahl CG, Postma DS et al. Comparison of formoterol and terbutaline for as needed treatment of asthma: a randomized trial. Lancet. 2001;357:257-261.
54. Hermansson BA, Jenkins RJ. A 4-week comparison of salmeterol and terbutaline in adult asthma. Allergy. 1995;50:551-558.

55. Bouros D, Bachlitzanakis N, Kottakis J et al. Formoterol and beclomethasone versus higher dose beclomethasone as maintenance therapy in adult asthma. Eur Respir J. 1999;14:627-632.
56. Estelle F, Simmons R. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. N Engl J Med. 1997;337:1659-1665.
57. Lazarus SC, Boushey HA, Fahy JV et al. Long-acting β_2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma. JAMA. 2001;285:2583-2593.
58. Hancox RJ, Cowan JO, Flannery EM et al. Randomized trial of an inhaled β2 agonist, inhaled corticosteroid and their combination in the treatment of asthma. Thorax. 1999;54:482-487.
59. Berkowitz R, Schwartz E, Bukstein D et al. Albuterol protects against exercise-induced asthma longer than metaproterenol sulfate. Pediatrics. 1986;77(2):173-178.
60. Shapiro GS, Yegen U, Xiang J et al. A randomized, double-blind, single-dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchospasm by formoterol and albuterol. Clin Ther. 2002;24(12):2077-2087.
61. Richter K, Janicki S, Jorres RA et al. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. Eur Respir J. 2002;19:865-871.
62. Edelman JM, Turpin JA, Brodsky EA et al. Oral montelukast compared with inhaled salmeterol to prevent exercise induced bronchoconstriction a randomized, double blind trial. Ann Intern Med. 2000;132:97-104.
63. Storms W, Czerwinski P, Ghana AF et al. A Comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. Respir Med. 2004;98:1051-1062.
64. Benhamou D, Cuvelier A, Muir JF et al. Rapid onset of bronchodilation in COPD: a placebo-controlled study comparing formoterol (Foradil Aerolizer) with salbutamol (Ventodisk). Respir Med. 2001;95:817-821.
65. Cazzola M, D'Amato M, Califano C et al. Formoterol as dry powder oral inhalation compared with salbutamol metered-dose inhaler in acute exacerbations of chronic obstructive pulmonary disease. Clin Ther. 2002;24:595-604.
66. Condemi J. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a multicenter, randomized, open label trial. Clin Ther. 2001;23:1529-1541.
67. Datta D, Vitale A, Lahiri B et al. An evaluation of nebulized levalbuterol in stable COPD. Chest. 2003;124:844-849.
68. Hanania N, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 mcg)/salmeterol (50 mcg) combined in the discus inhaler for the treatment of COPD. Chest 2003;124:834-43.
69. Papi A, Canonica GW, Maestrelli PN et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007 May 17; 356 (20):2040-52
70. Rabe KF, Atienza T, Magyar P et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study. Lancet 2006 Aug 26; 368 (9537): 744-53.
71. Pohunek P, Kuna P, Jorup C et al. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. Pediatr Allergy Immunol 2006 Sep 01; 17(6):458-65.
72. Wolfe J, Laforce C, Friedman B et al. Formoterol, 24 microg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 microg bid, with and without extra doses taken on demand, and placebo. Chest 2006 Jan 01; 129(1):27-38
73. Peters SP, Anthonisen N, Castro M et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med 2007 May 17; 356 (20): 2027-39
74. Baumgartner RA, Hanania NA, Calhoun WJ et al. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther 2007 Feb 01; 29(2):261-78.
75. Levenson M. Long-acting beta-agonists and adverse asthma events meta-analysis: statistical briefing package for joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee, December 10–11, 2008. Available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-00-index.htm. Accessed November 2010.
76. Berger WE, Milgrom H, Skoner DP, et al. Evaluation of levalbuterol metered dose inhaler in pediatric patients with asthma: a double-blind, randomized, placebo- and active-controlled trial. Curr Med Res Opin 2006;22:1217-1226.
77. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. American College of Chest Physicians /American College of Asthma, Allergy, and Immunology. Chest 2005;127:335-371.
78. Filuk R. Delivery system selection: clinical considerations. AHDB 2008;1(8S):13-17.
79. Rand CS. Patient adherence with COPD therapy. Eur Respir Rev 2005;14:97-101.

80. Bunnag C, Fuangtong R, Pothirat C, et al. A comparative study of patients' preferences and sensory perceptions of three forms of inhalers among Thai asthma and COPD patients. Asian Pac J Allergy Immunol 2007;25:99-109.
81. Ikeda A, Nishimura K, Koyama H, et al. Bronchodilating effects of combined therapy with clinical dosages of ipratropium bromide and salbutamol for stable COPD: comparison with ipratropium alone. Chest. 1995;107:401-405.
82. Combivent Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone an 85-day multicenter trial. Chest. 1994;105:1411-1419.
83. Dorinsky PM, Reisner C, Ferguson G, et al. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. Chest. 1999;115:966-971.
84. Friedman M, Serby CW, Menjoge SS, et al. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest. 1999;115:635-641.
85. Ralston ME, Euwema S, Knecht KR, et al. Comparison of levalbuterol and racemic albuterol combined with ipratropium bromide in acute pediatric asthma: a randomized controlled trial. J Emerg Med. 2005;29:29-35.
86. Tashkin DP, Klein GL, Colman SS et al. Comparing COPD treatment: nebulizer, metered dose inhaler, and concomitant therapy. Am J Med 2007;120:435-41.
87. Barta SK, Crawford A, Roberts CM. Survey of patients' views of domiciliary nebuliser treatment for chronic lung disease. Respir Med 2002;96:375-381.
88. Hamilos DL, D'Urzo A, Levy RJ, et al. Long-term safety study of levalbuterol administered via metered-dose inhaler in patients with asthma. Ann Allergy Asthma Immunol 2007;99:540-548.
89. Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med 2010;362:975-85.
90. Cates CJ, Lasserson TJ. Regular treatment with formoterol versus regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2009, Issue 4. Art. No.: CD007695. DOI: 10.1002/14651858.CD007695.
91. Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2010, Issue 1. Art. No.: CD007694. DOI: 10.1002/14651858.CD007694.pub2.
92. Welsh EJ, Cates CJ. Formoterol versus short-acting beta-agonists as relief medication for adults and children with asthma. Cochrane Database Syst Rev 2010 Sep 8;(9):CD008418.
93. Campbell LM, Anderson TJ, Parashchak MR, et al. A comparison of the efficacy of long-acting beta 2-agonists: eformoterol via Turbohaler and salmeterol via pressurized metered dose inhaler or Accuhaler, in mild to moderate asthmatics. Force Research Group. Respir Med 1999;93:236-44.
94. Everden P, Campbell M, Harnden C, et al. Eformoterol Turbohaler compared with salmeterol by dry powder inhaler in asthmatic children not controlled on inhaled corticosteroids. Pediatr Allergy Immunol 2004;15:40-7.
95. Lee-Wong M, Chou V, Ogawa Y. Formoterol fumarate inhalation powder vs. albuterol nebulizer for the treatment of asthma in the acute care setting. Ann Allergy Asthma Immunol 2008;100:146-152.
96. Pearlman D, Milgrom H, Till D, et al. Effect of formoterol fumarate treatment on exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol 2006;97:382-388.
97. Bouros D, Kottakis J, Le Gros V, et al. Effects of formoterol and salmeterol on resting inspiratory capacity in COPD patients with poor FEV(1) reversibility. Curr Med Res Opin 2004;20:581-586.
98. Schermer T, Hoff W, Greefhorst A, et al. Profiles of measured and perceived bronchodilation. A placebo-controlled cross-over trial comparing formoterol and salmeterol in moderate persistent asthma. Pulm Pharmol Ther 2004;17:205-212.
99. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm. Accessed December 2010.
100. Tripp K, McVicar W, Nair P, et al. A cumulative dose study of levalbuterol and racemic albuterol administered by hydrofluoroalkane-134a metered-dose inhaler in asthmatic subjects. J Allergy Clin Immunol 2008;122:544-549.
101. Nightingale J, Rogers D, Barnes P. Comparison of the effects of salmeterol and formoterol in patients with severe asthma. Chest 2002;121:1401-1406.
102. Donohue J, Parsey M, Andrews C, et al. Evaluation of the efficacy and safety of levalbuterol in subjects with COPD. COPD 2006;3:125-132.

103. Habib M, Campbell S, Shon B, et al. A comparison of albuterol and metaproterenol nebulizer solutions. Ann Allergy 1987;58:421-424.
104. Skoner D, Greos L, Kim K, et al. Evaluation of the safety and efficacy of levalbuterol in 2-5-year-old patients with asthma. Pediatr Pulmonol 2005;40:477-486.
105. Hanrahan J, Hanania N, Calhoun W, et al. Effect of nebulized arformoterol on airway function in COPD: results from two randomized trials. COPD 2008;5:25-34.
106. Donohue J, Hanania N, Fogarty C, et al. Long-term safety of nebulized formoterol: results of a twelve-month open-label clinical trial. Ther Adv Respir Dis 2008;2:199-208.
107. Cote C, Pearle J, Sharafkhaneh A, et al. Faster onset of action of formoterol versus salmeterol in patients with chronic obstructive pulmonary disease: a multicenter, randomized study. Pulm Pharmacol Ther 2009;22:44-49.
108. van Noord JA, Aumann JL, Janssens E et al. Combining tiotropium and salmeterol in COPD: Effects on airflow obstruction and symptoms. Respir Med 2010;104:995-1004.
109. Gappa M, Zachgo W, von Berg A et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatr Pulmonol. 2009 Nov; 44(11):1132-42.
110. Berton DC, Reis M, Siqueira AC et al. Effects of tiotropium and formoterol on dynamic hyperinflation and exercise endurance in COPD. Respir Med 2010;104:1288-1296.
111. Matera MG, Caputi M, Cazzola M, et al. A combination with clinical recommended dosages of salmeterol and ipratropium is not more effective than salmeterol alone in patients with chronic obstructive pulmonary disease. Respir Med. 1996;90(8):497-9.
112. Tashkin DP, Donohue JF, Mahler DA, et al. Effects of arformoterol twice daily, tiotropium once daily, and their combination in patients with COPD. Respir Med 2009;103:516-524.
113. Van Noord JA, de Munck DRAJ, Bantje ThA, et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J. 2000;15(5):878-85.
114. Rabe K, Timmer W, Sagkriotis A et al. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. Chest 2008; 134:255-62.
115. Brusasco V, Hodder R, Miravitlles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003;58:399-404.
116. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest. 2002;122(1):47-55.
117. Briggs DD Jr, Covelli H, Lapidus R, et al. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther 2005;18:397-404.
118. Chen AM, Bollmeier SG, Finnegan PM. Long-acting bronchodilator therapy for the treatment of chronic obstructive pulmonary disease. Ann Pharmacother 2008;42:1832-42.
119. Donohue JF, Hanania NA, Sciarappa KA, et al. Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: a one year evaluation of safety and tolerance. Ther Adv Respir Dis 2008;2:37-48.
120. Van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Resp J 2005;26:214-22.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Leukotriene Modifiers
AHFS Class 481024
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I. Overview

The leukotriene modifiers are approved for the long-term management of patients with asthma.[1-7] Montelukast is also approved for the treatment of symptoms of seasonal and perennial allergic rhinitis, as well as for the prevention of exercise-induced bronchoconstriction.[4] Cysteinyl leukotrienes play an important role in the pathophysiology of asthma and contribute to bronchoconstriction, increased airway responsiveness, mucous secretion, and the recruitment of inflammatory cells.[8] Blocking the action of cysteinyl leukotrienes has been shown to reduce or prevent airway obstruction and decrease the activation of inflammatory cells.[8]

The leukotriene modifiers can be divided into two subtypes: leukotriene receptor antagonists and 5-lipoxygenase inhibitors. The leukotriene receptor antagonists (montelukast and zafirlukast) block the leukotriene receptor and inhibit the action of cysteinyl leukotrienes.[4-5] Zileuton is the only 5-lipoxygenase inhibitor currently available. It inhibits the actions of the 5-lipoxygenase enzyme, thereby preventing the formation of leukotrienes.[6-7] All of the leukotriene modifiers elicit a similar biologic response, but differ in their dosing requirements, adverse events, drug interactions and pharmacokinetic parameters.

The leukotriene modifiers that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Zafirlukast is the only product available in a generic formulation. This class was last reviewed in December 2008.

Table 1. Leukotriene Modifiers Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Montelukast	chewable tablet, granules, tablet	Singulair®	Singulair®
Zafirlukast	tablet	Accolate®*	zafirlukast, Accolate®
Zileuton	sustained-release tablet, tablet	Zyflo®, Zyflo CR®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the leukotriene modifiers are summarized in Table 2. For a comprehensive overview of the treatment of asthma and allergic rhinitis, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Leukotriene Modifiers

Clinical Guideline	Recommendation(s)
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **Diagnosis and Management of Rhinitis: An Updated Practice Parameter[17] (2008)**	• Pharmacologic treatment options include oral and intranasal antihistamines, oral and topical decongestants, oral and intranasal corticosteroids, over-the-counter cough and cold medications for young children, intranasal cromolyn sodium, intranasal anticholinergics, leukotriene receptor antagonists, omalizumab, and nasal saline. • Intranasal corticosteroids are the most effective class of medications for the treatment of allergic rhinitis. • Leukotriene receptor antagonists (LTRA) have been proven to be useful in the treatment of allergic rhinitis, either alone or in combination with antihistamines. • There is no significant difference in efficacy between LTRA and antihistamines. • LTRA are less effective than intranasal corticosteroids.

Clinical Guideline	Recommendation(s)
World Health Organization (WHO)/Global Allergy and Asthma European Network (GA^2LEN)/AllerGen: **Allergic Rhinitis and its Impact on Asthma (ARIA)[12] (2008)**	Pharmacotherapy of Allergic Rhinitis • Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for the treatment of allergic rhinitis. • Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age. • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy and availability. • A stepwise approach depending on the severity and duration of rhinitis is proposed. • Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. Treatment Algorithm • Patients with mild intermittent allergic rhinitis should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, or leukotriene receptor antagonist. • Patients with moderate/severe intermittent symptoms or mild persistent symptoms should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, intranasal corticosteroid, or leukotriene receptor antagonist. • Patients with moderate/severe persistent symptoms should initially be treated with the following (in preferred order): intranasal corticosteroid, antihistamine (oral or nasal), or leukotriene receptor antagonist.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults[16] (2008)**	• Treatments for allergic rhinitis include corticosteroids, antihistamines, decongestants, cromolyn, anticholinergics, and leukotriene receptor antagonists. • Intranasal corticosteroids are considered the most effective treatment option. Therefore, they are recommended as first-line therapy in patients with moderate to severe symptoms of allergic rhinitis. • Leukotriene receptor antagonists are as effective as antihistamines, however are not as effective as intranasal corticosteroids.
International Primary Care Respiratory Group (IPCRG): **Management of Allergic Rhinitis[13] (2006)**	• Pharmacologic treatment should be individualized for each patient. • Mild intermittent allergic rhinitis may be treated with an antihistamine, decongestant, and intranasal saline. • Mild persistent and moderate/severe intermittent allergic rhinitis may be treated with antihistamines, decongestants, intranasal corticosteroids, intranasal saline, a mast-cell stabilizer, or a leukotriene receptor antagonist. • Moderate/severe persistent allergic rhinitis may be treated with intranasal corticosteroids, antihistamines, decongestants, intranasal saline, or a leukotriene receptor antagonist.
Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): **British Guideline on the Management of Asthma[14] (2009)**	General Treatment Considerations • Inhaled steroids are the recommended preventer drug for adults and children for achieving overall treatment goals. • Alternative preventer therapies in patients taking short-acting β_2-agonists alone are mast-cell stabilizers, leukotriene receptor antagonists and theophylline. In children <5 years of age who are unable to take inhaled corticosteroids, leukotriene receptor antagonists are an effective first-line preventer. • The first choice as add-on therapy to inhaled corticosteroids in adults and children (5-12 years of age) is an inhaled long-acting β_2-agonist. In children <5 years of age, the first choice as add-on therapy to inhaled

Clinical Guideline	Recommendation(s)
	corticosteroids is leukotriene receptor antagonists. • If control remains inadequate on an inhaled corticosteroid plus a long-acting β_2-agonist, consider the following interventions: leukotriene receptor antagonists, theophylline, slow release β_2-agonist tablets (adults). • There is limited evidence that leukotriene antagonists may be used intermittently in children with episodic asthma. Treatment is started at the onset of either asthma symptoms or of coryzal symptoms and continued for seven days. <u>Exercise-Induced Asthma</u> • The following treatments provide protection against exercise-induced asthma: inhaled corticosteroids, short-acting β_2-agonists, long-acting β_2-agonists, theophyllines, leukotriene receptor antagonists, chromones, and β_2-agonist tablets. • If exercise is a specific problem in patients who are well controlled on inhaled corticosteroids, consider the following therapies: leukotriene receptor antagonists, long-acting β_2-agonists, chromones, oral β_2-agonists, or theophyllines. • Inhaled short-acting β_2-agonists are the drug of choice immediately prior to exercise.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention**[11] **(2009)**	<u>Adults</u> • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. • Leukotriene modifiers are considered an alternative treatment option for adults with mild persistent asthma. Some patients with aspirin-sensitive asthma may also respond favorably to leukotriene modifiers. • Leukotriene modifiers are generally less effective than low doses of inhaled glucocorticosteroids when used as monotherapy. • When used as add-on therapy, leukotriene modifiers may reduce the dose of inhaled glucocorticosteroids in patients with moderate to severe asthma. They may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. However, leukotriene modifiers are less effective as add-on therapy than long-acting inhaled β_2-agonists. <u>Children</u> • Inhaled glucocorticosteroids are the most effective controller therapy and are the recommended treatment for children of all ages. • Leukotriene modifiers provide clinical benefit at all levels of asthma severity, but generally less than that of low-dose inhaled glucocorticosteroids. • Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction. • When used as add-on therapy in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers may provide moderate clinical improvements (including a reduction in exacerbations). Combination therapy is less effective than increasing to moderate doses of inhaled glucocorticosteroids in children with moderate persistent asthma.
Global Initiative for Asthma (GINA): **Global Strategy for the Diagnosis and Management of Asthma in Children 5 years and Younger**[10] **(2009)**	• A low-dose inhaled glucocorticosteroid is the recommended initial treatment option in children ≤5 years of age. Inhaled glucocorticosteroids have been shown to be more effective than other controller treatment for asthma. • The role of leukotriene modifiers as add-on therapy in children ≤5 years of age whose asthma is uncontrolled on inhaled glucocorticosteroids has not been specifically evaluated.

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[9] (2007)**	General Treatment Considerations • Inhaled corticosteroids (ICSs) are the most effective long-term therapy for mild, moderate, or severe persistent asthma. • Leukotriene receptor antagonists (LTRAs) are an alternative (not preferred) treatment option for mild persistent asthma. • LTRAs can also be used as an adjunctive treatment with ICS; however, for children ≥12 years of age and adults, they are not the preferred adjunct therapy (compared to the addition of long-acting bronchodilators). • Zileuton is an alternative treatment option; however it is less desirable than LTRAs due to more limited efficacy data and the need for liver function monitoring. Exercise-Induced Bronchospasm (EIB): • Appropriate long-term control of asthma with anti-inflammatory medication will reduce airway responsiveness, which is associated with a reduction in the frequency and severity of EIB. • Pretreatment before exercise with inhaled β_2-agonists will prevent EIB in >80% of patients. • Short-acting β_2-agonists used shortly before exercise (or as close to exercise as possible) may be helpful for 2–3 hours. Long-acting β_2-agonists can be protective up to 12 hours. • LTRAs can attenuate EIB in up to 50% of patients. The onset of action is generally hours after administration.
International Primary Care Respiratory Group (IPCRG): **Management of Asthma[15] (2006)**	• The most effective preventative therapy is inhaled corticosteroids. • For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting β_2-agonist. Alternatives are combinations of inhaled corticosteroids with sustained-release theophylline or with leukotriene receptor antagonists.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the leukotriene modifiers are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Leukotriene Modifiers[1-7]

Generic Name(s)	Montelukast	Zafirlukast	Zileuton
Allergic Rhinitis			
Relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older	✔		
Asthma			
Prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older	✔		
Prophylaxis and chronic treatment of asthma in adults and children 5 years of age and older		✔	
Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older			✔
Exercise-Induced Bronchoconstriction			
Prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older	✔		

IV. Pharmacokinetics

The pharmacokinetic parameters of the leukotriene modifiers are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Leukotriene Modifiers[1-7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Montelukast	60-78	>99	Liver, extensive	Feces (86)	2.7-5
Zafirlukast	Not reported	99	Liver, extensive	Renal (10) Feces (90)	13.3
Zileuton	Not reported	93	Liver	Renal (95)	IR: 2.5 SR: 3.2

IR=immediate-release, SR=sustained-release

V. Drug Interactions

Significant drug interactions with the leukotriene modifiers are listed in Table 5.

Table 5. Significant Drug Interactions with the Leukotriene Modifiers[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Zileuton	1	Pimozide	Zileuton may inhibit the metabolism of pimozide (possibly via CYP 450 3A4 enzyme), potentially causing fatal cardiac arrhythmias.
Zileuton	2	Theophylline	Zileuton may decrease the metabolism of theophylline compounds, and thereby increase theophylline levels.
Zileuton	2	H_1 Antagonists	Zileuton may increase plasma concentrations of H_1 antagonists. Substantial cardiovascular toxicity may result. Inhibition of cytochrome P450 3A4 isoenzymes by zileuton may decrease the metabolic elimination of H_1 antagonists.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the leukotriene modifiers are listed in Table 6. Treatment with zileuton has been associated with elevations in liver transaminases and hepatitis.[6-7] Long term post-marketing surveillance studies have shown elevations in liver function tests ≥3 times the upper limit of normal, which occurred more frequently in zileuton-treated patients than in patients taking other routine asthma medications.[6-7] Cases of life-threatening hepatic failure have been reported in patients treated with zafirlukast. In most cases, symptoms resolved and liver enzymes returned to normal after discontinuation of therapy.[5] Use of montelukast has also been associated with rare post-marketing reports of liver injury and cholestatic hepatitis. In general, montelukast has been associated with fewer reports of liver injury and risk compared to zafirlukast and zileuton.[4-7]

Table 6. Adverse Drug Events (%) Reported with the Leukotriene Modifiers[1-7]

Adverse Events	Montelukast	Zafirlukast	Zileuton
Cardiovascular			
Chest pain	-	-	>1
Edema	✔	✔	-
Palpitations	✔	-	-
Central Nervous System			
Agitation	✔	-	-
Aggressive behavior	✔	-	-
Dizziness	2	1.6	>1
Depression	✔	✔	-
Disorientation	✔	-	-
Dream abnormalities	✔	-	-
Drowsiness	✔	-	-
Hallucinations	✔	-	-
Headache	18	12.9	24.6
Irritability	✔	-	-
Insomnia	✔	✔	>1
Nervousness/anxiousness	✔	-	>1
Paraesthesia	✔	-	-
Restlessness	✔	-	-
Seizures	✔	-	-
Somnolence	-	-	>1
Suicidal ideation	✔	-	-
Dermatological			
Atopic dermatitis	≥2	-	-
Dermatitis	≥2	-	-
Eczema	≥2	-	-
Erythema nodosum	✔	-	-
Pruritus	✔	✔	>1
Rash	≥2	✔	✔
Rash with blistering	-	✔	-
Skin infection	≥2	-	-
Urticaria	≥2	✔	✔
Varicella	≥2	-	-
Gastrointestinal			
Abdominal pain	2.9	1.8	4.6
Constipation	-	-	>1
Diarrhea	≥2	2.8	-
Dyspepsia	2.1	1.3	8.2
Flatulence	-	-	>1
Gastroenteritis	≥2	-	-
Nausea	≥2	3.1	5.5
Pancreatitis	✔	-	-
Vomiting	✔	1.5	>1
Genitourinary			
Pyuria	1	-	-
Urinary tract infection	-	-	>1
Vaginitis	-	-	>1
Hematologic			
Agranulocytosis	-	✔	-
Bleeding abnormalities	✔	✔	-
Eosinophilia	✔	✔	-
Leukopenia	-	-	1
Hepatic			

Adverse Events	Montelukast	Zafirlukast	Zileuton
ALT elevations	2.1	1.5	1.9
AST elevations	1.6	-	-
Cholestatic hepatitis	✔	-	-
Hepatic eosinophilic infiltration	✔	-	-
Hepatic failure	-	✔	-
Hepatitis	-	✔	✔
Hyperbilirubinemia	-	✔	✔
Transaminase elevations	-	✔	✔
Musculoskeletal			
Arthralgia	✔	✔	>1
Back pain	-	1.5	-
Muscle cramps	✔	✔	-
Myalgia	✔	1.6	3.2
Neck pain	-	-	>1
Tremor	✔	-	-
Respiratory			
Anaphylaxis	✔	✔	-
Bronchitis	≥2	-	-
Cough	2.7	-	-
Influenza	4.2	-	-
Laryngitis	≥2	-	-
Nasal congestion	1.6	-	-
Pharyngitis	≥2	-	-
Pneumonia	≥2	-	-
Rhinitis	≥2	-	-
Rhinorrhea	≥2	-	-
Sinusitis	≥2	-	-
Upper respiratory infection	≥2	-	-
Wheezing	≥2	-	-
Other			
Accidental injury	-	1.6	3.4
Angioedema	✔	✔	-
Asthenia	1.8	1.8	3.8
Bruising	✔	✔	-
Conjunctivitis	≥2	-	>1
Ear pain	≥2	-	-
Eosinophilic pneumonia	-	✔	-
Epistaxis	✔	-	-
Fatigue	1.8	-	-
Fever	≥2	1.6	>1
Hypertonia	-	-	>1
Hypoesthesia	✔	-	-
Infection	-	3.5	-
Lymphadenopathy	-	-	>1
Malaise	-	✔	>1
Myopia	≥2	-	-
Otitis media	≥2	-	-
Pain	1.7	1.9	7.8
Tonsillitis	≥2	-	-
Tooth infection	≥2	-	-
Trauma	1	-	-
Vasculitis	✔	✔	-

✔ Percent not specified
\- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the leukotriene modifiers are listed in Table 7.

Table 7. Usual Dosing Regimens for the Leukotriene Modifiers[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Montelukast	Allergic Rhinitis: 10 mg daily at any time of day Asthma: 10 mg daily in evening Exercise-Induced Bronchospasm: 10 mg at least 2 hours before exercise - no additional dose within 24 hours of a previous dose. Not to be taken if patient is already taking daily dose for another indication (including chronic asthma).	Allergic Rhinitis: 6-23 months of age (perennial rhinitis): 4 mg once daily at any time 2-5 years of age: 4 mg once daily at any time 6-14 years of age: 5 mg once daily at any time Asthma: 12-23 months of age: 4 mg once daily in the evening 2-5 years of age: 4 mg once daily in the evening 6-14 years of age: 5 mg once daily in the evening	Chewable tablet: 4 mg 5 mg Granules: 4 mg Tablet: 10 mg
Zafirlukast	Asthma: 20 mg two times daily	Asthma: 5-11 years of age: 10 mg two times daily	Tablet: 10 mg 20 mg
Zileuton	Asthma: Tablet IR: 600 mg four times daily Tablet SR: 1,200 mg twice daily	Asthma: Tablet IR: ≥12 years of age: 600 mg four times daily Tablet SR: ≥12 years of age: 1,200 mg twice daily	Tablet (IR): 600mg Tablet (SR) 600 mg

IR=immediate-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the leukotriene modifiers are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Leukotriene Modifiers

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Rhinitis				
Pullerits et al.[36] (2002) Montelukast 10 mg QD vs fluticasone nasal spray 200 mcg QD vs montelukast 10 mg QD and loratadine 10 mg QD vs placebo	RCT, DB, PG PC Patients 15-50 years of age with allergic rhinitis during the grass pollen season for at least the 2 previous years	N=62 50 days	Primary: Daytime and nighttime nasal symptom score Secondary: EG^{2+} eosinophilic inflammation	Primary: There was a significant decrease in the development of daytime nasal symptoms with fluticasone and montelukast plus loratadine compared to placebo during period 1(fluticasone P=0.003, montelukast plus loratadine P=0.04), period 2 (fluticasone P=0.001, montelukast plus loratadine P=0.04), and period 3 (fluticasone P<0.001, montelukast plus loratadine P<0.001). There was no significant difference between fluticasone and montelukast plus loratadine. There was a significant decrease in nasal symptoms with fluticasone compared to the montelukast monotherapy (P=0.046). There was a significant decrease in nasal symptoms in the montelukast monotherapy group compared to placebo (P=0.03). Significantly lower nighttime symptom scores were reported in the fluticasone group compared to the placebo group during all periods (P=0.02, P=0.002, and P<0.001 respectively). Significantly lower symptom scores were reported in the fluticasone group compared to the montelukast plus loratadine group during peak season in period 2 (P=0.04). Significantly lower symptom scores were reported in the fluticasone group compared to the montelukast monotherapy group during periods 2 and 3 (P=0.01). Significantly lower symptom scores were reported in the montelukast plus loratadine group compared to the placebo group during period 3 (P=0.02). Secondary: A statistically significant increase in EG^{2+} eosinophils in the placebo, montelukast monotherapy, and montelukast plus loratadine groups was observed (P<0.01 for all groups). There was no significant increase in EG^{2+} eosinophils in the fluticasone group (P=0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Baena-Cagnani et al.[37] (2003) Montelukast 10 mg QD vs desloratadine 5 mg QD vs placebo	RCT, DB, PC Patients 15-75 years of age with SAR for at least 2 years with increased asthma symptoms during the autumn allergy season, $FEV_1 \geq 70\%$ predicted value, asthma controlled with as needed bronchodilators only, increase in FEV_1 of at least 12% following bronchodilator use, greater than weekly but no daily asthma symptoms and/or bronchodilator use	N=924 4 weeks	Primary: Total asthma symptom scores, individual asthma symptom scores, and FEV_1	Primary: There was a significant reduction in the total asthma symptom scores with montelukast and desloratadine compared to placebo ($P \leq 0.05$). There was no significant difference between montelukast and desloratadine. There was a significant reduction in individual symptom scores with montelukast and desloratadine compared to placebo ($P<0.05$). There was no significant difference between montelukast and desloratadine. There was a significant increase in FEV_1 with montelukast and desloratadine compared to placebo ($P<0.01$ and $P<0.05$ respectively). There was no significant difference between montelukast and desloratadine.
Saengpanich et al.[38] (2003) Montelukast 10 mg QD and loratadine 10 mg QD vs fluticasone nasal spray 200 mcg QD	RCT, DB, DD, PG Patients 21-54 years of age with a history of sensitivity to ragweed pollen for last 2 years	N=63 2 weeks	Primary: Rhino-conjunctivitis Quality of Life Questionnaire, daily nasal symptom scores, number of eosinophils, and level of eosinophil cationic protein (ECP) found in nasal lavage fluids	Primary: There was a significant improvement in questionnaire answers with fluticasone and montelukast plus loratadine ($P<0.01$). There was a significant reduction in nasal symptoms on the questionnaire with fluticasone compared to montelukast plus loratadine ($P=0.05$).There was no significant decrease in daily nasal symptom scores in either the fluticasone or montelukast plus loratadine groups. There was a significant decrease in number of eosinophils in nasal lavage with fluticasone compared to baseline ($P=0.05$). However, there was no decrease with montelukast plus loratadine compared to baseline. When compared between groups, this was not statistically significant. A significant decrease in ECP from baseline ($P=0.009$) and between groups ($P=0.04$) favored fluticasone.
Meltzer et al.[39] (2000)	RCT, DB, PC, MC	N=460	Primary: Daytime nasal	Primary: There was a significant improvement in daytime nasal symptom scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Montelukast 10 to 20 mg QD vs loratadine 10 mg QD vs montelukast 10 mg QD and loratadine 10 mg QD vs placebo	Patients 15-75 years of age with spring seasonal allergic rhinitis for 2 years	2 weeks	symptoms score Secondary: Eye symptoms, nighttime symptoms, individual daytime symptoms, global evaluations, and rhinoconjunctivitis quality of life scores	with montelukast plus loratadine compared to placebo and to either agent alone (P<0.001). There was no significant difference between montelukast or loratadine monotherapy groups compared to placebo. Secondary: There was a significant improvement in all secondary endpoints in the montelukast plus loratadine compared to placebo (P<0.05). There was a significant improvement in rhinoconjunctivitis quality of life with montelukast and loratadine monotherapy compared to placebo (P<0.05). There was a significant improvement in daytime eye symptom scores, nighttime symptom scores, and the composite daytime and nighttime symptom scores with montelukast monotherapy compared to placebo (P<0.05).
Mucha et al.[40] (2006) Montelukast 10 mg QD vs pseudoephedrine 240 mg QD	RCT, DB, PG Patients 18-45 years of age with allergic rhinitis during the ragweed season	N=58 2 weeks	Primary: Nasal symptoms, nasal peak inspiratory flow (NPIF), quality of life scores, and tolerability profiles	Primary: There was a significant improvement in all primary outcome measures in both groups compared to baseline (P<0.05). There was a significant improvement in nasal congestion in the pseudoephedrine group compared to the montelukast group (P=0.01).
Sardana et al.[50] (2010) Montelukast 10 mg once daily for 2 weeks vs	RCT, DB, PC, XO Patients 18 to 55 years of age with perennial allergic rhinitis	N=56 8 weeks	Primary: Changes in rhinitis severity scores (RSS)	Primary: Patients receiving montelukast experienced a significantly greater reduction in symptoms of itchy/watery eyes and itchy nose/throat/palate/ears compared to those receiving budesonide (P=0.0297 and P=0.0010, respectively). Patients receiving azelastine experienced a significantly greater improvement in rhinorrhea compared to montelukast (P=0.0044) and budesonide (P=0.0033).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide 28 mcg 2 sprays twice daily for 2 weeks vs azelastine 137 mcg 2 sprays twice daily for 2 weeks				
Jiang et al.[45] (2006) Zafirlukast 20mg BID vs loratadine 10 mg QD vs loratadine 5 mg and pseudoephedrine 120 mg BID	RCT Patients 15 to 70 years of age with at least a 2 year history of perennial allergic rhinitis	N=93 14 days	Primary: Subjective assessment of nasal symptoms Secondary: Objective assessment via rhinomanometry and acoustic rhinometry, performed 1 day before first dose and within 2 days after last dose on same day as nasal symptom scoring	Primary: All treatment groups demonstrated a lower mean score for rhinorrhea, nasal itching and nasal obstruction (P<0.05). Patients who took zafirlukast did not report a significant decrease in sneezing score (P=0.1456), but the decrease in nasal obstruction score was more pronounced than in those who took loratadine or loratadine-pseudoephedrine (P=0.014). Secondary: Results of rhinomanometry and acoustic rhinometry showed no significant difference among the three groups (P>0.05).
Asthma				
Knorr et al.[21] (1998) Montelukast 5 mg QD vs placebo	RCT, DB, PC, MC Patients 6 to 14 years of age with asthma, FEV_1 between 50%-85% of predicted value, ≥15% reversibility after inhaled β-agonist therapy,	N=336 8 weeks	Primary: Improvements in morning FEV_1 Secondary: Daytime asthma symptoms, morning and evening peak expiratory flow	Primary: A significant improvement in percent change from baseline in FEV_1 was reported in patients in the montelukast group compared to the placebo group (P<0.001). Secondary: A significant improvement in daily use of β-agonists was observed in the montelukast group (P=0.01). Significant improvements in percentage of days and percentage of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	daytime asthma symptoms, and reported daily β-agonist use		(PEF), daily use of inhaled short-acting β-agonists, nocturnal awakenings, pediatric asthma-specific quality of life questionnaire, global evaluations, changes in blood eosinophil count, school absences, asthma exacerbations, use of oral corticosteroids, discontinuations because of worsening of asthma, asthma control days	experiencing asthma exacerbations were reported in the montelukast group (P=0.049). A significant improvement in the pediatric asthma-specific quality of life questionnaire was noted in the montelukast group (symptoms: P=0.007; activity: P=0.001, emotions: P=0.002). A significant improvement in parental (P=0.049) and combined (P=0.04) global evaluations were observed in the montelukast group. A significant improvement in morning clinic-measured PEF was reported in the montelukast group (P=0.03). A significant decrease in blood eosinophil levels over 8 weeks was observed in the montelukast group (P=0.02). Other secondary endpoints did not reach statistical significance because the study was not powered appropriately to detect a difference.
Reiss et al.[22] (1998) Montelukast 10 mg QD vs placebo Patients could also use inhaled corticosteroids.	RCT, DB, PC, MC Patients 15 to 79 years with chronic stable asthma, FEV_1 50%-85% predicted value, 15% or better improvement of FEV_1 after β-agonist, minimum level of daytime asthma symptoms, and use of an inhaled β-agonist	N=681 12 weeks	Primary: Percent change in FEV_1 from baseline and daytime asthma symptom score Secondary: Morning and evening PEF, daily use of inhaled short-acting β-agonists, number of nocturnal awakenings per week, asthma-	Primary: There was a significant improvement in the percent change from baseline in FEV_1 with montelukast group compared to placebo (P<0.001). Secondary: A significant improvement in AM and PM PEF was reported in the montelukast group compared to placebo (P<0.001). A significant improvement in daytime asthma symptoms and β-agonist use was observed in the montelukast group compared to placebo (P<0.001). Improvement in nocturnal awakenings was observed in the montelukast group. A significant improvement in asthma specific quality of life questionnaire was reported in the montelukast group compared to placebo (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			specific quality of life, global assessment, blood eosinophil count, percentage of days with asthma exacerbation, use of oral corticosteroids, discontinuation because of worsening of asthma, and asthma control days	A significant improvement in global assessments was observed in the montelukast group compared to placebo (P<0.001). A significant improvement in days without asthma exacerbations and days with asthma control was reported in the montelukast group compared to placebo (P<0.001). A significant improvement in blood eosinophil count was observed in the montelukast group compared to placebo (P<0.001). The remainder of secondary endpoints (use of oral corticosteroids and discontinuation due to worsening of asthma) were not significantly different between the montelukast group and the placebo group.
Riccioni et al.[51] 2004 Montelukast 10 mg QD vs zafirlukast 40 mg/day	RCT, PG Adults with mild persistent asthma	N=40 12 weeks	Primary: FEV_1, FVC, PEF, use of rescue medications, and Asthma-Specific Quality-of-Life Questionnaire (AQLQ)	Primary: The values of the respiratory tests did not show statistical differences between the two agents. Statistically significant differences were seen with each groups baseline value compared with post-treatment (P<0.05). The amount of times that a rescue medication needed to be used was not statistically different (25 times for the montelukast vs 27 times for the zafirlukast group; P=NS). There was no difference in quality of life between montelukast and zafirlukast: overall AQLQ (5.5 vs 5.7, P=NS); symptoms (5.7 vs 5.6; P=NS); environment (5.3 vs 5.6; P=NS), emotions (5.3 vs 5.8; P=NS), and activities (5.9 compared with 5.7; P=NS).
Szefler et al.[25] (2005) Montelukast 5 to 10 mg QD vs fluticasone 100	RCT, DM, MC, XO Patients 6 to 17 years of age with mild to moderate persistent asthma, >12% improvement in FEV_1 after maximum	N=144 16 weeks	Primary: Percent change in pre-bronchodilator FEV_1 from baseline	Primary: A significantly greater percent change in FEV_1 was reported with fluticasone compared to montelukast (P<0.001). Seventeen percent of patients responded to both treatments, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither medication. Children with low pulmonary function or high levels of markers

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg BID	bronchodilation or 20% improvement in FEV_1 after methacholine dose of ≤12.5 mg/ml, and FEV_1 ≥70% of predicted value			associated with allergic inflammation responded better to inhaled corticosteroids than to montelukast.
Zeiger et al.[26] (2006) Montelukast 5 to 10 mg QD vs fluticasone 100 mcg BID	RCT, DB, XO (post-hoc analysis) Patients 6 to 17 years of age with mild to moderate persistent asthma, >12% improvement in FEV_1 after maximum bronchodilation or 20% improvement in FEV_1 after methacholine dose of ≤12.5 mg/ml, and FEV_1 ≥70% of predicted value	N=144 16 weeks	Primary: Asthma control days Secondary: Pulmonary function as measured by exhaled nitric oxide (eNO), FEV_1 and FEV_1/forced vital capacity (FVC), resistance of the respiratory system at 5 Hz (R5), and area of reactance (AX)	Primary: Significant improvements in asthma control days were reported compared to baseline in both groups (P<0.001). A significant improvement in asthma control days in the fluticasone group was reported compared to the montelukast group (P<0.001). Secondary: A significant decrease in eNO in both groups was reported compared to baseline (P<0.001), and the difference between groups was significant, favoring fluticasone (P=0.028). Significant improvements were noted in both groups in FEV_1, FEV_1/FVC, R5, and AX compared to baseline.
Garcia et al.[27] (2005) Montelukast 5 mg QD vs fluticasone 100 mcg BID	RCT, DB, NI Patients 6 to 14 years of age with mild persistent asthma, FEV_1 ≥80% predicted value, and FEV_1 or PEF ≥70% predicted value at visit 3	N=994 12 months	Primary: Change in the percent of asthma rescue-free days (RFD) Secondary: Percentage change from baseline in predicted FEV_1, percentage of patients requiring anti-asthma	Primary: Montelukast was shown to be equivalent to fluticasone in percentage of asthma RFDs. Secondary: A significant difference in change from baseline in percentage of predicted FEV_1 favoring fluticasone was observed (P=0.04). No significant difference in change from baseline in FEV_1 between fluticasone group and montelukast group was observed (when not expressed as change in percentage of predicted value). There was a significant difference in percentage of β-agonist use from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			medications other than β-agonists, percentage of patients with an asthma attack, average percentage of days with β-agonist use, change in blood eosinophil count Tertiary: Patient reports of asthma control, patient lost school days, and parental lost work days	baseline in both groups (P≤0.001). A significant decrease in percentage of β-agonist use in the fluticasone group was reported compared to the montelukast group (P=0.003). Significantly fewer patients in the fluticasone group used rescue asthma medications, other than β-agonists, compared to the montelukast group. Significantly fewer patients in the fluticasone group experienced an asthma attack compared to the montelukast group. There was no significant difference in the proportion of patients experiencing an asthma attack between the fluticasone group and montelukast group when analyzing only the patients who received no systemic corticosteroids during the previous year. A significant improvement in overall quality of life from baseline in both fluticasone and montelukast groups was reported (P≤0.001). A significant decrease in blood eosinophil count was reported in both fluticasone and montelukast groups from baseline (P≤0.001). Tertiary: There was a significant improvement in patient asthma control from baseline in both the fluticasone and montelukast groups (P≤0.001) though between-group comparison favored fluticasone. The proportion of patients with ≥1 lost school day during the 4 weeks preceding the 12 month visit was 8.8% in the montelukast group and 6.2% in the fluticasone group. The percentage of patients who lost >3 school days was 1.9% in the montelukast group and 2.1% in the fluticasone group. A ≥1 lost work day was reported in parents of 2.9% of montelukast patients and 2.0% of fluticasone patients during the 4 weeks prior to the 12 month visit, and the percentage whose parents lost >3 work days were reported as 0.4% in the montelukast group and 0.2% in the fluticasone group. The significance of these differences was not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Busse et al.[29] (2001) Montelukast 10 mg QD vs fluticasone 44 mcg BID	RCT, DB, DD, PG Patients 15 to 83 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 between 50%-80% of predicted value, increase in FEV_1 of 15% or greater after β-agonist use, regular or as needed use of inhaled or oral β-agonist in the 3 months prior to screening	N=533 24 weeks	Primary: Mean percentage change from baseline in morning pre-medication FEV_1 Secondary: Mean change in forced vital capacity (FVC), forced mid-expiratory flow ($FEF_{25\%-75\%}$), morning and evening PEF, percentage of symptom-free days, asthma symptom scores, nighttime awakenings, daily rescue albuterol use, percentage of rescue-free days	Primary: A significantly greater improvement in FEV_1 in the fluticasone group was reported compared to the montelukast group (P≤0.002). Secondary: A significantly greater improvement in all spirometric values in the fluticasone group was reported compared to the montelukast group (P≤0.002). A significant improvement in asthma symptom-free days in the fluticasone group was reported compared to montelukast group (P<0.001). A significant improvement in asthma symptom scores in the fluticasone group was observed compared to the montelukast group (P<0.001). A significant improvement in nighttime awakenings in the fluticasone group was observed compared to the montelukast group (P=0.023). A significant improvement in rescue albuterol use in the fluticasone group was observed compared to the montelukast group (P<0.001). Additional outcomes: The physician's global assessment significantly favored fluticasone compared to montelukast (P<0.001). Significantly greater improvements noted on the asthma quality of life questionnaire in the fluticasone group compared to the montelukast group (P≤0.001). Patient-rated satisfaction with treatment significantly favored the fluticasone group compared to the montelukast group (P<0.001).
Peters et al.[18] (2007) LOCSS Montelukast 5 to	DB, MC, RCT Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-	N=500 16 weeks	Primary: Time to treatment failure Secondary: Measures of	Primary: The rates of treatment failure were 20.2% in the fluticasone group, 20.4% in the fluticasone/salmeterol group, and 30.3% in the montelukast group (HR, 1.6; 95% CI, 1.1 to 2.6; P=0.03 for both comparisons). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 mg QD vs fluticasone 100 mcg BID vs fluticasone-salmeterol 100/50 mcg QHS	bronchodilator, reversibility of airway obstruction by ≥12% with the use of a β-agonist or provocative concentration of methacholine producing a 20% decrease in FEV_1 of ≤8 mg/ml within the previous 2 years. Patients were stable on fluticasone 100 mcg BID and step-down therapy was being attempted.		pulmonary function, measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients	Mean prebronchodilator FEV_1 values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone/salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value; P=0.002 and P<0.001, respectively). Asthma control, as measured with the use of the Asthma Control Questionnaire, was better in the fluticasone group and in the fluticasone/salmeterol group than in the montelukast group. The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone/salmeterol group (22.9% vs. 17.1%, P=0.06) and in the fluticasone group (22.9% vs. 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone group than in the montelukast group (16.7% vs. 25.4%; P=0.04), with a similar trend in the fluticasone/salmeterol group (17.3%, vs. 25.4% in the montelukast group; P=0.06). The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6% to 85.8%.
Sorkness et al.[43] (2007) Montelukast 5 mg QD vs fluticasone 100 mcg BID vs fluticasone 100 mcg/salmeterol 50 mcg BID	DB, PG, RCT Patients 6 to 14 years, with mild-moderate persistent asthma with >4 hour post-bronchodilator FEV_1 ≥80% of predicted at screening and ≥70% predicted at randomization plus methacholine FEV_1 ≤12.5 mg/ml.	N=285 48 weeks	Primary: Percent of asthma control days Secondary: Percent episode-free days, number of exacerbations requiring prednisone and time to first exacerbation requiring prednisone, time to treatment failure, and the 7-item	Primary: Asthma control days averaged 64.2% for fluticasone, 59.6% for PACT combination, and 52.5% for montelukast. The fluticasone monotherapy group gained an average of 42 asthma control days per year compared with the montelukast monotherapy group (P=0.004). The change in asthma control days from baseline to end of treatment was significantly greater for fluticasone monotherapy vs montelukast, and PACT combination vs montelukast, but not for fluticasone monotherapy vs PACT combination. Secondary: Compared with montelukast monotherapy, both fluticasone monotherapy and PACT combination led to a greater percentage of episode-free days. Time to first prednisone burst and time to treatment failure favored fluticasone treatment compared to montelukast (P=0.002 and P=0.015,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(PACT combination)			Asthma Control Questionnaire (ACQ), pulmonary function, and growth	respectively) but there was no differences noted between the PACT combination and montelukast groups. No significant difference in ACQ scores between the fluticasone and PACT combination groups, or between the PACT combination and montelukast groups. There was a significant difference with fluticasone compared to montelukast (P=0.018). Prebronchodilator FEV_1 and FEV_1/FVC increased more with fluticasone monotherapy than montelukast (P <0.001 for both measures) and PACT combination (P=0.01 for FEV_1). Treatment with montelukast did not improve these lung function measures. There was no difference in the mean increase in height between the three treatment groups.
Fish et al.[30] (2001) Montelukast 10 mg QD vs salmeterol 50 mcg BID	RCT, MC, DB, PG Patients ≥15 years of age with asthma who were symptomatic despite therapy with a stable dose of inhaled corticosteroids during the previous 30 days	N=948 12 weeks	Primary: Morning PEF values Secondary: Evening PEF, daytime asthma symptom score, supplemental albuterol use, nighttime awakenings	Primary: Significant increases in morning PEF in the salmeterol group were observed compared to the montelukast group (P<0.001). Secondary: A significant decrease in symptom scores in the salmeterol group was reported compared to the montelukast group (P=0.039). A significant decrease in supplemental albuterol use in the salmeterol group was reported compared to the montelukast group (P≤0.012). Significantly greater reductions in nighttime awakenings in the salmeterol group were reported compared to the montelukast group (P=0.015).
Calhoun et al.[33] (2001) Montelukast 10 mg QD vs fluticasone 100	RCT, DB, DD, MC Patients 15 to 72 years of age with asthma for ≥6 months who had been treated with oral or inhaled β-agonists for at least	N=423 12 weeks	Primary: Change from baseline in pre-dose FEV_1 values Secondary: Morning and evening PEF values, asthma	Primary: A statistically significant improvement in the percent change from baseline in FEV_1 in the fluticasone and salmeterol group was observed compared to the montelukast group (P≤0.001). Secondary: A statistically significant improvement in all secondary endpoints for the fluticasone and salmeterol group was observed compared to the montelukast group (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg and salmeterol 50 mcg BID	6 weeks prior to study, FEV_1 values of between 50%-80% of predicted value, and an increase in FEV_1 of at least 12% within 30 minutes of inhaled albuterol		symptom score, percentage of symptom-free days, β-agonist use, percentage of rescue-free days, percent of nights with no asthma-related awakenings, percentage of nights with no asthma-related awakenings in patients with ≥2 awakenings per week at baseline, and nights per week with no awakenings	
Maspero et al.[47] (2008) Montelukast 5 mg QD vs fluticasone-salmeterol 100-50 mcg BID	RCT, DB, DD, Patients 6 to 14 years of age with FEV_1 between 55% and 85% predicted who were receiving only short acting β_2-agonists	N=548 12 weeks	Primary: Change from baseline in AM PEF Secondary: Predose FEV_1, PM PEF, level of symptoms and rescue medication use, Pediatric Asthma Quality of Life Questionnaire	Primary: There was a significant improvement in AM PEF with fluticasone-salmeterol compared to montelukast (P<0.001). Secondary: The mean change in FEV_1 was greater in the fluticasone-salmeterol group than the montelukast group (P<0.001). The fluticasone-salmeterol group experienced significantly greater improvements in the percentage of symptom-free and rescue-free 24 hour periods compared to treatment with montelukast (P=0.025 and P<0.001, respectively) There was no significant difference in the Pediatric Asthma Quality of Life Questionnaire between the treatment groups.
Katial et al.[49] (2010)	RCT, DB, PC, MC,	N=1,081	Primary: Mean change from	Primary: There was no significant difference in AM PEF between FSC and FSC +

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Montelukast 10 mg QD (MON) vs fluticasone-salmeterol 100/50 mcg BID (FSC) vs fluticasone-salmeterol 100/50 mcg BID and montelukast 10 mg QD (FSC + MON) vs fluticasone-salmeterol 100/50 mcg BID and fluticasone nasal spray 200 mcg QD (FSC +FPANS)	Patients ≥15 years of age with asthma and a history of seasonal allergic rhinitis for at least two allergy seasons. All patients were stabilized on either SABA, LABA, anticholinergic, cromolyn alone or in combination with an ICS for ≥1 month prior to study entry	4 weeks	baseline in AM PEF between FSC and FSC + MON, as well as FSC and MON Secondary: Changes in AM predose FEV_1, percent of symptom free days and albuterol free days, difference in daytime and nighttime total nasal symptom score (D/N-TNSS)	MON. The mean change from baseline in AM PEF was greater with FSC than MON (P<0.001). There was no significant difference between FSC + FPANS and FSC + MON with regards to AM PEF. There was no difference in AM PEF between FSC + FPANS and FSC monotherapy. Secondary: There was no significant difference in other asthma secondary endpoints between FSC and FSC + MON. FSC was significantly more effective than MON on other asthma secondary endpoints (% symptom free days, % albuterol free days, morning FEV_1, and PM PEF). There was no significant difference between FSC + FPANS and FSC + MON with regards to other asthma secondary endpoints. There was no difference in other asthma secondary endpoints between FSC + FPANS and FSC monotherapy. For rhinitis outcomes, FSC + FPANS was more effective than FSC + MON, with a mean change in D-TNSS of -3.1 vs -2.4, respectively (P<0.001) and a mean change in N-TNSS of -0.20 vs -1.7, respectively (P<0.001).
Yildirim et al.[24] (2004) Montelukast 10 mg QD and budesonide 400 mcg/day vs budesonide 800	RCT, PG Patients with moderate persistent asthma for ≥6 months	N=30 6 weeks	Primary: Morning, daytime, and evening asthma symptoms, morning and evening PEF, FEV_1, blood eosinophil counts, frequency of short-acting β-agonist use, frequency of	Primary: A significant decrease in morning and daytime symptom scores were reported in both groups compared to baseline (P<0.05). There was no significant difference between the treatment groups. There was no significant difference in evening symptom scores in either treatment group compared to baseline. There were no significant differences in FEV_1 or PEF values from baseline or between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg/day			asthma exacerbations	There was a significant decrease in blood eosinophil counts in both groups compared to baseline (P<0.05). There was no significant difference between the treatment groups. There was a significant decrease in β-agonist use in the budesonide plus montelukast group compared to baseline (P<0.05), but there was no significant difference in β-agonist use in the high-dose budesonide group compared to baseline. No patients in either group experienced an asthma exacerbation during the study period.
Price et al.[28] (2003) Montelukast 10 mg QD and budesonide 800 mcg/day vs budesonide 1,600 mcg/day	RCT, DB, PG, NI Patients 15 to 75 years of age with asthma for ≥1 year and not optimally controlled on regular inhaled corticosteroids; patients were non-smokers or ex-smokers, FEV_1 values of ≥50% of predicted value at visits 1 and 3, ≥12% improvement in FEV_1 after β-agonist treatment of at least 1 puff per day during the last 2 weeks of the run in period	N=889 12 weeks	Primary: Morning PEF values Secondary: Initial treatment effect on PEF (days 1-3), daily self-reported β-agonist use, daytime symptoms, nocturnal awakenings, asthma exacerbations, asthma-free days, blood eosinophil counts, asthma specific quality of life	Primary: A significant improvement in morning PEF compared to baseline for both groups was reported (P<0.001), but differences between groups were not significant at the end of the study. Secondary: The change from baseline in PEF during the first 3 days of treatment was significantly more rapid in the montelukast plus budesonide group compared to the budesonide group alone (P<0.001). All other secondary endpoints were not significantly different from baseline or between groups.
Bjermer et al.[31] (2003) Montelukast 10	RCT, DB, PG, MC Patients 15 to 72 years of age with	N=1,490 52 weeks	Primary: Percentage of patients with at least one asthma	Primary: No significant difference between the 2 groups in percentage of patients with at least 1 asthma attack was reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD and fluticasone 100 mcg BID vs fluticasone 100 mcg BID and salmeterol 50 mcg BID	asthma for ≥1 year, baseline FEV_1 50%-90% predicted value, improvement of 12% or more in FEV_1 or in morning PEF after β-agonist use, regular use of inhaled corticosteroids for at least 8 weeks prior to study, average β-agonist use of at least 1 puff per day		exacerbation Secondary: Asthma specific quality of life, nocturnal awakenings, mean FEV_1 before and after β-agonist use, mean morning PEF, time to first asthma exacerbation, blood eosinophil counts	Secondary: A significant improvement in asthma specific quality of life compared to baseline in both groups was reported (P≤0.001), though there was no significant difference between the 2 groups. A significant decrease in nocturnal awakenings from baseline in both groups was reported (P≤0.001), though there was no significant difference between the 2 groups. A significant improvement in FEV_1 before β-agonist use in the salmeterol and fluticasone group was observed compared to the montelukast and fluticasone group (P≤0.001), though the improvement in FEV_1 after β-agonist use was similar between the 2 groups. A significantly larger increase in morning PEF in the salmeterol and fluticasone group was reported compared to the montelukast and fluticasone group (P≤0.001), though both groups significantly improved morning PEF values from baseline (P≤0.001). No significant differences between the groups regarding time to first asthma exacerbation were observed. A significant decrease in blood eosinophils in the montelukast and fluticasone group was reported compared to the salmeterol and fluticasone group (P=0.011).
Lemanske et al.[20] (2010) BADGER Montelukast 5 to 10 mg QD + fluticasone 100 mcg BID (LTRA step-up therapy) vs	RCT, DB, XO Patients 6 to 17 years of age with uncontrolled asthma (diary-reported symptoms, rescue use of an inhaled bronchodilator with ≥2 puffs/day, or peak flows <80% of the predetermined reference value)	N=165 48 weeks	Primary: Differential response to each of the three step-up therapies on the basis of fixed threshold criteria for the following three asthma-control measures: need for treatment with oral prednisone for	Primary: A differential response occurred in 161 of 165 patients (98%; P<0.001). The proportion of patients who had a better response to LABA step-up was higher than the proportion with a better response to LTRA step-up (52% vs. 34%, P=0.02), and the proportion with a better response to LABA step-up was higher than the proportion with a better response to ICS step-up (54% vs. 32%, P=0.004), whereas the responses to LTRA and ICS step-up therapies were similar. The response to LABA step-up therapy was significantly more likely to be the best response, as compared with the response to LTRA step-up (relative probability, 1.6; 95% CI, 1.1 to 2.3; P=0.004) and the response to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 mcg BID + fluticasone 100 mcg BID (LABA step-up therapy) vs fluticasone 250mcg BID (ICS step-up therapy)	while receiving fluticasone 100 mcg BID		acute exacerbations, number of asthma control days, FEV_1 (One treatment period was ranked as better than another if the total amount of prednisone received during the period was ≤180 mg, if the number of annualized asthma-control days during the final 12 weeks of the period was increased by at least 31 days, or if the FEV_1 at the end of the period was at least 5% higher)	ICS step-up (relative probability, 1.7; 95% CI, 1.2 to 2.4; P=0.002). Higher scores on the Asthma Control Test before randomization (indicating better control at baseline) predicted a better response to LABA step-up (P=0.009). White race predicted a better response to LABA step-up, whereas black patients were least likely to have a best response to LTRA step-up (P=0.005).
Suissa et al.[23] (1997) Zafirlukast 20 mg BID vs placebo	RCT, DB, PC, MC Patients ≥12 years of age who were non-smokers in the last 6 months, smoking history of <10 pack-years, FEV_1 at least 55% of predicted value, with bronchial hyper-responsiveness	N=146 13 weeks	Primary: Days without limitation of activity, days without use of β-agonists, days without episodes of asthma, days without sleep disturbance, unscheduled health care visits and contacts, total number of β-	Primary: Significantly more days without asthma symptoms was observed in the zafirlukast group compared to placebo (P=0.03). Significantly more days without β-agonist use were observed in the zafirlukast group compared to placebo (P=0.001). Significantly more days without episodes of asthma were reported in the zafirlukast group compared to placebo (P=0.003). More days without sleep disturbances were reported in the zafirlukast group compared to placebo; however, this was not significant (P>0.2). A significant decrease in health care contacts was reported in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			agonist inhalers used, number of prescriptions for non-asthma medications consumed, number of days absent from work or school	zafirlukast group compared to placebo (P=0.007). A significant decrease in asthma-related absenteeism was reported in zafirlukast group compared to placebo (P=0.04). A decrease in canisters of β-agonists used was observed in the zafirlukast group compared to placebo; however, this was not significant (P=0.17). A decrease in the use of non-asthma medications was observed in the zafirlukast group compared to placebo; however, this was not significant (P>0.2).
Busse et al.[32] (1999) Zafirlukast 20 mg BID vs salmeterol 42 mcg BID	RCT, DB, PG, MC Patients 12 to 73 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 between 50%-80% predicted value, at least 12% increase in FEV_1 within 30 min of inhalation of albuterol	N=289 4 weeks	Primary: Morning PEF values Secondary: Evening PEF values, asthma symptom scores, supplemental albuterol use, nighttime awakenings, FEV_1, and asthma exacerbations	Primary: A statistically significant improvement in morning PEF values in the salmeterol group was reported compared to the zafirlukast group (P=0.001). Secondary: A statistically significant improvement in evening PEF values in the salmeterol group was reported compared to the zafirlukast group (P=0.019). Statistically significant improvements in asthma symptom scores in the salmeterol group were reported compared to the zafirlukast group (P≤0.026). A statistically significant decrease in daytime and nighttime supplemental albuterol use in the salmeterol group was noted compared to the zafirlukast group (P=0.004 and P=0.013 respectively). No statistically significant difference in nighttime awakenings between the 2 groups was reported (P=0.142). A statistically significant improvement in FEV_1 compared to baseline in both groups was reported (P<0.001), but no statistically significant difference between groups at the end of the treatment period was observed (P=0.293).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Seven patients in the salmeterol group and 9 patients in the zafirlukast group experienced asthma exacerbations during the treatment period.
Israel et al.[34] (1993) Zileuton 600 mg QID vs zileuton 800 mg BID vs placebo	RCT, DB, PC Patients 18 to 65 years of age with asthma, FEV_1 40%-75% of predicted value, a 15% or greater increase in FEV_1 30 minutes after inhalation of albuterol, and who were not being treated with inhaled or oral corticosteroids	N=139 4 weeks	Primary: FEV_1, asthma symptoms, and frequency of β-agonist use	Primary: There was a significant 14.6% increase in baseline in FEV_1 within 1 hour in both zileuton groups compared to baseline (P<0.001). There was a significant change in FEV_1 in the zileuton 600 mg group after 4 weeks compared to placebo (P=0.02). There was a significant decrease in asthma symptoms in all 3 groups (P<0.01), but the change was the greatest in the zileuton 600 mg group compared to placebo (P=0.02). There was a significant decrease in β-agonist use in the zileuton 600 mg group and the 800 mg group (P<0.001 and P=0.005 respectively) from baseline. Compared to placebo, the change was only significant in the zileuton 600 mg group (P0.03).
Israel et al.[35] (1996) Zileuton 600 mg QID vs zileuton 400 mg QID vs placebo	RCT, DB, PG Patients with mild to moderate asthma, FEV_1 values of 40%-80% of predicted value, only being treated with inhaled β-agonists	N=401 13 weeks	Primary: Frequency of asthma exacerbations requiring corticosteroid treatment, use of inhaled β-agonists, FEV_1, asthma symptoms, and quality of life evaluations	Primary: There was a significantly lower percentage of patients requiring corticosteroid treatment for asthma in the zileuton 600 mg group compared to placebo (P=0.02). There was a significant increase in FEV_1 in the zileuton 600 mg group compared to the placebo group (P=0.006). There was a significant improvement in quality of life assessments in the zileuton group compared to the placebo group (P=0.007).
Wenzel et al.[46] (2007) Zileuton CR 1200 mg BID	DB, MC, PC, RCT Patients ≥12 years of age and non-smoking for at least 6 months; ex-	N=926 6 months	Primary: Mean change in PEFs Secondary: Improvement in	Primary: Sustained improvements in PEF were observed in the zileuton group compared to placebo. Secondary: Improvement in trough FEV1 was similar between zileuton and placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	smokers with ≤10-pack year history of cigarette smoking; FEV1 ≥40% predicted at least 48 hours after last theophylline use, at least 12 hours after long-acting β-agonist (salmeterol) use, and at least 6 hours after SABA use; ≥15%in FEV_1 at least 15 minutes after inhaled albuterol; and history of 15% reversibility documented within 1 year.		trough FEV1; change in number of daily doses of SABA; change from baseline in total score of Asthma QOL questionnaire measured at 3months and 6 months	groups. There was no significant difference in the number of daily doses of SABA with zileuton compared to placebo. Treatment with zileuton resulted in greater mean improvements in QOL than did treatment with placebo at 6 for the symptoms domain (0.74 versus 0.56, P=0.040) and the emotions domain (0.63 versus 0.42, P=0.043). The overall score improved by 0.71 for the zileuton group and 0.57 for the placebo group (P=0.083).
Exercise-Induced Bronchoconstriction				
Philip et al.[44] (2007) Montelukast 10 mg vs salmeterol 50 mcg vs placebo	R, DB, PC, XO Men and women who demonstrated a fall in FEV_1 following exercise (ΔFEV_1) of ≥20%	N=47 9-21 days	Primary: Maximum ΔFEV_1 observed after exercise challenge at 2 hours postdose for montelukast Secondary: Maximum ΔFEV_1 observed after the challenges at 8.5 and 24 hours postdose, recovery time and need for β-agonist rescue for montelukast	Primary and Secondary: Maximum ΔFEV_1 at 2, 8.5, and 24 hours were significantly smaller after montelukast administration than after placebo administration (least squares mean [± SE], 13.2 ± 1.2%, 11.7 ± 1.2%, and 10.0 ± 1.1% vs 21.8 ± 1.2%, 16.8 ± 1.3%, and 14.0 ± 1.1%, respectively; P≤0.001, P<0.01, and P<0.05). Montelukast and salmeterol had similar efficacy at 2 and 8.5 hours, but only montelukast was effective at 24 hours. Montelukast was associated with substantially less use of SABA rescue vs placebo at 2 hours postdose (P=0.031). Salmeterol vs placebo was accompanied by higher levels of FEV_1 before exercise, significant reductions in mean maximum ΔFEV_1, and fewer instances of SABA rescue.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fogel et al.[19] (2010) Montelukast 5 mg QD vs salmeterol 50 mcg BID All patients received open-label fluticasone 50 mcg 2 puffs BID throughout the study.	RCT, DB, MC, XO Patients 6 to 14 years of age with exercise-induced bronchoconstriction, FEV_1 ≥70%, who were receiving treatment with an ICS	N=154 8 weeks	Primary: Percent change in FEV_1 after exercise and before SABA administration Secondary: AUC for first 20 minutes after exercise, time to recovery within 5% of pre-exercise FEV_1, maximum FEV_1 % predicted after SABA, average percent change from pre-exercise baseline FEV_1 after SABA	Primary: Montelukast was significantly more effective than salmeterol for maximum percent decrease in FEV_1 after exercise (10.6% vs 13.8% P=0.009) and for mean percent change after exercise. Montelukast provided significantly more effective bronchoprotection than salmeterol as shown by a smaller $AUC_{0–20}$ (P=0.006) and a shorter time to recovery (P=0.04). Patients receiving montelukast had a significantly better response to SABA based on FEV_1 percent predicted (103.1% vs 100.9%; P<0.001). The average percent change in FEV_1 after SABA use was significantly greater in the montelukast group than the salmeterol group (P<0.001).

Drug regimen abbreviations: QD=once daily, BID=twice daily
Study abbreviations: DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multi-center, NI=non-inferiority, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: ED=Emergency Department, ECP=eosinophil cationic protein, EG^{2+}=mediator released by eosinophils in response to stimuli, FEV_1=forced expiratory flow in 1 second, FVC=forced vital capacity, LTRA=leukotriene receptor antagonist, NPIF=nasal peak inspiratory flow, PACT=Pediatric Asthma Controller Trial, PEF=peak expiratory flow, SABA=short-acting beta agonist, SAR=seasonal allergic rhinitis

Additional Evidence

Dose Simplification
Dorais et al. analyzed pharmacy claims to assess adherence with leukotriene modifiers and inhaled corticosteroids.[41] Compared to patients receiving inhaled corticosteroids, patients receiving a leukotriene modifier were more likely to refill their prescriptions at least once during the first year of treatment (67.9% vs. 52.7%), were less likely to discontinue treatment (RR=0.46; 95% CI: 0.85-0.98), and were more likely to be on treatment longer during the first year of therapy (38% vs. 19%; all, P<0.001).

Bukstein et al. evaluated preference with montelukast or inhaled cromolyn sodium in children with asthma.[42] More parents (87% vs 12%, respectively; P<0.001) and children (82% vs 17%, respectively; P<0.001) preferred montelukast to cromolyn. Parents and children expressed greater overall satisfaction with montelukast compared with cromolyn (P<0.001). The most prevalent reason for greater parental satisfaction with montelukast stemmed from its greater convenience and ease in getting the child to use the medication, as well as less interference with the parent's lifestyle. Additionally, significantly more patients were adherent while taking montelukast than while taking cromolyn (78% vs 42%, respectively; P<0.001). The mean albuterol use during montelukast therapy was significantly lower than that reported during cromolyn therapy (1.56 vs 1.92, respectively; P=0.003).

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Suissa et al. demonstrated a significant reduction in health care resource utilization in patients taking zafirlukast compared to those taking placebo.[23] Price et al. found no difference in health care resource utilization with montelukast compared to budesonide in patients with asthma.[28]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Leukotriene Modifiers

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Montelukast	chewable tablet, granules, tablet	Singulair®	$$$$	N/A
Zafirlukast	tablet	Accolate®*	$$$-$$$$	$$$$
Zileuton	sustained-release tablet, tablet	Zyflo®, Zyflo CR®	$$$$$	N/A

N/A=Not available

X. Conclusions

The leukotriene modifiers are approved for the long-term management asthma.[1-7] Montelukast is also approved for the treatment of allergic rhinitis, as well as for the prevention of exercise-induced bronchoconstriction.[4] Montelukast and zafirlukast are classified as leukotriene receptor antagonists, whereas zileuton is classified as a 5-lipoxygenase inhibitor. Zafirlukast is the only product available in a generic formulation.

For the treatment of asthma, guidelines recommend the use of an inhaled corticosteroid as initial therapy.[9-11,14] Leukotriene modifiers are considered an alternative treatment option in patients who are only using short-acting β_2-agonists.[9,11,14] They may be considered as a first-line treatment option in children <5 years of age who are unable to use inhaled corticosteroids.[14] When additional therapy is needed, it is recommended that a long-acting β_2-agonist be added to an inhaled corticosteroid in adults and children 5-12 years of age.[9,14-15] For children <5 years of age, a leukotriene receptor antagonist is the first choice as add-on therapy to inhaled corticosteroids.[14] Guidelines do not give preference to one leukotriene modifier over another for the treatment of asthma.

Clinical trials have demonstrated that the leukotriene modifiers improve asthma outcomes, including pulmonary function, daytime symptoms, nocturnal awakening, β_2-agonist use, exacerbations and quality of life.[18,20-35,43,46-47,49] However, they have generally been shown to be less effective than inhaled corticosteroids and long-acting β_2-agonists.[11,18,20,25-27,29-30,32-33,43,47,49] There are very few studies that directly compare the leukotriene modifiers for the treatment of asthma.[51]

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists and mast cell stabilizers.[12-13,16-17] When selecting an agent for the treatment of allergic rhinitis and conjunctivitis, clinicians should take into consideration the severity of symptoms, duration of disease, patient preference, as well as efficacy. Intranasal corticosteroids are considered the most effective treatment option for allergic rhinitis.[12,16-17] Leukotriene receptor antagonists have been shown to be useful for the treatment of allergic rhinitis, either alone or in combination with antihistamines. Guidelines do not give preference to one leukotriene modifier over another for the treatment of allergic rhinitis. In clinical trials, there was no difference in efficacy between montelukast and second-generation antihistamines; however, montelukast was found to be less effective than treatment with intranasal corticosteroids.[16-17,36-37,39]

There is insufficient evidence to support that one brand leukotriene modifier is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand leukotriene modifiers within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendation

No brand leukotriene modifier is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
4. Singulair® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; July 2010.
5. Accolate® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2004.
6. Zyflo® [package insert]. Cary, NC: Cornerstone Therapeutics, Inc.; July 2009.
7. Zyflo CR® [package insert]. Cary, NC: Cornerstone Therapeutics, Inc.; August 2009.
8. Laitinen A, Lindqvist A, Halme M et al. Leukotriene E_4-induced persistent eosinophilia and airway obstruction are reversed by zafirlukast in patients with asthma. J Allergy Clin Immunol. 2005;115(2):259-265.
9. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
10. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.
11. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.
12. Bousquet J, Khaltaev N, Cruz A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA^2LEN and AllerGen). Allergy 2008:63(S86):8–160.
13. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of allergic rhinitis. Primary Care Respiratory Journal 2006;15:58-70.
14. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
15. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
16. Institute for Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Respiratory Illness in Children and Adults. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); January 2008. Available at: http://www.icsi.org/respiratory_illness_in_children_and_adults__guideline_/respiratory_illness_in_children_and_adults__guideline__13116.html. Accessed October 2010.
17. Wallace DV, Dykewicz MS, Bernstein DI, et al., Joint Task Force on Practice, American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1-84.
18. Peters SP, Anthonisen N, Castro M et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med 2007;356:2027-39.
19. Fogel RB, Rosario N, Aristizabal G, et al. Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol 2010;104:511-7.
20. Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med 2010;362:975-85.
21. Knorr B, Matz J, Bernstein J, et al. Montelukast for chronic asthma in 6-14 year old children: a randomized, double blind trial. JAMA. 1998;279(15):1181-1186.
22. Reiss T, Chervinsky P, Dockhorn R, et al. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double blind trial. Arch Internal Med. 1998;158(11):1213-1220.
23. Suissa S, Dennis R, Ernst P, et al. Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma: a randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine. 1997;126(3):177-183.

24. Yildirim Z, Ozlu T, Bulbul Y, et al. Addition of montelukast versus double dose of inhaled budesonide in moderate persistent asthma. Respirology. 2004;9:243-248.
25. Szefler S, Phillips B, Martinez F, et al. characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005;115(2):233-242.
26. Zeiger R, Szefler S, Phillips B, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006;117(1);45-52.
27. Garcia M, Wahn U, Gilles L, et al. Montelukast compared with fluticasone for control of asthma among 6 to 14-year-old patients with mild asthma: the MOSAIC study. Pediatrics. 2005;116:360-369.
28. Price D, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax. 2003;58:211-216.
29. Busse W, Raphael G, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. J Allergy Clin Immunol. 2001;107(3):461-468.
30. Fish J, Elliot I, Murray J, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2001;120(2):423-430.
31. Bjermer L, Bisgaard H, Bousquet J, et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomized comparative trial. British Medical Journal. 2003;327(7420):891-896.
32. Busse W, Nelson H, Wolfe J, et al. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. J Allergy Clin Immunol. 1999;103(6):1075-1080.
33. Calhoun W, Nelson H, Nathan R, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short acting β_2 agonists alone. American J Resp and Critical Care Med. 2001;164:759-763.
34. Isreale E, Rubin P, Kemp J, et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. Annals of Internal Medicine. 1993;119(11):1059-1066.
35. Israel E, Cohn L, Dube L, et al. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. JAMA. 1996;275:931-936.
36. Pullerits T, Praks L, Ristioja V, et al. Comparison of nasal glucocorticoid, antileukotriene, and combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. 2002;109(6)949-955.
37. Baena-Cagnani C, Berger W, DuBuske et al. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of β_2 agonists in patients with seasonal allergic rhinitis and asthma. Int Arch Allergy Immunol. 2003;130:307-313.
38. Saengpanich S, deTineo M, Naclerio R, et al. Fluticasone nasal spray and the combination of loratadine and montelukast in seasonal allergic rhinitis. Arch Otolaryngol Head Neck Surg. 2003;129:557-562.
39. Meltzer E, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol. 2000;105(5):917-922.
40. Mucha S. deTineo M, Naclerio R, et al. Comparison of montelukast and pseudoephedrine in the treatment of allergic rhinitis. Arch Otolaryngol Head/Neck Surg. 2006;132:164-172.
41. Dorais M, Blais L, Chabot I, et al. Treatment persistence with leukotriene receptor antagonists and inhaled corticosteroids. Journal of Asthma. 2005;42:385-393.
42. Bukstein DA, Bratton DL, Firriolo KM, et al. Evaluation of parental preference for the treatment of asthmatic children aged 6 to 11 years with oral montelukast or inhaled cromolyn: a randomized, open-label, crossover study. J Asthma. 2003;40(5):475-485.
43. Sorkness CA, Lemanske RF Jr, Mauger DT et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol 2007;119:64-72.
44. Philip G, Pearlman DS, Villaran C et al. Single-dose montelukast or salmeterol as protection against exercise-induced bronchoconstriction. Chest 2007;132:875-83.
45. Jiang RS. Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis. J Otolaryngol 2006;35:117-21.
46. Wenzel S, Busse W, Calhoun W et al. The safety and efficacy of zileuton controlled-release tablets as adjunctive therapy to usual care in the treatment of moderate persistent asthma: a 6-month randomized controlled study. J Asthma 2007;44:305-10.
47. Maspero J, Guerra F, Cuevas F, et al. Efficacy and tolerability of salmeterol/fluticasone propionate versus montelukast in childhood asthma: A prospective, randomized, double-blind, double-dummy, parallel-group study. Clin Ther 2008;30:1492-504.

48. Papadopoulos NG, Philip G, Giezek H, Watkins M, Smugar SS, Polos PG. The efficacy of montelukast during the allergy season in pediatric patients with persistent asthma and seasonal aeroallergen sensitivity. J Asthma 2009;46:413-20.
49. Katial RK, Oppenheimer JJ, Ostrom NK, et al. Adding montelukast to fluticasone propionate/salmeterol for control of asthma and seasonal allergic rhinitis. Allergy Asthma Proc 2010;31:68-75.
50. Sardana N, Santos C, Lehman E, Craig T. A comparison of intranasal corticosteroid, leukotriene receptor antagonist, and topical antihistamine in reducing symptoms of perennial allergic rhinitis as assessed through the Rhinitis Severity Score. Allergy Asthma Proc 2010;31:5-9.
51. Riccioni G, Vecchia RD, Di Ilio C, et al. Effect of the two different leukotriene receptor antagonists montelukast and zafirlukast, on quality of life. Allergy and Asthma Proc 2004;25:445-448.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Inhaled Mast-Cell Stabilizers
AHFS Class 481032
February 9, 2011

I. Overview

Cromolyn sodium is the only inhaled mast-cell stabilizer that is currently available in this class. It is approved for the maintenance treatment of asthma, as well as for the prophylaxis of acute bronchospasm induced by exercise, exposure to cold air, or other environmental agents.[1-3] Cromolyn sodium has no intrinsic bronchodilator or antihistaminic activity; however, it inhibits mast cell degranulation after exposure to antigens.[1-3] It indirectly blocks calcium ions from entering the mast cell, which prevents the release of mediators and inhibits bronchoconstriction. Cromolyn sodium has been shown to reduce asthma symptoms, improve morning peak flow, and reduce the need for short-acting bronchodilators.

The inhaled mast-cell stabilizers that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Cromolyn sodium inhalation solution is available in a generic formulation. This class was last reviewed in December 2008.

Table 1. Inhaled Mast-Cell Stabilizers Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cromolyn sodium	inhalation solution*	N/A	cromolyn sodium

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the inhaled mast-cell stabilizers are summarized in Table 2. For a comprehensive overview of the treatment of asthma, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Inhaled Mast-Cell Stabilizers

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): **British Guideline on the Management of Asthma[4] (2009)**	General Treatment Considerations • Inhaled steroids are the recommended preventer drug for adults and children for achieving overall treatment goals. • Alternative preventer therapies in patients taking short-acting β_2-agonists alone are mast-cell stabilizers, leukotriene receptor antagonists and theophylline. • The first choice as add-on therapy to inhaled corticosteroids in adults and children (5-12 years of age) is an inhaled long-acting β_2-agonist. • If control remains inadequate on an inhaled corticosteroid plus a long-acting β_2-agonist, consider the following interventions: leukotriene receptor antagonists, theophylline, slow release β_2-agonist tablets (adults). Exercise-Induced Asthma • The following treatments provide protection against exercise-induced asthma: inhaled corticosteroids, short-acting β_2-agonists, long-acting β_2-agonists, theophyllines, leukotriene receptor antagonists, chromones, and β_2-agonist tablets. • If exercise is a specific problem in patients who are well controlled on inhaled corticosteroids, consider the following therapies: leukotriene receptor antagonists, long-acting β_2-agonists, chromones, oral β_2-

Clinical Guideline	Recommendation(s)
	agonists, or theophyllines. • Inhaled short-acting β_2-agonists are the drug of choice immediately prior to exercise.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention[6] (2009)**	• Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. • The role of mast-cell stabilizers in the long-term treatment of asthma is limited. • Efficacy has been reported in patients with mild persistent asthma and exercise-induced bronchospasm. • Their anti-inflammatory effect is weak and they are less effective than a low dose of inhaled glucocorticosteroid.
Global Initiative for Asthma (GINA): **Global Strategy for the Diagnosis and Management of Asthma in Children 5 years and Younger[11] (2009)**	• A low-dose inhaled glucocorticosteroid is the recommended initial treatment option in children ≤5 years of age. Inhaled glucocorticosteroids have been shown to be more effective than other controller treatment for asthma. • Mast-cell stabilizers are not recommended in children ≤5 years of age.
National Heart, Lung, and Blood Institute (NHLBI): **Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[5] (2007)**	• Inhaled corticosteroids (ICSs) are the most effective long-term therapy for mild, moderate, or severe persistent asthma. • Mast-cell stabilizers are alternative (not preferred) medications for the treatment of mild persistent asthma. • They can also be used as preventive treatment before exercise or unavoidable exposure to known allergens. • Cromolyn or nedocromil taken shortly before exercise is an alternative treatment to prevent EIB, but it is not as effective as short-acting bronchodilators.
International Primary Care Respiratory Group (IPCRG): **Management of Asthma[7] (2006)**	• This guideline does not provide recommendations regarding the use of the mast-cell stabilizers.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the inhaled mast-cell stabilizers are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Inhaled Mast-Cell Stabilizers[1-3]

Indication	Cromolyn Sodium
Asthma	
Maintenance treatment of asthma	✔
Exercised-Induced Bronchospasm	
Prophylaxis of acute bronchospasm induced by exercise, exposure to cold air, or other environmental agents	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the inhaled mast-cell stabilizers are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Inhaled Mast-Cell Stabilizers[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (minutes)
Cromolyn sodium	8	63-76	Not metabolized	Renal (30-50) Feces (80-87)	80-90

V. Drug Interactions

There are no significant drug interactions with the inhaled mast-cell stabilizers.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the inhaled mast-cell stabilizers are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Inhaled Mast-Cell Stabilizers[1-3]

Adverse Events	Cromolyn Sodium
Cardiovascular	
Pericarditis	<1
Central Nervous System	
Dizziness	<1
Drowsiness	✔
Headache	<1
Vertigo	<1
Dermatological	
Exfoliative dermatitis	<1
Photodermatitis	<1
Rash	<1
Urticaria	<1
Gastrointestinal	
Dyspepsia	✔
Nausea	<1
Genitourinary	
Dysuria	<1
Urinary frequency	<1
Musculoskeletal	
Joint swelling and pain	<1
Myalgia	<1
Polymyositis	<1
Respiratory	
Bronchospasm	<1
Cough	<1
Epistaxis	✔
Hoarseness	<1
Nasal burning	✔
Nasal congestion	<1
Nasal itching	✔
Pulmonary infiltrates with eosinophilia	<1
Sneezing	✔

Adverse Events	Cromolyn Sodium
Wheezing	✔
Other	
Anaphylaxis	<1
Anemia	<1
Angioedema	<1
Hemoptysis	<1
Lacrimation	<1
Laryngeal edema	<1
Nephrosis	<1
Peripheral neuritis	<1
Parotid gland swelling	<1
Serum sickness	✔

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the inhaled mast-cell stabilizers are listed in Table 6.

Table 6. Usual Dosing Regimens for the Inhaled Mast-Cell Stabilizers[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cromolyn sodium	Asthma: 20 mg four times daily Bronchospasm Prophylaxis: 20 mg administered shortly before exposure to the precipitating factor	Asthma: ≥2 years of age: 20 mg four times daily Bronchospasm Prophylaxis: ≥2 years of age: 20 mg administered shortly before exposure to the precipitating factor	Inhalation solution: 20 mg/2 ml

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the inhaled mast-cell stabilizers are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Inhaled Mast-Cell Stabilizers

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Leflein et al.[8] (2002) Cromolyn sodium 20 mg QID via nebulization for 8 weeks, followed by dose titration vs budesonide 0.5 mg daily via nebulization for 8 weeks, followed by dose titration	RCT, OL, PG, MC Children 2-6 years of age with persistent asthma treated with at least one long-term control medication, but no long-term or intermittent oral corticosteroids within 12 weeks and 15 days, respectively, of study entry	N=335 52 weeks	Primary: Rate of asthma exacerbations Secondary: Time to first asthma exacerbation, first use of additional asthma therapy, asthma symptom score, rescue medication use, health-care resource use, change in height standard deviation scores	Primary: Treatment with budesonide inhalation suspension significantly reduced the rate of asthma exacerbations per year compared with cromolyn sodium nebulizer solution (P<0.001). The mean exacerbation rate for patients who were receiving cromolyn sodium was estimated to be 1.27 times (27%) greater than for those who were receiving budesonide inhalation suspension. Secondary: Mean times to first asthma exacerbation and first use of additional long-term asthma medication were significantly longer in patients who were receiving budesonide than in patients receiving cromolyn sodium (P<0.001). Mean improvement in nighttime and daytime asthma symptom scores from baseline to study end were greater in the budesonide group compared to the cromolyn sodium group (P<0.001). Patients in the budesonide group were associated with a significantly decreased utilization of rescue medication from baseline compared with the cromolyn sodium group (P<0.001). Patients treated with budesonide were significantly less likely to have an urgent care visit compared to the cromolyn sodium group (P=0.02). Patients in the budesonide group were associated with a significantly lower rate and duration of oral corticosteroid utilization compared to the cromolyn sodium group (P<0.01). Patients randomized to budesonide exhibited a smaller increase in height

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				from baseline compared to the cromolyn group (P<0.001).
Murphy et al.[9] (2003) Cromolyn sodium 20 mg QID via nebulization for 8 weeks, followed by dose titration vs budesonide 0.5 mg daily via nebulization for 8 weeks, followed by dose titration	RCT, OL, PG, MC Children 2-6 years of age with persistent asthma treated with at least one long-term control medication, but no long-term or intermittent oral corticosteroids within 12 weeks and 15 days, respectively, of study entry	N=335 52 weeks	Primary: Impact of a child's asthma on the caregiver's quality of life (assessed by the pediatric asthma caregiver's quality of life questionnaire or PACQLQ), caregiver satisfaction, treatment convenience, ease of use, compliance, child health status (assessed by the Functional Status-II Questioner [FS-II], and the Modified Child Health Questionnaire-Parent Form 50 [CHQ-PF50])	Primary: Improvements in activities and emotional function as well as total PACQLQ scores were significantly greater for caregivers of patients in the budesonide group than in the cromolyn sodium group at all study time points (P<0.05). Mean scores for caregiver satisfaction, convenience, ease of use, and compliance were significantly greater for caregivers of children receiving budesonide, compared to the cromolyn group (P<0.001). Child health status improved from baseline in both study groups as evident by improvements in both FS-II and CHQ-PF50. There was no statistically significant difference between the groups in either questionnaire (P=0.635).
Hoshino et al.[10] (1998) Disodium cromoglycate* (DSCG) 2 mg QID vs ketotifen 1 mg tablet BID	RCT, PG Patients with mild-moderate atopic asthma, no anti-inflammatory drugs within 4 months of study onset, and no RTI within 2 weeks of study entry	N=32 12 weeks	Primary: Symptom score, FEV_1, PEF, bronchial responsiveness, eosinophil count, mast-cell count, CD3, CD4	Primary: Both DSCG and beclomethasone groups exhibited significant improvement in symptom score compared to the ketotifen group (P<0.05). PEF significantly increased in the DSCG group compared to the ketotifen (P<0.01) and BDP group (P<0.05). FEV_1 increased significantly in the DSCG (P<0.01) and beclomethasone (P<0.05) groups, in comparison to the ketotifen group. Compared with baseline, activated eosinophils, CD3, and CD4 counts

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs beclomethasone 100 mcg QID				were significantly decreased in all three treatment groups (P<0.01). Mast-cell count significantly decreased in the DSCG and BDP groups (P<0.05), but not in the ketotifen group.
Furusho et al.[12] (2002) Sodium cromoglycate* 1% BID via nebulization vs albuterol 0.5 to 1 mg BID via nebulizer vs albuterol 0.5 to 1 mg and sodium cromoglycate* 1% administered BID via nebulizer	R, OL, PRO, XO, MC Patients <20 years of age with moderate-severe, allergic or non-allergic perennial asthma, not on maintenance treatment with cromolyn, albuterol, or injected steroids	N=257 12 weeks	Primary: Change in asthma severity, measured by the mean asthma score Secondary: Patients' opinion of treatment effectiveness	Primary: The mean difference in the asthma score reduction was significantly greater in the combination compared to the individual treatments. The mean difference between the combination and albuterol was 7.5 (P<0.001). The mean difference between the combination and sodium cromoglycate was 8.5 (P<0.001). Secondary: Patients preferred combination therapy to treatment with either albuterol (P<0.001) or sodium cromoglycate alone (P<0.01).
Exercise-Induced Bronchospasm				
Kelly et al.[13] (2001) Sodium cromoglycate* (SCG) 4-10 mg vs nedocromil sodium	MA Patients ≥6 years of age with exercise-induced bronchoconstriction (EIB), with a fall in FEV_1 of >10% after an exercise challenge test	N=117 (8 trials) Variable duration	Primary: Pulmonary function Secondary: Complete protection from EIB, clinical protection, adverse events	Primary: There was no significant difference between SCG and nedocromil sodium with respect to the maximum percent decrease in FEV_1 analysis (95% CI, 4.49-2.74). Secondary: There was no significant difference between SCG and nedocromil sodium with respect to complete protection from EIB (OR 0.95; 95% CI, 0.50 to 1.81).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4-8 mg				There was no significant difference between SCG and nedocromil sodium with respect to clinical protection from EIB (OR 0.71; 95% CI 0.36-1.39). There was no significant difference between SCG and nedocromil sodium with respect to unpleasant taste (OR 6.85; 95% CI, 0.77-60.73) or sore throat (OR 3.46; 95% CI, 0.32-37.48).
Spooner et al.[14] (2003) Inhaled mast-cell stabilizers (cromolyn sodium or nedocromil sodium) vs short-acting β_2-agonist, anticholinergic agent, or short-acting β_2-adrenergic agonist in addition to inhaled mast-cell stabilizers	MA Patients $\geq$6 years of age with exercise-induced bronchoconstriction (EIB) with a fall in FEV_1 of $\geq$10% after an exercise challenge test	N=518 (24 trials) Variable duration	Primary: Pulmonary function Secondary: Complete protection from EIB, clinical protection, adverse events, symptom score or preference measure	Primary: On average, the maximum percent decrease in FEV_1 after a single dose of either mast-cell stabilizer was 7.1%, compared to a 13.8% fall observed in the anticholinergic group (95% CI, 3.3-10.0). On average, the maximum percent decrease in FEV_1 after a single dose of either mast-cell stabilizer was 11.2%, compared to a 4.3% fall observed in the β_2-adrenergic agonist group (95% CI, 4.5-9.2). Secondary: Mast cell stabilizers provided a greater number of patients with complete protection (73% vs 56%; 95% CI, 1.3-3.7) and clinical protection from EIB, compared with anticholinergic agents (73% vs 52%; 95% CI, 1.1 to 6.4). Mast cell stabilizers provided a fewer number of patients with complete protection (66 vs 85%; 95% CI, 0.2-0.5) and clinical protection from EIB, compared with β_2-adrenergic agonists (55% vs 77%; 95% CI, 0.2-0.8). Patients receiving a combination of a short-acting β_2-adrenergic agonist and a mast-cell stabilizer did not exhibit statistically significant difference in improvement of pulmonary function compared to patients on short-acting β_2-adrenergic agonist alone (5.3% and 3.5% fall, respectively; 95% CI, 0.2-1.4).

*Synonym for cromolyn
Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study design abbreviations: AC=active-controlled, DB=double-blind, DD=double dummy, MC=multi-center, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, PT=pragmatic trial, R=randomized, RCT=randomized trial, RETRO=retrospective, TA=three-arm, XO=crossover
Miscellaneous abbreviations: EIA=exercise-induced asthma, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, MDI= metered dose inhaler, RTI=respiratory tract infection, PACQLQ=pediatric asthma caregiver's quality of life questionnaire, PD15FEV1=provocative dose inducing fall of 15% in FEV_1, PEF=peak expiratory flow, PEFR=peak expiratory flow rate

Additional Evidence

Dose Simplification
Sherman et al. evaluated adherence rates with asthma medications in children with persistent asthma who were Medicaid recipients.[15] Maximum potential adherence was found to be 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn. Murphy et al. evaluated the differences in caregiver satisfaction and adherence to therapy with budesonide inhalation suspension administered once-daily and cromolyn sodium inhalation solution administered four-times-daily.[9] Adherence rates were 76% in the budesonide group compared to 57% in the cromolyn group. Additionally, 54.6% of caregivers rated budesonide as "highly or very convenient" compared with only 23% for cromolyn. While 77% of caregivers found the budesonide formulation easy to administer, only 47% reported ease of use with the cromolyn inhalation. The results of the survey indicated significantly higher parental satisfaction and improved compliance with budesonide compared to cromolyn due to ease of use and convenience of once-daily administration ($P \leq 0.001$).

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Inhaled Mast-Cell Stabilizers

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cromolyn sodium	inhalation solution*	N/A	N/A	$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

Cromolyn sodium inhalation solution is the only inhaled mast-cell stabilizer that is currently available in this class. It is approved for the maintenance treatment of asthma, as well as for the prophylaxis of acute bronchospasm induced by exercise, exposure to cold air, or other environmental agents.[1-3] Cromolyn sodium is available in a generic formulation.

For the treatment of asthma, guidelines recommend the use of an inhaled corticosteroid as initial therapy.[4-7,11] The mast-cell stabilizers are considered an alternative treatment option for patients with mild persistent asthma.[5-6] Clinical studies have demonstrated that inhaled corticosteroids are more effective than mast-cell stabilizers in patients with persistent asthma.[8-9] Mast-cell stabilizers are considered an alternative treatment option for the prevention of exercise-induced bronchospasm as they are not as effective as short-acting bronchodilators.[5-6,14]

Therefore, all brand inhaled mast-cell stabilizers within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand inhaled mast-cell stabilizer is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed October 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; October 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 2010.
4. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
5. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
6. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.
7. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
8. Leflein JG, Szefler SJ, Murphy KR, et al. Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. Pediatrics 2002;109:866-872.
9. Murphy KR, Fitzpatrick S, Cruz-Riviera M, et al. Effects of budesonide inhalation suspension compared with cromolyn sodium nebulizer solution on health status and caregiver quality of life in childhood asthma. Pediatrics 2003;112:212-219.
10. Hoshino M, Nakamura Y, Sim J, et al. A comparative study of the effects of ketotifen, disodium cromoglycate, and beclomethasone dipropionate on bronchial mucosa and asthma symptoms in patients with atopic asthma. Resp Med 1998;92:942-950.
11. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.
12. Furusho K, Kiyoshi N, Sasaki S. The combination of nebulized sodium cromoglycate and salbutamol in the treatment of moderate-to-severe asthma in children. Pediatr Allergy Immunol 2002;13:209-216.
13. Kelly KD, Spooner CH, Rowe BH, et al. Nedocromil sodium versus sodium cromoglycate in treatment of exercise-induced bronchoconstriction: a systemic review. Eur Respir J 2001;17:39-45.
14. Spooner CH, Spooner GR, Rowe BH. Mast-cell stabilizing agents to prevent exercise-induced bronchoconstriction. The Cochrane Database of Systematic Reviews.- 2003 - Issue 4. Art. No.: CD002307. DOI: 10.1002/14651858.CD002307.
15. Sherman J, Hutson A, Baumstein S, et al. Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for prescriptions. J Pediatr 2000;136(4):532-536.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Orally Inhaled Corticosteroids
AHFS Class 680400
February 9, 2011

I. Overview

The inhaled corticosteroids are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-15] They control airway inflammation by suppressing the migration of leukocytes and fibroblasts, reverse capillary permeability, and prevent phospholipid release at the cellular level. The inhaled corticosteroids are considered the most effective long-term control medication for the treatment of asthma. They have been shown to reduce the severity of symptoms, improve asthma control and quality of life, improve spirometric indices, decrease airway hyperresponsiveness, prevent exacerbations, reduce the use of systemic corticosteroids, reduce hospitalizations, and decrease mortality due to asthma.[17]

All of the inhaled corticosteroids are structurally related to endogenously produced corticosteroids, but differ in their mineralocorticoid and glucocorticoid activity. They also differ with regards to their potency, bioavailability, formulation and dosing schedules. The inhaled corticosteroids are available as single entity products, as well as in combination with a long-acting β_2- agonist (formoterol or salmeterol). Inhaled β_2-agonists dilate the airways by relaxing bronchial smooth muscle.

The inhaled corticosteroids that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Budesonide inhalation solution is the only product that is currently available in a generic formulation. This class was last reviewed in December 2008.

Table 1. Inhaled Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Beclomethasone	aerosol inhaler	QVAR®	QVAR®
Budesonide	dry powder inhaler, inhalation suspension	Pulmicort®*	budesonide
Budesonide and formoterol	aerosol inhaler	Symbicort®	Symbicort®
Ciclesonide	aerosol inhaler	Alvesco®	none
Flunisolide	aerosol inhaler	Aerobid®, Aerobid-M®	Aerobid®, Aerobid-M®
Fluticasone	aerosol inhaler, dry powder inhaler	Flovent Diskus®, Flovent HFA®	Flovent Diskus®, Flovent HFA®
Fluticasone and salmeterol	aerosol inhaler, dry powder inhaler	Advair Diskus®, Advair HFA®	Advair Diskus®, Advair HFA®
Mometasone	dry powder inhaler	Asmanex®	Asmanex®
Mometasone and formoterol	aerosol inhaler	Dulera®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the inhaled corticosteroids are summarized in Table 2. For a comprehensive overview of the treatment of asthma and chronic obstructive pulmonary disease, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Inhaled Corticosteroids

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): **British Guideline on the Management of Asthma[21] (2009)**	General Treatment Considerations • Inhaled corticosteroids are the recommended preventer drug for adults and children for achieving overall treatment goals. They should be considered for adults, children aged 5-12 and children <5 years of age with any of the following features: 1) using inhaled β_2-agonists ≥3 times/week; 2) symptomatic ≥3 times/week; or 3) waking ≥1 night/week. They should also be considered in adults and children aged 5-12 who have had an exacerbation of asthma requiring oral corticosteroids in the last two years. • The first choice as add-on therapy to inhaled corticosteroids in adults and children (5-12 years of age) is an inhaled long-acting β_2-agonist. In children <5 years of age, the first choice as add-on therapy to inhaled corticosteroids is leukotriene receptor antagonists. • Long-acting inhaled β_2-agonists should not be used without inhaled corticosteroids. • In selected adult patients at step 3 who are poorly controlled or in selected adult patients at step 2, the use of budesonide/formoterol in a single inhaler as rescue medication instead of a short-acting β_2-agonist, in addition to its regular use as controller therapy, has been shown to be an effective treatment regimen. • There is no difference in efficacy in giving inhaled corticosteroid and long-acting β_2-agonist in combination or in separate inhalers. Once a patient is stable, the combination inhalers might be advantageous as they may prevent the accidental use of the long-acting β_2-agonist without the inhaled corticosteroid. Device Selection • In children aged 5-12 years, a pressurized metered-dose inhaler (pMDI) + spacer is as effective as any dry powder inhaler (DPI). No recommendation can be given for nebulized therapy. • In adults, a pMDI ± spacer is as effective as any DPI. • There is no evidence relating to children aged <5 years. A pMDI + spacer are the preferred method of delivery of inhaled steroids. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. If ineffective, a nebulizer may be required.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention[18] (2009)**	Controller Medications - Adults • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. To achieve control, add-on therapy with another type of controller medication is preferred over increasing the dose of the inhaled glucocorticosteroid. • Long-acting β_2-agonists (LABAs) should not be used as monotherapy in asthma as they do not affect airway inflammation. They are most effective when combined with inhaled glucocorticosteroids. This combination is preferred when a medium dose of an inhaled glucocorticosteroid alone fails to achieve control of asthma. • Studies have shown that delivering an inhaled glucocorticosteroid and a LABA in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers may increase compliance and

Clinical Guideline	Recommendation(s)
	ensure that the LABA is always accompanied by a glucocorticosteroid. • LABAs, when used in combination with an inhaled glucocorticosteroid, can be used to prevent exercise-induced bronchospasm. They may also provide longer protection than rapid-acting inhaled β_2-agonists. Controller Medications - Children • Inhaled glucocorticosteroids are the most effective controller therapy and are the recommended treatment for children of all ages. • Inhaled LABAs should not be used as monotherapy in children with asthma. They are primarily used as add-on therapy in children >5 years of age whose asthma is insufficiently controlled by inhaled glucocorticosteroids, or as single-dose therapy for exercise-induced bronchoconstriction. Inhaled LABAs have not been adequately studied in children ≤5 years of age. • Combination products containing an inhaled glucocorticosteroid and a LABA are preferred to the coadministration of each component as separate inhalers. Fixed combination inhalers ensure that the LABA is always accompanied by a glucocorticosteroid. The combination of budesonide and formoterol has been shown to reduce asthma exacerbations in children ≥4 years of age with moderate to serve asthma. Device Selection – Children • Children <4 years of age o Preferred: pressurized MDI plus spacer with face mask o Alternate: nebulizer with face mask • Children 4 – 6 years of age o Preferred: pressurized MDI plus spacer with mouthpiece o Alternate: nebulizer with mouthpiece • Children >6 years of age o Preferred: DPI, or breath-actuated MDI, or pressurized MDI plus spacer with mouthpiece o Alternate: nebulizer with mouthpiece
Global Initiative for Asthma (GINA): **Global Strategy for the Diagnosis and Management of Asthma in Children 5 years and Younger[16] (2009)**	General Treatment Considerations • A low-dose inhaled glucocorticosteroid is the recommended initial treatment option in children ≤5 years of age (beclomethasone 100 mcg, budesonide MDI + spacer 200 mcg, budesonide nebulized 500 mcg, fluticasone 100 mcg). Inhaled glucocorticosteroids have been shown to be more effective than other controller treatment for asthma. • If the child is uncontrolled or only partly controlled on low-dose inhaled glucocorticosteroid, then the initial dose of the inhaled glucocorticosteroid should be doubled. The addition of a leukotriene modifier to the low-dose inhaled glucocorticosteroid may also be considered; however, this has not been studied in this age group. • The effect of long-acting inhaled β_2-agonists (LABAs) or combination products (LABA plus glucocorticosteroid) has not been adequately studied in children ≤5 years of age. Therefore, LABAs cannot be recommended in this age group. Device Selection • Children <4 years of age o Preferred: pressurized MDI plus spacer with face mask o Alternate: nebulizer with face mask • Children 4 – 5 years of age o Preferred: pressurized MDI plus spacer with mouthpiece o Alternate: pressurized MDI plus spacer with face mask or nebulizer with mouthpiece or face mask

Clinical Guideline	Recommendation(s)

National Heart, Lung, and Blood Institute (NHLBI): **Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[17] (2007)**	General Treatment Considerations
	• Inhaled corticosteroids are the most effective long-term therapy available for mild, moderate, or severe persistent asthma. Most benefit is achieved with relatively low doses, whereas the risk of adverse effects increases with dose.
	• Long-acting β_2-agonists (LABAs) are not recommended for use as monotherapy for long-term control of persistent asthma or to treat acute symptoms or exacerbations of asthma; however, they are used as an adjunct to inhaled corticosteroid (ICS) therapy. LABAs are the preferred treatment to combine with ICS in children ≥12 years of age and adults. For children ≥5 years of age, LABAs should be considered an adjunctive therapy in those who have asthma that requires more than low-dose ICS.
	Device Selection
	• Metered-dose inhaler (MDI):
	  o ≥5 years of age
	  o <5 years of age with a spacer or valved holding chamber (VHC) with face mask
	• Breath-actuated MDI:
	  o ≥5 years of age
	• Dry powder inhaler (DPI):
	  o ≥4 years of age
	• Spacer or VHC
	  o ≥4 years of age
	  o <4 years of age with VHC with face mask
	• Nebulizer:
	  o Patients of any age who cannot use MDI with VHC and face mask

International Primary Care Respiratory Group (IPCRG): **Management of Asthma[22] (2006)**	• The most effective preventative therapy is inhaled corticosteroids. • For moderate persistent asthma, the preferred treatment is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting β_2-agonist. • Alternatives are combinations of inhaled corticosteroids with sustained-release theophylline or with leukotriene receptor antagonists.

National Institute for Clinical Excellence (NICE): **Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care[24] (2010)**	• Inhaled agents are preferred over oral treatments because of the reduction in systemic side effects.
	• As needed short-acting bronchodilators should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
	• In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the following treatments are recommended as maintenance therapy::
	  o If FEV_1 ≥50% predicted: either long-acting β_2-agonist (LABA) or LAMA
	  o If FEV_1 <50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler or LAMA
	• In people with stable COPD and an FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
	  o Consider LABA+ICS in a combination inhaler
	  o Consider LAMA in addition to LABA where ICS is declined or not tolerated
	• Offer LAMA in addition to LABA+ICS to patients with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1.
	• Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have

Clinical Guideline	Recommendation(s)
	exacerbations despite maintenance therapy with LAMA, irrespective of their FEV_1.
Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[23] (2009)**	• Most studies have indicated that the existing medications for COPD do not modify the long-term decline in lung function. Therefore, pharmacotherapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. • Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis or on a regular basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. • The principal bronchodilator treatments are β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. • Regular treatment with long-acting bronchodilators, including nebulized formulations, are more effective than treatment with short-acting bronchodilators. • Regular use of a long-acting β_2-agonist or a short-or long-acting anticholinergic improves health status. • Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. • Most studies have demonstrated that regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD. However, one study in patients with an FEV_1 <60% predicted demonstrated that inhaled glucocorticosteroids decreased the rate of decline of lung function. • Regular treatment with inhaled glucocorticosteroids has been shown to reduce the frequency of exacerbations and improve health status for symptomatic COPD patients with an FEV_1 <50% predicted, as well as repeated exacerbations. • Treatment with inhaled glucocorticosteroids increases the likelihood of pneumonia and does not reduce overall mortality. • Treatment with inhaled glucocorticosteroids can be recommended for patients with more advanced COPD and repeated exacerbations. • An inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status.
American College of Physicians (ACP): **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease[25] (2007)**	• Clinicians should prescribe one of the following maintenance monotherapies for symptomatic patients with COPD and FEV_1 <60% predicted: long-acting inhaled β_2-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. • Monotherapy with a long-acting inhaled β_2-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. • Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness, but differ in adverse effects, reductions in deaths, and hospitalizations. • Evidence is insufficient to recommend one agent over another. • Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV_1 <60% predicted. • When to use combination therapy instead of monotherapy has not been clearly established. Studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy.

Clinical Guideline	Recommendation(s)
International Primary Care Respiratory Group (IPCRG): **Management of Chronic Obstructive Pulmonary Disease** [19] **(2006)**	• None of the current pharmacologic treatments for COPD have been shown to modify the long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. Treatment strategy is based on severity of COPD as follows: • Bronchodilators (anticholinergics and β_2-agonists) are central to symptom management in COPD. • For regular treatment, long-acting bronchodilators are more effective than short-acting bronchodilators. • Inhaled glucocorticosteroids are recommended in patients with 'Severe' (Stage III) and 'Very Severe' (Stage IV) COPD who have repeated exacerbations (three or more in the last three years) requiring oral corticosteroids or antibiotics. • Regular treatment with inhaled glucocorticosteroids reduces the frequency of exacerbations and improves health status in this group of patients.
American Thoracic Society (ATS)/European Respiratory Society (ERS): **Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease**[20] **(2004)**	• Medications for COPD can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present, no treatment has been shown to modify the rate of decline in lung function. • A short-acting bronchodilator as needed is recommended for symptom control in patients with intermittent symptoms. • For patients with persistent symptoms, a long- or short-acting bronchodilator is recommended. If symptoms are not controlled, consider using alternate classes or combine classes. • The initial trial data show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its components. The largest effects in terms of exacerbations and health status are seen in patients with an FEV_1<50% predicted, where combining treatment is clearly better than either component drug used by itself. • In patients with more advanced disease (usually classified as an FEV_1 <50% predicted) there is evidence that the number of exacerbations per year and the rate of deterioration in health status can be reduced by inhaled corticosteroids in COPD. • Evidence has shown no effect of inhaled corticosteroids on rate of change of FEV_1 in any severity of COPD.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the inhaled corticosteroids are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Inhaled Corticosteroids[1-15]

Indication	Beclomethasone	Budesonide	Budesonide/ Formoterol	Ciclesonide	Flunisolide	Fluticasone	Fluticasone/ Salmeterol	Mometasone	Mometasone/ Formoterol
Asthma									
Maintenance treatment of asthma as prophylactic therapy in children 12 months to 8 years of age		✔ ‡							
Maintenance treatment of asthma as prophylactic therapy in patients ≥4 years of age						✔	✔ †	✔	
Maintenance treatment of asthma as prophylactic therapy in patients ≥5 years of age	✔								
Maintenance treatment of asthma as prophylactic therapy in patients ≥6 years of age		✔ †			✔				
Maintenance treatment of asthma as prophylactic therapy in patients ≥12 years of age			✔	✔			✔ §		✔
Treatment of patients requiring systemic corticosteroid therapy, which may reduce or eliminate the need for the oral corticosteroids	✔				✔	✔			
COPD									
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema			✔				✔ †		
To reduce exacerbations of COPD in patients with a history of exacerbations							✔ †		

§Aerosol inhaler.
†Dry powder inhaler.
‡Inhalation solution/suspension.

IV. Pharmacokinetics

The pharmacokinetic parameters of the inhaled corticosteroids are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Inhaled Corticosteroids[1-15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Beclomethasone	Low	87	Liver, partial Lung, extensive	Renal (10-15) Feces (60)	3
Budesonide	39	85-90	Liver, extensive Lung, partial	Renal 60% Feces (15-30) Bile	2-3
Budesonide and formoterol	B: 27 F: Low	B: 85-90 F: 31-64	Liver, extensive	B: Renal (60) Feces (15-30) F: Renal (59-62) Feces (32-34)	B: 2-3 F: 7.9
Ciclesonide	22	99	Liver, extensive	Renal (<20) Feces (66)	6-7
Flunisolide	40	Not reported	Liver, extensive	Renal (50) Feces (50)	1-2
Fluticasone	18	91	Liver, extensive	Renal (<5) Feces (95)	7.8
Fluticasone and salmeterol	F: 18	F: 91 S: 96	Liver, extensive	F: Renal (<5) Feces (95) S: Renal (25) Feces (60)	F: 7.8 S: 5.5
Mometasone	<1	98-99	Liver, extensive	Renal (8) Feces (74) Bile	5.8
Mometasone and formoterol	M: <1 F: Low	M: 98-99 F: 31-64	Liver, extensive	M: Renal (8) Feces (74) F: Renal (59-62) Feces (32-34)	M: 5.8 F: 7.9

V. Drug Interactions

Significant drug interactions with the inhaled corticosteroids are listed in Table 5.

Table 5. Significant Drug Interactions with the Inhaled Corticosteroids[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Formoterol, salmeterol	1	Beta-adrenergic blockers	Pharmacologic effects of inhaled beta agonists may be decreased by beta-adrenergic blockers. Untoward physiologic effects, characterized by bronchospasm, may occur. Non-cardioselective beta-adrenergic blockers may block the bronchodilating effects of inhaled beta agonists.
Formoterol, salmeterol	1	HIV protease inhibitors	Pharmacologic effects of inhaled beta agonists may be increased by HIV protease inhibitors. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as

Generic Name(s)	Significance Level	Interaction	Mechanism
			QT prolongation, palpitations, and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of the swallowed portion of a salmeterol dose.
Formoterol, salmeterol	1	Imidazoles	Pharmacologic effects of inhaled beta agonists may be increased by imidazoles. Elevated plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by imidazoles may decrease the metabolic elimination of the swallowed portion of the dose.
Formoterol, salmeterol	1	Macrolides	Pharmacologic effects of inhaled beta agonists may be increased by macrolides. Elevated plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur. Inhibition of cytochrome P450 3A4 isoenzymes by macrolides may decrease the metabolic elimination of the swallowed portion of the dose.
Formoterol, salmeterol	1	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur. Formoterol and salmeterol are direct acting β-agonists and should be administered very cautiously in patients taking monoamine oxidase inhibitors (MAOIs) or who have taken them within 2 weeks prior to the start of therapy with formoterol or salmeterol.
Inhaled corticosteroids (budesonide, ciclesonide, fluticasone)	1	HIV Protease Inhibitors	Plasma concentrations and pharmacologic effects of specific inhaled steroids may be increased by HIV protease inhibitors. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur. Inhibition of cytochrome P450 3A4 isoenzymes by HIV

Generic Name(s)	Significance Level	Interaction	Mechanism
			protease inhibitors may decrease the metabolic elimination of specific inhaled steroids. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur.
Budesonide	2	Anticoagulants	Both an increase in the dosage requirement of anticoagulants and hemorrhagic episodes have been reported with this combination.
Budesonide	2	Barbiturates	Pharmacologic effects of budesonide may be decreased with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by barbiturates may increase the metabolic elimination of budesonide.
Budesonide	2	Carbamazepine	Pharmacologic effects of budesonide may be decreased by carbamazepine. Carbamazepine may increase the hepatic metabolism of budesonide.
Budesonide	2	Hydantoins	Pharmacologic effects of budesonide may be decreased, with possible exacerbation of the disease being treated. Plasma concentrations and therapeutic effects of hydantoins may be decreased by budesonide. Induction of hepatic microsomal enzymes by hydantoins may increase the metabolic elimination of budesonide.
Budesonide	2	Oral contraceptives	Pharmacologic effects of budesonide may be increased. Oral contraceptives decrease the hepatic metabolism of budesonide.
Budesonide	2	Quinolones	The risk of quinolones-induced tendon rupture may be increased by coadministration of budesonide especially in those 60 years of age or greater. Adverse effects of quinolones and budesonide may be additive or synergistic.
Budesonide	2	Rifamycins	Pharmacologic effects of budesonide may be decreased by rifamycins with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of

Generic Name(s)	Significance Level	Interaction	Mechanism
			budesonide. Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of budesonide.
Formoterol, salmeterol	2	COMT Inhibitors	The combination of inhaled beta agonists with COMT Inhibitors may result in inhibition of the pathway responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result.
Formoterol, salmeterol	2	Linezolid	Coadministration of linezolid and inhaled beta agonists may result in adverse cardiovascular effects characterized by hypertension. Inhibition of monoamine oxidase by linezolid may result in reversible enhancement of the pressor response with concomitant administration of beta agonists.
Inhaled corticosteroids (budesonide, ciclesonide, fluticasone)	2	Azole antifungals	Azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids (budesonide and fluticasone only) resulting in enhanced corticosteroid effects and toxicity.
Inhaled corticosteroids (ciclesonide, fluticasone)	2	Delavirdine	Plasma concentrations of specific inhaled steroids may be increased when co-administered with delavirdine. Inhibition of cytochrome P450 3A4 isoenzymes by delavirdine may decrease the metabolic elimination of these inhaled steroids.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the inhaled corticosteroids are listed in Tables 6–7. The boxed warnings for the inhaled corticosteroids containing a long-acting β_2-agonist are summarized in Table 8.

Table 6. Adverse Drug Events (%) Reported with the Inhaled Corticosteroids (Drugs B – C)[1-15]

Adverse Events	Beclomethasone	Budesonide	Budesonide/ Formoterol	Ciclesonide
Cardiovascular				
Arrhythmias	-	-	<1	-
Chest pain	-	1-3†	-	<1
Palpitations	-	-	1-3	<1
Syncope	-	1-3§	-	-

Adverse Events	Beclomethasone	Budesonide	Budesonide/ Formoterol	Ciclesonide
Tachycardia	-	-	<1	-
Central Nervous System				
Agitation	-	-	<1	-
Aggression	-	-	-	-
Anxiety	-	-	<1	-
Dizziness	-	-	-	≥3
Emotional lability	-	1-3†	-	-
Headache	12-15	13-14§	6-12	4.9-11
Hyperkinesia	-	1-3†	-	-
Hypertonia	-	1-3§	-	-
Insomnia	-	1-3§	-	-
Migraine	-	1-3§	1-3	-
Tremors	-	-	1-3	-
Dermatological				
Ecchymosis	-	1-3§	-	<1
Eczema	-	1-3†	-	-
Pruritus	-	1-3†	-	-
Purpura	-	1-3†	<1	-
Pustular rash	-	1-3†	-	-
Rash	-	1-4†	<1	<1
Gastrointestinal				
Angioedema	-	-	-	<1
Anorexia	-	1-3†	-	-
Diarrhea	-	2-4†	1-3	-
Dry mouth	-	1-3§	-	<1
Dyspepsia	-	1-4§	1-3	<1
Gastroenteritis	-	1-3§ 4-5†	-	≥3
Gastrointestinal pain	-	1-3§ 2-3†	1-7	-
Nausea	1-3	1-3§	1-3	<1
Oral candidiasis	-	2-4§	1-3	≥3
Taste alteration	-	1-3§	-	-
Vomiting	-	2-4†	-	-
Musculoskeletal				
Arthralgia	-	-	-	≤4
Fracture	-	1-3§†	-	-
Myalgia	-	1-3§†	1-3	-
Respiratory				
Bronchitis	-	-	1-3	-
Coughing	1-3	5-8†	-	<1
Dyspnea	-	✔ †	-	-
Increased asthma symptoms	3-8	-	-	-
Influenza	-	-	2-3	-
Lower respiratory infections	-	-	1-3	-
Nasal congestion	-	-	2-3	2-6
Pharyngitis	8-10	5-10§	6-11	7-11
Pneumonia	-	-	-	≥3
Rhinitis	6-11	7-12†	1-3	-
Rhinorrhea	-	-	-	<1
Sinusitis	-	2-11§	5-6	≤6
Stridor	-	1-3†	-	3-5
Throat irritation	-	-	-	<1

Adverse Events	Beclomethasone	Budesonide	Budesonide/ Formoterol	Ciclesonide
Upper respiratory tract infection	9-12	19-24§ 34-38†	7-11	4-7
Wheezing	-	✔ †	-	-
Other				
Back pain	1-4	2-6§	-	1-3
Cataract	-	-	-	<1
Conjunctivitis	-	1-2†	-	≥3
Dysmenorrhea	1-3	-	-	-
Dysphonia	2-4	1-6§ 1-3†	-	<1
Ear pain	-	1-3†	-	≤2
Ear infection	-	2-5†	-	-
Epistaxis	-	2-4†	-	-
Eye infection	-	1-3†	-	-
Fever	-	2-4§	1-3	-
Flu syndrome	-	6-14§ 1-3†	-	-
Hypersensitivity reaction	-	1-3†	-	-
Infection	-	1-3§†	-	-
Intraocular pressure increased	-	-	-	<1
Moniliasis	-	3-4†	-	-
Neck pain	-	1-3§	-	-
Otitis media	-	9-12†	-	-
Pain	2-3	5§	-	0-3
Poisoning/toxicity	-	-	1-3	-
Throat Pain	-	-	-	2-5
Viral infection	-	3-5†	-	-
Weight gain	-	1-3§	-	<1

✔ Percent not specified
- Event not reported
§Dry powder inhaler
†Inhalation suspension

Table 7. Adverse Drug Events (%) Reported with the Inhaled Corticosteroids (Drugs F – M)[1-15]

Adverse Events	Flunisolide	Fluticasone	Fluticasone/ Salmeterol	Mometasone	Mometasone/ Formoterol
Cardiovascular					
Arrhythmias	-	-	✔ § 1-3†	-	-
Chest pain	3-9	✔ § 1-3†	-	-	-
Hypertension	1-3	-	-	-	-
Palpitations	3-9	-	1-3§	-	-
Tachycardia	1-3	-	1-3†	-	-
Central Nervous System					
Agitation	-	-	✔ §†	-	-
Aggression	-	-	✔ §†	-	-
Anxiety	1-3	✔ §†	-	-	-
Depression	1-3	✔ §†	✔ §†	-	-
Dizziness	3-9	✔ § 1-3†	4§ 1-4†	-	-
Drowsiness	1-3	-	-	-	-
Emotional lability	-	✔ §†	-	-	-

Adverse Events	Flunisolide	Fluticasone	Fluticasone/ Salmeterol	Mometasone	Mometasone/ Formoterol
Headache	25	2-14§ 5-11†	12-20§ 15-21†	17-22	2-5
Hyperkinesia	1-3	✔ §†	✔ †	-	-
Insomnia	-	-	-	1-3	-
Migraine	-	✔ § 1-3†	1-3†	-	-
Nervousness	3-9	-	-	-	-
Sleep disorders		-	1-3§†	-	-
Tremors		-	1-3§	-	-
Vertigo	1-3	-	-	-	-
Dermatological					
Angioedema	-	✔ §†	-	-	-
Contusions	-	-	1-3§	-	-
Dermatitis	-	-	1-3†	-	-
Ecchymosis	-	✔ §†	✔ §	-	-
Eczema	3-9	-	1-3†	-	-
Pruritus	3-9	✔ §†	-	-	-
Rash	3-9	-	-	-	-
Sebum disorders	-	-	1-3§	-	-
Skin flakiness	-	-	1-3§	-	-
Sweat disorders	-	-	1-3§	-	-
Sweating	-	-	1-3§	-	-
Skin infection	-	✔ § 1-3†	1-3§	-	-
Urticaria	1-3	-	1-3§	-	-
Vasculitis	-	✔ §†	-	-	-
Endocrine and Metabolic					
Cushingoid features	-	✔ §†	✔ §†	-	-
Edema	3-9	✔ §†	✔ §†	-	-
Hyperglycemia	-	✔ §†	✔ §†	-	-
Hypothyroidism	-	-	1-3§	-	-
Osteoporosis	-	✔ §†	✔ §†	-	-
Weight gain	-	-	✔ §†	-	-
Gastrointestinal					
Anorexia	3-9	-	-	1-3	-
Constipation	1-3	-	1-3§†	-	-
Diarrhea	10	✔ § 1-3†	2-4§	-	-
Dyspepsia	3-9	✔ § 1-3†	✔ §†	3-5	-
Epigastric fullness	<1	-	-	-	-
Flatulence	1-3	-	-	1-3	-
Gastroenteritis	-	-	1-3§	1-3	-
Gastrointestinal pain	3-9	✔ § 1-3†	-	2-3	-
Nausea	-	-	4-6§ 3-5†	1-3	-
Oral candidiasis	3-9	1-9§ 2-5†	1-10§ 1-3†	4-6	<1
Taste alteration	10	-	1-3§	-	-
Vomiting	25	-	4-6§ 3-5†	1-3	-
Xerostomia	-	-	✔ §†	-	-

Adverse Events	Flunisolide	Fluticasone	Fluticasone/ Salmeterol	Mometasone	Mometasone/ Formoterol
Genitourinary					
Dysuria	-	<1§†	-	-	-
Irregular Menstrual Cycle	-	-	✔ §	-	-
Polyuria	-	✔ § <3†	-	-	-
Urinary tract infection	-	-	-	1-3	-
Hematologic					
Enlarged lymph nodes	1-3	-	1-3§	-	-
Musculoskeletal					
Myalgia	-	✔ §†	1-3§	2-3	-
Respiratory					
Bronchitis	1-3	0-8§ 2-6†	2-8§	-	-
Cold symptoms	15	-	-	-	-
Coughing	3-9	1-5§ 4-6†	3-6§ ✔ †	-	-
Dyspnea	✔	✔ §†	-	-	-
Hoarseness	3-9	✔ § 2-6†	2-5§ 1-3†	-	-
Increased asthma symptoms	-	✔ §†	-	-	-
Influenza	-	-	✔ §†	-	-
Nasal congestion	15	-	1-3§†	-	-
Pharyngitis	1-3	✔ §†	3-13§	11-13	5
Rhinitis	3-9	✔ §†	1-3§	11-15	-
Sinusitis	-	6-10§ 4-7†	3-5§	-	2-3
Throat infections	-	-	1-4§†	-	-
Throat irritation	-	-	8§ 7-9†	-	-
Upper respiratory inflammation	-	-	6-7§ 4†	-	-
Upper respiratory tract infection	25	14-20§ 16-18†	10-27§ 16-24†	8-15	-
Wheezing	✔	✔ §†	✔ §†	-	-
Other					
Back pain	-	-	1-3§	3-6	-
Blurred vision	1-3	-	-	-	-
Dysmenorrhea	3-9	-	1-3§	4-9	-
Dysphonia	-	-	1-3§	1-3	-
Ear ache	1-2	-	-	1-3	-
Ear infection	3-9	-	-	-	-
Epistaxis	1-3	-	-	1-3	-
Eye infection	1-3	-	1-3§	-	-
Fever	3-9	1-7§ 1-3†	4-5§ ✔ †	-	-
Flu syndrome	10	-	-	-	-
Hematomas	-	-	1-3§	-	-
Hives	-	-	1-3§	-	-
Hypersensitivity reactions	-	-	✔ §†	-	✔
Infection	-	-	1-3§†	1-3	-
Pain	-	✔ § 1-3†	-	1-3	-
Sore Throat	20	✔ §†	-	-	-

Adverse Events	Flunisolide	Fluticasone	Fluticasone/ Salmeterol	Mometasone	Mometasone/ Formoterol
Weight gain	-	✔ §†	-	-	-

✔ Percent not specified
- Event not reported
§Dry powder inhaler
†Aerosol inhaler

Table 8. Boxed Warning for Budesonide/Formoterol, Fluticasone/Salmeterol and Mometasone/Formoterol[1]

WARNING
Long-acting beta$_2$-adrenergic agonists (LABAs) may increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of hospitalization in pediatric and adolescent patients. When treating patients with asthma, only prescribe budesonide/formoterol, fluticasone/salmeterol, or mometasone/formoterol for patients not adequately controlled on a long-term asthma-control medication (e.g., inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use budesonide/formoterol, fluticasone/salmeterol, or mometasone/formoterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

VII. Dosing and Administration

The usual dosing regimens for the inhaled corticosteroids are listed in Table 9. The estimated comparative daily doses for the available products are listed in Table 10.

Table 9. Usual Dosing Regimens for the Inhaled Corticosteroids[1-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Beclomethasone	Asthma: 40 to 160 mcg twice daily; maximum, 320 mcg twice daily	Asthma: ≥5 years of age: 40 mcg twice daily; maximum, 80 mcg twice daily	Aerosol inhaler: 40 mcg 80 mcg
Budesonide	Asthma: Dry powder inhaler: 180 to 360 mcg twice daily; maximum, 720 mcg twice daily	Asthma: Dry powder inhaler: ≥6 years of age: 180 mcg twice daily; maximum, 360 mcg twice daily Inhalation suspension: 12 months to 8 years: 0.5 mg total daily dose administered once or twice daily; maximum, 1 mg total daily dose	Dry powder inhaler: 90 mcg 180 mcg Inhalation suspension: 0.25 mg/2 ml 0.5 mg/2 ml 1 mg/2 ml
Budesonide and formoterol	Asthma: 2 inhalations (80-4.5 mcg or 160-4.5 mcg) twice daily COPD: 2 inhalations (80-4.5 mcg or 160-4.5 mcg) twice daily	Asthma: ≥12 years of age: 2 inhalations (80-4.5 mcg or 160-4.5 mcg) twice daily	Aerosol inhaler: 80-4.5 mcg 160-4.5 mcg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ciclesonide	Asthma: 80 mcg twice daily; maximum, 320 mcg twice daily	Asthma: ≥12 years of age: 80 mcg twice daily; maximum, 320 mcg twice daily	Aerosol inhaler: 80 mcg 160 mcg
Flunisolide	Asthma: 2 inhalations twice daily; maximum, 4 inhalations twice daily	Asthma: ≥6 years of age: 2 inhalations twice daily; maximum, 2 inhalations twice daily	Aerosol inhaler: 250 mcg Aerosol inhaler (menthol): 250 mcg
Fluticasone	Asthma: Aerosol inhaler: 88 to 220 mcg twice daily; maximum, 880 mcg twice daily Dry powder inhaler: 100 to 250 mcg twice daily; maximum, 1,000 mcg twice daily	Asthma: Aerosol inhaler: 4-11 years of age: 88 mcg twice daily; maximum, 88 mcg twice daily ≥12 years of age: 88 to 220 mcg twice daily; maximum, 880 mcg twice daily Dry powder inhaler: 4-11 years of age: 50 mcg twice daily; maximum, 100 mcg twice daily ≥12 years of age: 100 to 250 mcg twice daily; maximum, 1,000 mcg twice daily	Aerosol inhaler: 44 mcg 110 mcg 220 mcg Dry powder inhaler: 50 mcg 100 mcg 250 mcg
Fluticasone and salmeterol	Asthma: Aerosol inhaler: 2 inhalations twice daily (based on patient's current asthma therapy); maximum, 2 inhalations (of 230/21 mcg formulation) twice daily Dry powder inhaler: 1 inhalation (100-50 mcg, 250-50 mcg, 500-50 mcg) twice daily COPD: Dry powder inhaler: 1 inhalation (250-50 mcg) twice daily	Asthma: Aerosol inhaler: ≥12 years of age: 2 inhalations twice daily (based on prior asthma therapy); maximum, 2 inhalations (230/21 mcg) twice daily Dry powder inhaler: 4-11 years of age: 1 inhalation (100-50 mcg) twice daily ≥12 years of age: 1 inhalation (100-50 mcg, 250-50 mcg, 500-50 mcg) twice daily	Aerosol inhaler: 45-21 mcg 115-21 mcg 230-21 mcg Dry powder inhaler: 100-50 mcg 250-50 mcg 500 -50 mcg
Mometasone	Asthma: 220 mcg once daily in the evening; maximum, 880 mcg per day	Asthma: 4-11 years of age: 110 mcg once daily in the evening; maximum, 110 mcg once daily ≥12 years of age: 220 mcg once daily in the evening; maximum, 880 mcg per day	Dry powder inhaler: 110 mcg 220 mcg
Mometasone and formoterol	Asthma: 2 inhalations (100-5 mcg or 200-5 mcg) twice daily based on prior asthma therapy; maximum, 800-20 mcg	Asthma: ≥12 years of age: 2 inhalations (100-5 mcg or 200-5 mcg) twice daily based on prior asthma therapy; maximum, 800-20 mcg	Aerosol inhaler: 100-5 mcg 200-5 mcg

Table 10. Estimated Comparative Daily Doses for the Inhaled Corticosteroids[17-18]

Adolescents ≥12 Years of Age and Adults*			
Generic Name	**Low Daily Dose (mcg)**	**Medium Daily Dose (mcg)**	**High Daily Dose (mcg)**
Beclomethasone HFA	80-240	>240-480	>480
Budesonide DPI	180-600	>600-1,200	>1,200
Ciclesonide HFA	80-160	>160-320	>320-1,280
Flunisolide	500-1,000	>1,000-2,000	>2,000
Fluticasone HFA	88-264	>264-440	>440
Fluticasone DPI	100-300	>300-500	>500
Mometasone DPI	200	400	>400
Triamcinolone	300-750	>750-1,500	>1,500
Children 5-11 Years of Age*			
Generic Name	**Low Daily Dose (mcg)**	**Medium Daily Dose (mcg)**	**High Daily Dose (mcg)**
Beclomethasone HFA	80-160	>160-320	>320
Budesonide DPI	180-400	>400-800	>800
Budesonide neb	0.5 mg	1.0 mg	2.0 mg
Ciclesonide	80-160	>160-320	>320
Flunisolide	500-750	>750-1,250	>1,250
Fluticasone HFA	88-176	176-352	>352
Fluticasone DPI	100-200	>200-400	>400
Mometasone	NA	NA	NA
Triamcinolone	300-600	>600-900	>900
Children 0-4 Years of Age*			
Generic Name	**Low Daily Dose (mcg)**	**Medium Daily Dose (mcg)**	**High Daily Dose (mcg)**
Beclomethasone HFA	NA	NA	NA
Budesonide DPI	NA	NA	NA
Budesonide neb	0.25-0.5 mg	>0.5-1.0 mg	>1.0 mg
Ciclesonide	NA	NA	NA
Flunisolide	NA	NA	NA
Fluticasone HFA	176	>176-352	>352
Fluticasone DPI	NA	NA	NA
Mometasone	NA	NA	NA
Triamcinolone	NA	NA	NA

*Comparative dosages are based on published comparative clinical trials.[17]
NA=not approved

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the inhaled corticosteroids are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Inhaled Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Busse et al.[42] (1999) Beclomethasone HFA 100 mcg/day vs beclomethasone HFA 400 mcg/day vs beclomethasone HFA 800 mcg/day vs beclomethasone CFC 100 mcg/day vs beclomethasone CFC 400 mcg/day vs beclomethasone CFC 800 mcg/day	MC, RCT, PG, DB Asthmatic subjects who had deteriorated in their asthma control after discontinuation of inhaled corticosteroids	N=323 6 weeks	Primary: Change from baseline in FEV1 percent predicted at week 6 Secondary: Percent change from baseline in $FEF_{25-75\%}$, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings, daily albuterol use	Primary: For each treatment group, FEV_1 percent predicted increased over the first 4 weeks of treatment and tended to reach a plateau by week 6. Change from baseline at week 6 in FEV_1 percent predicted was greater with 800 mcg/day beclomethasone HFA (-32.7%; P=0.049) than 400 mcg/day (-25.1%) and marginally, but not significantly greater (P=0.09) with 800 mcg/day (-31.3%) of the beclomethasone CFC than 400 mcg/day (-22.6%). Secondary: ANOVA showed significant dose effects across both products for $FEF_{25-75\%}$, FVC, and morning PEF. Evening PEF, asthma symptom scores, nighttime sleep disturbances, and daily albuterol use were similar in all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Papi et al.[144] (2007) Beclomethasone 250 mcg BID and albuterol 100 mcg as needed (regular beclomethasone) vs beclomethasone-albuterol 250/100 mcg in a single inhaler as needed (as needed combination) vs beclomethasone-albuterol 250/100 mcg BID in a single inhaler and albuterol 100 mcg as needed (regular combination) vs albuterol 100 mcg as needed (as needed albuterol)	MC, DB, DD, PG, RCT Patients 18-65 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 ≥75% of predicted value, associated with either an increase in FEV_1 ≥12% of predicted value after inhalation of 200 mcg of albuterol or a positive methacholine challenge	N=455 6 months	Primary: Mean rate of morning PEFR Secondary: Lung function, symptom scores, and number/severity of exacerbations	Primary: The morning peak expiratory flow rate at 6 months was significantly higher among patients receiving as-needed combination therapy and in for patients receiving regular beclomethasone therapy compared to the use of as-needed albuterol therapy. The morning peak expiratory flow rate did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy. Secondary: The evening peak expiratory flow rate was significantly higher in the group receiving regular beclomethasone therapy, but not in the group receiving as-needed combination therapy compared to as-needed albuterol therapy. The prebronchodilator FEV_1 and forced vital capacity (FVC) were significantly higher after as-needed combination therapy, but not after regular beclomethasone therapy compared with as-needed albuterol therapy. These values did not differ significantly between patients receiving as-needed combination therapy and those receiving regular beclomethasone therapy or regular combination therapy. The FEV_1 and FVC increased significantly in the as-needed combination group and in the regular combination group, and evening peak expiratory flow rate increased significantly in the regular combination group. The evening peak expiratory flow rate and FEV_1 (percentage of the predicted value) increased significantly in the regular beclomethasone group. The group receiving as-needed combination therapy had fewer nocturnal awakenings, and the group receiving regular beclomethasone had less daily use of rescue medication compared to as-needed albuterol therapy. The percentage of symptom-free days was significantly higher in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy. The percentage of symptom-free days increased significantly in all groups, except the group receiving as-needed albuterol therapy, in which the number of nocturnal awakenings increased significantly. The regular beclomethasone group had fewer daytime asthma symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 237 exacerbations occurred during the study, 38 in patients receiving as-needed combination therapy, 83 in those receiving as-needed albuterol therapy, 33 in those receiving regular beclomethasone therapy, and 83 in those receiving regular combination therapy. The mean number of exacerbations per patient per year was lower in the as-needed combination group (0.74) and in the regular beclomethasone group (0.71) than in the as-needed albuterol group (1.63, P<0.001) and in the regular combination group (1.76, P<0.001). The percentage of patients with at least one exacerbation was not significantly different in the group receiving as-needed combination therapy (4.92%) and the group receiving regular beclomethasone therapy (5.66%, P=0.802) or the group receiving regular combination therapy (10.09%, P=0.133). The percentage of patients with at least one exacerbation was significantly lower both in the group receiving as-needed combination therapy and in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy (17.80%) (P=0.002 and P=0.005, respectively). The time to first exacerbation differed significantly between groups, with the shortest time to first exacerbation in the as-needed albuterol group (P=0.003 by the log-rank test).
Berkowitz et al.[39] (1998) Beclomethasone 336 mcg/day vs triamcinolone 800 mcg/day vs placebo	RCT, DB, DD, PC Patients aged 18 – 65 years with a documented history of bronchial asthma	N=339 56 days	Primary: Change from baseline in FEV_1 Secondary: Forced expiratory flow at 25%-75% of FVC ($FEF_{25-75\%}$), peak expiratory flow rate (PEFR), and forced viral capacity (FVC)	Primary: For both active treatment groups, increases in baseline FEV_1 were evident at all time points; these results were statistically significant when compared to placebo (P<0.05). At endpoint, FEV_1 had increased by 10.3% in the beclomethasone group and 11.2% in the triamcinolone group ($P \leq 0.05$ vs placebo). Secondary: Mean increases in $FEF_{25-75\%}$ and PEFR were similar in both active treatment groups. The same trend was noticed for FVC. All results were numerically and statistically significant when compared to placebo (P<0.05)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bronsky et al.[41] (1998) Beclomethasone 336 mcg/day vs triamcinolone 800 mcg/day vs placebo	RCT, DB, PG, PC, MC Adults with mild to moderately severe asthma maintained on inhaled corticosteroids	N=328 56 days	Primary: Mean changes in FEV_1 from baseline Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25-75\%}$, and FVC	Primary: Throughout the study, mean change and percent mean change in FEV_1 for both active treatment groups were significantly greater than placebo (0.27 L for beclomethasone, 0.16 L for triamcinolone, and -0.10 for placebo; $P \leq 0.01$). A pairwise comparison showed that mean percent change and mean change (SD) were consistently greater in the beclomethasone group throughout the study, with the difference statistically significant at day 28 (P=0.042 and P=0.036, respectively). Both active treatments were better than placebo ($P \leq 0.003$). Secondary: At each visit and at study endpoint, mean reductions in total symptom severity scores were significantly greater in the beclomethasone group compared with the triamcinolone group (P=0.028) and at endpoint in both active treatment groups compared with placebo (-1.37, -0.58, 0.83; $P<0.001$). The mean average daily use of albuterol calculated weekly tended to be least in the beclomethasone group (2.86), greatest in placebo group (4.43), and intermediate in triamcinolone group (3.61). Nighttime awakenings were not significantly different among the treatment groups. Mean change from baseline in $FEF_{25-75\%}$, and FVC showed both active treatment groups better than placebo, with beclomethasone being clinically better than triamcinolone throughout the study.
Baker et al.[31] (1999) Budesonide 0.25mg BID via nebulizer vs	MC, RCT, DB, PC, PG Children, ages 6 months to 8 years, with a diagnosis of asthma	N=480 12 weeks	Primary: Changes in asthma symptom improvement score from baseline, peak expiratory flow (PEF), improvements in	Primary: Symptom scores within 2 weeks after starting treatment showed separation between active treatment groups and placebo. When symptom scores for all active treatment groups were combined, a statistically significant difference between active treatment compared with placebo was seen as early as day 2 for nighttime asthma symptoms, and day 5 for daytime asthma symptoms ($P<0.05$)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide 0.5mg BID via nebulizer vs budesonide 1mg AM and placebo PM via nebulizer vs placebo			FEV_1	There were statistically significant improvements in morning PEF in the 0.25 mg BID (10.9 L/min), 0.5 mg BID (24.8 L/min), and 1.0 mg QD 917.1 L/min) treatment groups compared with placebo (P<0.030) and in evening PEF for each active treatment (16.8 L/min for 0.25 mg QD; P<0.05, 19.2 L/min for 0.25 mg BID; P<0.05, and 21.0 L/min for 0.5 mg BID; P<0.010) except 1.0 mg QD (14.1 L/min; no P value provided). All treatment groups showed numerical improvement in FEV_1 but the only improvement that was statistically significant for FEV_1 compared with placebo was for the 0.5 mg BID group (0.04 L/min vs 0.17 L/min; P=0.031).
Rowe et al.[34] (1999) Budesonide 1,600 mcg/day via DPI vs placebo	RCT, PC, DB Patients aged 16 to 60 years presenting to the emergency department with acute asthma who were discharged with a non-tapering course of oral prednisone (50 mg/day) for 7 days	N=1,006 21 days	Primary: Rates of relapse Secondary: Quality of life (QOL), rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects, compliance	Primary: The budesonide group experienced fewer relapses (12 patients [12.8%]; 95% CI; 7-21%) than the placebo group (23 patients [24.5%]; 95% CI; 16% to 34%) by 21 days (P=0.049). This represents a 48% relapse reduction and suggests as few as 9 patients would require treatment with budesonide to prevent 1 relapse. Secondary: QOL scores were higher in the budesonide than that for the placebo group (P=0.001). The budesonide patients were using fewer mean albuterol inhalations in 24 hours compared with placebo patients (2.4 vs 4.2, P=0.01) at 21 days. Mean and percent predicted peak flow and spirometry findings revealed no differences between the groups. At the conclusion of the study, the budesonide group had fewer symptoms of cough (P=0.004), breathlessness (P=0.001), wheezing (P=0.001), and nighttime awakenings (P=0.001) compared with placebo. Patients in the budesonide group assessed their asthma as more improved than those in the placebo group at 21-day follow-up (6.2 vs 5.2, P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse effects were greater in the placebo group for both hoarseness and sore throat (P=0.02). The overall incidence of adverse effects associated with ICS use (insomnia, fluid retention, acne) was equal between the two groups. Self-reported compliance with the use of oral prednisone was high within the first week of care in both groups (94% for budesonide vs 96% for placebo; P=0.73). Self-reported compliance with budesonide was similar between the groups at 7 (100% for both groups) and 21 days (92% for budesonide vs 93% for placebo; P=0.95).
Sheffer et al.[35] (2005) START Budesonide 200 to 400 mcg once daily via DPI vs placebo Treatment was added to existing asthma therapy.	RCT, PC, DB Patients 5 to 66 years of age with mild persistent asthma, with asthma symptoms at least weekly, but not daily, in the 3 months before enrollment, increase in FEV_1 >12% after the use of a SABA, decrease in FEV_1 of >15% after exercise challenge, or variation of >15% between the 2 highest and 2 lowest PEF rates in 14 days	N=7,221 3 years	Primary: Time to the first severe asthma-related event; change in post-bronchodilator FEV_1 percent predicted from baseline to the end of the 5-year study period Secondary: Number of asthma-related events during the double-blind period; time to first addition of a steroid treatment (systemic or inhaled); symptom- free days, data on healthcare utilization, days off work, and lost school days	Primary: Budesonide reduced the risk of a first severe asthma-related event in patients with mild persistent asthma by 44% (hazard ratio 0.56; CI 0.45 to 0.71; P<0.001). A significant improvement in both prebronchodilator and postbronchodilator FEV_1 percent values was observed after year 1 and year 3 of the study for the budesonide treatment group compared with the placebo arm. After 1 year the differences were 2.24% prebronchodilator and 1.48% postbronchodilator (P<0.0001 for both) and after 3 years, 1.71%, (P<0.0001) and 0.88% (P=0.0005). Secondary: Of the 1,241 serious adverse events reported, 162 in the budesonide group and 276 in the placebo group were related to asthma. Significantly fewer patients in the budesonide group received additional glucocorticosteroids over time compared with the placebo group (31% versus 45%, respectively, P<0.001). An improvement in symptom-free days for both budesonide and placebo groups from baseline was seen over time. However, patients receiving budesonide had significantly more symptom-free days over the 3-year study period (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Busse et al.[65] (2008) START Budesonide 200 to 400 mcg once daily via DPI vs placebo Treatment was added to existing asthma therapy. Randomization was for 3 years, followed by open-label treatment for 2 years.	DB, OL, RCT Patients 5 to 66 years of age with mild persistent asthma, with asthma symptoms at least weekly, but not daily, in the 3 months before enrollment, increase in FEV_1 >12% after the use of a SABA, decrease in FEV_1 of >15% after exercise challenge, or variation of >15% between the 2 highest and 2 lowest PEF rates in 14 days	N=7,221 5 years	Primary: Change from baseline in postbronchodilator percent predicted FEV_1 Secondary : Change in prebronchodilator percent predicted FEV_1;the number of SAE; change in asthma-related symptoms; use of concomitant asthma medication to achieve asthma control	Primary: During the full 5-year study period, the postbronchodilator percent predicted FEV_1 decreased, irrespective of randomized treatment during the double-blind phase (P=0.74), by an average of 2.22%. However, in adults (age ≥18 years), ignoring sex, there was a statistically significant treatment difference of 0.85% (P=0.044) in favor of budesonide. Secondary: During the full 5-year study period, prebronchodilator percent predicted FEV_1 increased, irrespective of randomized treatment during the double-blind phase (P=0.20), by an average of 3.24%. The increase was more pronounced in the pediatric age groups (age <18 years) than in adults. In adults, a statistically significant treatment difference of 1.21% (P=0.018) in favor of budesonide was seen between the 2 treatment groups. The incidence rate of SAE decreased in each group over the 5-year treatment period. During the 3-year double-blind phase, 315 patients (117 in the budesonide group and 198 in the reference group) experienced 1 or more SAE, with the risk being significantly lower in the budesonide group than in the reference group (OR, 0.57; P<0.001). Excluding the 315 patients, 30 patients (16 in the budesonide group and 14 in the reference group) experienced 1 or more SAE during the 2-year open-label phase, with the risk being similar in the 2 treatment groups (OR, 1.12; P=0.76). The cumulative risk of having 1 or more SAE during the full 5 years of START was significantly lower in the budesonide group than in the reference group (OR, 0.61; P<0.001). The reductions in the percentages of patients with symptoms, restrictions in normal activities, and sleep problems caused by asthma from baseline to the end of the double-blind treatment phase were maintained or further improved during the subsequent 2 years of open-label budesonide treatment. Between-group differences, which existed during the double-blind phase, were, however, no longer statistically significant during the open-label phase. The percentage of symptom-free days increased among patients in both treatment groups throughout the 5-year study period, and the differences between groups were no longer significant during the open-label phase.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients who received budesonide during the double-blind treatment phase used significantly less additional asthma medication during the open-label treatment phase. Significantly fewer patients in the budesonide group required additional ICS (10.4% vs 14.6%, P<0.001) or long-acting β-adrenergic agonists (6.3% vs 9.3%, P<0.001) in addition to their budesonide treatment by year 5.
Tinkelman et al.[36] (2003) Budesonide 100-800 mcg QD via DPI	OL Adults with persistent asthma not receiving corticosteroids, adults and children previously maintained on inhaled corticosteroids, and adults previously maintained on oral corticosteroids	N=1,133 52 weeks	Primary: Percentage of predicted FEV_1, oral corticosteroid use Secondary: Plasma cortisol levels, adverse events	Primary: FEV_1 values continued to improve in all patient populations through week 6 of open-label treatment and were sustained for the remainder of the 52 week study. Patients who had not received prior inhaled corticosteroid treatment demonstrated the greatest improvement in FEV_1 (67.1±18% to 81.2±14.8%). Of the 144 oral corticosteroid-dependent patients, 64 entered the open-label study free of oral corticosteroids, and 58 (91%) of those patient remained free of long-term oral corticosteroid use throughout the course of the study. Secondary: There was no evidence of clinically significant suppression of basal or stimulated cortisol levels as a result of treatment with 100, 200, or 400 mcg BID of budesonide. Basal and stimulated cortisol levels increased by 20.7±183.3 nmol/L and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 mcg BID of budesonide. Thirty-three patients discontinued treatment because of adverse events. Of these patients, the relationship between budesonide therapy and the adverse events was none in 18 patients, unlikely in 4 patients, possible in 8 patients, probably in 1 patient, and highly probable in 2 patients. Ninety-two patients (8%) reported serious adverse events, of which the most commonly reported was asthma exacerbation (30 patients). No substantial or unexpected changes in vital signs were observed throughout the open-label study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weiss et al.[53] (2004) Budesonide 200-1,600 mcg/day vs triamcinolone 1,200-1,600 mcg/day	RCT, OL Patients ≥18 years of age with persistent asthma	N=945 52 weeks	Primary: Mean change from baseline to the end of treatment in symptom-free days Secondary: Changes from baseline in number of episode-free days, episode-free days at 52 weeks, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), asthma symptom scores, breakthrough bronchodilator use, health-related quality of life (HRQOL)	Primary: Increase in mean estimated symptom- and episode-free days from baseline was observed in both treatment groups by month 1, and were maintained throughout the treatment period. These increases were consistently greater with budesonide treatment than with triamcinolone treatment (7.74 and 5.73 for the budesonide group compared to 3.78 and 2.12 for the triamcinolone group; P<0.001). Secondary: The adjusted mean increase in symptom- and episode-free days from baseline to month 12 and the estimated mean number of symptom- and episode-free days over the 52-week treatment period were significantly greater in the budesonide group than in the triamcinolone group (P<0.001). FEV_1 and FVC improved from baseline to week 52 in both treatment groups. Patients receiving budesonide treatment experienced a greater improvement in FEV_1 than patients receiving triamcinolone (0.35 L vs 0.25 L; P=0.005). The difference between the 2 treatment groups in FVC was not statistically significant. Mean daytime and nighttime asthma symptom scores decreased from baseline in both groups. Decreases were significantly greater in patients receiving budesonide at month 12 (P=0.001 and P<0.001, respectively). The mean amount of breakthrough bronchodilator use decreased from 4.42 to 2.58 puffs/week in the budesonide group (95% CI; -2.17 to -1.58) and from 4.56 to 3.68 puffs/week in the triamcinolone group (95% CI; -1.36 to -0.52) (P<0.001). Patients in both treatment groups reported significant improvements from baseline over the course of the study in overall quality of life and the individual domains of the HRQOL questionnaire. Compared with the triamcinolone group, the budesonide group reported significantly greater improvements in SF-36 general health scores at weeks 26 and 52 (P<0.05 and P=0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Szefler et al.[64] (2007) Budesonide 500 mcg QD (BIS group) vs montelukast 4 to 5 mg QD	OL, MC, RCT Children 2 to 8 years of age with symptoms of mild persistent asthma	N=695 52 weeks	Primary: Time to first additional medication for asthma worsening over 52 weeks Secondary: Time to first additional asthma medication measured at 12 and 26 weeks; time to first asthma exacerbation measured at 12, 26, and 52 weeks; exacerbation rates over a period of 52 weeks; diary variables: daily AM and PM PEF, and symptom scores; patient/caregiver-reported outcomes via standardized questionnaires	Primary: Time to first additional asthma medication over a period of 52 weeks was not significantly different (P=0.285) between the 2 groups. Secondary: Percentages of subjects who received ≥1 course of additional asthma medication over the 52-week treatment period in BIS group vs montelukast group were as follows: 12 weeks (29.1% vs 38.6%, respectively), 26 weeks (41.3% vs 48.2%, respectively), and 52 weeks (52.0% vs 56.9%, respectively). Subjects treated with BIS experienced a lower rate of exacerbations (number/subject/year) that required step-up BIS therapy or oral corticosteroids vs subjects treated with montelukast (1.23 vs 1.63, respectively; unadjusted P=0.034; a 24.5% reduction in the total number of exacerbations). Percentages of subjects who received oral corticosteroids for an acute severe exacerbation over the 52-week treatment period in BIS group vs montelukast group were as follows: week 12 (10.7% vs 14.7%, respectively), week 26 (17.3% vs 22.3%, respectively), and week 52 (25.5% vs 32.0%, respectively). Rate (number/subject/year) of acute severe exacerbations requiring treatment with oral corticosteroids was lower in BIS group vs montelukast group (0.52 vs 0.67, respectively; P=0.149), with an estimated reduction in the total number of courses of additional oral corticosteroid therapy of 22.7% in BIS group vs montelukast group. Diary variables: short-term results Mean changes from baseline to the average over the first 12 weeks in secondary diary variables generally were similar in both treatment groups, with the exception of AM & PM PEF, for which improvements were greater in BIS group vs montelukast group (morning PEF, unadjusted P=0.007; evening PEF, unadjusted P=0.005). Mean daytime and nighttime asthma symptom scores showed greater improvements in BIS group vs montelukast group, although the differences were not significant (adjusted

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mean change from baseline, –0.40 vs –0.35 and –0.43 vs –0.35, respectively). Mean changes from baseline to the average over the first 12 weeks in the daily use of rescue medication were similar in both treatment groups). Diary variables: long-term results Improvements from baseline in all diary variables were greater over a period of 52 weeks compared with 12 weeks in both treatment groups. Similar results were observed in BIS and montelukast groups on all variables over a period of 52 weeks, with the exception of AM & PM PEF, for which the mean changes from baseline were greater with BIS compared with montelukast (AM PEF, 28.39 vs 20.63, respectively; PM PEF, 25.25 vs 16.85, respectively). Improvements from baseline to the average over the first 12 weeks in spirometry variables (FEV_1, FVC and % predicted FEV_1) were small in both treatment groups, with no significant differences observed between the groups. Patient-reported outcomes and global assessments were evaluated by using the Child Health Questionnaire Parent Form-50 (CHQ-PF50), the Children's Health Survey for Asthma (CSHA), the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ), and the Global Physician and Caregiver Assessments. Results of Physician and Caregiver Global Assessments were significantly better ($P \leq 0.0164$) for BIS compared with montelukast at week 12. The results of Physician Global Assessments also were significantly better ($P \leq 0.0171$) for BIS compared with montelukast at the end of treatment. The results of the CHQ-PF50 questionnaire, the CHSA, and the PACQLQ generally were similar between the groups at the end of week 12.
Pohl et al.[117] (2006) Budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (AMD)	DB, PG, RT Patients >19 years of age with asthma, FEV_1 reversibility of ≥15% (or 200 mL) within 1 month	N=133 20 weeks	Primary: Treatment failures Secondary: Health-related quality of life measured by the	Primary: The rate of treatment failures were comparable between the 2 treatment groups with 5/63 patients in the budesonide-formoterol group and 2/63 patients in the budesonide group experiencing treatment failure throughout the duration of the study. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 320 mcg, 2 inhalations BID (AMD)	prior to enrollment, FEV_1 40%-85% of predicted normal, requirement of ICS or ICS-LABA combination within given starting dose range		SF-36, dose of study medication, days of reliever medication use, treatment satisfaction	Patients in the budesonide-formoterol group had a statistically significant improvement in health-related quality of life and treatment satisfaction (for patients and physicians) versus those in the budesonide group (P<0.05). Patients in the budesonide-formoterol group also had a lower use of daily inhalations of study drug versus budesonide (P=0.024). Both groups had minimal use of reliever medications.
Tal et al.[119] (2002) Budesonide-formoterol 80/4.5 mcg, 2 inhalations BID vs budesonide 100 mcg, 2 inhalations BID	DB, DD, MC, PG, RCT Asthmatic children (mean age, 11 years) with mean predicted FEV_1 of 75% and treated with an ICS (average baseline dose, 548 mcg/day)	N=286 12 weeks	Primary: PEF Secondary: FEV_1, asthma symptoms, use of rescue medications, adverse events	Primary: Patients receiving budesonide-formoterol had greater increases in morning and evening PEF than with those treated with budesonide (P<0.001). Secondary: Patients in the budesonide-formoterol group had greater increases in mean FEV_1 and serial FEV_1 measured over 12 hours than those treated with budesonide (P<0.05). There were no significant differences in asthma symptoms and use of rescue medications observed between treatment groups. Adverse events reported by ≥5% of patients were pharyngitis (8% vs 12%), respiratory infection (8% vs 6%), rhinitis (7% vs 4%), coughing (5% vs 5%), headache (6% vs 4%), viral infection (7% vs 3%), fever (6% vs 2%), and aggravated asthma (5% vs 3%) in the budesonide-formoterol and budesonide groups, respectively.
Lalloo et al.[120] (2003) Budesonide-formoterol 80/4.5 mcg BID vs budesonide 200 mcg BID	DB, MC, PG, RCT Adult patients with mild-to-moderate asthma not fully controlled on low doses of ICS alone, mean baseline predicted FEV_1 of 82%	N=467 12 weeks	Primary: PEF Secondary: Asthma symptoms, use of reliever medication, adverse events	Primary: The budesonide-formoterol group showed greater improvements from baseline in morning PEF (P=0.002), and evening PEF (P<0.001). Secondary: Patients receiving budesonide-formoterol showed greater improvements from baseline in symptom-free days (P=0.007), asthma-control days (P=0.002) and use of rescue medications (P=0.025) than the budesonide group. Fewer patients in the budesonide-formoterol group experienced at least one mild asthma exacerbation (48% vs 57%; no P value reported) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				nighttime awakenings due to asthma (33% vs 44%; no P value reported) compared with budesonide group. The rate of severe exacerbations (7% of each group) and time to first severe exacerbation were similar for both treatment groups. There were no between group differences in adverse events observed with respiratory infection, pharyngitis, and rhinitis being the most common.
Berger et al.[142] (2010) Budesonide-formoterol 160/4.5 mcg BID vs budesonide 200 mcg BID	RCT, OL, MC Patients 6-11years of age with asthma for ≥ 6 months who previously received daily ICS for ≥4 weeks prior to randomization and had FEV_1 ≥50%	N=187 26 weeks	Primary: Safety analysis, urinary cortisol, EKG's Secondary: Pulmonary function, health care resource utilization, health-care related quality of life (HRQL)	Primary: The incidence of adverse reactions was similar between both groups, with 84.6% of events occurring in the budesonide-formoterol group and 85.7% of events occurring in the budesonide group. No serious adverse events were considered related to the treatment drug. No hyperglycemia, hypokalemia or differences in urinary cortisol were detected and no other significant differences were noted on physical exam. Secondary: There was a mean improvement of FEV_1 from baseline favoring budesonide-formoterol versus budesonide (0.15L vs 0.07L; P<0.01). There were significant improvements from baseline to end of therapy in both groups, and a greater improvement in the budesonide-formoterol group compared to budesonide, in the Pediatric asthma caregiver quality of life questionnaire (PACQLQ). These differences did not meet the prespecified minimally important differences. Patients in the budesonide-formoterol group had significantly fewer visits to urgent care facilities compared to budesonide group (3.3% vs 11.1%, respectively; P<0.05).
Kuna et al.[127] (2006) Budesonide-formoterol 80/4.5 mcg, 2 inhalations in the evening	AC, DB, DD, PG, RT Adult patients with mild to moderate persistent asthma who were not	N=617 12 weeks	Primary: Morning PEF Secondary: Evening PEF, symptom-free days, reliever-free	Primary: Patients in both budesonide-formoterol regimens showed greater improvements in morning PEF (P<0.05). Secondary: Patients in both budesonide-formoterol regimens showed greater improvement in evening PEF, symptom-free days, reliever-free days, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide-formoterol 80/4.5 mcg, 1 inhalation BID vs budesonide 200 mcg, 1 inhalation in the evening	optimally controlled on ICS dose of 200-500 mcg/day, mean predicted FEV_1 at baseline was 78.5%		days, asthma-control days, adverse events	asthma-control days than budesonide alone (P<0.05). Both the twice-daily and once-daily budesonide-formoterol regimens were similar in all efficacy variables, except for evening PEF which was higher with the twice-daily regimen (18.3 L/min vs 9.6 L/min; P<0.05). There were no between-group differences in nighttime awakenings due to asthma, or in the number and nature of adverse events.
Morice et al.[129] (2007) Budesonide-formoterol pMDI 160/4.5 mcg vs budesonide-formoterol DPI 160/4.5 mcg vs budesonide pMDI 200 mcg	DB, DD, MC, PG, RCT Patients ≥12 years with asthma for ≥6 months with inadequate control on ICS alone, FEV_1 of 50%-90% predicted normal, reversibility of >12% after inhalation of terbutaline 1 mg, and daily ICS use history ≥3 months	N=680 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, nighttime awakenings, asthma symptom score, symptom-free days, and asthma-control days	Primary: Patients in the budesonide-formoterol DPI and budesonide-formoterol pMDI groups had improved morning PEF compared with those in the budesonide group by 31.4 L/min and 28.6 L/min, respectively (P<0.001). Secondary: Patients in the budesonide-formoterol group had greater improvements observed compared to those in the budesonide group. Endpoints were similar between the two budesonide-formoterol devices, with the exception of symptom-free and asthma-control days, which were slightly improved with the DPI.
Pauwels et al.[132] (1997) FACET Budesonide 100 mcg and	DB, MC, PC, PG, RCT Adult patients with persistent asthma (mean ICS dose 829 mcg/day, mean	N=852 1 year	Primary: Frequency of asthma exacerbations, lung function, asthma symptoms	Primary: The estimated yearly rates of severe asthma exacerbations were as follows: 0.34 for higher dose budesonide plus formoterol, 0.46 for those receiving higher dose budesonide, 0.67 for those receiving lower dose budesonide plus formoterol, and 0.91 for those receiving lower dose budesonide (P=0.01 for formoterol vs placebo, P<0.001 for lower vs higher dose of budesonide, no P value reported for lower dose budesonide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
formoterol 12 mcg BID vs budesonide 400 mcg and formoterol 12 mcg BID vs budesonide 100 mcg BID vs budesonide 400 mcg BID	predicted FEV_1 of 76%, mean reversibility of 21%)		Secondary: Adverse events	plus formoterol vs higher dose budesonide plus placebo). The estimated yearly rates of mild asthma exacerbations were as follows: 13.4 for patients receiving higher dose budesonide plus formoterol, 22.3 for higher dose budesonide plus placebo, 21.3 for those receiving lower dose budesonide plus formoterol, and 35.4 for those receiving lower dose budesonide plus placebo (P<0.001 for formoterol vs placebo, P<0.001 for lower vs higher dose of budesonide, no P value reported for lower dose budesonide plus formoterol vs higher dose budesonide plus placebo). Secondary: All treatments were well tolerated throughout the study.
Kerwin et al.[137] (2009) Budesonide-formoterol 80/4.5 mcg, 2 inhalations BID (320/18 mcg/day) vs budesonide-formoterol 160/4.5 mcg, 2 inhalations QPM (320/9 mcg/day) vs	AC, DB, RCT Patients ≥12 years of age with mild to moderate asthma for ≥6 months who were on a stable dose of budesonide-formoterol 80/4.5 mcg, 2 inhalations BID	N=619 12 weeks	Primary: Evening predose FEV_1 Secondary: Morning predose PEF, evening predose PEF, daytime and nighttime asthma symptom scores, daytime and nighttime rescue medication use, and nighttime awakenings due to asthma	Primary: All budesonide-formoterol groups maintained significantly better evening predose FEV_1, morning PEF, daytime/nighttime asthma symptoms, nighttime rescue medication use, and rescue medication-free days compared to budesonide monotherapy (P<0.05 for each). Twice-daily budesonide-formoterol groups maintained significantly better evening predose FEV_1, evening PEF, daytime asthma symptoms, and daytime rescue medication use than the once-daily groups (P<0.05 for each).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide-formoterol 80/4.5 mcg, 2 inhalations QPM (160/9 mcg/day) vs budesonide 160 mcg, 2 inhalations QD (320 mcg/day)				
Corren et al.[106] (2007) Budesonide-formoterol pMDI 80/4.5 mcg, 2 inhalations BID vs budesonide pMDI* 80 mcg, 2 inhalations BID vs formoterol DPI 4.5 mcg, 2 inhalations BID vs placebo	DB, DD, MC, PC, RCT Patients ≥12 with predominantly mild to moderate persistent asthma treated with an ICS for ≥4 weeks before screening and with a prebronchodilator FEV_1 60%-90% of predicted normal on ICS at screening	N=480 12 weeks	Primary: Changes from baseline in morning predose FEV_1 and 12-hour mean FEV_1 after morning dose Secondary: Morning and evening predose PEF, daytime and nighttime symptom scores, nighttime awakenings, daily rescue medication use, and worsening asthma	Primary: The mean change from baseline in predose FEV_1 was greater in patients who received budesonide-formoterol compared with those who received budesonide, formoterol, and placebo (P<0.005). Observed mean changes from baseline in 12-hour FEV_1 were greater in patients who received budesonide-formoterol compared with those who received budesonide or placebo (P<0.001). There was no evidence of diminution of the 12-hour bronchodilatory effect of budesonide-formoterol during the study period. Secondary: Patients who received treatment with budesonide-formoterol had greater mean increases from baseline in morning and evening predose PEF compared with budesonide or formoterol (P<0.001). Mean decreases in symptom scores were greater with the budesonide-formoterol treatment group compared with formoterol and placebo (P<0.046). Active treatments were associated with greater mean increases in awakening-free nights compared with placebo (P<0.012). Patients who received budesonide-formoterol had a greater mean reduction from baseline in daily rescue medication use compared with formoterol (P=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentage of patients experiencing worsening asthma was reduced with budesonide-formoterol compared with formoterol or placebo (P≤0.01).
Murphy et al.[107] (2008) Budesonide-formoterol pMDI 80/4.5 mcg, 2 inhalations BID vs budesonide pMDI* 80 mcg, 2 inhalations BID vs formoterol DPI 4.5 mcg, 2 inhalations BID vs placebo	DB, DD, MC, PC, RCT Patients ≥18 with predominantly mild to moderate persistent asthma	N=405 12 weeks	Primary: AQLQ, MOS Sleep Scale, asthma control variables (daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, and percentage of asthma control days), PSAM	Primary: A significantly greater improvement from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores, and asthma control variables was seen in the budesonide-formoterol group compared to placebo (P<0.033). A significantly greater improvement from baseline in AQLQ overall and domain scores, daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, and percentage of asthma control days was seen in the budesonide-formoterol group compared to formoterol (P<0.042). A significantly greater PSAM scores were reported in the budesonide-formoterol group compared to all other treatment arms (P<0.004).
Scicchitano et al.[112] (2004) Budesonide-formoterol 160/4.5 mcg, 2 inhalations QD with additional inhalations as needed	DB, PG, RT Patients 11-80 years of age with symptomatic asthma, mean FEV_1 70% of predicted, mean ICS dose 746 mcg/day	N=1,890 12 months	Primary: Time to first severe exacerbation (defined as hospital/ER visit, oral steroids, or fall in morning PEF to <70% of baseline for 2 consecutive days)	Primary: Patients in the budesonide-formoterol group had prolonged time to first exacerbation, and a 39% lower risk of having a severe exacerbation compared to budesonide (P<0.001). Secondary: Patients in the budesonide-formoterol group had 45% fewer severe exacerbations resulting in medical interventions per patient compared to those in the budesonide group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 160 mcg, 2 inhalations BID plus terbutaline 0.4 mg inhalations as needed			Secondary: Number of severe exacerbations, use of as-needed medication, mean daily ICS dose, number of asthma control days	Patients in the budesonide-formoterol group also had less utilization of as needed medication compared to those in the budesonide group (P<0.001), and a lower mean daily ICS dose (466 mcg/day vs 640 mcg/day, respectively). Overall, those in the budesonide-formoterol group experienced 31 more asthma control days and 12 more undisturbed nights per patient-year versus those in the high-dose budesonide group (no P value reported).
Rabe et al.[113] (2006) Budesonide-formoterol 80/4.5 mcg, 2 inhalations QD in the evening with additional inhalations as needed vs budesonide 160 mcg, 2 inhalations QD in the evening plus terbutaline 0.4 mg as needed	AC, DB, MC, PG, RCT Patients 11-79 years of age with asthma for ≥6 months, FEV_1 60%-100% predicted normal, >12% reversibility of baseline FEV_1 15 min after terbutaline 1 mg inhalation, who were receiving ICS 200-500 mcg/day for ≥3 months at a constant dose for ≥30 days prior to study and were required to have had ≥7 inhalations of as-needed medication during the last 10 days of the run-in period, but <10 inhalations on any single day	N=697 6 months	Primary: Morning PEF Secondary: FEV_1, evening PEF, PRN inhalations, PRN medication-free days, asthma symptom score, nighttime awakenings, symptom free days, asthma control days, risk of exacerbation	Primary: Patients in the budesonide-formoterol maintenance and relief group had greater improvements in morning PEF from baseline than those in the budesonide group and was maintained throughout the 6 month treatment period (34.5 L/min vs 9.5 L/min, respectively; P<0.001). Secondary: Both treatment groups were associated with an increase in mean FEV_1, but those in the budesonide-formoterol group had statistically significant greater improvements compared to those receiving budesonide alone (P<0.001). Patients in the budesonide-formoterol maintenance and relief group also had greater improvements in evening PEF from baseline than those in the budesonide group. Patients in the budesonide-formoterol maintenance and relief group had statistically significantly lower asthma symptom scores in comparison to those who were receiving budesonide (P<0.001). There was also a statistically significant improvement in both symptom free days and asthma control-days observed in the budesonide-formoterol maintenance and relief group versus those in the budesonide group (P<0.01). Those in the budesonide-formoterol maintenance and relief group had less utilization of as-needed medication, along with 8% more as-needed medication-free days versus those in the budesonide group (P<0.001). Patients in the budesonide-formoterol maintenance and relief group had a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				54% lower risk in having an exacerbation in comparison to those in the budesonide group (P=0.0011), as well as 90% fewer hospitalizations/ED treatments versus those in the budesonide group (P=0.026).
Sears et al.[26] (2008) Budesonide-formoterol 160/4.5 mcg, 1 inhalation BID and additional doses as needed vs conventional best practice therapy (could include any therapy including either ICS-LABA combination product, but not the use of budesonide-formoterol as both maintenance and reliever therapy)	MC, OL, PG, RCT Patients ≥12 with asthma for a minimum of 3 months, use of ≥400 mcg of ICS daily, treatment with ICS alone and a history of uncontrolled disease (≥3 inhalations of as needed rescue therapy during the last 7 days prior to enrollment) or daily maintenance treatment with an ICS and LABA	N=1,538 6 months	Primary: Time to first severe asthma exacerbation Secondary: Number of severe asthma exacerbations, mean use of as needed medication, PEF, ACQ-5	Primary: No significant difference was found between the two treatment groups in time to first severe exacerbation (HR, 0.99; 95% CI, 0.70 to 1.41; P=0.95). Secondary: The mean number of exacerbations per patient per year was 0.19 for the budesonide-formoterol group compared to 0.21 for the convention treatment group (HR, 0.92; 95% CI, 0.67 to 1.28; P=0.63). Total days of oral corticosteroid use were 17% lower in the budesonide-formoterol group compared to the conventional group (590 vs 709 days). Mean as-needed reliever use decreased from 1.25 to 0.94 inhalations per day with budesonide-formoterol compared to a decrease from 1.22 to 1.09 inhalations per day in the conventional therapy (P=0.0036). There were a total of 15 patients in the budesonide-formoterol group who required >8 as needed inhalations on at least one day, compared to 30 subjects in the conventional treatment group (P=0.028). PEF increased from 94.8% to 98.0% predicted in the budesonide-formoterol group compared to an increase from 84.1% to 96.3% in the conventional group a difference that was not significant (P=0.46). The ACQ-5 score decreased from 1.27 to 1.08 in the budesonide-formoterol group compared to a decrease from 1.24 to 1.09 in the conventional treatment group, a difference that was not significant (P=0.46).
Bateman et al.[124] (2003) Budesonide-formoterol 160/4.5 mcg, 1 inhalation BID	DB, DD, PG, RT Patients with asthma (average age of 42 years, FEV_1 78% predicted, reversibility 21%)	N=373 12 weeks	Primary: Morning PEF Secondary: Evening PEF, clinic FEV_1, use of reliever	Primary: Patients in the budesonide-formoterol group had significantly greater increases in morning PEF than those in the fluticasone group (27.4 L/min vs 7.7 L/min, respectively; P<0.001). Secondary: Those in the budesonide-formoterol group had a significant improvement

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone 250 mcg, 1 inhalation BID			medication, symptom-free days, asthma-control days, night-time awakenings, risk of having an exacerbation	in their evening PEF and FEV_1 compared to the fluticasone group. Also, patients in the budesonide-formoterol group utilized less reliever medication (P=0.04) and had a greater proportion of reliever-free days (P<0.001). Patients in the budesonide-formoterol group had a 32% risk reduction of having an exacerbation compared to those in the fluticasone group (P<0.05). Although not statistically significant, patients in the budesonide-formoterol group had improvements in regards to symptom-free days, asthma-control days, and nighttime awakenings versus those in the fluticasone treatment group (60.4% vs 55.5%; 57.8% vs 52.4%; and 7.9% vs 9.6%, respectively).
Ericsson et al.[125] (2006) Budesonide-formoterol 160/4.5 mcg BID vs fluticasone propionate 250 mcg BID	DB, DD, MC, PG, RT Patients ≥18 years of age with moderate-persistent asthma, diagnosis ≥6 months, on ICS (200-1,000 mcg) ≥30 days, FEV_1 60%-90% predicted normal, ≥12% reversibility after inhalation of terbutaline or salbutamol†	N=339 12 weeks	Primary: Morning PEF Secondary: Time to first exacerbation, asthma symptom score, rescue medication use	Primary: Patients in the budesonide-formoterol treatment group had a statistically significant greater improvement in morning PEF of 27.4 L/min in comparison to 7.7 L/min observed in the fluticasone propionate treatment group (19.7% difference; 95% CI, 13.6 to 25.9; P<0.001). Secondary: Patients in the budesonide-formoterol treatment group had a statistically significant greater increase in the time to first mild exacerbation in comparison to those in the fluticasone propionate treatment group (P=0.04). Budesonide-formoterol was associated with a greater reduction in the use of rescue medications in comparison to fluticasone propionate –0.31 inhalations/day versus –0.13 inhalations/day, respectively; P=0.04).
Pohunek et al.[100] (2006) Budesonide-formoterol 80/4.5mcg BID (fixed-dose	RCT, DB, PG, AC, MC Patients 4-11 years of age with PEF >50% of predicted normal who had	N=630 12 weeks	Primary: Change in morning PEFR Secondary: Change from baseline in:	Primary: The change in morning PEFR was significantly greater with budesonide/formoterol compared with budesonide (mean difference 10.9 L/min; P<0.001). There was no significant difference in morning PEF between patients treated with budesonide/formoterol and those who received budesonide + formoterol in separate inhalers (P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhaler) vs budesonide 200 mcg BID and formoterol 9 mcg BID (separate inhalers) vs budesonide 200 mcg BID	received stable treatment with an inhaled corticosteroid, and history of an average of ≥1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study		evening PEF; total asthma-symptom score; night-time awakenings due to asthma symptoms; use of reliever medication; reliever-free days; symptom-free days; change in FEV_1, change in health-related quality of life (Pediatric Asthma Quality of Life Questionnaire [PAQLQ])	Significantly greater changes in evening PEF were seen in patients treated with budesonide/formoterol compared to budesonide (mean difference 9.1 L/min; P<0.001). There was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers. Patients treated with budesonide/formoterol had significantly greater changes in FEV_1 compared with budesonide (mean difference 0.078 L; P<0.001). There was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers. Asthma symptoms improved from baseline with all treatments, with no significant between-group differences. Overall PAQLQ(S) scores improved in all treatment groups, with adjusted mean changes of 0.437, 0.494 and 0.501 for the budesonide/ formoterol, budesonide + formoterol in separate inhalers and budesonide treatment groups, respectively. No significant between-group differences were observed. Scores were also improved for the individual domains, indicating improvements with regard to symptoms, emotional function and activity limitation; there were no differences between the treatment groups.
Noonan et al.[108] (2006) Budesonide-formoterol pMDI 160/4.5 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide pMDI* 160 mcg, 2 inhalations plus formoterol DPI 4.5	DB, DD, MC, PC, RCT Patients ≥12 years, documented diagnosis of asthma for ≥6 months, moderate to high ICS use for ≥4 weeks, prebronchodilator FEV_1 45%-85% of predicted normal	N=596 12 weeks	Primary: Mean change from baseline in morning predose FEV_1, mean change from baseline in 12-hour FEV_1 after administration of morning dose Secondary: PEF, asthma symptoms, rescue medications use, and worsening	Primary: Greater improvements in morning predose FEV_1 were obtained in patients treated with budesonide-formoterol (0.19 L) than those with budesonide (0.10 L), formoterol (-0.12 L), and placebo (-0.17 L); P≤0.049. Patients who received budesonide-formoterol also demonstrated a greater improvement in 12-hour FEV_1 than budesonide, formoterol, and placebo at 2 weeks and end of treatment (P≤0.001). Secondary: Budesonide-formoterol treatment resulted in greater improvements in morning and evening PEF, daytime and nighttime symptoms, worsening asthma, and percentage of symptom-free days than budesonide, formoterol, and placebo (P≤0.05). Patients receiving budesonide-formoterol demonstrated reduction in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg, 2 inhalations, both BID (separate inhalers) vs budesonide pMDI* 160 mcg, 2 inhalations BID vs formoterol DPI 4.5 mcg, 2 inhalations BID vs placebo			asthma	asthma symptoms, use of rescue medication and improvement in PEF within the first day, and effects were maintained over the course of the 12-week study. Significant reductions in the use of rescue medication were observed in patients with budesonide-formoterol treatment compared with formoterol (P<0.001) and placebo but not with budesonide (P=0.066). Awakenings due to asthma were not significantly different between active treatment groups. Results were similar in the budesonide/formoterol pMDI group and the budesonide pMDI + formoterol DPI group on all measures. No clinically significant differences in adverse events were observed between treatment groups. Patients who received budesonide-formoterol had clinically significant bronchodilation, defined as >15% improvement in FEV_1, within 15 minutes and effect was maintained over 12 hours.
Zetterström et al.[126] (2001) Budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 200 mcg plus formoterol 4.5 mcg, 2 inhalations BID (separate inhalers)	DB, DD, MC, PG, RCT Adult patients with moderate persistent asthma (mean ICS dose 960 mcg/day, mean predicted FEV_1 of 73.8%)	N=362 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, asthma control/symptoms, use of reliever medication, night-time awakenings, exacerbations, safety	Primary: Patients in the budesonide-formoterol and budesonide plus formoterol groups had greater improvements in morning PEF compared with those in the budesonide group (35.7 L/min vs 32.0 L/min vs 0.2 L/min, respectively; P<0.001). Secondary: Evening PEF, total asthma symptom score, use of reliever medication, reliever use-free days, percentage of symptom-free days, percentage of asthma control days, and risk of mild exacerbations were all significantly improved in the budesonide-formoterol and budesonide plus formoterol groups compared with budesonide (P<0.01). No significant differences between treatment groups in night-time asthma awakenings or adverse events were observed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 200 mcg, 2 inhalations BID				
Rosenhall et al.[122] (2002) Budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 mcg and formoterol 4.5 mcg, 2 inhalations BID (separate inhalers)	MC, OL, RT Patients with moderate persistent asthma	N=586 6 months	Primary: Safety and efficacy (FEV_1, Mini Asthma Quality of Life Questionnaire, Asthma Control Questionnaire, exacerbations	Primary: Patients in both treatment groups had a mean FEV_1 increase of 5%-6% from baseline. There was no significant change in response using the Mini Asthma Quality of Life Questionnaire and the Asthma Control Questionnaire from baseline in both treatment groups. Both treatment groups were well tolerated, with asthma exacerbations occurring at a low frequency. The withdrawal rate in both groups was also similar (P=0.085).
Rosenhall et al.[121] (2003) Budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 mcg and formoterol 4.5	MC, OL, PG, RCT Adult patients with asthma of ≥6 months duration, predicted FEV_1 ≥50%, receiving constant ICS dose of ≥400-1,200 mcg for ≥30 days, and daily use of inhaled short- and/or long-acting β_2-agonists	N=321 6 months	Primary: Lung function, asthma control, health-related quality of life Secondary: Adverse events	Primary: There were no significant differences in lung function measurements, time to first exacerbation (defined as first use of oral glucocorticosteroids), or health-related quality of life observed between treatment groups. Secondary: There were no significant differences in incidence and severity of adverse events observed between treatment groups. More patients from the budesonide-formoterol group than the budesonide plus formoterol group remained in the study (P=0.008).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg, 2 inhalations BID (separate inhalers)				
Rosenhall et al.[111] (2006) Budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 mcg and formoterol 4.5 mcg, 2 inhalations BID (separate inhalers)	ES, MC, OL, PG, RCT Adult patients with asthma	N=320 12 months	Primary: Efficacy and safety parameters	Primary: There were no significant differences observed between the two treatment groups in regards to safety and efficacy. There was a lower withdrawal rate in patients treated with budesonide-formoterol via a single inhaler compared to those using separate inhalers (9.2% and 19.4%, respectively; P=0.008).
Jenkins et al.[128] (2006) Budesonide-formoterol 320/9 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 400 mcg plus formoterol 9 mcg, 2 inhalations BID (separate inhalers)	DB, DD, MC, RCT Patients ≥12 years of age with asthma for ≥6 months who used ICS for ≥4 months at a constant daily dose of ≥750 mcg for at least 4 weeks prior to study entry	N=456 24 weeks	Primary: PEF Secondary: Use of rescue medications, asthma symptoms, FEV_1, adverse events	Primary: Patients in both the budesonide-formoterol and budesonide plus formoterol groups had significantly improved morning PEF, and evening PEF (P<0.01). No significant difference was observed in morning PEF and evening PEF between budesonide-formoterol and budesonide plus formoterol (P=NS). Secondary: Patients in both the budesonide-formoterol and budesonide plus formoterol groups had significantly improved symptom-free days, reliever-free days, FEV_1, asthma-control days, and risk of mild asthma exacerbation compared with those in the budesonide group (P<0.01). No significant differences in total asthma symptoms, symptom-free days, reliever-free days, asthma-control days, or risk of mild exacerbation were observed between budesonide-formoterol and budesonide plus formoterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 400 mcg, 2 inhalations BID for 12 weeks, followed by either budesonide-formoterol or budesonide plus formoterol via separate inhalers for 12 weeks				(P=NS). The frequency and profile of adverse events were similar for all treatment groups.
Chervinsky et al.[136] (2008) Budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 mcg and formoterol 4.5 mcg, 2 inhalations BID (separate inhalers) vs budesonide 160 mcg, 2 inhalations BID	DB, PC, MC, RCT Patients ≥12 years of age with moderate to severe persistent asthma for ≥6 months	N=553 12 weeks	Primary: Asthma Quality of Life Questionnaire (AQLQ) Secondary: Medical Outcomes Study (MOS) Sleep Scale, PSAM questionnaire, diary variables	Primary: Mean AQLQ overall scores were 5.71 for budesonide-formoterol, 5.80 for budesonide plus formoterol, 5.35 for budesonide, 5.08 for formoterol, and 4.98 for placebo. Mean AQLQ(S) overall scores improved from baseline to end of therapy in all treatment groups except for the formoterol and placebo groups. Mean improvements from baseline to end of treatment in AQLQ overall scores were significantly greater for patients receiving budesonide-formoterol compared to those receiving budesonide (P<0.047), formoterol (P<0.001), or placebo (P<0.001). There was no significant difference between budesonide-formoterol and budesonide plus formoterol in any outcome. Secondary: No significant differences were observed among the treatment groups for the MOS Sleep Scale scores. Patients receiving budesonide-formoterol reported awakening with shortness of breath or headache significantly less often than patients receiving formoterol (P=0.009) or placebo (P<0.001). Mean PSAM scores for control relief, perception of medication, and comparison with other medications at end of therapy were significantly higher in patients receiving budesonide-formoterol compared to those receiving budesonide, formoterol, or placebo (all, P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs formoterol 4.5 mcg, 2 inhalations BID vs placebo				A greater percentage of patients receiving budesonide-formoterol reported higher satisfaction ratings for items in the control relief index, the perception of medication index, and the comparison with other medication index than patients receiving budesonide, formoterol, or placebo. Patients receiving budesonide-formoterol experienced greater improvements in daily asthma symptom scores, daily rescue medication use, and the percentages of symptom-free days, rescue medication-free days, and asthma control days compared to patients receiving budesonide, formoterol, or placebo (all P≤0.004). Patients reporting improvements in overall health at end of therapy was significantly higher in the budesonide-formoterol group (58.9%) compared to the formoterol (40.2%; P=0.01) and placebo (12.9%; P<0.001) groups. The percentage of patients reporting easier management of their asthma during treatment was significantly higher in the budesonide-formoterol group (61.7%) compared to the budesonide (46.2%; P=0.03) and placebo (19.4%; P<0.001) groups.
Rabe et al.[99] (2006) Budesonide-formoterol 160/4.5 mcg BID and terbutaline MDI 0.4 mg as needed vs budesonide-formoterol 160/4.5 mcg BID and formoterol MDI 4.5 mcg as needed	DB, PG, RCT, MC Patients >12 years of age with asthma who had >1 severe asthma exacerbation in the 12 months before entry, use of inhaled corticosteroids for >3 months and at a constant dose for ≥4 weeks immediately before entry, FEV_1 50–100% of predicted normal (prebronchodilator) with 12%	N=3,394 12 months	Primary: Time to first severe exacerbation Secondary: Total number of severe exacerbations, time to first and total number of emergency treatment or hospitalizations, asthma symptom scores—asthma control questionnaire score; mild	Primary: The time to first severe exacerbation was longer with as needed budesonide-formoterol vs formoterol (P=0.0048) or terbutaline (P<0.0001). As-needed formoterol prolonged the time to first severe exacerbation versus terbutaline (P=0.0051). Secondary: As-needed budesonide-formoterol reduced the risk of a severe exacerbation by 27% (95% CI, 10–41%) versus formoterol and by 45% (95% CI, 32–55%) versus terbutaline. The risk reduction with as-needed formoterol versus terbutaline was 24% (95% CI, 8–37%). The yearly rate of severe exacerbations per patient was reduced with as-needed budesonide-formoterol by 33% versus formoterol (P<0.0001), by 48% versus terbutaline (P<0.0001), and by 22% with as-needed formoterol versus terbutaline (P=0.012). Rates of exacerbations needing emergency room treatment or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide-formoterol 160/4.5 mcg BID and budesonide-formoterol 160/4.5 mcg as needed	reversibility or more after inhalation of terbutaline 1 mg		exacerbations; FEV1; morning and evening peak expiratory flow (PEF); and reliever medication use	hospitalization were reduced with as-needed budesonide-formoterol by 27% (P=0.046) versus formoterol and by 39% (P=0.0010) versus terbutaline, respectively. There was no significant difference between formoterol and terbutaline. The proportion of patients with more than one exacerbation was lowest in the as-needed budesonide-formoterol group (3%, 7%, and 7% of patients in the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively). Mild exacerbation days were reduced by 10–18% with as-needed budesonide-formoterol compared with both formoterol P=0.043) and terbutaline (P<0.0001). The time to first mild exacerbation was longer with as-needed budesonide-formoterol versus terbutaline (P=0.0080), but the difference between as-needed budesonide-formoterol and formoterol was not significant (P=0.059). Mean asthma symptom scores decreased for all groups, with a greater reduction in the budesonide-formoterol for maintenance and reliever therapy group versus maintenance therapy plus formoterol (P=0.0002) or terbutaline (P=0.0007). Night-time awakenings were reduced by 2% (7 nights per year) with as-needed budesonide-formoterol versus formoterol (P=0.018) and by 3% versus terbutaline (P=0.0025). No between-group differences were seen with as-needed formoterol compared with terbutaline for asthma symptom scores or night-time awakenings. Asthma-control days increased in all groups with no between-group differences. Overall ACQ-5 scores improved to a greater extent with as-needed budesonide-formoterol than with formoterol (P=0.0009) and terbutaline (P<0.0001). No difference in overall ACQ-5 scores was seen with formoterol versus terbutaline. Mean FEV_1 improved in each of the treatment groups when all patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				used maintenance budesonide-formoterol plus as-needed terbutaline (run-in). Additional increases in FEV_1 of 0.05 L and 0.08 L were seen with as-needed budesonide-formoterol versus formoterol (P=0.0001) and terbutaline (P<0.0001). Mean morning PEF increased from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol versus both formoterol (4.8 L per min; P=0.004) and terbutaline (7.5 L per min; P<0.0001). Similar improvements were noted with as-needed budesonide-formoterol for mean evening PEF compared with formoterol (5.4 L per min; P=0.0011) and terbutaline (6.3 L per min; P=0.0001). There was no significant difference in morning or evening PEF between as-needed formoterol and terbutaline. The mean reliever use decreased to 1.02 inhalations per day in the budesonide-formoterol group and to 1.23 and 1.26 inhalations per day in the formoterol and terbutaline groups, respectively. Patients receiving budesonide-formoterol used fewer as-needed inhalations per day than those receiving formoterol or terbutaline (P<0.0001 for both) and on 52% of treatment days patients in the budesonide-formoterol group did not use any as-needed medication compared with 48% in both comparator groups. There was no significant difference in reliever use between the formoterol and terbutaline groups.
Canonica et al.[133] (2004) CAST Budesonide-formoterol 80/4.5 mcg, 2 inhalations BID (AMD) vs budesonide-formoterol 160/4.5	RCT Patients with persistent asthma	N=2,358 12 weeks	Primary: Frequency of asthma exacerbations, changes in asthma symptom severity Secondary: Asthma control, safety and health economics	Primary: Both fixed dosing and adjustable maintenance dosing budesonide-formoterol treatment groups had similar low frequency of exacerbations, as well as improved comparable lung function. However, results did not reach statistical significance (P=NS). Secondary: Both treatment groups had improved lung function, less asthma symptoms, and fewer nighttime awakenings compared to the mean value of run-in period (P value not reported). Patients in the adjustable maintenance budesonide-formoterol dose group utilized 24% less of the study drug in comparison to those in the fixed maintenance dose group (2.95 vs 3.86 daily inhalations, respectively;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg, 2 inhalations BID (AMD) vs budesonide-formoterol 80/4.5 mcg, 2 inhalations BID (FD) vs budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (FD)				P<0.0001).
Fitzgerald et al.[96] (2005) Budesonide-formoterol 200/6 mcg BID via DPI vs salmeterol-fluticasone 50/250 mcg BID via DPI	RCT, DB, DD Patients 18 to 70 years of age with a history of asthma and an FEV_1 between 60% and 90% of projected normal value	N=706 1 year	Primary: Percentage of symptom-free days Secondary: Daily asthma symptom scores, morning PEF, percentage of days free of rescue medication use, nighttime awakenings due to asthma	Primary: The percentage of symptom-free days was higher with salmeterol/fluticasone propionate compared to formoterol/budesonide (58.8% vs 52.1%, P=0.034). The percentage of symptom-free days was significantly higher in the salmeterol/fluticasone group compared to the formoterol/budesonide during weeks 5 through 52 (73.8% vs 64.9%, P=0.030). Secondary: In the salmeterol/fluticasone group, there was a significant difference in the adjusted annual mean exacerbation rate compared to formoterol/budesonide group (0.18 vs 0.33, P=0.008). The median value for the percentage of days free of rescue medication over weeks 5 through 52 was 94.5% for the salmeterol/fluticasone group compared to 90.7% in the formoterol/budesonide group (P=0.008). Over the 52-week treatment period the mean morning PEF was significantly higher in the salmeterol/fluticasone group compared to the formoterol/budesonide group (400.1 L/min vs 390.6 L/min, P=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Palmqvist et al.[109] (2001) Budesonide-formoterol 160/4.5 mcg, 1 inhalation as a single dose vs budesonide-formoterol 160/4.5 mcg, 2 inhalations as a single dose vs fluticasone-salmeterol 250/50 mcg, 1 inhalation as a single dose vs placebo	DB, PC, RCT, XO Adult asthmatic patients (mean predicted FEV_1 of 78%, mean reversibility of 19%)	N=30 4 days	Primary: Mean FEV_1 at 15 minutes after inhalation Secondary: Time to bronchodilation (defined as >15% increase in FEV_1 from baseline), absolute FEV_1 at 3 minutes, FEV_1 at time points ≤60 minutes	Primary: Both budesonide-formoterol doses demonstrated improvements in FEV_1 compared with fluticasone-salmeterol and placebo at 15 minutes postdose (P<0.001). Secondary: At 1 hour, bronchodilation was achieved in 47% of patients in the fluticasone-salmeterol group, 73% of those in the budesonide-formoterol one inhalation group, and 77% of those in the budesonide-formoterol two inhalations group. Both doses of budesonide-formoterol also demonstrated significant improvements in FEV_1 at 3 minutes (P<0.001) and at 60 minutes compared with fluticasone-salmeterol and placebo.
Kuna et al.[130] (2007) Budesonide-formoterol 160/4.5 mcg, 1 inhalation BID, and additional inhalations as needed vs	DB, DD, MC, PG, RCT Patients ≥12 years of age with asthma diagnosis of at least 6 months, use of an ICS for at least 3 months, FEV_1 ≥50% predicted normal, ≥12% reversibility	N=3,335 6 months	Primary: Time to first severe exacerbation (defined as hospitalization or ER visit, or ≥3 days of oral corticosteroids) Secondary: Number of severe exacerbations,	Primary: Patients in the maintenance and relief budesonide-formoterol group had a significant prolonged time to first severe exacerbation compared to those in the fixed dose fluticasone-salmeterol and budesonide-formoterol groups (P=0.0034, P=0.023, respectively). There was no difference in time to first exacerbation observed between the two fixed-dose groups. Secondary: There was a 39% reduction in the number of severe exacerbations observed in the maintenance and relief budesonide-formoterol group in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide-formoterol 320/9 mcg, 1 inhalation BID and terbutaline as needed vs fluticasone-salmeterol 125/25 mcg, 2 inhalations BID and terbutaline as needed	following terbutaline use, ≥1 asthma exacerbation in past 1-12 months		number of mild exacerbations, asthma symptom score, inhalations of PRN medication, change in morning and evening PEF, FEV_1, night awakenings, symptom-free days, as-needed-free days, asthma-control days	comparison to the fixed-dose fluticasone-salmeterol group (RR, 0.61; 95% CI, 0.49 to 0.76; P<0.001) There was a 28% reduction in the number of severe exacerbation observed in the maintenance and relief budesonide-formoterol group versus the fixed-dose budesonide-formoterol group (RR, 0.72; 95% CI, 0.57 to 0.90; P=0.0048). There were similar findings in the total number of severe exacerbations observed between the two fixed-dose groups. There were no significant differences in the number of mild exacerbations, asthma symptoms, asthma symptom scores, use of as-needed medications, and lung function between the maintenance and relief budesonide-formoterol group and the two fixed-dose groups.
Price et al.[114] (2007) Budesonide-formoterol 200/6 mcg, 2 inhalations BID (adjustable maintenance dose) vs fluticasone-salmeterol 250/50 mcg, 1 inhalation BID (stable dose)	DB, DD, MC, PG, RT Patients 18-70 years of age with asthma, FEV_1 60%-90% predicted normal, who were receiving an ICS dose equal to 200-500 mcg/day BDP plus LABA, or ICS alone at dose equal to >500-1,000 mcg BDP	N=688 1 year	Primary: Symptom-free days Secondary: Rate of exacerbations	Primary: Patients in the fluticasone-salmeterol group had a significantly greater percentage of symptom-free days (58.8%) over the entire year, compared to budesonide-formoterol (52.1%; P=0.034). Secondary: The adjusted annual mean exacerbation rate was significantly lower in the fluticasone-salmeterol group compared to the budesonide-formoterol group (47%; P=0.008).
Aalbers et al.[131] (2004) Budesonide-formoterol 160/4.5	DB, ES Patients with moderate-severe asthma, mean	N=658 4 weeks (DB) and 6 months (OL)	Primary: Odds of achieving a well-controlled asthma week (WCAW)	Primary: There was no difference in the odds of achieving a well-controlled asthma week in the fixed dosing (FD) treatment groups. There was a significant increase in the odds of achieving a well-controlled asthma week in the budesonide-formoterol adjustable maintenance dosing (AMD) group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg, 2 inhalations BID (AMD) vs budesonide-formoterol 160/4.5 mcg, 2 inhalations BID (FD) vs fluticasone-salmeterol 250/50 mcg, 1 inhalation BID (FD)	symptom score 1.5, mean FEV_1 84% predicted, mean ICS dose 735 mcg/day		Secondary: Exacerbation rate, use of reliever medication	compared to the budesonide-formoterol FD group during the open-label period, regardless of a 15% decrease in the average use of study drug (OR, 1.335; 95% CI, 1.001 to 1.783; P=0.049). Secondary: Patients in the budesonide-formoterol AMD group had a significantly lower exacerbation rate (40%) compared to those in the fluticasone-salmeterol group, and a 32% lower exacerbation rate compared to those in the budesonide-formoterol FD group (P=0.018 and P=NS, respectively). Patients in the budesonide-formoterol AMD group used significantly less reliever medication during the open study period versus those in the budesonide-formoterol and fluticasone-salmeterol FD groups (P=0.001 and P=0.011, respectively).
Edwards et al.[134] (2007) Budesonide vs budesonide-formoterol (FD) vs budesonide-formoterol (AMD) vs fluticasone-salmeterol (FD)	MA Patients with moderate to severe asthma	15 trials 12-52 weeks	Primary: Treatment failure Secondary: Hospitalizations, emergency visits, use of oral steroids	Primary: Patients in the budesonide-formoterol group demonstrated 50% less treatment failure in comparison to those who received budesonide treatment alone (RR 1.50; 95% CI, 1.12 to 2.02; P=0.007). Although there seemed to be a favorable trend in the reduction of treatment failure observed in the budesonide-formoterol (AMD) group versus the budesonide-formoterol FD group, there was no significant difference detected (RR, 0.88; 95% CI, 0.77 to 1.02; P=0.09). There was no significant difference observed between those in the budesonide-formoterol group and those in the fluticasone-salmeterol group in regards to treatment failure (P=0.86). Secondary: Patients in the fluticasone-salmeterol group had a 49% greater risk of hospitalizations/accident and emergency visits compared to those in the FD budesonide-formoterol group (RR, 1.49; 95% CI, 1.07 to 2.08; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients in the budesonide-formoterol-AMD treatment group had a 28% risk reduction in hospitalizations/accident and emergency visits versus those treated with FD budesonide-formoterol (RR, 0.72; 95% CI, 0.52 to 0.99; P=0.04). Budesonide alone, was associated with a greater risk (51%) in the use of oral steroids in comparison to budesonide-formoterol (RR, 1.51; 95% CI, 1.10 to 2.09; P=0.01). Patients in the budesonide-formoterol-AMD group had a lower requirement for oral steroids than those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; P=0.01). Patients in the budesonide-formoterol-AMD treatment group experienced a 19% decreased risk in use of oral steroids versus those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; P=0.01).
Remington et al.[118] (2002) Budesonide (range: 200, 400, and 800 mcg) vs budesonide (range: 200, 400, and 800 mcg) plus formoterol (range: 9-24 mcg)	MA Patients ≥12 years of age with mild to severe asthma	N=4,079 (5 trials) 12 weeks to 12 months	Primary: Frequency of mild and severe exacerbations, time to first severe exacerbation, poorly controlled asthma days, PEF, asthma symptoms, rescue medication use	Primary: The addition of formoterol to high-dose budesonide resulted in a greater reduction in both mild and severe exacerbation rates compared to low-dose budesonide (P<0.001). High-dose budesonide monotherapy was more efficacious in reducing the rates of severe exacerbations in comparison to low-dose budesonide and formoterol (P=0.03), but similar results were observed between the two groups in regards to the rate of mild exacerbations. The addition of formoterol to either budesonide 200 or 400 mcg in patients who were previously on low-medium doses of ICS led to a greater reduction in the risk of first severe exacerbation, as well as a reduction in the frequency of poorly controlled asthma days compared to budesonide alone. Combination of budesonide and formoterol in separate devices or a single inhaler had significantly greater improvements in morning PEF compared to budesonide alone (P<0.0001), and improvements were maintained over the entire study period. Combination therapy was associated with grater improvements in symptom scores, symptom-free days, and rescue medication use. There were no observed differences between the treatment groups in regard to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the number of severe exacerbations. Budesonide and formoterol were equally efficacious, whether in a single or separate inhaler, and were more effective than budesonide alone. Patients in the high dose budesonide plus formoterol group had improved AQLQ scores during both the run-in period and during the treatment period (P<0.001 and P=0.028, respectively).
Erin et al.[135] (2008) Ciclesonide 320 mcg, 1 inhalation QD vs ciclesonide 640 mcg,1 inhalation BID vs placebo	PC, DB, XO, RCT Adults 18 to 45 years of age with stable persistent asthma for ≥6 months and a FEV_1 ≥70% predicted	N=21 7 days	Primary: Nitric oxide (NO) exhalation (2 h after inhalation), pulmonary function test (2 to 5 min after inhalation), adenosine monophosphate (AMP) challenge 5 h after inhalation) and sputum induction	Primary: Ciclesonide 320 mcg and 640 mcg produced significantly greater improvements in FEV_1 compared with placebo on days 1, 3, and 7 (all P<0.0001). Compared with placebo, ciclesonide 320 mcg and 640 mcg improved median exhaled NO levels by -22.6 and -20.7 parts per billion after 7 days, respectively (P<0.001 for both). Although not statistically significant, sputum eosinophils decreased after 7 days of ciclesonide treatment.
Hansel et al.[146] (2006) Ciclesonide 80 mcg QD vs ciclesonide 320 mcg QD vs	RCT, MC, DB, OL Patients 12-75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: Change in FEV_1 Secondary: Changes from baseline in morning peak expiratory flow (PEF), asthma symptom scores, and rescue medication use	Primary: Significant increases from baseline in FEV_1 were achieved in all 3 groups (all, P<0.001). Ciclesonide was found to be non-inferior to budesonide with regard to mean changes from baseline in FEV_1 (ITT: 97.5% CI, -0.192 to 0.015 for ciclesonide 80 mcg vs budesonide; 97.5% CI, -0.200 to 0.001for ciclesonide 320 mcg vs budesonide). Similar findings were seen in the PP population. There was no significant difference between the 2 ciclesonide groups. Secondary: Morning PEF was improved significantly in the ciclesonide 80 mcg and 320 mcg groups, as well as the budesonide group (all, P<0.008). Ciclesonide was found to be non-inferior to budesonide. No significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide 200 mcg BID				differences in morning PEF were found between the 2 ciclesonide groups. Significant improvements were found in median daily asthma symptom scores in all 3 treatment groups (all, P<0.001). Significant improvements were found in median daytime and nighttime asthma symptom scores in all 3 groups (all, P<0.001). Comparisons between treatments for daily, daytime, and nighttime asthma symptom scores did not demonstrate any significant differences throughout the study. Overall, the percentages of patients without any asthma symptoms (score, 0) increased from -20% to -40% after 3 days of treatment; these percentages were similar across all 3 treatment groups throughout the study. The onset of effect for ciclesonide and budesonide, based on asthma symptom scores, occurred during the first week of treatment. However, in smokers treated with budesonide 200 mcg BID (4 patients), the mean onset of action was 4 weeks, whereas in smokers treated with ciclesonide 80 mcg QD (23 patients) or 320 mcg QD (15), onset was within 1 week. There were significant decreases in rescue medication use in all 3 groups by day 1 of treatment (all, P<0.001). These decreases remained significant throughout the study in all 3 treatment groups (all, P<0.001). AEs were reported in 36.8 % of patients receiving ciclesonide 80 mcg QD, 80 (40.8%) patients receiving ciclesonide 320 mcg QD, and 60 (33.9%) patients receiving budesonide 200 mcg BID.
Niphadkar et al.[147] (2005) Ciclesonide 160 mcg QAM or QPM vs budesonide 200	RCT, DB, OL, MC Patients 18-69 years of age with persistent asthma for ≥6 months that was maintained on a constant dose of ICS and FEV_1 ≥70% predicted	N=405 12 weeks	Primary: Change in FEV_1 Secondary: FVC, PEF, asthma symptom scores, rescue medication use	Primary: Ciclesonide and budesonide maintained FEV_1 as compared with baseline. Ciclesonide was non-inferior to budesonide with regard to maintenance of FEV_1 (PP analysis: 95% CI, -0.075 to 0.095 for ciclesonide 160 mcg QAM vs budesonide, 95% CI, -0.051 to 0.123 for ciclesonide 160 mcg QPM vs budesonide). No significant differences were found among the 3 treatment groups with regard to the change in FEV_1 at the end of treatment. Similar results were obtained in the ITT analysis. Secondary:

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mcg BID				Ciclesonide was found to be non-inferior to budesonide with regard to maintenance of FVC in all treatment groups, and no significant differences were found among the groups. The mean change in morning PEF was 8.0 L/min in the ciclesonide 160 mcg PM group, compared with -5.7 L/min in the ciclesonide 160 mcg AM group and -1.3 L/min in the budesonide (all groups, P=NS). Evening PEF was maintained in all treatment groups. No significant differences were found among the 3 treatment groups for the secondary endpoints FVC, PEF by spirometry, and morning and evening PEF by diary. Ciclesonide 160 mcg QAM, ciclesonide 160 mcg QPM, and budesonide maintained asthma symptom scores, and no significant differences were found between the treatment groups. The percentages of days that were free of asthma symptoms and need for rescue medication were 89%, 91%, and 93% for patients taking ciclesonide 160 mcg QAM, ciclesonide 160 mcg QPM, and budesonide, respectively, with no differences between the treatment groups. The percentage of days that were free of nocturnal awakening was 100% in all treatment groups. Rescue medication use, days with control of asthma symptoms, and days without PEF fluctuation, were maintained versus baseline, and no significant differences were found between the treatment groups. Both treatments were well tolerated.
von Berg et al.[148] (2007) Ciclesonide 160 mcg QPM vs budesonide 400	RCT, DB, PG, MC Patients 6-11 years of age with asthma for ≥6 months, FEV_1 50-90%, reversibility of FEV_1 ≥12% of initial after	N=621 12 weeks	Primary: Change in FEV_1, PEF, FVC, asthma symptoms, rescue medication use, quality of life	Primary: Both ciclesonide and budesonide significantly increased FEV_1 (232 and 250 ml, respectively, ITT; P<0.0001 vs. baseline). Non-inferiority of ciclesonide vs. budesonide was demonstrated for FEV1 (P=0.8158 ITT). Ciclesonide and budesonide significantly increased morning PEF, evening PEF and FVC (P<0.0001 vs. baseline, ITT and PP). There was no significant difference between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg QPM	inhalation of salbutamol 200–400 mcg, and asthma symptom scores ≥1 on at least six of the previous 10 consecutive days or use of ≥8 puffs of rescue medication during the previous 10 consecutive days			Treatment with ciclesonide and budesonide led to significant improvements in asthma symptom score sum (all P<0.0001 vs. baseline). There was no significant difference between the treatment groups (P=0.8379, ITT). There was a significant reduction in the need for rescue medication with ciclesonide and budesonide (P<0.0001 vs. baseline). There was no significant difference between the treatment groups (P=0.8593). The percentage of days without asthma symptoms and without need for rescue medication was 73% and 70% for patients in the ciclesonide and budesonide treatment groups, respectively. There was no significant difference between the treatment groups. The percentage of nocturnal awakening-free days was 98.5% in both treatment groups. The percentage of patients with asthma exacerbations was small in both treatment groups (2.6% and 1% in the ciclesonide and budesonide treatment groups, respectively). There was no significant difference between the treatment groups. Ciclesonide and budesonide achieved significant improvements in overall scores vs. baseline on the PAQLQ(S) (P<0.0001) and PACQLQ (P<0.0001). Non-inferiority of ciclesonide vs. budesonide was demonstrated in the PAQLQ(S) and PACQLQ (P=0.5738, ITT). The increase in body height was significantly greater in ciclesonide-treated patients than in budesonide-treated patients (P=0.0025). Treatment with ciclesonide and budesonide resulted in significant decreases in 24-h urinary cortisol adjusted for creatinine (P<0.0001 vs. baseline). The decrease in 24-h urinary cortisol was significantly greater in the budesonide group compared with the ciclesonide group (P<0.0001). Adverse events occurred in approximately 38% of patients in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Boulet et al.[149] (2006) Ciclesonide 320 mcg QD vs budesonide 320 mcg QD	RCT, MC, DB, MC Patients 12-75 years of age with persistent asthma for ≥6 months, FEV_1 65-95% of predicted value, receiving treatment with budesonide 320-640 mcg, fluticasone 175-440 mcg/day or equivalent. patients entering the treatment period had to fulfill inclusion criteria and demonstrate improvement in FEV1 during the pretreatment period of either ≥7% or 0.15 L following the increase in their daily ICS dose from budesonide 320–640 mg (or the equivalent) to budesonide 1,280 mg.	N=359 12 weeks	Primary: Change in FEV_1, FVC, PEF, asthma symptom scores, rescue medication use	Primary: During the pretreatment period with budesonide 1,280 mg daily, mean FEV_1 levels increased by 0.352 L for the ciclesonide group and 0.319 L for the budesonide group. After patients were randomized to either ciclesonide 320 mg or budesonide 320 mg once daily, FEV_1 decreased by 0.18 and 0.23 L, respectively, over 12 weeks of treatment (P<0.0001; PP analysis). Ciclesonide was non-inferior to budesonide with regard to maintenance of FEV_1 (95% CI, -0.015 to 0.121 for ciclesonide versus budesonide; PP analysis). Similar results were obtained by ITT analysis. There were no significant differences between the two treatment groups with regard to change in FEV_1 at the end of treatment. Mean FVC levels decreased in both treatment groups, the decrease in ciclesonide patients (0.12 L; P<0.0001, within-treatment comparison) compared with that in budesonide patients (0.21 L; P<0.0001, within-treatment comparison) was significantly less (95% CI, 0.02 to 0.147; P=0.011 for ciclesonide versus budesonide; ITT analysis). Similar results were obtained after PP analysis. There was no significant difference in morning PEF between the treatment groups. Mean evening PEF levels did not significantly change with ciclesonide or budesonide. There were no significant differences between the two treatment groups in median asthma symptom score sums, night scores, and daytime scores over the treatment period. The percentage of asthma symptom-free days was 43.6% in the ciclesonide group compared with 25.8% in the budesonide group. Patients treated with ciclesonide experienced a significant reduction in the median rescue medication use over the course of treatment (P=0.009) compared to no change in those treated with budesonide (P=0.626). There was a significant difference between treatment groups in median rescue medication use (P=0.026). The median percentage of rescue medication-free days was similar in both groups (57.5% versus 53.6% for ciclesonide and budesonide group, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences between treatment groups with regard to lack of efficacy, physician assessments, or patient self-assessments. A total 52% of patients in the budesonide group and 42% of patients in the ciclesonide group experienced an adverse event.
Ukena et al.[150] (2007) Ciclesonide 320 mcg QPM vs budesonide 400 mcg QPM	RCT, DB, MC, PG Patients 12-75 years of age with asthma for ≥6 months, FEV_1 50-90%	N=399 12 weeks	Primary: Change in FEV_1 Secondary: FVC, PEF, asthma symptom scores, use of rescue medication	Primary: After 12 weeks, FEV_1 increased by 416 ml in the ciclesonide group and by 321 ml in the budesonide group (P<0.0001 versus baseline for both). Ciclesonide was significantly more effective than budesonide demonstrated (P=0.019). Secondary: Patients experienced significant improvements in FVC and PEF with ciclesonide and budesonide (P<0.0001 versus baseline for both). Patients treated with ciclesonide achieved a significantly greater increase in FVC (P=0.034) and PEF by spirometry (P=0.019) compared with budesonide. Significant increases in asthma symptom scores and decreases in use of rescue medication were observed with ciclesonide and budesonide. Ciclesonide and budesonide significantly improved asthma symptom scores from baseline (both P<0.0001). There was no significant difference between the treatment groups (P=0.863). Ciclesonide and budesonide improved rescue medication use compared to baseline (P<0.0001). There was no significant difference between the treatment groups. Ciclesonide treatment achieved a significant improvement in morning PEF by day 2 (P=0.039 versus baseline) compared with day 7 for budesonide (P=0.047 versus baseline). Adverse events occurred with a similar incidence in both treatment groups.
Vermeulen et al.[151] (2007) Ciclesonide 320	RCT, DB, MC, PG Patients 12-17 years of age with asthma	N=403 12 weeks	Primary: Change in FEV_1 and percentage of days without any	Primary: There were significant increases in FEV_1 in the ciclesonide group (505 mL) and the budesonide group (536 mL; both P<0.0001 versus baseline). There was no significant difference between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg QPM vs budesonide 800 mcg QPM	for ≥6 months who were not well controlled on budesonide 400 mcg/day or equivalent with FEV_1 50-80% of predicted		asthma symptoms and without use of rescue medication Secondary: Change in FEV_1% of predicted, FVC, PEF, asthma symptom scores, use of rescue medications, exacerbations, nighttime symptoms, quality of life	Secondary: FEV_1% predicted increased in the ciclesonide group from 73.1% at baseline to 89.4% at study end, and in the budesonide group from 73.0% to 90.7%. There was no significant difference between the treatment groups. There was a significant increase in FVC from baseline with ciclesonide and budesonide (P<0.0001). There was no significant difference between the treatment groups. PEF significantly increased with ciclesonide and budesonide (P<0.0001). There was no significant difference between the treatment groups. Morning and evening PEF increased in both treatment groups. In the ITT population, the increases were significant in the ciclesonide group for both morning and evening assessments (P=0.0424 and P=0.0263, respectively), but not in the budesonide group. There was no significant difference between the treatment groups. Asthma exacerbations occurred in 2.6% of patients receiving ciclesonide and 1.5% of patients receiving budesonide. There was no difference between the ciclesonide and budesonide groups. For time to first asthma exacerbation, there was no statistically significant difference between the treatments. The median percentage of days without any asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group. There was no significant difference between the treatment groups. Median asthma symptom scores were significantly reduced during the study in both treatment groups (P<0.05). There was no significant difference between the treatment groups. The percentage of nocturnal awakening-free days was 100% in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Ciclesonide and budesonide significantly improved QoL overall, and the individual domains of activities, symptoms and emotions, by a comparable amount (all P<0.05). There was no significant difference between the treatment groups. Pharyngitis and asthma were the most frequently documented AEs. The majority of AEs in both treatment groups were mild or moderate in intensity.
Buhl et al.[152] (2006) Ciclesonide 160 mcg QD vs fluticasone 88 mcg BID	RCT, MC, DB, MCG Patients 12-75 years of age with asthma for ≥6 months, FEV_1 50-90% predicted after rescue medication was withheld for at least 4 hours, a decrease in FEV_1 ≥10% after ICS withdrawal, reversibility of FEV_1 ≥15% after inhaling 200-400 mcg of salbutamol or have shown a diurnal PEF fluctuation of ≥15%	N=529 12 weeks	Primary: Changes in FEV_1, FVC, PEF, $FEF_{25-75\%}$, asthma symptom scores, rescue mediation use	Primary: Ciclesonide produced similar improvements in FEV_1 as fluticasone (0.489 and 0.499 L for ciclesonide and fluticasone, respectively; P=0.801; ITT). Similar improvements in FEV_1 were observed in the PP analysis (0.506 and 0.536 L for ciclesonide and fluticasone, respectively; P=0.477). FVC and morning PEF increased to a similar extent in both treatment groups and there were no differences for these parameters between the groups (P=0.468 and P=0.582, respectively; ITT). Evening PEF values significantly improved over the 12 weeks following treatment with ciclesonide and fluticasone. $FEF_{25-75\%}$ increased in both the ciclesonide and fluticasone treatment groups by 0.519 and 0.601 L/s, respectively (P<0.0001 for both), and no significant differences were observed between treatment groups (P=0.264). PP analysis of all lung function variables revealed comparable results with the ITT analysis. There were no significant differences between asthma symptom scores in the ciclesonide and fluticasone groups. Ciclesonide and fluticasone also significantly reduced rescue medication use with no significant differences between the groups. There was no significant difference between ciclesonide and fluticasone with regards to rescue medication-free days, asthma symptom-free days, and nights without awakenings due to asthma.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 270 treatment-emergent AEs were experienced by 186 of the 529 patients (36% of patients in the ciclesonide group and 34% of patients in the fluticasone group).
Magnussen et al.[153] (2007) Ciclesonide 80 mcg QPM vs ciclesonide 160 mcg QPM vs fluticasone 88 mcg BID	RCT, DB, PG Patients 12-75 years of age with persistent asthma for ≥6 months	N=808 12 weeks	Primary: Change in FEV_1 and change in nighttime asthma symptoms score Secondary: PEF, FVC, asthma symptoms, rescue medication use, and days with asthma control	Primary Ciclesonide 80 mcg, ciclesonide 160 mcg and fluticasone achieved similar improvements in FEV_1 (P<0.0001 for all groups and time points versus baseline; ITT). PP analysis revealed similar results. Both doses of ciclesonide were found to be non-inferior to fluticasone and led to similar improvements in FEV_1 from baseline. Non-inferiority of both ciclesonide 80 mcg and 160 mcg versus fluticasone was achieved for PEF and FVC, as well as evening PEF. For morning PEF, the within-treatment improvements were statistically significant for all 3 treatment groups (P<0.0001). Non-inferiority was demonstrated for ciclesonide 160 mcg versus fluticasone, but not for ciclesonide 80 mcg. Treatment with ciclesonide 80 mcg, ciclesonide 160 mcg and fluticasone led to significant decreases in median asthma symptom scores (P<0.0001 vs baseline). Nighttime asthma symptom score significantly improved for all treatment groups, as well as daytime asthma symptom scores (P<0.0001 versus baseline). There were no significant differences among groups for asthma symptom scores. Similar results were obtained in the PP analysis. All 3 treatment groups significantly reduced rescue medication use (all P<0.0001 versus baseline), with no significant differences among treatment groups. The percentage of days with asthma control was similar in all treatment groups with no significant differences between groups. Only 2 patients in each of the ciclesonide 80 mcg and 160 mcg groups and 1 patient in the fluticasone group experienced an asthma exacerbation that required treatment with oral steroids.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 25% of patients in the ciclesonide 80 mcg group, 24% of patients in the ciclesonide 160 mcg group and 27% of patients in the fluticasone group experienced AEs.
Pedersen et al.[154] (2009) Ciclesonide 80 mcg QD vs ciclesonide 160 mcg QD vs fluticasone 88 mcg BID	RCT, DB, PG Patients 6-11 years of age with persistent asthma for ≥6 months, FEV_1 50-90% of predicted and FEV_1 reversibility of ≥12% predicted after salbutamol 200-400 mcg	N=744 12 weeks	Primary: Change in FEV_1, PEF, exacerbations, asthma symptom scores, rescue medication use, quality of life	Primary: FEV_1 increased significantly in all treatment groups (P<0.0001). Non-inferiority was demonstrated for ciclesonide 160 mcg versus fluticasone (95% CI, -0.079 to 0.027; P=0.0030, whereas ciclesonide 80 mcg was not shown to be non-inferior to fluticasone. Morning PEF increased significantly in all treatment groups (all P<0.0001). Both ciclesonide doses were non-inferior to fluticasone (P<0.0063 for both doses). Asthma exacerbations occurred in 7.1% of patients receiving ciclesonide 80 mcg, 2.9% of patients receiving ciclesonide 160 mcg, and 2.0% of patients receiving fluticasone. The difference between the higher-dose treatments was not statistically significant, but both these treatments were significantly superior to ciclesonide with respect to time to onset of first exacerbation (P<0.021). All three treatments significantly decreased asthma symptom score sums and need for rescue medication (all P<0.0001). Between-treatment analyses confirmed non-inferiority of both ciclesonide groups to fluticasone for asthma symptom score sums (P>0.5713). No significant differences were found between treatment groups for asthma symptom score sums and rescue medication use. The percentage of asthma symptom-free days, rescue medication- free days and nocturnal awakening-free days did not differ significantly between the treatment groups. Quality of life significantly improved for overall scores and all sub-categories of the questionnaires in all treatment groups (P<0.0001 for all). Between-treatment analyses for the overall PACQLQ and PAQLQ scores confirmed non-inferiority of ciclesonide 80 mcg and ciclesonide 160 mcg to fluticasone (P<0.0001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentage of patients experiencing AEs was comparable across all treatment groups (CIC80, 46.4%; CIC160, 41.7%; FP176, 47.6%).
Boulet et al.[155] (2007) Ciclesonide 320 mcg QPM vs fluticasone 200 mcg BID	RCT, OL. MC, MCG Patients 12-75 years of age with moderate asthma for ≥6 months and FEV_1 60-80% of predicted. Patients had to have been on a constant dose and type of asthma medication (except rescue medication) during the 4 weeks prior to the run-in period.	N=474 12 weeks	Primary: Change in FEV_1, FVC, PEF, FEV_1% predicted, SVC, asthma symptom scores, rescue medication use, asthma control days, exacerbations, health-related quality of life	Primary: FEV_1 increased significantly from baseline with ciclesonide and fluticasone in the ITT and PP analyses (all P<0.0001). Treatment difference was -31 ml (95% CI, -121 to 59) in the PP analysis, demonstrating non-inferiority of ciclesonide. FVC improved significantly with both treatments with ciclesonide showing a similar effect to fluticasone (-0.034; 95% CI, -0.134 to 0.066 in the PP population and -0.017; 95% CI, -0.105 to 0.070 in the ITT population). A significant increase in morning PEF was seen in the ciclesonide-treated group (ITT and PP; both P<0.050) and a significant decrease in evening PEF was seen in the fluticasone -treated group (ITT population only; P=0.020). Non-inferiority was seen for ciclesonide in morning and evening PEF for both the ITT and PP populations. FEV_1% predicted and SVC improved significantly with both treatments in both populations. There were no significant between-treatment differences in any of these lung function parameters. In the ITT population, daytime and total median asthma symptom scores were reduced in the ciclesonide group by 0.25 (P<0.0001) and 0.29 (P<0.0001), and in the fluticasone group by 0.29 (P<0.0001) and 0.29 (P<0.0001), respectively. The median values for nighttime scores were 0 at baseline and end of study. The PP analysis yielded similar results. There were no significant differences in asthma symptom scores between the treatment groups. In the ITT population, the use of rescue medication decreased by 0.29 puffs/day (P<0.0001) in both treatment groups and there was no significant difference between treatments. The percentage of days with asthma control was achieved at similar rates in the two groups (85% and 84% in the ciclesonide and fluticasone groups,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively, in both the ITT and PP analyses). Asthma exacerbations were recorded in 1.3% of patients in the ciclesonide group and 2.1% of patients in the fluticasone group (ITT). The mean AQLQ(S) overall score increased from 5.85 at baseline to 6.14 (P<0.0001) in the ciclesonide group and from 5.85 to 5.96 (P=0.030) in the fluticasone group. The improvement with ciclesonide was significantly greater than with fluticasone (P=0.005). Both ciclesonide and fluticasone produced significant increases in all of the individual AQLQ(S) domain scores. Non-inferiority of ciclesonide to fluticasone was seen in all domain scores (all P<0.0001) in the PP and ITT analyses. The improvement in the scores for the domains of 'activities' and 'symptoms' was significantly greater with ciclesonide versus fluticasone (P<0.01). The overall frequency of adverse events was similar in the two treatment groups (36.1% in the ciclesonide group and 39.3% in the fluticasone group).
Bateman et al.[156] (2008) Ciclesonide 160 mcg, 2 inhalations BID vs fluticasone 110 mcg, 3 inhalations BID Patients using LABAs, oral β_2-agonists, theophylline, leukotriene antagonists or	RCT, OL, MCG, MC Patients 12-75 years of age with ≥6 month history of asthma, FEV_1 ≥80% of predicted, reversibility of FEV_1 ≥12% after 200-400 mcg salbutamol, and ≥1 day without asthma symptoms during the last 7 days. Patients were receiving fluticasone 500-1000 mcg/day.	N=528 6 months	Primary: Change in FEV_1 and drop-out rate due to asthma exacerbation Secondary: Morning and evening PEF; asthma symptom scores; use of rescue medication; percentage of days free from asthma symptoms, rescue medication and nocturnal awakenings; percentage of days	Primary: FEV_1 was maintained from baseline to study end in both groups (mean increase: ciclesonide 11 ml, fluticasone 24 ml; ITT analysis). The least squares mean of the mean for the treatment difference was -13 (95% CI, -70 to 44) in the ITT analysis and -27 (95% CI, -93 to 40) in the PP analysis, demonstrating non-inferiority of ciclesonide to fluticasone. Six patients in the ciclesonide group and seven in the fluticasone group in the ITT analysis experienced an asthma exacerbation that required treatment with oral corticosteroids. Similar findings were seen in the PP data set (ITT: 95% CI, -0.031 to 0.028; PP: 95% CI, -0.016 to 0.043). Secondary: Both treatments significantly decreased asthma symptom score sum (ITT and PP analyses: all P<0.0001) and rescue medication use (ITT and PP analyses: all P<0.05). The treatment differences between ciclesonide and fluticasone were not statistically significant for any of the asthma symptom scores or rescue medication use.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lipoxygenase inhibitors could continue treatment provided the dose was kept constant throughout the trial.			with asthma control; and AQLQ(S)	Median values for percentages of symptom-free days, rescue-medication-free days and nocturnal-awakening-free days did not differ significantly between the two treatment groups. The percentage of days with asthma control was 74.1% in the ciclesonide group and 73.2% in the fluticasone group. There was no significant difference between the treatment groups. There were significant improvements in health-related quality of life (HRQoL) in the two treatment groups for the overall AQLQ(S) score, as well as for all domain scores (ITT and PP analyses, all P<0.05). The frequency of AEs was comparable in both treatment groups.
Brenner et al.[32] (2000) Flunisolide 2 mg/day vs placebo At discharge, all patients were given prednisone 40 mg/d x 5 days and inhaled β-agonists as needed.	RCT, PC Patients aged 18-50 years old with a diagnosis of asthma presenting to the emergency department with an acute asthma exacerbation	N=104 24 days	Primary: Peak expiratory flow rates (PEFR) Secondary: Overall symptoms and albuterol use	Primary: PEFR was similar between the two groups throughout the trial (P=0.36 on day 24). There was a mean difference of 4 units, favoring flunisolide, between the groups (95% CI). Secondary: Both symptoms and albuterol use were similar in both groups for the duration of the trial. 75% of patients in the flunisolide group reported symptom improvement vs 70% in the placebo group (95% CI, -17-27).
Sheikh et al.[51] (1999) Flunisolide 1,500 mcg/day for a period of one year then crossed over	XO, OL Children with moderate to sever asthma, mean age of 12.7 years	N=30 2 years	Primary: Mean percent predicted values for FVC, FEV_1, $FEF_{25\%-75\%}$, and PEFR	Primary: Significant improvement in all clinical parameters was found while patients were receiving fluticasone as compared with flunisolide. There was significant improvement in FVC during the 2 to 6 month and 7- to 12-month time periods after the switch.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to fluticasone 880 mcg/day for one year				Significant improvement was noted in FEV_1 and $FEF_{25\%-75\%}$ at 1 month after the switch, and this improvement persisted during the 2 to 6 months and 7 to 12 month time periods. There was no significant difference in PEFR at any time period.
Lee-Wong et al.[55] (2002) Flunisolide 2,000 mcg BID via spacer vs placebo Patients were also randomized to receive oral prednisone or placebo.	RCT, DB, PC Patients aged 18-55 years admitted to the emergency department for an acute asthma exacerbation	N=40 7 days	Primary: Peak expiratory flow rate (PEFR), FEV_1 Secondary: Change in asthma symptom scores	Primary: From day 1 to day 7, mean PEFR increased from 190 to 379 L/min in the inhaled corticosteroid group, and from 207 to 347 L/min in the prednisone (P=0.95; 95% CI, -66.3 to ∞). Mean FEV_1 increased from 1.6 to 2.3 L in the ICS group and from 1.4 to 2.1 L in the prednisone group (P=0.33; 95% CI; -21.7 to ∞). Secondary: Mean symptom scores declined from 1.4 to 0.7 in the ICS group and decreased from 1.3 to 0.4 in the prednisone group (P=0.39).
Nakanishi et al.[56] (2003) Flunisolide 1 mg BID via valved holding chamber vs prednisone 2mg/kg	RCT, PC, PG, Masked Children aged 6 to 16 years seeking emergent care for an acute exacerbation of asthma	N=58 7 days	Primary: Percentage of predicted FEV_1 Secondary: Symptom score, initial vital signs and oximetry, side effects, recurrence rate for acute asthma symptoms, and daily peak expiratory flow (PEF)	Primary: The FEV_1 percentage of predicted for the inhaled corticosteroids group was lower on day 3 (65% vs 78% for oral corticosteroids, P=0.03) and on day 7 (77% vs 95%, P=0.002). Both groups continued to improve over the 7-day study period, with the most improvement in those patients receiving oral corticosteroids. Secondary: There was no significant difference in symptom severity between the two groups at any time during the study. There was no significant difference in initial vital signs or oximetry between the two groups at any time during the study. One patient in the inhaled corticosteroid group required additional corticosteroids after the 7-day study period to control symptoms. One

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patient in the oral corticosteroid group required hospital admission for asthma within 24 hours following enrollment. There was no significant difference in PEF between the two groups at any time during the study.
Newhouse et al.[48] (2000) Flunisolide 750 mcg BID (administered via AeroChamber®) vs budesonide 600 mcg BID (administered via Turbuhaler®)	MC, RCT, PG Patients with moderate asthma (FEV_1 of 40% to 85% of predicted)	N=176 6 weeks	Primary: Change in prebronchodilator FEV_1 from week 0 to week 6, change in mean albuterol usage during the weeks preceding week 0 and week 6 Secondary: Changes in PEF, asthma scores, nocturnal awakenings	Primary: There were no statistically significant differences between the two treatment groups in the changes in FEV_1 during the six week treatment period (difference of -0.031 L in percent predicted favoring flunisolide, P=0.544). There were no significant changes in albuterol use between the two groups (difference of 0.261 puffs/day favoring budesonide, P=0.333). Secondary: There were no statistically significant differences between the two treatment groups in the change in PEF, asthma symptoms scores, and nocturnal awakenings during the treatment period.
Nelson et al.[33] (1999) Fluticasone 500 mcg BID vs fluticasone 1,000 mcg BID vs placebo	RCT, DB, PG, PC Patients ≥12 years of age with chronic asthma who were receiving oral corticosteroid treatment during the preceding 6 months	N=111 16 weeks	Primary: Percentage of patients with a change in maintenance prednisone dose, mean change from baseline in maintenance dose of prednisone Secondary: Changes in FEV_1, patient-measured morning and evening PEF, patient-rated	Primary: At study endpoint, oral prednisone use was eliminated by 75% and 89% of patients treated twice daily with 500 or 1,000 mcg of fluticasone, respectively, compared with 9% in the placebo group. Mean maintenance dose of oral prednisone decreased significantly in both fluticasone groups compared with placebo, with decreases of 12.0 mg and 13.0 mg in the 500 and 100 mcg groups, respectively, compared with 5.2 mg in the placebo group (P<0.001). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone 500 mcg group (8.37±3.84) and the 1,000 mcg group (24.21±5.67) vs placebo (0.56±5.56, P≤0.05 for all) Both morning and evening PEF improved in the fluticasone 500 mcg (23+10 AM, 3±7 PM) and 1,000 mcg (67±12 AM, 48±10 PM). The placebo group did not improve (-23±11 AM and -9±12 PM; P≤0.05 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			asthma symptoms, number of nighttime awakenings requiring albuterol	all). Asthma symptom scores improved in both the fluticasone 500 mcg (-0.26±0.08) and the 1,000 mcg groups (-0.47±0.13, P≤0.05); symptom scores worsened in the placebo group (0.26±0.12, P≤0.05) Nighttime awakenings requiring albuterol decreased in both the fluticasone 500 mcg (-0.19±0.11) and the 1,000 mcg groups (-0.42±0.13); nighttime awakenings increased in the placebo group (0.26±0.15, P≤0.05 for all)
Qaqundah et al.[67] (2006) Fluticasone HFA 88 mcg BID vs placebo	RCT Children age 1 to <4 years with a history of symptomatic asthma and ≥2 episodes of increased asthma symptoms requiring medical attention/asthma treatment within the year before screening	N=359 12 weeks	Primary: Mean percent change from baseline to endpoint in 24-hour daily asthma symptom scores Secondary: Mean change from baseline to endpoint in daily rescue SABA use; time to treatment failure; mean change in 24-hour daily asthma symptom scores; clinic morning PEF.	Primary: Fluticasone group had a significantly greater mean percent (P=0.036) reduction in 24-hour daily asthma symptom scores vs placebo. Secondary: Fluticasone group had significantly greater (P<0.05) reduction in nighttime asthma symptom scores over the treatment period vs placebo; mean change in 24-hour daily asthma symptom scores was also significantly increased in fluticasone group. Fluticasone group had improved daily SABA use, daytime symptom scores, and nighttime symptoms scores vs placebo; however, the differences were not statistically significant. A total of 65 children (18%) were able to produce technically acceptable morning PEF measurements. At treatment week 12, mean change from baseline was 14.1 L/min in the fluticasone group (n=34) vs 8.3 L/min for the placebo group (n=23). The number of children able to perform PEF measures was too low to allow meaningful comparisons between the treatment groups.
Berend et al.[38] (2001) Fluticasone (at ~50% of the ICS dose during the run-in phase)	MC, RCT, OL, PG Patients ≥18 years of age with a history of severe asthma who were currently receiving at least	N=133 6 months	Primary: Changes in morning peak expiratory flow (PEF), changes in FEV_1 at clinic visits	Primary: At week 6, patients in the fluticasone group showed a significant improvement in morning PEF and this improvement was maintained until the end of the study (adjusted difference between two groups=26±32 L/min; 95% CI: 8-45, P=0.006). Changes in FEV_1 measured at clinic visits paralleled those values of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs beclomethasone or budesonide (at the same dose used during the run-in phase)	1,750 mcg/day of inhaled beclomethasone or budesonide		Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations, quality of life	morning PEF (fluticasone=1.87±0.70 L; beclomethasone/budesonide 2.03±0.86 L). Secondary: Serum osteocalcin levels increased significantly only in the fluticasone group (adjusted mean [SD]=2.6 [4.0] mcg/L, 95% CI: 0.2-4.9, P=0.03). There were no clinically significant changes during the study in plasma creatinine, plasma glucose, serum insulin, serum fasting lipids, or in any parameter associated with the calcium-parathyroid axis or the renal handling of calcium. There was no significant difference in the analysis of change in hoarseness between the two treatment groups. There was a low incidence of oropharyngeal candidiasis during the study in both treatment groups. By week 24, four patients (6%) in the fluticasone group and one patient (2%) in the beclomethasone / budesonide group had evidence of candidiasis. An analysis of change did not show any significant difference between the two groups. Thirty-four patients (51%) in the fluticasone group and 36 patients (55%) in the beclomethasone/budesonide group reported one or more exacerbations during the course of the trial. No significant difference seen in the incidence of asthma between the groups. There was a significant increase in the overall asthma quality of life score in the fluticasone group (4.8±1.1 to 5.5±1.1 units; P<0.001); no significant change was seen in the beclomethasone/ budesonide group (4.9±1.1 to 5.0±1.2 units, P=0.13).
Raphael et al.[50] (1999) Fluticasone 88 mcg BID vs	RCT, DB, PG Patients ≥12 years of age with asthma requiring daily inhaled corticosteroid therapy for at least 6	N=399 14 weeks	Primary: Changes in morning predose FEV_1 Secondary: Forced expiratory flow ($FEF_{25-75\%}$),	Primary: The FEV_1 for all treatment groups improved with respect to baseline; however, a significant drug effect was observed in favor of fluticasone compared with beclomethasone in the mean change in FEV_1 from baseline to endpoint (0.3L1 to 0.36 L vs 0.18L to 0.21 L; P=0.006). At endpoint, mean FEV_1 values in the low-and medium-dose fluticasone treatment groups improved by 0.31 L (14%) and 0.36 L (15%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone 220 mcg BID vs beclomethasone 168 mcg BID vs beclomethasone 336 mcg BID	months before the study		forced vital capacity (FVC), morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings, asthma symptoms	respectively, compared with improvements of 0.18 L (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively. Secondary: Forced expiratory flow ($FEF_{25-75\%}$) and FVC were improved from baseline in all treatment groups; fluticasone showed greater improvements than beclomethasone ($P \leq 0.034$). Fluticasone provided significantly greater improvement in morning PEF when compared with beclomethasone treatment at endpoint and in all of the other time points except week 2 ($P<0.004$). The fluticasone group also experienced a significant improvement in morning PEF relative to baseline (15.8 L to 22.8 L), but the beclomethasone groups did not (0.7 L to 7.2 L). A similar trend was seen in evening PEF, but the improvement observed in response to fluticasone compared with beclomethasone did not achieve statistical significance. There were no significant differences noted in the analysis of the probability of remaining in the study. The percentage of days in which no albuterol was used was significantly higher with fluticasone treatment than with beclomethasone (P=0.01 at endpoint). Albuterol use declined by 0.9 (26%) and 0.5 (16%) puffs/day in the low and moderate fluticasone treatment groups, respectively, whereas it was unchanged in the beclomethasone low-dose group and decreased by 0.3 (9%) puffs/day in the moderate-dose group. There were no significant differences noted in the analysis of nighttime awakenings. Significant drug effects were observed at endpoint in favor of fluticasone for asthma symptom scores (P=0.024) and in the percentage of days in which no symptoms were recorded (P=0.027).
Ferguson et al.[45] (1999)	DB, DD, RCT, PG Patients 4-12 years	N=442 22 weeks	Primary: Mean morning PEF during the last	Primary: The adjusted mean morning PEF, measured over the last 7 treatment days, were 271±82 and 259±75 L/min, for the fluticasone and budesonide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone 200 mcg BID via DPI vs budesonide 400 mcg BID via DPI	of age with a history of moderate to severe asthma who required moderate to high doses of ICS to control symptoms for at least 1 month preceding the start of the run in period		7 treatment days, obtained from the daily record cards assessed by analysis of covariance Secondary: Adverse events	treatment groups, respectively. The difference in means was 12 L/min (90% CI 6-19 L/min, P=0.002). For the purpose of this study, the two treatment regimens were considered to be equivalent if the 90% CI for the difference in mean morning PEFs for the last 7 days of the 20-week treatment period was within ± 15 L/min. The 90% upper and lower confidence limits for the treatment difference were 6 and 9 L/min, respectively, indicating that the treatments were not equivalent, with fluticasone showing improved outcomes. Secondary: There was no significant difference in the number of children who experienced an adverse event in the 2 treatment groups.
Fitzgerald et al.[46] (1998) Fluticasone 375 mcg BID vs budesonide 750 mcg BID	RCT, DB, XO Patients 5-16 years of age with persistent severe asthma (requiring 1,000-2,000 mcg/day of inhaled beclomethasone or budesonide continuously for symptom control over the previous 12 months)	N=30 12 weeks	Primary: Daily mean morning and evening PEF and day and night symptom scores Secondary: Physician/patient/ parent assessment of efficacy, total number of exacerbations requiring systemic steroids, adrenal function, growth, adverse events	Primary: There was no significant difference between the treatment groups PEF and symptoms scores. Secondary: There was no difference in physician or patient/parent assessment of efficacy with 90% rating both fluticasone and budesonide effective or very effective. The total number of exacerbations (fluticasone=33, budesonide=35) and those exacerbations requiring systemic steroids (fluticasone=9, budesonide=11) suggested no difference between the treatment groups. There were no significant differences in adjusted means for urinary free cortisol levels at 8 or 12 weeks, ACTH levels, or baseline and peak serum cortisol levels between the treatment phases. There was no significant treatment effect on growth which remained normal in either group. Most of the adverse events were related to exacerbations of asthma or upper respiratory tract infections in both groups. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to inhaled

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				corticosteroids between the treatment groups.
Condemi et al.[43] (1997) Fluticasone 250 mcg BID vs triamcinolone 200 mcg QID vs placebo	RCT, PC, DB, PG Patients ≥12 years of age with asthma (FEV_1 between 50-80 percent of predicted value) who had previously received maintenance therapy with beclomethasone or triamcinolone	N=291 24 weeks	Primary: Morning predose FEV_1, probability of remaining in the study over time, patient-measured morning peak expiratory flow (PEF), albuterol use, number of nighttime awakenings requiring albuterol, asthma symptom scores Secondary: Adverse events, morning plasma cortisol levels	Primary: Patients in both the fluticasone and triamcinolone groups experienced significant improvements in FEV_1 compared with the placebo group (-0.18 L for placebo, 0.07 for triamcinolone, 0.27 for fluticasone; $P \leq 0.001$). Only 27% of patients in the placebo group remained in the study over time compared with 66% in the fluticasone group and 55% in the triamcinolone group. Survival analysis suggested that patients in both active treatment groups had a significantly greater probability of remaining in the study over time than patients in the placebo group ($P<0.001$). There was no significant difference seen between the two active treatment groups. Significant differences in mean change in PEF between the triamcinolone and fluticasone groups were observed by week 1 and maintained throughout the treatment period ($P<0.05$). At endpoint, the mean increase over baseline values in patients who switched to fluticasone was 21 L/min compared with mean decreases of 6 L/min and 28 L/min in the triamcinolone and placebo groups, respectively ($P<0.001$). Patients treated with fluticasone had reduced albuterol use by 30% and those in the triamcinolone group by 6%. Patients in the placebo group increased their albuterol use by 50% ($P<0.05$). The number of nighttime awakenings requiring albuterol significantly decreased ($P \leq 0.001$ vs placebo) with either fluticasone (-0.03 SEM) or triamcinolone (-0.01 SEM). Nighttime awakenings increased after treatment with placebo (0.27 SEM; $P<0.05$). There were no significant differences between the treatment groups with respect to symptom scores. Secondary: A total of 13% of patients in the placebo group, 15% of the fluticasone group, and 8% of the triamcinolone group experienced at least one adverse event that was considered to be potentially related to treatment during the study (sore throat, oral candidiasis, hoarseness).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 1% of patients in the placebo group, 3% in the triamcinolone group, and 1% in the fluticasone group has morning plasma cortisol concentrations less than 5 mcg/ml.
Peters et al.[63] (2007) LOCSS Fluticasone-salmeterol 100/50 mcg QHS vs fluticasone 100 mcg BID vs montelukast 5-10 mg QD	DB, MC, RCT Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-bronchodilator, reversibility of airway obstruction by ≥12% with the use of a β-agonist or provocative concentration of methacholine producing a 20% decrease in FEV_1 of ≤8 mg/ml within the previous 2 years. Patients were stable on fluticasone 100 mcg BID and step-down therapy was being attempted.	N=500 16 weeks	Primary: Time to treatment failure Secondary: Measures of pulmonary function, measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients	Primary: The rates of treatment failure were 20.2% in the fluticasone group, 20.4% in the fluticasone/salmeterol group, and 30.3% in the montelukast group (HR, 1.6; 95% CI, 1.1 to 2.6; P=0.03 for both comparisons). Secondary: Mean prebronchodilator FEV_1 values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone/salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value; P=0.002 and P<0.001, respectively). Asthma control, as measured with the use of the Asthma Control Questionnaire, was better in the fluticasone group and in the fluticasone/salmeterol group than in the montelukast group. The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone/salmeterol group (22.9% vs. 17.1%, P=0.06) and in the fluticasone group (22.9% vs. 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone group than in the montelukast group (16.7% vs. 25.4%; P=0.04), with a similar trend in the fluticasone/salmeterol group (17.3%, vs. 25.4% in the montelukast group; P=0.06). The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6% to 85.8%.
Covar et al.[66] (2008) Fluticasone-salmeterol 100/50 mcg QAM and	DB, PC, PG, RCT Children 6 to 14 years of age with documented mild-moderate persistent	N=285 48 weeks	Primary: Regression modeling was used to look for factors predictive of exacerbation	Primary: Treatment with montelukast versus FP monotherapy (OR, 2.00; P=0.005) was a positive predictor for exacerbations.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 mcg QPM vs fluticasone 100 mcg BID vs montelukast 5mg QD	asthma			
Nguyen et al.[77] (2005) Fluticasone-salmeterol 100/50 to 250/50 mcg BID vs usual care (all patients received inhaled corticosteroids at some point during the study)	RCT, DB Patients 4-17 years of age with asthma, parent reported emergency room visits ≥5 in the past 2 years or 2-3 in the past 2 months, enrolled in Medicaid in Tennessee, Mississippi, or Arkansas	N=39 12 months	Primary: Number of emergency department visits and hospitalizations in minority inner-city children	Primary: There was a significant decrease in the number of emergency department visits per year in the study group compared to the control group (1.2 to 0.8, P=0.017). The risk of experiencing at least one hospitalization was reduced by 43% in the treatment group compared to placebo (risk ratio, 0.57; 95% CI, 0.19-1.71; P=0.31). The risk of experiencing an asthma exacerbation was reduced by 23% in the treatment group compared to placebo (P=0.09).
Strand et al.[78] (2004) Fluticasone-salmeterol 100/50 mcg BID vs fluticasone 100	RCT, DB, PG, MC Patients 23-54 years of age with persistent asthma who were using short acting bronchodilators one or more times per week for asthma for	N=150 24 weeks	Primary: Percentage of symptom free days and nights Secondary: Morning and evening PEF, daytime symptom score, nighttime	Primary: Statistically significant increase in percentage of symptom free days and nights in fluticasone/salmeterol group compared to fluticasone group (P=0.008). Secondary: Statistically significant improvement in morning PEF (P=0.0011) and evening PEF (P=0.011) in the fluticasone/salmeterol group compared to fluticasone group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg BID	symptom relief		symptom score, days and nights without symptoms, β-agonist use, episode free days and night, and asthma exacerbations	Statistically significant improvement in percentage of episode-free days and nights in the fluticasone/salmeterol group compared to fluticasone group (P=0.015). Statistically significant increase in percentage of days and nights without β-agonist use in the fluticasone/salmeterol group compared to fluticasone group (P<0.05). No statistically significant difference observed in asthma exacerbations between groups.
Bateman et al.[79] (2004) Fluticasone-salmeterol 100/50 mcg BID vs fluticasone 100 mcg BID NOTE: all patients were "stepped up" every 12 weeks until asthma totally controlled or highest dose reached (fluticasone-salmeterol 500/50 mcg BID or fluticasone 500 mcg BID)	RCT, DB, MC, PG Patients ≥12 years of age with asthma	N=3,421 12 months	Primary: Asthma control, symptoms, and rescue albuterol use Secondary: Dose of inhaled corticosteroid, exacerbations	Primary: In the fluticasone/salmeterol group, 71% of the patients achieved well-controlled asthma compared to 65% with the fluticasone group. Compared to fluticasone, individuals in the fluticasone/salmeterol group were significantly faster to achieve asthma control (P≤0.002). Secondary: At a lower corticosteroid dose with fluticasone/salmeterol, control was achieved more rapidly than fluticasone alone. There were a significantly lower amount of exacerbations requiring oral corticosteroids and or hospitalizations or emergency visits in the fluticasone/salmeterol group in each stratum (P≤0.009).
Bateman et al.[80] (2006)	RCT, DB, MC, PG Patients 12-80 years	N=484 12 weeks	Primary: Mean morning PEF	Primary: Patients in the fluticasone/salmeterol group maintained the improved PEF values achieved in the open-label treatment period compared to those in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone-salmeterol 100/50 mcg BID vs fluticasone 250 mcg BID NOTE: all patients were stabilized on fluticasone-salmeterol 250/50 mcg BID during open-label treatment for 12 weeks and were "stepping down" therapy	of age with asthma who were treated with only a β-agonist over the last 6 months, ≤10 pack year smoking history, FEV_1 of between 60-80% predicted value, demonstrated reversibility in lung function, combined daytime and nighttime symptom scores of ≥2 on ≥4 of the last 7 days of the run-in period and no exacerbations in the run-in period. Patients received 12 weeks of open-label fluticasone plus salmeterol 250/50 mcg BID before being randomized to the other treatment groups		Secondary: Asthma control, symptoms, and rescue albuterol use	the fluticasone group, whose PEF values decreased. The difference between the groups (63 L/min) was statistically significant (P<0.001). Secondary: Portion of patients with well controlled asthma remained higher in fluticasone/salmeterol group compared with the fluticasone group (no P value reported). The odds of a patient achieving total control of their asthma were 62% greater in fluticasone/salmeterol group compared to the fluticasone group (P=0.017). Statistically significant difference in daytime symptom score, daytime and nighttime rescue use, and percent symptom free and rescue-free days and nights seen in favor of fluticasone/salmeterol (P<0.05).
de Blic et al.[141] (2009) Fluticasone-salmeterol 100/50 mcg BID vs	RCT, DB, MC Patients 4-11years of age with asthma who were previously uncontrolled on a low dose inhaled ICS (equivalent to	N=321 12 weeks	Primary: Change in mean PEF, asthma control, percent rescue free days, percent symptom free days, nighttime awakenings	Primary: Change from baseline in mean morning PEF increased following both treatments, but was significantly greater in the fluticasone-salmeterol group compared with fluticasone (P=0.012). There was no significant difference in time to 'well controlled' asthma status between each group. Mean pre-bronchodilator maximal-expiratory flow at 50% vital capacity

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone 200 mcg BID	beclomethasone 400 mcg/day)			and percentage rescue-free days showed significantly greater improvements in the fluticasone-salmeterol group compared with fluticasone monotherapy. All other efficacy indices showed comparable improvements in each group.
Lundback et al.[85] (2006) Fluticasone-salmeterol 250/50 mcg BID vs fluticasone 250 mcg BID vs salmeterol 50 mcg BID	RCT, DB, PG Patients 18-70 years of age with mild to moderate asthma, symptoms at least twice per week, and at least one of the following: airway hyper-responsiveness, diurnal variability in PEF of ≥20% in >3 days during the last 14 days of the run-in, ≥30% difference between the highest and second highest PEF reading during any 7 days of the run-in, or reversible increase of ≥15% in FEV_1 or PEF after β-agonist administration	N=282 12 months	Primary: Number of patients requiring increase in study medication Secondary: Number of patients experiencing ≥2 asthma exacerbations during 12 months, clinic lung function tests (FEV_1 and FVC), airway hyper-responsiveness, and diary card data containing information on morning and evening PEF, rescue medication use, daytime and nighttime asthma symptom scores	Primary: Statistically significant lower percentage of patients in the fluticasone/salmeterol group required increase in study medication compared with fluticasone monotherapy and salmeterol monotherapy (P<0.001). Secondary: Statistically significant lower number of patients having ≥2 asthma exacerbations in fluticasone/salmeterol group compared to fluticasone monotherapy (P<0.01) and salmeterol monotherapy (P<0.001). Statistically significant improvement in morning PEF values in fluticasone/salmeterol group compared to fluticasone monotherapy and salmeterol monotherapy (P<0.001). Statistically significant improvement in FEV_1 (P<0.001) and FVC (P<0.05) from baseline in fluticasone/salmeterol group compared to salmeterol monotherapy. No statistically significant difference in FEV_1 or FVC from baseline in fluticasone/salmeterol group compared to fluticasone monotherapy (P value not reported). Statistically significant improvement in airway hyper-responsiveness in fluticasone/salmeterol group compared to fluticasone monotherapy (P<0.05) and salmeterol monotherapy (P<0.001). Statistically significant increase in symptom-free days in fluticasone/salmeterol group and fluticasone monotherapy group than in salmeterol monotherapy group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Statistically significant increase in symptom-free nights in the fluticasone/salmeterol group and fluticasone monotherapy group than in salmeterol monotherapy group (P<0.001). Statistically significant increase in rescue-medication-free days in fluticasone/salmeterol group and fluticasone monotherapy group compared to salmeterol group (P<0.05). Rescue-medication-free nights was 100% for all treatment groups.
Pearlman et al.[91] (2004) Fluticasone-salmeterol 44/21 mcg, 2 inhalations BID (HFA) vs fluticasone 44 mcg, 2 inhalations BID (CFC) vs salmeterol 21 mcg, 2 inhalations BID (CFC) vs placebo	RCT, DB, PG, PC Patients ≥12 years of age with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40%-85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration	N=360 12 weeks	Primary: Area under the curve (AUC) of the 12-hour serial FEV_1 relative to baseline, morning pre-dose FEV_1 at endpoint, and the probability of patients remaining in the study without being withdrawn for worsening of asthma Secondary: Morning and evening PEF, patient-rated asthma symptom scores, albuterol use, nighttime awakenings requiring albuterol, and Asthma Quality of Life Questionnaire	Primary: At week 12, the average percent change in serial FEV_1 compared to baseline was significantly greater for fluticasone plus salmeterol HFA compared to fluticasone CFC, salmeterol CFC, and placebo (P≤0.007). The AUC of the 12-hour serial FEV_1 was significantly higher on day 1 (baseline) and week 12 for the fluticasone plus salmeterol HFA group compared to the fluticasone CFC group and the placebo group (P<0.001) and at week 12 only for the salmeterol CFC group (P=0.006). There was a significant improvement in morning pre-dose FEV_1 from baseline in the fluticasone plus salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC, and placebo groups (P≤0.0112). There were significantly fewer patients withdrawn due to worsening of asthma in the fluticasone plus salmeterol group compared to the salmeterol CFC group and the placebo group (P<0.001). The difference was not significant when comparing the fluticasone plus salmeterol HFA group and the fluticasone CFC group (P value not reported). Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone plus salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC, and placebo groups (P≤0.006). There was a significantly greater percentage of day without asthma symptoms in the fluticasone plus salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC, and placebo groups (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(AQLQ) scores	There was a significant decrease in nighttime awakenings in patients in the fluticasone plus salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC, and placebo groups (P≤0.007). There was a significant reduction in the need for albuterol in the fluticasone plus salmeterol HFA group compared to fluticasone CFC, salmeterol CFC, and placebo groups (P≤0.002). There were no results reported for Asthma Quality of Life Questionnaire scores.
Nathan et al.[92] (2006) Fluticasone-salmeterol 110/21 mcg, 2 inhalations BID (HFA) vs fluticasone 110 mcg, 2 inhalations BID (CFC) vs salmeterol 21 mcg, 2 inhalations BID (CFC) vs placebo	RCT, DB, PC, PG Patients ≥12 years of age with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40%-85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration, history of inhaled corticosteroid ≥3 months with no change in regimen for at least one month prior to screening	N=365 12 weeks	Primary: Area under the curve (AUC) of the 12-hour serial FEV_1 relative to baseline, morning pre-dose FEV_1 at endpoint, and the probability of patients remaining in the study without being withdrawn for worsening of asthma Secondary: Morning and evening PEF, asthma symptom scores, albuterol use, nighttime awakenings requiring albuterol use	Primary: The AUC of the 12-hour serial FEV_1 was significantly higher on day 1 (baseline) and week 12 for the fluticasone-salmeterol HFA group compared to the fluticasone CFC group and the placebo group (P<0.001) and at week 12 when compared to the salmeterol CFC group (P≤0.020). There was a significantly greater improvement in morning pre-dose FEV_1 at endpoint in the fluticasone-salmeterol HFA group compared to the improvements seed in the fluticasone CFC and salmeterol CFC groups (P≤0.001). There was a significant decrease in morning pre-dose FEV_1 in patients in the placebo group (P≤0.001). Significantly fewer patients in the fluticasone-salmeterol HFA group withdrew due to worsening of asthma compared to the salmeterol CFC and placebo groups (P<0.001). The difference was not significant when comparing fluticasone-salmeterol HFA group and the fluticasone CFC group. Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone-salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC, and placebo groups (P≤0.001). There was a significant improvement in asthma symptom scores in the fluticasone-salmeterol HFA group compared to placebo (P<0.001), but the difference when compared to the fluticasone CFC and the salmeterol CFC

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups was not significant. There was a significant increase in the proportion of days with no asthma symptoms in the fluticasone-salmeterol HFA group compared to placebo (P<0.001), but the difference when compared to the fluticasone CFC and the salmeterol CFC groups was not significant. The number of nighttime awakenings decreased in the fluticasone-salmeterol HFA group and increased in the fluticasone CFC, salmeterol CFC, and placebo groups, but only the difference between the fluticasone-salmeterol HFA and placebo groups was statistically significant (P<0.001). There was a significant reduction in the need for albuterol use in the fluticasone-salmeterol HFA group compared to the fluticasone CFC and placebo groups (P≤0.005), but there was no significant difference when compared to the salmeterol CFC group.
Nelson et al.[93] (2003) Fluticasone-salmeterol 88/42 mcg (HFA) vs fluticasone 88 mcg (CFC) vs salmeterol 42 mcg (CFC)	RCT, DB, PG MC Patients diagnosed with asthma	N=283 12 weeks	Primary: Are under the FEV_1 curve relative to baseline	Primary: Morning pre-dose FEV_1 was significantly improved in the fluticasone plus salmeterol HFA group compared to the fluticasone CFC and salmeterol CFC groups (P≤0.016). Fewer patients in the fluticasone plus salmeterol HFA group withdrew due to worsening of asthma compared to the fluticasone CFC and salmeterol CFC groups (P=0.024). Morning and evening PEF values were significantly increased in the fluticasone plus salmeterol HFA group compared to the fluticasone CFC and salmeterol CFC groups at endpoint (P≤0.002).
Bateman et al.[94] (2001) Fluticasone-	RCT, DB, DD, PG Patients 12 years of age and older with	N=497 12 weeks	Primary: Mean morning PEF	Primary: Mean morning PEF values were equivalent between the fluticasone-salmeterol HFA and DPI groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50/25 mcg, 2 inhalations BID (HFA) vs fluticasone-salmeterol 100/50 mcg, 1 inhalation BID (DPI) vs fluticasone 50 mcg, 2 inhalations BID (CFC)	diagnosis of reversible airway obstruction, smoking history of <10 pack-years, using inhaled corticosteroids (beclomethasone, budesonide, or flunisolide at a dose of 400 mcg-500 mcg per day or fluticasone 200 mcg-250 mcg per day) for at least 4 weeks prior to randomization, mean morning PEF 50%-85% of value measured after albuterol during the last 7 days of the run-in period, symptomatic for the last 7 days of the run-in period, and be taking albuterol ≤800 mcg per day, and FEV_1 >50% of predicted value		Secondary: Evening PEF, daytime and nighttime symptom scores, albuterol use, clinic FEV_1 values	There was a significant improvement in mean morning PEF values in the fluticasone-salmeterol HFA group compared to the fluticasone CFC group (P<0.001). Comparisons were not made between the fluticasone-salmeterol DPI and the fluticasone CFC groups. Secondary: Mean evening PEF improved in all 3 groups compared to baseline. The greatest improvements were seen in the fluticasone-salmeterol HFA and DPI groups, and the difference was significant in the fluticasone-salmeterol HFA group compared to the fluticasone CFC group (P<0.001). The number of symptom free days and nights increased in all 3 treatment groups. The proportion of symptom free days and nights were similar in the fluticasone-salmeterol HFA and CPI groups. The fluticasone-salmeterol HFA group reported significantly more symptom free days compared to the fluticasone CFC group (P=0.001). The fluticasone-salmeterol HFA group reported more symptom free nights compared to the fluticasone CFC group, but this difference was not significant (P=0.063). The increase in albuterol free days and nights was similar in the fluticasone-salmeterol HFA and DPI groups. The increase in albuterol free days and nights was significantly higher in the fluticasone-salmeterol HFA group compared to the fluticasone CFC group (P<0.033) for every assessment period except for weeks 5-8 (P=0.093). Clinic FEV_1 values improved in all 3 treatment groups and the differences between groups was not significant.
Gappa et al.[160] (2009) Fluticasone 200 mcg BID	RCT, DB, MC, PG Patients 6-14 years of age with persistent asthma	N=283 8 weeks	Primary: Change in mean morning PEF, asthma symptom scores, number of	Primary: Mean increase in morning PEF was 30.4 L/min in SFC group and 16.7 L/min in fluticasone group. The mean improvement from baseline in morning PEF was significantly larger after SFC (+8.6 L/min, 95% CI, 1.3 to infinity).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs salmeterol-fluticasone 50/100 mcg BID (SFC)	uncontrolled by standard ICS doses		days without asthma symptoms, use of rescue albuterol, asthma control, and exacerbations	Patients in the SFC group experienced more days without asthma symptoms (8.7%; 95% CI, 1.2 to 16.3) and more days without albuterol use (8.0%; 95% CI, 0.6-15.3) than patients receiving fluticasone. Good asthma control was achieved for a longer period in SFC group (3.4 weeks) than in the fluticasone group (2.7; P=0.02). Asthma exacerbations were recorded in 3 and 6 patients receiving SFC and fluticasone, respectively. Both treatments were generally well tolerated. Serious adverse events were reported in 2 and 1 patients in the SFC and fluticasone groups, respectively.
Maspero et al.[138] (2008) Fluticasone-salmeterol 100/50 mcg, 1 inhalation BID vs montelukast 5 mg QD	DB, AC, RCT Patients 6 to 14 years of age with asthma for at least 6 months	N=548 12 weeks	Primary: Change from baseline in morning PEF Secondary: Tolerability was assessed by recording adverse events and asthma exacerbations	Primary: The mean changes from baseline in morning PEF was 45.8 ± 2.82 L/min with salmeterol/fluticasone and 28.7 ± 2.86 L/min with montelukast (treatment difference 17.16 L/min; P<0.001). Secondary: Both treatments were well tolerated with a similar number of patients reporting adverse events (155/281 [55%] in the salmeterol/fluticasone group; 153/267 [57%] in the montelukast group). The mean exacerbation rates over 12 weeks were 0.12 in the salmeterol/fluticasone group and 0.30 in the montelukast group (P<0.001).
Sorkness et al.[103] (2007) Fluticasone-salmeterol 100/50 mcg QAM and salmeterol 50 mcg QPM (PACT combination) vs	DB, PG, RCT Patients 6 to 14 years of age with mild to moderate asthma, >4 hour post-bronchodilator FEV_1 ≥80% of predicted normal and ≥70% at randomization plus	N=285 48 weeks	Primary: Percent of asthma control days; use of oral corticosteroids; use of non-study asthma medications; daytime symptoms; nighttime	Primary Percent of asthma control days averaged 64.2% for fluticasone monotherapy, 59.6% for PACT combination, and 52.5% for montelukast monotherapy. The fluticasone monotherapy group gained an average of 42 asthma control days per year compared with the montelukast monotherapy group (P=0.004). The change in asthma control days from baseline to end of treatment was significantly greater for fluticasone monotherapy vs montelukast, and PACT combination vs montelukast, but not for fluticasone monotherapy vs PACT combination. During the 48 weeks, the percentages of patients who achieved 20% more

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fluticasone 100 mcg BID (fluticasone monotherapy) vs montelukast 5 mg QPM (montelukast monotherapy)	methacholine FEV_1 ≤12.5 mg/ml		awakenings; unscheduled health care visits; ED visits, or hospitalizations for asthma; and school absenteeism for asthma. Secondary: Percent of episode-free days; number of exacerbations requiring prednisone; time to first exacerbation requiring prednisone; time to treatment failure; Asthma Control Questionnaire (ACQ); pulmonary function and growth	asthma control days during the treatment period compared with the run-in period were 65% for fluticasone monotherapy, 66% for PACT combination, and 50% for montelukast. The number needed to treat for both fluticasone monotherapy and PACT combination compared with montelukast was approximately 6.5, meaning that 7 patients would need to be treated with fluticasone monotherapy or PACT combination instead of montelukast to achieve 1 additional treatment response defined as a 20% increase in asthma control days. Secondary: Compared with montelukast monotherapy, both fluticasone monotherapy and PACT combination led to a greater percentage of episode-free days. Significant superiority of fluticasone vs montelukast monotherapies (in favor of the former) for time to first prednisone burst (P=0.002) and time to treatment failure (P=0.015) but no differences for PACT combination vs montelukast. Twenty-eight treatment failures occurred, 5 with fluticasone, 8 with PACT combination, and 15 with montelukast, with the comparison for fluticasone versus montelukast monotherapies significant (P=0.04). No significant difference between fluticasone monotherapy vs PACT combination, or PACT combination vs montelukast in regard to ACQ score improvement, there was a significant difference with fluticasone compared with montelukast (P=0.018). Prebronchodilator FEV_1 (% predicted) and FEV_1/FVC (%) increased more with fluticasone monotherapy than montelukast (P<0.001 for both measures) and PACT combination (P=0.01 for FEV_1). Treatment with montelukast did not improve these lung function measures. The mean change in FEV_1 % predicted from baseline was 6.32% with fluticasone monotherapy and 3.62% with PACT combination (P=0.06 for difference). For FEV_1/FVC, the mean change from baseline was 3.95% for fluticasone monotherapy, compared with 1.76% for PACT combination (P=0.015 for difference). Change in bronchodilator response at 36 weeks compared with baseline was a mean decrease of 3.6% with fluticasone

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				monotherapy, compared with a 0.3% increase with PACT combination and a 1.69% increase with montelukast (P<0.001, fluticasone vs montelukast). For the participant-measured outcome of percent predicted prebronchodilator AM and PM PEFs, fluticasone monotherapy and PACT combination resulted in comparable increases in mean change from baseline (5.1% and 5.4%, respectively, for AM recordings, and 2.9% and 4.3%, respectively, for PM recordings). Montelukast treatment did not significantly improve PEFs. Both fluticasone and PACT combination were significantly superior to montelukast for change from baseline in both PEF measurements. Mean increase in height from baseline over 48 weeks was 5.3 ± 1.8 cm with fluticasone monotherapy, 5.3 ± 1.5 cm with PACT combination, and 5.7 ± 2.0 cm with montelukast monotherapy). Differences among the therapies in this outcome were about 0.4 to 0.46 cm less for fluticasone monotherapy and PACT combination compared with montelukast monotherapy respectively, but of no statistical significance.
Ringdal et al.[89] (2003) Fluticasone-salmeterol 100/50 mcg BID plus oral placebo vs fluticasone 100 mcg BID and montelukast 10 mg QD	RCT, DB, PG, MC Patients 14-79 years of age with asthma, history of receiving inhaled corticosteroids for at least 4 weeks prior to randomization, reversible airway obstruction, ≥15% increase in FEV_1 after β-agonist use, mean morning PEF between 50-85% predicted value (predicted value	N=806 14 weeks	Primary: Mean morning PEF value Secondary: Evening PEF values, β-agonist use, daytime and nighttime symptom scores, changes in asthma medications, FEV_1, incidence and severity of asthma exacerbations, patient assessment of satisfaction with treatment, and	Primary: Statistically significant improvement in morning PEF values in fluticasone/salmeterol group compared to the fluticasone and montelukast group (361 L/min vs 191 L/min, P<0.05). Secondary: Statistically significant improvement in FEV_1 values in fluticasone/salmeterol group compared to the fluticasone and montelukast group (mean treatment difference 0.11 l, P<0.05). Fluticasone/salmeterol group significantly more likely to have a symptom-free day compared to fluticasone and montelukast group (odds ration 1.32; 95% CI 1.05-1.65; P<0.05). Fluticasone/salmeterol group significantly more likely to have a rescue free day compared to fluticasone and montelukast group (odds ratio 1.29; 95% CI 1.02-1.63; P=0.03), but rescue-free nights did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	was that obtained after β-agonist administration in clinic), cumulative symptom score of ≥8 during last 7 days of run-in period, and symptoms on at least 4 of last 7 days of run-in		physician assessment of effectiveness of treatment	Significantly lower number of patients in the fluticasone/salmeterol group had an asthma exacerbation compared to the fluticasone and montelukast group (9.6% vs 14.6%; P<0.05), but no significant difference between groups in percentage of patients having moderate or severe asthma exacerbation (P=0.07). Time to first exacerbation longer in the fluticasone/salmeterol group compared to the fluticasone and montelukast group (P<0.05). Patient and physician satisfaction and assessment of treatment higher in fluticasone/salmeterol group compared to the fluticasone and montelukast group (P<0.05).
You-Ning et al.[95] (2005) Fluticasone-salmeterol 125/25 mcg, 2 inhalations BID (HFA) vs fluticasone-salmeterol 250/50 mcg, 1 inhalation BID (DPI)	RCT, OL, PG, MC Patients 18-70 years of age with asthma, receiving stable doses of budesonide or beclomethasone up to 1200 mcg per day or fluticasone up to 600 mcg per day for at least 1 month, or required therapy with inhaled corticosteroids, total score of ≥8 for daytime and nighttime symptoms, and ≥15% reversibility and 200 ML elevation in FEV_1 following albuterol administration	N=270 4 weeks	Primary: Morning PEF Secondary: Rescue medication use, daytime and nighttime symptom scores, evening PEF, FEV_1, and patient self-evaluation of efficacy	Primary: Morning PEF improved significantly in both the fluticasone-salmeterol HFA and DIP groups compared to baseline (P<0.05), but the differences between groups was not significant (P>0.05). Secondary: All secondary endpoint improved significantly compared to baseline in both the fluticasone-salmeterol HFA and DPI groups (P<0.05), but the difference between groups was not significant for any secondary endpoint (P>0.05). Patient self-evaluation of efficacy at visit 3 which was significantly higher in the DPI group compared to the HFA group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chapman et al.[86] (1999) Fluticasone-salmeterol 250/50 mcg BID (fixed-dose inhaler) vs fluticasone 250 mcg and salmeterol 50 mcg BID (separate inhalers)	RCT, DB, DD Individuals between the ages of 13 to 75 years with symptomatic asthma	N=371 28 weeks	Primary: Change in PEFR	Primary: PEFR was 43 L/min for the fixed-dose combination group and 36 L/min for the concurrent therapy group (difference: 6 L/Min; 95% CI, -13 to 0 L/min; P=0.114). Secondary: A total of 35% of patients in the fixed-dose combination group had a mean daytime symptom score of 0 compared to 31% of patients receiving concurrent therapy. No statistically significant difference in FEV_1 between combination and concurrent therapy groups was noticed.
Nelson et al.[87] (2003) Fluticasone-salmeterol 100/50 to 500/50 mcg BID vs fluticasone 100 to 500 mcg BID and salmeterol 50 mcg BID	MA Patients ≥4 years of age with asthma	N=1,375 (4 trials) 12 weeks	Primary: Change from baseline in mean PEF over 12 weeks Secondary: Mean change in evening PEF and clinic FEV_1 median percentage of days, nights, or both symptom and rescue inhaler free	Primary: A significant advantage (5.4 L/min) was seen for PEF in the fixed-dose combination therapy over the 12 week treatment period (P=0.006). Secondary: There was a difference in favor of the fixed-dose combination therapy in the mean difference in FEV_1 (40 mL) compared to concurrent therapy (P=0.054). The difference was statistically significant (6.11 L/min) in the mean evening PEF in favor of the fixed-dose combination product (P<0.001). There was no significant difference seen in the percentage of symptom-free and/or rescue inhaler free days and nights (P=0.165-0.635).
Lötvall et al.[110] (2006) <u>Study A</u> Fluticasone-salmeterol 100/50 mcg as a single dose	Study A: DB, PC, RT, SC, 3-way XO Study B: DB, MC, RT, XO Patients ≥18 years of age with asthma	<u>Study A</u> N=33 3 weeks <u>Study B</u> N=75 12 weeks	<u>Study A</u> Primary: Mean change from predose FEV_1 to 16 hours postdose Secondary: Mean change in FEV_1 from predose	<u>Study A:</u> Primary: Patients in both the fluticasone-salmeterol and budesonide-formoterol groups had statistically significant greater FEV_1 values at 16 hours postdose in comparison to those in the placebo group (-0.5 L difference; P<0.001). There was no statistically significant difference in FEV_1 values at 16 hours postdose between the active treatment groups (P=0.617).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide-formoterol 160/4.5 mcg as a single dose vs placebo Study B Fluticasone-salmeterol 100/50 mcg, 1 inhalation BID vs budesonide-formoterol 160/4.5 mcg, 1 inhalation BID	for ≥6 months, prebronchodilator FEV_1 of >50% predicted of normal, FEV_1 ≥15% of predicted value 15 min after receiving 400 mcg salbutamol. In Study A, patients were receiving budesonide 400-1,200 mcg (or equivalent) at least 4 weeks prior to study. In Study B, patients were receiving budesonide or beclomethasone 800-1,200 mcg/day or fluticasone 400-600 mcg/day for at least 4 weeks prior to study		over 24 hours postdose Study B Primary: Slope of decline in FEV_1 from 2 hours postdose, area under FEV_1 curve, mean change from predose FEV_1 at 12 hours postdose Secondary: Serial FEV_1 measurements following single dose after 4 weeks treatment	Secondary: Patients in both the fluticasone-salmeterol and budesonide-formoterol groups had a statistically significant mean change in FEV_1 at each scheduled evaluation compared to those in the placebo group. There was no statistically significant difference in mean change of FEV_1 between the active treatment groups. Study B: There were no statistically significant differences between the fluticasone-salmeterol and budesonide-formoterol groups in regards to all primary endpoints. Secondary: There was no statistically significant difference in mean FEV_1 from baseline or FEV_1 from predose over 24 hours after 4 weeks treatment between the active treatment groups.
Dahl et al.[115] (2006) Fluticasone-salmeterol 250/50 mcg, 1 inhalation BID vs budesonide-formoterol 200/6	DB, MC, PG, RCT Patients with persistent asthma, currently receiving 1,000-2,000 mcg/day of ICS, FEV_1 reversibility of ≥12% (and ≥200 mL), 15 min after salbutamol† 200-400 mcg, and an	N=1,391 24 weeks	Primary: Rate of exacerbations Secondary: Lung function, asthma symptoms, use of rescue medications, adverse events	Primary: There were no statistically significant differences in mean rate of exacerbations over 24 weeks, or severity of exacerbations observed between treatment groups. The adjusted mean rates of moderate/severe exacerbations per year calculated at weeks 1-24, 1-8, and 9-16 were similar between treatment groups (P=NS). The adjusted mean rate of moderate/severe exacerbations per year calculated at weeks 17-24 of fluticasone-salmeterol was lower than budesonide-formoterol (P=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg, 2 inhalations BID	asthma symptom score of at least 2 on at least 4 of the last 7 evaluable days of the run-in period			Secondary: There were no statistically significant differences in morning and evening PEF, asthma symptoms, symptom-free days, symptom-free nights, rescue medication usage, asthma control, and incidence and types of adverse events observed between treatment groups.
Ringdal et al.[116] (2002) EDICT Fluticasone-salmeterol 250/50 mcg, 1 inhalation BID vs budesonide 800 mcg and formoterol 12 mcg, 1 inhalation BID	DB, DD, PG, RCT Patients 16-75 years of age with clinical history of reversible airway obstruction, symptomatic on 1,000-1,600 mcg/day of budesonide, BDP, or flunisolide, or 500-800 mcg/day of fluticasone, FEV_1 50%-85%, increased symptom scores or reliever use	N=428 12 weeks	Primary: Mean morning PEF (during week 12 of treatment) Secondary: Morning and evening PEF, day and nighttime symptom scores, nighttime awakenings, FEV_1, rate and severity of exacerbations, use of rescue medication, withdrawals from study	Primary: Patients in the per-protocol population had an increase in mean morning PEF of 343 L/min to 386 L/min with fluticasone-salmeterol treatment compared to an increase of 348 L/min to 389 L/min observed with budesonide-formoterol treatment (-3.2 L/min mean difference; 95% CI, –15.0 to 8.6; P=0.593). Similar results in mean morning PEF were seen in the intent to treat population for both treatment groups. Secondary: The mean rate of exacerbation per patient per 84 days of treatment was significantly lower in those in the fluticasone-salmeterol group in comparison to the budesonide-formoterol treatment group with a risk reduction of 36% (0.472 vs 0.735, respectively; 95% CI, 0.51 to 0.80; P<0.001). Over the entire treatment period, patients in the fluticasone-salmeterol treatment group had a greater percentage of nights with no awakenings, without symptoms, and a symptom score of <2 in comparison to those in the budesonide-formoterol treatment group (P=0.02, P=0.04, and P=0.03, respectively). There was no significant difference in morning and evening PEF, clinic-measured FEV_1, improvement in day-time symptoms, and use of relief medication (salbutamol) between the two treatment groups.
Marceau et al.[88] (2006) Fluticasone-salmeterol or	RETRO Patients 16-44 years of age who had not been on	N=5,118 1 year	Primary: Number of prescription renewals during the first year of	Primary: An estimation of 44.2% of patients started on a combination therapy and 51.5% of patients started on concurrent therapy did not renew their prescription during the first year of treatment (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide-formoterol (fixed-dose inhaler) vs combination of inhaled corticosteroid (fluticasone, budesonide, or beclomethasone) and a long-acting inhaled β_2-agonist (salmeterol or formoterol)	combination or concurrent inhaled corticosteroid (ICS) and long-acting β_2-agonist therapy within the past year		treatment Secondary: The rate of moderate to severe asthma exacerbations (defined as a filled prescription of an ICS, an emergency department (ED) visits or hospitalization for asthma) during the first year of treatment, and weekly number of doses of short-acting inhaled β_2-agonists	The number of prescriptions filled on average during the first year after treatment initiation was 3.5 for combination therapy and 2.7 for concurrent therapy (P value not reported). Secondary: Concurrent users had more exacerbations (1.1 vs, 0.7; P<0.0001) ED visits (0.4 vs 0.2; P<0.0001), hospitalizations (0.03 vs 0.01; P=0.78), and mean number of doses per week of short-acting inhaled β_2-agonists (7.0 vs 5.7; P<0.0001) compared to combination users.
Fish et al.[54] (2000) Mometasone 400 to 800 mcg BID vs placebo	RCT, PC, MC Patients with severe persistent, oral corticosteroid-dependent asthma	N=132 12 weeks, followed by 9 month open-label phase	Primary: percentage change in daily oral corticosteroid (OCS): prednisone requirement Secondary: spirometric measurements (FEV_1, FVC, forced expiratory flow, midexpiratory phase), morning and evening peak expiratory flow	Primary: OCS requirements were reduced by 46.0% for the mometasone 400 mcg BID group and 23.9% for mometasone 800 mcg BID group compared with the placebo group that had an increase in OCS requirements by 164.4% (P<0.01). OCS requirements were eliminated in 40%, 37%, and 0% of the patients after 12 weeks and 71%, 62%, and 58% at the end of the 9 month open-label phase in the mometasone 400 mcg and 800 mcg BID and placebo groups, respectively. Secondary: Nocturnal awakenings fell by 57% and 66% in the mometasone 400 and 800 mcg bid groups, respectively and increased by 62% in the placebo group (P<0.01). Daily rescue medication use was significantly reduced in the mometasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(PEF), rescue albuterol use, asthma symptom scores, number of nocturnal awakenings caused by asthma that required albuterol use, and general and asthma-specific quality-of-life measures	400 mcg group (P<0.01), but not in the mometasone 800 mcg group when compared with placebo. All other secondary endpoints did not exhibit any statistically differences between the active treatment groups.
Schmier et al.[57] (2003) Mometasone 400 to 800 mcg BID vs placebo	RCT, DB, PC, MC Patients with severe persistent asthma previously maintained on oral steroids	N=132 12 weeks, followed by a 9 month open-label extension	Primary: Corticosteroid use, Marks Asthma Quality of Life Questionnaire (AQLQ-M)	Primary: Mometasone treated patients had a reduction in oral steroids requirement and a significant improvement in the SF-36 physical component summary score and the physical function subscale (p<0.05) compared with placebo. Mometasone treated patients also showed a significant improvement in each of the four subscales of the AQLQ-M (p<0.05).
Bernstein et al.[37] (1999) Mometasone 100 mcg BID vs mometasone 200 mcg BID vs mometasone 400 mcg BID	MC, RCT, DB, DD Patients with asthma previously being treated with inhaled corticosteroids	N=365 12 weeks	Primary: Mean change from baseline to endpoint for FEV_1 Secondary: FVC, $FEF_{25\%-75\%}$, PEFR, patient evaluation of asthma symptoms, physician evaluation of asthma symptoms	Primary: The difference in FEV_1, FVC, $FEF_{25\%-75\%}$, and PEFR from baseline was significantly greater in all the active treatment groups compared with placebo (P<0.01). Mometasone 200 mcg bid group showed greater improvement than mometasone 100 mcg bid group, with the mometasone 400 mcg bid group showing no additional benefit. Secondary: Changes in lung function from baseline for mometasone 100 mcg bid and beclomethasone 168 mcg bid groups were similar. Asthma symptoms as evaluated subjectively by patients and physicians were similarly improved for the mometasone 200 (P<0.01) and 400 (P=0.05) mcg bid groups, which were slightly better than that of the mometasone 100 mcg bid (P=0.01) and beclomethasone 168 mcg bid (P=0.02) groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs beclomethasone 168 mcg BID vs placebo				
Nathan et al.[47] (2001) Mometasone 100 mcg BID vs mometasone 200 mcg BID vs beclomethasone 168 mcg BID vs placebo	RCT, DB, DD, PC, MC Patients with moderate persistent asthma previously maintained on inhaled corticosteroids	N=227 12 weeks	Primary: Changes in FEV_1 Secondary: PEFR, asthma symptoms, nocturnal awakenings, albuterol use	Primary: FEV_1 significantly improved for all three active treatment groups compared with placebo (P<0.01). There was no statistical significant difference in FEV_1 between the treatment groups mometasone 200 and beclomethasone (P=0.07) or mometasone 200mcg and mometasone 100 mcg (P=0.08). Secondary: Improvement in FEV_1, PEFR, asthma symptoms, nocturnal awakenings, and albuterol use were approximately twice as large for the mometasone 200 group as the response for mometasone 100 mcg and beclomethasone group, but did not reach statistical significance.
Bousquet et al.[40] (2000) Mometasone 100 to 400 mcg BID vs budesonide 400 mcg BID	MC, RCT, DB Patients with moderate persistent asthma previously maintained on daily inhaled corticosteroids	N=730 12 weeks	Primary: Mean change from baseline to endpoint in forced expiratory volume in one second (FEV_1) Secondary: Self-rated asthma	Primary: FEV_1 was significantly improved in the mometasone 200 and 400 mcg bid treatment group compared with the budesonide 400 mcg bid treatment group (P<0.05). Secondary: The a.m. wheezing scores were significantly improved in the mometasone 400 mcg bid group compared with the budesonide 400 mcg bid group or mometasone 100 mcg bid group (P values not provided).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use, physician evaluation of response to therapy	Patients treated with mometasone 200 and 400 mcg bid required significantly less albuterol than did patients treated with budesonide 400 mcg bid. Physicians reported a significant improvement in asthma symptoms scores in the mometasone 400 and 200 mcg bid group compared with budesonide group (63% and 65% vs 50%, P values not provided).
Corren et al.[44] (2003) Mometasone 440 mcg QD vs budesonide 400 mcg QD vs placebo	RCT, DB, DD, PC, MC Patients with moderate persistent asthma previously using twice daily inhaled corticosteroids	N=262 8 weeks	Primary: Percent change in FEV_1 from baseline to endpoint Secondary: Morning and evening peak expiratory flow rates (PEFR), FVC, forced expiratory flow $FEF_{25\%-75\%}$, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy, asthma symptom scores	Primary: The percent change in FEV_1 was significantly greater in the mometasone group compared with the budesonide group (P<0.01) and placebo group (P<0.001). Secondary: Pulmonary function ($FEF_{25\%-75\%}$, FVC), evening asthma symptoms scores, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were significantly improved in the mometasone group compared with both the budesonide and placebo groups (P<0.05).
O'Connor et al.[49] (2001)	RCT, DB, PG, MC Patients with	N=733 12 weeks	Primary: Change in FEV_1	Primary: At study endpoint, all treatment groups showed improvement in FEV_1. No statistical difference was observed between the mometasone 200, 400, or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mometasone 100 to 400 mcg BID vs fluticasone 250 mcg BID	moderate persistent asthma previously treated with inhaled corticosteroids		Secondary: Mean changes from baseline in PEFR, $FEF_{25\%-75\%}$, FVC, asthma symptom scores, albuterol use, nocturnal awakenings due to asthma, and physician-evaluation of response to therapy	fluticasone group. The mometasone 400 mcg BID group showed significant improvement in FEV_1 compared with the mometasone 100 mcg BID group (P=0.02). Mometasone 200 mcg BID and fluticasone groups showed similar improvements in FEV_1. Secondary: $FEF_{25\%-75\%}$ and PEFR were significantly improved in the mometasone 200 mcg BID, 400 mcg BID, and fluticasone groups compared with the mometasone 100 mcg BID group. All other results showed no significant differences between the treatment groups.
Wardlaw et al.[52] (2004) Mometasone 400 mcg every evening vs fluticasone 250 mcg BID	RCT, OL, PG Patients with moderate persistent asthma previously using fluticasone	N=167 8 weeks	Primary: Percent change in FEV_1 from baseline to endpoint Secondary: FVC, PEFR, asthma symptom scores, albuterol use, and device evaluation	Primary: No significant difference in the percent change in FEV_1 (P≥0.14) was observed between treatment groups at any point in the study (2, 4, and 8 weeks of treatment). Secondary: No significant difference in the percent change in FVC (P≥0.24), PEFR (P=0.60), albuterol use or asthma symptom scores (P≥0.06) was observed between treatment groups at any point in the study (2, 4, and 8 weeks of treatment). There was a greater number of subjects that showed improvement in their asthma symptoms in the mometasone group compared with the fluticasone group (P=0.007) as reported by physicians' evaluations of response to therapy. A significantly greater number of subjects reported having "liked the inhaler a lot" in the mometasone group versus the fluticasone group (P=0.01).
Weinstein et al.[157] (2010) Mometasone-formoterol 200/10	RCT, DB, MC, PG Patients ≥12 years of age with asthma for ≥12 months,	N=728 12 weeks	Primary: Mean change from baseline to week 12 in FEV_1 area under the curve	Primary: There were significant improvements in FEV_1 AUC_{0-12h} for both MF/F doses compared to MF (P<0.001). Treatment with MF/F 400/10 mcg produced greater changes in FEV_1 AUC_{0-12h} than did MF/F 200/10 mcg treatment across all time points; however, this was not significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 400/10 mcg BID (MF/F) vs mometasone 400 mcg BID (MF)	history of asthma deterioration within the preceding 2–12 months requiring treatment with oral corticosteroids, receiving a high daily dose of ICS (beclomethasone >1,000 mcg or equivalent) with or without a LABA for ≥12 weeks, and on a stable asthma treatment regimen for ≥2 weeks. Patients also had to have FEV_1 of 50–85% of predicted, as well as ≥12% and ≥200 ml of FEV_1 β_2-reversibility 15–20 minutes after 4 inhalations of albuterol, or ≥20% diurnal variation of PEF between morning predose PEF and postdose PEF from the previous evening		measured by serial spirometry over 12 hours (AUC_{0-12h}) Secondary: Change in the Asthma Control Questionnaire (ACQ) total score, change in the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) total score, change in the proportion of nocturnal awakenings requiring SABA rescue medication, predose FEV_1, changes in AM and PM PEF, and number of severe asthma exacerbations	(P=0.096). Secondary: Trough FEV_1 values showed significant improvement with MF/F 400/10 mcg over MF 400 mcg at week 12 (P=0.006) and at all other time points (P=0.04). MF/F 200/10 mcg was significantly better than MF 400 mcg only at week 4 (P=0.027). Compared with the MF group, both MF/F groups demonstrated significant improvement in predose AM PEF (P=0.003). Improvements in PM PEF were significantly greater for MF/F groups versus the MF group (P=0.004). Daily total rescue medication use decreased more with MF/F 400/10 mcg than MF (P=0.043). Treatment with MF/F 200/10 mcg was significantly better than MF (P=0.019). Compared with MF alone, both doses of MF/F reduced the proportion of nights in which patients experienced nocturnal awakenings requiring SABA rescue medication (P<0.006). Both doses of MF/F reduced mean total asthma symptom scores more than MF alone (P<0.001). Patients in the MF/F 200/10 mcg treatment group had significantly fewer asthma deteriorations compared with the MF group (P=0.038). The difference between MF/F 400/10 mcg and MF groups was only marginally statistically significant (P=0.053). A combined analysis of MF/F 400/10 mcg and MF/F 200/10 mcg versus MF 400 mcg showed that MF/F was superior to MF (P=0.029). Both doses of MF/F combination therapy were significantly more effective than MF alone in improving ACQ total scores (P<0.014). Mean AQLQ(S) score changes were similar between treatment groups. There were no significant differences between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All treatments were well tolerated; no new or unexpected safety signals were observed.
Nathan et al.[158] (2010) Mometasone-formoterol 100/5 mcg, 2 inhalations BID (MF/F) vs mometasone 100 mcg, 2 inhalations BID (MF) vs formoterol 5 mcg, 2 inhalations BID (F) vs placebo	RCT, DB, PG, PC, MC Patients ≥12 years of age with asthma for ≥12 months, who were on a stable asthma regimen for ≥2 weeks and with a history of medium-dose ICS use for ≥12 weeks, with or without additional LABA. Patients also had FEV_1 of ≥12% or a volume increase of ≥200 ml after 15–20 minutes of albuterol-salbutamol administration or of a nebulized SABA, PEF variability of ≥20%, or a diurnal variation PEF of ≥20%	N=781 26 weeks	Primary: Time to first asthma deterioration Secondary: FEV_1 $AUC_{0–12h}$, trough FEV_1, PEF, asthma control, quality of life, asthma symptom scores, nocturnal awakenings, rescue medication use	Primary: There was a delay in time to first asthma deterioration with MF/F and MF compared to F and placebo (both P<0.001). The median times to first asthma deterioration were days 92 and 131 for those receiving F and placebo, respectively. Because <50% of the patients in the MF/F and MF groups experienced an asthma deterioration, median times to first asthma deterioration could not be determined. The proportion of patients experiencing asthma deteriorations was 30.4% with MF/F, 33.9% with MF, 54% with F, and 55.6% with placebo (P<0.001). Secondary: Mean FEV_1 $AUC_{0–12h}$ improved more with MF/F than with MF (P<0.001) or placebo (P<0.001) at all time points throughout the study and with F at week 12 (P<0.017). Trough FEV_1 showed significant improvement with MF/F versus F and placebo. Treatment with MF/F was significantly better than treatment with F after week 1 (P<0.001) and placebo at all time points (P<0.006). Treatment with MF/F was also statistically better than treatment with MF at several time points, including week 26 (P<0.023). The change from baseline in A.M. PEF was significantly greater for the MF/F group than for the other groups (P<0.008), and treatment with MF alone was statistically significant versus placebo (P<0.001). There was a significant improvement in asthma control for patients treated with MF/F versus F or versus placebo (P<0.001 for both). There was a significantly greater mean improvement in AQLQ(S) score between baseline and week 26 for MF/F versus F (P<0.001) and placebo (P=0.004). Mean improvement from baseline in AQLQ(S) score at week 26 was statistically significantly greater for MF versus F (P=0.039), but similar for MF and placebo (P=0.130). AQLQ(S) outcomes did not differ

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly for F versus placebo at any time point during treatment. The 24-hour asthma symptom scores were significantly improved in the MF/F group compared with both the F and placebo groups (P<0.001). Treatment with MF also showed significant improvements over both F and placebo (P<0.001). Both MF/F and MF groups exhibited greater changes for nocturnal awakenings due to asthma requiring the use of SABA versus F (MF/F, P<0.001; MF, P<0.001), and placebo (MF/F, P<0.001; MF, P<0.003). There was no significant difference between F and placebo. The 24-hour SABA use was significantly reduced in both the MF/F (-61.1%) and the MF (-22.1%) groups versus either the F (+184.1%) or the placebo (+79.1%) groups (P<0.001). The most common AEs were nasopharyngitis (MF/F, 6.3%; MF, 7.8%; F, 6.4%; placebo, 3.6%), upper respiratory tract infection (MF/F, 5.8%; MF, 8.3%; F, 5.9%; placebo, 8.7%), and headache (MF/F, 4.7%; MF, 5.2%; F, 3.0%; placebo, 3.6%).
Chronic Obstructive Pulmonary Disease				
Weir et al.[30] (1999) Beclomethasone 750 to 1,000 mcg BID vs placebo	RCT, PC, DB, PG Patients with COPD	N=98 24 months	Primary: Change in FEV_1, number of exacerbations Secondary: Change in histamine reactivity, respiratory symptoms	Primary: Decline in FEV_1 was less in the beclomethasone treated group although the difference did not reach statistical significance (mean FEV_1 decline: placebo 45.2 mL/year, budesonide 12.1 mL/year; [95% CI; -80 to 8 mL/year]). The actively treated group had fewer exacerbations per year although the difference was not statistically significant (mean exacerbation rates per year: placebo 0.57, budesonide 0.36). Secondary: Bronchial reactivity to inhaled histamine showed no significant change in either active or placebo groups (placebo -0.09, budesonide -0.13). There was no significant effect of active treatment on the Mahler dyspnea index over the study period (placebo 5.4, beclomethasone 6.7, P values not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported).
Bourbeau et al.[73] (1998) Budesonide 400 mcg BID vs placebo	RCT, DB, PC, PG Patients with COPD aged 40 years or older who did not respond to oral corticosteroids	N=79 6 months	Primary: Decline in FEV_1 Secondary: Exercise capacity, dyspnea with exertion, quality of life, peak expiratory flow rate (PEFR), respiratory symptom scores	Primary: There was no difference in the change in FEV_1 from baseline between the treatment and placebo groups (-4 units difference; -95 to 87). Secondary: None of the secondary endpoints differed significantly between the two groups: (treatment difference: budesonide vs placebo). Exercise capacity as measured by the 6-minute walking test: (-28 units difference; -45 to -10). Dyspnea with exertion: (0.1 units difference; -1.0 to 1.1) Quality of life: (1.3 units difference; -4.1 to 1.5) Morning PEFR increased more from baseline in the budesonide group than in the placebo group, but this was observed after only four weeks of treatment and the difference was no longer apparent after one month of treatment. Symptom scores with budesonide did not produce a significant improvement compared with placebo.
Pauwels et al.[28] (1999) Budesonide 400 mcg BID vs placebo	RCT, PG, DB, MC, PC Current smokers aged 30 to 65 years with COPD	N=1,277 36 months	Primary: Change in FEV_1 over time Secondary: Adverse events	Primary: The median decline in FEV_1 over the three-year period was 140 mL in the budesonide group and 180 mL in the placebo group (P=0.05), or 4.3% and 5.3% of their respective predicted values (P=0.04). Secondary: More subjects in the budesonide group had skin bruising (10%) than the placebo group (4%) (P<0.001). Serious adverse events were equally distributed between the groups. Seventy patients were withdrawn from the study in the budesonide group as compared with 62 in the placebo group (P=0.51).
Vestbo et al.[29] (1999)	PG, RCT, DB, PC	N=290	Primary: Rate of FEV_1	Primary: No significant effect of budesonide was found on the rate of FEV_1 decline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide 800 mcg QAM and 400 mcg QPM for six months, followed by 400 mcg BID for 30 months vs placebo	Patients with COPD	36 months	decline Secondary: Decrease in symptoms	The crude rate of loss of lung function was 41.8 mL per year in the placebo group and 45.1 mL per year in the budesonide group. The difference in estimated rates of decline (3.1 mL per year [95% CI, -12.8 to 19.0]) was not significant (P=0.70). Secondary: In both treatment groups, symptoms decreased substantially during the study period but no differences between the two groups was observed.
Welte et al.[143] (2009) Budesonide-formoterol 320/9 mcg BID and tiotropium 18 mcg QD vs tiotropium 18 mcg QD	RCT, DB, MC, PG Patients >40 years of age with COPD and FEV_1<50%	N=660 12 weeks	Primary: Pre- and postdose FEV_1, pre- and postdose FVC and inspiratory capacity, health status Secondary: Peak expiratory flow, morning symptoms and activities, morning reliever use, exacerbations, tolerability	Primary: Budesonide-formoterol treatment significantly increased pre- and postdose FEV_1 by 6% and 11%, respectively compared to tiotropium alone (P<0.001). SGRQ-C total score improved by 3.8 units in the budesonide-formoterol group compared to 1.5 units in the tiotropium monotherapy group (mean difference -2.3; 95% CI, -4.23 to 0.32; P=0.023). Morning PEF and FEV_1 were improved with budesonide-formoterol therapy compared to tiotropium monotherapy as early as week 1, and maintained statistical significant to week 12 (P<0.001 for all weeks). Morning symptoms and activities were significantly better in the budesonide-formoterol group compared to the tiotropium group (P<0.001). There were significant improvements in reliever medication in the budesonide-formoterol group. A total of 7.6% of patients in the budesonide-formoterol group experienced exacerbations compared to 18.5% in the tiotropium group (RR, 0.38; 95% CI, 0.25 to 0.57; P<0.001). Hospitalizations and ED visits were decreased by 65% in the budesonide-formoterol group compared to the tiotropium group (RR, 0.35; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.16 to 0.78; P=0.011). There were no differences in tolerability between the regimens.
Lindberg et al.[104] (2007) Budesonide-formoterol 160/4.5 mcg vs fluticasone-salmeterol 250/25 mcg vs salbutamol 100 mcg vs placebo	DB, DD, MC, RCT, XO Patients ≥40 years of age with COPD and FEV_1 30-70% predicted	N=90 17 days	Primary: Change in FEV_1 5 minutes after drug inhalation Secondary: Change in FEV_1 at 3 minutes and 180 minutes; maximal change in FEV_1; change in inspiratory capacity (IC) at 15 minutes; maximal change in IC and average effect on IC during observation interval; yes or no answer by patient to perception of onset of effect (POE) question; adverse events	Primary: Budesonide-formoterol improved FEV_1 at 5 min to a greater extent than either fluticasone-salmeterol (ratio, 105% [95% CI: 103–108%]; P=0.0001) or placebo (ratio, 116% [95% CI: 113–119%]; P<0.0001) and to a similar extent as salbutamol (ratio, 99% [95% CI: 97–101%]; P=0.35). Secondary: Findings similar to above were observed for FEV_1 at 3 minutes. Compared with placebo, FEV_1 was significantly improved over 180 minutes after all three active treatments (all P<0.0001), although improvements were maintained more effectively with budesonide-formoterol and fluticasone-salmeterol than with salbutamol, as demonstrated by FEV_1 at 180 minutes, ratio 107% (95% CI: 104–109%) for budesonide-formoterol and 106% (95% CI: 103–108%) for fluticasone-salmeterol vs salbutamol; both P<0.0001). Maximal increases in FEV_1 were 0.35 L, 0.32 L, 0.34 L and 0.14 L for budesonide-formoterol, fluticasone-salmeterol, salbutamol and placebo respectively, with no statistically significant differences among the three active treatments in maximal FEV_1 or average FEV_1 over 180 minutes. All three active treatments were superior to placebo for both variables (all P<0.0001). IC was significantly improved at 15 minutes following all three active treatments compared with placebo (all P<0.0001), with no significant differences among the active treatments. Maximal increases in IC were 0.65 L, 0.53 L, 0.54 L and 0.28 L for budesonide-formoterol, fluticasone-salmeterol, salbutamol and placebo respectively, representing a 4% greater increase for budesonide-formoterol versus fluticasone-salmeterol (ratio, 104% [95% CI: 101–107%]; P=0.0184) and a 13% greater increase vs placebo (ratio,113% [95% CI: 110–117%]); P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no differences between the active treatments in average IC over 185 min. The effect of budesonide-formoterol and fluticasone-salmeterol on IC was of longer duration than that of salbutamol. POE: The proportion of patients answering 'yes' to the question regarding whether they felt their medication working was 84%, 81%, 84% and 61% following treatment with budesonide-formoterol, fluticasone-salmeterol, salbutamol and placebo, respectively. Time to POE was 10 min faster (95% CI: -75.0, -3.5) for budesonide-formoterol and 10.5 minutes faster (95% CI: -80.0, -3.5) for salbutamol compared with placebo; time to POE was slightly slower with fluticasone-salmeterol, being observed 5 minutes faster (95% CI: -75.0, 0.0) than placebo All active treatments resulted in a significantly faster time to POE than placebo (all P<0.001). Median time to POE was 5 minutes for each of the three active treatments and 20 minutes for placebo, with no statistically significant differences among active treatments. All treatments were well tolerated and no new or unexpected safety concerns were identified. There were 24 adverse events in total, all mild to moderate, of which none was considered to be related to study treatment. No serious adverse events or deaths were reported, nor were clinically important differences between treatments, changes over time or abnormalities reported with respect to vital signs and physical findings.
Burge et al.[145] (2000) Fluticasone 500 mcg BID vs placebo	RCT, PC, DB Patients with COPD with a mean FEV_1 50% of predicted normal	N=751 36 months	Primary: Rate of decline in FEV_1 Secondary: Frequency of exacerbations, changes in health status, withdrawals due to respiratory	Primary: The annual rate of decline in FEV_1 was 59 mL per year in the placebo group and 50 mL per year in the fluticasone group (P=0.16). The predicted mean FEV_1 at three and 36 months in the fluticasone group was 76 mL and 100 mL higher, respectively, than in the placebo group (P<0.001). Secondary: The median yearly exacerbation rate was lower in the fluticasone group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			disease, morning serum cortisol levels, adverse events	(0.99 per year) compared with the placebo group (1.32 per year), a reduction of 25% in those receiving fluticasone (P=0.026). The respiratory health questionnaire score increased (i.e., health status declined) after the first six months of treatment and this increase was linear (P<0.001). The respiratory score worsened at a faster rate in the placebo group (3.2 units per year) than in the fluticasone group (2.0 units per year) (P=0.004). More patients in the placebo group than in the fluticasone group withdrew because of respiratory disease (25% vs 19%, respectively, P=0.034). There was a small decrease in mean cortisol concentrations with fluticasone compared with placebo (P≤0.032). No decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects. Reported events were similar between treatments overall, with the exception of side effects secondary to inhaled glucocorticoids: hoarseness (35 vs 16), throat irritation (43 vs 27), and candidiasis of the mouth and throat (41 vs 24) were more common in the fluticasone group than with placebo.
Paggiaro et al.[27] (1998) Fluticasone 500 mcg BID vs placebo	RCT, DB, PC Patients 50-75 years of age with COPD	N=281 6 months	Primary: Number of patients who had at least one exacerbation at the end of the study period Secondary: Mean change from baseline in peak expiratory flow rate (PEFR), daily symptom scores, frequency of adverse events	Primary: More patients in the placebo group (37%) experienced at least one exacerbation than in the fluticasone group (32%) (P<0.001). Secondary: The adjusted mean change from baseline daily PEFR in the placebo group was -2 L/min compared with 15 L/min in the fluticasone group ([9-26], P<0.001). Symptom scores showed a distribution of significantly lower median daily cough scores in the fluticasone group compared with the placebo group (P=0.004). The overall frequency of adverse events during treatment was similar in the two treatment groups, occurring in 68% of patients receiving placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 64% of patients receiving fluticasone.
Hanania et al.[82] (2003) Fluticasone-salmeterol 250/50 mcg BID vs fluticasone 250 mcg BID vs salmeterol 50 mcg BID vs placebo	RCT, DB, PC, MC Patients 40-87 years of age, current or former smokers with ≥20 pack year history, diagnosed with COPD, FEV_1/FVC ratio of ≤70%, baseline FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and 2 hour post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, chronic respiratory disease questionnaire (CRDQ), chronic bronchitis symptom questionnaire (CBSQ), exacerbations, and supplemental albuterol use	Primary: Statistically significant increase in pre-dose FEV_1 in fluticasone/salmeterol group compared to the salmeterol group (91 mL; P=0.012) and placebo (1 mL; P<0.001). No significant difference between fluticasone/salmeterol group and fluticasone group. Statistically significant increase in 2 hour post-dose FEV_1 in fluticasone/salmeterol group compared to the salmeterol group (281 mL vs 200 mL; P<0.001), placebo (281 mL vs 58 mL; P<0.001), and fluticasone group (281 mL vs 147 mL; P<0.001). Secondary: Statistically significant increase in morning PEF values in fluticasone/salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (P≤0.034), though improvements were also seen from baseline in salmeterol and fluticasone monotherapy groups (P<0.001). Statistically significant improvements in dyspnea index observed in fluticasone/salmeterol group (P=0.023) compared to placebo, in addition to improvements in fluticasone (P=0.057) and salmeterol (P=0.043) monotherapy groups compared to placebo (NOTE: difference in fluticasone monotherapy group not significant). Statistically significant reduction in supplemental albuterol use in fluticasone/salmeterol group compared to fluticasone monotherapy group (-1.0 vs -0.2; P=0.036) and placebo (-1.0 vs 0.1; P=0.002). Numerical reduction in supplemental albuterol use in fluticasone/salmeterol group compared to salmeterol monotherapy group. Statistically significant increase in CBSQ scores in fluticasone/salmeterol group and fluticasone monotherapy group compared to placebo (P≤0.017). There was significant difference between treatment groups in terms of exacerbations or time to first exacerbation.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calverley et al.[83] (2003) Fluticasone-salmeterol 500/50 mcg BID vs fluticasone 500 mcg BID vs salmeterol 50 mcg BID vs placebo	RCT, DB, PC, PG Patients with COPD, pre-dose FEV_1 25-70% predicted, <10% increase in FEV_1 after β-agonist use, pre-bronchodilator FEV_1/FVC ratio of 70% or less, smoking history of at least 10 pack years, a history of chronic bronchitis, at least 1 COPD exacerbation per year for previous 3 years, and at least 1 exacerbation in previous year requiring oral corticosteroids, antibiotics, or both	N=1,465 12 months	Primary: Pre-dose FEV_1 after 12 months of treatment and after abstaining from bronchodilators for at least 6 hours and from study medication by at least 12 hours Secondary: Pre-dose FVC, post-bronchodilator FEV_1 and FVC, morning PEF, use of relief medication, symptom scores, nighttime awakenings, acute COPD exacerbations, and St. George's Respiratory Questionnaire (SGRQ) scores	Primary: Statistically significant improvement in pre-dose FEV_1 in all treatment groups compared to placebo (P<0.001 for salmeterol, P=0.0063 for fluticasone, and P<0.001 for fluticasone/salmeterol) and statistically significant improvement in fluticasone/salmeterol group compared to fluticasone and salmeterol monotherapy groups (P<0.001). Secondary: Predose FVC improved significantly in all groups compared to placebo (P=0.0004 for salmeterol, P=0.013 for fluticasone, and P<0.001 for fluticasone/salmeterol) and there was a statistically significant improvement in pre-dose FVC in fluticasone/salmeterol group when compared to fluticasone and salmeterol monotherapy groups (P=0.006 for salmeterol and P<0.001 for fluticasone). Postbronchodilator FEV_1 improved significantly in fluticasone and fluticasone/salmeterol group compared to placebo (P=0.013 for fluticasone and P<0.001 for fluticasone/salmeterol) and there was a statistically significant difference between fluticasone/salmeterol group compared to salmeterol and fluticasone monotherapy (P=0.039 and P=0.0014 respectively). Statistically significant improvement in PEF in all treatment groups compared to placebo (P<0.001), and there was a statistically significant improvement in fluticasone/salmeterol group compared to fluticasone and salmeterol monotherapy (P<0.001). All active treatment groups significantly decreased the number of exacerbations per patient per year compared to placebo (P=0.003) but there was no significant difference between the groups. Statistically significant reduction in the use of relief medication in fluticasone/salmeterol group compared to placebo and other treatment groups (P<0.001 for placebo, P=0.004 for salmeterol, and P=0.003 for fluticasone). Statistically significant reduction in nighttime awakenings in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				fluticasone/salmeterol group compared to placebo and salmeterol groups (P=0.006 and P=0.011 respectively) but there was no significant difference between fluticasone/salmeterol and fluticasone monotherapy groups (P=0.591). Fluticasone/salmeterol combination therapy showed significant improvement in SGRQ scores compared to placebo and fluticasone groups (P=0.0003 and P=0.021 respectively), but no difference between fluticasone/salmeterol and salmeterol monotherapy groups (P=0.071).
Vestbo et al.[84] (2005) Fluticasone-salmeterol 500/50 mcg BID vs fluticasone 500mcg BID vs salmeterol 50 mcg BID vs placebo	RCT, PC, DB, PG, Patients with COPD, pre-dose FEV_1 25-70% predicted, <10% increase in FEV_1after β-agonist use, pre-bronchodilator FEV_1/FVC ratio of 70% or less, smoking history of at least 10 pack years, history of chronic bronchitis, at least 1 COPD exacerbation per year for previous 3 years, and one of them requiring oral corticosteroids, antibiotics, or both	N=1,465 12 months	Primary: Time to first observation of treatment effects in each arm of study, analyzed for the first 14 days after initial treatment	Primary: Significant increase in PEF in fluticasone/salmeterol and salmeterol monotherapy groups over placebo after 1 day (P<0.001). This was also observed in the fluticasone group on day 2 (P<0.001). Increase in PEF values in the fluticasone/salmeterol group was significantly better than the other treatment arms after day 1 (P<0.001). No other mention of comparison between groups. Significant increase in FEV_1 values in all treatment arms compared to placebo by day 14 (P<0.001 for salmeterol monotherapy and fluticasone/salmeterol groups and P=0.016 for fluticasone monotherapy group). No mention of comparison between groups.
Calverley et al.[105] (2007) Fluticasone-salmeterol 500/50	DB, MC, PC, PG, RCT Patients 40-80 years of age with COPD,	N=6112 3 years	Primary: Death from any cause Secondary:	Primary: The proportions of deaths from any cause at 3 years were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The absolute risk reduction for death in the combination-therapy group as compared with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg BID vs salmeterol 50 mcg BID vs fluticasone 500 mcg BID vs placebo	current or former smokers, ≥10 pack-year history, prebronchodilator FEV_1 <60% of predicted value, an increase of FEV_1 <10% of predicted value with use of 400 mcg of albuterol, and FEV1/FVC ratio of ≤0.70		Frequency of SAE, defined as a symptomatic deterioration requiring treatment with antibiotics, systemic corticosteroids, hospitalization, or a combination of the above; health status accessed via the St. George's Respiratory Questionnaire; lung function as accessed via post-bronchodilator spirometry ; adverse events and safety	the placebo group was 2.6% (HR, 0.825; 95% CI, 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, 0.2 to 31.9). The risk of death in the salmeterol group and in the fluticasone group did not differ significantly from that in the placebo group, and was similar among patients who died while receiving a study medication. The risk of death in the combination-therapy group did not differ significantly from that in the salmeterol group, but patients receiving the combination regimen were less likely to die than those receiving fluticasone (HR, 0.774; 95% CI, 0.641 to 0.934; P=0.007). Secondary: Annual rate of exacerbations was 0.85 (95% CI, 0.80 to 0.90) in the combination-therapy group and 1.13 (95% CI, 1.07 to 1.20) in the placebo group, a rate ratio for exacerbations of 0.75 (95% CI, 0.69 to 0.81; P<0.001), a reduction of 25% and corresponding to a number needed to treat of four to prevent one exacerbation in 1 year. Annual rates of exacerbations in the salmeterol group and the fluticasone group were significantly lower than in the placebo group. Overall, 26% of the patients were hospitalized at least once during the 3-year study period. Annual admission rates were 17% lower in the combination-therapy and salmeterol groups than in the placebo group (P=0.03), corresponding to a number needed to treat of 32 to prevent one hospitalization in 1 year. Total scores on the St. George's Respiratory Questionnaire initially improved from baseline in all groups, with the greatest changes occurring in the combination-therapy group (mean score at baseline, 48.7, with a mean reduction of 3.0 units averaged over 3 years), as compared with the placebo group (a mean score of 48.4 at baseline, with an increase of 0.2 unit in the placebo group). For lung function, the mean baseline FEV1 in the combination-therapy group was 1.236 liters with an average increase of 0.029 liter; in the placebo group, the mean baseline FEV1 was 1.257 liters and a decrease of 0.062 liter.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Averaged over 3 years, the health status (a reduction of 3.1 units in the score for the St. George's Respiratory Questionnaire) and spirometric measurements (an increase in FEV1 of 0.092 liter) in the combination-therapy group were significantly better than in the groups receiving placebo, salmeterol alone, or fluticasone propionate alone). The most frequently reported adverse event was an exacerbation of COPD. The probability of having pneumonia reported as an adverse event during the 3-year study period was significantly greater among patients receiving a study medication containing fluticasone propionate: the probability was 19.6% in the combination-therapy group, 12.3% in the placebo group, 13.3% in the salmeterol group, and 18.3% in the fluticasone group (P<0.001 for the comparison between both the combination-therapy and fluticasone groups and the placebo group). There was no significant difference in the probability of fractures among the groups. There was no excess of cardiac disorders among patients treated with the combination regimen or salmeterol alone. In the safety substudy, there were no significant differences in bone mineral density or in the numbers of patients in whom cataracts developed.
Dal Negro et al.[81] (2003) Fluticasone-salmeterol 250/50 mcg BID vs salmeterol 50 mcg BID vs placebo	RCT, DB, PG, PC Patients 53-78 years of age with moderate COPD who were naïve to inhaled corticosteroids, FEV_1 ≤80% predicted value but >800mL, FEV_1/ FVC ratio ≤70% predicted value, FEV_1 change of ≤12% following β-agonist administration, receiving regular	N=18 52 weeks	Primary: FEV_1, morning PEF values, COPD symptom scores, number of exacerbations, and β-agonist use	Primary: Increase in FEV_1 percent predicted noted in fluticasone/salmeterol group but this increase was not significant (49.9 % to 53.4%; P=0.07). However, if the increase is expressed as a percent over baseline value, it is significant in the fluticasone/salmeterol group (1.1 to 6.6; P<0.001), but not in the salmeterol group (P=0.79). Statistically significant increase in morning PEF values in fluticasone/salmeterol group compared to placebo (180 L/min to 255.4 L/min compared to 18606 L/min to 173.3 L/min; P<0.001), but values did not change in salmeterol and placebo groups. Statistically significant reduction in daily symptom scores in fluticasone/salmeterol group (P=0.008), but not in salmeterol group. Statistically significant reduction in β-agonist use in fluticasone/salmeterol group (4.2 to 1.9; P<0.001), but not in salmeterol group 4.1 to 4.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	treatment with oral theophylline 200 mg BID, short acting β-agonist as needed current or ex-smokers with history of at least 10 pack years			Statistically significant decrease in exacerbations in fluticasone/salmeterol group (P<0.001), but not in salmeterol group.
Make et al.[90] (2005) Fluticasone-salmeterol 250/50 mcg BID vs ipratropium-albuterol 36/206 mcg QID	RCT, DB, PG, MC Patients 40-85 years of age with moderate to severe COPD, FEV_1/FVC ratio ≤70%, FEV_1 >0.70 L and ≤70% predicted normal value (or if ≤0.70 L, then ≥40% predicted), smoking history of ≥10 pack years, use of inhaled short acting bronchodilator for COPD for ≥30 days	N=361 8 weeks	Primary: Morning pre-dose FEV_1 Secondary: Morning PEF values, 6-hour FEV_1 AUC, percentage of symptom free nights, dyspnea, overall combined daytime symptom score	Primary: Statistically significant improvement in morning pre-dose FEV_1 in fluticasone/salmeterol group compared to ipratropium/albuterol group (P<0.001). Secondary: Statistically significant improvement in mean FEV_1 AUC in fluticasone/salmeterol group at week 8 compared to ipratropium/albuterol group (P=0.002). Statistically significant improvement in morning PEF values in fluticasone/salmeterol group compared to ipratropium/albuterol group at week 1 and throughout study (P<0.001). Mean post-administration FEV_1 values significantly higher in the ipratropium/albuterol group at 0.5, 1, and 2 hours compared to fluticasone/salmeterol group (P<0.001), but higher in the fluticasone/salmeterol group at 6 hours (P=0.003). Dyspnea scores significantly higher in fluticasone/salmeterol group compared to ipratropium/albuterol group (P=0.026), though improvements over baseline observed in both groups. Significantly greater reduction in overall daytime symptom score in fluticasone/salmeterol group compared to ipratropium/albuterol group (change from baseline is -46.7 vs -28.1; P=0.024). Statistically significant increase in albuterol-free nights in fluticasone/salmeterol group compared to ipratropium/albuterol group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(change from baseline is 19% vs7.3%; P<0.001), and a similar increase in albuterol-free days (change from baseline is 34.7% vs 26.7%; P=0.021).
Aaron et al.[101] (2007) Fluticasone-salmeterol 250/25 mcg, 2 inhalations BID and tiotropium 18 mcg QD vs tiotropium 18 mcg QD and salmeterol 25 mcg, 2 inhalations BID vs tiotropium 18 mcg QD	DB, MC, PC, RCT Patients ≥ 35 years of age with ≥ 1 COPD exacerbation in last 12 months requiring systemic steroids or antibiotics; history of ≥10 pack-years of cigarette smoking; documented chronic airflow obstruction with FEV_1 –FVC ratio <0.70 and a postbronchodilator $FEV_1 \leq 65\%$ of the predicted value	N=449 1 year	Primary: Proportion of patients who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics	Primary: The proportion of patients in the tiotropium group who experienced an exacerbation (62.8%) did not differ from that in the tiotropium + salmeterol group (64.8%; difference, -2.0 percentage points [95% CI, -12.8 to 8.8 percentage points]). The proportion of patients in the tiotropium group who experienced an exacerbation (62.8%) did not differ from that in the tiotropium + fluticasone-salmeterol group (60.0%; difference, 2.8 percentage points [CI, -8.2 to 13.8 percentage points]). Tiotropium + fluticasone-salmeterol improved lung function (P=0.049) and disease-specific quality of life (P=0.01) and reduced the number of hospitalizations for COPD exacerbation (incidence rate ratio, 0.53 [CI, 0.33 to 0.86]) and all-cause hospitalizations (incidence rate ratio, 0.67 [CI, 0.45 to 0.99]) compared with tiotropium. Tiotropium + salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo. NOTE: More than 40% of patients who received tiotropium + placebo and tiotropium + salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or long-acting beta-agonists.
Rabe et al.[102] (2008) Fluticasone 500 mcg and salmeterol 50 mcg BID vs tiotropium 18 mcg QD and formoterol 12mcg BID	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, and stable airway obstruction	N=605 6 weeks	Primary: FEV_1 area under the curve for the time period 0 to 12 h (AUC_{0-12}) and peak FEV_1	Primary: Lung function profiles in the group receiving tiotropium plus formoterol were superior to those in the group receiving salmeterol plus fluticasone (mean difference in FEV_1 AUC_{0-12}, 78ml; P=0.0006; mean difference in FVC AUC_{0-12}, 173ml; P<0.0001). Peak responses were in favor of tiotropium plus formoterol (difference in peak FEV_1, 103ml; P<0.0001; difference in peak FVC, 214ml; P<0.0001), as were FEV_1 and FVC at each individual time point after dose (P<0.05). Both treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wedzicha et al.[139] (2008) Fluticasone-salmeterol 500/50 mcg BID vs tiotropium 18 mcg QD	AC, DB, MC, RCT Patients 40 to 80 years of age with COPD, smoking history, and post-bronchodilator FEV_1 of <50%	N=1,323 2 years	Primary: Exacerbations Secondary: All-cause mortality	Primary: Over 2 years, 62% of the fluticasone-salmeterol group and 59% of the tiotropium group had at least one exacerbation requiring therapeutic intervention. The overall rates of exacerbations were 1.28/year for the fluticasone-salmeterol group and 1.32/year for the tiotropium group, with no difference between rates (P=0.656). Secondary: Mortality was significantly lower among the fluticasone-salmeterol group, 21 (3%), than the tiotropium group, 38 (6%), during the study period (P=0.032). Specifically, cardiac disorders were associated with death in 9 (1%) of fluticasone-salmeterol treated patients and 19 (3%) tiotropium treated patients.

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
MDI=metered-dose inhaler, DPI=dry-powder inhaler, HFA=hydrofluoroalkane, CFC=chlorofluorocarbon
Study abbreviations: AMD=adjustable maintenance dose, CI=confidence interval, DB=double-blind, DD=double-dummy, FD=fixed dosing regimen, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, ICS=inhaled corticosteroids, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PEF=peak expiratory flow, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SABA=short-acting ß-agonist, SAE=severe asthma exacerbations, SEM=standard error of the mean, XO=crossover

Additional Evidence

Dose Simplification
Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. Evidence-based guidelines for the selection of the appropriate inhalation delivery device have been published. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[69] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[69] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[69] Incorrect technique can result in decreased drug delivery and potentially decreased efficacy. The ability of a patient to use a particular inhalation device correctly may be affected by a number of factors. These factors include age, cognitive status, coordination, manual dexterity/strength, severity of respiratory disease, and visual acuity.[70] Adherence to inhaled therapy is often poor, with rates of 40% to 72% being reported.[71] Patient preference should be considered when selecting an inhalation delivery device.[69] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.[69]

Dorais et al. analyzed pharmacy claims to assess adherence with leukotriene modifiers and inhaled corticosteroids.[60] Compared to patients receiving inhaled corticosteroids, patients receiving a leukotriene modifier were more likely to refill their prescriptions at least once during the first year of treatment (67.9% vs. 52.7%), were less likely to discontinue treatment (RR=0.46; 95% CI: 0.85-0.98), and were more likely to be on treatment longer during the first year of therapy (38% vs. 19%; all, P<0.001). Stoloff et al. evaluated refill persistence with fluticasone/salmeterol, fluticasone plus salmeterol in separate inhalers, fluticasone plus montelukast, fluticasone monotherapy, and montelukast monotherapy.[97] Patients in the fluticasone/salmeterol group had significantly more refills compared to patients receiving other fluticasone preparations, and had similar refill rates as patients in the montelukast group. In a similar study, Stempel et al. reported the same findings with regards to refill persistence.[98] In addition, the mean number of short-acting bronchodilator prescriptions was significantly lower in patients receiving fluticasone/salmeterol compared to those receiving montelukast monotherapy (P<0.0001). Sovani et al. evaluated adherence rates with budesonide/formoterol compared to budesonide plus a short-acting β_2-agonist.[68] Adherence with budesonide was found to be approximately 60% of the prescribed dose. Patients receiving budesonide/formoterol used approximately 80% more budesonide than participants in the control group (P<0.001). Sherman et al. assessed adherence rates in children with persistent asthma who were Medicaid recipients.[61] Adherence was 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn. Murphy et al. evaluated the differences in caregiver satisfaction and adherence to therapy with budesonide inhalation suspension administered once-daily and cromolyn sodium inhalation solution administered four-times-daily.[62] Adherence rates were 76% in the budesonide group compared to 57% in the cromolyn group. Additionally, 54.6% of caregivers rated budesonide as "highly or very convenient" compared with only 23% for cromolyn. While 77% of caregivers found the budesonide formulation easy to administer, only 47% reported ease of use with the cromolyn inhalation. The results of the survey indicated significantly higher parental satisfaction and improved compliance with budesonide compared to cromolyn due to ease of use and convenience of once-daily administration (P≤0.001).

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Sheikh et al. evaluated health care resource utilization in patients receiving flunisolide and fluticasone.[51] There was a significant improvement in emergency room visits with fluticasone compared to flunisolide (P=0.004). Mean hospital admissions for asthma were also lower in the fluticasone group compared to the flunisolide group (P<0.002). A retrospective study of approximately 17,000 patients demonstrated that inhaled corticosteroids significantly reduced emergency department visits and hospitalizations due to asthma.[59]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Inhaled Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Beclomethasone	aerosol inhaler	QVAR®	$$$	N/A
Budesonide	dry powder inhaler, inhalation suspension	Pulmicort ®*	$$$$-$$$$$	$$$$$
Budesonide and formoterol	aerosol inhaler	Symbicort®	$$$$	N/A
Ciclesonide	aerosol inhaler	Alvesco®	$$$-$$$$	N/A
Flunisolide	aerosol inhaler	Aerobid®, Aerobid-M®	$$$	N/A
Fluticasone	aerosol inhaler, dry powder inhaler	Flovent Diskus®, Flovent HFA®	$$$-$$$$	N/A
Fluticasone and salmeterol	aerosol inhaler, dry powder inhaler	Advair Diskus®, Advair HFA®	$$$$-$$$$$	N/A
Mometasone	dry powder inhaler	Asmanex®	$$$-$$$$	N/A
Mometasone and formoterol	aerosol inhaler	Dulera®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The inhaled corticosteroids are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-15] They are available as single entity products, as well as in combination with a long-acting β_2- agonist (formoterol or salmeterol). Budesonide inhalation solution is the only product that is currently available in a generic formulation.

The inhaled corticosteroids are the most effective long-term medications for the treatment of mild, moderate or severe persistent asthma; therefore, they are consistently recommended as first-line therapy.[16-18,21-22] Guidelines do not give preference to one inhaled corticosteroid over another for the treatment of asthma. Most of the benefit is achieved using relatively low doses, and increasing the dose provides little additional benefit.[17] However, due to variability in individual responses and poor adherence, some patients may need higher doses to achieve adequate control of their asthma symptoms.[18] Higher doses may also be needed in patients who smoke. When additional therapy is needed, guidelines recommend a long-acting β_2-agonist (LABA) be added to an inhaled corticosteroid

in children 5-12 years of age and adults.[17,21-22] However, an increased risk of asthma-related death has been reported with the use of a LABA.[7,12-13,15] The data are insufficient to determine whether concurrent use of inhaled corticosteroids mitigates the increased risk of asthma-related death. According to the prescribing information, the use of a fixed-dose combination product containing an inhaled corticosteroid and LABA (budesonide/formoterol, fluticasone/salmeterol, and mometasone/formoterol) should only be considered for patients who are not adequately controlled on a long-term asthma control medication (e.g., an inhaled corticosteroid) or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.[7,12-13.15] Once asthma control is achieved and maintained, the patient should be assessed at regular intervals and therapy should be stepped down (e.g., discontinue the LABA) if possible. Patients should then be maintained on a long-term asthma control medication (e.g., an inhaled corticosteroid). The fixed-dose combination products should not be used in patients whose asthma is adequately controlled on a low or medium dose of an inhaled corticosteroid.[7,12-13,15] The available data also suggest that the LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.[159] For pediatric and adolescent patients with asthma who require the addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product should be considered to ensure adherence with both drugs. If the use of a separate long-term asthma control medication and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be ensured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.[159]

Numerous trials have been conducted with the inhaled corticosteroids.[26-158,160] They have been shown to improve pulmonary function, prevent symptoms and exacerbations, reduce the need for emergency department treatment, and reduce asthma mortality compared to other maintenance therapies (e.g., leukotriene modifiers, long-acting β_2-agonists, cromolyn or theophylline). When administered at equipotent doses via comparable delivery devices, the inhaled corticosteroids do not appear to differ in their ability to control asthma symptoms, prevent exacerbations, or reduce the need for rescue medication use. When comparing combination therapy to monotherapy, the more aggressive treatment regimens improved asthma outcomes to a greater extent than the less-intensive treatment regimens.[78-80,85,91-94,106-108,112-113,117,119-120,124-127,129,132,136,141-142,157-158] Several studies have demonstrated similar outcomes with the fixed-dose combination inhalers compared to the coadministration of their individual components as separate inhalers.[18,21,86,100,108,111,121-122,126,128,136] Studies directly comparing the fixed-dose combination products (budesonide/formoterol vs fluticasone/salmeterol) have shown conflicting results with regards to asthma outcomes.[96,109-110,113-114,116,130-131,161]

Most studies have indicated that the existing medications to treat COPD do not modify the long-term decline in lung function.[23] Therefore, the goal of treatment is to decrease symptoms and complications. Bronchodilators are central to the symptomatic management of COPD. The principal bronchodilators are β_2-agonists, antimuscarinics and xanthines. For the treatment of mild airflow obstruction, guidelines recommend the use of a short-acting bronchodilator as needed to relieve breathlessness and exercise limitation.[19-20,23-24] For patients who require daily maintenance therapy to control symptoms, the use of an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic). The inhaled corticosteroids have been shown to reduce the frequency of exacerbations and improve health status in symptomatic patients with an FEV_1 <50% predicted.[19-20,23-24] Therefore, they are recommended in patients with more advanced disease and for those with repeated exacerbations. The combination of an inhaled corticosteroid and a long-acting β_2-agonist is more effective than monotherapy in reducing exacerbations, improving lung function and improving health status.[23,81-84,105] Guidelines do not give preference to one inhaled corticosteroid over another for the treatment of COPD.

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. According to the ACCP/ACAAI guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[69] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[69] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability, clinical setting, patient age and the ability to use the selected device correctly, device use with multiple medications, drug administration time, convenience in both outpatient and inpatient settings, as well as physician and patient preference.[69]

Given the role of the single entity inhaled corticosteroids in the management of asthma, one or more brand products within the class reviewed offers significant clinical advantage in general use over the generics and OTC products (if applicable), but is comparable to all other brands in the same class. All brand fixed-dose combination

inhaled corticosteroids within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. The fixed-dose combination inhaled corticosteroids should be available through the medical justification portion of the prior authorization process for patients who require the combination of an inhaled corticosteroid and long-acting β_2-agonist (LABA) to control their respiratory symptoms.

XI. Recommendations

Alabama Medicaid should work with manufacturers of brands in the class on cost proposals so that at least one single entity brand inhaled corticosteroid is selected as a preferred agent.

No brand fixed-dose combination inhaled corticosteroid is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
4. QVAR® [package insert]. Northridge, CA: 3M Drug Delivery Systems; August 2008.
5. Pulmicort Flexhaler® [package insert]. Wilmington, DE: AstraZeneca; July 2010.
6. Pulmicort Respules® [package insert]. Wilmington, DE: AstraZeneca; July 2010.
7. Symbicort® [package insert]. Wilmington, DE: AstraZeneca; June 2010.
8. Alvesco® [package insert]. Marlborough, MA: Sepracor Inc.; July 2008.
9. Aerobid®, Aerobid-M® [package insert]. St. Louis, MO: Forest Pharmaceuticals; March 2002.
10. Flovent Diskus® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2010.
11. Flovent HFA® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2008.
12. Advair Diskus® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2010.
13. Advair® HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; June 2010.
14. Asmanex® Twisthaler® [package insert]. Kenilworth, NJ: Schering Corporation; September 2010.
15. Dulera® [package insert]. Kenilworth, NJ: Schering Corporation; June 2010.
16. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.
17. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
18. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.
19. Bellamy D, Bouchard J, Henrichsen S, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J 2006;15:48-57.
20. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
21. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
22. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
23. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009. 93 p. Available at: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed October 2010.
24. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 June. 61 p. Available at: http://guidance.nice.org.uk/CG101. Accessed October 2010.
25. Qaseem A, Snow V, Shekelle P, et al., Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians (ACP). Ann Intern Med 2007;147:633-8.
26. Sears MR, Boulet LP, Laviolette M, Fitzgerald JM, Bai TR, Kaplan A, Smiljanic-Georgijev N, Lee JS. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. Eur Respir J. 2008;231:982-989.
27. Paggiaro PL, Dahle R, Bakran I, et al. Multicentre randomized placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. Lancet. 1998;351(9105):773-80.

28. Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long – term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. NEJM. 1999;340(25):1948-53.
29. Vestbo J, Sorensen T, Lange P, et al. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomized controlled trial. Lancet. 1999;353(9167):1819-23.
30. Weir DC, Bale GA, Bright P, et al. A double-blind placebo-controlled study of the effect of inhaled beclomethasone dipropionate for 2 years in patients with nonasthmatic chronic obstructive pulmonary disease. Clin Exp Allergy. 1999;29(suppl 2):125-8.
31. Baker JW, Mellon M, Wald J, et al. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. Pediatrics. 1999;103(2):414-21.
32. Brenner BE, Chavda KK, Camargo CA. Randomized trial of inhaled flunisolide versus placebo among asthmatic patients discharged from the emergency department. Ann Emerg Med. 2000;36(5):417-26.
33. Nelson HS, Busse WW, deBoisblanc BP, et al. Fluticasone propionate powder: Oral corticosteroid-sparing effect and improved lung function and quality of life in patients with severe chronic asthma. J Allergy Clin Immunol. 1999;103(2 pt 1):267-75.
34. Rowe BH, Bota GW, Fabris L, et. al. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department. JAMA. 1999;281(22):2119-26
35. Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. Ann Allergy Asthma Immunol. 2005;94(1):48-54.
36. Tinkelman DG, Bronsky EA, Gross G, et al. Efficacy and safety of budesonide inhalation powder (Pulmicort Turbuhaler®) during 52 weeks of treatment in adults and children with persistent asthma. J of Asthma. 2003;40(3):225 -36.
37. Bernstein DI, Berkowitz RB, Chervinsky P, et al. Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler. Respir Med 1999;93:603-12.
38. Berend N, Kellett B, Kent N, et al. Improved safety with equivalent asthma control in adults with chronic severe asthma on high-dose fluticasone propionate. Respirology. 2001;6(3):237-46.
39. Berkowitz K, Rachelefsky G, Harris AG, et al. A comparison of triamcinolone MDI with a built-in tube extended and beclomethasone dipropionate MDI in adult asthmatics. Chest 1998;114:757-65.
40. Bousquet J, D'Urzo A, Hebert J, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler®. Eur Respir J 2000;16:808-16.
41. Bronsky E, Korenblat P, Harris AG, et al. Comparative clinical study of inhaled beclomethasone dipropionate and triamcinolone acetonide in persistent asthma. Ann Allergy Asthma Immunol 1998;90:295-302.
42. Busse WW, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 1999;104(6):1215-22.
43. Condemi JJ, Chervinsky P, Goldstein MF, et al. Fluticasone propionate powder administered through Diskhaler versus triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. J Allergy Clin Immunol. 1997;100(4):467-74.
44. Corren J, Berkowitz R, Murray JJ, et al. Comparison of once-daily mometasone furoate versus once-daily budesonide in patients with moderate persistent asthma. Int J Clin Pract 2003;57(7):567-72.
45. Ferguson AC, Spier S, Manjra A, et. al. Efficacy and safety of high-dose inhaled steroids in children with asthma: A comparison of fluticasone propionate with budesonide. J Pediatr. 1999;134(4):422-27.
46. Fitzgerald D, Van Asperen P, Mellis C, et. al. Fluticasone propionate 750 mcg/day versus beclomethasone dipropionate 1500 mcg/day: comparison of efficacy and adrenal function in pediatric asthma. Thorax. 1998;53(8):656-61.
47. Nathan RA, Nayak AS, Graft DF, et al. Mometasone furoate: efficacy and safety in moderate asthma compared with beclomethasone dipropionate. Ann Allergy Asthma Immunol 2001;86:203-10.
48. Newhouse M, Knight A, Wang S, et al. Comparison of efficacy and safety between flunisolide/Aerochamber® and budesonide/Turbuhaler® in patients with moderate asthma. Ann Allergy Asthma Immunol 2000; 84:313-19.
49. O'Connor B, Bonnaud G, Haahtela T, et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. Ann Allergy Asthma Immunol 2001;86:397-404.

50. Raphael GD, Lanier RQ, Baker J, et. al. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. J Allergy Clin Immunol. 1999;103(5):796-803.
51. Sheikh S, Goldsmith LJ, Howell L. Comparison of the efficacy of inhaled fluticasone propionate, 880 mcg/day, with flunisolide, 1500 mcg/day, in moderate-to-severe persistent asthma. Ann Allergy Asthma Immunol 1999; 83:300-04.
52. Wardlaw A, Larivee P, Eller J, et al. Efficacy and safety of mometasone furoate dry powder inhaler vs. fluticasone propionate metered-dose inhaler in asthma subjects previously using fluticasone propionate. Ann Allergy Asthma Immunol 2004;93:49-55.
53. Weiss KB, Liljas B, Schoenwetter W, et. al. Effectiveness of budesonide administered via dry-powder inhaler versus triamcinolone acetonide administered via pressurized metered-dose inhaler for adults with persistent asthma in managed care settings. Clinical Therapeutics. 2004;26(1):102-14.
54. Fish JE, Karpel JP, Craig TJ, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. J Allergy Clin Immunol 2000;106:852-60.
55. Lee-Wong M, Dayrit FM, Kohli AR, et al. Comparison of high-dose inhaled flunisolide to systemic corticosteroids in severe adult asthma. Chest 2002;122(4):1208-13.
56. Nakanishi AK, Klasner AK, Rubin BK. A randomized controlled trial of inhaled flunisolide in the management of acute asthma in children. Chest 2003;124(3):790-4.
57. Schmier J, Leidy NK, Gower R. Reduction in oral corticosteroid use with mometasone furoate dry powder inhaler improves health-related quality of life in patients with severe persistent asthma. J Asthma 2003;40(4):383-93.
58. Sin DD, Man J, Sharpe H, et al. Pharmacological management to reduce exacerbations in adults with asthma: a systemic review and meta-analysis. JAMA 2004;292:367-76.
59. Donahe JG, Weiss ST, Livingston JM, et al. Inhaled steroids and the risk of hospitalization for asthma. JAMA 1997;277(11):887-91.
60. Dorais M, Blais L, Chabot I, et al. Treatment persistence with leukotriene receptor antagonists and inhaled corticosteroids. Journal of Asthma 2005;42:385-393.
61. Sherman J, Hutson A, Baumstein S, et al. Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for prescriptions. J Pediatr 2000;136(4):532-536.
62. Murphy KR, Fitzpatrick S, Cruz-Riviera M, et al. Effects of budesonide inhalation suspension compared with cromolyn sodium nebulizer solution on health status and caregiver quality of life in childhood asthma. Pediatrics 2003;112:212-219.
63. Peters SP, Anthonisen N, Castro M et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med 2007 May 17; 356 (20): 2027-39
64. Szefler SJ, Baker JW, Uryniak T et al. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol 2007; 120(5):1043-50.
65. Busse WW, Pedersen S, Pauwels RA et al. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy Clin Immunol 2008 May 01; 121(5):1167-74.
66. Covar R, Szefler S, Zeiger R et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. J Allergy Clin Immunol 2008;122:741-47.
67. Qaqundah PY, Sugerman RW, Ceruti E et al. Efficacy and safety of fluticasone propionate hydrofluoroalkane inhalation aerosol in pre-school-age children with asthma: a randomized, double-blind, placebo-controlled study. J Pediatr 2006;149(5):663-670.
68. Sovani MP, Whale CI, Oborne J, Cooper S, Mortimer K, Ekström T, Tattersfield AE, Harrison TW. Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help? Br J Gen Pract. 2008 Jan;58(546):37-43.
69. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. American College of Chest Physicians / American College of Asthma, Allergy, and Immunology. Chest 2005;127:335-371.
70. Filuk R. Delivery system selection: clinical considerations. AHDB 2008;1(8S):13-17.
71. Rand CS. Patient adherence with COPD therapy. Eur Respir Rev 2005;14:97-101.
72. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932-46.
73. Bourbeau J, Rouleau MY, Boucher S. Randomized controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax. 1998;53(6):477-82.

74. Bellamy D, Bouchard J, Henrichsen S, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J. 2006;15:48-57.
75. Nelson HS, Weiss ST, Bleeker ER et al. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129:15-26.
76. Salpeter SR et al. Meta-Analysis: Effect of Long-Acting B-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths, Annals of Internal Medicine. 2006, 144: 904-913.
77. Nguyen WT, Stewart C, Fisher K, et al. Maintenance asthma treatment with fluticasone/salmeterol combination via diskus: effect on outcomes in inner-city children enrolled in TennCare. Allergy and Asthma Proc. 2005;26:129-134.
78. Strand A, Luckow A. Initiation of maintenance treatment of persistent asthma: salmeterol/fluticasone propionate combination treatment is more effective than steroid alone. Respiratory Medicine. 2004;98:1008-1015.
79. Bateman E, Boushey H, Bousquet J et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. Am J Respir Crit Care Med. 2004;170:836-844.
80. Bateman E, Jacques L, Goldfrad C, et al. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006;117(3):563-570.
81. Dal Negro R, Pomari C, Tognella S, et al. Salmeterol and fluticasone 50 mcg/250 mcg bid in combination provides a better long term control than salmeterol 50 mcg bid alone and placebo in COPD patients already treated with theophylline. Pulmonary Pharmacology and Therapeutics. 2003;16:241-246.
82. Hanania N, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 mcg)/salmeterol (50 mcg) combined in the discus inhaler for the treatment of COPD. Chest. 2003;125(3):834-843.
83. Calverley P, Pauwels R, Vestbo J et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. Lancet. 2003;361:449-456.
84. Vestbo J, Pauwels R, Anderson J, et al. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax. 2005;60:301-304.
85. Lundback B, Ronmark E, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. Respiratory Medicine. 2006;100:2-10.
86. Chapman KR, Ringdal N, Backer V, et al. Salmeterol and fluticasone propionate (50/250 microg) administered via combination diskus inhaler: as effective as when given via separate diskus inhalers. Canadian Respiratory Journal. 1999:6:45-51.
87. Nelson HS, Chapman KR, Pyke SD et al. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J Allergy Clin Immunol. 2003;112:29-36.
88. Marceau C, Lemiere C, Berbiche D, et al. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol. 2006;118:574-581.
89. Ringdal N, Eliraz A, Pruzinec P, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respiratory Medicine. 2003;97:234-241.
90. Make B, Hanania N, ZuWallack R, et al. The efficacy and safety of inhaled fluticasone propionate/salmeterol and ipratropium/albuterol for the treatment of chronic obstructive pulmonary disease: an eight week, multicenter, randomized, double blind, double dummy, parallel-group study. Clinical Therapeutics. 2005;27(5):531-542.
91. Pearlman DS, Peden D, Condemi JJ et al. Efficacy and safety of fluticasone propionate/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. Journal of Asthma. 2004;41:797-806.
92. Nathan RA, Rooklin A, Schoaf L et al. Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. Clin Ther. 2006;28:73-85.
93. Nelson HS, Wolfe JD, Gross G et al. Efficacy and safety of fluticasone propionate 44 mcg/salmeterol 21 mcg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. Annals of Allergy, Asthma, & Immunology. 2003;91:263-269.
94. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 mcg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med. 2001;95:136-146.
95. You-Ning L, Humphries M, Du X et al. Efficacy and safety of salmeterol/fluticasone propionate delivered via a hydrofluoroalkane metered dose inhaler in Chinese patients with moderate asthma poorly controlled with inhaled corticosteroids. Int J Clin Pract. 2005;59:754-759.

96. Fitzgerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clinical Therapeutics. 2005;36:116-120.
97. Stoloff S, Stempel D, Meyer J, et al. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. J Allergy Clin Immunol. 2004;113(2):245-251.
98. Stempel D, Stoloff S, Rosenzweig C et al. Adherence to asthma controller medication regimens. Respiratory Medicine. 2005;99:1263-1267.
99. Rabe KF, Atienza T, Magyar P et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006 Aug 26; 368 (9537): 744-53.
100. Pohunek P, Kuna P, Jorup C et al. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. Pediatr Allergy Immunol 2006 Sep 01; 17(6):458-65.
101. Aaron SD, Vandemheen KL, Fergusson D et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007 Apr 17; 146 (8): 545-55.
102. Rabe K, Timmer W, Sagkriotis A et al. Comparison of a Combination of Tiotropium Plus Formoterol to Salmeterol Plus Fluticasone in Moderate COPD. Chest 2008 Aug 1; 134 (2): 255-62.
103. Sorkness CA, Lemanske RF Jr, Mauger DT et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol 2007 Jan 01; 119(1): 64-72.
104. Lindberg A, Szalai Z, Pullerits T et al. Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction. Respirology 2007 Sep 01; 12 (5):732-9.
105. Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007 Feb 22; 356 (8):775-89.
106. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther. 2007 May;29(5):823-43.
107. Murphy K, Nelson H, Parasuraman B, Boggs R, Miller C, O'Dowd L. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. Curr Med Res Opin. 2008 Feb 8; [Epub ahead of print].
108. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma. Drugs. 2006;66(17):2235-54.
109. Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther. 2001;14(1):29-34.
110. Lötvall J, Langley S, Woodcock A. Inhaled steroid/long-acting b2 agonist combination products provide 24 hours improvement in lung function in adult asthmatic patients. Respir Res. 2006 Aug 18;7:110.
111. Rosenhall L, Borg S, Andersson F, Ericsson K l. Budesonide/formoterol in a single inhaler (Symbicort) reduces healthcare costs compared with separate inhalers in the treatment of asthma over 12 months. Int J Clin Pract. 2003 Oct;57(8):662-7.
112. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004 Sep;20(9):1403-18.
113. Rabe KF, Pizzichini E, Ställberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma. Chest. 2006 Feb;129(2):246-56.
114. Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. Respir Res. 2007 Jul 4;8:46.
115. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. Respir Med. 2006 Jul;100(7):1152-62.
116. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ; EDICT Investigators. Evaluation of different inhaled combination therapies (EDICT): a randomized, double-blind, comparison of Seretide (50/250 µg bd Diskus) vs formoterol (12 µg bd) and budesonide (800 µg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. Respir Med. 2002 Nov;96(11):851-61.

117. Pohl WR, Vetter N, Zwick H, Hrubos W. Adjustable maintenance dosing with budeosnide/formoterol or budesonide: double blind study. Respir Med. 2006 Mar;100(3):551-60.
118. Remington TL, Heaberlin AM, DiGiovine B. Combined budesonide/formoterol turbuhaler treatment of asthma. Ann Pharmacother. 2002 Dec;36(12):1918-28.
119. Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol. 2002 Nov;34(5):342-50.
120. Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest. 2003 May;123(5):1480-7.
121. Rosenhall L, Elvstrand A, Tilling B, Vinge I, Jemsby P, Ståhl E, et al. One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort® Turbuhaler®) for the treatment of asthma. Respir Med. 2003 Jun;97(6):702-8.
122. Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Ståhl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. Int J Clin Pract. 2002 Jul-Aug;56(6):427-33.
123. Papi A, Paggiaro PL, Nicolini G, Vignola AM, Fabbri LM; Inhaled Combination Asthma Treatment versus SYmbicort (ICAT SY) Study Group. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. Eur Respir J. 2007; 29: 682-9.
124. Bateman ED, Bantje TA, Joao Gomes M, Toumbis MG, Huber RM, Naya I, et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. Am J Respir Med. 2003;2(3):275-81.
125. Ericsson K, Bantje TA, Huber RM, Borg S, Bateman ED. Cost-effectiveness analysis of budesonide/formoterol compared with fluticasone in moderate-persistent asthma. Respir Med. 2006 Apr;100(4):586-94.
126. Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S, et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. Eur Respir J. 2001 Aug;18(2):262-8.
127. Kuna P, Creemers JPHM, Vondra V, Black PN, Lindqvist A, Nihlen U, et al. Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. Respir Med. 2006 Dec;100(12):2151-9.
128. Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006 May;11(3):276-86.
129. Morice AH, Peterson S, Beckman O, et al. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. Int J Clin Pract. 2007 Nov; 61(11): 1874-83.
130. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martínez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007 May; 61(5):725-36.
131. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandström T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40.
132. Pauwels RA, Lofdahl C-G, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med. 1997 Nov 13;337(20):1405-11.
133. Canonica GW, Castellani P, Cazzola M, Fabbri LM, Fogliani V, Mangrella M, et al; The CAST (Control Of Asthma By Symbicort Turbuhaler) Study Group. Adjustable maintenance dosing with budesonide/formoterol in a single inhaler provides effective asthma symptom control at lower dose than fixed maintenance dosing. Pulm Pharmacol Ther. 2004;17(4):239-47.
134. Edwards SJ, Gruffydd-Jones K, Ryan DP. Systemic review and meta-analysis of budesonide/formoterol in a single inhaler. Curr Med Res Opin. 2007 Aug;23(8):1809-20.
135. Erin EM, Zacharasiewiez AS, Nicholson GC, Tan AJ, Neighbour H, Engelstatter R, et al. Rapid effect of inhaled ciclesonide in asthma: a randomized, placebo-controlled study. Chest 2008;134:740-5.
136. Chervinsky P, Baker J, Bensch G, Parasuraman B, Boggs R, Martin P, et al. Patient-reported outcomes in adults with moderate to severe asthma after use of budesonide and formoterol administered via 1 pressurized metered-dose inhaler. Ann Allergy Asthma Immunol 2008;101:463-73.

137. Kerwin EM, Oppenheimer JJ, LaForce C, Parasuraman B, Miller CJ, O'Dowd L, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice daily budesonide/formoterol dosing. Ann Allergy Asthma Immunol 2009;103:62-72.
138. Maspero J, Guerra F, Cuevas F, Gutierrez JP, Soto-Ramos M, Anderton S, et al. Efficacy and tolerability of of salmeterol/fluticasone propionate versus montelukast in childhood asthma: a prospective, randomized, double-blind, double-dummy, parallel-group study. Clin Ther 2008;30:1492-1504.
139. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19-26.
140. Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. Chest 2008;134:255-62.
141. de Blic J, Ogorodova L, Klink R et al. Salmeterol/fluticasone propionate vs double dose fluticasone propionate on lung function and asthma conrol in children. Pediatr Allergy Immunol 2009;20:763-771.
142. Berger WE, Leflein JG, Geller DE et al. The safety and clinical benefit of budesonide/formoterol pressurized metered dose inhaler versus budesonide alone in children. Allergy Asthma Proc 2010;31:26-39.
143. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-750.
144. Papi A, Canonica GW, Maestrelli PN et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52
145. Burge PA, Calverley PM, Jones PW, et al. Randomized, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.
146. Hansel TT, Benezet O, Kafé H, et al. A multinational, 12-week, randomized study comparing the efficacy and tolerability of ciclesonide and budesonide in patients with asthma. Clin Ther 2006;28:906-20.
147. Niphadkar P, Jagannath K, Joshi JM, et al. Comparison of the efficacy of ciclesonide 160 microg QD and budesonide 200 microg BID in adults with persistent asthma: a phase III, randomized, double-dummy, open-label study. Clin Ther 2005;27:1752-63.
148. von Berg A, Engelstätter R, Minic P, et al. Comparison of the efficacy and safety of ciclesonide 160 microg once daily vs. budesonide 400 microg once daily in children with asthma. Pediatr Allergy Immunol 2007;18:391-400.
149. Boulet LP, Drollmann A, Magyar P, et al. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. Respir Med 2006;100:785-94.
150. Ukena D, Biberger C, Steinijans V, et al. Ciclesonide is more effective than budesonide in the treatment of persistent asthma. Pulm Pharmacol Ther 2007;20:562-70.
151. Vermeulen JH, Gyurkovits K, Rauer H, et al. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. Respir Med 2007;101:2182-91.
152. Buhl R, Vinkler I, Magyar P, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. Pulm Pharmacol Ther 2006;19:404-12.
153. Magnussen H, Hofman J, Staneta P, et al. Similar efficacy of ciclesonide once daily versus fluticasone propionate twice daily in patients with persistent asthma. J Asthma 2007;44:555-63.
154. Pedersen S, Engelstätter R, Weber HJ, et al. Efficacy and safety of ciclesonide once daily and fluticasone propionate twice daily in children with asthma. Pulm Pharmacol Ther 2009;22:214-20.
155. Boulet LP, Bateman ED, Voves R, et al. A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. Respir Med 2007;101:1677-86.
156. Bateman ED, Linnhof AE, Homik L, et al. Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma. Pulm Pharmacol Ther 2008;21:264-75.
157. Weinstein SF, Corren J, Murphy K, et al. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. Allergy Asthma Proc 2010;31:280-9.
158. Nathan RA, Nolte H, Pearlman DS, et al. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. Allergy Asthma Proc 2010;31:269-79.
159. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). Available at:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm. Accessed December 2010.

160. Gappa M, Zachgo W, von Berg A et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatr Pulmonol. 2009 Nov; 44(11):1132-42.
161. Lasserson TJ, Cates CJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004106. DOI: 10.1002/14651858.CD004106.pub3.

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I. Overview

The respiratory smooth muscle relaxants (xanthines) are approved for the treatment of asthma, chronic bronchitis and emphysema.[1-7] Their respiratory effects are thought to be mediated through competitive inhibition of phosphodiesterase with a resultant increase in cyclic AMP. This produces relaxation of bronchial smooth muscle (bronchodilation) and suppresses the response of the airway to stimuli.

The respiratory smooth muscle relaxants are available as single entity products, as well as in combination with guaifenesin and pseudoephedrine. Guaifenesin increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. It increases the efficiency of the cough reflex and ciliary action in removing accumulated secretions from the trachea and bronchi.[1-3] Pseudoephedrine directly stimulates beta-adrenergic receptors causing bronchial relaxation.

Theophylline is the reference xanthine derivative from which aminophylline and dyphylline were developed. Aminophylline is a 2:1 complex of theophylline and ethylenediamine. Dyphylline is a xanthine derivative with pharmacologic actions similar to theophylline; however, it is not converted to free theophylline *in vivo*.[4] Xanthines are often carefully titrated according to weight-based dosing due to their narrow therapeutic index. For bronchodilatory effects, therapeutic serum levels of theophylline should fall between 10-20 mcg/ml. Of the xanthines, dyphylline has the shortest serum half-life.[1-3] The xanthines generally share similar side effect profiles, precautions and contraindications.

The respiratory smooth muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation, with the exception of guaifenesin/theophylline/pseudoephedrine. This class was last reviewed in December 2008.

Table 1. Respiratory Smooth Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aminophylline	injection, tablet	N/A	aminophylline
Dyphylline	tablet, elixir*	Lufyllin®	dyphylline
Guaifenesin and dyphylline	elixir, liquid, syrup, tablet	Difil-G®, Difil-G Forte®*, Dilex-G®, Lufyllin-GG®*	guaifenesin and dyphylline
Guaifenesin and theophylline	liquid	N/A	guaifenesin and theophylline
Guaifenesin, theophylline and pseudoephedrine	elixir	Bronchomar-1®	none
Theophylline	elixir, extended-release capsule, injection*, solution*, sustained-release tablet*	Elixophyllin®, Theo-24®	theophylline

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the respiratory smooth muscle relaxants are summarized in Table 2. For a comprehensive overview of the treatment of asthma and chronic obstructive pulmonary disease, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Respiratory Smooth Muscle Relaxants

Clinical Guideline	Recommendation(s)
Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): **British Guideline on the Management of Asthma[13] (2009)**	General Treatment Considerations • Inhaled corticosteroids are the recommended preventer drug for adults and children for achieving overall treatment goals. • Alternative preventer therapies in patients taking short-acting β_2-agonists alone are mast-cell stabilizers, leukotriene receptor antagonists and theophylline. • The first choice as add-on therapy to inhaled corticosteroids in adults and children (5-12 years of age) is an inhaled long-acting β_2-agonist. • If control remains inadequate on an inhaled corticosteroid plus a long-acting β_2-agonist, consider the following interventions: leukotriene receptor antagonists, theophylline, slow release β_2-agonist tablets (adults). There are no controlled trials indicating which treatment option is best; however, the potential for adverse events is greater with theophylline and β_2-agonist tablets. Exercise-Induced Asthma • The following treatments provide protection against exercise-induced asthma: inhaled corticosteroids, short-acting β_2-agonists, long-acting β_2-agonists, theophyllines, leukotriene receptor antagonists, chromones, and β_2-agonist tablets. • If exercise is a specific problem in patients who are well controlled on inhaled corticosteroids, consider the following therapies: leukotriene receptor antagonists, long-acting β_2-agonists, chromones, oral β_2-agonists, or theophyllines. • Inhaled short-acting β_2-agonists are the drug of choice immediately prior to exercise.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention[12] (2009)**	• Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. • In adults, sustained-release theophylline has little effect as a first-line controller. It may provide benefit as add-on therapy in patients who do not achieve control on inhaled glucocorticosteroids alone. Theophylline is less effective than long-acting inhaled β_2-agonists. • In children >5 years of age, theophylline has been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids. Sustained-release products with reliable absorption profiles and complete bioavailability (with and without concomitant food intake) are preferable for maintenance therapy.
Global Initiative for Asthma (GINA): **Global Strategy for the Diagnosis and Management of Asthma in Children 5 years and Younger[9] (2009)**	• A low-dose inhaled glucocorticosteroid is the recommended initial treatment option in children ≤5 years of age. Inhaled glucocorticosteroids have been shown to be more effective than other controller treatment for asthma. • The efficacy of theophylline is less than that of low-dose inhaled glucocorticosteroids and adverse events are more common.
National Heart, Lung, and Blood Institute (NHLBI): **Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[11] (2007)**	• Inhaled corticosteroids (ICSs) are the most effective long-term therapy for mild, moderate, or severe persistent asthma. • Sustained-release theophylline is an alternative (not preferred) treatment for mild persistent asthma. It may also be used as alternative (not preferred) adjunctive therapy with ICS.

Clinical Guideline	Recommendation(s)
International Primary Care Respiratory Group (IPCRG): **Management of Asthma[14] (2006)**	• The most effective preventative therapy is inhaled corticosteroids. • For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting β_2-agonist. Alternatives are combinations of inhaled corticosteroids with sustained-release theophylline or with leukotriene receptor antagonists.
National Institute for Clinical Excellence (NICE): **Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care[17] (2010)**	• Inhaled agents are preferred over oral treatments because of the reduction in systemic side effects. • As needed short-acting bronchodilators should be the initial empirical treatment for the relief of breathlessness and exercise limitation. • Initial therapy includes either an inhaled long-acting β_2-agonist (LABA) or long-acting muscarinic antagonist (LAMA), with or without an inhaled corticosteroid, depending on the severity of the disease. • Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions.
Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[15] (2009)**	• Bronchodilator medications are central to the symptomatic management of COPD. • The principal bronchodilator treatments are β_2-agonists, anticholinergics and xanthines used as monotherapy or in combination. • Theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.
American College of Physicians (ACP): **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease[10] (2007)**	• Clinicians should prescribe one of the following maintenance monotherapies for symptomatic patients with COPD and FEV_1 <60% predicted: long-acting inhaled β_2-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids. • Monotherapy with a long-acting inhaled β_2-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations. • Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness, but differ in adverse effects, reductions in deaths, and hospitalizations. • Evidence is insufficient to recommend one agent over another. • Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV_1 <60% predicted. However, when to use combination therapy instead of monotherapy has not been clearly established. Studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy. • This guideline does not provide recommendations regarding the use of the smooth muscle relaxants.
International Primary Care Respiratory Group (IPCRG): **Management of Chronic Obstructive Pulmonary Disease[18] (2006)**	• None of the current pharmacologic treatments for COPD have been shown to modify the long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • This guideline does not provide recommendations regarding the use of the smooth muscle relaxants.
American Thoracic Society (ATS)/European Respiratory Society (ERS): **Standards for the Diagnosis and Treatment**	• At present no treatment is shown to modify the rate of decline in lung function. • The initial trial data show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination

Clinical Guideline	Recommendation(s)
of Patients with Chronic Obstructive Pulmonary Disease[16] (2004)	therapy compared with its components. The largest effects in terms of exacerbations and health status are seen in patients with an FEV_1<50% predicted, where combining treatment is clearly better than either component drug used by itself. • Three types of bronchodilators are in common clinical use: β-agonists, anticholinergic drugs and xanthines. • Combining long-acting β-agonists and theophylline appears to produce a greater spirometric change than either drug alone.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory smooth muscle relaxants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Respiratory Smooth Muscle Relaxants[1-7]

Indication	Aminophylline	Dyphylline	Guaifenesin/ Dyphylline	Guaifenesin/ Theophylline	Guaifenesin/ Theophylline/ PSE	Theophylline
Asthma						
Treatment of the symptoms and reversible airflow obstruction associated with asthma	✔	✔	✔	✔	✔	✔
Chronic Bronchitis and Emphysema						
Treatment of the symptoms and reversible airflow obstruction associated with chronic bronchitis and emphysema	✔	✔	✔	✔	✔	✔

PSE=pseudoephedrine

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Respiratory Smooth Muscle Relaxants[1-7]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aminophylline	PO: 1-2 IV: 0.5	Variable	100	40	Liver (90)	Renal (10)	Variable* 3.7-12
Dyphylline	0.75	Variable	Rapidly absorbed	Not Reported	Not reported	Renal (82-88)	2
Theophylline	IR: 1-2 ER: 8 SR: 8	Variable	Complete	40%	Liver (90)	Renal (10)	Variable* 3.7-12
Guaifenesin	0.5	4-6	Well absorbed	Not Reported	Blood (60)	Renal	1
Pseudoephedrine	1.5-2.4	3-8	Not Reported	Not Reported	Liver (10-30)	Renal (70-90)	9-16

*Elimination half-life highly variable and dependent upon age, liver function, cardiac function, presence of lung disease, and smoking history.

V. Drug Interactions

Significant drug interactions with the respiratory smooth muscle relaxants are listed in Table 5.

Table 5. Significant Drug Interactions with the Respiratory Smooth Muscle Relaxants[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Dyphylline	1	Acitretin	Dyphylline may increase plasma concentrations and toxic effects of acitretin.
Dyphylline	1	Disulfiram	The combination of dyphylline and disulfiram may produce acute alcohol intolerance. Inhibition of aldehyde dehydrogenase by disulfiram leads to the development of toxic intermediate metabolites.
Dyphylline	1	Insulin	Dyphylline may increase the hypoglycemic effect of insulin.
Pseudoephedrine	1	Furazolidone	Furazolidone may increase pressor sensitivity to pseudoephedrine due to liberation of large amounts of norepinephrine.
Pseudoephedrine	1	Linezolid	Pharmacologic effects of pseudoephedrine may be increased by linezolid due to MOA inhibition. Headache, hyperpyrexia, and hypertension may occur.
Pseudoephedrine	1	MAO inhibitors	MAO inhibitors may increase pressor response at receptor sites due to accumulation of norepinephrine from MAO-inhibitor blocking of norepinephrine metabolism and normal release of norepinephrine from pseudoephedrine.
Theophyllines (all)	1	Halothane	Halothane may cause catecholamine-induced arrhythmias in a patient who has taken theophylline.
Theophyllines (aminophylline, theophylline)	1	Quinolones	Inhibition of cytochrome P450 1A2 isoenzymes by quinolones may decrease the metabolic elimination of theophylline. Additional theophylline plasma concentration and clinical monitoring are indicated, as a dose reduction may be needed during concurrent therapy.
Dyphylline	2	Acetaminophen	The risk of acetaminophen-induced hepatotoxicity may be increased by chronic intake of dyphylline.
Dyphylline	2	Benzodiazepines	The CNS depressant effects of benzodiazepines and dyphylline may be increased. Excessive

Generic Name(s)	Significance Level	Interaction	Mechanism
			sedation and impaired psychomotor function may occur.
Dyphylline	2	Furazolidone	The combination of dyphylline and furazolidone may produce acute alcohol intolerance in some patients.
Dyphylline	2	Metronidazole	Combination of metronidazole and dyphylline may produce alcohol intolerance since metronidazole may inhibit aldehyde dehydrogenase-mediated metabolism of ethanol.
Dyphylline	2	Metformin	The hypoglycemic effects of metformin may be increased by dyphylline.
Dyphylline	2	Probenecid	The renal excretion of dyphylline is decreased by probenecid.
Dyphylline	2	Sodium Oxybate	Concurrent use of sodium oxybate and dyphylline may result in an increase in sleep duration and CNS depression.
Pseudoephedrine	2	Guanethidine	Guanethidine may decrease the effects of pseudoephedrine which is dependent on norepinephrine since guanethidine depletes norepinephrine stores.
Pseudoephedrine	2	Urinary alkalinizers	Urinary alkalinizers may increase the serum levels of pseudoephedrine resulting in increased pharmacologic and toxic effects of theophylline. The mechanism is thought to be due to an increased urinary pH leading to increased tubular reabsorption of pseudoephedrine.
Theophyllines (all)	2	Adenosine	The pharmacologic effects of adenosine may be decreased by xanthines. Adenosine may lose its pharmacologic effect in patients treated with xanthines.
Theophyllines (all)	2	Barbiturates	Barbiturates may increase the metabolism and clearance of xanthines by inducing cytochrome P450 enzymes resulting in decreased asthma control.
Theophyllines (all)	2	β-blockers (non-selective)	Non-selective β-blockers may decrease the elimination of xanthines by inhibiting the n-demethylation process resulting in increased pharmacologic and toxic effects of theophylline.

Generic Name(s)	Significance Level	Interaction	Mechanism
			However, the use of a non-selective β-blocker may also decrease the therapeutic effects of xanthine derivatives by pharmacologic antagonism resulting in increased airway resistance and poor asthma control.
Theophyllines (aminophylline, theophylline)	2	Cimetidine	The pharmacologic effects of xanthines may be increased by cimetidine. Elevated plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (all)	2	Dipyridamole	Xanthines may attenuate the pharmacologic action of intravenous dipyridamole, leading to false negative dipyridamole-thallium-201 cardiac imaging studies.
Theophyllines (aminophylline, theophylline)	2	Erythromycin	The pharmacologic effects of xanthines may be increased by erythromycin. Elevated plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (aminophylline, theophylline)	2	Febuxostat	Plasma concentrations and pharmacologic effects of xanthines may be increased by febuxostat.
Theophyllines (aminophylline, theophylline)	2	Fluvoxamine	Fluvoxamine may increase the pharmacologic effects of xanthines. Elevated plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (all)	2	Hydantoins	Pharmacologic effects of xanthines and hydantoins may be decreased since reduced plasma concentrations of xanthines and phenytoin may occur.
Theophyllines (all)	2	Lithium	The pharmacologic effects of lithium may be decreased by xanthines. The renal excretion of lithium may be increased by xanthines.
Theophyllines (all)	2	Mexiletine	Mexiletine may impair hepatic elimination and increase plasma concentrations of xanthines.

Generic Name(s)	Significance Level	Interaction	Mechanism
			Additive arrhythmogenic effects may also occur.
Theophyllines (all)	2	Nondepolarizing muscle relaxants	Xanthines may cause a dose-dependent reversal of neuromuscular blockade induced by a nondepolarizing relaxant.
Theophyllines (aminophylline, theophylline)	2	Oral contraceptives	Pharmacologic effects of xanthines may be increased by oral contraceptives. Elevated theophylline plasma levels with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (aminophylline, theophylline)	2	Rifamycins	Rifamycins may increase xanthine metabolism and clearance by inducing cytochrome P450 resulting in decreased asthma control.
Theophyllines (all)	2	Tacrine	Xanthines given concomitantly with tacrine increases the half-life of xanthines and plasma concentrations by approximately two-fold.
Theophyllines (aminophylline, theophylline)	2	Thiabendazole	Thiabendazole may increase serum levels of xanthines resulting in increased pharmacologic and toxic effects through an unknown mechanism.
Theophyllines (aminophylline, theophylline)	2	Ticlopidine	Ticlopidine may decrease the elimination of xanthines resulting in increased pharmacologic and toxic effects.
Theophyllines (aminophylline, theophylline)	2	Troleandomycin	Pharmacologic effects of xanthines may be increased. Elevated plasma levels with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (all)	2	Zileuton	Zileuton increases serum levels of xanthines resulting in increased pharmacologic and toxic effects, possibly through the inhibition of theophylline metabolism.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the respiratory smooth muscle relaxants are listed in Table 6. Adverse drugs events reported with guaifenesin and pseudoephedrine are listed in Table 7. Due to the narrow therapeutic index of the xanthines, adverse events are dependent on the peak serum concentration. They are generally mild and transient with serum levels <20 mcg/ml, whereas they are more common and severe when the serum concentration exceeds 20 mcg/ml.[1-3]

Table 6. Adverse Drug Events (%) Reported with the Respiratory Smooth Muscle Relaxants[1-7]

Adverse Events	Aminophylline	Dyphylline	Theophylline
Cardiovascular			
Arrhythmia	✔	✔	✔
Bradycardia	✔	-	-
Cardiac arrest	✔	-	-
Circulatory failure	✔	✔	✔
Extrasystoles	✔	✔	✔
Hypotension	✔	✔	✔
Palpitations	✔	✔	✔
Premature ventricular contraction	✔	-	✔
Tachycardia	1-10	1-10	1-10
Central Nervous System			
Dizziness	✔	✔	✔
Headache	✔	✔	✔
Insomnia	<1	✔	<1
Irritability	<1	✔	<1
Nervousness	1-10	1-10	1-10
Reflex hyperexcitability	✔	✔	✔
Restlessness	1-10	1-10	1-10
Seizure	<1	✔	<1
Syncope	✔	-	-
Dermatological			
Allergic skin reactions	<1	-	-
Angioedema	✔	-	-
Flushing	✔	✔	✔
Injection site pain	✔	-	-
Pruritus	✔	-	-
Rash	<1	-	-
Tissue sloughing	✔	-	-
Urticaria	✔	-	-
Endocrine and Metabolic			
Elevated SGOT	✔	✔	✔
Hyperglycemia	✔	✔	✔
SIADH	✔	✔	✔
Gastrointestinal			
Abdominal cramping	✔	✔	✔
Anorexia	✔	✔	✔
Diarrhea	✔	✔	✔
Epigastric pain	✔	✔	✔
Hematemesis	✔	✔	✔
Nausea	1-10	1-10	1-10
Vomiting	1-10	1-10	1-10
Genitourinary			
Albuminuria	✔	✔	✔
Diuretic effect	✔	✔	✔
Excretion of renal tubular cells	✔	✔	✔

Adverse Events	Aminophylline	Dyphylline	Theophylline
Hematologic			
Bone marrow suppression	✔	✔	✔
Hemorrhagic diathesis	✔	✔	✔
Leukopenia	✔	✔	✔
Thrombocytopenia	✔	✔	✔
Laboratory Test Abnormalities			
Elevated plasma glucose	-	-	✔
Elevated uric acid	✔	✔	✔
Elevated free fatty acid	-	-	✔
Elevated total cholesterol	-	-	✔
Elevated HDL	-	-	✔
Elevated HDL/LDL ratio	-	-	✔
Elevated urinary free cortisol excretion	-	-	✔
Musculoskeletal			
Muscle cramps	-	-	✔
Respiratory			
Tachypnea	✔	✔	✔
Other			
Dehydration	✔	✔	✔
Tremor	<1	-	<1
Twitching of fingers/hands	✔	✔	✔

✔ Percent not specified
- Event not reported

Table 7. Adverse Drug Events (%) Reported with Guaifenesin and Pseudoephedrine[1-7]

Adverse Events	Guaifenesin	Pseudoephedrine
Cardiovascular		
Arrhythmia	-	✔
Bradycardia	-	✔
Palpitations	-	✔
Tachycardia	-	✔
Transient hypertension	-	✔
Central Nervous System		
Dizziness	✔	✔
Drowsiness	-	✔
Headache	✔	✔
Insomnia	-	✔
Nervousness	-	✔
Prolonged psychosis	-	✔
Restlessness	-	✔
Dermatological		
Rash	-	✔
Urticaria	✔	✔
Gastrointestinal		
Gastric irritation	-	✔
Hematemesis	-	✔
Nausea	✔	-
Vomiting	✔	-
Genitourinary		
Urinary retention	-	✔
Hematologic		
Agranulocytosis	-	✔
Leukopenia	-	✔
Thrombocytopenia	-	✔

Adverse Events	Guaifenesin	Pseudoephedrine
Musculoskeletal		
Orofacial dystonia	-	✔
Weakness	-	✔
Respiratory		
Tachypnea	-	✔
Other		
Blepharospasm	-	✔
Sweating	-	✔
Tremor	-	✔
Uric levels decreased	✔	-

VII. Dosing and Administration

The usual dosing regimens for the respiratory smooth muscle relaxants are listed in Table 8.

Table 8. Usual Dosing Regimens for the Respiratory Smooth Muscle Relaxants[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aminophylline	Reversible Airway Disease: Injection: initial, 6 mg/kg IV over 20-30 minutes; maintenance, 0.5 mg/kg/hour continuous infusion ; maximum, 900 mg/day theophylline or 13 mg/kg/day theophylline, whichever is less Tablet: initial, 380 mg/day (equivalent to 300 mg theophylline/day) in divided doses every 6 to 8 hours; maintenance, 928 mg/day (equivalent to theophylline 800 mg/day) in divided doses every 6 to 8 hours; maximum, 900 mg/day theophylline or 13 mg/kg/day theophylline, whichever is less	Reversible Airway Disease: Injection: initial, 6 mg/kg IV over 20-30 minutes; maintenance, 0.5-1 mg/kg/hour; maximum, 900 mg/day theophylline or 13-24 mg/kg/day theophylline, whichever is less Tablet: >45 kg: refer to adult dosing <45 kg: initial, 15-17.7 mg/kg/day in divided doses every 4 to 6 hours; maintenance, titrate to effect up to 20 mg/kg/day in divided doses every 4 to 6 hours; maximum, 760 mg/day aminophylline	Injection: 250mg/10 ml 500 mg/20 ml Tablet: 100 mg 200 mg
Dyphylline	Reversible Airway Disease: 15 mg/kg every 6 hours	Safety and efficacy in children have not been established	Elixir: 100 mg/15 ml Tablet: 200 mg 400 mg
Guaifenesin and dyphylline	Reversible Airway Disease: 100-100 mg or 200-200 mg three to four times daily	Safety and efficacy in children have not been established.	Elixir: 100-100 mg/15 ml Liquid: 100-100 mg/5 ml Syrup: 50-100 mg/5 ml 200-100 mg/5 ml Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			200-200 mg 300-200 mg 400-200 mg
Guaifenesin and theophylline	Reversible Airway Disease: 16 mg/kg/day or 400 mg theophylline/day, in divided doses every 6 to 8 hours	Safety and efficacy in children have not been established.	Liquid: 100-150 mg/15 ml
Guaifenesin, theophylline and pseudoephedrine	Reversible Airway Disease: No dosing information available	Safety and efficacy in children have not been established.	Elixir: 150-150 mg/15 ml
Theophylline	Reversible Airway Disease: Capsule (ER): Initial, 300-400 mg once daily; maintenance, may increase dose to 400-600 mg once daily after 3 days, if dose greater then 600mg/day, titrate according to blood levels Elixir/solution: Initial loading dose, 5 mg/kg; maintenance, 300 mg/day anhydrous theophylline in divided doses every 6 to 8 hours (may increase dose to 400 mg/day after 3 days, may increase dose to 600 mg/day after 3 more days); maximum: 900 mg/day, unless serum levels indicate need for larger doses Injection: Initial, 4.6 mg/kg) over 20-30 minutes; maintenance, 0.3-0.4 mg/kg/hour continuous infusion; maximum: 900 mg/day unless serum levels indicate need for larger doses Tablet (SR): Initial, 150 mg twice daily; maintenance, may increase dose to 200 mg twice daily after 3 days, may increase dose to 300 mg/day after 3 more days; maximum: 900 mg/day unless serum levels indicate need for larger doses	Reversible Airway Disease: Capsule (ER): Initial, 12-14 mg/kg/day; maintenance, may increase to 16 mg/kg once daily after 3 days, may increase to 20 mg/kg/day after 3 more days; if dose greater then 600 mg/day, titrate according to blood levels Elixir/solution: Initial, 12 to 14 mg/kg/day in divided doses every 4 to 6 hours (maximum, 300 mg/day); after 3 days (if tolerated), increase to 16 mg/kg/day in divided doses every 4 to 6 hours, (maximum, 400 mg/day); after 3 more days (if tolerated and needed), increase to 20 mg/kg/day in divided doses every 4 to 6 hours, (maximum, 600 mg/day) Injection: Initial, 4.6 mg/kg over 20-30 minutes; maintenance, 0.5-0.8 mg/kg/hour; maximum: 900 mg/day unless serum levels indicate need for larger doses Tablet (SR): Initial, 12-14 mg/kg/day divided every 12 hours ; maintenance, may increase to 16 mg/kg/day divided every 12 hours after 3 days, may increase to 20 mg/kg/day divided every 12 hours after 3 more days; (maximum: 600 mg/day)	Capsule (ER): 100 mg 200 mg 300 mg 400 mg Elixir: 80 mg/15 ml Injection: 200 mg/50 ml 200 mg/100 ml 400 mg/250 ml 400 mg/500 ml 800 mg/250 ml 800 mg/500 ml 800 mg/L Solution: 80 mg/15 ml Tablet (SR): 100 mg 200 mg 300 mg 400 mg 450 mg 600 mg

ER=extended-release, IR=immediate-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory smooth muscle relaxants are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Respiratory Smooth Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Roberts et al.[44] (2003) Aminophylline infusion (5 mg/kg over 20 minutes), followed by 0.9 mg/kg/h infusion vs albuterol IV bolus (15 mcg/kg over 20 minutes), followed by saline infusion	RCT, DB Patients 1 to 16 years of age with acute severe asthma that is unresponsive to treatment with three nebulizers (combined albuterol [2.5 mg, 5 mg if ≥5 years] and ipratropium [125 mcg, 250 mcg if ≥5 years]) administered over 1 hour and systemic steroids	N=44 3 to 4 days	Primary: Asthma severity score, supplemental oxygen Secondary: Adverse effects	Primary: There was no significant difference in both treatment groups relative to asthma severity score at 2 hours (P=0.93) or change in this score from time 0 to 2 hours (P=0.85). Secondary: There was a significant difference in the albuterol group in terms of requiring a longer hospital stay (P=0.02). There was no significant difference in both treatment groups relative to adverse events (P=0.50) or longer duration of oxygen therapy (P=0.07).
Ream et al.[23] (2001) Aminophylline 7 mg/kg IV bolus, followed by theophylline infusion (to achieve serum levels between 12 to 17 mcg/mL; age-related dosing protocol: 6-12 months 0.5	PRO, DB, RCT Patients between 13 months and 17 years with severe status asthmaticus admitted to the pediatrics intensive care unit for ≤2 hours with intractable wheezing and a modified Wood-Downes clinical	N=47 29 to 189 days	Primary: Time to reach clinical asthma score ≤3 Secondary: Time required to meet predetermined criteria for discharge from pediatric intensive care unit, adverse events	Primary: The patients receiving theophylline showed a statistically significant decrease in time to reach a clinical asthma score ≤3 (P<0.05), regardless of mechanical ventilation use. Secondary: There was a significant difference in time required to meet discharge criteria (P<0.05) and shortened length of intensive care unit stay observed in patients taking theophylline who were receiving mechanical ventilation relative (P<0.05). Theophylline was associated with more emesis (P<0.05) and the control regimen was associated with more tremor (P<0.05). Theophylline showed no statistically significant effect relative to the total incidence of side

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/h, 1-9 years 0.8 mg/kg/h, ≥10 years 0.65 mg/kg/h) in addition to continuous albuterol nebulization, intermittent, inhaled ipratropium, and IV methyl-prednisolone vs continuous albuterol nebulization, intermittent, inhaled ipratropium, and IV methyl-prednisolone	asthma score of ≥5 and treated with an aggressive regimen consisting of continuous albuterol nebulization 0.3 mg/kg/h at 7-8 L/min, intermittent inhaled ipratropium during first 48 hours of hospitalization at 250 to 500 mcg every 6 hours, and IV methylprednisolone with bolus dose of 2 mg to 4 mg/kg, then 0.5 mg to 1.0 mg/kg/dose every 6 hours until discharge from intensive care unit			effects.
Yung et al.[22] (1998) Aminophylline IV 10 mg/kg loading dose, followed by continuous infusion of 1.1 mg/kg/h (<10 years old) or 0.7 mg/kg/h (≥10 years old)	RCT, PC, DB Patients aged 1 and 19 years old with severe acute asthma currently unresponsive to three 5 mg doses of nebulized albuterol and treated with large doses of inhaled albuterol (5 mg/dose in 4 mL at	N=163 3 days	Primary: Length of hospital stay Secondary: Spirometry, FEV_1, FVC, maximum mid-expiratory flow, and PEFR, saturated oxygen, supplemental oxygen use, albuterol doses,	Primary: The effects of aminophylline on the mean length of hospital stay was not statistically significant compared to placebo (2.69, 2.87, days, respectively, P=0.53). Secondary: Compared to placebo, there was a statistically significant difference in patients receiving aminophylline relative to improved FEV_1, maximum mid-expiratory flow, and PEFR at 6 hours, 12-18 hours, and 24 hours (except for maximum expiratory flow at 24 hours). P values ranged from 0.0016 to 0.043. Patients receiving aminophylline experienced a higher saturated oxygen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	8-10 L/min), inhaled ipratropium (250 mcg every 4 to 6 hours), and intravenous steroids (1mg/kg every 6 hours, followed by oral prednisone 1 mg/kg BID during convalescence)		intubation duration	level up to 30 hours compared to placebo. Exact P values not reported. Patients receiving placebo required a longer duration of supplemental oxygen compared to placebo (P=0.015), longer duration (P=0.045) and higher total dose (P=0.009) of IV albuterol. There was no statistical difference between the treatment groups in terms of number of doses of albuterol or reduction in intubation duration.
Vieira et al.[46] (1998) Aminophylline IV 6 mg/kg loading dose, followed by 1.2 mg/kg/hour vs placebo	PRO, RCT, DB. PC Patients 1 to 7 years of age with moderate bronchoconstriction despite 3 sequential fenoterol* nebulizations, history of 2 similar episodes, and Wood-Downes score between 3 and 6, persisting symptoms lasting ≥2 days	N=43 12-14 hours	Primary: Wood-Downes clinical score Secondary: Protocol discharge, hospital admission rates	Primary: There is no significant difference between the aminophylline and placebo groups relative to hours needed to reach Wood-Downes score ≤2 in order to be discharged (12.5 and 14.6, respectively, P=0.13). Secondary: There is no significant difference between the treatment groups relative to protocol discharge (P=0.33) or hospital admission rates (P=0.59).
Yamauchi et al.[21] (2005) Theophylline 200 mg IV vs placebo	RCT, PG, SB Patients with mild acute exacerbation of bronchial asthma who were currently treated with oral sustained-release theophylline and theophylline levels <13 mcg/mL	N=22 2 hours	Primary: Spirometry and asthma symptoms (Borg Scale, wheezing index, coughing, and sputum production)	Primary: There was a significant improvement in PEFR (from 313±82 L/min to 356±111 L/min, P<0.005) and FEV_1 (from 1.66±0.48 L to 1.83±0.45 L, P<0.005) in patients receiving intravenous theophylline. There was a significant improvement in asthma symptoms, severity of asthma, Borg scale (P<0.05), wheezing index (P<0.05), coughing, and sputum production in patients receiving intravenous theophylline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wheeler at al.[43] (2005) Theophylline IV bolus (6.4 mg/kg), followed by a continuous infusion and terbutaline IV bolus (20 mcg/kg), followed by continuous infusion (0.4 mcg/kg/hour) vs terbutaline IV bolus (20 mcg/kg), followed by continuous infusion (0.4 mcg/kg/hour) vs theophylline IV bolus (6.4 mg/kg), followed by a continuous infusion	PRO, DB, RCT Patients between 3 and 15 years old who are critically ill with status asthmaticus and potential respiratory failure, admitted ≤2 hours; receiving continuous nebulized albuterol (10mg/hr) and IV methylprednisolone (2 mg/kg every 6 hours for 24 hours followed by 1 mg/kg every 6 hours until discharge)	N=40 4-5 days	Primary: Change in clinical asthma score over time Secondary: Length of time to a clinical asthma score of ≤3, length of pediatric intensive care unit stay, progressive mechanical ventilation, incidence of adverse effects	Primary: There was no clinically significant difference among the study groups in terms of improved change (P<0.05) in clinical asthma score over time. Secondary: With the exception of more reported nausea in patients receiving both theophylline/terbutaline, there was no clinically significant difference among the study groups in terms of the incidence of adverse effects. There was also no significant difference in terms of the length of hospital stay. No patient required mechanical ventilation. When 4 patients were excluded from data analysis, a significant difference was seen in the shorter length of time to achieving ≤3 clinical asthma scores in patients receiving theophylline/placebo compared to terbutaline/placebo and theophylline/terbutaline (24.2±121 hours vs 51.6±33.3 hours vs 47.1±38.3.hours, respectively, P<0.05).
Helms et al.[25] (1983) Theophylline 10 mg/kg TID, followed by	PG, DB, XO Children between 7 and 13 years old with chronic asthma and mean daily	N=25 8 weeks	Primary: Pharmacokinetics and therapeutic effects (morning and evening PEFRS, weighted	Primary: There was no statistically significant difference in peak theophylline levels (P>0.05), morning and evening PEFRs (P>0.05), drug score (P>0.05), day wheeze (P>0.05), and cough (P>0.05) among treatment groups. There was a statistically significant difference in the increased daytime

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aminophylline SR 14 mg/kg BID vs aminophylline SR 14 mg/kg BID, followed by theophylline 10 mg/kg TID vs theophylline 10 mg/kg TID vs aminophylline CR 14 mg/kg BID	PEFR <75% of that predicted on stature over a 4-week assessment period		drug score, daily symptoms scores)	activity scores (P<0.05) and in the reduction of nighttime wheezing (P<0.05) in patients receiving the controlled release aminophylline compared to the standard oral theophylline.
Dombrowski et al.[27] (2004) Theophylline 400 to 800 mg/day day (to achieve serum level between 8-12 mcg/mL) vs beclomethasone inhaler 4 puffs TID	PRO, RCT, DB, PC Pregnant women <26 weeks' gestation with mild or moderate asthma	N=385 Less than 26 weeks' gestation until delivery	Primary: Proportion of patients with at least 1 asthma exacerbation required medical intervention, oral corticosteroids, or hospitalization Secondary: Treatment failures, participant withdrawal, delivery and perinatal outcomes	Primary: There was no significant difference in the proportion of women receiving either theophylline tablets or inhaled beclomethasone (20.4%, 18.0%, respectively; P=0.554) relative to experiencing at least 1 validated asthma exacerbation during the study. Secondary: There was no significant difference in the proportion of women receiving either theophylline tablets or inhaled beclomethasone relative to treatment failure (3.7%, 2.1%, respectively; P=0.896) and all obstetric outcomes (P values ranged from 0.160 to 0.962). Women receiving theophylline tablets were more likely to discontinue their medications due to side effects compared to those women receiving inhaled beclomethasone (RR=0.3, 95% CI=0.1-0.9; P=0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Reed et al.[28] (1998) Theophylline SR 100 to 300 mg (to achieve a serum level between 8-15 mcg/mL) vs beclomethasone inhaler 2 inhalations (42 mg/inhalation) QID	MC, DB, DD, RCT Patients between 6 and 65 years old with asthma associated with symptoms of dyspnea, cough, and wheezing, and the need for a bronchodilator despite allergen avoidance; FEV_1 greater than 50% of predicted value before bronchodilator use and FEV_1 increased by 15% after bronchodilator use	N=747 12 months	Primary: Daily diary symptoms; PEFR; supplemental bronchodilator use; doctor's office or hospital visits and absence from work or school; spirometry; methacholine testing; adverse experiences; cortical blood measurements	Primary: Compared to theophylline, treatment with beclomethasone resulted in a greater reduction in symptom scores (P=0.002 at 6 months), symptoms days (P=0.002 at 6 months), supplemental bronchodilator use (P=0.038 at 6 months), systemic glucocorticoid doses (P=0.009 at 6 months), bronchial hyperresponsiveness (P<0.05 at 6 months; P<0.001 at 1 year), and eosinophilia (P=0.001 at 1 year). There was no overall statistical difference between theophylline and beclomethasone in all other primary study parameters. Compared to beclomethasone, theophylline use was associated with a greater discontinuation of therapy (3%, 6%, respectively) due to side effects, including headache, nervousness, insomnia, and gastrointestinal problems. Compared to theophylline, beclomethasone use was associated with more oropharyngeal candidiases, hoarseness, and reduced morning plasma cortisol levels before and after cosyntropin.
Tinkleman et al.[30] (1994) Theophylline SR administered BID (to achieve serum levels between 8-15 mcg/mL) vs beclomethasone inhaler 2 inhalations (42 mcg/inhalation) QID	MC, DB, DD, RCT Children between 6 and 16 years old with mild to moderate chronic asthma, FEV_1 greater than 50% of predicted and increased FEV_1 by 15% after bronchodilator use	N=195 12 months	Primary: Daily diary symptom record, PEFR, supplemental bronchodilator and glucocorticoid use, doctor/hospital visits, school/work absence, physician's global evaluation, side effects	Primary: Theophylline and beclomethasone led to improvements in overall asthma control (symptom diaries, PEFR, methacholine response, pre-/post-bronchodilator FEV_1, doctor/hospital visits, school/work absences, and physician's global evaluation). Compared to theophylline, beclomethasone use was associated with less bronchodilator use (P=0.004 at month 5, P=0.025 at month 6, P=0.003 at month 10) and fewer milligrams of systemic corticosteroid use (123.9 mg, 58.4 mg, respectively; P=0.002). Compared to beclomethasone, theophylline use was associated with more adverse events: headache (P=0.001), central nervous system changes (P=0.008), tremor (P=0.003), gastric irritation (P=0.013), and nausea/vomiting (P=0.016). Beclomethasone was associated with a slower of growth velocity compared to theophylline in all children (4.2 centimeters/year, 5.5 centimeters/year, respectively; P=0.005) and in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				prepubescent males only (4.3 centimeters/year, 6.2 centimeters/year, respectively; P=0.005).
Ukena et al.[38] (1997) Theophylline 250 to 375 mg BID and beclomethasone inhaler 200 mcg BID vs beclomethasone inhaler 400 mcg BID	DB, PG, RCT Patients with mild to moderate asthma with FEV_1 of 50-85% predicted normal and FEV_1 increase of 15% after bronchodilator who remained symptomatic on beclomethasone 400 mcg/day or equivalent ICS dose	N=133 6 weeks	Primary: Improvement of PEFR at 6 weeks over baseline Secondary: Asthma symptoms, albuterol use	Primary: Both theophylline/beclomethasone and beclomethasone regimens demonstrated equal efficacy in increasing FEV_1 and PEFR at week 6 (P<0.01). There was no significant difference between the treatment groups (P=0.960). Secondary: There was no significant difference in daytime (P=0.575) or nighttime (P=0.196) asthma symptoms between theophylline/beclomethasone and beclomethasone regimens. There was no significant difference in the reduction of albuterol use during the daytime (P=0.392) or nighttime (P=0.814) between theophylline/beclomethasone and beclomethasone regimens.
Lim et al.[40] (2000) Theophylline SR 200 mg BID and beclomethasone inhaler 200 mcg BID vs beclomethasone inhaler 200 mcg BID vs beclomethasone inhaler 500 mcg BID	RC, DB, PG Patients between 18 and 65 years old with asthma, with PEFR greater than 50% of predicted normal and PEFR increase of 15% after bronchodilator use and who remained symptomatic despite use of low-dose inhaled steroids and as needed albuterol	N=155 6 months	Primary: Mean morning and evening PEFR Secondary: Diurnal variation of PEFR, use of short-acting β_2-agonists, symptom scores, asthma exacerbations, and quality of life	Primary: Significant improvement was observed in mean morning PEFR in patients receiving high-dose beclomethasone (P=0.007) and low-dose beclomethasone/theophylline (P=0.006). Significant improvement was observed in mean evening PEF in patients receiving low-dose beclomethasone/theophylline (P=0.002). There was no significant difference among the three study groups relative to change in morning and evening PEFR. Secondary: There was no significant difference among the three study groups relative to diurnal variation of PEFR, symptom scores, or short-acting β_2-agonist usage, asthma exacerbations, quality of life, or side effects.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wang et al.[42] (2005) Theophylline SR 200 mcg BID and beclomethasone inhaler 250 mcg BID vs beclomethasone inhaler 500 mcg BID	RCT OL, PG Patients between 18 and 70 years old with asthma showing FEV_1 increase of greater than 15% and 20 mL over baseline after bronchodilator use and use of an ICS with a dose ≤1,000 mcg	N=41 6 weeks	Primary: Lung function testing, sputum induction (cell differential counts and interleukin-5), PEFR, symptom score, and β_2-agonist use	Primary: Both the beclomethasone and beclomethasone/theophylline groups experienced improved mean morning and evening PEFR (P<0.001, P<0.05, respectively) and FEV_1 (P<0.05), as well as a reduction in symptom score (P<0.001), β_2-agonist usage (P<0.01), percentage eosinophils (P<0.001), and interleukin-5 levels (P<0.05). There was no significant difference in all primary study parameters between the two treatment groups. Both treatment regimens were well tolerated.
Spears et al.[63] (2009) Theophylline 400 mg QD and beclomethasone inhaler 200 mcg QD vs theophylline 400 mg QD vs beclomethasone inhaler 200 mcg QD	RCT, DB, DD, PG Patients 18 to 60 years of age with mild to moderate asthma who were current smokers and who were receiving ≤1,000 mcg/day of beclometasone (or equivalent)	N=68 4 weeks	Primary: Change in lung function and Asthma Control Questionnaire (ACQ) scores Secondary: Inflammatory biomarkers in sputum	Primary: The addition of theophylline to inhaled beclometasone resulted in statistically significant improvements in morning peak expiratory flow (P=0.008) and ACQ scores (-0.47, 95% CI -0.91 to -0.04). Theophylline monotherapy did not improve lung function, except for post-bronchodilator forced vital capacity (304 mL; P=0.046). However, it did improved the ACQ scores after 4 weeks (-0.55, 95% CI -0.99 to -0.11). Secondary: Treatment with the combination of theophylline and inhaled beclometasone was associated with a reduction in the mean absolute (-10.99; P=0.018) and percentage sputum lymphocyte count. Theophylline alone was associated with reductions in sputum supernatant IL-8 (P=0.009) and myeloperoxidase (P=0.026).
Morali et al.[29] (2001) Theophylline 200	RCT, DB, PG Patient between 18 and 45 years old	N=38 4 weeks	Primary: Clinical, functional, anti-inflammatory	Primary: Budesonide use was associated with a significant reduction in serum interleukin levels (P<0.0005), eosinophil counts (P<0.005), daytime (P<0.01) and nighttime (P<0.005) symptom scores; increase in morning

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID vs budesonide inhaler 2 inhalations (800 mcg) BID	with mild to moderate asthma with baseline FEV_1 greater than 60% of predicted value and FEV_1 increased by 20% after bronchodilator use		effects	(P<0.005) and evening PEFR (P<0.05 and FEV_1 (P<0.01). Theophylline use was associated with a statistically significant reduction in serum interleukin levels (P<0.05), nasal eosinophil counts (P<0.01) blood eosinophil counts (P<0.02), and daytime/nighttime symptom scores (P<0.05). There were no significant differences between theophylline and budesonide.
Evans et al.[39] (1997) Theophylline 250 to 375 mg BID and budesonide inhaler 400 mcg BID vs budesonide inhaler 800 mcg BID	DB, PC, RCT Patients 18-67 years of age with asthma, FEV_1 of 50% predicted and FEV_1 increase of 15% after bronchodilator, who were uncontrolled despite 800 to 1000 mcg budesonide or equivalent ICS dose	N=62 3 months	Primary: PEFR, albuterol usage, 4-point scale for symptom severity	Primary: Compared to budesonide, the budesonide/theophylline group demonstrated greater improvements in FEV_1 (P=0.03) and FVC (P=0.03). There was no significant difference in PEFR (P=0.16), daytime (P=0.57) and nighttime (P=0.97) bronchodilator use, daytime (P=0.26) and nighttime (P=0.59) symptoms. Budesonide reduced serum cortisol concentrations; however, this was no significantly different than budesonide/theophylline therapy (P=0.09). Both treatment groups were well tolerated.
Yurdakul et al.[34] (2003) Theophylline SR 400 mg QD vs budesonide inhaler 400 mcg QD vs montelukast tablet 10 mg QD	RCT, PG Patients aged 23 and 45 years old with mild persistent asthma, FEV_1 at least 80% of the predicted normal value and FEV_1 increase of 15% after 400 mcg of albuterol	N=74 3 months	Primary: Lung function (PEFR, FEV_1), asthma symptom scores, supplemental β_2-agonist use, adverse events, asthma exacerbations	Primary: FEV_1 and PEFR values were not significantly different among treatment groups at the end of the study (P >0.05 and P >0.05, respectively). Asthma symptom scores and supplemental β_2-agonist use were not significantly different (P >0.05) among treatment groups. The adverse events for montelukast, theophylline, and budesonide were 12%, 16%, and 16.7%, respectively. Asthma exacerbation percentage for montelukast, theophylline, and budesonide were 16%, 12.5%, and 0%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Furukawa et al.[35] (1984) Theophylline SR 100 to 300 mg BID (to achieve serum levels between 10-15 mcg/mL) vs cromolyn sodium inhaler QID	DB, PC, RCT Patients between 5 and 15 years old with daily asthma symptoms of coughing, chest congestion, or wheezing and FEV_1 greater than 20% at methacholine challenge and naïve to regular asthma medication	N=46 3 months	Primary: Home assessment (symptom, PEFR), office assessment (FVC, FEV_1, PEFR, and forced mid-expiratory flow rate, asthma score)	Primary: Both theophylline and cromolyn demonstrated similar effects relative to symptom scores, increased pulmonary function, and decreased use of the bronchodilator. Compared to cromolyn, theophylline use was associated with more side effects (nausea, nervousness, P<0.02) and doctor visits (P<0.01).
Hendeles et al.[36] (1995) Theophylline SR every morning (to achieve serum levels between 10-20 mcg/mL) vs cromolyn inhaler 2 inhalations QID vs placebo	RCT, DB, DD, XO Patients between 18 and 35 years old with intermittent to mild chronic asthma with an allergic component, FEV_1 greater than 65% of predicted, 20% decrease in FEV_1 after 8 mg/mL inhaled histamine, and a dual response to inhaled allergen and histamine	N=16 7 days	Primary: FEV_1, airway responsiveness to histamine	Primary: During the late phase, decrease in mean FEV_1 for placebo, theophylline, and cromolyn were 30%, 16%, and 13%, respectively. There was a significant difference in the mean FEV_1 for theophylline and cromolyn compared to placebo (P=0.0001), but no significant difference for theophylline vs cromolyn (P=0.1). Geometric mean fold rise in airway responsiveness for placebo, theophylline and cromolyn were 3.0, 1.7, and 1.5, respectively. There was a significant difference in the mean airway responsiveness with theophylline and cromolyn compared to placebo (P=0.0001), but no significant difference for theophylline vs cromolyn (P=0.1).
Burki et al.[37] (1997) Theophylline 300 to 700 mg (to achieve serum	DB, PC, XO, RCT Patients with mild to moderate stable asthma with FEV_1 of 70% of the	N=19 7 days	Primary: Efficacy	Primary: Both theophylline and ipratropium were effective in management of asthma control by increasing FVC (P<0.05) and FEV_1 (P<0.05). After 3 hours, treatment with theophylline/ipratropium led to a significantly greater increase in FEV_1 than theophylline or ipratropium

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levels between 10-20 mcg/mL) and ipratropium inhaler (40 mcg) vs theophylline 300 to 700 mg (to achieve serum levels between 12-18 mcg/mL) vs ipratropium inhaler (40 mcg) vs placebo	predicted normal and a FEV_1 increase of 15% within 30 minutes of 2 inhalations of isoproterenol			monotherapy (3 L, 2.48 L, 2.61 L, respectively; P<0.05). There were no significant differences in side effects when comparing all study regimens.
Yurdakul et al.[41] (2002) Theophylline SR 400 mg QD and budesonide inhaler 400 mcg BID vs formoterol inhaler 9 mcg BID and budesonide inhaler 400 mcg BID vs	RCT, OL, PG Patients with moderate persistent asthma with symptoms despite treatment with moderate to high doses of ICS, who demonstrated FEV_1 increase of 15% after bronchodilator use	N=64 3 months	Primary: PEFR variability, FEV_1, daytime and nighttime asthma symptom scores, supplemental terbutaline use, asthma exacerbations, adverse effects	Primary: Overall, there was no statistical difference between the treatment groups in terms of study outcome parameters (P>0.05). A greater percentage of patients receiving zafirlukast experienced medication-related side effects compared to formoterol and theophylline (31.6%, 20%, 20%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
zafirlukast 20 mg BID and budesonide inhaler 400 mcg BID				
Vatrella et al.[31] (2005) Theophylline SR 600 mg x 1 dose vs salmeterol 50 mcg x 1 dose vs theophylline SR 600 mg and salmeterol 50 mcg x 1 dose vs placebo	RCT, SB, PC, XO Patients with moderate to severe asthma	N=10 4 days	Primary: Changes in FEV_1	Primary: Patients receiving salmeterol had a better clinical response compared to theophylline (based on earlier onset, greater magnitude, and longer duration). There were no P values reported comparing active treatments to each other for the mentioned parameters. Theophylline offered a synergistic improvement in FEV_1 values when taken concurrently with salmeterol in the 4th, 6th, and 8th hours of the study, at which therapeutic plasma concentrations of theophylline were reached (P=0.05, P=0.03, P=0.05, respectively).
Nutini et al.[32] (1998) Theophylline SR 150 mg BID (to achieve plasma levels between 10-20 mcg/mL) vs	RCT, MC, OL, PG Patients ≥18 years of age with asthma, FEV_1 between 50%-80% predicted value, FEV_1 increase of 15% after 200 mcg of albuterol, and total symptom score ≥2	N=112 12 months	Primary: PEFR, symptom score, and additional albuterol use Secondary: The effects on quality of life of salmeterol and theophylline were	Primary: There was no significant difference in morning and evening PEFRs among the treatment groups. Salmeterol demonstrated greater efficacy compared to theophylline in controlling both daytime and nighttime asthma symptoms (P<0.001) and in reducing additional albuterol requirement (P<0.001). Secondary: The effects of salmeterol and theophylline in increasing quality of life showed no significant difference; both agents improved quality of life.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 mcg BID			evaluated by examining a synthetic score ranging from a minimum of 0 to maximum of 20	
Dawson et al.[24] (1986) Theophylline SR 10 mg/kg BID vs theophylline syrup 5 mg/kg QID	PRO, OL Children with chronic asthma requiring continuous bronchodilator therapy	N=61 3 months	Primary: Symptoms (night wheeze and cough, exercise-induced symptoms, daytime cough and wheeze), compliance, side effects, β_2-agonist usage	Primary: There was no statistical difference in compliance or symptom control among treatment groups. There was a significant difference in greater side effects (P<0.015) and increased need for nebulizations with a β_2-agonist (P<0.05) in patients receiving theophylline microspheres compared to theophylline syrup.
Schwartz et al.[33] (1998) Theophylline SR 200 to 400 mg BID (to achieve serum levels of 8-15 mcg/mL) vs zileuton 400 mg QID	MC, RCT, DB, AC, PG Patients 18 and 60 years old with moderate asthma, FEV_1 40%-80% of the predicted normal value and FEV_1 increase of 15% after β_2-agonist	N=377 13 weeks	Primary: Mean percentage change in FEV_1 from baseline to maximum improvement on days 36 and 92 of study Secondary: morning/evening PEFR, β_2-agonist use, asthma symptom scores, quality of life indexes (activity, symptoms, emotional changes, allergen exposure), drug tolerability	Primary: Mean percentage change in FEV_1 from baseline values to any postdose time-point was not significantly different among the treatment groups. Secondary: Morning and evening PEFR were not significantly different among treatment groups, although the mean evening change in PEFR for theophylline was greater than for zileuton 600 mg in the first 2-week comparison (95% CI, -33.5 - 4.9). On day 64 of the study, the difference in FEV_1 percentage change after β_2-agonist use was clinically significant for the theophylline and zileuton 400 mg groups (23% and 30%, respectively, P=0.01) The use of a β_2-agonist was significantly less in the theophylline group compared to the zileuton group within the first 10 weeks of the study only. Asthma symptom scores and quality-of-life indexes were not significantly different among the treatment groups. One or more adverse events associated with treatment were reported in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				zileuton 400 mg, zileuton 600 mg, and theophylline groups (121, 117, and 110, respectively). The clinical significance is unknown.
Faillers et al.[20] (1978) Theophylline elixir (150 mg) 5.5 mg/kg, ephedrine HCl (25 mg) 0.93 mg/kg, guaifenesin 100 mg, and butabarbital 20 mg/15 mL; complete dosing regimen not specified vs theophylline elixir (150 mg) 5.5 mg/kg and guaifenesin 90 mg/ 15 mL; complete dosing regimen not specified vs elixir with ephedrine HCl (25 mg) 0.93 mg/kg and butabarbital 20 mg/ 15 mL; complete dosing regimen not specified	DB, XO Children between 6 to 15 years old diagnosed with uncomplicated bronchial asthma with a FEV_1 between 30% - 75% and improved FEV_1 by $\geq$20% after inhaled isoproterenol	N=20 18 days	Primary: Pulmonary function tests (FEV_1, FVC, $FEV_{25\%-75\%}$, FEF_{max}, FRC, Raw, TGV, Gaw/V_L)	Primary: There was no statistical difference in all pulmonary function test parameters (FEV_1, FVC, $FEV_{25\%-75\%}$, FEF_{max}, FRC, Raw, TGV, Gaw/V_L) in patients receiving guaifenesin compared to placebo. Compared to placebo, patients receiving the theophylline- ephedrine-guaifenesin-butabarbital combination product experienced statistically significant improvements in FEV_1 (P<0.05), FVC (P<0.05), $FEV_{25\%-75\%}$ (P<0.05), FEF_{max} (P<0.05), FRC (P<0.05), Raw (P<0.05), TGV(P<0.05), and Gaw/V_L (P<0.05). Compared to placebo, patients receiving the theophylline-guaifenesin combination product only experienced statistically significant improvements in FEV_1 (P<0.05), FVC (P<0.05), $FEV_{25\%-75\%}$ (P<0.05), FEF_{max} (P<0.05), FRC (P<0.05), Raw (P<0.05), and Gaw/V_L (P<0.05). Compared to placebo, patients receiving ephedrine-butabarbital experienced statistically significant improvements in FEV_1 (P<0.05), $FEV_{25\%-75\%}$ (P<0.05), FEF_{max} (P<0.05), FRC (P<0.05), Raw (P<0.05), TGV (P<0.05), and Gaw/V_L (P<0.05). Compared to placebo, patients receiving ephedrine experienced statistically significant improvements in FEV_1 (P<0.05), FVC (P<0.05), and $FEV_{25\%-75\%}$ (P<0.05). Compared to patients receiving ephedrine-butabarbital, patients receiving theophylline-ephedrine-guaifenesin-butabarbital experienced statistically significant improvements in FEV_1 (P<0.05), FVC (P<0.05), $FEV_{25\%-75\%}$ (P<0.05), FEF_{max} (P<0.05), FRC (P<0.05), Raw (P<0.05), TGV(P<0.05), and Gaw/V_L (P<0.05). Compared to patients receiving ephedrine-butabarbital, patients receiving ephedrine experienced statistically significant improvements in only FEV_1 (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs elixir with guaifenesin 100 mg / 15 mL; complete dosing regimen not specified vs elixir with ephedrine HCl (25 mg / 15 mL) 0.93 mg/kg; complete dosing regimen not specified vs placebo elixir				Compared to patients receiving ephedrine, patients receiving theophylline-guaifenesin experienced statistically significant improvements in FEV_1 ($P<0.05$), FEF_{max} ($P<0.05$), Raw ($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to patients receiving guaifenesin, patients receiving theophylline-guaifenesin experienced statistically significant improvements in FEV_1 ($P<0.05$), FVC ($P<0.05$), $FEV_{25\%-75\%}$ ($P<0.05$), FEF_{max} ($P<0.05$), Raw ($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to patients receiving theophylline-guaifenesin, patients receiving theophylline-ephedrine-guaifenesin-butabarbital experienced statistically significant improvements in FRC ($P<0.05$) only.
COPD				
Duffy et al.[45] (2005) Aminophylline IV 5 mg/kg loading dose, followed by 0.5 mg/kg/hour infusion (to achieve goal theophylline serum levels) vs	RCT, DB, PC Patients between 40 and 80 years old admitted due to a non-acidotic exacerbations of chronic obstructive pulmonary disease with FEV_1<70% predicted, FEV_1/FVC <7% predicted, 20 pack-years smoking	N=132 5 days	Primary: Change in post-bronchodilator FEV_1 Secondary: Self-reported breathlessness, arterial blood gas tensions, FVC, length of hospital stay	Primary: There was no significant difference between the treatment groups relative to FEV_1 ($P=0.49$). Secondary: Compared to placebo, aminophylline demonstrated a significant difference in its effects relative to increased arterial pH ($P=0.001$) and reduction on arterial carbon dioxide tension ($P=0.01$). There was no significant difference between the treatment groups relative to self-reported breathlessness ($P=0.56$), FVC ($P=0.49$), or length of hospital stay ($P=0.19$). Aminophylline was associated with more nausea compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	history, COPD symptoms for the last 24 hours			(44%, 22%, respectively, P<0.05).
Rice et al.[47] (1987) Aminophylline IV 0 mg/kg (if last theophylline dose <6 hours ago) or 3 mg/kg (if last theophylline dose ≥6 hours ago) or 6 mg/kg (theophylline-naïve or if last theophylline dose >12 hours ago) as a loading dose, followed by a 0.5 mg/kg/hour infusion (to achieve adequate theophylline serum levels) vs placebo Patients were also treated with metaproterenol, methyl-prednisolone, ampicillin, and supplemental	RCT, DB, PC Patients admitted due to an exacerbation of chronic obstructive pulmonary disease with FEV_1 greater than 2 standard deviations below the predicted and FEV_1/FVC <60%;	N=30 2 hours	Primary: FEV_1, FVC, dyspnea index, side effects	Primary: Both treatment groups demonstrated statistically significant improvements in FEV_1, FVC, and dyspnea (P<0.05). However, there was no significant difference between the treatment groups relative to these improvements (P>0.5). Aminophylline was associated with more gastrointestinal side effects compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oxygen (as needed)				
Jenkins et al.[49] (1982) Aminophylline SR 325 mg BID vs theophylline SR 250 mg BID vs placebo	SB, XO Male patients between 51 to 73 years old with chronic bronchitis and 5%-15% reversibility of airway obstruction after 200 mcg of inhaled albuterol	N=20 6 weeks	Primary: PEFR, daily symptom score (cough, wheeze, chest tightness), β-agonist inhaler usage	Primary: There was no significant difference in morning or evening PEFRs (P value range of 0.58 to 0.95), β_2-agonist inhaler usage, and symptoms scores among treatment groups.
Rossi et al.[52] (2002) Theophylline SR 200 to 300 mg BID (to achieve serum levels between 8-20 mcg/mL) vs formoterol inhaler 12 mcg BID vs formoterol inhaler 24 mcg BID vs	MC, RCT, PC, PG Patients >40 years of age with symptomatic COPD (FEV_1 <70% of predicted value and ≥0.75L, FEV_1/FVC <88% predicted [men] or <89% predicted [women])	N=854 12 months	Primary: AUC for FEV_1 Secondary: Standardized AUC for FVC, FEV_1, PEFR, symptom score, daily puffs of rescue inhaler, frequency of exacerbations, quality of life	Primary: Compared to placebo, there was a significant improvement in the AUC for FEV_1 over 12 hours for both doses of formoterol and theophylline treatment groups after 3 to 12 months of treatment (P<0.001). Secondary: Compared to placebo, there was a significant improvement for both formoterol and/or theophylline treatment groups in terms of quality of life symptom sub-scores (P=0.009 for 12 mcg, P=0.016 for 24 mcg, P=0.003 for theophylline), AUC for FVC (P<0.001, P≤0.007, respectively), 12-month PEF values (P<0.001, P<0.007, respectively), reduction in bronchodilator use (P≤0.003 for formoterol), frequency of exacerbations (P<0.008, no P value, respectively), need for additional COPD therapy (P=0.043 for 24 mcg dose, P=0.019, respectively). Compared to theophylline, formoterol use was associated with a significantly greater reduction in AUC for FVC at 3 months (P≤0.016) and 12-month PEF values (P≤0.020). There was no significant difference between the treatment groups relative to average symptoms score.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Patients receiving theophylline experienced a significant increased risk for discontinuing treatment compared to placebo (P=0.002), formoterol 12 mcg (P=0.001), and formoterol 24 mcg (P=0.001). Compared to theophylline, both doses of formoterol was overall more effective (P≤0.026).
Crimi et al.[50] (1995) Theophylline SR 250 mg BID for 4 days, then 350 mg BID thereafter (to achieve serum levels of 10-20 mcg/mL) vs nedocromil sodium 2 inhalations QID	RCT, DB, DD, PG Patients between 18 and 76 years old with chronic reversible obstructive airway disease	N=105 6 weeks	Primary: Daytime and nighttime symptoms, inhaled bronchodilator use, morning tightness, cough, PEFR	Primary: There was no overall significant difference in improvements in patients receiving either theophylline or nedocromil relative to mean pulmonary function measurements, inhaled bronchodilator use, symptom severity, or clinician's assessment of disease severity. Theophylline demonstrated a greater reduction in morning tightness and nighttime inhaled bronchodilator use at weeks 1 and 2 when compared to nedocromil. There was a greater number of gastrointestinal side effects (P<0.05) and central nervous system related events (P<0.01) in patients receiving theophylline compared to nedocromil.
Broseghini et al.[51] (2005) Theophylline SR (to achieve serum levels between 10-20 mcg/mL) vs salmeterol 50 mcg BID vs	RCT, DB, DD, XO Patients with stable moderate to severe COPD with cough and sputum history, FEV_1 between 30% and 70% of predicted normal, and poor reversibility (FEV_1 increase <12% and <200 mL from baseline after bronchodilator use)	N=13 22 weeks	Primary: Pulmonary function tests, PEFR, adverse effects	Primary: Compared to placebo, there was a greater increase in FEV_1 (P<0.01), FVC (P<0.05), and morning PEFR (P<0.01 for salmeterol 100 mcg) in patients receiving salmeterol. Compared to placebo, there was a significant improvement in FEV_1 in patients receiving salmeterol (P<0.01) and theophylline (P<0.05). There was no significant difference between salmeterol and theophylline relative to FEV_1. There was no statistical difference in primary study endpoints between the two inhaled salmeterol doses (P=0.867). Overall, both treatment regimens were well tolerated with no significant difference.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 100 mcg BID vs placebo				
ZuWallack et al.[53] (2001) Theophylline SR 100 mg BID (to achieve serum levels between 10-20 mcg/mL) and salmeterol 42 mcg BID vs theophylline SR 100 mg BID (to achieve serum levels between 10-20 mcg/mL) vs salmeterol 42 mcg BID	RCT, DB, DD, PG Patients >45 years of age with COPD, $FEV_1 \geq 0.7$ L, $FEV_1 \leq 65\%$ of predicted, and FEV_1/FVC ratio $\leq 70\%$	N=943 12 weeks	Primary: Change from baseline in AUC for FEV_1, predose FEV_1 and FVC Secondary: PEFR, symptoms scores, albuterol use, COPD exacerbations, quality of life	Primary: There was a significant improvement observed with salmeterol/theophylline, salmeterol monotherapy, and theophylline monotherapy treatment groups in terms of mean pre-dose FEV_1 and FVC ($P<0.001$, $P<0.001$, $P \leq 0.021$ except for FVC at week 12, respectively). Treatment with salmeterol/theophylline was associated with greater improvement in FEV_1 and FVC ($P<0.020$) compared to salmeterol monotherapy and theophylline monotherapy. Secondary: Treatment with salmeterol/theophylline was associated with a greater improvement in dyspnea symptom reduction ($P \leq 0.048$), albuterol use reduction ($P \leq 0.048$), COPD exacerbations ($P=0.023$ vs placebo), more symptom-free days ($P=0.023$ vs theophylline), and mean overall change from baseline in quality of life ($P \leq 0.019$) compared to salmeterol only and theophylline only treatment groups. There was a significant association with fewer side effects in patients receiving salmeterol compared to either treatment containing theophylline ($P \leq 0.028$).
Cazzola et al.[54] (2004) Theophylline SR BID (to achieve serum levels between 10-20 mcg/mL) and	RCT, OL Patients >50 years of age with at least a 20-year smoking history, $FEV_1<70\%$ of predicted but more than 0.5 L and	N=66 4 months	Primary: Pulmonary function, dyspnea, supplemental albuterol use	Primary: Both treatment groups demonstrated improvements in FEV_1 ($P<0.05$); there was no difference between the groups relative to pulmonary function tests ($P>0.05$). The salmeterol/fluticasone group experienced statistically significant greater reduction in dyspnea episodes and supplemental albuterol use compared to the theophylline/fluticasone group ($P=0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone 500 mcg BID vs salmeterol-fluticasone 50/500 mcg BID	FEV_1/FVC ratio <70% after albuterol 400 mcg			
Cazzola et al.[55] (2000) Theophylline BID (to achieve goal serum levels) and salmeterol 50 mcg BID vs salmeterol 50 mcg BID vs salmeterol 50 mcg and fluticasone 250 mcg BID vs salmeterol 50 mcg and fluticasone 500 mcg BID	RCT, OL Patients ≥50 years of age with at least a 20-year smoking history and well-controlled COPD that was previously treated with slow-release theophylline; change in FEV_1 ≤12% of predicted normal after albuterol 400 mcg, FEV_1 post-bronchodilator <85%, and good metered-dose inhaler technique	N=80 3 months	Primary: FEV_1, FVC	Primary: All treatment groups demonstrated statistically significant gradual improvements in FEV_1 (P<0.05). Salmeterol 50 mcg/fluticasone 500 mcg group demonstrated a statistically significant difference in its greater effect on FEV_1 compared to salmeterol/theophylline and salmeterol only treatment groups (P<0.05).
Lee et al.[62] (2009) Theophylline-	RETRO Male patients aged 45 years or older	N=183,573 4 years	Primary: All cause mortality, COPD Exacerbations, and	Primary: Overall, patients receiving a theophylline-containing regimen were found to have a small, but significant increased risk of death. The risk ranged from 1.11 to (95% CI, 1.04-1.18) for the combination of ipratropium plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
containing drug regimens vs drug regimens not containing theophylline	with a diagnosis of COPD who received respiratory medications who were identified through the National Veterans Affairs inpatient, outpatient, pharmacy, and mortality databases		COPD-related hospitalizations	theophylline to 1.31 (95% CI, 1.11-1.55) for inhaled corticosteroid plus long acting β_2-agonist and theophylline. Theophylline regimens containing solely ipratropium or an inhaled corticosteroid, or a combination of them both had significantly higher COPD exacerbations compared to similar therapy without theophylline. Theophylline was associated with an increased hospitalization rate for two regimens (ipratropium and ipratropium plus inhaled corticosteroid).
Exercise-Induced Bronchospasm				
Furukawa et al.[26] (1983) Dyphylline 10 mg/kg administered 1 hour prior to exercise vs dyphylline 15 mg/kg administered 1 hour prior to exercise vs dyphylline 20 mg/kg administered 1 hour prior to exercise	RCT, DB, PC, XO Patients between 12 and 17 years old with exercise-induced bronchospasm ($\geq$20% decrease in FEV_1 during treadmill exercise test)	N=20 1 day	Primary: Spirometry, PEFR, physical examination, subjective symptoms	Primary: After exercise, there was a mean reduction for placebo, theophylline, dyphylline 10 mg/kg, dyphylline 15 mg/kg, and dyphylline 20 mg/kg in FEV_1 (30.5%, 8.8%, 26.3%, 23.5%, 21.5%, respectively). There was a significant difference in efficacy for preventing exercise-induced bronchospasm in patients receiving theophylline 6 mg/kg, dyphylline 15mg/kg, and dyphylline 20mg/kg compared to placebo ($P<0.05$). There was no statistically significant difference in blood pressure, pulse, hematologic, chemistry, or urine test among treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs theophylline 6 mg/kg administered 2 hours prior to exercise vs placebo				

*Agent not available in the United States
Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=crossover
COPD=chronic obstructive pulmonary disease, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, GINA=Global Strategy for Asthma Management and Prevention Program Report, ICS=inhaled corticosteroid, PEFR=peak expiratory flow rate, AUC=area under the curve

Additional Evidence

Dose Simplification
Kelloway et al. analyzed pharmacy claims to assess adherence with theophylline and inhaled anti-inflammatory medications.[60] Adherence was found to be better with theophylline than inhaled treatments (P=0.001). Sherman et al. evaluated adherence rates with asthma medications in children with persistent asthma who were Medicaid recipients.[19] Maximum potential adherence was 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn. These findings indicate poor compliance with asthma therapy, especially evident with nebulized cromolyn. According to this study, physicians were only able to identify 50% of patients who were non-compliant with therapy, and approximately one third of patients who were excessively refilling their inhaled albuterol.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Reed et al. evaluated health care resource utilization rates.[28] Over a 12-month period, 1.3% to 4.7% of patients in the theophylline study group required ≥1 physician visit, emergency room department visit, or hospitalization compared to 1.2% to 4.1% for patients receiving beclomethasone. There was no significant difference between the treatment groups. Tinkelman et al. also demonstrated comparable efficacy for theophylline and beclomethasone in decreasing physician visits and hospitalizations.[30] The available data demonstrates that aminophylline does not reduce the length of hospital stay during the acute management of asthma or COPD.[34-36,51-52]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Respiratory Smooth Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aminophylline	injection, tablet	N/A	N/A	$
Dyphylline	Tablet, elixir*	Lufyllin®	$$$$$	$$$$$
Guaifenesin and dyphylline	elixir, liquid, syrup, tablet	Difil-G, Difil-G Forte®*, Dilex-G®, Lufyllin-GG®*	$-$$	$-$$
Guaifenesin and theophylline	liquid	N/A	N/A	$
Guaifenesin, theophylline and pseudoephedrine	elixir	Bronchomar-1®	$$-$$$$	N/A
Theophylline	elixir, extended-release capsule, injection*, solution*, sustained-release tablet*	Elixophyllin®, Theo-24®	$$-$$$	$-$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The respiratory smooth muscle relaxants are approved for the treatment of asthma, chronic bronchitis and emphysema.[1-7] They are available as single entity products, as well as in combination with guaifenesin and pseudoephedrine. All of the products are available in a generic formulation, with the exception of guaifenesin/theophylline/pseudoephedrine.

For the treatment of asthma, guidelines recommend the use of an inhaled corticosteroid (ICS) as initial therapy.[11-14] When additional therapy is needed, it is recommended that a long-acting β_2-agonist (LABA) be added to the regimen.[11-14] Theophylline is considered an alternative treatment option for the management of asthma. For the treatment of mild airflow obstruction associated with COPD, guidelines recommend the use of a short-acting bronchodilator as needed to relieve breathlessness and exercise limitation.[18-21] For patients who require daily maintenance therapy to control symptoms, an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic).[18,20-21] Theophylline should only be used after a trial of inhaled bronchodilators or in patients who are unable to use inhaled therapy due to its potential toxicity.[15,17]

Numerous clinical trials have been conducted evaluating the efficacy and safety of the respiratory smooth muscle relaxants. While the majority of these trials have compared active treatment to placebo, or combination therapy to monotherapy, few studies have directly compared the xanthine derivatives. For the treatment of asthma and COPD, sustained-release theophylline has been shown to be either slightly less, or equally effective, when compared to ICS, inhaled LABAs, leukotriene modifiers, nedocromil, cromolyn, or ipratropium.[27-30,32-38,40-42,50-55] Studies comparing the various dosage forms of xanthines are limited; most dosage form comparison studies have evaluated pharmacokinetic data.[56-59] The use of theophylline and aminophylline is often associated with a greater discontinuation rate due to adverse events than comparator drugs.[27-28,30,32,35,43,45,47,50,52-53]

Widespread use of the respiratory smooth muscle relaxants is limited by their narrow therapeutic index. Toxicity is a significant concern and close monitoring is essential. These agents must be carefully titrated according to therapeutic response and serum levels. Theophylline serum concentrations of 10-20 mcg/ml are generally needed to produce bronchodilation. Serum levels >20 mcg/ml are associated with unacceptable adverse events. The most common adverse events reported with theophylline include anorexia, nausea, vomiting and headache. Cardiac arrhythmias, tachycardia, diarrhea and seizures may occur with higher doses. A severe overdose with theophylline can be fatal.

There is insufficient evidence to support that one brand respiratory smooth muscle relaxant is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand respiratory smooth muscle relaxants within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand respiratory smooth muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
4. Lufyllin® [package insert]. Somerset, NJ: Meda Pharmaceuticals; August 2007.
5. Lufyllin-GG® [package insert]. Somerset, NJ: Meda Pharmaceuticals; January 2009.
6. Elixophyllin® [package insert]. St. Louis, MO: Forest Pharmaceuticals; September 2004.
7. Theo-24® [package insert]. Caugus, PR: Pfizer Pharmaceuticals; April 2005.
8. Hendeles, L. Theophylline use in asthma. In:Rose, BD, ed. UpToDate. Waltham MA: UpToDate, 2006.
9. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.
10. Qaseem A, Snow V, Shekelle P, et al., Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians (ACP). Ann Intern Med 2007;147:633-8.
11. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
12. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.
13. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
14. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
15. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009. 93 p. Available at: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed October 2010.
16. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
17. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 June. 61 p. Available at: http://guidance.nice.org.uk/CG101. Accessed October 2010.
18. Bellamy D, Bouchard J, Henrichsen S, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J 2006;15:48-57.
19. Sherman J, Hutson A, Baumstein S, et al. Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for prescriptions. J Pediatr. 2000;136(4):532-536.
20. Faillers CJ, Cato AE, Harris JR. Controlled assessment of oral bronchodilators for asthmatic children. J Int Med Res. 1978;6(4):326-336.
21. Yamauchi K, Kobayashi H, Tanifuji, et al. Efficacy and safety of intravenous theophylline administration for treatment of mild acute exacerbation of bronchial asthma. Respirology. 2005;10:491-496.
22. Yung M, South M. Randomized controlled trial of aminophylline for severe acute asthma. Arch Dis Child. 1998;79(5):405-410.
23. Ream RS, Loftis LL, Albers GM, et al. Efficacy of IV theophylline in children with severe status asthmaticus. Chest. 2001;119:1480-1488.
24. Dawson KP. A comparative study of theophylline in a slow-release 'sprinkle' format with a standard syrup preparation in young children with asthma. Pharmacotherapeutica. 1986;4(7):442-444.

25. Helms P, Pearl K, Wilson R. A comparative trial of choline theophyllinate and controlled release aminophylline in chronic childhood asthma. Eur J Pediatr. 1983;141:89-91.
26. Furukawa CT, Shapiro GG, Pierson WE, et al. Dyphylline versus theophylline: a double-blind comparative evaluation. J Clin Pharmacol. 1983;23:414-418.
27. Dombrowski MP, Schatz MS, Wise R, et al. Randomized trial of inhaled beclomethasone dipropionate versus theophylline for moderate asthma during pregnancy. Am J Obstet Gynecol. 2004;190:737-44.
28. Reed CE, Offord KP, Nelson HS, et al. Aerosol beclomethasone dipropionate spray compared with theophylline as primary treatment for chronic mild-to moderate asthma. J Allergy Clin Immunol. 1998;101(1):14-23.
29. Morali T, Yilmaz A, Erkan F, et al. Efficacy of inhaled budesonide and oral theophylline in asthmatic subjects. J Asthma. 2001;38(8):673-679.
30. Tinkleman DG, Reed CE, Nelson HS, et al. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderate severe asthma in children. Pediatrics. 1994;92(1):64-77.
31. Vatrella A, Ponticiello A, Pelaia G, et al. Bronchodilating effects of salmeterol, theophylline and the combination in patients with moderate to severe asthma. Pulm Pharmacol Ther. 2005;18:89-92.
32. Nutini S, Martini T, Righi R. Long-term treatment of asthmatic patients with salmeterol vs slow-release theophylline. Resp Med. 1998;92:683-90.
33. Schwartz HJ, Petty T, Dube LM, et al. A randomized controlled trial comparing zileuton with theophylline in moderate asthma. Arch Intern Med. 1998;158(2):141-48.
34. Yurdakul AS, Taci N, Eren A, et al. Comparative efficacy of once-daily therapy with inhaled corticosteroids, leukotriene antagonist or sustained release theophylline in patients with mild persistent asthma. Respir Med. 2003;97:1313-19.
35. Furukawa CT, Shapiro GG, Bierman CW, et al. A double-blind study comparing the effectiveness of cromolyn sodium and sustained-release theophylline in childhood asthma. Pediatrics. 1984;74(4):453-459.
36. Hendeles L, Harman E, Huang D, et al. Theophylline attenuation of airway response to allergen: comparison with cromolyn metered-dose inhaler. J Allergy Clin Immunol. 1995;95(2):505-514.
37. Burki, NK. The effects of the combination of inhaled ipratropium and oral theophylline in asthma. Chest 1997;111(6):1509-1513.
38. Ukena D, Harnest U, Sakalauskas, et al. Comparison of addition of theophylline to inhaled steroid with doubling the dose of inhaled steroid in asthma. Eur Respir J. 1997;10:2754-2760.
39. Evans DJ, Taylor DA, Zetterstrom O, et al. A comparison of low-dose inhaled budesonide plus theophylline and high-dosed inhaled budesonide for moderate asthma. N Engl J Med. 1997;337(20):1412-1418.
40. Lim S, Jatakanon A, Gordon D, et al. Comparison of high dosed inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. Thorax. 2000;55:837-841.
41. Yurdakul AS, Calisir HC, Tunctan B, et al. Comparison of second controller medications in addition to inhaled corticosteroids in patients with moderate asthma. Respir Med. 2002;96:322-329.
42. Wang Y, Wang CZ, Lin KX, et al. Comparison of inhaled corticosteroid combined with theophylline and double-dose inhaled corticosteroid in moderate to severe asthma. Respirology. 2005;10:189-195.
43. Wheeler DS, Jacobs BR, Kenreigh CA, et al. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. Pediatr Crit Care Med. 2005;6(2):142-147.
44. Roberts G, Newsom D, Gomez K, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomized controlled trial. Thorax. 2003;58:306-310.
45. Duffy N, Walker P, Diamantea F, et al. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. Thorax. 2005;60:713-717.
46. Vieira SE, Lotufo JP, Ejzenberg B, et al. Efficacy of IV aminophylline as a supplemental therapy in moderate broncho-obstructive crisis in infants and preschool children. Pulm Pharmacol Therap. 2000;13:189-194. (UKPDS 33). Lancet. 1998;352(9131):837-853.
47. Rice KL, Leatherman JW, Duane PG et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;107:305-309.
48. Chen CY, Yang KY, Lee YC, et al. Effect of oral aminophylline on pulmonary function improvement and tolerability in different age groups of COPD patients. Chest. 2005;128:2088-2092.
49. Jenkins PF, White JP, Jariwalla AJ, et al. A controlled study of slow-release theophylline and aminophylline in patients with chronic bronchitis. Br J Dis Chest. 1982;76:57-60.

50. Crimi E, Orefice U, De Benedetto F, et al. Nedocromil sodium versus theophylline in the treatment of reversible obstructive airway disease. Ann Allergy Asthma Immunol. 1995;74:501-508.
51. Broseghini C, Testi R, Polese G et al. A comparison between inhaled salmeterol and theophylline in the short-term treatment of chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2005;18:103-108.
52. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest. 2002;121(4):1058-1069.
53. ZuWallack RL, Mahler DA, Reilly D, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest. 2001;119(6):1661-1670.
54. Cazzola M, Noschese P, Centanni S, et al. Salmeterol/fluticasone propionate in a single inhaler device versus theophylline + fluticasone propionate in patients with COPD. Pulm Pharmacol Ther. 2004;17:141-145.
55. Cazzola M, Di Lorenzo G, Di Perna F, et al. Additive effects of salmeterol and fluticasone in COPD. Chest 2000;118(6):1576-1581.
56. Kjellman NIM, Croner S, Leijon I, et al. Theophylline pharmacokinetics in children comparing sustained-release spheres (Theo-Dur sprinkle) with elixir. Eur J Pediatric. 1988;148:278-280.
57. Gupta S, Raina RK, Samotra K, et al. Pharmacokinetics of sustained release and conventional tablets of theophylline plus hydroxyethyltheophylline and its comparison with tablet aminophylline. Indian J Chest Dis Allied Sci. 1991;33(1):1-8.
58. Muittari A, Allonen H. Comparison of serum theophylline with plan and slow-release aminophylline in patient with airway obstruction. J Int Med Res. 1981;9(5):378-380.
59. Subramaniam S, Dhand R, Garg SK, et al. A steady state comparison of three theophylline formulations in adult stable asthmatics. Indian J Med Res. 1988;87:509-515.
60. Kelloway J, Wyatt R, Adlis S. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. Arch Intern Med. 1994;154(12):1349-1352.
61. Wiggins J, Arbab OA, Stableforth DE, et al. Intravenous aminophylline in patients already taking oral theophylline effect on calculated dose of knowledge of serum theophylline concentration on admission. Thorax. 1986;41(10):759-765.
62. Lee TA, Schumock GT, Bartle B, et al. Mortality risk in patients receiving drug regimens with theophylline for chronic obstructive pulmonary disease. Pharmacotherapy. 2009;29(9):1039-1053.
63. Spears M, Donnelly I, Jolly L, et al. Effect of low-dose theophylline plus beclomethasone on lung function in smokers with asthma: a pilot study. Eur Respir J. 2009;33(5):1010-1017.

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I. Overview

The intranasal corticosteroids are approved for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis.[1-10] Allergic rhinitis is characterized by inflammation of the nasal passages in response to an allergen. Symptoms include nasal congestion, rhinorrhea, sneezing, and/or nasal itching.[11] The intranasal corticosteroids downregulate the inflammatory response by binding to glucocorticosteroid receptors of inflammatory cells, which causes a conformational change. This controls the rate of protein synthesis and suppresses the transcription of cytokine and chemokine genes.[12] Symptomatic relief is usually evident after 1-2 days of continuous use; however, it may take up to two weeks for the maximum effects to be seen.

Beclomethasone and mometasone are also approved for the treatment of nasal polyps.[4,9] The topical administration of corticosteroids reduces the size of polyps, which reestablishes the nasal airway, improves the sense of smell, and prevents the recurrence of nasal polyps. However, intranasal corticosteroids do not completely eliminate polyps that are located in the upper part of the nasal cavity, which cannot be reached by the use of a nasal spray. Another limitation to the use of intranasal corticosteroids is that the presence of large polyps may make administration of the medication difficult. Therefore, surgery or a short course of systemic corticosteroids may be required.[13]

Beclomethasone and fluticasone propionate are also approved for the management of nonallergic rhinitis.[4,8] Nonallergic rhinitis is characterized by sporadic or persistent symptoms of rhinitis that are not mediated by immunoglobulin E.[15] Examples of nonallergic rhinitis include infectious rhinitis, hormonal rhinitis, vasomotor rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, and drug-induced rhinitis.

The intranasal corticosteroids that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Flunisolide and fluticasone propionate are available in a generic formulation. This class was last reviewed in December 2008.

Table 1. Intranasal Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Beclomethasone	nasal spray	Beconase AQ®	Beconase AQ®
Budesonide	nasal spray	Rhinocort Aqua®	none
Ciclesonide	nasal spray	Omnaris®	none
Flunisolide	nasal spray	N/A	flunisolide
Fluticasone furoate	nasal spray	Veramyst®	none
Fluticasone propionate	nasal spray	Flonase®*	fluticasone propionate
Mometasone	nasal spray	Nasonex®	Nasonex®
Triamcinolone	nasal spray	Nasacort AQ®	Nasacort AQ®

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the intranasal corticosteroids are summarized in Table 2. For a comprehensive overview of the treatment of allergic rhinitis, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Intranasal Corticosteroids

Clinical Guideline	Recommendation(s)
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **Diagnosis and Management of Rhinitis: An Updated Practice Parameter**[15] **(2008)**	• Pharmacologic treatment options include oral and intranasal antihistamines, oral and topical decongestants, oral and intranasal corticosteroids, cough and cold medications for young children, intranasal cromolyn sodium, intranasal anticholinergics, leukotriene receptor antagonists, omalizumab, and nasal saline. • Intranasal corticosteroids are the most effective class of medications for the treatment of allergic rhinitis. They can be used continuously or intermittently. Continuous use is generally more effective. • In most studies, intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis. • When comparing the available intranasal corticosteroids, the overall clinical response does not appear to vary significantly between products irrespective of the differences in topical potency, lipid solubility, and binding affinity.
World Health Organization (WHO)/Global Allergy and Asthma European Network (GA^2LEN)/AllerGen: **Allergic Rhinitis and its Impact on Asthma (ARIA)**[17] **(2008)**	• Patients with mild intermittent allergic rhinitis should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, or leukotriene receptor antagonist. • Patients with moderate/severe intermittent symptoms or mild persistent symptoms should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, intranasal corticosteroid, or leukotriene receptor antagonist. • Patients with moderate/severe persistent symptoms should initially be treated with the following (preferred order): intranasal corticosteroid, antihistamine (oral/nasal), or leukotriene receptor antagonist. • Intranasal glucocorticosteroids are the most effective drugs for the treatment of allergic rhinitis. Intranasal glucocorticosteroids are significantly more effective than oral or topical H_1-antihistamines for the treatment of allergic rhinitis and, in particular, for nasal congestion. • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy and availability. A stepwise approach depending on the severity and duration of rhinitis is proposed.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults**[16] **(2008)**	• Treatment includes corticosteroids, antihistamines, decongestants, cromolyn, anticholinergics, and leukotriene receptor antagonists. • Intranasal corticosteroids are considered the most effective treatment option. They are recommended as first-line therapy in patients with moderate to severe symptoms of allergic rhinitis.
International Primary Care Respiratory Group (IPCRG): **Management of Allergic Rhinitis**[18] **(2006)**	• Mild intermittent allergic rhinitis may be treated with an antihistamine, decongestant, and intranasal saline. • Mild persistent and moderate/severe intermittent allergic rhinitis may be treated with antihistamines, decongestants, intranasal corticosteroids, intranasal saline, a mast cell stabilizer, or a leukotriene receptor antagonist. • Moderate/severe persistent allergic rhinitis may be treated with intranasal corticosteroids, antihistamines, decongestants, intranasal saline, or a leukotriene receptor antagonist.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the intranasal corticosteroids are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Intranasal Corticosteroids[1-10]

Indication	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone	Triamcinolone
Allergic Rhinitis								
Prophylaxis of the nasal symptoms of seasonal allergic rhinitis							✔	
Relief of nasal congestion associated with seasonal allergic rhinitis							✔	
Treatment of nasal symptoms of seasonal and perennial allergic rhinitis	✔	✔	✔	✔	✔	✔	✔	✔
Nasal Polyps								
Prevention of recurrence of nasal polyps following surgical removal	✔							
Treatment of nasal polyps							✔	
Nonallergic Rhinitis								
Relief of the symptoms of nonallergic rhinitis	✔					✔		

IV. Pharmacokinetics

The pharmacokinetic parameters of the intranasal corticosteroids are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Intranasal Corticosteroids[1-10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Beclomethasone	44	87	Not reported	Renal (12) Feces (60)	0.5-2.7
Budesonide	34	85-90	Liver	Renal (66) Feces	2-3
Ciclesonide	<1	≥99	Liver	Renal (20) Feces (66)	5-7**
Flunisolide	50	Not reported	Liver	Renal (50) Feces (50)	1-2
Fluticasone furoate	0.5	>99	Liver	Renal (2)* Feces (90)*	15.1*
Fluticasone propionate	<2	91	Liver	Renal (<5) Feces (>95)	7.8
Mometasone	Minimal	98-99	Liver	Renal Feces	5.8
Triamcinolone	Minimal	Not reported	Liver	Renal (40) Feces (60)	3.1

*Data from intravenous administration.
**Data from oral inhalation.

V. Drug Interactions

Significant drug interactions with the intranasal corticosteroids are listed in Table 5.

Table 5. Significant Drug Interactions with the Intranasal Corticosteroids[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Intranasal corticosteroids (budesonide, ciclesonide fluticasone)	1	HIV protease inhibitors	Plasma concentrations and pharmacologic effects of certain intranasal corticosteroids may be increased by HIV protease inhibitors. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur.
Intranasal corticosteroids (ciclesonide, fluticasone)	2	Delavirdine	Plasma concentrations of ciclesonide may be increased when co-administered with delavirdine.
Intranasal corticosteroids (ciclesonide, fluticasone)	2	Imidazoles	Plasma concentrations and pharmacologic effects of ciclesonide may be increased by imidazoles. Adrenal suppression and Cushing's Syndrome may occur.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the intranasal corticosteroids are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Intranasal Corticosteroids[1-10]

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone[†]	Mometasone	Triamcinolone
Central Nervous System							
Dizziness	-	-	>3	-	1-3	-	-
Fatigue	-	-	≥3	-	-	-	-
Headache	<5	-	>11	-	7-16	17-26	≥2
Lightheadedness	<5	-	-	-	-	-	-
Gastrointestinal							
Abdominal pain	-	-	-	-	1-3	-	-
Diarrhea	-	-	-	-	1-3	2-<5	-
Dyspepsia	-	-	-	-	-	2-<5	-
Gastroenteritis	-	-	≥3	-	-	-	-
Nausea	<5	-	-	>1	3-5	2-<5	-
Vomiting	-	-	-	-	3-5	1-5	≥2
Hypersensitivity reactions							
Anaphylaxis	-	-	-	-	<1	✔	-
Angioedema	✔	<1	-	-	<1	✔	-
Bronchospasm	✔	-	-	-	<1	-	-
Dyspnea	-	-	-	-	<1	-	-
Facial edema	-	-	>3	-	<1	-	-
Pruritus	-	-	-	-	<1	-	-
Rash	✔	-	-	-	<1	-	-
Wheezing	✔	✔	-	-	<1	2-<5	-
Urticaria	✔	-	>3	-	<1	-	-
Respiratory							
Asthma symptoms	-	-	-	-	3-7	2-<5	≥2
Bronchitis	-	-	-	-	1-3	2-<5	-
Bronchospasm	-	2	2	-	-	-	-
Cough	-	2	-	>1	4	7-13	2
Epistaxis	<3	8	<8	3-9	6-7	8-11	2.7
Nasal burning/stinging	-	-	-	13	2-3	✔	-
Nasal congestion	<3	-	<6	-	-	-	-
Nasal dryness	✔	-	-	>1	-	-	-
Nasal irritation	✔	2	-	-	2-3	2-<5	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone†	Mometasone	Triamcinolone
Nasal mucosal ulceration	✔	-	-	✔	✔	<1	-
Nasal septal perforation	✔	<1	-	✔	<1	✔	✔
Nasopharyngeal irritation	24	-	-	-	-	-	-
Nasopharyngitis	-	-	<11	-	-	-	-
Pharyngolaryngeal pain	-	-	<5	-	-	-	-
Rhinitis	-	-	-	-	-	2-<5	≥2
Pharyngitis	-	4	-	-	6-8	10-12	5
Rhinorrhea	<3	-	-	-	1-3	-	-
Sinusitis	-	-	<6	≤1	-	4-5	≥2
Sneezing	4	-	-	-	-	-	-
Throat discomfort	-	<1	-	-	<1	-	-
Throat dryness/irritation	✔	<1	-	-	<1	-	-
Upper respiratory tract infection	-	-	<9	-	-	5-7	-
Special senses							
Aftertaste	-	-	-	17	-	-	-
Blurred vision	-	-	-	-	✔	-	-
Cataracts	✔	-	-	-	<1	-	-
Conjunctivitis	-	-	>3	-	✔	2-<5	-
Dry/irritated eyes	-	-	-	-	✔	-	-
Earache	-	-	2	-	-	2-<5	-
Glaucoma	✔	-	-	-	<1	-	-
Hoarseness	-	-	>3	≤1	<1	-	-
Increased intraocular pressure	✔	✔	-	-	<1	✔	-
Loss of taste/smell	✔	✔	-	≤1	✔	✔	-
Otitis media	-	-	-	-	-	2-<5	≥2
Unpleasant taste/smell	✔	-	-	-	-	-	-
Watery eyes	<3	-	-	-	-	-	-
Other							
Aches and pains	-	-	>3	-	1-3	-	-
Arthralgia	-	-	<4	-	-	2-<5	-
Chest pain	-	-	>3	-	-	2-<5	-
Dysmenorrhea	-	-	-	-	-	1-5	-
Fever	-	-	-	-	1-3	-	-
Flu-like symptoms	-	-	>3	-	1-3	2-<5	-
Growth suppression	✔	✔	-	-	✔	-	-
Infection	✔	✔	-	✔	<1	<1	✔
Myalgia	-	-	-	-	-	2-<5	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone†	Mometasone	Triamcinolone
Palpitations	-	✔	-	-	-	-	-
Viral infection	-	-	-	-	-	8-14	-
Voice changes	-	-	-	-	<1	-	-

†Fluticasone furoate and fluticasone propionate.
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the intranasal corticosteroids are listed in Table 7.

Table 7. Usual Dosing Regimens for the Intranasal Corticosteroids[1-10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Beclomethasone	Rhinitis and Nasal Polyps: 42-84 mcg (1-2 sprays) in each nostril twice daily	Rhinitis and Nasal Polyps: ≥6 years of age: 42 mcg (1 spray) in each nostril twice daily	Nasal spray: 42 mcg
Budesonide	Allergic Rhinitis: 32 mcg (1 spray) in each nostril once daily	Allergic Rhinitis: ≥6 years of age: 32 mcg (1 spray) in each nostril once daily	Nasal spray: 32 mcg
Ciclesonide	Allergic Rhinitis: 200 mcg (2 sprays) in each nostril once daily	Seasonal Allergic Rhinitis: ≥6 years of age: 200 mcg (2 sprays) in each nostril once daily Perennial Allergic Rhinitis: ≥12 years of age: 200 mcg (2 sprays) in each nostril once daily	Nasal spray: 50 mcg
Flunisolide	Allergic Rhinitis: 58 mcg (2 sprays) in each nostril twice daily	Allergic Rhinitis: 6-14 years of age: 29 mcg (1 spray) in each nostril three times daily or 58 mcg (2 sprays) in each nostril twice daily if response to lower dose is inadequate	Nasal spray: 0.25% 29 mcg
Fluticasone furoate	Allergic Rhinitis: 55 mcg (2 sprays) in each nostril once daily	Allergic Rhinitis: 2-11 years of age: 27.5 mcg (1 spray) in each nostril daily or 55 mcg (2 sprays) in each nostril once daily if response to lower dose is inadequate	Nasal spray: 27.5 mcg
Fluticasone propionate	Rhinitis: 100 mcg (2 sprays) in each nostril once daily or 50 mcg (1 spray) in each nostril twice daily	Rhinitis: ≥4 years: 50 mcg (1 spray) in each nostril once daily	Nasal spray: 50 mcg
Mometasone	Nasal Polyps: 100 mcg (2 sprays) in each nostril once to twice daily Allergic rhinitis: 100 mcg (2 sprays) in each nostril daily	Allergic rhinitis: 2-11 years: 50 mcg (1 spray) in each nostril daily	Nasal spray: 50 mcg
Triamcinolone	Allergic Rhinitis: 110 mcg (2 sprays) in each nostril once daily	Allergic Rhinitis: 2-5 years of age: 55 mcg (1 spray) in each nostril once daily 6-12 years of age: 55 mcg (1 spray) in each nostril once daily or 110 mcg (2 sprays) in each nostril once daily	Nasal spray: 55 mcg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the intranasal corticosteroids are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Intranasal Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Rhinitis				
Khanna et al.[50] (2005) Beclomethasone vs budesonide vs fluticasone vs mometasone	SB, XO Patients with allergic rhinitis	N=114 Duration not specified	Primary: Sensory perceptions and patient preference	Primary: Significantly more patients preferred mometasone because of less irritation, odor, and aftertaste. Fluticasone was reported by patients as having a significantly higher odor strength and amount of irritation. Eighty percent of the patients predicted better compliance with their preferred drug.
Svendsen et al.[31] (1989) Beclomethasone vs flunisolide	RCT, DB, XO Patients with perennial rhinitis	N=23 8 weeks	Primary: Rhinitis symptoms and patient preference	Primary: There were no statistically significant differences in rhinitis symptoms or patient preference between treatments.
Welsh et al.[35] (1987) Beclomethasone 336 mcg/day, administered as 2	RCT, PC Patients 12-50 years of age, with at least 2 year history of seasonal rhinitis and	N=120 8 weeks	Primary: Symptomatic relief Secondary: Adverse events	Primary: Beclomethasone, flunisolide, and cromolyn significantly reduced the use of supplemental antihistamines or decongestants and hay fever symptoms such as sneezing, nasal symptoms, eye symptoms, itchy nose, and throat symptoms compared with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sprays in each nostril BID vs flunisolide 200 mcg/day, administered as 2 sprays in each nostril BID vs cromolyn 41.6 mg/day, administered as 1 spray in each nostril QID vs placebo	positive skin test to crude short ragweed extract			Beclomethasone and flunisolide significantly reduced hay fever symptoms compared to cromolyn (P<0.001). There were no statistically significant differences between beclomethasone and flunisolide in relief of hay fever symptoms. Secondary: There was significantly more nasal burning with flunisolide than the other treatments (P<0.001).
McArthur et al.[30] (1994) Budesonide 200 mcg BID vs beclomethasone 200 mcg BID	RCT, DB Adults with seasonal allergic rhinitis	N=88 3 weeks	Primary: Nasal and non-nasal symptom score Secondary: Adverse events	Primary: Budesonide treatment resulted in significantly lower scores for runny nose, itchy nose, and sneezing compared with beclomethasone at all time points (P<0.05), but the greatest difference was towards the end of the treatment period. There was no statistically significant difference between treatment groups in scores for nasal blockage, runny eyes, and sore eyes. Secondary: Adverse events for both treatments were mild and transient.
Al-Mohaimeid et al.[42] (1993)	RCT, SB Patients 18-70 years of age with	N=120 3 weeks	Primary: Nasal symptoms	Primary: There were significantly fewer reports of sneezing with budesonide than beclomethasone (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide 200 mcg BID vs beclomethasone 200 mcg BID	perennial allergic rhinitis			No statistically significant differences in the other symptoms, such as blocked nose, runny nose, itchy nose, runny eyes, and sore eyes, were reported (P>0.05). After 3 weeks of treatment, more patients reported being totally free of symptoms with budesonide than with beclomethasone (38% vs 27%). More patients reported the treatment as noticeably, very, or totally effective with budesonide than with beclomethasone (72% vs 58%).
Vanzieleghem et al.[44] (1987) Budesonide as needed, up to 2 sprays of 50 mcg/spray in each nostril QID vs beclomethasone as needed, up to 2 sprays of 50 mcg/spray in each nostril QID	RCT, DB, DD Patients with seasonal allergic rhinitis during the ragweed-pollen season	N=61 7 weeks	Primary: Nasal symptoms, use of chlorpheniramine as rescue medication Secondary: Adverse events	Primary: Less budesonide was administered by the subjects than beclomethasone to maintain good control of nasal symptoms (P=0.016). No statistically significant difference was observed between treatment groups in the amount of oral chlorpheniramine used as rescue medication (P=NS). Secondary: Reported adverse events with both treatments were mild and transient.
Stern et al.[33] (1997) Budesonide 128 mcg or 256 mcg QD vs fluticasone propionate 200	RCT, PC, MC, PG Patients 18-72 years of age with ≥2 year history of allergic rhinitis	N=635 4-6 weeks	Primary: Nasal and eye symptoms Secondary: Adverse events	Primary: Budesonide and fluticasone resulted in significant improvements in individual nasal symptoms such as blocked nose, runny nose, and sneezing (P<0.001), combined nasal symptoms (P<0.001), eye symptoms, and overall substantial or total control of symptoms (P<0.001) compared to placebo. Budesonide 256 mcg produced significant reduction in sneezing compared with fluticasone (P=0.04).There were no other significant differences in individual nasal symptoms, combined nasal symptoms, eye symptoms, or overall substantial or total control of symptoms between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg QD vs placebo				Secondary: Budesonide and fluticasone were well tolerated, with reported adverse events mild to moderate in severity.
Day et al.[41] (1998) Budesonide 256 mcg QD vs fluticasone propionate 200 mcg QD	RCT, MC, DB, PG, PC Patients ≥18 years of age with a ≥1 year history of allergic perennial rhinitis and positive skin test to one or more perennial allergens	N=273 6 weeks	Primary: Nasal symptoms, patients' overall evaluation of efficacy, and use of rescue medication Secondary: Adverse events	Primary: Both treatments resulted in significantly greater improvement in combined nasal symptom scores, runny nose, and sneezing from baseline compared with placebo (P≤0.0012). Budesonide showed greater improvement in combined nasal symptom scores (P=0.031) and nasal blockage than fluticasone, but no statistically significant differences in runny nose or sneezing symptoms were detected. Significant improvements in nasal symptoms were seen at 36 hours with budesonide and 60 hours with fluticasone. At 6 weeks of treatment, there were no statistically significant differences in patients' overall evaluation of efficacy (P=0.44) or use of antihistamines as rescue medication between treatment groups. Secondary: The rates of reported adverse events were 46% with budesonide, 37% with fluticasone, and 36% with placebo. No signs of fungal infection were detected in the study population.
Andersson et al.[47] (1995) Budesonide 200 or 400 mcg QD vs fluticasone propionate 200 mcg QD vs	RCT, PG, PC, MC Patients with perennial allergic rhinitis	N=98 6 weeks	Primary: Rhinitis symptoms, use of terfenadine as rescue medication Secondary: Safety as assessed by rhinoscopy, urine cortisol, adverse events	Primary: There were no significant differences in nasal symptoms or eye symptoms between active treatment groups. All active treatments reduced the use of terfenadine when compared with baseline, but this was significantly significant with budesonide only (P<0.05). Secondary: Reported adverse events were few and minor. No significant differences in adverse events or 24-hour cortisol levels were reported between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Shah et al.[52] (2003) Study 1: Budesonide 32 mcg in each nostril for one dose vs fluticasone propionate 100 mcg in each nostril for one dose Study 2: Budesonide 32 mcg in each nostril for one dose vs fluticasone propionate 50 mcg in each nostril for one dose	MC, RCT, SB, XO Patients ≥18 years of age with ≥1 year history of allergic rhinitis and experiencing mild to moderate symptoms	Study 1, N=181 1 day Study 2 N=190 1 day	Primary: Sensory Perceptions Questionnaire and patients' product preference Secondary: Adverse events	Primary: In study 1, significantly fewer patients perceived the scent (P<0.001), taste (P<0.001), aftertaste (P<0.001), throat rundown (P<0.001), and nose run out (P<0.019) with budesonide than with fluticasone. In study 2, significantly fewer patients detected an altered scent or taste with budesonide than with fluticasone (P<0.001). There were no significant differences between budesonide and fluticasone in aftertaste, throat rundown, and nose run out. More patients perceived the spray in the throat as less wet (P<0.004 for study 1 and P<0.002 for study 2) and therefore preferred the feel of the spray in the throat (P<0.001 for both studies) of budesonide to that of fluticasone. More patients perceived the spray in the nose as less wet (P<0.001 for both studies) and therefore preferred the feel of the spray in the nose (P<0.001 for both studies) of budesonide to fluticasone. Significantly more patients perceived a less forceful spray with budesonide and therefore preferred budesonide to fluticasone (P<0.001). Overall, significantly more patients preferred budesonide to fluticasone (P=0.02). Secondary: Budesonide and fluticasone were both well tolerated.
Naclerio et al.[25] (2003) Budesonide 32 mcg in each nostril QD vs	RCT, PG Patients >18 years of age with perennial allergic rhinitis who were symptomatic on the majority of days of	N=20 2 weeks	Primary: Symptomatic relief and quality of life as assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and nasal	Primary: The RQLQ scores showed that both budesonide and mometasone resulted in a significant improvement in quality of life compared with baseline. There were no significant differences between treatment groups for any of the individual domains in the RQLQ. Data on nasal clearance could not be interpreted by the authors.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mometasone 100 mcg in each nostril QD	each year and have a positive skin test to dust mites		clearance	
Ratner et al.[60] (2006) Ciclesonide 200 mcg once daily vs placebo	RCT, DB, MC, PC, PG Patients ≥12 yrs with ≥2 yr history of seasonal allergic rhinitis and demonstrated sensitivity to mountain cedar pollen (skin prick test).	N=327 28 days	Primary: Change from baseline in the morning and evening patient-assessed reflective total nasal symptom scores (TNSS) Secondary: Patient-assessed instantaneous TNSS; physician-assessed overall nasal signs and symptoms severity (PANS); total nonnasal symptom scores; Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ); individual nasal symptoms; time to onset of effect.	Primary: The average of morning and evening reflective TNSS decreased from baseline by 2.69 ± 0.17 in the ciclesonide group and 1.87 ± 0.17 in the placebo group (P<0.001 vs placebo) over the 28 days of the study. Secondary (all data for 28 days): The average of morning and evening instantaneous TNSS decreased from baseline by 2.43 ± 0.16 in the ciclesonide group and 1.63 ± 0.16 in the placebo group (P<0.001 vs placebo). Statistically significant differences from placebo were not observed in overall PANS and RQLQ scores and in the average of morning and evening reflective nonnasal symptoms. Time to onset of effect was determined by hourly measurements of instantaneous TNSS during day 1. The first time point with a P<0.05 for the difference in instantaneous TNSS was at hour 12. Significant differences were seen at 14 days for the individual nasal symptoms of nasal congestion, runny nose, sneezing and nasal itching; evaluation at 28 days not reported.
Sipila et al.[23] (1983) Flunisolide 50 mcg in each nostril BID	OL, PG Patients with allergic rhinitis and seasonal symptoms for at least two	N=45 4 weeks	Primary: Daily symptoms and severity of nasal symptoms Secondary:	Primary: There were no significant differences between the treatment groups in the change from baseline in daily symptoms such as runny nose, stuffiness, sneezing, and eye symptoms. Improvement in the severity of nasal symptoms compared with baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs beclomethasone 50 mcg in each nostril QID	years		Adverse events	was similar in both treatment groups. Secondary: The reported side effects were mild and primarily consisted of local irritation.
Sahay et al.[24] (1980) Flunisolide 50 mcg in each nostril BID vs beclomethasone 50 mcg in each nostril QID	OL, PG Patients with perennial allergic rhinitis, with or without seasonal allergic rhinitis	N=56 4 weeks	Primary: Symptom relief Secondary: Detection of Candida growths and safety	Primary: Flunisolide and beclomethasone resulted in significant reductions in sneezing, stuffiness, runny nose, nose blowing, postnasal drip, epistaxis, and interference by symptoms with routine life or sleep when compared to baseline (P<0.01 for all). There were no statistically significant differences in control of symptoms between the two treatment groups. Secondary: There were no signs of adrenal suppression or Candida growths in either group. There were four side effects in the flunisolide group and five side effects in the beclomethasone group that were considered to be probably drug related.
Langrick et al.[32] (1984) Flunisolide 200 mcg daily, administered as 2 sprays in each nostril BID vs beclomethasone 400 mcg daily, administered as 2 sprays in each nostril BID	RCT, SB, PG Patients 18-60 of age with a history of moderate to severe hay fever	N=69 7 weeks	Primary: Signs and symptoms of hay fever, severity of symptoms, and physicians' and patients' evaluation of overall effect of treatment Secondary: Adverse events	Primary: There were no significant differences between treatment groups in severity of symptoms, overall treatment effect, or patients' self-assessment of symptoms such as sneezing, runny nose, and blocked nose. Secondary: One patient in the flunisolide reported a dry throat of moderate severity. One patient in the beclomethasone group reported a mild tickling sensation inside the nose.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McAllen et al.[39] (1980) Flunisolide 50 mcg in each nostril BID vs beclomethasone 50 mcg in each nostril QID	SB, XO Patients 19-58 years of age who had perennial rhinitis with or without seasonal exacerbations and had moderate to severe symptoms of 6 months to 50 years in duration	N=34 8 weeks	Primary: Rhinitis symptoms Secondary: Adverse events and Candida growth	Primary: Treatment with flunisolide and beclomethasone significantly reduced sneezing, stuffiness, runny nose, nose-blowing, and interference with routine life when compared with baseline. There were no statistical differences between the flunisolide and beclomethasone treatment groups in nasal symptoms, physicians' and patients' preference, and interference with routine life. Secondary: Neither treatment resulted in Candida growth. Reported side effects were minor and mostly nasal irritation or dryness.
Aasand et al.[40] (1982) Flunisolide 50 mcg in each nostril BID vs beclomethasone 50 mcg in each nostril QID	SB, PG, MC Patients with ≥2 year history of seasonal rhinitis	N=47 4 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: Flunisolide and beclomethasone improved nasal rhinitis symptoms (88% of patients showed improvement with flunisolide vs 91% with beclomethasone). No statistical differences were observed between treatment groups. Secondary: The only reported adverse event with both medications was mild stinging of transient duration.
Kaiser et al.[61] (2007) Fluticasone furoate 110 mcg once daily vs placebo	RCT, DB, MC, PC, PG Patients ≥12 yrs with moderate or severe seasonal allergic rhinitis caused by ragweed pollen	N=299 2 weeks	Primary: Mean change from baseline in daily reflective total nasal symptom scores (rTNSS) Secondary: Change in daily reflective total ocular symptom scores (rTOSS); change in morning	Primary: Fluticasone furoate significantly reduced nasal symptoms (rTNSS) compared with placebo with an observed treatment difference of – 1.473 (P<0.001). Secondary: The observed difference in rTOSS was –0.600 between the treatment groups (P=0.004). Morning predose iTNSS was significantly reduced compared to placebo, with an observed difference of – 0.696 (P<0.001); this supports once-daily dosing.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			predose instantaneous TNSS; response to therapy; health related quality of life (RQLQ); change in total and individual reflective and instantaneous nasal and ocular symptoms; time to onset of effect; change in daily rTNSS and rTOSS and morning predose iTNSS and instantaneous total scores for ocular symptoms	Improvement was reported by 73% of fluticasone furoate patients compared with 52% of placebo patients (P<0.01). Significant improvements in overall RQLQ was seen in patients treated with fluticasone compared to placebo (P<0.001). Mean change from baseline in total and individual reflective (rTNSS) and instantaneous nasal (iTNSS) and ocular (iTOSS) symptoms: greater reductions for fluticasone furoate than for placebo (P<0.001 and P ≤0.033, respectively). The first significant treatment difference in morning predose iTNSS was observed at 8 hours after the first dose (observed treatment difference – 0.696, P<0.028).
Meltzer et al.[64] (2008) Fluticasone furoate 110 mcg as a single dose (FF) vs fluticasone propionate 200 mcg as a single dose (FP)	RCT, DB, MC, XO Patients ≥18 years of age with allergic rhinitis, determined by respiratory symptoms and positive skin test to perennial and/or seasonal allergens within 12 months prior to study	N=127 Single dose	Primary: Sensory attributes and patient preference	Primary: A total of 64% of patients preferred FF with respect to odor, while 29% preferred FP (P<0.001), and 7% had no preference. Between 43% and 49% of patients preferred FF with respect to the attributes of immediate taste (47% vs 21%; P<0.001), aftertaste (44% vs 22%; P=0.002), less dripping down the throat (43% vs 27%; P=0.037), and less running out of the nose (49% vs 19%; P<0.001), while 19% to 27% of patients preferred FP, and 30% to 34% had no preference regarding these attributes. There were no significant differences between FF and FP in preferences for attributes related to the medication being soothing, irritating, or making patients want to sneeze. A greater proportion of patients preferred FF overall compared with FP (60% vs 33%; P=0.003). A total of 8% of patients indicated no preference. Patient ratings favored FF over FP with respect to odor, taste, running down the throat, and running out of the nose both immediately and 2

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				minutes after dosing. There were no statistically significant differences between drugs either immediately or 2 minutes after dosing in patient ratings for FF and FP with respect to whether the medication felt soothing, caused nasal irritation, or made patients sneeze. A total of 52% of patients replied that they were very likely to comply with FF treatment versus FP treatment if the medications were prescribed (38 %; P=0.02). The overall incidence of adverse events was 2%, all of which occurred during treatment with FF.
Meltzer et al.[66] (2010) Fluticasone furoate 100 mcg QD for 1 week vs fluticasone propionate 200 mcg QD for 1 week vs placebo	RCT, DB, PC, XO Patients with moderate to severe allergic rhinitis	N=360 2 weeks	Primary: Change from baseline during 1 week in daily reflective total nasal symptom score (rTNSS), patient preference	Primary: Fluticasone furoate and fluticasone propionate significantly reduced daily rTNSS compared with placebo (P<0.001 and P=0.01, respectively). Fluticasone furoate and fluticasone propionate were also significantly more effective than placebo in improving daytime rTNSS and nighttime rTNSS. More patients preferred fluticasone furoate to fluticasone propionate based on the primary preference endpoint of scent or odor (58% vs 27%, P<0.001). A total of 15% of patients had no preference for either product with respect to scent or odor. Significantly (P<0.001) more patients preferred fluticasone furoate compared with fluticasone propionate because less medication leaked out of the nose or down the throat (59% vs 21%), because of the gentleness of the mist (57% vs 26%), and because of less aftertaste (60% vs 18%). No statistically significant differences were found in preferences for fluticasone furoate and fluticasone propionate with respect to attributes related to ease of use, consistency of medication delivered, the delivery method, or device comfort. The proportions of patients with any adverse event were similar among treatments. Headache was the most frequently reported adverse event and occurred in 4% of patients during fluticasone furoate treatment, 9% during fluticasone propionate treatment, and 7% during each placebo treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Okubo et al.[67] (2009) Fluticasone furoate 110 mcg QD (FFNS) vs fluticasone propionate 100 mcg BID (FPNS) vs placebo	RCT, DB, PC, MC, PG Patients ≥16 years of age with cedar pollinosis	N=446 2 weeks	Primary: Mean change in 3TNSS (the sum of 3 individual symptom scores for sneezing, rhinorrhea and nasal congestion), mean change in 4TNSS (the sum of scores for sneezing, rhinorrhea, nasal congestion and nasal itching), mean change in individual nasal symptom scores and rhinoscopy scores, patients' impression of treatment effect, and number of days until onset of action	Primary: The mean change from baseline in 3TNSS over the entire treatment period was significantly greater for FFNS than for placebo (P<0.001). A significant decrease in 3TNSS was also observed in the FPNS group compared to placebo (P<0.001). Fluticasone furoate was non-inferior to fluticasone propionate in mean change from baseline in 3TNSS. There were similar mean changes in 4TNSS in the FFNS and FPNS groups. Mean changes from baseline in 4TNSS were significantly greater with FFNS and FPNS compared to placebo (both P<0.001). There were similar mean changes in individual nasal symptom scores (sneezing, rhinorrhea, nasal congestion, and nasal itching) in the FFNS and FPNS groups. There was a significant decrease in all symptom scores with FFNS compared with placebo (P<0.001). There were similar improvements in rhinoscopy findings, activity of daily life interference, and patient-rated overall evaluation to therapy in both groups. After 2 weeks of treatment, the number of patients who felt "improved (improved, remarkably improved)" was highest with FFNS (50%), followed by FPNS (45%), FPNS placebo (14%), and then FFNS placebo (10%). There was a significant difference between the FFNS and FFNS placebo groups (P<0.001), suggesting improvement of ADL in the patients treated with FFNS.
Ratner et al.[34] (1992) Fluticasone propionate 200 mcg QD vs beclomethasone 168 mcg BID	RCT, DB, PC, PG, MC Adults with ≥2 year history of seasonal allergic rhinitis, who have moderate to severe symptoms and positive skin test to mountain cedar	N=313 2 weeks	Primary: Nasal symptoms, overall response to treatment, and use of rescue medication (chlorpheniramine maleate) Secondary: Adverse events	Primary: When compared with placebo, significant improvements in nasal symptoms and overall response to treatment were seen with fluticasone and beclomethasone as evaluated by the clinicians and the patients (P<0.05 for all). There were no significant differences between treatment groups in nasal symptoms as rated by the clinicians or the patients or overall response to treatment. When compared with placebo, there was a significant reduction in the use of rescue medication with fluticasone and beclomethasone (P<0.05).There was no statistically significant difference between treatment groups in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				amount of rescue medication used. Secondary: No clinically significant differences in any of the safety variables between treatment groups were reported.
LaForce et al.[37] (1994) Fluticasone propionate 100 mcg BID or 200 mcg QD vs beclomethasone 168 mcg BID vs placebo	RCT, DB, MC, PC, PG Patients at least 12 years of age, with at least a 2-year history of seasonal allergic rhinitis, who have positive skin test to at least one spring allergen and moderate to severe symptoms	N=238 4 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: Fluticasone reduced patient-rated nasal symptom scores significantly better than beclomethasone (P<0.05) and placebo (P<0.01) at all time points measured. There were no statistically significant differences in clinician-rated nasal symptom scores between treatment groups (P=NS). Secondary: There were no significant differences in adverse events between treatment groups.
Van As et al.[45] (1993) Fluticasone propionate 100 mcg BID or 200 mcg QD vs beclomethasone 168 mcg BID vs placebo	RCT, DB, MC, PC, PG Patients 12-71 years of age with perennial allergic rhinitis and moderate to severe symptoms, nasal eosinophils, and positive skin test to a perennial allergen	N=466 6 months	Primary: Nasal symptoms and use of antihistamine as rescue medication Secondary: Adverse events	Primary: Fluticasone and beclomethasone reduced nasal obstruction, rhinorrhea, sneezing, nasal itching, and nasal eosinophilia. There were no significant differences between active treatment groups in nasal symptoms, number of patients who used rescue medication, amount of rescue medication consumed, or incidences of adverse events. Secondary: No evidence of systemic effects with drug treatment was reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Haye et al.[46] (1993) Fluticasone propionate 200 mcg BID vs beclomethasone 200 mcg BID	RCT, MC, DB, PG Patients ≥16 years of age with perennial rhinitis	N=251 1 year	Primary: Rhinitis symptoms Secondary: Safety	Primary: Fluticasone treatment resulted in significantly less nasal blockage (P=0.002), nasal discharge (P=0.002), and eye watering/irritation (P=0.048) than beclomethasone. No significant differences were observed in the amount of sneezing (P=0.114) or nasal itching (P=0.052) between treatment groups. Secondary: There were no significant differences in nasal itching (P=0.052), sneezing, nasal examination by rhinoscopy, hematologic, biochemical, and urinary parameters, plasma cortisol level, or adverse events between treatment groups.
Scadding et al.[48] (1995) Fluticasone propionate 200 mcg QD or BID vs beclomethasone 200 mcg BID vs placebo	RCT, DB, MC, PG, PC Patients with allergic and nonallergic perennial rhinitis	N=not specified 12 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: There were no significant differences between active treatment groups in nasal symptoms. Secondary: Few adverse events and no treatment-related abnormalities in laboratory measurements were reported.
Bachert et al.[49] (2004) Fluticasone propionate 200 mcg QD vs	RCT, DB, PC, XO Healthy volunteers 18-65 years of age	N=23 12 days	Primary: Suppression of the hypothalamic-pituitary-adrenal (HPA) axis as measured by 12 hour overnight urinary cortisol excretion and	Primary: Overnight urinary cortisol concentrations showed that there was no significant difference in HPA axis suppression with fluticasone (P=0.609) or triamcinolone (P=0.194) compared with placebo. Neither fluticasone (P=0.999) and triamcinolone (P=0.521) showed a significant effect on the HPA axis activity when compared with placebo, as assessed by the mean peak serum cortisol concentrations before and after adrenocorticotropic hormone (ACTH) stimulation.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triamcinolone 220 mcg QD vs placebo			serum cortisol concentrations Secondary: Adverse events	Secondary: Both medications were well tolerated. There were no significant differences in the number of subjects that experienced adverse events between treatment groups.
Drouin et al.[26] (1996) Mometasone 100 mcg in each nostril QD vs beclomethasone 100 mcg in each nostril BID vs placebo	RCT, DB, PC, PG, MC Patients 12 years of age and older, who are allergic to at least one perennial allergen, with adequate symptomatology	N=427 12 weeks	Primary: Change from baseline in total morning (AM) plus evening (PM) diary nasal symptom score over the first 15 days of treatment Secondary: Total diary nasal symptom scores averaged over 15-day intervals beyond day 15, composite total and individual diary symptom scores, physician evaluation of response to therapy, and adverse events	Primary: When compared to placebo, both mometasone and beclomethasone produced significantly greater improvements in the total AM plus PM diary nasal symptom scores over the first 15 days of treatment (P≤0.01). The difference in reduction from baseline in nasal symptom scores between mometasone and beclomethasone was not significant at any time point (P≥0.32). Secondary: Physician evaluations of nasal symptoms for mometasone and beclomethasone were not statistically different from each other at any time point. The rates of adverse events were similar for all groups (43% for mometasone, 42% for beclomethasone, 36% for placebo).
Hebert et al.[28] (1996) Mometasone 100 to 200 mcg QD, administered as 2 sprays of 25 or 50	RCT, DB, PC, PG, MC Patients 18 years of age and older, with moderate to severe seasonal allergic	N=501 4 weeks	Primary: Nasal symptom score, physicians' and patients' evaluation of response to therapy, and use of	Primary: Nasal symptoms (P≤0.01) and use of rescue medication (P≤0.05) were significantly improved in all three treatment groups compared with placebo. There were no significant differences between treatment groups in nasal symptom score, physicians' evaluation of nasal symptoms, overall

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg/spray in each nostril QD vs beclomethasone 100 mcg in each nostril BID vs placebo	rhinitis for at least 2 years, who have a positive skin test to at least one tree and/or grass aeroallergen		loratadine as rescue medication Secondary: Adverse events	condition, and response to treatment, or use of rescue medication. Secondary: The rate of adverse events were similar in all groups (25% with mometasone 100 mcg, 26% with mometasone 200 mcg, 30% with beclomethasone, 28% with placebo).
Graft et al.[29] (1996) Mometasone 100 mcg in each nostril QD vs beclomethasone 84 mcg in each nostril BID vs placebo	RCT, DB, PG, MC, PC Patients at least 12 years of age who have at least a 2-year history of moderate to severe seasonal allergic rhinitis and a positive skin test response to ragweed	N=349 8 weeks	Primary: Severity score of nasal and non-nasal symptoms Secondary: Adverse events	Primary: Both treatments resulted in a significantly higher percentage of days with minimal symptoms, longer duration to the first occurrence of a non-minimal symptom day, and total nasal symptom scores compared with placebo (P≤0.01 for all). There was no significant difference in the percentage of days with minimal symptoms between treatment groups. Nasal symptom scores for the treatment period before the allergy season onset were significantly lower with mometasone than beclomethasone (P=0.05). Secondary: The percentages of patients experiencing at least one adverse event that was considered possibly related to treatment are as follows: 16% of the mometasone group, 14% of the beclomethasone group, and 19% of the placebo group. The adverse events were generally mild to moderate and of short duration.
Ratner et al.[65] (2009) Mometasone 100 mcg QD vs	MC, SC, SB Children 6-11 years of age with ≥1 year history of perennial allergic rhinitis (PAR)	N=255 12 months	Primary: Changes in overall PAR symptoms and response to treatment, as well as safety	Primary: Physician-rated reductions in PAR symptoms were -42.1% for mometasone compared with -44.0% for beclomethasone. Subject-rated overall condition of PAR was -39.7% for mometasone compared with -39.0% for beclomethasone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
beclomethasone 168 mcg QD				A total of 94% of patients in the mometasone group reported mostly mild to moderate adverse reactions compared with 100% in the beclomethasone group. Epistaxis, headache, and pharyngitis were the most frequently reported events. There was no evidence of hypothalamic-pituitary-adrenal axis suppression in children.
Meltzer et al.[54] (2005) Mometasone vs fluticasone propionate 200 mcg	RCT, DB, XO Patients with allergic rhinitis	N=100 Duration not specified	Primary: Individual product sensory attributes and overall sensory preference	Primary: Significantly more patients preferred mometasone to fluticasone for its scent (P=0.0005), immediate taste (P=0.005), aftertaste (P=0.005), and overall (54% vs 33%, P=0.03). Patients rated mometasone as significantly better than fluticasone in individual sensory attributes, which included fewer perceived scent/odor (P<0.001), taste (P=0.002), and aftertaste (P=0.007). Patients reported significantly larger percentage of expected compliance with mometasone than fluticasone (47% vs 25%, P=0.03).
Mandl et al.[27] (1997) Mometasone 100 mcg in each nostril QD vs fluticasone propionate 100 mcg in each nostril QD vs placebo	RCT, DB, PG, PC Patients 12-77 years of age who are allergic to at least one perennial allergen, and have moderate to severe symptomatology	N=550 12 weeks	Primary: Nasal symptom score Secondary: Physicians' evaluation of nasal symptoms and response to therapy and adverse events	Primary: Both mometasone and fluticasone produced significantly greater improvements in nasal symptoms than placebo (P<0.01). The difference in reduction of nasal symptom score between mometasone and fluticasone was not significant at any time point (P≥0.43). Secondary: Physicians' evaluation of nasal symptoms and response to therapy were similar for mometasone and fluticasone. The rates of adverse events were similar for all groups (33% for mometasone, 38% for fluticasone, and 37% for placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weinstein et al.[63] (2009) Triamcinolone 110 mcg, 1 spray per nostril QD vs placebo	MC, RCT, DB, PG Patients 2-5 years of age with at least 1 year history of perennial allergic rhinitis	N=474 28 days	Primary: Change from baseline in the mean daily instantaneous TNSS and change in individual treatment scores Secondary: Change from baseline in the mean daily reflective TNSS	Primary: Adjusted mean change for instantaneous TNSS was -2.28 for triamcinolone and -1.92 for the placebo group (P=0.09). The individual symptom score showed a significantly greater reduction with triamcinolone than placebo (P=0.02). Secondary: There was a significantly greater reduction in reflective TNSS from baseline in the triamcinolone group (-2.31) than the placebo group (1.87; P=0.03).
Winder et al.[36] (1993) Triamcinolone 220 mcg QD vs beclomethasone 84 mcg BID	RCT, SB, PG, MC Patients 18-64 years of age with at least a 2-year history of perennial allergic rhinitis who have positive skin tests to indoor allergens and nasal eosinophilia or basophilia	N=169 4 weeks	Primary: Rhinitis symptoms and global evaluations of treatment by patients and physicians Secondary: Adverse events	Primary: No statistically significant differences were found in rhinorrhea, congestion, sneezing, sum of primary symptom scores, and physicians' global evaluations between treatment groups. Patients' global evaluation of treatment with triamcinolone were significantly higher than with beclomethasone (P<0.05). Secondary: There were no statistically significant differences between treatments in burning/stinging, nasal dryness, nasal bleeding, bloody mucus, nasal congestion, throat discomfort, and bad taste (P=NS). There were significantly more medication-induced sneezing with triamcinolone than beclomethasone (P=0.024). There was significantly more medication runoff from the nose and throat with beclomethasone than triamcinolone (P<0.05).
Lumry et al.[38] (2003) Triamcinolone 220 mcg QD	RCT, MC, SB, PG Patients at least 18 years of age with at least a 2-year	N=152 3 weeks	Primary: Nasal symptoms, eye symptoms, health-related quality of life, and	Primary: Significant improvement from baseline in rhinitis related-nasal and eye symptoms were seen with triamcinolone and beclomethasone. There were no significant differences in nasal stuffiness, nasal discharge,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs beclomethasone 168 mcg BID	history of seasonal allergic rhinitis to ragweed pollen		patient preference for sensory attributes Secondary: Adverse events	nasal index, nasal itching, total eye symptoms, patients' or physicians' overall assessment of efficacy, or health-related quality of life between treatment groups. Patients rated the taste and odor of triamcinolone as significantly better than beclomethasone (P≤0.05). Otherwise, there were no statistically significant differences between treatment groups in the other sensory attributes such as medication running down to throat, medication running out of nose, medication induced sneezing, stinging/burning sensation, nose bleed, and blood in mucus (P>0.05). Secondary: The rates of reported adverse events were comparable between treatment groups (34.7% with triamcinolone vs 35.1% with beclomethasone).
Small et al.[22] (1997) Triamcinolone 110 mcg in each nostril QD vs fluticasone 100 mcg in each nostril QD	RCT, PG, SB, MC Patients 12-70 years of age with spring pollen allergic rhinitis for at least 2 years, who had at least two nasal symptoms (rhinorrhea, congestion, sneezing, and itching) at baseline, and who had a Rhinitis Index Score of at least 24 out of 48	N=233 21 days	Primary: Rhinitis Index Score and individual symptom score Secondary: Physicians' and patients' global evaluations, patients' acceptance of the study medications, and safety	Primary: There were no significant differences between treatment groups in the changes from baseline in Rhinitis Index Score (P=0.23) or individual symptoms, such as congestion (P=0.58), rhinorrhea (P=0.08), sneezing (P=0.51), and nasal itching (P=0.64). Secondary: There were no statistically significant differences between treatment groups in physicians' and patients' global evaluations. Patients' acceptance of the study medication varied. Fluticasone was rated as significantly more intolerable than triamcinolone with respect to medication "running down the throat" and "medication running out of nose" (P<0.01), while triamcinolone was rated as significantly more intolerable than fluticasone with respect to "medication causing dry nostril" and "medication causing stuffed-up nose" (P<0.01). Adverse events were experienced by 26% of the patients receiving triamcinolone and 22% of the patients receiving fluticasone.
Gross et al.[43] (2002) Triamcinolone 110	RCT, SB, PG, AC Patients 12-70 years of age, with fall	N=352 3 weeks	Primary: Nasal symptoms, effects on health-related quality of	Primary: No statistically significant differences were reported between the treatment groups in daily total nasal symptom scores (P=0.332), individual symptom scores, treatment-related side effects, overall HRQL scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mcg in each nostril QD vs fluticasone 100 mcg in each nostril QD	seasonal allergic rhinitis and positive skin test to ragweed		life (HRQL) as measured by the Rhino-conjunctivitis Quality of Life (QOL) questionnaire, adverse events	(P=0.4), or overall Rhinoconjunctivitis QOL Questionnaire scores.
Bachert et al.[51] (2002) Triamcinolone 110 mcg in each nostril QD vs fluticasone 100 mcg in each nostril QD vs mometasone 100 mcg in each nostril QD	RCT, DB, XO, MC Patients at least 18 years of age with at least a 2- year history of allergic rhinitis	N=95 1 day	Primary: Sensory perceptions, patient preferences, and likelihood of compliance	Primary: Overall, more patients preferred triamcinolone to fluticasone (P≤0.05) and mometasone (P≤0.001). Patients preferred the odor, sensation of greater moisture, less aftertaste, and less irritation of triamcinolone to that of fluticasone and mometasone (P<0.05 for all). Triamcinolone was significantly preferred more than mometasone for the taste, comfort, and less irritation (P<0.05 for all). Fluticasone was also significantly preferred more than mometasone in terms of taste, comfort and amount of irritation (P≤0.05). There were no significant differences between fluticasone and mometasone in aftertaste and amount of irritation. Patients reported a higher likelihood of compliance with triamcinolone (67.4%) than with fluticasone (54.7%) and mometasone (49.5%).
Stokes et al.[53] (2004) Triamcinolone 220 mcg one time vs fluticasone 200 mcg one time	RCT, DB, XO, MC Patients 18-70 years of age with at least a 2-year history of allergic rhinitis, who were symptomatic at baseline	N=215 1 day	Primary: Patients' sensory perception measured by the Nasal Spray Evaluation Questionnaire (NSEQ), patients' preference measured by the	Primary: The NSEQ scores for triamcinolone were significantly higher than fluticasone and mometasone (78.6 for triamcinolone, 72.3 for fluticasone, 69.3 for mometasone, P <0.001 for all). Based on the ONSEQ scores, significantly more patients preferred triamcinolone (50% for triamcinolone vs 25% for fluticasone and 25% mometasone, P<0.001 for all). A larger percentage of the patients reported a Likert score of 1 or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mometasone 200 mcg one time			Overall Nasal Spray Evaluation Questionnaire (ONSEQ), and patients' self reported expected compliance score using the 4-point Likert scale	"definitely complying" with triamcinolone (62.5% for triamcinolone, 49.0% for fluticasone, 51.0% for mometasone, P<0.01 for all).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, TB=triple-blind, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Corren et al. demonstrated that asthmatic patients with concomitant allergic rhinitis who were treated with nasal corticosteroids had a significantly lower risk of asthma exacerbations that resulted in emergency room visits (OR, 0.75; 95% CI, 0.62-0.91) and hospitalizations (OR, 0.56; 95% CI, 0.42-0.76).[55] Bonfils et al. conducted a retrospective review of medical records and determined that 85% of patients were successfully treated with a short-term combination therapy of prednisolone and intranasal beclomethasone; therefore, they did not have to undergo surgery for nasal polyps.[56]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Intranasal Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Beclomethasone	nasal spray	Beconase AQ®	$$$$	N/A
Budesonide	nasal spray	Rhinocort Aqua®	$$$$	N/A
Ciclesonide	nasal spray	Omnaris®	$$$	N/A
Flunisolide	nasal spray	N/A	N/A	$-$$
Fluticasone furoate	nasal spray	Veramyst®	$$$	N/A
Fluticasone propionate	nasal spray	Flonase®*	$$$	$
Mometasone	nasal spray	Nasonex®	$$$	N/A
Triamcinolone	nasal spray	Nasacort AQ®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The intranasal corticosteroids are approved for the treatment of allergic and nonallergic rhinitis, as well as nasal polyps.[1-10] Flunisolide and fluticasone propionate are both available in a generic formulation.

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists and mast cell stabilizers.[15,17-18] The selection of therapy should be individualized and take into consideration the severity and duration of the disease, patient preference, efficacy and safety.[17] Intranasal corticosteroids are considered first-line therapy for the treatment of allergic rhinitis, especially in patients with moderate to severe persistent symptoms.[15-18]

Comparative clinical trials have demonstrated similar efficacy with the intranasal steroids for the majority of the endpoints assessed in patients with allergic rhinitis.[22-49,54,64-65,67] The differences in potencies, systemic bioavailabilities and onset of action did not translate to improved efficacy. However, there were subtle differences reported among the various agents in tolerability and patient preference. Guidelines do not give preference to one intranasal corticosteroid over another for the treatment of allergic rhinitis.

There is insufficient evidence to support that one brand intranasal corticosteroid is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand intranasal corticosteroids within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand intranasal corticosteroid is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
4. Beconase AQ® [package insert]. Research Park Triangle, NC: GlaxoSmithKline; April 2005.
5. Rhinocort Aqua® [package insert]. Wilmington, DE: AstraZeneca; May 2009.
6. Omnaris® [package insert]. Marlborough, MA: Sepracor, Inc; July 2009.
7. Veramyst® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2010.
8. Flonase® [package insert]. Research Park Triangle, NC: GlaxoSmithKline; August 2007.
9. Nasonex® [package insert]. Kenilworth, NJ: Schering Corporation; May 2010.
10. Nasacort AQ® [package insert]. Bridgewater, NJ: sanofi-aventis Pharmaceuticals, Inc; September 2008.
11. Plaut M, Valentine MD. Allergic rhinitis. N Engl J Med. 2005;353:1934-1944.
12. DeShazo RD, Kemp SF. Management of allergic rhinitis (rhinosinusitis). In: Rose, BD, ed. UpToDate. Waltham, Mass: UpToDate, 2006.
13. Badia L, Lund V. Topical corticosteroids in nasal polyposis. Drugs. 2001;61(5):573-578.
14. Allen DB, Meltzer EO, Lemanske RF, et al. No growth suppression in children treated with the maximum recommended dose of fluticasone propionate aqueous nasal spray for one year. Allergy Asthma Proc. 2002;23:407-413.
15. Wallace DV, Dykewicz MS, Bernstein DI, et al., Joint Task Force on Practice, American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1-84.
16. Institute for Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Respiratory Illness in Children and Adults. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); January 2008. Available at: http://www.icsi.org/respiratory_illness_in_children_and_adults__guideline_/respiratory_illness_in_children_and_adults__guideline__13116.html. Accessed October 2010.
17. Bousquet J, Khaltaev N, Cruz A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA^{2}LEN and AllerGen). Allergy 2008:63(S86):8–160.
18. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of allergic rhinitis. Primary Care Respiratory Journal 2006;15:58-70.
19. Van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy. 2000;55:116-134.
20. Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis – superior relief? Drugs. 2001;61(1):1563-1579.
21. Demoly P, Piette V, Daures J. Treatment of allergic rhinitis during pregnancy. Drugs. 2003;63(17):1813-1820.
22. Small P, Houle PA, Day JH, et al. A comparison of triamcinolone acetonide nasal aerosol spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. J Allergy Clin Immunol. 1997;100(5):592-595.
23. Sipila P, Sorri M, Ojala K, et al. Comparative trial of flunisolide and beclomethasone dipropionate nasal sprays in patients with seasonal allergic rhinitis. Allergy. 1983;38:303-307.
24. Sahay JN, Chatterjee SS, Engler C. A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin Allergy. 1980;10:65-70.
25. Naclerio RM, Baroody FM, Bidani N, et al. A comparison of nasal clearance after treatment of perennial allergic rhinitis with budesonide and mometasone. Otolaryngol Head Neck Surg. 2003;128:220-227.
26. Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol. 1996:77(2):153-160.
27. Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. The 194-079 Study Group. Ann Allergy Asthma Immunol. 1997:79(3):237-245.
28. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex™) in seasonal allergic rhinitis: an active- and placebo-controlled study. Allergy. 1996;51:569-576.

29. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. Journal of Allergy and Clinical Immunology. 1996:98(4):724-731.
30. McArthur JG. A comparison of budesonide and beclomethasone dipropionate sprays in the treatment of seasonal allergic rhinitis [abstract]. Clin Otolaryngol Allied Sci. 1994;19(6):537-542.
31. Svendsen UG, Frolund L, Madsen F, et al. Beclomethasone dipropionate versus flunisolide as topical steroid treatment in patients with perennial rhinitis [abstract]. Clin Otolaryngol Allied Sci. 1989;14(5):441-445.
32. Langrick AF. Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. Curr Med Res Opin. 1984;9:290-295.
33. Stern MA, Dahl R, Nielsen LP, et al. A comparison of aqueous suspensions of budesonide nasal spray (128 mcg and 256 mcg once daily) and fluticasone propionate nasal spray (200 mcg once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol. 1997;11(4):323-330.
34. Ratner PH, Paull BR, Findlay SR, et al. Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily. J Allergy Clin Immunol. 1992;90:285-291.
35. Welsh PW, Stricker WE, Chu C, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc. 1987;62:125-134.
36. Winder J, Bell T, Brodsky L, et al. A comparative study of intranasal triamcinolone acetonide aerosol and intranasal beclomethasone dipropionate aqueous spray in perennial allergic rhinitis. Immunol Allergy Pract. 1993;15(7):203-209.
37. LaForce CF, Dockhorn RJ, Findlay SR, et al. Fluticasone propionate: an effective alternative treatment for seasonal allergic rhinitis in adults and adolescents. J Fam Pract. 1994;38:145-152.
38. Lumry W, Hampel F, LaForce C, et al. A comparison of once-daily triamcinolone acetonide aqueous and twice-daily beclomethasone dipropionate aqueous nasal sprays in the treatment of seasonal allergic rhinitis. Allergy Asthma Proc. 2003;24:203-210.
39. McAllen MK, Portillo PR, Parr EJ, et al. Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. Br J Dis Chest. 1980;74:32-36.
40. Aasand G, Etholm BO, Skjostad M, et al. Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis [abstract]. Rhinology. 1982;20(4):205-211.
41. Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol. 1998;102(6):902-908.
42. Al-Mohaimeid H. A parallel-group comparison of budesonide and beclomethasone dipropionate for the treatment of perennial allergic rhinitis in adults. J Int Med Res. 1993;21(2):67-73.
43. Gross G, Jacobs RL, Woodworth TH, et al. Comparative efficacy, safety, and effect on quality of life of triamcinolone acetonide and fluticasone propionate aqueous nasal sprays in patients with fall seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89(1):56-62.
44. Vanzieleghem MA, Juniper EF. A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis. J Allergy Clin Immunol. 1987;79(6):887-892.
45. Van As A, Bronsky EA, Dockhorn RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. J Allergy Clin Immunol. 1993;91(6):1146-1154.
46. Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology. 1993;31(4):169-174.
47. Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology. 1995;33(1):18-21.
48. Scadding GK, Lund VJ, Jacques LA, et al. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis [abstract]. Clin Exp Allergy. 1995;25(8):737-743.
49. Bachert C, Lukat KF, Lange B. Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity in healthy volunteers. Clin Exp Allergy. 2004;34:85-90.
50. Khanna P, Shah A. Assessment of sensory perceptions and patient preference for intranasal corticosteroid sprays in allergic rhinitis. Am J Rhinol. 2005;19(3):316-321.
51. Bachert C, El-Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89:292-297.
52. Shah SR, Miller C, Pethick N, et al. Two multicenter, randomized, single-blind, single-dose, crossover studies of specific sensory attributes of budesonide aqueous nasal spray and fluticasone propionate nasal spray. Clin Ther. 2003;25(8):2198-2214.

53. Stokes M, Amorosi SL, Thompson D, et al. Evaluation of patients' preferences for triamcinolone acetonide aqueous, fluticasone propionate, and mometasone furoate nasal sprays in patients with allergic rhinitis. Otolaryngol Head Neck Surg. 2004;131:225-231.
54. Meltzer EO, Bardelas J, Goldsobel A, et al. A preference evaluation study comparing the sensory attributes of mometasone furoate and fluticasone propionate nasal sprays by patients with allergic rhinitis [abstract]. Treat Respir Med. 2005;4(4):289-296.
55. Corren J, Manning BE, Thompson SF, et al. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. J Allergy Clin Immunol. 2004;113:415-419.
56. Bonfils P, Nores JM, Halimi P, et al. Corticosteroid treatment in nasal polyposis with a three-year follow-up period. Laryngoscope. 2003;113(4):683-687.
57. Waddell AN, Patel SK, Toma AG, et al. Intranasal steroid sprays in the treatment of rhinitis: is one better than the other? J Laryngol Otol. 2003;117(1):843-845.
58. Passalacqua G, Albano M, Canonica GW, et al. Position paper – inhaled and nasal corticosteroids: safety aspects. Allergy. 2000;55:16-33.
59. Gradman J, Caldwell MF, Wolthers OD. A 2-week, crossover study to investigate the effect of fluticasone furoate nasal spray on short-term growth in children with allergic rhinitis. Clin Ther 2007;29:1738-1747.
60. Ratner PH, Wingertzahn MA, van Bavel JH, et al. Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2006;118(5):1142-1148
61. Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: A single treatment option for the symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol 2007;119(6):1430-1437.
62. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics. 2000;105(2):E22-E29.
63. Weinstein S, Qaqundah P, Georges G et al. Efficacy and safety of triamcinolone acetonide aquaeous nasal spray in children aged 2-5 years with perennial allergic rhinitis: a randomized double blind placebo controlled study with an open label extension. Ann Allergy Asthma Immunol 2009;102:339-347.
64. Meltzer EO, Stahlman JE, Leflein J, et al. Preferences of adult patients with allergic rhinitis for the sensory attributes of fluticasone furoate versus fluticasone propionate nasal sprays: A randomized, multicenter, double-blind, single-dose, crossover study. Clin Ther 2008;30:271-9.
65. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. Int J. Pediatr Otorhinolaryngol 2009;73:651-7.
66. Meltzer EO, Andrews C, Journeay GE et al. Comparison of patient preference for sensory attributes of fluticasone furoate or fluticasone propionate in adults with seasonal allergic rhinitis: a randomized, placebo-controlled, double-blind study. Ann Allergy Asthma Immunol 2010;104:331-38.
67. Okubo K, Nakashima M, Miyake N et al. Comparison of fluticasone furoate and fluticasone propionate for the treatment of Japanese cedar pollinosis. Allergy Asthma Proc 2009;30:84-94.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Antiallergic Agents
AHFS Class 520200
February 9, 2011

I. Overview

The eye, ear, nose, and throat (EENT) antiallergic agents include nasal and ophthalmic formulations, which are approved for the treatment of allergic conjunctivitis and rhinitis.[1-16] Conjunctivitis is an inflammatory condition of the conjunctiva, which may be classified as infectious or non-infectious. The types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic.[17] Seasonal allergic conjunctivitis is precipitated by environmental allergens and the symptoms are usually mild and recurrent.[17] Vernal conjunctivitis usually occurs in hot, dry environments. Potential sequelae include 1) eyelid thickening, 2) ptosis, 3) conjunctival scarring, 4) corneal neovascularization, thinning, ulceration, and infection, 5) vision loss, and 6) keratoconus.[17] It is a chronic condition with acute exacerbations during spring and summer. The onset of vernal conjunctivitis typically occurs during childhood, with a gradual decrease in activity observed within 2 to 30 years. Allergic rhinitis is an inflammatory condition involving the nasal passages in response to an allergen. The severity of symptoms range from mild and intermittent to seriously debilitating.[18] Nasal symptoms include congestion, rhinorrhea (anterior and posterior), sneezing and itching. Patients may also experience symptoms of allergic conjunctivitis. The symptoms may decrease quality of life by causing headache, cognitive impairment and fatigue.

Emedastine is a relatively selective, histamine H_1-receptor antagonist. Cromolyn, lodoxamide, nedocromil and pemirolast are mast cell stabilizers. Azelastine, bepotastine, epinastine, ketotifen and olopatadine are antihistamines with mast cell stabilizing properties.[1-3]

The EENT antiallergic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Azelastine, cromolyn and ketotifen are available in a generic formulation. Cromolyn and ketotifen are also available over-the-counter. This class was last reviewed in December 2008.

Table 1. EENT Antiallergic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Azelastine	solution†§	Astelin®*†, Astepro®†, Optivar®*§	azelastine†§, Astelin®*†, Astepro®†
Bepotastine	solution§	Bepreve®	none
Cromolyn	solution‡†§	N/A	cromolyn†§
Emedastine	solution§	Emadine®	none
Epinastine	solution§	Elestat®	none
Ketotifen	solution‡§	Refresh®*‡, Zaditor®*‡	ketotifen, Refresh®*‡, Zaditor®*‡
Lodoxamide	solution§	Alomide®	none
Nedocromil	solution§	Alocril®	none
Olopatadine	solution†§	Pataday®§, Patanase®†, Patanol®§	Pataday®§, Patanase®†, Patanol®§
Pemirolast	solution§	Alamast®	none

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
†Nasal formulation.
§Ophthalmic formulation.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the EENT antiallergic agents are summarized in Table 2. For a comprehensive overview of the treatment of allergic rhinitis, please refer to the Appendix.

Table 2. Treatment Guidelines Using the EENT Antiallergic Agents

Clinical Guideline	Recommendation(s)
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter[18] (2008)**	Allergic Conjunctivitis • Allergic rhinitis is often accompanied by symptoms of allergic conjunctivitis. Many treatments used for allergic rhinitis can benefit associated symptoms of allergic conjunctivitis, and a variety of topical ophthalmic agents are useful for specific treatment of associated ocular symptoms. • Intranasal corticosteroids, oral antihistamines, and intranasal antihistamines have similar effectiveness in relieving ocular eye symptoms associated with rhinitis. • Oral antihistamines, intranasal antihistamines, oral anti-leukotriene agents, intranasal corticosteroids, and allergen immunotherapy are treatments for allergic rhinitis that have been reported to relieve associated ocular allergy symptoms in controlled trials. • Use of cold compresses and irrigation with saline solution or artificial tears relieves mild symptoms of allergic conjunctivitis. • Topical ophthalmic agents are indicated for specific treatment of itching or symptoms of allergic conjunctivitis. • Vasoconstrictors are indicated for relief of ocular redness, although they do not reduce the allergic response. Prolonged use of ocular decongestants may lead to rebound hyperemia. Use limited to 10 days does not appear to induce this condition. • The combination of an ocular antihistamine and a vasoconstrictor works better than either agent alone. • Mast cell stabilizers, also approved for vernal and atopic keratoconjunctivitis, have a slow onset of action and may require several days of treatment before optimal symptom relief is achieved, making them more suitable for prophylactic or longer-term treatment of chronic ocular allergies than for acute symptom relief. • Topical NSAIDs reduce prostaglandin production involved in mediating ocular allergy. • Multiple-action agents possess both antihistamine and mast cell stabilizer activities, generally have onset of action within 30 minutes, and are suitable for acute and long-term treatment of allergic conjunctivitis symptoms. • Ocular corticosteroids should be reserved for more severe symptoms of allergic conjunctivitis considering that the ocular side effects from their use can threaten vision because of the increased risk of cataract formation, elevated intraocular pressure (IOP), and secondary infections. The modified steroid loteprednol is indicated for the temporary relief of symptoms and signs of seasonal allergic conjunctivitis and has a greatly reduced risk of causing increased IOP compared with many other ocular corticosteroids. • Oral antihistamines are generally less effective in relieving ocular allergy symptoms than topical ophthalmic agents and have slower onset of action. Oral agents have also been associated with excessive drying of the tear film. Allergic Rhinitis • Pharmacologic treatment options include oral and intranasal antihistamines, oral and topical decongestants, oral and intranasal

Clinical Guideline	Recommendation(s)
	corticosteroids, over-the-counter cough and cold medications for young children, intranasal cromolyn sodium, intranasal anticholinergics, leukotriene receptor antagonists, omalizumab, and nasal saline. • Intranasal corticosteroids are the most effective class of medications for the treatment of allergic rhinitis. • Oral and intranasal antihistamines effectively treat rhinorrhea, sneezing, itching, and allergic conjunctivitis, but have little effect on nasal congestion. • Intranasal antihistamines may be considered as first-line therapy for the treatment of allergic rhinitis and are equal to or more efficacious than oral second-generation antihistamines. However, intranasal antihistamines are less effective than intranasal corticosteroids. • Antihistamines are more effective when used continuously for seasonal and perennial allergic rhinitis than intermittent use. • Intranasal cromolyn may be effective in some groups for controlling allergic rhinitis and is associated with minimal adverse events. However, this agent is less effective than intranasal corticosteroids.
World Health Organization (WHO)/Global Allergy and Asthma European Network (GA^2LEN)/AllerGen: **Allergic Rhinitis and its Impact on Asthma (ARIA): 2008 Update**[19] **(2008)**	<u>Pharmacotherapy of Allergic Rhinitis and Conjunctivitis</u> • Second-generation oral or intranasal H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First-generation oral H_1-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Topical H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis. • Intranasal H_1-antihistamines are effective at the site of their administration in reducing itching, sneezing, runny nose and nasal congestion. They are effective in allergic eye symptoms. They can be effective within 20 min of administration. In general, topical H_1-antihistamines are well tolerated. • Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for the treatment of allergic rhinitis. Intranasal glucocorticosteroids are significantly more effective than oral or topical H_1-antihistamines for the treatment of allergic rhinitis and, in particular, for nasal congestion. • Intramuscular glucocorticosteroids and the long-term use of oral glucocorticosteroids are not recommended due to safety concerns. • Topical cromones (cromolyn and nedocromil) are recommended in the treatment of allergic rhinitis and conjunctivitis. They are modestly effective in nasal symptoms and effective in ocular symptoms. They are particularly safe. • Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age. • Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis. • Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction. • Oral decongestants (and their combination with oral H_1-antihistamines) may be used in the treatment of allergic rhinitis in adults, but side effects are common. • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy and availability.

Clinical Guideline	Recommendation(s)
	• A stepwise approach depending on the severity and duration of rhinitis is proposed. • Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. Treatment Algorithm • Patients with mild intermittent allergic rhinitis should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, or leukotriene receptor antagonist. • Patients with moderate/severe intermittent symptoms or mild persistent symptoms should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, intranasal corticosteroid, or leukotriene receptor antagonist. • Patients with moderate/severe persistent symptoms should initially be treated with the following (in preferred order): intranasal corticosteroid, antihistamine (oral or nasal), or leukotriene receptor antagonist.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults**[20] **(2008)**	• Antihistamines are effective for the treatment of allergic rhinitis, however are somewhat less effective than intranasal corticosteroids. • Antihistamines can be used in patients who are not candidates for intranasal corticosteroids. Second-generation antihistamines are preferred due to safety concerns. • Antihistamines or antihistamine/decongestant combinations can be used initially in patients with mild or episodic allergic rhinitis for rapid relief of symptoms. They can be used on a daily basis or as needed. • Topical cromolyn is an alternative treatment option in patients who are not candidates for intranasal corticosteroids.
International Primary Care Respiratory Group (IPCRG): **Management of Allergic Rhinitis**[21] **(2006)**	• Treatment recommendations are consistent with the ARIA guidelines. • Mild intermittent allergic rhinitis may be treated with an antihistamine, decongestant, and intranasal saline. • Mild persistent and moderate/severe intermittent allergic rhinitis may be treated with antihistamines, decongestants, intranasal corticosteroids, intranasal saline, a mast cell stabilizer, or a leukotriene receptor antagonist. • Moderate/severe persistent allergic rhinitis may be treated with intranasal corticosteroids, antihistamines, decongestants, intranasal saline, or a leukotriene receptor antagonist.
American Academy of Ophthalmology (AAO): **Preferred Practice Pattern Guidelines: Conjunctivitis**[17] **(2008)**	Seasonal Allergic Conjunctivitis • Mild allergic conjunctivitis can be treated with an OTC antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1-receptor antagonists. • If the condition is frequently recurrent or persistent, mast cell stabilizers can be utilized. • If the symptoms are not adequately controlled, a brief course of low-potency topical corticosteroid can be added to the regimen. • A nonsteroidal anti-inflammatory agent (ketorolac) has also been FDA-approved for the treatment of allergic conjunctivitis. • Additional measures include using artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful. Vernal/Atopic Conjunctivitis • General treatment measures include minimizing exposure to allergens or irritants, cool compresses and ocular lubricants. • Topical/oral antihistamines and topical mast cell stabilizers can be used to maintain comfort.

Clinical Guideline	Recommendation(s)
	• For acute exacerbations, topical corticosteroids are usually necessary to control severe signs and symptoms. • Topical cyclosporine 2% is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, systemic immunosuppression may be necessary. Eyelid involvement can be treated with pimecrolimus cream or tacrolimus ointment.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the EENT antiallergic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the EENT Antiallergic Agents[1-16]

Indication	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Ketotifen	Lodoxamide	Nedocromil	Olopatadine	Pemirolast
Conjunctivitis										
Prevention of itching due to allergic conjunctivitis					✔	✔				✔
Temporary relief of signs and symptoms of allergic conjunctivitis				✔						
Treatment of itching associated with allergic conjunctivitis	✔ §	✔						✔	✔ §	
Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis			✔ §				✔			
Rhinitis										
Prevent and relieve nasal symptoms of hay fever and other nasal allergies			✔ †							
Treatment of the symptoms of seasonal allergic rhinitis	✔ †								✔ †	
Treatment of the symptoms of seasonal and perennial allergic rhinitis	✔ †									
Treatment of the symptoms of vasomotor rhinitis	✔ †									

†Nasal formulation.
§Ophthalmic formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the EENT antiallergic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the EENT Antiallergic Agents[1-16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Azelastine	N: 40	O: 78-97	Liver, extensive	Renal (25) Feces (50-75)	22-25*
Bepotastine	Not reported	55	Liver, minimal	Renal (75-90)	Not reported
Cromolyn	N: <7 O: <1	Not reported	Not metabolized	Renal (30-50) Feces (80-87)	<1*
Emedastine	Negligible	Negligible	Liver, extensive	Renal (44)	2-7*
Epinastine	Minimal	64	Liver	Renal (55)*	12
Ketotifen	Not reported	Not reported	Liver, extensive	Renal (60-70) Feces (30-40)	21
Lodoxamide	Not detectible	Not reported	Not reported	Not reported	8.5
Nedocromil	<4	Not reported	Not metabolized	Renal (70)	1.5-3.3*
Olopatadine	N: 57 O: Minimal	N: 55	Not reported	N: Renal (70) Feces (17) O: Renal (60-70)	N: 8-12 O: 3
Pemirolast	Significant	Not reported	Liver	Renal (84-90)	4-5

N=nasal formulation, O=ophthalmic formulation
*Based on oral, inhalation or intravenous administration.

V. Drug Interactions

There are no significant drug interactions with the EENT antiallergic agent.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the EENT antiallergic agents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the EENT Antiallergic Agents[1-16]

Adverse Events	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Ketotifen	Lodoxamide	Nedocromil	Olopatadine	Pemirolast
Cardiovascular										
Atrial fibrillation	<1†	-	-	-	-	-	-	-	-	-
Chest pain	<1†	-	-	-	-	-	-	-	-	-
Flushing	<2†	-	-	-	-	-	-	-	-	-
Hypertension	<2†	-	-	-	-	-	-	-	-	-
Palpitation	<1†	-	-	-	-	-	-	-	-	-
Tachycardia	<2†	-	-	-	-	-	-	-	-	-
Central Nervous System										
Abnormal dreams	-	-	-	<5	-	-	-	-	-	-
Abnormal thinking	<2†	-	-	-	-	-	-	-	-	-
Anxiety	<2†	-	-	-	-	-	-	-	-	-
Confusion	<1†	-	-	-	-	-	-	-	-	-
Depersonalization	<2†	-	-	-	-	-	-	-	-	-
Depression	<2†	-	-	-	-	-	-	-	-	-
Dizziness	2†	-	-	-	-	-	<1	-	-	-
Drowsiness	<2†	-	-	-	-	-	-	-	-	-
Dysesthesia	8†	-	-	-	-	-	-	-	-	-
Fatigue	2† 1-10§	-	-	-	-	-	-	-	-	-
Fever	<2†	-	-	-	-	-	-	-	-	<5
Headache	8-15†* 1-3†** 15§	2-5	1-10†	11	1-3	10-25	<2	40	<7§	10-25
Heat sensation	-	-	-	-	-	-	<1	-	-	-
Hypoesthesia	<2†	-	-	-	-	-	-	-	-	-
Malaise	<2†	-	-	-	-	-	-	-	-	-
Nervousness	<2†	-	-	-	-	-	-	-	-	-
Paresthesia	<1†	-	-	-	-	-	-	-	-	-
Sleep disorder	<2†	-	-	-	-	-	-	-	-	-
Somnolence	<1-12†	-	-	-	-	-	<1	-	1†	-
Vertigo	<2†	-	-	-	-	-	-	-	-	-
Dermatological										

Adverse Events	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Ketotifen	Lodoxamide	Nedocromil	Olopatadine	Pemirolast
Contact dermatitis	<2†	-	-	-	-	-	-	-	-	-
Dermatitis	-	-	-	<5	-	-	-	-	-	-
Eczema	<2†	-	-	-	-	-	-	-	-	-
Facial edema	<1†	-	-	-	-	-	-	-	-	-
Furunculosis	<2†	-	-	-	-	-	-	-	-	-
Hair and follicle infection	<2†	-	-	-	-	-	-	-	-	-
Pruritus	<1†	-	-	<5	-	-	-	-	-	-
Rash	-	-	-	-	-	-	<1	-	-	-
Skin irritation	<1†	-	-	-	-	-	-	-	-	-
Skin laceration	<2†	-	-	-	-	-	-	-	-	-
Endocrine and Metabolic										
Amenorrhea	<2†	-	-	-	-	-	-	-	-	-
Breast pain	<2†	-	-	-	-	-	-	-	-	-
Dysmenorrhea	-	-	-	-	-	-	-	-	-	<5
Gastrointestinal										
Abdominal pain	<2†	-	-	-	-	-	-	-	-	-
Aphthous stomatitis	<2†	-	-	-	-	-	-	-	-	-
Appetite increased	<2†	-	-	-	-	-	-	-	-	-
Bitter taste	8-20†* 6-7†** 10§	-	-	-	-	-	-	-	13†	-
Constipation	<2†	-	-	-	-	-	-	-	-	-
Diarrhea	<2†	-	-	-	-	-	-	-	-	-
Gastroenteritis	<2†	-	-	-	-	-	-	-	-	-
Glossitis	<2†	-	-	-	-	-	-	-	-	-
Loss of taste	<2†	-	-	-	-	-	-	-	-	-
Nausea	3†	-	-	-	-	-	<1	-	≤5§	-
Stomach discomfort	-	-	-	-	-	-	<1	-	-	-
Taste abnormality	-	25	1-10†	<5	-	-	-	10-30	≤5§	-
Toothache	<2†	-	-	-	-	-	-	-	-	-
Vomiting	<2†	-	-	-	-	-	-	-	-	-
Ulcerative stomatitis	<2†	-	-	-	-	-	-	-	-	-
Xerostomia	3†	-	-	-	-	-	-	-	1†	-
Genitourinary										
Albuminuria	<2†	-	-	-	-	-	-	-	-	-
Hematuria	<2†	-	-	-	-	-	-	-	-	-

Adverse Events	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Ketotifen	Lodoxamide	Nedocromil	Olopatadine	Pemirolast
Polyuria	<2†	-	-	-	-	-	-	-	-	-
Urinary retention	<1†	-	-	-	-	-	-	-	-	-
Urinary tract infection	-	-	-	-	-	-	-	-	1†	-
Hepatic										
ALT increased	<2†	-	-	-	-	-	-	-	-	-
Transaminases increased	<1†	-	-	-	-	-	-	-	-	-
Musculoskeletal										
Back pain	<2†	-	-	-	-	-	-	-	≤5§	<5
Extremity pain	<2†	-	-	-	-	-	-	-	-	-
Hyperkinesia	<2†	-	-	-	-	-	-	-	-	-
Involuntary muscle contractions	<1†	-	-	-	-	-	-	-	-	-
Myalgia	≤2†	-	-	-	-	-	-	-	-	-
Rheumatoid arthritis	<2†	-	-	-	-	-	-	-	-	-
Temporomandibular dislocation	<2†	-	-	-	-	-	-	-	-	-
Weakness	-	-	-	<5	-	-	-	-	≤5§	-
Ocular										
Anterior chamber cells	-	-	-	-	-	-	<1	-	-	-
Blepharitis	-	-	-	-	-	-	<1	-	-	-
Blurred vision	<1† 1-10§	-	-	<5	-	-	1-5	-	≤5§	-
Burning/stinging	30§	-	-	<5	1-10	<5	15	10-30	≤5§	<5
Chemosis	-	-	-	-	-	-	<1	-	-	-
Conjunctival injection	-	-	✔ §	-	-	10-25	-	-	-	-
Conjunctivitis	≤2-5† 1-10§	-	-	-	-	<5	-	1-10	≤5§	-
Corneal abrasion	-	-	-	-	-	-	<1	-	-	-
Corneal erosion/ulcer	-	-	-	-	-	-	<1	-	-	-
Corneal infiltrates	-	-	-	<5	-	-	-	-	-	-
Corneal staining	-	-	-	<5	-	-	-	-	-	-
Crystalline deposits	-	-	-	-	-	-	1-5	-	-	-
Discharge	-	-	-	-	-	<5	-	-	-	-
Discomfort	-	-	-	-	-	-	15	-	-	<5
Dry eyes	<1†	-	✔ §	<5	-	<5	1-5	-	≤5§	<5
Epitheliopathy	-	-	-	-	-	-	<1	-	-	-
Eye pain	<2† 1-10§	-	-	-	-	<5	<1	-	≤5§	-
Eye redness	-	-	-	-	-	-	-	1-10	-	-

Adverse Events	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Ketotifen	Lodoxamide	Nedocromil	Olopatadine	Pemirolast
Eyelid disorder	-	-	-	-	-	<5	-	-	-	-
Eyelid edema	-	-	✔ §	-	-	-	<1	-	≤5§	-
Folliculosis	-	-	-	-	1-10	-	-	-	-	-
Foreign body sensation	-	-	-	<5	-	-	1-5	-	≤5§	<5
Hyperemia	-	-	-	<5	1-10	-	1-5	-	≤5§	-
Hypersensitivity reactions	-	-	✔ §	-	-	-	-	-	-	-
Irritation	-	2-5	✔ §	-	-	-	-	10-30	-	-
Keratitis	-	-	-	<5	-	<5	<1	-	≤5§	-
Mydriasis	-	-	-	-	-	<5	-	-	-	-
Ocular fatigue	-	-	-	-	-	-	<1	-	-	-
Photophobia	-	-	-	-	-	<5	-	1-10	-	-
Pruritus	1-10§	-	✔ §	-	1-10	<5	1-5	-	≤5§	-
Puffy eyes	-	-	✔ §	-	-	-	-	-	-	-
Rash	<1†	-	-	-	-	<5	-	-	-	-
Scales on lid/lash	-	-	-	-	-	-	<1	-	-	-
Styes	-	-	✔ §	-	-	-	-	-	-	-
Tearing	<2†	-	✔ §	<5	-	<5	1-5	-	-	-
Visual disturbances	<1†	-	-	-	-	-	-	-	-	-
Warming sensation	-	-	-	-	-	-	<1	-	-	-
Respiratory										
Asthma	5† 1-10§	-	-	-	-	-	-	1-10	-	-
Bronchitis	<2†	-	-	-	-	-	-	-	-	<5
Bronchospasm	<2†	-	-	-	-	-	-	-	-	-
Cold/flu syndrome	2-17† 1-10§	-	-	-	-	<5	-	-	<10§	10-25
Cough	11†	-	1-10†	-	1-3	-	-	-	1† ≤5§	<5
Dyspnea	<1† 1-10§	-	✔ §	-	-	-	-	-	-	-
Epistaxis	2-3†	-	<1†	-	-	-	-	-	3†	-
Hoarseness	-	-	1-10†	-	-	-	-	-	-	-
Laryngitis	<2†	-	-	-	-	-	-	-	-	-
Loss of smell	<1†	-	-	-	-	-	-	-	-	-
Nasal burning	4†	-	>10†	-	-	-	-	-	-	-
Nasal congestion	<2†	-	-	-	-	-	-	10-30	-	<5
Nasal dryness	-	-	-	-	-	-	<1	-	-	-

Adverse Events	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Ketotifen	Lodoxamide	Nedocromil	Olopatadine	Pemirolast
Nasal ulceration	-	-	-	-	-	-	-	-	9†	-
Nasopharyngitis	-	2-5	-	-	-	-	-	-	-	-
Nocturnal dyspnea	<2†	-	-	-	-	-	-	-	-	-
Paroxysmal sneezing	3†	-	-	-	-	-	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	-	-	-	-	2†	-
Pharyngitis	4† 1-10§	-	-	-	1-3	<5	-	-	<10§	-
Postnasal drip	<2†	-	1-10†	-	-	-	-	-	2†	-
Rhinitis	2-17† 1-10§	-	-	<5	1-3	10-25	-	1-10	≤5§	10-25
Sinus hypersecretion	<2†	-	-	-	-	-	-	-	-	-
Sinusitis	3†	-	-	<5	1-3	-	-	-	≤5§	<5
Sneezing	-	-	>10†	-	-	-	<1	-	-	<5
Throat burning/irritation	<2†	-	-	-	-	-	-	-	1†	-
Other										
Allergic reaction	<2†	-	-	-	-	<5	<1	-	-	-
Anaphylaxis	<1†	-	-	-	-	-	-	-	-	-
Application site irritation	<1†	-	-	-	-	-	-	-	-	-
CPK increased	-	-	-	-	-	-	-	-	1†	-
Hypersensitivity	-	-	-	-	-	-	-	-	≤5§	-
Infection	-	-	-	-	10	-	-	-	≤5§	-
Influenza	-	-	-	-	-	-	-	-	1†	-
Parosmia	<1†	-	-	-	-	-	-	-	-	-
Tolerance	<1†	-	-	-	-	-	-	-	-	-
Viral infection	<2†	-	-	-	-	-	-	-	-	-
Weight gain	2†	-	-	-	-	-	-	-	✔ †	-

✔ Percent not specified
- Event not reported
†Nasal formulation.
§Ophthalmic formulation.
*Astelin®
**Astepro®

VII. Dosing and Administration

The usual dosing regimens for the EENT antiallergic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the EENT Antiallergic Agents[1-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Azelastine	Allergic Conjunctivitis: Optivar®: 1 drop twice daily Allergic Rhinitis (Perennial): Astepro® 0.15%: 2 sprays per nostril once daily Allergic Rhinitis (Seasonal): Astelin®: 1 to 2 sprays per nostril twice daily Astepro® 0.1% and 0.15%: 1 to 2 sprays per nostril twice daily Astepro® 0.15%: 2 sprays per nostril once daily Vasomotor Rhinitis: Astelin®: 2 sprays per nostril twice daily	Allergic Conjunctivitis: >3 years of age (Optivar®): 1 drop twice daily Allergic Rhinitis (Perennial): >12 years of age (Astepro®): 0.15%: 2 sprays per nostril once daily Allergic Rhinitis (Seasonal): >5 years of age (Astelin®): 1 spray per nostril twice daily >12 years of age (Astepro®): 0.1% and 0.15%: 1 to 2 sprays per nostril twice daily 0.15%: 2 sprays per nostril once daily Vasomotor Rhinitis: >12 years of age (Astelin®): 2 sprays per nostril twice daily	Nasal spray: 137 mcg 205.5 mcg Ophthalmic drops: 0.05%
Bepotastine	Allergic Conjunctivitis: 1 drop twice daily	Allergic Conjunctivitis: >2 years of age: 1 drop twice daily	Ophthalmic drops: 1.5%
Cromolyn	Allergic Rhinitis : 1 spray in each nostril 3 to 6 times per day Vernal Conjunctivitis, Vernal Keratoconjunctivitis, Vernal Keratitis: 1 to 2 drops in each eye 4 to 6 times per day	Allergic Rhinitis: ≥2 years of age: 1 spray in each nostril 3 to 6 times per day Vernal Conjunctivitis, Vernal Keratoconjunctivitis, Vernal Keratitis: ≥4years of age: 1 to 2 drops in each eye 4 to 6 times per day	Nasal spray: 40mg/ml Ophthalmic drops: 4%
Emedastine	Allergic Conjunctivitis: 1 drop in each eye up to 4 times daily	Allergic Conjunctivitis: ≥3 years of age: 1 drop in each eye up to 4 times daily	Ophthalmic drops: 0.05%
Epinastine	Allergic Conjunctivitis: 1 drop in each eye twice daily	Allergic Conjunctivitis: ≥3 years of age: 1 drop in each eye twice daily	Ophthalmic drops: 0.05%
Ketotifen	Allergic Conjunctivitis: 1 drop in each eye twice daily, every 8 to 12 hours	Allergic Conjunctivitis: ≥3 years of age: 1 drop in each eye twice daily, every 8 to 12 hours	Ophthalmic drops: 0.025%
Lodoxamide	Vernal Conjunctivitis, Vernal Keratoconjunctivitis, Vernal Keratitis: 1 to 2 drops in each eye 4 times daily for up to 3 months	Vernal Conjunctivitis, Vernal Keratoconjunctivitis, Vernal Keratitis: ≥2 years of age: 1 to 2 drops in each eye 4 times daily for up to 3 months	Ophthalmic drops: 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Nedocromil	Allergic Conjunctivitis: 1 to 2 drops in each eye twice daily	Allergic Conjunctivitis: ≥3 years of age: 1 to 2 drops in each eye twice daily	Ophthalmic drops: 2%
Olopatadine	Allergic Conjunctivitis: Pataday®: 1 drop in each eye once daily Patanol®: 1 drop in each eye twice daily every 6 to 8 hours Allergic Rhinitis: Patanase®: 2 sprays per nostril twice daily	Allergic Conjunctivitis: ≥3 years of age (Pataday®): 1 drop in each eye once daily ≥3 years of age (Patanol®): 1 drop in each eye twice daily every 6 to 8 hours Allergic Rhinitis: 6-11 years of age (Patanase®): 1 spray per nostril twice daily ≥12 years of age (Patanase®): 2 sprays per nostril twice daily	Nasal spray: 0.6% Ophthalmic drops: 0.1% 0.2%
Pemirolast	Allergic Conjunctivitis: 1 to 2 drops in each eye 4 times daily	Allergic Conjunctivitis: ≥3 years of age: 1 to 2 drops in each eye 4 times daily	Ophthalmic drops: 0.1%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the EENT antiallergic agents are summarized in Table 7.

Table 7. Comparative Clinical Trials with the EENT Antiallergic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Conjunctivitis				
Abelson et al.[30] (2009) Bepotastine 1.0% 1 drop in each eye vs bepotastine 1.5% 1 drop in each eye vs placebo	RCT, DB, PC, SC Patients ≥10 years of age with a history of allergic conjunctivitis	N=107 3 doses	Primary: Patient-assessed ocular itching and investigator-assessed conjunctival hyperemia following conjunctival allergen challenge (CAC)	Primary: The differences in mean ocular itching scores between bepotastine 1.0% or 1.5% and the placebo group were significant at all time points measured in the 15-minute onset-of-action and the 8-hour duration-of-action CAC tests (all, P<0.001). The clinical significance associated with bepotastine 1.5% was similar between the 15-minute and 8-hour CAC tests, whereas the 1.0% solution appeared to be less effective at 8 hours compared with 15 minutes after administration. At visit 5, the rates of complete relief of ocular itching at the 3-, 5-, and 7-minute time points in the 15-minute onset-of-action CAC test were significant with bepotastine 1.0% (44.3%, 42.9%, and 50.0% of eyes, respectively) and 1.5% (67.2%, 48.4%, and 53.1%) compared with placebo (1.5%, 0%, and 1.5%; all, P≤0.003). Mean conjunctival hyperemia scores were improved with bepotastine 1.0% versus placebo at all 3 time points in the 15-minute onset-of-action CAC test (all, P≤ 0.001). With the 1.5% solution, improvement was found at the 7- and 15-minute time points on the 15-minute onset-of-action CAC (P<0.001 and P=0.017, respectively) and at 7 minutes on the 8-hour CAC (P=0.01).
Macejko et al.[31] (2010) Bepotastine 1.0% 1 drop in each eye vs	RCT, DB, PC, MC Patients ≥10 years of age with a positive allergen skin test	N=130 Single dose	Primary: Ocular itching and conjunctival hyperemia following conjunctival allergen challenge (CAC)	Primary: Bepotastine (1.0% and 1.5%) demonstrated a reduction in ocular itching (P<0.0001) compared to placebo (within 3 minutes after a CAC and at every other time point after a CAC performed 15 minutes or 8 hours after test agent instillation). Bepotastine 1.5% demonstrated a slightly higher degree of reduced ocular itching than seen for the 1.0% formulation. An improvement in conjunctival redness was observed at most time points

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bepotastine 1.5% 1 drop in each eye vs placebo				at the onset of action CAC test for both bepotastine formulations (P<0.0125). There was less conjunctival redness improvement seen at the 8- and 16-hour duration-of-action CAC tests.
Torkildsen et al.[32] (2010) Bepotastine 1.5% 1 drop in each eye vs placebo	RCT, DB, SC, PC Patients ≥10 years of age with a history of allergic conjunctivitis	N=70 Single dose	Primary: Non-ocular effectiveness following conjunctival allergen challenge (CAC)	Primary: Treatment with bepotastine led to a significant reduction in rhinorrhea and nasal congestion compared to placebo at all time points (P≤0.01). There was a significant reduction in nasal pruritus and ear or palate pruritus with bepotastine (P≤0.025 for visits 3 and 4 and P≤0.05 for visit 5) compared to placebo. The summed non-ocular composite symptom (NOCS) score was improved with bepotastine compared to placebo at most time points for at least 16 hours after dosing (P≤0.01).
Figus et al.[33] (2010) Cromolyn sodium 4% and chlorpheniramine 0.2% twice daily vs diclofenac 0.1% twice daily vs epinastine 0.05% twice daily vs	RCT, SB, MC Patients ≥18 years of age with allergic conjunctivitis	N=240 1 month	Primary: Percentage of patients achieving at least a “small” or “good” improvement of signs and symptoms	Primary: Naphazoline/antazoline induced significantly higher discomfort compared to the other study treatments (P<0.0001). Ketotifen was associated with the least discomfort. All study treatments induced a significant reduction in mean scores for both signs and symptoms compared to baseline (P<0.0001). At the end of the study, the mean score for signs was similar in the study groups (P>0.5). Diclofenac and naphazoline/antazoline showed less efficacy in decreasing symptoms compared to the other treatments (P<0.05). At the end of the study, good improvement of symptoms was obtained in at least 70% of patients by epinastine, ketotifen, fluorometholone, and olopatadine, whereas a 70% improvement in signs was obtained only by fluorometholone and ketotifen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluorometholone 0.2% twice daily vs ketotifen 0.05% twice daily vs levocabastine 0.05% twice daily vs naphazoline 0.25-antazoline 5 mg/ml twice daily vs olopatadine 0.1% twice daily				
D'Arienzo et al.[34] (2002) Emedastine 0.05% in one eye and placebo in the contralateral eye vs ketotifen 0.025% in one eye and placebo in the contralateral eye	RCT, DB, PC, SC Patients with allergic conjunctivitis	N=45 Single dose	Primary: Signs and symptoms following conjunctival allergen challenge (CAC)	Primary: Treatment with emedastine and ketotifen resulted in significant reductions in raw mean itching scores at all time points compared with placebo ($P<0.05$). This was seen at both the 5- and 15-minute challenges. There were no significant differences in itching scores between emedastine and ketotifen at either the 5- or 15-minute challenge.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs emedastine 0.05% in one eye and ketotifen 0.025% in the contralateral eye				
Torkildsen et al.[35] (2008) Epinastine 0.05% vs azelastine 0.05% vs ketotifen 0.025% Patients were randomized to receive a single drop of epinastine in 1 eye and either azelastine or ketotifen in the other eye (contralateral dosing).	RCT, DB, XO Patients ≥18 years of age with allergic conjunctivitis	N=40 Single dose	Primary: Ocular comfort	Primary: The mean comfort score was significantly lower (indicating more comfort) with epinastine than azelastine at 0.5, 1, 2, and 5 minutes after instillation (P<0.001, P<0.001, P=0.001, and P=0.019, respectively) and compared with ketotifen immediately after instillation (P=0.014). The mean comfort score was significantly lower with ketotifen compared with azelastine at 0.5, 1, and 2 minutes (P=0.001, P=0.023, and P=0.028). With epinastine, 85% of descriptors were positive and 5% were negative; with azelastine, 41% and 34%, respectively; with ketotifen, 55% and 28%. Neutral descriptors were used for epinastine, azelastine, and ketotifen in 10%, 25%, and 17% of cases, respectively. There were no significant differences between treatments in fluorescein staining scores and OPI values.
Greiner et al.[36] (2002) Ketotifen 0.025% as a single dose	RCT, SB, AC Patients ≥18 years of age with a history of allergy to environmental	N=56 Single dose	Primary: Signs and symptoms following conjunctival allergen challenge	Primary: Ketotifen was more effective than cromolyn in the prevention of itching at the 7-minute evaluation (P<0.001). Ketotifen was more effective than cromolyn in preventing redness (ciliary, conjunctival and episcleral) at both 7 and 15 minutes (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cromolyn sodium 4% administered 4 times daily for 2 weeks (as a loading dose) One eye was treated with the study drug and the other eye was treated with placebo.	allergens not currently in season		(CAC)	Following the 15 minute challenge, cromolyn-treated eyes exhibited more tearing than ketotifen-treated eyes at 7 minutes (28% vs 9%) and 15 minutes (13% vs 4%). Following the 4-hour challenge, more tearing occurred in cromolyn-treated than in ketotifen-treated eyes at 7 minutes (13% vs 6%) and 15 minutes (15% vs 9%).
Greiner et al.[37] (2003) Ketotifen 0.025% in one eye and nedocromil 2% in the contralateral eye vs ketotifen 0.025% in one eye and artificial tears in the contralateral eye vs nedocromil 2% in one eye and artificial tears in	RCT, PC, AC, SC, DB Patients ≥10 years of age with a history of allergic hypersensitivity	N=59 Single dose	Primary: Ocular itching following conjunctival allergen challenge (CAC)	Primary: Peak itching occurred in the range of 4 to 10 minutes after the allergen challenge. The itching response diminished after 10 minutes. At both 5 minutes and 12 hours after medication administration, placebo and nedocromil exhibited similar responses. Ketotifen controlled itching better than both placebo and nedocromil at every time point after 30 seconds post-challenge in the 5-minute data and every time point after 90 seconds post-challenge in the 12-hour data. These treatment differences were significant from 2 to 18 minutes in the 5-minute data (all, $P<0.05$) and from 3 to 12 minutes in the 12-hour data (all, $P<0.05$). Onset of action: The comparison of ketotifen-treated eyes with those that received placebo showed a significant difference from 2 through 19.5 minutes post-challenge ($P<0.05$). Scores of nedocromil-treated eyes were not difference from those that received placebo at any time point. Ketotifen mean itching scores were significantly lower than nedocromil mean itching scores from 2 to 18 minutes post-challenge ($P<0.05$). Duration of action (12-hour data): The comparison of ketotifen-treated eyes with those that received placebo showed a significant difference from 3 to 12 minutes post-challenge ($P<0.05$). Scores of nedocromil-treated eyes were not different from those that received placebo at any time point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
the contralateral eye				Ketotifen mean itching scores were significantly lower than nedocromil mean itching scores from 2.5 to 14 minutes post-challenge (P<0.05). Ketotifen-treated eyes were more comfortable than nedocromil-treated eyes at all time points. The comfort differences between ketotifen and nedocromil were significant at 1 minute, 2 minutes, 5 minutes, and 10 minutes after eye drop instillation (P<0.05). Ketotifen showed no difference from placebo in terms of comfort. The percentage of the comfortable responses was 52% for both ketotifen and placebo and 37% for nedocromil. Immediately after instillation, unfavorable terms (burning, stinging, or irritating) were used to describe nedocromil in 48% of instances, compared with 26% and 12% for ketotifen and placebo, respectively. Five minutes after the medication was instilled, comfortable was the most common descriptive term for ketotifen and placebo (72% and 49%, respectively, compared with 27% for nedocromil); stinging was the most common descriptive term for nedocromil (31%). The proportion of unfavorable descriptive terms (burning, stinging, or irritating) was 6% for ketotifen, 12% for placebo, and 55% for nedocromil. The patient satisfaction rates were 60% with ketotifen treatment, 21% with nedocromil treatment, and 19% with placebo.
Avunduk et al.[38] (2005) Ketotifen 0.025% 2 drops in each eye twice daily vs olopatadine 0.1% 2 drops in each eye twice daily vs	RCT, DB Patients ≥18 years of age with a history of seasonal allergic conjunctivitis over the previous 2 years, including moderate to severe ocular itching (severity based on patient's history); and had at least 1 of the following	N=39 30 days	Primary: Clinical scores (itching, tearing, redness, eyelid, swelling, and chemosis)	Primary: In the ketotifen group, the mean itching scores were significantly lower on days 15 and 30 compared with the mean score obtained on day 0 (both, P=0.001). In the olopatadine group, the mean itching scores were significantly lower on days 15 and 30 compared with that on day 0 (P=0.016 and P=0.017, respectively). On days 15 and 30, the mean itching scores in the ketotifen-treated patients and those who received olopatadine were significantly lower compared with those in the ATS group (ketotifen, P=0.042 and P=0.028, respectively; olopatadine, P=0.032 and P=0.026, respectively). There was no significant difference between ketotifen and olopatadine groups at any time point. Mean tearing scores in the ketotifen group were significantly lower on days 15 and 30 compared with the baseline score (P=0.008 and P=0.014,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
artificial tears (ATS) 2 drops in each eye twice daily	bilateral signs of at least moderate severity: conjunctival redness, conjunctival chemosis, and eyelid swelling			respectively). The mean tearing scores were significantly lower in the ketotifen-treated patients compared with those in the ATS group on days 15 and 30 (P=0.017 and P=0.02, respectively). In the olopatadine group, the mean tearing scores were significantly lower on days 15 and 30 compared with that on day 0 (P=0.018 and P=0.016, respectively). Olopatadine-treated patients had a significantly lower mean tearing score compared with that in the ATS group on day 15 (P=0.038). There was no significant difference between the ketotifen- and olopatadine-treated patients in mean tearing scores at any time point. No significant within-group or between-group differences were found in terms of mean scores for redness, eyelid swelling, or chemosis at any time point.
Spangler et al.[22] (2001) Olopatadine 0.1% in one eye and artificial tears in the contralateral eye vs azelastine 0.05% in one eye and artificial tears in the contralateral eye vs olopatadine 0.1% in one eye and azelastine 0.05% in the contralateral eye	RCT, DB, MC Patients with allergic conjunctivitis	N=111 Single dose	Primary: Ocular itching following conjunctival allergen challenge (CAC)	Primary: Olopatadine and azelastine were both significantly more effective than placebo at reducing itching post-challenge. Olopatadine was significantly more effective than azelastine in preventing itching at 3.5 minutes through 20 minutes post challenge (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Katelaris et al.[24] (2002) Olopatadine 0.1% twice daily vs cromolyn sodium 2% four times daily	MC, RCT Patients with seasonal allergic conjunctivitis	N=185 6 weeks	Primary: Ocular itching and conjunctival redness	Primary: By day 42, olopatadine was significantly more effective in reducing itching and redness compared to cromolyn sodium (P<0.05).
Lanier et al.[29] (2004) Olopatadine 0.1% in one eye and epinastine 0.05% in the contralateral eye vs olopatadine 0.1% in one eye and placebo in the contralateral eye vs epinastine 0.05% in one eye and placebo in the contralateral eye	RCT, DB, SC Patients with allergic conjunctivitis	N=66 Single dose	Primary: Itching and conjunctival redness following conjunctival allergen challenge (CAC)	Primary: Olopatadine-treated eyes showed significantly lower mean itching and conjunctival redness scores than epinastine-treated eyes (P=0.003 and P<0.001, respectively). Olopatadine-treated eyes showed significantly less chemosis (P<0.001), ciliary redness (P<0.001), and episcleral redness (P<0.001) than epinastine-treated eyes.
Mah et al.[39] (2007) Olopatadine 0.2%	RCT, DB, PC Patients with allergic	N=92 Single dose	Primary: Efficacy and comfort following conjunctival	Primary: Both active treatments were more effective than placebo at preventing ocular itching at all assessment time points (P<0.001 for both treatments). Olopatadine 0.2% was associated with significantly lower mean ocular

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in one eye and epinastine 0.05% in the contralateral eye vs olopatadine 0.2% in one eye and placebo in the contralateral eye vs epinastine 0.05% in one eye and placebo in the contralateral eye vs placebo	conjunctivitis		allergen challenge (CAC)	itching scores in comparison to epinastine 0.05% at 5 minutes (P=0.024) and 7 min (P=0.003). There was no significant difference in mean itching scores at 3 min post-challenge. Compared to placebo, epinastine 0.05% demonstrated lower mean ciliary redness scores at 7 minutes (P<0.002). Olopatadine 0.2% demonstrated lower mean redness scores for all three vessel beds at all assessment time points (ciliary: P<0.001, conjunctival: P<0.0012, and episcleral: P<0.001). Olopatadine 0.2% was associated with lower mean redness scores in comparison to epinastine 0.05% in all three vessel beds at all assessment time points (ciliary: P≤0.013, conjunctival: P≤0.015, and episcleral: P≤0.006). When paired with placebo-treated eyes, olopatadine 0.2%-treated eyes were significantly more comfortable (P<0.05) at 2 and 5 minutes post-dose. The differences between mean comfort scores for the epinastine 0.05% and placebo-paired eyes were not significantly different. In the group of patients receiving contralateral olopatadine 0.2% and epinastine 0.05%, comfort scores for olopatadine 0.2%-treated eyes were statistically better at the 1 minute time point (P=0.030). There were no significant differences in eye drop comfort scores at 2 and 5 minutes post-instillation.
Aguilar et al.[40] (2000) Olopatadine 0.1% 1 drop every 12 hours (OHC) vs ketotifen 0.05% 1 drop every 12 hours (KF)	OL Patients 19 to 68 years of age with a history of allergy who were showing signs/symptoms of allergic conjunctivitis	N=80 14 days	Primary: Signs and symptoms of allergic conjunctivitis	Primary: In the OHC group, 42.5% to 62.5% of patients showed improvement in signs and symptoms assessed between 0 min and 30 min after initial instillation of the study medication; however, there was no improvement in mucous discharge. At 48 hours, improvements in every evaluated parameter were observed in 57.5% to 75% of patients. After 7 days of treatment, complete control of all evaluated signs and symptoms was achieved in 80% to 87.5% of patients. In the KF group, 20.0% to 47.5% of patients showed improvement in the signs and symptoms assessed between 0 min and 30 min after initial instillation of the study medication; however, there was no improvement in mucous discharge. At 48 hours, improvements in every evaluated parameter were observed in 27.5% to 48% of patients. After 7 days of treatment, 60% to 75% of patients showed improvements. With continued

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment through day 14, control of all signs and symptoms evaluated was observed in 67.5% to 75% of patients.
Berdy et al.[41] (2000) Olopatadine 0.1% vs ketotifen 0.025%	RCT, DB, SC Patients with allergic conjunctivitis	N=32 Single dose	Primary: Ocular itching and patient satisfaction following conjunctival allergen challenge (CAC)	Primary: Olopatadine was significantly more effective than ketotifen at all time points (3, 5, and 10 minutes) in reducing the itching induced by the CAC (P<0.05). The mean efficacy scores for olopatadine were significantly higher than those for ketotifen at 3 and 5 minutes post-challenge (P<0.05). Olopatadine-treated eyes were rated as significantly more comfortable than those treated with ketotifen (P<0.05). Of the patients who had a preference, 73% identified olopatadine and 27% were more satisfied with ketotifen and identified ketotifen as the more tolerable formulation.
Ganz et al.[42] (2003) Olopatadine 0.1% twice daily vs ketotifen 0.025% twice daily	RCT, DB, PG, SC, AC Patients ≥12 years of age with seasonal allergic conjunctivitis	N=66 3 weeks	Primary: Responder rates Secondary: patient and investigator assessments of global efficacy, as well as signs and symptoms	Primary: More patients responded to treatment with ketotifen than to olopatadine, according to both patient and investigator assessments. The difference between groups was significant for the investigator evaluation at visit 2 (P<0.0001) and for the patient (P=0.0001) and investigator (P<0.0001) evaluations at visit 3. Secondary: The patient-assessed mean global efficacy scores were significantly lower with ketotifen than olopatadine at day 5 (P=0.03) and day 21 (P=0.0005). The investigator-assessed mean global efficacy scores were significantly lower with ketotifen than olopatadine at day 5 (P=0.001) and day 21 (P<0.0001). The ketotifen group had significantly lower scores for conjunctival hyperemia at day 5 (right, P=0.048; left, P=0.032), and day 21 (right, P=0.003; left, P=0.003) compared to olopatadine. The ketotifen group had significantly lower scores for itching at day 5 (right, P=0.007; left, P=0.008), and day 21 (right, P<0.0001; left, P<0.0001) compared to olopatadine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in tearing among the treatment groups at day 5 or day 21. Between baseline and visit 2 (days 5–8), treatment with ketotifen significantly decreased conjunctival hyperemia, itching, and tearing, along with total signs and symptoms; treatment with olopatadine significantly decreased itching, tearing, and total symptom scores. At all visits, ketotifen and olopatadine were rated between 0 (comfortable, no sensation) and 1 (mild, slightly perceptible sensation). No significant differences were found between treatments.
Borazan et al.[43] (2009) Olopatadine 0.1% twice daily vs ketotifen 0.025% twice daily vs epinastine 0.05% twice daily vs emedastine 0.05% twice daily vs	RCT, DB, PC Patients with seasonal allergic conjunctivitis	N=100 2 weeks	Primary: Patient-assessed signs and symptoms	Primary: Scores for ocular itching, conjunctival redness, tearing, chemosis and eyelid swelling were significantly improved in drug-treated eyes compared with placebo-treated eyes in all treatment groups (P<0.001). Ocular itching and conjunctival redness were significantly less improved in eyes in the fluorometholone group compared with all other groups. Although scores for tearing, chemosis and eyelid swelling showed a clinical improvement in all groups, there were no significant between-group differences. There were no significant differences in itching and tearing scores between days 7 and 14 in the placebo-treated eyes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluorometholone 0.1% twice daily One eye was treated with study drug and the other eye was treated with placebo.				
Leonardi et al.[44] (2004) Olopatadine 0.1% 2 drops per eye per day vs ketotifen 0.025% 2 drops per eye per day Patients were required to use both bottles during the study, but were allowed to use their own discretion to determine the number of times required to use each medication to determine preference.	MC, DB Patients with seasonal or perennial allergic conjunctivitis	N=100 4 weeks	Primary: Patient preference	Primary: Patients reported a significant preference for using olopatadine, with 81% indicating this preference, 17% preferring ketotifen, and 2% indicating no preference (P<0.0001). When asked which medication provided better relief of signs and symptoms of ocular allergy, such as itching, redness, and lid swelling, 81% of patients chose olopatadine, 19% selected ketotifen, and zero indicated no preference (P<0.0001). A significant percentage of patients selected olopatadine as more comfortable (81%) compared to ketotifen (18%; P<0.0001); 1% indicated no preference. In response to the question regarding the drop patients would request if visiting the doctor's office during allergy season, 81% would request olopatadine, 18% ketotifen, and 1% had no preference. The difference between olopatadine and ketotifen was significant (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Butrus et al.[23] (2000) Olopatadine 0.1% as a single dose vs nedocromil 2% administered for 2 weeks (loading dose)	SC, RCT, DB Patients with allergic conjunctivitis	N=52 Single dose	Primary: Ocular itching and comfort following conjunctival allergen challenge (CAC)	Primary: Olopatadine was more efficacious than nedocromil at reducing itching at all time points (3, 5, 10 min; P<0.0001). Olopatadine was more comfortable than nedocromil (P=0.034).
Alexander et al.[45] (2000) Olopatadine 0.1% 1 drop into each eye twice daily for 1 week vs nedocromil 2% 1 drop into each eye twice daily for 1 week	RCT, XO, OL Patients ≥7 years of age with perennial allergic conjunctivitis and use of olopatadine within the previous 12 months	N=28 2 weeks	Primary: Patient satisfaction, severity of ocular symptoms, clinical signs, quality of life, and global assessments of effectiveness	Primary: Mean symptom scores for seven ocular symptoms were comparable with nedocromil and olopatadine, except that light sensitivity was significantly lower with nedocromil (P=0.012). In the physicians' evaluations, there was a significant and comparable reduction in erythema, conjunctival injection and overall conjunctival signs with both treatments from baseline. Improvement in edema and discharge were not significant with either drug. Quality of life scores (as measured by RQLQ) improved following treatment with nedocromil (P=0.0001) and olopatadine (P=0.0001). The improvement was comparable with the two drugs (P=0.603). Nedocromil and olopatadine were similarly effective in preventing onset of allergic signs and symptoms. Both physicians and patients rated nedocromil as moderately or completely effective in 18 patients and olopatadine as moderately or completely effective in 17 patients.
Shulman et al.[46] (2003) Pemirolast 0.1% 1 drop in each eye twice daily	RCT, DB, AC, PG Patients ≥18 years of age with a history of seasonal allergic conjunctivitis	N=80 8 weeks	Primary: Worst itching scores Secondary: Bedtime redness, bedtime itching,	Primary: Diary data on highest-pollen-count days: There was no significant difference in worst itching scores among the treatment groups (P=0.033), except on day 1 when pemirolast users had significantly lower scores than nedocromil users. Bedtime itching and bedtime redness did not differ significantly between the treatment groups, except on 1 day when nedocromil users had significantly lower scores than pemirolast users

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nedocromil 2% 1 drop in each eye twice daily			redness, chemosis, lid swelling, tearing, and mucous discharge	(P=0.045 and P=0.033, respectively). Secondary: Daily diary data: No significant differences in worst itching, bedtime itching, or bedtime redness were evident at any time during the study. This was also the case for percentage of days with a score of zero in worst itching (P=0.501), bedtime itching (P=0.833), and bedtime redness (P=0.584). Compared to baseline, there were no significant differences between the pemirolast and nedocromil groups in ciliary, conjunctival or episcleral redness, chemosis, itching, or eyelid swelling. The pemirolast group reported 27 adverse events: 12 ocular and 15 non-ocular events. The most common ocular adverse event was mild redness and the most common non-ocular adverse event was headache. The nedocromil treatment group reported 39 adverse events: 15 ocular and 24 non-ocular events. The most common ocular adverse event was mild to moderate stinging immediately after drop instillation and the most common non-ocular adverse event was taste perversion. At visits 2, 3, and 4, pemirolast also was rated significantly more comfortable than nedocromil (visit 2, P=0.01; visit 3, P<0.001; visit 4, P<0.001).
Allergic Rhinitis				
Stern et al.[26] (1998) Azelastine nasal spray vs budesonide nasal spray	MC, RCT, PC, PG, DB Patients with perennial allergic rhinitis	N=195 6 weeks	Primary: Daily nasal symptom scores (combined nasal symptoms, blocked nose, rhinorrhea, sneezing), patients' overall assessment of treatment efficacy, use of terfenadine tablets as rescue	Primary: The reduction in all individual nasal symptoms from baseline was greater with the budesonide group compared with those treated with azelastine (P≤0.05). Azelastine did not produce a significant improvement in either combined or individual nasal symptoms (P >0.05). The patients' overall assessments of treatment efficacy after 6 weeks of therapy showed that budesonide was significantly more effective compared with both azelastine and placebo (P=0.013 and P=0.0003 respectively). There was no significant difference between azelastine and placebo with respect to the degree of symptom control achieved (P=0.20).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			medication	The reduction in the use of terfenadine from baseline was significantly greater for budesonide (P=0.0033) and azelastine (0.0015) compared with placebo, but there was no difference between the two active treatments (P=0.80).
Corren et al.[25] (2005) Azelastine nasal spray vs cetirizine 10 mg tablets	MC, RCT, DB, PG Patients with moderate to severe seasonal allergic rhinitis	N=229 2 weeks	Primary: Change from baseline to day 12 in the 12-hour reflective total nasal symptom score (TNSS), including rhinorrhea, sneezing, itchy nose, nasal congestion	Primary: Both groups had significant improvements in the TNSS compared with baseline (P<0.001). The overall TNSS was significantly greater with azelastine nasal spray compared with cetirizine (P=0.015). Azelastine nasal spray significantly improved the instantaneous TNSS compared with cetirizine at 60 and 240 minutes after the initial dose (P=0.040).
Meltzer et al.[47] (2008) Olopatadine 0.6% 2 sprays in each nostril (OLO) vs azelastine 0.1% 2 sprays in each nostril (AZE)	RCT, MC, DB, XO Patients ≥18 years of age with a ≥2 year history of allergic rhinitis (seasonal or perennial) who were symptomatic at the time of enrollment	N=110 Single dose	Primary: Patient preference based on overall aftertaste of each medication	Primary: Overall, 60.6% of the patients favored OLO, 30.3% favored AZE, and 9.2% indicated no preference. OLO was more effective than AZE in patient perceptions of aftertaste (P<0.0005). For overall patient preference, OLO was more effective than AZE at visit 4 was (P=0.0001). The mean response for likelihood of use (0.8 U) indicated a preference for OLO over AZE (P=0.0004). Overall, 62.4% and 60.9% of patients favored OLO in regards to patient preference and likelihood of use, respectively. OLO was shown to be statistically superior to AZE in patient perceptions of taste immediately after study drug administration (P<0.0001). Immediately after dosing, patients reported a significant difference in favor of OLO relative to AZE with regard to several attributes: the smell of the medication (P=0.0002); nasal irritation (P<0.0001); urge to sneeze (P=0.0146); dripping out of the nose (P=0.0008); dripping down the throat (P=0.0004); and overall satisfaction (P<0.0001). No significant difference was observed for moistness of the nose or throat (P=0.1723). When assessed at 45 minutes post-dosing, a difference in favor of OLO relative to AZE was observed for nasal irritation (P=0.0048), urge to sneeze

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.0174), and overall satisfaction (P=0.0487). No significant differences were observed for the remaining variables at this time point (P≥0.0933 for each of the remaining variables). At visit 4, after having received both treatments, patients indicated a favorable preference for OLO in all of the assessed variables (P≤0.0036 for each variable).
Shah et al.[48] (2009) Olopatadine 0.6% 2 sprays in each nostril twice daily (OLO) vs azelastine 0.1% 2 sprays in each nostril twice daily (AZE) vs placebo	RCT, MC, DB, AC, PC, PG Patients ≥12 years of age with a history of seasonal allergic rhinitis	N=544 16 days	Primary: Total nasal symptom scores (TNSS), quality of life (RQLQ), tolerability	Primary: The mean change from baseline in overall TNSS was significantly greater with OLO (26.8%) compared to placebo (18.4%; P=0.003). The mean change from baseline in overall TNSS was 29.9% with AZE. The difference between active treatments was nonsignificant (95% CI, -2.5% to 8.7%). The mean change in overall RQLQ score was significantly greater with OLO compared with placebo (P=0.005). There was no significant difference between active treatments. The most commonly reported adverse event in the OLO and AZE groups was bitter taste (12.2% and 19.7%, respectively). In the placebo group, bitter taste (1.7%) and nasal discomfort (1.7%) were the most frequently reported adverse events. The prevalence of bitter taste was significantly lower in the OLO treatment group compared with the AZE group (P=0.05). Among patients who reported bitter taste, the proportion who rated the event as severe was significantly lower in the OLO group compared with the AZE group (0% vs 8.1%; P=0.005). The majority of bitter taste events reported in the OLO group were mild (72.7%), whereas the majority of these events in the AZE group were reported as moderate (56.8%).
Miscellaneous				
Shulman et al.[49] (2003) Study 1 Pemirolast 0.1% 1-2 drops in each eye vs	Study 1 RCT, DB, XO, PG Study 2 RCT, DB, SC, AC Patients ≥18 years of age with asymptomatic eyes	Study 1 N=45 Single dose Study 2 N=48 Single dose	Primary: Ocular comfort variables and preference	Study 1 Primary: The mean change in overall discomfort with pemirolast was 0.27 units lower than with cromolyn and 0.34 units lower than with ketorolac. Mean changes favoring pemirolast were significant versus cromolyn (P=0.001) and ketorolac (P<0.001). Mean changes in score compared with pre-instillation were consistently lower with pemirolast than with cromolyn for both burning/stinging

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ketorolac 0.5% 1-2 drops in each eye vs cromolyn 4% 1-2 drops in each eye <u>Study 2</u> Pemirolast 0.1% 1 drop in one eye vs nedocromil 2% 1 drop in one eye				(P<0.001) and tearing (P=0.014). The discomfort level in the pemirolast-treated subjects was significantly lower compared with ketorolac-treated subjects (P=0.021). Pemirolast treatment resulted in fewer reports of burning/stinging (2%) compared to cromolyn (20%; P=0.011), and ketorolac (11%; P=0.103). No notable differences were found in the incidence of adverse events between the 3 treatments. <u>Study 2</u> Primary: Overall discomfort was significantly lower with pemirolast compared to nedocromil (P<0.001). The number of subjects with a clinically significant increase (>1 unit) in overall discomfort score was significantly lower in pemirolast- than in nedocromil-treated eyes (P=0.007). Mean changes in other ocular comfort parameters were significantly lower with pemirolast compared with nedocromil: burning/stinging (P<0.001), foreign-body sensation (P=0.043), and tearing (P=0.039). Photophobia demonstrated no significant difference between the 2 treatments. Pemirolast treatment resulted in fewer clinically significant increases (>1 unit) in burning/stinging than nedocromil (15% vs 40%, respectively; P=0.005). For foreign-body sensation, this difference was also significant, occurring in only 2% of pemirolast eyes versus 13% of nedocromil eyes (13%; P=0.025). The differences for tearing and photophobia were not significant. Seventy-five percent of subjects preferred the pemirolast-treated eye to the nedocromil-treated eye (P<0.001).

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, SB=single-blind, DB=double-blind, TB=triple-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the EENT Antiallergic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Azelastine	solution†§	Astelin®*†, Astepro®†, Optivar®*§	$$$-$$$$	$$$
Bepotastine	solution§	Bepreve®	$$$$	N/A
Cromolyn	solution‡†§	N/A	N/A	$
Emedastine	solution§	Emadine®	$$$	N/A
Epinastine	solution§	Elestat®	$$$$	N/A
Ketotifen	solution‡§	Refresh®*‡, Zaditor®*‡	$	$
Lodoxamide	solution§	Alomide®	$$$	N/A
Nedocromil	solution§	Alocril®	$$$	N/A
Olopatadine	solution†§	Pataday®§, Patanase®†, Patanol®§	$$$$	N/A
Pemirolast	solution§	Alamast®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
†Nasal formulation.
§Ophthalmic formulation.
N/A=Not available

X. Conclusions

The EENT antiallergic agents are approved for the treatment of allergic conjunctivitis and rhinitis.[1-16] They are available in both nasal and ophthalmic formulations. Emedastine is a relatively selective, histamine H_1-receptor antagonist. Cromolyn, lodoxamide, nedocromil and pemirolast are mast cell stabilizers. Azelastine, bepotastine, epinastine, ketotifen and olopatadine have dual actions that offer a combination of these two mechanisms (i.e., they are antihistamines with mast cell stabilizing properties).[1-3] The ophthalmic products that are available in a generic formulation include azelastine, cromolyn and ketotifen. The nasal products that are available in a generic formulation include azelastine and cromolyn.

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists and mast cell stabilizers.[17-21] Many of these agents can also benefit associated symptoms of allergic conjunctivitis. The selection of therapy should be individualized and take into consideration the severity and duration of the disease, patient preference, efficacy and safety. In general, guidelines do not give preference to one EENT antiallergic agent over another.[17-21] Ophthalmic products may be preferred to oral formulations if ocular symptoms are the primary manifestation of the disease as they are faster-acting and are less likely to cause systemic adverse events. The dual action antiallergic agents treat signs and symptoms of allergic conjunctivitis during the acute phase (antihistaminic action) and prevent mast cell degranulation (membrane stabilizing action). Thus, they are suitable for both the acute and long-term management of allergic conjunctivitis. The onset of action for mast cell stabilizers is 5 to 14 days; therefore, they are not useful for treating acute symptoms.

There are relatively few comparative studies that have been conducted with the EENT antiallergic agents in a 'real-life' setting.[24,35,38,40,42-49] While some of these trials have demonstrated similar outcomes with regards to ocular symptoms, nasal symptoms and patient preference, other studies have demonstrated greater efficacy with one agent over another. Many comparative studies have been performed using environmental challenge chambers.[22-23,29,34,36-37,39,41] However, the antiallergic agents are typically administered as a single dose and the clinical outcomes are assessed after several minutes or hours.

There is insufficient evidence to support that one brand EENT antiallergic agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand EENT antiallergic agents within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand EENT antiallergic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed October 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; October 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 2010.
4. Astelin® [package insert]. Somerset, NJ: MedPointe Healthcare, Inc; April 2007.
5. Astepro® [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; September 2009.
6. Optivar® [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; July 2008.
7. Bepreve® [package insert]. Irvine, CA: ISTA Pharmaceuticals, Inc.; August 2009.
8. Emadine® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; August 2002.
9. Elestat® [package insert]. Irvine, CA: Allergan, Inc.; August 2008.
10. Zaditor® [package insert]. Duluth, GA: Novartis Ophthalmics; October 2002.
11. Alomide® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; 2003.
12. Alocril® [package insert]. Irvine, CA: Allergan, Inc.; 2008.
13. Pataday® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; 2006.
14. Patanase® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; April 2010.
15. Patanol® [package insert]. Alcon Laboratories. December 2003.
16. Alamast® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; January 2007.
17. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Conjunctivitis; September 2008. Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=9d9650fb-39a3-439c-9225-5fbb013cf472. Accessed October 2010.
18. Wallace DV, Dykewicz MS, Bernstein DI, et al., Joint Task Force on Practice, American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1-84.
19. Bousquet J, Khaltaev N, Cruz A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). Allergy 2008:63(S86):8–160.
20. Institute for Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Respiratory Illness in Children and Adults. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); January 2008. Available at: http://www.icsi.org/respiratory_illness_in_children_and_adults__guideline_/respiratory_illness_in_children_and_adults__guideline__13116.html. Accessed October 2010.
21. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of allergic rhinitis. Primary Care Respiratory Journal 2006;15:58-70.
22. Spangler D, Bensch G, Berdy G. Evaluation of the efficacy of olopatadine hydrochloride 0.1% ophthalmic solution and azelastine hydrochloride 0.05% ophthalmic solution in the conjunctival allergen challenge model. Clin Ther 2001 Aug;23(8):1272-80.
23. Butrus S, Greiner J, Discepola M, Finegold I. Comparison of the clinical efficacy and comfort of olopatadine hydrochloride 0.1% ophthalmic solution and nedocromil sodium 2% ophthalmic solution in the human conjunctival allergen challenge model. Clin Ther 2000 Dec;22(12):1462-72.
24. Katelaris CH, Ciprandi G, Missotten L, Turner D, Bertin D, Berdeaux G. A comparison of the efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and cromolyn sodium 2% ophthalmic solution in seasonal allergic conjunctivitis. Clin Ther 2002;24(10):1561-75.
25. Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. Clin Ther 2005;27(5):543-553.
26. Stern M, Wade A, Ridout S, Cambell L. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. Ann Allergy Asthma Immunol 1998;81:354-358.
27. Kamis U, Ozturk BT, Ozkagnici A et al. Comparison of the efficacy of olopatadine hydrochloride 0.1% ophthalmic solution and artificial tears in seasonal allergic conjunctivitis. Acta Ophthalmol Scand 2006 Feb 01; 84 (1):148-49.
28. Abelson MB, Gomes PJ, Pasquine T et al. Efficacy of olopatadine ophthalmic solution 0.2% in reducing signs and symptoms of allergic conjunctivitis. Allergy Asthma Proc 2007 Jul-Aug; 28 (4):427-33.

29. Lanier BQ, Finegold I, D'Arienzo P, et al. Clinical efficacy of olopatadine vs epinastine ophthalmic solution in the conjunctival allergen challenge model. Curr Med Res Opin 2004;20(8):1227-33.
30. Abelson MB, Torkildsen GL, Williams JI, et al. Time to onset and duration of action of the antihistamine bepotastine besilate ophthalmic solutions 1.0% and 1.5% in allergic conjunctivitis: a phase III, single-center, prospective, randomized, double-masked, placebo-controlled, conjunctival allergen challenge assessment in adults and children. Clin Ther 2009;31:1908-21.
31. Macejko TT, Bergmann MT, Williams JI, et al. Multicenter clinical evaluation of bepotastine besilate ophthalmic solutions 1.0% and 1.5% to treat allergic conjunctivitis. Am J Ophthalmol 2010;150:122-127.
32. Torkildsen GL, Williams JI, Gow JA, et al. Bepotastine besilate ophthalmic solution for the relief of nonocular symptoms provoked by conjunctival allergen challenge. Ann Allergy Asthma Immunol 2010;105:57-64.
33. Figus M, Fogagnolo P, Lazzeri S, et al. Treatment of allergic conjunctivitis: results of a 1-month, single-masked randomized study. Eur J Ophthalmol 2010;20:811-8.
34. D'Arienzo PA, Leonardi A, Bensch G, et al. Randomized, double-masked, placebo-controlled comparison of the efficacy of emedastine difumarate 0.05% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the human conjunctival allergen challenge model. Clin Ther 2002;24:409-16.
35. Torkildsen GL, Ousler GW 3rd, Gomes P, et al. Ocular comfort and drying effects of three topical antihistamine/mast cell stabilizers in adults with allergic conjunctivitis: a randomized, double-masked crossover study. Clin Ther 2008;30:1264-71.
36. Greiner JV, Michaelson C, McWhirter CL, et al. Single dose of ketotifen fumarate 0.025% vs 2 weeks of cromolyn sodium 4% for allergic conjunctivitis. Adv Ther 2002;19:185-93.
37. Greiner JV, Minno G. A placebo-controlled comparison of ketotifen fumarate and nedocromil sodium ophthalmic solutions for the prevention of ocular itching with the conjunctival allergen challenge model. Clin Ther 2003;25:1988-2005.
38. Avunduk AM, Tekelioglu Y, Turk A, et al. Comparison of the effects of ketotifen fumarate 0.025% and olopatadine HCl 0.1% ophthalmic solutions in seasonal allergic conjunctivities: a 30-day, randomized, double-masked, artificial tear substitute-controlled trial. Clin Ther 2005;27:1392-402.
39. Mah FS, Rosenwasser LJ, Townsend WD, et al. Efficacy and comfort of olopatadine 0.2% versus epinastine 0.05% ophthalmic solution for treating itching and redness induced by conjunctival allergen challenge. Curr Med Res Opin 2007;23:1445-52.
40. Aguilar AJ. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. Acta Ophthalmol Scand Suppl 2000;230:52-5.
41. Berdy GJ, Spangler DL, Bensch G, et al. A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. Clin Ther 2000;22:826-33.
42. Ganz M, Koll E, Gausche J, et al. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. Adv Ther 2003;20:79-91.
43. Borazan M, Karalezli A, Akova YA, et al. Efficacy of olopatadine HCI 0.1%, ketotifen fumarate 0.025%, epinastine HCI 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions for seasonal allergic conjunctivitis: a placebo-controlled environmental trial. Acta Ophthalmol 2009;87:549-54.
44. Leonardi A, Zafirakis P. Efficacy and comfort of olopatadine versus ketotifen ophthalmic solutions: a double-masked, environmental study of patient preference. Curr Med Res Opin 2004;20:1167-73.
45. Alexander M, Allegro S, Hicks A. Efficacy and acceptability of nedocromil sodium 2% and olopatadine hydrochloride 0.1% in perennial allergic conjunctivitis. Adv Ther 2000;17:140-7.
46. Shulman DG. Two mast cell stabilizers, pemirolast potassium 0.1% and nedocromil sodium 2%, in the treatment of seasonal allergic conjunctivitis: a comparative study. Adv Ther 2003;20:31-40.
47. Meltzer EO, Garadi R, Laforce C, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy Asthma Proc 2008;29:659-68.
48. Shah SR, Nayak A, Ratner P, et al. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Ther 2009; 31:99-107.
49. Shulman DG, Amdahl L, Washington C, et al. A combined analysis of two studies assessing the ocular comfort of antiallergy ophthalmic agents. Clin Ther 2003;25:1096-106.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Antibacterials
AHFS Class 520404
February 9, 2011

I. Overview

The eye, ear, nose, and throat (EENT) antibacterials are used to treat a variety of infections. The agents in this class are administered topically and include aminoglycosides, macrolides, quinolones, sulfonamides, as well as several miscellaneous antibacterials. The products are available as single entity formulations, as well as in combination with other antibacterial agents or corticosteroids. Oral doxycycline (subantimicrobial dose formulation) is also included in this review as it is approved for the treatment of periodontal disease.

The ophthalmic antibacterials are used to treat infections of the eye, including blepharitis, conjunctivitis, keratitis, as well as others. Bacterial overgrowth plays a role in the pathophysiology of blepharitis, and *Staphylococcus* species, *Corynebacterium* species and *Propionibacterium acnes* are the most common pathogens.[24,31] Patient education on self-care hygiene is an essential component of treatment and topical antibacterials are frequently used to reduce bacterial load.[24,31] Bacterial conjunctivitis is highly contagious and symptoms include redness of the eye and thick, purulent discharge.[25,32] Common pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*.[32] Bacterial conjunctivitis is a self-limiting condition; however, the use of topical antibacterials may shorten the clinical course and reduce transmission to others.[25,32] Soft contact lens wearers with conjunctivitis have a high incidence of infection with *Pseudomonas* and quinolones are the preferred treatment option in this patient population.[32] Antibacterials containing corticosteroids are generally not appropriate for the acute treatment of bacterial conjunctivitis.[32] Corneal abrasions may occur spontaneously or may be due to trauma, the presence of a foreign body, or contact lenses.[30] The prophylactic use of topical antibacterials is often employed to prevent superinfections.[30] Keratitis is an inflammatory condition affecting the cornea and is associated with moderate to intense pain.[33] Common pathogens include *Staphylococcus* species, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* and polymicrobial isolates.[26,33] Corneal scarring and loss of vision may occur very quickly; therefore, patients should be evaluated by an ophthalmologist on the same day and receive prompt treatment with a topical broad-spectrum antibacterial agent.[26,33] Antibacterials containing corticosteroids should not be used in the initial treatment of bacterial keratitis.[33] Bacterial endophthalmitis is a vision-threatening bacterial infection of the aqueous or vitreous humor of the eye, which may occur following intraocular surgery or perforating trauma.[26,38] Staphylococci are the major pathogens in endophthalmitis.[38] Treatment is emergent and may include direct injection of antibiotics into the vitreous humor or systemic administration. The role of topical antibacterials in the treatment of endophthalmitis is less clear.[38]

The otic antibacterials are approved for the treatment of otitis externa and otitis media. Otitis externa is an inflammatory condition of the external ear canal which may be classified as infectious or non-infectious. Common infectious pathogens include *Staphylococcus aureus* and *Pseudomonas aeruginosa*; however, polymicrobic infections occur frequently.[27,34] Topical antibacterials (alone or in combination with a corticosteroid) are very effective and systemic therapy is generally not required.[27,34] Acute otitis media is an inflammatory condition of the middle ear with middle ear effusion and symptoms include otalgia, hearing loss and vertigo.[28,36] Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.[28,36] Oral antibacterials are generally the initial treatment option; however, topical antibacterials may be used in patients with perforated tympanic membranes, tympanostomy tubes or chronic suppurative otitis media.[35-36]

Mupirocin nasal ointment is indicated for the eradication of nasal colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) in adult patients and health care workers during institutional outbreaks.[16] Nasal colonization with MRSA is common among certain groups of people, including healthcare workers, hospitalized patients, individuals on dialysis, diabetic patients, and in those with HIV infection.[87,89] Although these individuals are often asymptomatic, they are at increased risk for developing an infection with MRSA. In addition, nasal colonization increases the risk of transmission from one patient to another via colonized hands of healthcare workers.[87,89]

Periodontitis is an inflammatory condition of the periodontium, which is due to the presence of bacterial plaque on adjacent teeth.[29] Treatment includes scaling and root planing, as well as adjunctive therapy with an antimicrobial agent to reduce the bacterial load. Doxycycline has been shown to reduce collagenase activity in gingival tissues and fluid, and may prevent further breakdown of connective tissue and alveolar bone.[9,42] The dose of doxycycline used for the treatment of periodontitis (20 mg twice daily) differs from that used to treat infections. This subantimicrobial dose is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis.

The EENT antibacterials that are included in this review are listed in Table 1. This review encompasses all EENT antibacterial dosage forms and strengths. The topical antibacterials (AHFS 840404) and systemic antibacterials (AHFS 081200) were previously reviewed and are not included in this review. Many of the products are available in a generic formulation.

Table 1. EENT Antibacterials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Azithromycin	solution†	AzaSite®	AzaSite®
Bacitracin	ointment†	N/A	bacitracin
Bacitracin and polymyxin B	ointment†	N/A	bacitracin and polymyxin B
Besifloxacin	suspension†	Besivance®	Besivance®
Ciprofloxacin	ointment†, solution†§	Cetraxal®, Ciloxan®*	ciprofloxacin
Ciprofloxacin and dexamethasone	suspension§	Ciprodex®	none
Ciprofloxacin and hydrocortisone	suspension§	Cipro HC®	none
Doxycycline	oral tablet	Periostat®*	doxycycline
Erythromycin base	ointment†	Ilotycin®*	erythromycin base
Gatifloxacin	solution†	Zymar®, Zymaxid®	none
Gentamicin	ointment†, solution†	Garamycin®*‡	gentamicin
Gentamicin and prednisolone	ointment†, suspension†	Pred-G®	none
Levofloxacin	solution†	Iquix®, Quixin®*	levofloxacin
Moxifloxacin	solution†	Vigamox®	none
Mupirocin	nasal ointment	Bactroban Nasal®	Bactroban Nasal®
Neomycin, bacitracin and polymyxin B	ointment†	N/A	neomycin, bacitracin and polymyxin B
Neomycin, bacitracin, polymyxin B and hydrocortisone	ointment†	N/A	neomycin, bacitracin, polymyxin B and hydrocortisone
Neomycin, colistin, hydrocortisone and thonzonium	suspension§	Coly-Mycin S®, Cortisporin-TC®	none
Neomycin, polymyxin B and dexamethasone	ointment†, suspension†	Maxitrol®*	neomycin, polymyxin B and dexamethasone
Neomycin, polymyxin B and gramicidin	solution†	Neosporin®*	neomycin, polymyxin B and gramicidin, Neosporin®*
Neomycin, polymyxin B and hydrocortisone	solution§, suspension†§	Cortisporin®*	neomycin, polymyxin B and hydrocortisone
Neomycin, polymyxin B and prednisolone	suspension†	Poly-Pred®	Poly-Pred®
Ofloxacin	solution†§	Ocuflox®*	ofloxacin
Polymyxin B and trimethoprim	solution†	Polytrim®*	polymyxin B and trimethoprim
Sulfacetamide	solution†	Bleph-10®*	sulfacetamide, Bleph-10®*
Sulfacetamide and prednisolone	ointment†, solution†*, suspension†	Blephamide®, Blephamide S.O.P.®	sulfacetamide and prednisolone, Blephamide®, Blephamide S.O.P.®

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Tobramycin	ointment†, solution†	Tobrex®*	tobramycin, Tobrex®*
Tobramycin and dexamethasone	ointment†, suspension†	TobraDex®*, TobraDex ST®	tobramycin and dexamethasone
Tobramycin and loteprednol	suspension†	Zylet®	none

*Generic is available in at least one dosage form or strength.
‡Product was added to Medicaid's drug file after the meeting's drug list was approved.
†Ophthalmic formulation
§Otic formulation
N/A=Not available

The EENT antibacterials have been shown to be active against the strains of microorganisms indicated in Tables 2-4. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the EENT antibacterials that are noted in Tables 6-8. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the EENT Antibacterials (Drugs A-G)[1-23,92-94]

Organism	Azithro-mycin	Bacitracin	Bacitracin/ Polymyxin B	Besi-floxacin	Cipro-floxacin	Ciprofloxacin/ Dexamethasone	Ciprofloxacin/ Hydrocortisone	Erythro-mycin	Gati-floxacin
Gram-Positive Aerobes									
CDC coryneform group g	✔			✔					
Corynebacterium propinquum									✔
Corynebacterium pseudodiphtheriticum				✔					
Corynebacterium striatum				✔					
Corynebacterium species		✔	✔					✔	
Staphylococcus aureus	✔	✔	✔	✔	✔	✔	✔	✔	✔
Staphylococcus epidermidis				✔	✔				✔
Staphylococcus hominis				✔					
Staphylococcus lugdunensis				✔					
Staphylococcus species		✔	✔						
Streptococcus mitis group	✔			✔					✔
Streptococcus oralis				✔					✔
Streptococcus pneumoniae	✔	✔	✔	✔	✔	✔		✔	✔
Streptococcus pyogenes		✔	✔					✔	
Streptococcus salivarius				✔					
Streptococcus species		✔	✔						
Streptococcus (Viridans Group)					✔			✔	
Gram-Negative Aerobes									
Chlamydia trachomatis								✔	
Enterobacter aerogenes			✔						
Escherichia coli			✔						
Haemophilus influenzae	✔		✔	✔	✔	✔		✔	✔
Klebsiella pneumoniae			✔						
Moraxella catarrhalis						✔			
Moraxella lacunata				✔					
Neisseria gonorrhea		✔	✔					✔	
Neisseria species		✔	✔						
Proteus mirabilis							✔		
Pseudomonas aeruginosa			✔		✔	✔	✔		
Serratia marcescens					✔				

Table 3. Microorganisms Susceptible to the EENT Antibacterials (Drugs G-N)[1-23]

Organism	Genta-micin	Gentamicin/ Prednisolone	Levo-floxacin	Moxi-floxacin	Mupirocin	NEO/ BAC/ POLY	NEO/ BAC/ POLY/ HYDRO	NEO/ COL/ HYDRO/ THON	NEO/ POLY/ DEX	NEO/ POLY/ GRAM	NEO/ POLY/ HYDRO	NEO/ POLY/ PRED
Gram-Positive Aerobes												
Corynebacterium species			✔	✔								
Micrococcus luteus				✔								
Staphylococcus aureus	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔
Staphylococcus aureus (methicillin-resistant)					✔							
Staphylococcus epidermidis	✔		✔	✔								
Staphylococcus haemolyticus				✔								
Staphylococcus hominis				✔								
Staphylococcus warneri				✔								
Streptococcus pneumoniae	✔	✔	✔	✔		✔	✔			✔		
Streptococcus pyogenes	✔	✔										
Streptococcus (Groups C/F)			✔									
Streptococcus (Group G)			✔									
Streptococcus (Viridans Group)			✔	✔								
Gram-Negative Aerobes												
Acinetobacter lwoffi			✔	✔								
Chlamydia trachomatis				✔								
Enterobacter aerogenes	✔	✔										
Enterobacter species						✔	✔	✔	✔	✔	✔	✔
Escherichia coli	✔	✔				✔	✔	✔	✔	✔	✔	✔
Haemophilus influenzae	✔	✔	✔	✔		✔	✔		✔	✔	✔	✔
Haemophilus parainfluenzae				✔								
Klebsiella pneumoniae	✔	✔				✔	✔	✔				
Klebsiella species									✔	✔	✔	✔
Neisseria gonorrhoeae	✔	✔										
Neisseria species						✔	✔		✔	✔	✔	✔
Pseudomonas aeruginosa	✔	✔	✔			✔	✔	✔	✔	✔	✔	✔
Serratia marcescens	✔	✔	✔									

NEO/BAC/POLY=neomycin, bacitracin and polymyxin B; NEO/BAC/POLY/HYDRO=neomycin, bacitracin, polymyxin B and hydrocortisone; NEO/COL/HYDRO/THON=neomycin, colistin, hydrocortisone and thonzonium; NEO/POLY/DEX=neomycin, polymyxin B and dexamethasone; NEO/POLY/GRAM=neomycin, polymyxin B and gramicidin; NEO/POLY/HYDRO=neomycin, polymyxin B and hydrocortisone; NEO/POLY/PRED=neomycin, polymyxin B and prednisolone

Table 4. Microorganisms Susceptible to the EENT Antibacterials (Drugs O-Z)[1-23,92-94]

Organism	Ofloxacin	Polymyxin B/ Trimethoprim	Sulfacetamide	Sulfacetamide/ Prednisolone	Tobramycin	Tobramycin/ Dexamethasone	Tobramycin/ Loteprednol
Gram-Positive Aerobes							
Staphylococcus aureus	✔	✔	✔	✔	✔	✔	✔
Staphylococcus epidermidis	✔				✔	✔	✔
Streptococcus pneumoniae	✔	✔	✔	✔	✔	✔	✔
Streptococcus species					✔	✔	✔
Streptococcus (Viridans Group)			✔	✔			
Gram-Negative Aerobes							
Acinetobacter calcoaceticus					✔	✔	✔
Enterobacter aerogenes		✔			✔	✔	✔
Enterobacter cloacae	✔						
Enterobacter species			✔	✔			
Escherichia coli	✔	✔	✔	✔	✔	✔	✔
Haemophilus aegyptius					✔	✔	✔
Haemophilus influenzae	✔	✔	✔	✔	✔	✔	✔
Klebsiella pneumoniae		✔	✔	✔	✔	✔	✔
Moraxella catarrhalis	✔						
Moraxella lacunata					✔	✔	✔
Morganella morganii					✔	✔	✔
Neisseria species					✔	✔	✔
Proteus mirabilis	✔				✔	✔	✔
Proteus species		✔					
Proteus vulgaris					✔	✔	✔
Pseudomonas aeruginosa	✔	✔			✔	✔	✔
Serratia marcescens	✔						
Anaerobic Species							
Propionibacterium acnes	✔						

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the EENT antibacterials are summarized in Table 5.

Table 5. Treatment Guidelines Using the EENT Antibacterials

Clinical Guideline	Recommendation(s)
American Academy of Ophthalmology: **Preferred Practice Pattern Guidelines: Blepharitis[24] (2008)**	• There is insufficient evidence to make definitive recommendations for the treatment of blepharitis, and cure is not possible in most cases. • Treatments that are helpful include the following: o Warm compresses o Eyelid hygiene o Antibiotics (topical and/or systemic) o Topical anti-inflammatory agents (e.g., corticosteroids, cyclosporine) • These treatment options are often used in combination. Eyelid hygiene is especially useful for anterior blepharitis, while warm compresses are especially helpful for posterior blepharitis. • The optimal treatment regimen often requires a trial and error approach. An initial step in treating patients with blepharitis is to recommend warm compresses and eyelid hygiene. • A topical antibiotic ointment such as bacitracin or erythromycin can be prescribed and applied on the eyelid margins one or more times daily or at bedtime for 1 or more weeks. The frequency and duration of treatment should be guided by the severity of the blepharitis and response to treatment. • For patients with meibomian gland dysfunction (MGD), whose chronic symptoms and signs are not adequately controlled with eyelid hygiene, an oral tetracycline can be prescribed. Macrolide antibiotics also have anti-inflammatory activity. Treatments can be intermittently discontinued and reinstated, based on the severity of the patient's blepharitis and tolerance for the medication, and to allow re-colonization of normal flora. • Corticosteroid eye drops or ointments are typically applied several times daily to the eyelids or ocular surface. Once the inflammation is controlled, the corticosteroid can be tapered and discontinued and then used intermittently to maintain patient comfort. The minimal effective dose of corticosteroid should be utilized, and long-term corticosteroid therapy should be avoided if possible. Patients should be informed of the potential adverse effects of corticosteroid use, including the risk for developing increased intraocular pressure and cataract. These adverse effects may be minimized by using a site-specific corticosteroid such as loteprednol etabonate and corticosteroids with limited ocular penetration, such as fluorometholone. • Artificial tears may improve symptoms when used as an adjunct to eyelid hygiene and medications. If used more than four times per day, non-preserved tears should be used to avoid preservative toxicity.
American Academy of Ophthalmology: **Preferred Practice Pattern Guidelines: Conjunctivitis[25] (2008)**	• Mild bacterial conjunctivitis may be self-limited and resolve spontaneously without specific treatment in immunocompetent adults. • Use of topical antibacterial therapy is associated with earlier clinical and microbiological remission compared with placebo in days 2 to 5 of treatment. These advantages persist over days 6 to 10, but the extent of benefit over placebo lessens over time. • The choice of antibiotic is usually empirical. Since a 5-to-7-day course of a broad-spectrum topical antibiotic is usually effective, the most convenient or least expensive option can be selected. • Severe bacterial conjunctivitis is characterized by copious purulent discharge, pain, and marked inflammation of the eye. The choice of

Clinical Guideline	Recommendation(s)
	antibiotic is guided by the results of laboratory tests. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated with increasing frequency from patients with bacterial conjunctivitis. Methicillin-resistant *S. aureus* organisms are resistant to many commercially available topical antibiotics. • Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Topical therapy, while not necessary, is usually used. If corneal involvement is present, the patient should also be treated topically as for bacterial keratitis.
American Optometric Association (AOA): **Care of the Patient with Conjunctivitis[96] (2002)**	• The ideal method of treating bacterial conjunctivitis is to identify the causative organism and initiate specific antimicrobial treatment known to be effective against the offending organism. • In the absence of a culture or smear, the etiologic agent should be considered in the context of the patient's age, environment, and related ocular findings. • In most cases, a broad-spectrum topical antibiotic is the treatment of choice. • Although most cases of bacterial conjunctivitis are self-limited, treatment with effective antibiotics can lessen the patient's symptoms, decrease the duration of the infection, and reduce the chances of its recurrence.

American Academy of Ophthalmology: **Preferred Practice Pattern Guidelines: Bacterial Keratitis[26] (2008)**	Initial Treatment
	• Topical antibiotic eye drops are capable of achieving high tissue levels and are the preferred method of treatment in most cases. Ocular ointments may be useful at bedtime in less severe cases and also may be useful for adjunctive therapy.
	• Topical broad-spectrum antibiotics are used initially in the empiric treatment of bacterial keratitis. The recommended topical empiric treatments include:
	  o No organism identified or multiple types of organisms: cefazolin (with tobramycin or gentamicin) or fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin than other fluoroquinolones)
	  o Gram-positive cocci: cefazolin, vancomycin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), bacitracin(for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), or fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin than other fluoroquinolones)
	  o Gram-negative rods: tobramycin or gentamicin, ceftazidime, or fluoroquinolones
	  o Gram-negative cocci: ceftriaxone, ceftazidime, or fluoroquinolones (systemic therapy is necessary for suspected gonococcal infection)
	  o Nontuberculous mycobacteria: Amikacin, clarithromycin, azithromycin, or fluoroquinolones
	  o Nocardia: sulfacetamide, amikacin, or trimethoprim/sulfamethoxazole
	• Single-drug therapy using a fluoroquinolone has been shown to be as effective as combination therapy utilizing antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics.
	• Some pathogens (e.g., Streptococci, anaerobes) reportedly have variable susceptibility to fluoroquinolones and the prevalence of resistance to the fluoroquinolones appears to be increasing.
	• Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to initial treatment.

Clinical Guideline	Recommendation(s)
	• Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with LASIK. • Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated with increasing frequency from patients with bacterial keratitis and has been reported following kerato-refractive surgery. Fluoroquinolones are generally poorly effective against MRSA ocular isolates. Methicillin-resistant *Staphylococcus aureus* isolates generally are sensitive to vancomycin. • Systemic antibiotics are rarely needed, but they may be considered in severe cases where the infectious process has extended to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. • Systemic therapy is necessary in cases of gonococcal keratitis. <u>Modification of Therapy</u> • The efficacy of the therapeutic regimen is judged primarily by the clinical response. The results of cultures and sensitivity testing may have an impact on therapeutic decision making, especially if the patient is not responding to initial therapy. Dual antibiotic treatment designed to achieve broad-spectrum coverage may become unnecessary once the causative organism has been isolated. In general, the initial therapeutic regimen should be modified when the eye shows a lack of improvement or stabilization within 48 hours. • Modification of therapy may mean a change in the type, concentration, or frequency of antibiotic treatment. • Most antibiotic eye drops should not be tapered below three to four times a day, because low doses are subtherapeutic and may increase the risk of antibiotic resistance developing. <u>Corticosteroid Therapy</u> • Topical corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis. The potential advantage is the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. Potential disadvantages include recrudescence of infection, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased intraocular pressure. • There is no conclusive scientific evidence indicating that corticosteroids alter clinical outcome. • Despite the risks involved, many experts believe that the judicious use of topical corticosteroids can reduce morbidity. Patients being treated with ocular topical corticosteroids at the time of presentation of suspected bacterial keratitis should have their corticosteroid regimen reduced or eliminated until the infection has been controlled. • Inflammation may temporarily increase as corticosteroids are reduced. The objective in topical corticosteroid therapy is to use the minimum amount of corticosteroid required to achieve control of inflammation. Successful treatment requires optimal timing, careful dose regulation, use of adequate concomitant antibacterial medication, and close follow-up. • Corticosteroids should not be part of initial treatment of presumed bacterial ulcers, and ideally they should not be used until the organism has been determined by cultures. • The use of corticosteroids in the initial treatment of corneal ulcers has been determined to be a risk factor for requiring a penetrating keratoplasty. • Topical antibiotics, which are generally administered more frequently than corticosteroids during treatment of active infection, are continued at high

Clinical Guideline	Recommendation(s)
	levels and tapered gradually. Patient compliance is essential, and the intraocular pressure must be monitored frequently. The patient should be examined within 1 to 2 days after initiation of topical corticosteroid therapy.
American Optometric Association (AOA): **Care of the Patient with Ocular Surface Disorders**[97] **(2002)**	Blepharitis • For acute blepharitis, lid hygiene alone may not resolve the problem. An anti-infective drug can be administered topically, systemically, or in combination. • For chronic blepharitis, there is no complete cure. Aggressive therapy should initially include a minimum of 6 weeks of lid hygiene and appropriate anti-infective medications to gain control of the condition, followed by continuing treatment to maintain control of chronic blepharitis. Staphylococcal Blepharitis • Treatment includes an antibiotic ointment to control the infection, as well as lid hygiene. Erythromycin, bacitracin, polymyxin B/bacitracin, gentamicin, and tobramycin are all effective antibiotics for treatment of staphylococcal blepharitis. Antibiotic eye drops can be used, but they do not work as well as ointments due to reduced contact time. • Tear supplements may also be required to alleviate symptoms. • If peripheral corneal infiltrates are present without epithelial defects, topical steroids may be used for a limited time.
American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF): **Clinical Practice Guideline: Acute Otitis Externa**[27] **(2006)**	• Clinicians should use topical preparations for initial therapy of diffuse, uncomplicated acute otitis externa (AOE). Systemic antimicrobial therapy should not be used unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. • Topical preparations are recommended as initial therapy for diffuse, uncomplicated AOE because of safety, efficacy over placebo in randomized trials, and excellent clinical and bacteriologic outcomes in comparative studies. • The choice of topical antimicrobial for initial therapy of diffuse AOE should be based upon efficacy, low incidence of adverse events and likelihood of adherence to therapy. • Clinicians should use a topical drop that is efficacious for diffuse AOE. Efficacy is best summarized with meta-analysis of randomized controlled trials. In a systematic review, there were no significant differences in clinical outcomes of AOE for antiseptic vs antimicrobial, quinolone antibiotic vs non-quinolone antibiotic(s), or steroid-antimicrobial vs antimicrobial alone. Regardless of topical agent used, about 65% to 90% of patients had clinical resolution within 7 to 10 days. The meta-analysis results suggest minimal or no difference in clinical or bacteriologic cure rates among topical agents. • The lack of differences in efficacy among most topical antimicrobial and steroid preparations suggests that patient preference and clinician experience are important aspects in selecting therapy. • When the patient has a tympanostomy tube or known perforation of the tympanic membrane, the clinician should prescribe a non-ototoxic topical preparation. Substances with ototoxic potential (e.g., aminoglycosides) should not be used when the tympanic membrane is perforated and the middle ear space is open, because the risk of ototoxic injury outweighs the benefits compared with non-ototoxic antimicrobials with equal efficacy. • Appropriate treatment of uncomplicated AOE should be followed by symptom improvement (otalgia, itching and fullness) within 48 to 72 hours.
American Academy of Otolaryngology–Head and	• When possible, topical antibiotic preparations free of potential ototoxicity should be used in preference to ototopical preparations that have the

Clinical Guideline	Recommendation(s)
Neck Surgery (AAO-HNS): **Consensus Panel on Role of Potentially Ototoxic Antibiotics for Topical Middle Ear Use[95] (2004)**	potential for otologic injury if the middle ear or mastoid are open. • If used, potentially ototoxic antibiotic preparation should be used only in infected ears. Use should be discontinued shortly after the infection has resolved. • If potentially ototoxic antibiotic drops are prescribed for use in the open middle ear or mastoid, the patient/parent should be warned of the risk of ototoxicity. • If potentially ototoxic antibiotics are prescribed, the patient should be instructed to call the physician or return to his or her office if the patient develops 1) dizziness or vertigo; 2) hearing loss (or additional hearing loss if hearing impairment was part of the original condition); or 3) tinnitus. • If the tympanic membrane is known to be intact and the middle ear and mastoid are closed, then the use of potentially ototoxic preparations present no risk of ototoxic injury.

Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Otitis Media in Children[98] (2008)**	Watch and Wait
	• Low-risk children six months to two years without severe disease and an uncertain diagnosis should be treated with oral and topical analgesics and may be observed for 48-72 hours.
	• If symptoms do not resolve or are worse, child should be rechecked and/or antibiotics prescribed.
	• Low-risk children are defined as otherwise healthy, do not attend day care and have had no prior ear infections within the last month.
	• Severe disease is defined as fever greater than or equal to 39ºC in the past 24 hours and moderate to severe otalgia.
	• A diagnosis of acute otitis media meets any of the following criteria: sudden onset of symptoms, signs of middle-ear effusion, and signs and symptoms of middle-ear inflammation.
	Antibiotic Treatment
	• When antibiotics are necessary, the initial treatment is amoxicillin.
	• Indications for using another medication include:
	  o Failure to respond to initial treatment drug (resistant or persistent acute otitis media)
	  o History of lack of response to initial treatment drug (failure of medication on at least two occasions in the current respiratory season)
	  o Hypersensitivity to initial treatment medications
	  o Presence of resistant organism determined by culture
	  o Coexisting illness requiring a different medication
	• Other recommended treatments include amoxicillin/clavulanate potassium, cefuroxime axetil, ceftriaxone sodium, cefprozil, loracarbef, cefdinir, cefixime, and cefpodoxime proxetil.
	• Other treatments that are currently used but are not as strongly supported in the literature are: trimethoprim/sulfamethoxazole, clarithromycin, erythromycin ethylsuccinate and sulfisoxazole acetyl, or azithromycin. These medications are not recommended when the patient has failed a course of amoxicillin.

American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP), Subcommittee on Management of Acute Otitis Media: **Diagnosis and Management of Acute Otitis Media[28]**	Observation Option • Observation without use of antibacterial agents in a child with uncomplicated acute otitis media (AOM) is an option for selected children based on diagnostic certainty, age, illness severity, and assurance of follow-up. The "observation option" for AOM refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children 6 months to 2 years of age with non-severe illness at presentation and an uncertain diagnosis and to children 2 years of age and older without

Clinical Guideline	Recommendation(s)
(2004)	severe symptoms at presentation or with an uncertain diagnosis. Antibacterial Options - Temperature <39°C Without Severe Otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin 80-90 mg/kg/day. • For treatment failures at 48-72 hours after initial management with observation option, the recommended agent is amoxicillin 80-90 mg/kg/day. • For treatment failures at 48-72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. Antibacterial Options - Temperature ≥39°C and/or Severe Otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48-72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48-72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for 3 days.
Society for Healthcare Epidemiology of America (SHEA)/ Infectious Diseases Society of America (IDSA): **Strategies to Prevent Transmission of Methicillin-Resistant *Staphylococcus aureus* in Acute Care Hospitals[100] (2008)**	• Active surveillance testing: MRSA screening program for patients • Active surveillance testing for MRSA among healthcare personnel • Routine bathing with chlorhexidine • MRSA decolonization therapy for MRSA-colonized persons. The optimal decolonization therapy regimen has not been determined. Most experience has been with the use of 2% mupirocin administered intranasally with or without chlorhexidine bathing.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the EENT antibacterials are noted in Tables 6-8. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 6. FDA-Approved Indications for the EENT Antibacterials (Drugs A-G)[1-23,92-94]

Indication	Azithro-mycin	Bacitracin	Bacitracin/ Polymyxin B	Besi-floxacin	Cipro-floxacin	Ciprofloxacin/ Dexamethasone	Ciprofloxacin/ Hydrocortisone	Doxy-cycline	Erythro-mycin	Gati-floxacin
Ocular Disorders										
Prophylaxis of ophthalmia neonatorum due to *N gonorrhoeae* or *C trachomatis*									✔	
Treatment of bacterial conjunctivitis	✔	✔	✔	✔	✔ ‡				✔	✔
Treatment of corneal infections		✔	✔						✔	
Treatment of corneal ulcers					✔ ‡					
Otic Disorders										
Treatment of acute otitis externa					✔ †	✔	✔			
Treatment of acute otitis media in patients with tympanostomy tubes						✔				
Miscellaneous Disorders										
Adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis								✔		

†Otic formulation only.
‡Ophthalmic formulation only.

Table 7. FDA-Approved Indications for the EENT Antibacterials (Drugs G-N)[1-23,92-94]

Indication	Genta-micin	Gentamicin/ Prednisolone	Levo-floxacin	Moxi-floxacin	Mupirocin	NEO/ BAC/ POLY	NEO/ BAC/ POLY/ HYDRO	NEO/ COL/ HYDRO/ THON	NEO/ POLY/ DEX	NEO/ POLY/ GRAM	NEO/ POLY/ HYDRO	NEO/ POLY/ PRED
Ocular Disorders												
Treatment of bacterial conjunctivitis			✔	✔								
Treatment of chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies		✔					✔		✔		✔ ‡	✔
Treatment of corneal ulcers			✔									

Indication	Genta-micin	Gentamicin/ Prednisolone	Levo-floxacin	Moxi-floxacin	Mupirocin	NEO/ BAC/ POLY	NEO/ BAC/ POLY/ HYDRO	NEO/ COL/ HYDRO/ THON	NEO/ POLY/ DEX	NEO/ POLY/ GRAM	NEO/ POLY/ HYDRO	NEO/ POLY/ PRED
Treatment of corticosteroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists		✔					✔		✔		✔ ‡	✔
Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation		✔					✔		✔		✔ ‡	✔
Treatment of ocular bacterial infections, including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis	✔											
Treatment of superficial infections of the external eye and its adnexa						✔				✔		
When the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye		✔							✔			✔
Otic Disorders												
Treatment of infections of mastoidectomy and fenestration cavities								✔			✔ †	
Treatment of superficial bacterial infections of the external auditory canal								✔			✔ †	
Miscellaneous Disorders												
Eradication of nasal colonization with methicillin-resistant *S. aureus* in adult patients and health care					✔							

NEO/BAC/POLY=neomycin, bacitracin and polymyxin B; NEO/BAC/POLY/HYDRO=neomycin, bacitracin, polymyxin B and hydrocortisone; NEO/COL/HYDRO/THON=neomycin, colistin, hydrocortisone and thonzonium; NEO/POLY/DEX=neomycin, polymyxin B and dexamethasone; NEO/POLY/GRAM=neomycin, polymyxin B and gramicidin; NEO/POLY/HYDRO=neomycin, polymyxin B and hydrocortisone; NEO/POLY/PRED=neomycin, polymyxin B and prednisolone
†Otic formulation only.
‡Ophthalmic formulation only.

Table 8. FDA-Approved Indications for the EENT Antibacterials (Drugs O-Z)[1-23,92-94]

Indication	Ofloxacin	Polymyxin B/ Trimethoprim	Sulfacetamide	Sulfacetamide/ Prednisolone	Tobramycin	Tobramycin/ Dexamethasone	Tobramycin/ Loteprednol
Ocular Disorders							
Adjunctive treatment in systemic sulfonamide therapy of trachoma			✔				
Treatment of bacterial conjunctivitis	✔ ‡	✔					
Treatment of blepharoconjunctivitis		✔					
Treatment of conjunctivitis and other superficial ocular infections			✔				
Treatment of corneal ulcers	✔ ‡						
Treatment of corticosteroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists				✔		✔	✔
Treatment of chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies						✔	✔
Treatment of external infections of the eye and its adnexa					✔		
Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation						✔	✔
When the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye						✔	✔
Otic Disorders							
Treatment of acute otitis media in patients with tympanostomy tubes	✔ †						
Treatment of chronic suppurative otitis media in patients with perforated tympanic membranes	✔ †						
Treatment of otitis externa	✔ †						

†Otic formulation only.
‡Ophthalmic formulation only.

IV. Pharmacokinetics

There is limited or no data available regarding the pharmacokinetic properties of the nasal, ophthalmic or otic antibacterial agents. The pharmacokinetic parameters of oral doxycycline are listed in Table 9.

Table 9. Pharmacokinetic Parameters of the EENT Antibacterials[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Doxycycline	well absorbed	80-93	Liver (50)	Renal (35-45)	15-24

V. Drug Interactions

In general, drug interaction studies have not been completed with the nasal, ophthalmic or otic antibacterial agents. Significant drug interactions with oral doxycycline are listed in Table 10.

Table 10. Significant Drug Interactions with the EENT Antibacterials[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Doxycycline	1	Acitretin	Concurrent administration of acitretin and doxycycline may increase the risk for development of pseudotumor cerebri. The mechanism of this interaction is unknown.
Doxycycline	1	Anticoagulants	Hypoprothrombinemic effects of anticoagulants may be increased by doxycycline. Bleeding may occur.
Doxycycline	1	Isotretinoin	Concurrent administration of isotretinoin and doxycycline may increase the risk of pseudotumor cerebri. The mechanism of this interaction is unknown.
Doxycycline	1	Vaccines, live	Doxycycline may decrease the effectiveness of live vaccines when the two are coadministered. Although the exact mechanism of this interaction is unknown, doxycycline may be active against the bacterial strain and decrease the immune response.
Doxycycline	2	Aluminum salts	The antimicrobial effectiveness of doxycycline may be decreased by aluminum salts. Oral and enterohepatic absorption of doxycycline may be decreased due to formation of poorly soluble chelates with aluminum.
Doxycycline	2	Barbiturates	The antimicrobial effectiveness of doxycycline may be decreased by barbiturates. Induction of hepatic microsomal enzymes by barbiturates may increase the metabolic elimination of doxycycline.
Doxycycline	2	Carbamazepine	The antimicrobial effectiveness of doxycycline may be decreased. Carbamazepine may increase the hepatic metabolism of doxycycline.

Generic Name(s)	Significance Level	Interaction	Mechanism
Doxycycline	2	Digoxin	Tetracyclines may reverse the GI metabolism of digoxin to inactive metabolites by altering GI flora, allowing for more digoxin to be absorbed and increasing digoxin serum levels.
Doxycycline	2	Hydantoins	Stimulation of hepatic microsomal enzymes by hydantoins induces metabolism of doxycycline; displacement of doxycycline from plasma proteins may contribute to this phenomenon.
Doxycycline	2	Iron and magnesium salts	The antimicrobial effectiveness of doxycycline may be decreased by iron and magnesium salts. The formation of poorly soluble chelates decreases gastrointestinal absorption and enterohepatic recycling of doxycycline.
Doxycycline	2	Oral contraceptives	Pharmacologic effects of oral contraceptives may be decreased by doxycycline in a small unidentifiable subpopulation of patients. Breakthrough bleeding and pregnancy may occur. Doxycycline may alter gut flora and/or cause other GI disturbances (vomiting and diarrhea). Lower plasma concentrations of certain contraceptive steroids (because of reduced enterohepatic circulation/reabsorption) may result.
Doxycycline	2	Penicillins	The antimicrobial effectiveness of penicillins may be decreased. Doxycycline may interfere with the bactericidal activity of penicillins.
Doxycycline	2	Urinary alkalinizers	The antimicrobial effectiveness of doxycycline may be decreased.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the EENT antibacterials are listed in Tables 11-13.

Table 11. Adverse Drug Events (%) Reported with the EENT Antibacterials (Drugs A–G)[1-23,92-94]

Adverse Events	Azithro-mycin	Bacitracin	Bacitracin/ Polymyxin B	Besi-floxacin	Cipro-floxacin	Ciprofloxacin/ Dexamethasone	Ciprofloxacin/ Hydrocortisone	Doxycycline	Erythro-mycin	Gatifloxacin
Central Nervous System										
Headache	-	-	-	1-2	2-3	-	✔	26	-	1-4
Migraine	-	-	-	-	-	-	✔	-	-	-
Dermatological										
Alopecia	-	-	-	-	-	-	✔	-	-	-
Contact dermatitis	<1	-	-	-	-	-	-	-	-	-
Edema	-	-	✔	-	-	-	-	-	-	-
Fungal dermatitis	-	-	-	-	-	-	✔	-	-	-
Pruritus	-	-	✔	-	-	-	✔	-	-	-
Rash	-	-	-	-	-	-	✔	4	-	-
Urticaria	-	-	-	-	-	-	✔	-	-	-
Gastrointestinal										
Acid indigestion	-	-	-	-	-	-	-	4	-	-
Diarrhea	-	-	-	-	-	-	-	6	-	-
Dysgeusia	-	-	-	-	-	-	-	-	-	≥1
Dyspepsia	-	-	-	-	-	-	-	6	-	-
Nausea	-	-	-	-	<1	-	-	8	-	-
Taste disturbance	<1	-	-	-	<10	<1	-	-	-	1-4
Ophthalmic/Otic										
Blurred vision	-	-	-	1-2	-	-	-	-	-	-
Burning	<1	-	-	-	✔	-	-	-	-	-
Chemosis	-	-	-	-	-	-	-	-	-	1-4
Conjunctival hemorrhage	-	-	-	-	-	-	-	-	-	1-4
Conjunctival redness	-	-	✔	2	<10	-	-	-	✔	5-10
Corneal erosion	<1	-	-	-	-	-	-	-	-	-
Corneal infiltrates	-	-	-	-	<1	-	-	-	-	-
Corneal staining	-	-	-	-	<1	-	-	-	-	-
Crystals/scales	-	-	-	-	<10	-	-	-	-	-
Decreased vision	-	-	-	-	<1	-	-	-	-	1-4
Discomfort	-	-	-	-	✔	-	-	-	-	-
Dry eyes	<1	-	-	-	-	-	-	-	-	1-4

Adverse Events	Azithro-mycin	Bacitracin	Bacitracin/ Polymyxin B	Besi-floxacin	Cipro-floxacin	Ciprofloxacin/ Dexamethasone	Ciprofloxacin/ Hydrocortisone	Doxycycline	Erythro-mycin	Gatifloxacin
Ear congestion	-	-	-	-	-	<1	-	-	-	-
Ear debris	-	-	-	-	-	<1	-	-	-	-
Ear discomfort	-	-	-	-	-	3	-	-	-	-
Ear erythema	-	-	-	-	-	<1	-	-	-	-
Ear infection	-	-	-	-	-	<1	-	-	-	-
Ear pain	-	-	-	-	-	<2	-	-	-	≥1
Ear precipitate	-	-	-	-	-	<1	-	-	-	-
Ear pruritus	-	-	-	-	-	1	-	-	-	-
Eye discharge	<1	-	-	-	-	-	-	-	-	1-4
Eye irritation	1-2	-	✔	1-2	-	-	-	-	-	≥1
Eye pain	-	-	-	1-2	-	-	-	-	-	1-4
Eye pruritus	-	-	-	1-2	<10	-	-	-	-	-
Foreign body sensation	-	-	-	-	<10	-	-	-	-	-
Irritation	<1	-	✔	-	-	-	-	-	✔	-
Keratopathy/keratitis	-	-	-	-	<1	-	-	-	-	-
Lid edema	-	-	-	-	<1	-	-	-	-	1-4
Lid margin crusting	-	-	-	-	<10	-	-	-	-	-
Papillary conjunctivitis	-	-	-	-	-	-	-	-	-	5-10
Photophobia	-	-	-	-	<1	-	-	-	-	-
Punctate keratitis	<1	-	-	-	-	-	-	-	-	-
Stinging	<1	-	-	-	-	-	-	-	-	-
Tearing	-	-	-	-	<1	-	-	-	-	5-10
White crystalline precipitates	-	-	-	-	17	-	-	-	-	-
Worsening of conjunctivitis	-	-	-	-	-	-	-	-	-	≥1
Other										
Allergic reactions	-	-	✔	-	<1	-	-	-	-	-
Application site pain	-	-	-	-	2-3	-	-	-	-	-
Back ache	-	-	-	-	-	-	-	2	-	-
Back pain	-	-	-	-	-	-	-	3	-	-
Bronchitis	-	-	-	-	-	-	-	3	-	-
Common cold	-	-	-	-	-	-	-	22	-	-
Cough	-	-	-	-	-	-	✔	4	-	-
Flu symptoms	-	-	-	-	-	-	-	11	-	-
Fungal ear superinfection	-	-	-	-	2-3	-	-	-	-	-
Gum pain	-	-	-	-	-	-	-	<1	-	-
Hypersensitivity	-	-	-	-	-	-	-	-	✔	-

Adverse Events	Azithro-mycin	Bacitracin	Bacitracin/ Polymyxin B	Besi-floxacin	Cipro-floxacin	Ciprofloxacin/ Dexamethasone	Ciprofloxacin/ Hydrocortisone	Doxycycline	Erythro-mycin	Gatifloxacin
Infection	-	-	-	-	-	-	-	2	-	-
Injury	-	-	-	-	-	-	-	5	-	-
Joint pain	-	-	-	-	-	-	-	6	-	-
Menstrual cramp	-	-	-	-	-	-	-	4	-	-
Muscle pain	-	-	-	-	-	-	-	1	-	-
Nasal congestion	<1	-	-	-	-	-	-	-	-	-
Pain	-	-	-	-	-	-	-	4	-	-
Periodontal abscess	-	-	-	-	-	-	-	4	-	-
Sinus congestion	-	-	-	-	-	-	-	5	-	-
Sinus headache	-	-	-	-	-	-	-	4	-	-
Sinusitis	<1	-	-	-	-	-	-	3	-	-
Sore throat	-	-	-	-	-	-	-	5	-	-
Tooth ache	-	-	-	-	-	-	-	7	-	-
Tooth disorder	-	-	-	-	-	-	-	6	-	-

✔ Percent not specified
- Event not reported

Table 12. Adverse Drug Events (%) Reported with the EENT Antibacterials (Drugs G–N)[1-23,92-94]

Adverse Events	Genta-micin	Gentamicin/ Prednisolone	Levo-floxacin	Moxi-floxacin	Mupirocin	NEO/ BAC/ POLY	NEO/ BAC/ POLY/ HYDRO	NEO/ COL/ HYDRO/ THON	NEO/ POLY/ DEX	NEO/ POLY/ GRAM	NEO/ POLY/ HYDRO	NEO/ POLY/ PRED
Central Nervous System												
Hallucinations	✔	-	-	-	-	-	-	-	-	-	-	-
Headache	-	-	1-10	-	9	-	-	-	-	-	-	-
Dermatological												
Edema	-	-	-	-	-	✔	✔	-	-	✔	-	✔
Pruritus	-	-	-	-	1	✔	✔	-	-	✔	-	✔
Rash	-	-	-	1-4	<1	-	-	-	-	-	-	-
Skin sensitization	-	-	-	-	-	-	-	✔	-	-	✔	✔
Gastrointestinal												
Diarrhea	-	-	1-2	-	<1	-	-	-	-	-	-	-
Dyspepsia	-	-	1-2	-	-	-	-	-	-	-	-	-
Nausea	-	-	1-2	-	<1	-	-	-	-	-	-	-
Ophthalmic/Otic												
Blepharitis	-	-	-	-	<1	-	-	-	-	-	-	-
Blurred vision	-	-	1-2	-	-	-	-	-	-	-	-	-
Burning	✔	✔	1-2	1-6	-	-	✔	-	-	-	-	-

Adverse Events	Genta-micin	Gentamicin/ Prednisolone	Levo-floxacin	Moxi-floxacin	Mupirocin	NEO/ BAC/ POLY	NEO/ BAC/ POLY/ HYDRO	NEO/ COL/ HYDRO/ THON	NEO/ POLY/ DEX	NEO/ POLY/ GRAM	NEO/ POLY/ HYDRO	NEO/ POLY/ PRED
Chemosis	-	-	<1	-	-	-	-	-	-	-	-	-
Conjunctival epithelial defects	✔	-	-	-	-	-	-	-	-	-	-	-
Conjunctival hemorrhage	-	-	-	1-6	-	-	-	-	-	-	-	-
Conjunctival redness	-	-	-	1-6	-	✔	✔	-	-	✔	-	✔
Conjunctivitis	✔	-	-	-	-	-	-	-	-	-	-	-
Corneal erosion/ulceration	-	-	<1	-	-	-	-	-	-	-	-	-
Decreased visual acuity	-	-	-	1-6	-	-	-	-	-	-	-	-
Diplopia	-	-	<1	-	-	-	-	-	-	-	-	-
Discomfort	-	✔	1-2	1-6	-	-	-	-	-	-	-	-
Dry eyes	-	-	-	1-6	-	-	-	-	-	-	-	-
Ear pain	-	-	-	-	<1	-	-	-	-	-	-	-
Elevated intraocular pressure with possible glaucoma	-	✔	-	-	-	-	✔	-	✔	-	-	-
Floaters	-	-	<1	-	-	-	-	-	-	-	-	-
Foreign body sensation	-	-	1-3	-	-	-	-	-	-	-	-	-
Hyperemia	✔	-	<1	1-6	-	-	-	-	-	-	-	-
Irritation	✔	✔	1-2	1-6	-	✔	✔	-	-	-	-	-
Lid edema	-	-	<1	-	-	-	-	-	-	-	-	-
Lid erythema	-	-	<1	-	-	-	✔	-	-	-	-	-
Ocular infection	-	✔	1-2	-	-	-	-	-	✔	-	-	-
Ocular pain	-	-	1-2	1-6	-	-	-	-	-	-	-	-
Optic nerve damage	-	✔	-	-	-	-	✔	-	✔	-	-	-
Otitis media	-	-	-	1-4	-	-	-	-	-	-	-	-
Ototoxicity	-	-	-	-	-	-	✔	✔	✔	✔	✔	✔
Posterior subcapsular cataract formation	-	✔	-	-	-	-	✔	-	✔	-	-	-
Punctate keratitis	-	✔	-	1-6	-	-	-	-	-	-	-	-
Stinging	-	✔	1-2	1-6	-	-	✔	-	-	-	-	-
Tearing	-	-	-	1-6	-	-	-	-	-	-	-	-
Other												
Allergic reactions	✔	✔	-	-	-	✔	✔	✔	✔	✔	✔	✔
Anaphylaxis	-	-	-	-	-	✔	✔	-	-	-	-	-
Burning/stinging (nasal)	-	-	-	-	2	-	-	-	-	-	-	-

Adverse Events	Genta-micin	Gentamicin/ Prednisolone	Levo-floxacin	Moxi-floxacin	Mupirocin	NEO/ BAC/ POLY	NEO/ BAC/ POLY/ HYDRO	NEO/ COL/ HYDRO/ THON	NEO/ POLY/ DEX	NEO/ POLY/ GRAM	NEO/ POLY/ HYDRO	NEO/ POLY/ PRED
Cough	-	-	-	1-4	2	-	-	-	-	-	-	-
Delayed wound healing	-	✔	-	-	-	-	✔	-	✔	-	-	-
Epistaxis	-	-	-	-	<1	-	-	-	-	-	-	-
Fever	-	-	1-3	1-4	-	-	-	-	-	-	-	-
Hypersensitivity	-	✔	<1	-	-	-	✔	-	-	-	-	-
Infection (systemic)	-	-	-	1-4	-	-	-	-	-	-	-	-
Nephrotoxicity	-	-	-	-	-	✔	✔	✔	✔	✔	✔	✔
Pharyngitis	-	-	1-3	1-4	4	-	-	-	-	-	-	-
Respiratory disorder	-	-	-	-	5	-	-	-	-	-	-	-
Rhinitis	-	-	-	1-4	6	-	-	-	-	-	-	-
Taste disturbance	-	-	8-10	-	3	-	-	-	-	-	-	-
Throat irritation	-	-	1-2	-	-	-	-	-	-	-	-	-
Thrombocytopenic purpura	✔	-	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	1-4	-	-	-	-	-	-	-	-

NEO/BAC/POLY=neomycin, bacitracin and polymyxin B; NEO/BAC/POLY/HYDRO=neomycin, bacitracin, polymyxin B and hydrocortisone; NEO/COL/HYDRO/THON=neomycin, colistin, hydrocortisone and thonzonium; NEO/POLY/DEX=neomycin, polymyxin B and dexamethasone; NEO/POLY/GRAM=neomycin, polymyxin B and gramicidin; NEO/POLY/HYDRO=neomycin, polymyxin B and hydrocortisone; NEO/POLY/PRED=neomycin, polymyxin B and prednisolone

✔ Percent not specified

- Event not reported

Table 13. Adverse Drug Events (%) Reported with the EENT Antibacterials (Drugs O–Z)[1-23,92-94]

Adverse Events	Ofloxacin	Polymyxin B/ Trimethoprim	Sulfacetamide	Sulfacetamide/ Prednisolone	Tobramycin	Tobramycin/ Dexamethasone	Tobramycin/ Loteprednol
Central Nervous System							
Dizziness	≤1	-	-	-	-	-	-
Headache	≤1	-	-	-	-	<1	14
Paresthesia	1	-	-	-	-	-	-
Vertigo	≤1	-	-	-	-	-	-
Dermatological							
Pruritus	1-4	-	-	-	-	-	-
Rash	1	-	-	-	-	-	-
Ophthalmic/Otic							
Application site reaction	1-17	-	-	-	-	-	-
Burning	✔	✔	✔	✔	-	-	9
Cataract formation	-	-	-	✔	-	✔	✔
Conjunctival redness	✔	-	✔	✔	✔	✔	✔
Corneal deposits	-	-	-	-	-	-	<4

Adverse Events	Ofloxacin	Polymyxin B/ Trimethoprim	Sulfacetamide	Sulfacetamide/ Prednisolone	Tobramycin	Tobramycin/ Dexamethasone	Tobramycin/ Loteprednol
Corneal erosion/ulceration	-	-	✔	✔	-	-	-
Discharge	-	-	-	-	-	-	<4
Dry eyes	✔	-	-	-	-	-	-
Earache	≤1	-	-	-	-	-	-
Elevated intraocular pressure	-	-	-	✔	-	✔	10
Foreign body sensation	✔	-	-	-	-	-	-
Injection	-	-	-	-	-	-	20
Irritation	✔	✔	✔	✔	-	-	-
Lacrimation disorder	-	-	-	-	-	-	<4
Lid edema	✔	-	-	-	✔	✔	✔
Lid disorder	-	-	-	-	-	-	<4
Lid erythema	-	-	-	✔	✔	✔	✔
Lid pruritus	-	-	-	-	✔	✔	✔
Ocular infection	-	-	✔	✔	-	✔	✔
Ocular pain	✔	-	-	-	-	-	<4
Optic nerve damage	-	-	-	✔	-	✔	✔
Papillary conjunctivitis	✔	-	-	-	-	-	-
Photophobia	-	-	-	-	-	-	<4
Pruritus	-	-	-	-	-	-	<4
Punctate keratitis	✔	-	-	✔	-	-	15
Stinging	✔	✔	✔	✔	-	✔	9
Tearing	✔	-	-	-	-	-	-
Vision disorders	-	-	-	-	-	-	<4
Other							
Delayed wound healing	-	-	-	✔	-	✔	✔
Hypersensitivity	-	✔	✔	-	✔	✔	✔
Hypertension	-	-	-	-	-	<1	-
Photosensitivity	-	✔	-	-	-	-	-
Taste perversion	7	-	-	-	-	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the EENT antibacterials are listed in Table 14.

Table 14. Usual Dosing Regimens for the EENT Antibacterials[1-23,92-94]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Azithromycin	Bacterial Conjunctivitis: Instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first two days and then instill 1 drop in the affected eye(s) once daily for the next five days	Bacterial Conjunctivitis: ≥1 year of age: Instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first two days and then instill 1 drop in the affected eye(s) once daily for the next five days	Ophthalmic solution: 1%
Bacitracin	Bacterial Conjunctivitis or Corneal Infections: Instill ¼ inch to ½ inch ribbon every 3-4 hours into conjunctival sac for acute infections, or 2-3 times per day for mild-to-moderate infections for 7-10 days	Bacterial Conjunctivitis or Corneal Infections: Instill ¼ inch to ½ inch ribbon every 3-4 hours into conjunctival sac for acute infections, or 2-3 times per day for mild-to-moderate infections for 7-10 days	Ophthalmic ointment: 500 units/G
Bacitracin and polymyxin B	Bacterial Conjunctivitis or Corneal Infections: Apply every 3-4 hours for 7 to 10 days, depending on severity of infection	Bacterial Conjunctivitis or Corneal Infections: Apply every 3-4 hours for 7 to 10 days, depending on severity of infection	Ophthalmic ointment: 500-10KU/G
Besifloxacin	Bacterial Conjunctivitis: Instill 1 drop into the affected eye(s) 3 times per day, four to twelve hours apart for 7 days	Bacterial Conjunctivitis: ≥1 year of age: Instill 1 drop into the affected eye(s) 3 times per day, four to twelve hours apart for 7 days	Ophthalmic suspension: 0.6%
Ciprofloxacin	Acute Otitis Externa Otic solution: The contents of one single use container should be instilled into the affected ear twice daily for 7 days Bacterial Conjunctivitis: Ophthalmic ointment: Apply a ½ inch ribbon into the conjunctival sac three times daily for 2 days, then twice daily for 5 days Ophthalmic solution: Instill 1-2 drops into the affected eye(s) every 2 hours while awake for 2 days, then every 4 hours while awake for the next 5 days. Corneal ulcers: Ophthalmic solution: Instill two drops into the affected eye every 15 minutes for the	Acute Otitis Externa Otic solution: ≥1 year of age: The contents of one single use container should be instilled into the affected ear twice daily for 7 days Bacterial Conjunctivitis: Ophthalmic ointment: ≥2 years of age: Apply a ½ inch ribbon into the conjunctival sac three times daily for 2 days, then twice daily for 5 days Ophthalmic solution: ≥1 year of age: Instill 1-2 drops into the affected eye(s) every 2 hours while awake for 2 days, then every 4 hours while awake for the next 5 days Corneal ulcers:	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3% Otic solution: 0.2%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	first six hours and then every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. Thereafter, instill two drops in the affected eye every four hours for the remainder of treatment (14 days).	Ophthalmic solution: ≥1 year of age: Instill two drops into the affected eye every 15 minutes for the first six hours and then every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. Thereafter, instill two drops in the affected eye every four hours for the remainder of treatment (14 days).	
Ciprofloxacin and dexamethasone	Acute Otitis Externa: Instill 4 drops into affected ear(s) twice daily for 7 days	Acute Otitis Externa: ≥6 months of age: Instill 4 drops into affected ear(s) twice daily for 7 days Acute Otitis Media (Tympanostomy Tubes): ≥6 months of age: Instill 4 drops into affected ear(s) twice daily for 7 days	Otic suspension: 0.3%-0.1%
Ciprofloxacin and hydrocortisone	Acute Otitis Externa: Instill 3 drops into affected ear 2 times a day for 7 days	Acute Otitis Externa: ≥1 year of age: Instill 3 drops into affected ear 2 times a day for 7 days	Otic suspension: 0.2%-1%
Doxycycline	Periodontitis: 20 mg twice daily for up to 9 months	Safety and effectiveness have not been established in pediatric patients.	Oral tablet: 20 mg
Erythromycin base	Superficial Ocular Infections: Apply approximately 1cm to the affected eye(s) up to 6 times daily, depending on the severity of the infection	Superficial Ocular Infections: Apply approximately 1cm to the affected eye(s) up to 6 times daily, depending on the severity of the infection Prophylaxis of Neonatal Gonococcal or Chlamydial Ophthalmia: Apply approximately 1 cm into each lower conjunctival sac	Ophthalmic ointment: 5 mg/G
Gatifloxacin	Bacterial Conjunctivitis: Instill 1 drop into affected eye(s) every 2 hours (up to 8 times daily) for the first 2 days, then four times daily for 5 days	Bacterial Conjunctivitis: Ophthalmic solution (0.3%) ≥1 year of age: Instill 1 drop into affected eye(s) every 2 hours while awake (up to 8 times daily) for the first 2 days. Then, instill 1 drop up to 4 times daily on days 3 through 7. Ophthalmic solution (0.5%) ≥1 year of age: Instill 1 drop	Ophthalmic solution: 0.3% 0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		into affected eye(s) every 2 hours while awake (up to 8 times on day 1). Then, instill 1 drop 2 to 4 times daily on days 2 through 7.	
Gentamicin	Ocular Infections: Ophthalmic ointment: Apply approximately ½ inch to the affected eye(s) 2 to 3 times a day Ophthalmic solution: Instill 1 or 2 drops into the affected eye every 4 hours. In severe infections, dosage may be increased to as much as 2 drops once every hour.	Ocular Infections: Ophthalmic ointment: Apply approximately ½ inch to the affected eye(s) 2 to 3 times a day Ophthalmic solution: Instill 1 or 2 drops into the affected eye every 4 hours. In severe infections, dosage may be increased to as much as 2 drops once every hour.	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%
Gentamicin and prednisolone	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Ophthalmic ointment: Apply ½ inch in the conjunctival sac 1-3 times per day Ophthalmic suspension: Instill 1 drop into affected eye(s) 2-4 times daily; dosing frequency may be increased if necessary up to 1 drop every hour.	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Ophthalmic ointment: Apply ½ inch in the conjunctival sac 1-3 times per day Safety and effectiveness of the ophthalmic solution in pediatric patients have not been established.	Ophthalmic ointment: 0.3%-0.6% Ophthalmic suspension: 0.3%-1%
Levofloxacin	Bacterial Conjunctivitis: Ophthalmic solution (0.5%): Instill 1-2 drops into affected eye(s) every 2 hours while awake (up to 8 times per day) for 2 days, then 1-2 drops every 4 hours while awake (up to 4 times per day) for 5 days Corneal Ulcers: Ophthalmic solution (1.5%): Instill 1-2 drops in the affected eye(s) every 30 minutes to 2 hours while awake and approximately 4 to 6 hours after retiring for 3 days, then 1-2 drops every 1 to 4 hours while awake until therapy is completed	Bacterial Conjunctivitis: Ophthalmic solution (0.5%): ≥1 year of age: Instill 1-2 drops into affected eye(s) every 2 hours while awake (up to 8 times per day) for 2 days, then 1-2 drops every 4 hours while awake (up to 4 times per day) for 5 days Corneal Ulcers: Ophthalmic solution (1.5%): ≥6 years of age: Instill 1-2 drops in the affected eye(s) every 30 minutes to 2 hours while awake and approximately 4 to 6 hours after retiring for 3 days, then 1-2 drops every 1 to 4 hours while awake until therapy is completed	Ophthalmic solution: 0.5% 1.5%
Moxifloxacin	Bacterial Conjunctivitis: Instill 1 drop into affected	Bacterial Conjunctivitis: ≥1 year of age: Instill 1 drop	Ophthalmic solution: 0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	eye(s) three times daily for 7 days	into affected eye(s) three times daily for 7 days	
Mupirocin	Eradication of Nasal Colonization with MRSA: Divide approximately ½ of ointment from single-use tube between nostrils and apply twice daily for 5 days	Eradication of nasal colonization with MRSA: ≥12 years of age: Divide approximately ½ of ointment from single-use tube between nostrils and apply twice daily for 5 days	Nasal ointment: 2%
Neomycin, bacitracin and polymyxin B	Superficial Infections of the External Eye: Apply ointment to affected eye(s) every 3-4 hours for 7 to 10 days, depending on the severity of the infection	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic ointment: 3.5 mg-400
Neomycin, bacitracin, polymyxin B and hydrocortisone	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Apply ointment to the affected eye(s) every 3-4 hours, depending on the severity of the condition	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic ointment: 3.5 mg-10,000 units-1%
Neomycin, colistin, hydrocortisone and thonzonium	Bacterial Infections of the External Auditory Canal: Instill 5 drops into affected ear(s) 3-4 times daily	Bacterial Infections of the External Auditory Canal: ≥1 year of age: Instill 4 drops into affected ear(s) 3-4 times daily	Otic suspension: 3.3-3-10-0.5 mg/ml
Neomycin, polymyxin B and dexamethasone	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Instill 1-2 drops into affected eye(s). In severe disease, drops may be used hourly. In mild disease, drops may be used up to 4 to 6 times per day.	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: ≥2 years of age: Instill 1-2 drops into affected eye(s). In severe disease, drops may be used hourly. In mild disease, drops may be used up to 4 to 6 times per day.	Ophthalmic ointment: 3.5 mg-10,000 units-0.1% Ophthalmic suspension: 0.1%
Neomycin, polymyxin B and gramicidin	Superficial Infections of the External Eye: Instill 1-2 drops into affected eye(s) every 4 hours for 7-10 days. In severe infections, dosage may be increased to as much as 2 drops every hour.	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic solution: 1.75 mg-10,000 units
Neomycin, polymyxin B and hydrocortisone	Bacterial Infections of the External Auditory Canal: Instill 4 drops into affected ear(s) 3-4 times daily Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Instill 1-2 drops into	Bacterial Infections of the External Auditory Canal: ≥2 years of age: Instill 3 drops into affected ear(s) 3-4 times daily	Ophthalmic suspension: 3.5 mg-10,000 units-1% Otic solution: 3.5 mg-10,000 units-1% Otic suspension: 3.5 mg-10,000 units-

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	affected eye(s) 2-4 times per day, or more frequently as required for severe infections		1%
Neomycin, polymyxin B and prednisolone	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Instill 1-2 drops into affected eye(s) every 3-4 hours; acute infections may require every 30 minute instillation initially with frequency of administration reduced as the infection is brought under control To treat the lids: Instill 1-2 drops into affected eye(s) every 3-4 hours	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Instill 1-2 drops into affected eye(s) every 3-4 hours; acute infections may require every 30 minute instillation initially with frequency of administration reduced as the infection is brought under control To treat the lids: Instill 1-2 drops into affected eye(s) every 3-4 hours	Ophthalmic suspension: 0.5%
Ofloxacin	Bacterial Conjunctivitis: Ophthalmic solution: Instill 1-2 drops every 2-4 hours into the affected eye(s) for 2 days, then 1-2 drops 4 times daily for 5 days Bacterial Corneal Ulcer: Ophthalmic solution: Days 1-2: Instill 1-2 drops into the affected eye(s) every 30 minutes while awake. Awaken at ~4 and 6 hours after retiring and instill 1-2 drops. Days 3 through 7-9: Instill 1-2 drops hourly while awake Days 7-9 through treatment completion: Instill 1-2 drops 4 times daily Chronic Suppurative Otitis Media (Perforated Tympanic Membranes): Otic solution: Instill 10 drops into affected ear(s) twice daily for 14 days Otitis Externa: Otic solution: Instill 10 drops into affected ear(s) once daily for 7 days	Acute Otitis Media (Tympanostomy Tubes): ≥1 year of age: Instill 5 drops into affected ear(s) twice daily for 10 days Bacterial Conjunctivitis: Ophthalmic solution: ≥1 year of age: Instill 1-2 drops every 2-4 hours into the affected eye(s) for 2 days, then 1-2 drops 4 times daily for 5 days Bacterial Corneal Ulcer: Ophthalmic solution: ≥1 year of age: Days 1-2: Instill 1-2 drops into the affected eye(s) every 30 minutes while awake. Awaken at ~4 and 6 hours after retiring and instill 1-2 drops. Days 3 through 7-9: Instill 1-2 drops hourly while awake Days 7-9 through treatment completion: Instill 1-2 drops 4 times daily Chronic Suppurative Otitis Media (Perforated Tympanic Membranes): Otic solution: ≥12 years of age: Instill 10	Ophthalmic solution: 0.3% Otic solution: 0.3%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		drops into affected ear(s) twice daily for 14 days Otitis Externa: Otic solution: ≥6 months to 13 years of age: Instill 5 drops into affected ear(s) once daily for 7 days ≥13 years of age: Instill 10 drops into affected ear(s) once daily for 7 days	
Polymyxin B and trimethoprim	Ocular Bacterial Infections: Instill 1 drop in the affected eye(s) every 3 hours for 7 to 10 days	Ocular Bacterial Infections: ≥2 months of age: Instill 1 drop in the affected eye(s) every 3 hours for 7 to 10 days	Ophthalmic solution: 10,000 units-0.1%
Sulfacetamide	Conjunctivitis and other Superficial Ocular Infections: Instill 1-2 drops into the affected eye(s) every 2-3 hours for 7-10 days Trachoma: Instill 1-2 drops into the affected eye(s) every 2 hours	Conjunctivitis and other Superficial Ocular Infections ≥2 months of age: Instill 1-2 drops into the affected eye(s) every 2-3 hours for 7-10 days Trachoma: Instill 1-2 drops into the affected eye(s) every 2 hours	Ophthalmic solution: 10%
Sulfacetamide and prednisolone	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Ophthalmic ointment: Apply ½ inch to affected eye(s) 3-4 times per day and 1-2 times at night Ophthalmic solution: Instill 2 drops into affected eye(s) every 4 hours Ophthalmic suspension: Instill 2 drops into affected eye(s) every 4 hours during the day and at bedtime	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Ophthalmic ointment: ≥6 years of age: Apply ½ inch to affected eye(s) 3-4 times per day and 1-2 times at night Ophthalmic solution: ≥6 years of age: Instill 2 drops into affected eye(s) every 4 hours Ophthalmic suspension: ≥6 years of age: Instill 2 drops into affected eye(s) every 4 hours during the day and at bedtime	Ophthalmic ointment: 10%-0.2% Ophthalmic solution: 10%-0.25% Ophthalmic suspension: 10%-0.2%
Tobramycin	Bacterial Ocular Infections: Ophthalmic solution: Mild to moderate infections: Instill 1-2 drops into the affected eye(s) every 4 hours	Bacterial Ocular Infections: Ophthalmic solution: ≥2 months of age: Mild to moderate infections: Instill 1-2 drops into the affected eye(s) every 4 hours	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Severe infections: Instill 2 drops into the affected eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation Ophthalmic ointment: Mild to moderate infections: Apply ½ inch into the affected eye(s) 2-3 times per day Severe infections: Apply ½ inch into the affected eye(s) every 3-4 hours until improvement, following which treatment should be reduced prior to discontinuation	Severe infections: Instill 2 drops into the affected eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation Ophthalmic ointment: ≥2 months of age: Mild to moderate infections: Apply ½ inch into the affected eye(s) 2-3 times per day Severe infections: Apply ½ inch into the affected eye(s) every 3-4 hours until improvement, following which treatment should be reduced prior to discontinuation	
Tobramycin and dexamethasone	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Ophthalmic ointment: Apply ½ inch into the affected eye(s) 3-4 times per day Ophthalmic suspension (0.3%-0.05%): Instill 1 drops into affected eye(s) every 4-6 hours Ophthalmic suspension (0.3%-0.1%): Instill 1-2 drops into affected eye(s) every 4-6 hours	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Ophthalmic ointment: ≥2 years of age: Apply ½ inch into the affected eye(s) 3-4 times per day Ophthalmic suspension (0.3%-0.05%): ≥2 years of age: Instill 1 drops into affected eye(s) every 4-6 hours Ophthalmic suspension (0.3%-0.1%): ≥2 years of age: Instill 1-2 drops into affected eye(s) every 4-6 hours	Ophthalmic ointment: 0.3%-0.1% Ophthalmic suspension: 0.3%-0.05% 0.3%-0.1%
Tobramycin and loteprednol	Steroid-responsive Inflammatory Conditions and Superficial Ocular Infections: Instill 1-2 drops into the affected eye(s) every 4-6 hours	In a trial to evaluate the safety and efficacy in pediatric patients aged zero to six years with lid inflammation, tobramycin/loteprednol with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. There were no differences in safety assessments between the treatment groups.	Ophthalmic suspension: 0.3%-0.5%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the EENT antibacterials are summarized in Table 15.

Table 15. Comparative Clinical Trials with the EENT Antibacterials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Blepharitis				
John et al.[75] (2008) Azithromycin 1% ophthalmic solution (frequency not available) vs erythromycin ophthalmic ointment (frequency not available)	PRO Patients with chronic mixed anterior blepharitis	N=75 (150 eyes) 8 weeks	Primary: Clinical response	Primary: Sixty-six patients treated with azithromycin ophthalmic solution (132 eyes) showed complete recovery. One patient did not show complete recovery at the completion of the study, but showed an improvement in the blepharitis (Grade 3 to Grade 2) after one month of treatment, and at two months, the blepharitis grade decreased from Grade 2 to Grade 1 and subsequently resolved. The total clinical resolution after 4 weeks was 98.5% with azithromycin and 37.5% with erythromycin. At eight weeks, total clinical resolution was 98.5% for the azithromycin treatment group and 50% for the erythromycin treated group. In the 8 patients treated with topical erythromycin ophthalmic ointment, 5 patients (10 eyes) had unresolved blepharitis with inadequate clinical improvement after 1 month of treatment. Fifty percent (8 of 16 eyes) of patients treated with erythromycin required 8 weeks of treatment as compared to 1.5% (2 of 134 eyes) of patients treated with azithromycin. The average initial blepharitis grade of patients and the average blepharitis grade taken at 4 and 8 week intervals of treatment showed that patients treated with azithromycin had a better clinical response during a shorter treatment duration as compared to patients treated with erythromycin. The results after 4 weeks of treatment was statistically significant in favor of azithromycin (P=0.0237).
Blepharo-keratoconjunctivitis				
Rhee et al.[60] (2007)	RCT, DB, SC Patients with	N=40 (40 eyes)	Primary: Ocular signs and symptoms	Primary: Tobramycin/dexamethasone significantly decreased clinical signs of ocular inflammation, including blepharitis (P=0.017), conjunctivitis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tobramycin 0.3% and dexamethasone 0.1% ophthalmic solution administered twice daily for 3-5 days vs tobramycin 0.3% and loteprednol 0.5% ophthalmic solution administered twice daily for 3-5 days	moderate blepharo-kerato-conjunctivitis in at least 1 eye	3-5 days		(P=0.013), ocular discharge (P=0.025) and total posttreatment symptom scores (P<0.05) compared to tobramycin/loteprednol. Mean keratitis scores did not differ between the treatment groups (P=0.065). Mean total ocular scores for tobramycin/dexamethasone were greater than those for tobramycin/loteprednol at the postvisit evaluation. No patients in either treatment group required additional therapy or a longer course of treatment. No adverse events were reported in any patient in either treatment group.
White et al.[58] (2008) Tobramycin 0.3% and dexamethasone 0.1% ophthalmic solution administered 4 times daily for 3-5 days vs tobramycin 0.3% and loteprednol 0.5% ophthalmic solution administered 4 times daily for 3-5 days	RCT, SB, MC Patients with blepharokerato-conjunctivitis	N=276 15 days	Primary: Change from baseline to day 15 for ocular signs/ symptoms and investigator's global assessment Secondary: Percentage of eyes that were cured or not cured based on the investigator's global assessment; change from baseline to day 7 and day 3 in the signs/symptoms composite score; change from baseline to each visit in the signs	Primary: At day 15, the mean change from baseline in the signs and symptoms composite score for the ITT population was –15.2 for patients treated with tobramycin/loteprednol and –15.6 for tobramycin/dexamethasone treated patients, representing a 78% reduction from baseline for both treatments. There was no significant difference between the treatment groups. At day 3 and day 7, the mean change from baseline in the signs and symptoms composite score for the ITT population was –7.1 and –12.3 for tobramycin/loteprednol treated patients and –7.6 and –13.2 for tobramycin/dexamethasone treated patients. There was no significant difference between the treatment groups. In the per protocol analysis, the mean change from baseline in the signs and symptoms composite score was –7.2 and –7.4 on day 3, –13.0 and –13.2 on day 7, and –15.8 and –15.7 on day 15 for tobramycin/loteprednol treated patients and tobramycin/dexamethasone treated patients, respectively. There was no significant difference between the treatment groups. Secondary: Based on the investigator global assessment, the percentage of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			composite score and symptoms composite score, adverse events	tobramycin/loteprednol and tobramycin/dexamethasone study eyes considered 'cured' was 2.2% and 0.7% at day 3, 20.1% and 16.5% at day 7, and 43.6% and 40.9% at day 15, respectively. There was no significant difference between the treatment groups. The mean change from baseline in the signs composite score for the ITT population for tobramycin/loteprednol and tobramycin/dexamethasone was –3.3and –3.4 at day 3, –6.1 and –6.4 at day 7, and –7.4 and –7.6 at day 15, respectively. There was no significant difference between the treatment groups. The mean change from baseline in the symptoms composite score for tobramycin/loteprednol and tobramycin/dexamethasone was –3.8 and –4.2 at day 3, –6.2 and –6.8 at day 7, and –7.8 and –8.0 at day 15, respectively. There was no significant difference between the treatment groups. There was no significant difference in the mean change from baseline in the blepharitis, conjunctivitis, and keratitis signs composite scores for the ITT population. A total of four patients (2.9%) in each treatment group reported a non-ocular treatment-emergent adverse event (AE), with one subject in the tobramycin/dexamethasone group reporting a serious AE. Most non-ocular AEs were considered mild to moderate in severity, with the exception of hypertension in the tobramycin/dexamethasone group and one instance of headache in the tobramycin/loteprednol group, which were considered severe. A total of four patients (2.9%) in the tobramycin/loteprednol group and nine patients (6.5%) in the tobramycin/dexamethasone group reported treatment-emergent ocular adverse events in the study eye. All treatment-emergent ocular AEs were considered mild to moderate in severity, and most were considered related to the treatment. There were no clinically significant changes in the proportion of eyes with 'none', 'minimal/trace', 'mild', or 'moderate' cataract over the course of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the study. Patients treated with tobramycin/dexamethasone experienced a statistically significant increase in intraocular pressure (IOP) compared to patients treated with tobramycin/loteprednol at day 7 (0.6 vs –0.1, P=0.0339), at day 15 (1.0 vs –0.1, P=0.0091), and overall (2.3 vs 1.6, P=0.0208).
Conjunctivitis				
Abelson et al.[71] (2007) Azithromycin 1% ophthalmic solution administered twice daily on days 1-2, then once daily for 3 days vs tobramycin 0.3% ophthalmic solution administered 4 times daily for 5 days	RCT, DB, AC Patients ≥1 year of age with purulent conjunctival discharge and conjunctival or palpebral injection of no more than 3 days' duration	N=743 5 days	Primary: Clinical resolution of the signs and symptoms of infective bacterial conjunctivitis Secondary: Bacterial eradication	Primary: Treatment with 1% azithromycin achieved clinical resolution in 79.9% of participants; treatment with tobramycin achieved clinical resolution in 78.3% of participants (P=0.783). At day 3, 93.9% of infections that were treated with 1% azithromycin were resolved or improved. There were no statistically significant differences between the treatment groups (P=0.949). Secondary: Treatment with 1% azithromycin achieved bacterial eradication in 88.1% of participants. Treatment with tobramycin achieved bacterial eradication in 94.3% (P=0.073).
Protzko et al.[76] (2007) Azithromycin 1% ophthalmic solution administered twice daily on days 1-2, then once daily for 3 days vs tobramycin 0.3% ophthalmic solution	RCT, DB, AC Patients ≥1 year of age with a diagnosis of bacterial conjunctivitis of less than 3 days' onset	N=743 5 days	Primary: Safety and tolerability	Primary: There was no significant difference in the frequency of adverse events between the two treatment groups. Among all adverse events reported, 3% were deemed treatment-related in the 1% azithromycin group and 5.6% in the tobramycin group. The most frequently observed ocular adverse events in the overall study population were eye irritation (1.9%), conjunctival hyperemia (1.1%), and worsening conjunctivitis (1.1%). The percentage of participants with a clinically significant decline in visual acuity of 3 lines or more at any visit (schedule or unscheduled) was 0.8% in either treatment arm. More than 96% of participants had no change in visual acuity at any visit during the course of treatment. Few patients experienced any worsening of ophthalmic signs. The most

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered 4 times daily for 5 days				frequent treatment-emergent outcome was swelling of the eyelid, which was seen in 3.3% of participants in each treatment group. Other findings in the conjunctiva, lids, and cornea were equally distributed at relatively low frequencies in both treatment groups. The treatments were equally capable of eradicating the predominant Gram-negative and Gram-positive pathogens.
Karpecki et al.[50] (2009) Besifloxacin 0.6% ophthalmic suspension administered 3 times daily for 5 days vs placebo	RCT, DB, MC, PC Patients ≥1 year of age with a diagnosis of bacterial conjunctivitis	N=269 8 days	Primary: Clinical resolution and eradication of bacterial infection Secondary: Clinical resolution of conjunctivitis at visit 2; eradication of baseline bacterial infection at visit 2; and improvements in investigators' ratings of individual signs and symptoms, global change in clinical signs and symptoms, microbiologic outcomes, and clinical outcomes	Primary: Clinical resolution of baseline conjunctivitis at visit 3 was significantly better in patients who received besifloxacin compared with placebo (73.3% vs 43.1%, respectively; P<0.001). Eradication of bacterial infection at visit 3 also was significantly greater in the besifloxacin group compared with placebo (88.3% vs 60.3%; P<0.001). Secondary: There was no difference in clinical resolution of conjunctivitis at visit 2 between the treatment groups (33.3 % vs 17.2%, respectively). Eradication of bacterial infection at visit 2 was significantly greater in the besifloxacin group compared with placebo (90.0% vs 46.6%; P<0.001). Investigators' ratings of individual signs and symptoms were significantly better with besifloxacin compared with placebo at visit 2 (ocular discharge: P=0.008; bulbar conjunctival injection: P=0.014) and visit 3 (P=0.003 and P=0.013, respectively), as were investigators' ratings of global changes in signs and symptoms at visit 2 (P=0.004) and visit 3 (P<0.001). There was no difference between the besifloxacin and placebo groups in the cumulative frequency of patients with ≥1 adverse event (50.4% and 53.0%, respectively). Most adverse events in both treatment groups were of mild or moderate severity (98.7% and 100%), and most were considered unrelated or unlikely to be related to treatment (50% and 53.9%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tepedino et al.[77] (2009) Besifloxacin 0.6% ophthalmic suspension administered every 6 hours for 5 days vs placebo	RCT, DB, PC, MC Patients ≥1 year of age with bacterial conjunctivitis	N=390 9 days	Primary: Clinical resolution and microbiological eradication of baseline infection at visit 2 (day 5) Secondary: Clinical resolution and microbial eradication at visit 3 (day 8 or 9), individual clinical outcomes at follow-up visits, and safety	Primary: Clinical resolution in the baseline-designated study eye was significantly higher in the besifloxacin ophthalmic suspension group than in the vehicle group at visit 2 (45.2% vs 33.0%; P=0.0084). Microbial eradication in the baseline-designated study eye was significantly greater with besifloxacin ophthalmic suspension treatment group than with vehicle at visit 2 (91.5% and 59.7%, respectively; P<0.0001). Secondary: Clinical resolution in the baseline-designated study eye was significantly higher in the besifloxacin ophthalmic suspension group than in the vehicle group at visit 3 (84.4% vs 69.1%; P=0.0011). Microbial eradication in the baseline-designated study eye was significantly greater with besifloxacin ophthalmic suspension treatment group than with vehicle at visit 3 (88.4% and 71.7%, respectively; P<0.0001). The percentage of patients treated with besifloxacin ophthalmic suspension who had resolution of ocular discharge was significantly greater at visit 2 (73.9% vs 57.6%; P=0.0012) and at visit 3 (93.0% vs 79.1%; P=0.0002) compared with those treated with vehicle. Significantly greater percentages of patients treated with besifloxacin ophthalmic suspension had normal bulbar conjunctival injection than those treated with vehicle at both visit 2 (52.3% vs 36.1%; P=0.0007) and visit 3 (84.9% vs 70.7%; P=0.0011). At visit 2, 39.2% and 29.3% of patients randomized to besifloxacin ophthalmic suspension or vehicle, respectively, were considered cured by the investigator (P=0.02). At visit 3, the respective rates were 83.9% and 66.0% (P=0.0002). Treatment with besifloxacin ophthalmic suspension was well tolerated. The majority of ocular adverse events were mild to moderate in severity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A significantly greater percentage of eyes treated with vehicle experienced at least one ocular adverse event compared with those treated with besifloxacin ophthalmic suspension (13.9% vs 9.2%; P=0.0047).
McDonald et al.[106] (2009) Besifloxacin 0.6% ophthalmic suspension administered three times daily for 5 days vs moxifloxacin 0.5% ophthalmic solution administered three times daily for 5 days	RCT, DB, MC, PG Patients ≥1 year of age with bacterial conjunctivitis	N=1,161 8 days	Primary: Clinical resolution and microbial eradication of baseline bacterial infection on day 5 in patients with culture-confirmed bacterial conjunctivitis Secondary: Clinical resolution and microbial eradication on day 8, individual clinical outcomes, microbial and clinical outcomes by bacterial species, and safety	Primary: On day 5 in the modified ITT population (culture confirmed), 58.3% and 59.4% of patients treated with besifloxacin and moxifloxacin had clinical resolution, respectively (P=0.6520). Secondary: On day 8, clinical resolution was seen in 84.5% and 84.0% of patients treated with besifloxacin and moxifloxacin, respectively (P=0.5014). Non-inferiority was also demonstrated in the ITT population for clinical resolution. Besifloxacin was shown to be non-inferior to moxifloxacin with regard to microbial eradication in the modified ITT population. On day 5, microbial eradication occurred in 93.3% of patients receiving besifloxacin and 91.1% of patients receiving moxifloxacin (P=0.1238). On day 8, 87.3% and 84.7% of patients treated with besifloxacin or moxifloxacin, respectively, had microbial eradication (P=0.0608). According to the investigator's global assessment of response, 56.7% and 57.3% of patients treated with besifloxacin and moxifloxacin, respectively, were considered cured on day 5 (P=0.9303). A greater percentage of patients were considered to be cured on day 8: 84.9% of patients receiving besifloxacin compared to 84.7% of patients receiving moxifloxacin (P>0.9999). Similar results were noted in the ITT population for the investigator's global assessment. Clinical resolution and microbial eradication by baseline infection with either gram-positive or gram-negative organisms did not differ significantly from the overall study results. There were no differences between groups in the frequency of eyes that had at least 1 ocular AE (12.0% for besifloxacin and 14.0% for moxifloxacin; P=0.2238). Only eye irritation was statistically different between treatment groups, occurring in 0.3% of eyes treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				besifloxacin and in 1.4% treated with moxifloxacin (P=0.0201).
Comstock et al.[107] (2010) Besifloxacin 0.6% ophthalmic suspension one drop three times daily for 5 days vs moxifloxacin 0.5% ophthalmic solution (1 study) vs placebo (2 studies)	RCT, DB, PG, MC (post hoc analysis) Patients 1-17 years of age with bacterial conjunctivitis	N=815 (3 trials) 8-9 days	Primary: Clinical resolution and microbial eradication	Primary: <u>Placebo-Controlled Studies</u> The percentage of eyes with clinical resolution was significantly higher (P<0.05) in the besifloxacin group than in the placebo group at visit 2 (53.7% vs 41.3%) and visit 3 (88.1% vs 73.0%). Microbial eradication was significantly better (P<0.05) with besifloxacin than with placebo at visit 2 (85.8% vs 56.3%) and visit 3 (82.8% vs 68.3%). <u>Moxifloxacin-Controlled Study</u> High rates of clinical resolution and microbial eradication were seen in both the besifloxacin- and moxifloxacin-treated groups, with rates ranging from 69.9% to 89.8% for clinical resolution and from 66.7% to 94.2% for microbial eradication. There were no significant differences between the two treatments. <u>Adverse Events</u> The overall incidence of adverse events was similar between treatment groups (besifloxacin 11.0%; placebo 14.2%; moxifloxacin 10.6%). Rates of individual ocular adverse events were low in all treatment groups. The most commonly reported ocular adverse events among all besifloxacin-treated eyes, i.e. conjunctivitis (2.9%), bacterial conjunctivitis (2.1 %), and eye pain (1.8%), were consistent with the underlying condition being treated.
Gross et al.[65] (1997) Ciprofloxacin 0.3% ophthalmic solution administered every 2 hours for 2 days, then every 4 hours for 3-7 days vs	RCT, DB, MC Children 0-12 years of age with a diagnosis of acute (<7 days) bacterial conjunctivitis	N=257 7 days	Primary: Microbiological efficacy, physician's impression of condition, and severity of signs/symptoms	Primary: Microbiological eradication on follow-up was observed in 90.1% of the ciprofloxacin group and 84.3% of the tobramycin group (P=0.29). Microbiological reduction was observed in 2.8% of the ciprofloxacin group and 2.9% of the tobramycin group (P=0.29). No significant treatment difference was found for physician's judgment on day 3 (P=0.63) or day 7 (P=0.60). Physicians judged 87.0% of the ciprofloxacin patients and 89.9% of the tobramycin patients clinically cured on day 7.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tobramycin 0.3% ophthalmic solution administered every 2 hours for 2 days, then every 4 hours for 3-7 days				No significant treatment differences were found for the three cardinal signs of bacterial conjunctivitis. The changes for erythema/swelling, discharge/exudate, and bulbar conjunctiva between day 1 and days 3 and 7 were comparable (P>0.05). There were no significant differences between treatment groups for the other signs and symptoms evaluated (P>0.05). Ciprofloxacin and tobramycin were safe and well tolerated. No serious adverse events that were determined to be related to the study medications occurred during the study. No clinically significant differences in visual acuity were observed between the two treatment groups.
Yee et al.[48] (2005) Gatifloxacin 0.3% ophthalmic solution administered twice daily (BID) for 5 days vs gatifloxacin 0.3% ophthalmic solution administered 4 times daily (QID) for 5 days	RCT, SB, MC Patients ≥5 years of age and ≥10 kg with bacterial conjunctivitis, as well as at least +1 (mild) bulbar conjunctival hyperemia and at least +1 (mild) discharge in the same eye (5-point scale)	N=104 5 days	Primary: Clinical cure on day 5 in the intent-to-treat population Secondary: Clinical cure on day 5 in the per protocol (PP) population and safety	Primary: The clinical cure rates in the BID group were 86.5% and 71.2% in the QID group on day 5 (95% CI, –0.03 to 30.80; P=0.096). Secondary: Clinical cure rates at day 5 in the PP population were 95.5% in the BID group and 85.7% in the QID group (95% CI, –7.57 to 27.05; P=0.294). No serious adverse events were reported in either group. The most common adverse event was conjunctivitis. There were no significant differences in the incidence of any adverse event (P>0.999). The overall incidence of adverse events was the same (9.6%) in both the BID and the QID groups (P>0.999).
Hwang et al.[47] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1–2, then every 4 hours on days 3–5.	RCT, DB, MC, PC Patients ≥2 years of age with bacterial conjunctivitis, characterized by purulent ocular discharge and redness in at least	N=117 5 days	Primary: Antimicrobial efficacy, clinical efficacy, resolution of ocular signs and symptoms, safety	Primary: At each visit, approximately twice as many patients in the levofloxacin group as in the placebo group achieved microbial eradication (P<0.001). In the levofloxacin treatment group, 88% of children (2-11 years of age) achieved microbial eradication, compared with 24% of children receiving placebo (P<0.001). Corresponding microbial eradication rates in adults were 90% vs 65%, respectively (P=0.007). There was no significant difference in microbial eradication rates between treatment groups in the subset of adolescents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	one eye			Clinical cure rates were significantly greater in the levofloxacin treatment group than in the placebo group at both the final visit (P=0.020) and at end point (P=0.026). Subgroup analysis by age revealed a significant difference in favor of levofloxacin in children; clinical cure rates were 88% and 53% for children receiving 0.5% levofloxacin and placebo, respectively (P=0.034). Resolution rates for ocular signs and symptoms were higher in the levofloxacin treatment group than in the placebo group at all study visits. Statistically significant differences favoring levofloxacin were observed for resolution of the ocular signs of conjunctival discharge (P=0.027), bulbar conjunctival injection (P=0.029), and palpebral conjunctival injection (P=0.018), and for the ocular symptoms of burning/stinging (P=0.008), itching (P=0.037), and photophobia (P=0.023). There were no significant differences between treatment groups in the incidence of overall adverse events or treatment related events. Most adverse events were mild to moderate in severity. Conjunctivitis, primarily in the non-study eye, was the most common overall adverse event. Treatment related adverse events were predominantly ocular and occurred in 9% and 6% of patients in the levofloxacin and placebo treatment groups, respectively. The most common treatment related adverse events in the levofloxacin treatment group were transient burning (2.4%) and transient decreased vision (2.4%).
Lichtenstein et al.[63] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 and 2, then every 4 hours on days 3 through 5 vs ofloxacin 0.5%	RCT, DB, MC (Subset analysis of 2 trials) Pediatric patients aged 1-16 years old with bacterial conjunctivitis	N=167 10 days	Primary: Microbial eradication, physicians' clinical impression of change from baseline in cardinal signs, change from baseline in ocular signs/symptoms, and safety	Primary: The 5-day dosing regimen with 0.5% levofloxacin ophthalmic solution demonstrated microbial eradication rates in pediatric patients that were greater than those observed with either 0.3% ofloxacin ophthalmic solution or placebo treatment. In children (2 to 11 years of age), this finding was statistically significant in favor of 0.5% levofloxacin compared with 0.3% ofloxacin (87% vs 62%, $P \leq 0.032$) and for 0.5% levofloxacin compared with placebo (88% vs 24%, $P < 0.001$). Treatment with 0.5% levofloxacin ophthalmic solution resulted in a clinical cure rate in pediatric patients (81%) that was similar to that achieved with 0.3% ofloxacin ophthalmic solution (86%). Treatment with 0.5% levofloxacin ophthalmic solution resulted in a clinical cure rate in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ophthalmic solution administered every 2 hours on days 1 and 2, then every 4 hours on days 3 through 5 vs placebo				pediatric patients (89%) that was greater than that attained with placebo treatment (50%). This finding was statistically significant in children (2 to 11 years) with clinical cure rates of 88% with 0.5% levofloxacin versus 53% with placebo ($P \leq 0.034$). Physicians judged 99% of pediatric patients treated with 0.5% levofloxacin to be resolved or improved compared with 94% of patients in the 0.3% ofloxacin treatment group and 85% of patients in the placebo group. Resolution rates from baseline in ocular signs and symptoms were higher in patients who received active drug compared with placebo; resolution rates achieved in the 0.5% levofloxacin and the 0.3% ofloxacin treatment groups were similar. All three treatments were safe and well tolerated. There were no differences between treatment groups in the incidence of adverse events, and no serious adverse events were reported in pediatric patients. Overall, the most common ocular and non-ocular adverse events in the active-treatment groups, regardless of relationship to study medication, were transient burning (2%) and fever (3%).
Schwab et al.[46] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours for the first 2 days, then every 4 hours on days 3 through 5 vs ofloxacin 0.3% ophthalmic solution administered every 2	RCT, DB, AC Patients ≥1 year of age with a clinical diagnosis of bacterial conjunctivitis, characteristic purulent conjunctival discharge, and redness in at least one eye	N=423 6-10 days	Primary: Microbial eradication and clinical cure Secondary: Resolution of ocular signs and symptoms	Primary: A significantly greater proportion of patients receiving 0.5% levofloxacin experienced microbial eradication compared with patients receiving 0.3% ofloxacin at both the final visit (89% vs 80%, P=0.034) and at end point (90% vs 81%, P=0.038). A subgroup analysis by age revealed a difference in microbial eradication rates in children (2–11 years of age) that was statistically significant in favor of 0.5% levofloxacin. Microbial eradication was achieved in 87% of children treated with 0.5% levofloxacin, compared with 61.5% of children treated with 0.3% ofloxacin (P=0.032). There were no significant differences in microbial eradication rates between treatment groups for any of the other age subgroups. Clinical cure rates were similar between the 0.5% levofloxacin and 0.3% ofloxacin treatment groups at all time points assessed. At end point, 76%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours for the first 2 days, then every 4 hours on days 3 through 5				of patients in each treatment group were considered to be clinically cured. Secondary: No significant differences were noted between the treatment groups in resolution of baseline ocular signs at either the final visit or end point. In the 0.5% levofloxacin treatment group, 94% of patients had a resolution of photophobia compared with 73% of patients in the 0.3% ofloxacin treatment group (P=0.006). There were no significant differences between treatment groups in the overall incidence of adverse events. The most frequently reported non-ocular adverse event was headache (3%). The most common ocular adverse events were conjunctivitis in the non-study eye or worsening conjunctivitis in the infected eye (8%), burning (2%), eye pain (2%), and decrease in visual acuity (2%). Treatment-related adverse events were reported by 7.3% and 4.9% of patients receiving treatment with 0.5% levofloxacin and 0.3% ofloxacin, respectively. There were no significant differences between treatment groups in the incidence of treatment related adverse events. All treatment-related non-ocular adverse events were mild in severity. There were no notable differences between treatment groups for best-corrected visual acuity results or ophthalmoscopic findings over the course of the study. At end point, there was a statistically significant difference between treatment groups favoring 0.5% levofloxacin in the proportion of patients experiencing a change from baseline in palpebral conjunctival injection (P=0.009). There were no other significant differences between treatments in mean changes from baseline in biomicroscopy variables groups during the study. Ocular symptoms resolved more often in patients treated with 0.5% levofloxacin compared with patients treated with 0.3% ofloxacin. At end point, 64% of patients in the 0.5% levofloxacin treatment group experienced resolution of burning/stinging compared with 58% of patients in the 0.3% ofloxacin treatment group (P=0.025). Burning/stinging

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				worsened in more patients treated with 0.3% ofloxacin (5%) compared with patients treated with 0.5% levofloxacin (1%). The mean changes from baseline in burning/stinging scores were -0.93 for 0.5% levofloxacin and -0.89 for 0.3% ofloxacin. There were no other notable differences between treatment groups for the safety evaluation of ocular symptoms during the study. When safety variable composite scores were analyzed to determine the number of patients who experienced a worsening from baseline at end point, significantly more patients in the 0.3% ofloxacin treatment group demonstrated a worsening of biomicroscopy results than in the 0.5% levofloxacin treatment group (8.2% vs 2%, P<0.05).
Szaflik et al.[62] (2009) Levofloxacin 0.5% ophthalmic solution administered 3 times daily for 5 days vs levofloxacin 0.5% ophthalmic solution administered every 2 hours for the first 2 days, the every 4 hours for the next 3 days	RCT, OL, SB Patients ≥18 years of age with clinical diagnosis of bacterial conjunctivitis and the presence of three cardinal signs (purulent conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection)	N=120 7 days	Primary: Clinical cure Secondary: Microbiological eradication	Patients' disposition There was no significant difference between the groups in the frequency of patients with a resolved clinical outcome (RR 1.85, 95% CI, 0.50–6.87; P=0.48). Secondary: There was no significant difference between groups in the frequency of patients with a resolved microbiology outcome (RR 1.39, 95% CI, 0.25–7.85; P=1.00). No adverse events were reported in the studied groups. No significant changes in the patients' body temperature, blood pressure, and pulse were observed during the study.
Granet et al.[81] (2008) Moxifloxacin 0.5% ophthalmic solution administered 3 times daily for 7 days	RCT, DB, MC Patients ≥1 month and <18 years of age with bacterial conjunctivitis	N=56 (84 eyes) 7 days	Primary: Clinical cure (defined as complete resolution of all ocular signs and symptoms at the 48-hour	Primary: <u>Culture-positive eyes</u> A significantly greater percentage of culture-positive eyes in the moxifloxacin group achieved clinical cure compared with eyes in the polymyxin/trimethoprim group (81% vs 44%, respectively; P=0.001). The non-responder rate was significantly different at the 48-hour visit between the two treatment groups (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs polymyxin B and trimethoprim ophthalmic solution administered 4 times daily for 7 days (strength not available)			visit), clinical improvement (defined as at least 1 unit lower for each of the three cardinal ocular signs [bulbar conjunctival injection, palpebral conjunctival injection, and conjunctival discharge] at the 48-hour visit), non-responder rates (defined as a patient who did not meet success criteria at the time point evaluated) microbiological success (defined as eradication of all pre-therapy pathogens at the 48-hour visit)	At the 24-hour visit, more eyes treated with moxifloxacin showed a combined clinical cure and improvement (77.8%) than eyes treated with polymyxin/ trimethoprim (59.4%; P=0.1011). <u>Culture-positive and culture-negative eyes</u> An analysis of all eyes showed moxifloxacin to be more effective at 48 hours than polymyxin/trimethoprim (P=0.0001). Non-resolution was significantly different at the 48-hour visit between the two treatment groups (P=0.0001). Of the eyes treated with moxifloxacin, only 2.3% were reported as not responding by 48 hours compared with 19.5% in the polymyxin/ trimethoprim group. A telephone interview on day 7 found that the three main symptoms of bacterial conjunctivitis were absent in both eyes of all patients in the two treatment groups. No treatment-related adverse events were reported in this study.
Lohr et al.[59] (1988) Polymyxin B and trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours while awake for 10 days (TP)	RCT, DB Patients between the ages of 2 months and 22 years of age with bacterial conjunctivitis	N=158 10 days	Primary: Clinical and bacteriological responses	Primary: At the first follow-up visit, clinical cure or improvement was seen in 92%, 95%, and 89% of the patients treated with TP, GS and SS, respectively. At the final follow-up visit, the number of patients clinically cured, improved or failed was not statistically different for the three treatment groups (P>0.1). The overall bacteriologic response was not statistically different for the three treatment groups (83%, 68%, and 72% for TP, GS and SS, respectively; P>0.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gentamicin 0.3% ophthalmic solution administered every 3 hours while awake for 10 days (GS) vs sulfacetamide 10% ophthalmic solution administered every 3 hours while awake for 10 days (SS)				
Gibson et al.[67] (1983) Polymyxin B and trimethoprim 10,000 units-0.1% administered 4 times daily for 7 days (TP) vs Polymyxin B, neomycin and gramicidin 5000 units-1700 units-25 units/ml administered 4 times daily for 7 days (NPG) vs	RCT, DB, MC Patients between 1 and 70 years of age with presumptive bacterial conjunctivitis	N=272 10-14 days	Primary: Signs and symptoms of bacterial conjunctivitis	Primary: There was no significant difference between TP and NPG (P>0.05) in reducing overall initial scores by 100% (cure) and 90% (very good improvement). TP was significantly more effective than chloramphenicol (P=0.03) in reducing overall initial scores by 100% (cure) and 90% (very good improvement.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chloramphenicol 5 mg/ml administered 4 times daily for 7 days				
Genée et al.[72] (1982) Polymyxin B and trimethoprim (strength not provided) administered 6 times daily for 10 days (TP) vs Polymyxin B, neomycin and gramicidin (strength not provided) administered 6 times daily for 10 days (NPG)	RCT, DB Patients between the age of 8 and 80 years with a presumptive diagnosis of bacterial conjunctivitis	N=48 12-15 days	Primary: Microbiological eradication and sign/symptoms of bacterial conjunctivitis	Primary: Bacteria were eradicated in all except 2 of the patients receiving NPG and in all patients receiving TP (in whom bacteria were cultured at baseline). There was no significant difference between TP and NPG in reducing sign and symptom scores during the follow-up period. Photographic differences between the treatment groups did not achieve significance either prior to or following treatment. However, a significant difference (P<0.05) was detected between mean scores of photographs taken before and after treatment with NPG and before and after treatment with TP. No patient reported adverse reactions from either antibacterial preparation.
Eradication of Nasal Colonization with *Staphylococcus aureus*				
Mody et al.[56] (2003) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for up to 2 weeks vs placebo	RCT, DB, PC Residents of Veterans Affairs (VA) and community long-term facilities with *S. aureus* colonization	N=127 6 months	Primary: Nosocomial *S. aureus* infection, nasal carriage of *S. aureus*	Primary: By the end of the treatment period, 93% of patients randomized to receive mupirocin ointment were no longer colonized with *S. aureus*, compared with 15% of patients in the placebo group (P<0.001). One month after study entry, 88% of the patients on mupirocin therapy and 13% of patients in the control group remained free of *S. aureus* colonization (P<0.001). *S. aureus* colonization did not differ between the two study groups at 6 months after study onset (P<0.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no statistically significant difference in the incidence of *S. aureus* infection between patients receiving placebo and those on mupirocin therapy (15% vs 5%; P<0.1).
Wertheim et al.[53] (2004) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs placebo	RCT, DB, PC, MC Adult patients ≥18 years old with *S. aureus* colonization hospitalized in non-surgical departments	N=1,602 2 weeks	Primary: Incidence of nosocomial *S. aureus* infection Secondary: Time to nosocomial *S. aureus* infection, duration of hospitalization, in-hospital mortality	Primary: There was no significant difference in the overall incidence of nosocomial *S. aureus* infections between the mupirocin group (1.9%) and the placebo group (2.4%; 95% CI, –1.5 to1.9). Secondary: The mupirocin and placebo groups did not significantly differ in hospital mortality (3.0% vs 2.8%, respectively; 95% CI,–1.9 to 1.5). The mupirocin and placebo groups did not significantly differ in duration of hospitalization, median of 8 days in both groups. Mupirocin group exhibited a delay in onset of nosocomial *S. aureus* infection from 12 to 25 days, compared to placebo (P>0.2).
Harbarth et al.[51] (1999) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs placebo	RCT, DB, PC Patients ≥16 years old with methicillin resistant *S. aureus* (MRSA) colonization admitted to the hospitals	N=98 30 days	Primary: Incidence of overall MRSA carriage eradication Secondary: Nasal MRSA carriage eradication, MRSA infection rate, development of mupirocin resistance	Primary: There was no statistically significant difference in the overall MRSA eradication rate between the mupirocin group (25%) and the placebo group (18%; RR 1.39; 95% CI, 0.64-2.99; P=0.40). Secondary: The was no statistically significant difference in the nasal MRSA eradication rate between the mupirocin group (44%) and the placebo group (23%) (RR, 0.57; 95% CI, 0.31-1.04; P=0.06). There was no statistically significant difference in the incidence of MRSA infections between the two groups (1.48 vs 2.82 infections per 1,000 patient days, respectively; RR, 0.52; 95% CI, 0.14-2.02; P=0.53). There was an association between low-level mupirocin resistance at study entry and subsequent treatment failure in both study groups (P=0.003). High-level mupirocin resistance was not identified in the study groups.
Perl et al.[61] (2002)	RCT, DB, PC Adult patients	N=3,864 30 days	Primary: Nosocomial *S. aureus* infection,	Primary: The rates of *S. aureus* infection at surgical sites among patients receiving mupirocin ointment (2.3%) and placebo (2.4%) were similar.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for up to 5 days prior to operative procedure vs placebo	undergoing elective, nonemergency, cardiothoracic, general, oncologic, gynecologic, or neurologic surgical procedure, no *S. aureus* infection within 1 month of study onset, no nasal or facial bone disruption		nasal carriage of *S. aureus*	Among patients colonized with *S. aureus*, the risk for developing a nosocomial *S. aureus* infection at any site was significantly lower in patients receiving mupirocin ointment (4%) as compared to the placebo group (7.7%; OR 0.49; 95% CI, 0.25-0.92; P=0.02). Nasal carriage was eliminated in 83.4% of patients randomized to mupirocin ointment as compared to 27.4% of patients receiving placebo therapy (P=0.001). Patients receiving 6 or more doses of mupirocin exhibited a greater rate of *S. aureus* elimination (93.3%) compared to patients getting 3-5 doses of mupirocin ointment (81.3).
van Rijen et al.[70] (2008) Mupirocin calcium nasal ointment vs placebo, no treatment or alternative topical treatment	MA Studies of nasal carriers of *S. aureus* that were using hospital services (either as inpatient or outpatient)	N=3,396 (9 RCT) Variable duration	Primary: *S. aureus* infection rate Secondary: Mortality, adverse events, infection rate caused by other microorganisms than *S. aureus*	Primary: A pooled analysis of trials comparing mupirocin to placebo or no treatment demonstrated a significant reduction in *S. aureus* infection rate associated with mupirocin (RR 0.69, 95% CI 0.47 to 1.00). A planned subgroup analysis of surgical trials demonstrated a significant reduction in the rate of nosocomial *S. aureus* infection rate with mupirocin (RR 0.55, 95% CI 0.34 to 0.89); however, this effect disappeared if the analysis only included surgical site infections caused by *S. aureus* (RR 0.63, 95% CI 0.38 to 1.04). There was no statistically significant difference in rates of *S. aureus* infection between mupirocin-treated patients and neomycin-treated patients. Secondary: There was no significant difference in mortality between treated and untreated carriers (RR 0.91, 95% CI 0.64 to 1.31). No serious adverse events were observed or reported. The infection rate caused by microorganisms other than *S. aureus* was significantly higher in patients treated with mupirocin compared with control patients (RR 1.38, 95% CI 1.118 to 1.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Soto et al.[88] (1999) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs bacitracin ointment, 0.5 cm applied to each nostril TID for 5 days	RCT Healthcare workers colonized with *S. aureus*	N=35 30 days	Primary: Rate of *S. aureus* eradication at 72-96 hours, and 30 days post topical antibiotic administration	Primary: Nasal carriage was eradicated in 44% of patients randomized to bacitracin ointment as compared to 94% of patients receiving mupirocin therapy, as assessed 72-96 hours after administration of the topical antibiotic (P<0.01). Nasal carriage remained eradicated 30 days after study onset in 23% of patients randomized to bacitracin ointment as compared to 80% of patients receiving mupirocin therapy (P<0.01). Mild side effects occurred in 31% of patients in each of the two study groups and included itching, rhinitis, burning, congestion, unpleasant taste, and headache.
Sit et al.[79] (2007) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days every 4 weeks vs no treatment	RCT Patients undergoing continuous ambulatory peritoneal dialysis (CAPD) for at least 6 mo	N=49 1 year	Primary: Eradication of *S aureus* nasal carriage, incidence of peritonitis, exit site infection rates	Primary: At the beginning of the study, the frequency of *S aureus* nasal carriage was similar in the 2 groups (47.9% in the mupirocin group, 50% in the control group). By the end of the study, *S aureus* had been eradicated in 13 of 23 (56.5%) patients in the mupirocin group, and 7 of 24 patients (29%) in the control group remained free of *S aureus*, as detected on nasal smear culture. By study completion, *S aureus* was not cultured from the nasal smear in patients in the mupirocin group, but in the control group, it was cultured at a rate of 20.8%. Peritonitis occurred at rates of 4.3% in the mupirocin group and 4.1% in the control group (P>0.05). In both groups, the same species of *Staphylococcus* was detected upon culture of the nasal smear and dialysate. No exit site infections were reported in either group during the study.
Loeb et al.[89] (2003) Topical regimens	MA Patients with nasal or extra-nasal	N=384 (6 RCT) Up to 6	Primary: MRSA eradication from all sites and incidence of	Primary: <u>Mupirocin vs placebo</u> No significant difference was demonstrated in eradication of MRSA from all sites between the two groups on day 26 (RR 1.39; 95% CI 0.64 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(antibiotic or antiseptic ointments, antiseptic detergents) vs systemic antimicrobial agents vs placebo Results in this table are specific to mupirocin therapy.	MRSA colonization	months	MRSA infections	2.99). No evidence of a difference was demonstrated in eradication of MRSA from nasal sites alone on day 26 (RR 1.77; 95% CI 0.96 to 3.26). Ten MRSA infections occurred in this study, 3 of 46 in the mupirocin group and 7 of 50 in the placebo group (RR 0.47; 95% CI 0.13 to 1.70). <u>Mupirocin vs topical fusidic acid and oral trimethoprim-sulfamethoxazole</u> There was no significant difference in nasal eradication of MRSA between the two groups at 14 days (RR 1.04; 95% CI 0.93 to 1.15), 21 days (RR 1.09; 95% CI 0.97 to 1.23), 28 days (RR 1.01; 95% CI 0.88 to 1.16), and 90 days (RR 1.10; 95% CI 0.64 to 1.89). The investigators report that no evidence of differences in participants with extra-nasal eradication of MRSA was detected between the mupirocin and fusidic acid/trimethoprim-sulfamethoxazole groups at days 14 (83% and 76% eradication) and 28 (45% and 69%, respectively).
van Rijen et al.[68] (2008) Mupirocin nasal ointment administered before surgery vs placebo or no treatment	MA Mupirocin-treated surgical patients with *S. aureus* nasal carriage	N=1,372 (4 RCT) 5 days	Primary: Post-operative *S. aureus* infection rate	Primary: <u>Eradication of carriage</u> Perl et al. showed that nasal carriage of *S. aureus* was eliminated in 83% of patients who received mupirocin, as compared with 27% of patients who received placebo (P<0.05). Kalmeijer et al. demonstrated that eradication occurred in 82% of patients who were initially carrying *S. aureus* in the mupirocin group and in 29% of patients in the placebo group (P<0.05). Konvalinka et al demonstrated that nasal carriage was eliminated in 81.5% of patients receiving mupirocin and 46.5% of patients receiving placebo (P<0.0001). <u>Post-operative *S. aureus* infection rate</u> Perl et al. showed a significant effect of mupirocin on the rate of *S. aureus* infection following surgery. Garcia et al., Kalmeijer et al. and Konvalinka et al. found no significant difference with mupirocin. Analysis of these four studies together showed a significant effect of mupirocin on the *S. aureus* infection rate after surgery in carriers (RR 0.55, 95% CI 0.34 to 0.89).
Ammerlaan et al.[66] (2009)	MA	N=2,114 (23 RCT)	Primary: Eradication of *S.*	Primary: <u>Topical treatments</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Topically applied antibiotics (mupirocin nasal ointment, bacitracin nasal ointment, tea tree oil) vs oral antibiotics (tetracyclines, fusidic acid, macrolides, ciprofloxacin, rifampin, and trimethoprim-sulfamethoxazole) vs topical and oral antibiotic combination therapy	Methicillin-resistant *S. aureus* (MRSA) carriage in healthy individuals, health care workers, hospitalized patients and patients visiting outpatient clinics, and nursing home patients	Variable duration	*aureus* carriage	The efficacy of mupirocin was comparable among studies that included only methicillin-sensitive *S. aureus* (MSSA) carriers or included both MRSA and MSSA carriers, and efficacy was also comparable among studies that included patients or healthy patients. The estimated pooled relative risk of treatment failure with mupirocin was 0.10 (range, 0.07 to 0.14). Mupirocin eradicates MRSA and MSSA carriage 11 times more effectively than no treatment, with successful eradication in 94% of carriers one week after treatment. The effects of mupirocin, compared with placebo, appeared to be effective on carriage at the end of follow-up, with estimated pooled RRs of treatment failure of 0.44 (range, 0.39–0.50). Eradication had been successful in 65% (range, 25%–90%) of carriers after a follow-up period of at least 14 days. Overall, the efficacy of mupirocin was comparable among studies that included only MSSA carriers and studies that included both MRSA and MSSA carriers with pooled RRs at the end of follow-up of 0.52 (range, 0.43–0.64) and 0.40 (range, 0.34–0.48, respectively. Efficacy of mupirocin nasal ointment appeared to be lower in studies that included multiple body sites for evaluation (pooled RRs, 0.60; range, 0.49–0.74) compared with studies that only tested for nasal carriage (pooled RRs, 0.38; range, 0.32–0.45). Bacitracin nasal ointment only eradicated carriage in 29% of MRSA and MSSA carriers at 1 week after treatment (range, 13%–44%), and tea tree oil eliminated MRSA carriage in 44% of carriers at 2 weeks after treatment. Compared with mupirocin, estimated pooled RRs of treatment failure of bacitracin and tea tree oil at the end of treatment was 1.88 (range, 0.57–6.15). <u>Systemic treatments</u> The overall pooled RRs of treatment failure of oral antibiotics, compared with placebo or no treatment, was 0.47 (range, 0.39– 0.57) one week after treatment and 0.54 (range, 0.33–0.87) at the end of the follow-up period. Efficacies at the end of the follow-up period appeared to be comparable in studies that included only MSSA carriers or only MRSA carriers. In contrast with the results of mupirocin studies, the efficacy of systemic treatment, when compared with that of placebo or no treatment, was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				higher in studies that determined eradication by means of nasal cultures only (pooled RRs, 0.74; range, 0.65–0.85), compared with those using cultures samples from multiple body sites (pooled RR, 0.40; range, 0.11 to 0.42). Trimethoprim-sulfamethoxazole in combination with rifampin or nasal fusidic acid eradicated MRSA carriage in 62% patients. Of the macrolides, monotherapy with clarithromycin reduced nasal MSSA carriage in 88% of patients at the end of 8 weeks of follow-up, but it was also associated with a rapid and prolonged increase in macrolide resistance in oropharyngeal nonstaphylococcal flora. Combined treatment with doxycycline, rifampin, mupirocin, and chlorhexidine was associated with MRSA eradication in 74% of patients after 3 months. Rifampin as part of combination therapy with other oral and/or topical antibiotics was associated with eradication of MRSA in 62% of carriers.
Keratitis				
Leibowitz et al.[54] (1991) Ciprofloxacin 0.3% ophthalmic solution administered every 15 minutes for the first 6 hours, then every 30 minutes for the remainder of day 0, then every hour on day 1, then every 4 hours on days 2-14	PRO, OL, MC Patients with a presumed bacterial corneal ulcer	N=210 14 days	Primary: Physician's overall clinical impression of efficacy and clinical resolution of symptoms and signs	Primary: Clinical success was achieved in 91.9% of patients treated with ciprofloxacin. There was no significant difference in the rate of clinical success among patients with mild, moderate and severe bacterial keratitis. Twelve (8.1%) of patients did not respond to ciprofloxacin and were considered treatment failures. There was a progressive resolution of symptoms and sings with ciprofloxacin over the course of the study. No serious adverse events were associated with the use of ciprofloxacin.
Parmar et al.[90] (2006) Gatifloxacin 0.3% (GAT) ophthalmic solution (frequency not defined)	RCT, DB Patients with a diagnosis of bacterial keratitis	N=104 (104 eyes) Duration not specified	Primary: Healing of ulcers and microbiological outcomes	Primary: Of the 41 eyes in the GAT group in which a complete follow-up was possible, 39 eyes (95.1%) exhibited a good response to treatment with complete healing of ulcer as compared to 38/47 eyes (80.9%) in the CIP group (P=0.042). There was one severe ulcer with complete follow-up in each group. The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ciprofloxacin 0.3% (CIP) ophthalmic solution (frequency not defined)				severe ulcer treated with gatifloxacin healed completely, whereas the ulcer treated with ciprofloxacin failed to heal and ultimately required evisceration. The numbers were too small to analyze statistically. There was no significant difference in nonsevere ulcer healing rates with GAT or CIP (95% vs 82.6%, respectively; P=0.08). Among the larger nonsevere ulcers (4 to 6 mm in size), there was no significant difference in the proportion of ulcers healing in the GAT group compared to the CIP group (93.3% 77.4%, respectively; P=0.08). There was no significant difference in the number of smaller nonsevere ulcers (2 to 4 mm in size) that healed in the GAT group compared to the CIP group (100% vs 93.3%, respectively; P=0.40). Considering culture-positive eyes alone, there was no significant difference between GAT and CIP in the number of eyes that healed (92.9% vs 78.8%, respectively; P=0.165). The mean time to healing of ulcer in the GAT group was 13.9 days which did not differ significantly from that in the CIP group (16. 8 days P=0.43). The number of ulcers caused by gram-positive cocci that healed in the GAT group were significantly higher than in the CIP group (P=0.009). When considering individual pathogens, keratitis caused by *Staphylococcus epidermidis* (P=0.043) and by *Streptococcus pneumoniae* (P=0.007) showed a significantly better response to gatifloxacin than to ciprofloxacin. However, gram-positive bacilli and gram-negative organisms showed a similar sensitivity pattern to gatifloxacin and ciprofloxacin, and the percentages of ulcers caused by these organisms that healed in the GAT and CIP groups did not differ significantly.
Prajna et al.[49] (2001) Ofloxacin 0.3% ophthalmic solution administered every 30 minutes on day 1, every hour on days	RCT, DB, PG Patients with a microbiologic diagnosis of bacterial keratitis	N=217 3 weeks	Primary: Time to healing and reepithelialization accompanied by no progression of infiltration	Primary: No significant differences were observed between the ofloxacin and ciprofloxacin treatment groups with regard to ulcer healing (85% versus 77%, respectively; P=0.32). Improvement in healing rates was observed in 6% of ofloxacin-treated patients and 10% of ciprofloxacin-treated patients; although the endpoint of total healing was not achieved in these patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2-4, and every 2 hours on days 5-21 vs ciprofloxacin 0.3% ophthalmic solution administered every 30 minutes on day 1, every hour on days 2-4, and every 2 hours on days 5-21			Secondary: Biomicroscopic findings, microbiologic findings on organism susceptibility and resistance, and patient reported symptoms	The average time to corneal healing was comparable in patients treated with either ofloxacin or ciprofloxacin, 13.7 ± 0.7 days and 14.4 ± 0.8 days, respectively (P=0.80). Within 7 days of treatment initiation, one third of the patients in each treatment group exhibited keratitis healing. By day 26 of treatment, 85% of the ofloxacin-treated patients and 77% of the ciprofloxacin-treated patients exhibited keratitis healing (P=0.32). Secondary: Treatment was discontinued prematurely in six patients in each treatment group because of perforation and in nine patients in each treatment group because of an insufficient therapeutic response. Ulcers that perforated had a significantly larger mean epithelial defect at baseline compared with those that healed (P=0.003). The stromal infiltration was also significantly larger in those patients who experienced perforation compared with those who did not (P=0.002). The etiologic pathogens were similar between those patients who experienced perforation and those who were discontinued from treatment prematurely because of an insufficient therapeutic response. No patient was discontinued from the study because of an adverse event. The most frequently reported events were burning and stinging after instillation of either study medication.
Miscellaneous Ocular Evaluations				
Bloom et al.[82] (1994) Ciprofloxacin 0.3% ophthalmic solution administered every 2 hours on days 0-1, then every 4 hours on days 2-6	RCT, DB, MC Patients with blepharitis or blepharo-conjunctivitis	N=464 7 days	Primary: Efficacy, signs and symptoms, physicians' impression of efficacy	Primary: There were no significant differences in the treatment groups with regards to bacterial eradication, reduction, persistence, or proliferation after 7 days of treatment. The majority of cases of blepharoconjunctivitis organisms were eradicated by treatment and blepharitis was either reduced or eradicated. Over the 7 day period, significant reductions in scores for clinically apparent symptoms and signs were observed in both ciprofloxacin and tobramycin treated groups. There were no significant differences between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tobramycin 0.3% ophthalmic solution administered every 2 hours on days 0-1, then every 4 hours on days 2-6				the two treatments (P<0.05). The physicians' overall impression of efficacy after 7 days of treatment were as follows: improved or cured was noted in 82% of ciprofloxacin-treated patients and 84% of tobramycin-treated patients; unchanged was noted in 18% (ciprofloxacin) and 15% (tobramycin) of patients; worse was noted in one tobramycin treated case (1 %) and no ciprofloxacin-treated cases. There were no significant differences between the two treatments. Ciprofloxacin was discontinued in one patient (0.4%) because of ocular discomfort. Treatment was discontinued in 3.5% of tobramycin-treated patients. Adverse events led to the discontinuation of tobramycin in a significantly higher proportion of cases than of ciprofloxacin (P<0.05).
Foulks et al.[52] (1988) Polymyxin B and trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours for 10 days (TP) vs Polymyxin B, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (TSP)	RCT, DB Patients ≥2 months of age with bacterial ocular surface infections (conjunctivitis, blepharitis or blepharo-conjunctivitis)	N=39 3-6 days	Primary: Clinical improvement, cure rates, microbiological cure rates	Primary: Clinical improvement was similar in both treatment arms (TP=20%; TSP=29%) as were the cure rates (TP=80%; TSP=71%). Microbiologic cure rates were similar among the treatment groups with TP showing a pathogen eradication rate of 87% and TSP an eradication rate of 93%. Differences in clinical and microbiologic responses were not statistically significant. Adverse events were similar between the treatment groups.
Lamberts et al.[55] (1984)	RCT, DB Patients ≥2 months	N=68 17 days	Primary: Cure or clinical improvement,	Primary: <u>Study 1</u> Clinical cure or improvement was observed in 95% of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study 1 Polymyxin B, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (Solution 1) vs neomycin, polymyxin B and gramicidin 2.5 mg-5,000 units-0.025 mg/ml ophthalmic solution administered every 3 hours for 10 days (Solution 2) Study 2 Polymyxin B, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (Solution 1) vs polymyxin B and	of age with conjunctivitis, blepharitis, or blepharo-conjunctivitis		microbiological cure, adverse events	Solution 1 compared to 72% of patients receiving Solution 2. There was no significant difference between the treatment groups. The numbers of microbiologic cures for Solutions 1 and 2 were 82% and 90%, respectively. There was no significant difference between the treatment groups. Of the 35 patients treated with Solution 2, three had adverse reactions and left the study. Of the 33 patients using Solution 1, four had reactions of similar severity. There was no significant difference between the treatment groups. Study 2 Clinical cure or improvement was observed in 82% of patients receiving Solution 1 compared to 77% of patients receiving Solution 3. There was no significant difference between the treatment groups. The numbers of microbiologic cures for Solutions 1 and 3 were 62% and 85%, respectively. There was no significant difference between the treatment groups. Three of the patients using Solution 3 and two of the patients using Solution 1 had adverse reactions. There was no significant difference between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours for 10 days (Solution 3)				
Gwon et al.[84] (1992) Ofloxacin 0.3% ophthalmic solution administered 6 times daily on days 1-2, then 4 times daily on days 3-10 vs gentamicin 0.3% ophthalmic solution administered 6 times daily on days 1-2, then 4 times daily on days 3-10	RCT, DB Patients with suspected external ocular bacterial infection, including conjunctivitis, blepharitis, and blepharo-conjunctivitis	N=191 11 days	Primary: Cure or clinical improvement, signs and symptoms, microbiological improvement, adverse events	Primary: Among patients treated with ofloxacin, 98% were either clinically cured or improved by day 11, compared with 92% of the gentamicin group. There were no significant differences between the groups in any of the improvement rates (P=0.089). The signs and symptoms of infection were judged to be completely resolved in 52% of the ofloxacin group compared with 44% of the gentamicin group at day 11. There were no differences in clinical improvement rates between patients with different baseline diagnoses. Ninety-eight percent of ofloxacin-treated patients with conjunctivitis were found to have improved by day 11, compared with 100% of those with other diagnoses. Among the gentamicin group, 91% and 100% of the patients with conjunctivitis and other diagnoses, respectively, had improved by day 11. None of the differences between the groups showed statistical significance. Microbiological improvement was achieved in 78% of the ofloxacin patients compared with 67% of the gentamicin group. There was no significant difference between the treatment groups. Ofloxacin treatment eradicated the infecting bacteria in 67% of patients at day 11, compared with 58% after gentamicin treatment. Proliferation occurred in 16% of the ofloxacin group vs 27% of gentamicin-treated patients. Among the ofloxacin patients, 78% improved overall (both clinically and microbiologically) compared with 63% of gentamicin patients. The observed differences in clinical, microbiological, or overall improvement rates between the ofloxacin and gentamicin groups were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse reactions were reported by in 3.2% of ofloxacin patients and 7.1% of gentamicin patients.
Laibson et al.[43] (1981) Tobramycin 0.3% ophthalmic solution administered every 2 hours for 2 days, then every 4 hours for 8 days vs gentamicin 0.3% ophthalmic solution administered every 2 hours for 2 days, then every 4 hours for 8 days	RCT, DB Patients with acute superficial ocular inflammations of presumed bacterial origin	N=66 10 days	Primary: Cure or clinical improvement	Primary: The cure and improvement frequencies of the two drugs were similar, 93% for tobramycin and 92% for gentamicin sulfate. The differences in degree of improvement obtained with the two antibiotics were not statistically significant. Four of 28 patients (14.3%) treated with gentamicin sulfate and three of 38 patients (7.9%) treated with tobramycin had adverse reactions. The difference was not statistically significant.
Leibowitz et al.[80] (1981) Tobramycin 0.3% ophthalmic ointment administered 5 times per day on days 1-3, then 3 times per day on days 4-10 vs gentamicin 0.3% ophthalmic ointment administered 5 times per day on days 1-3, then 3 times per day	RCT, DB Patients with superficial bacterial infections	N=93 10 days	Primary: Clinical response, physicians' judgment of clinical response to therapy, antibacterial efficacy, adverse reactions	Primary: Patients in both treatment groups had similar reduction in sign and symptom scores following 10 days of treatment. There was no significant difference between the treatment groups. Based on the physician's judgment of response to therapy, 97% of the tobramycin-treated patients were judged to be cured or better vs 91% of gentamicin-treated patients. There was no significant difference between the treatment groups. Results of the antibacterial efficacy of the two treatments at the lid margin were similar (P>0.05). Among the tobramycin-treated patients, 9.3% experienced adverse reactions compared to 17.6% of patients in the gentamicin treatment group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
on days 4-10				
Cagle et al.[69] (1981) Tobramycin 0.3% ophthalmic solution administered every 2 hours on days 1-2, then 4 times daily on days 3-10 vs tobramycin 0.3% ophthalmic ointment administered 5 times per day on days 1-3, then 3 times per day on days 4-10 vs gentamicin 0.3% ophthalmic solution administered every 2 hours on days 1-2, then 4 times daily on days 3-10 vs gentamicin 0.3% ophthalmic ointment administered 5 times per day on days 1-3, then 3 times per day on days 4-10	RCT, DB, MC Patients with acute bacterial infections with ocular inflammation, including conjunctivitis, blepharitis, blepharo-conjunctivitis and blepharo-kerato-conjunctivitis	N=511 11 days	Primary: Cure or clinical improvement, microbiological improvement, adverse events	Primary: There were no significant differences in efficacy between the gentamicin solution and ointment formulations or between the tobramycin solution and ointment formulations. Tobramycin (combined data for both formulations) was clinically more effective than gentamicin (combined data for both formulations) when evaluating the number of patients that were cured, improved, or unimproved (P=0.038). However, there was no significant difference between tobramycin and gentamicin when the two solutions or ointments were compared separately. Tobramycin solution and ointment eradicated or controlled 91.4% of the invasive bacteria on the conjunctiva compared to 84.2% with gentamicin treatment (P=0.011). There was no significant difference between the treatment groups when evaluating the antibacterial effect of tobramycin and gentamicin on the skin-lash margin (P=0.879). When comparing one ointment vs the other, or the two solutions, the results were not statistically different. Adverse events occurred in 10.6% of patients receiving gentamicin ointment and 3.7% of patients receiving tobramycin ointment (P=0.017).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Otitis Externa				
Drehobl et al.[57] (2008) Ciprofloxacin 0.2% otic solution administered twice daily for 7 days vs neomycin, polymyxin B and hydrocortisone (PNH) 3.5 mg-10,000 units-1% otic solution administered 3 times daily for 7 days	RCT, MC, PG, SB Patients ≥2 years of age with acute diffuse otitis externa of less than 3 weeks' duration	N=630 15-17 days	Primary: Clinical cure of otitis symptoms at the test-of-cure (TOC) visit Secondary: Clinical cure at the end-of-treatment (EOT) visit, percentage of patients with clinical improvement, resolution and/or improvement of otalgia at EOT and TOC visits, adverse events (AEs)	Primary: The percentage of patients with clinical cure at the TOC visit in the clinical intent-to-treat (CITT) population was 81.4% in the ciprofloxacin group and 76.7% in the PNH group. In the clinical per-protocol (CPP) population, clinical cure at the TOC visit was 86.6% in the ciprofloxacin group and 81.1% in the PNH group. There were no significant differences between the treatment groups for either outcome. Secondary: The percentage of patients with clinical cure at the EOT visit was 70.0% in the ciprofloxacin group and 60.5% in the PNH group. There was no significant difference between the treatment groups. Clinical improvement at the EOT visit was reported in 92.7% of patients in ciprofloxacin group compared with 88.5% in the PNH group. At the TOC visit, clinical improvement was similar in the ciprofloxacin group (89.5%) and the PNH group (83.1%). Patients treated with ciprofloxacin and PNH had similar percentages of resolution of otalgia at the EOT and TOC visits. The percentage of patients with clinical microbiologic cure in the EOT visit was 69.5% in the ciprofloxacin group compared with 59.8% in the PNH group. At the TOC visit, the percentage of patients with clinical microbiologic cure increased to 85.1% in the ciprofloxacin group and 78.2% in the PNH group. In both treatment groups, most treatment-emergent AEs were of mild intensity and unrelated to the study medication. The incidence of treatment-related adverse events was 3.8% and 3.6% for ciprofloxacin and PNH, respectively.
Roland et al.[64] (2004) Ciprofloxacin 0.3% and	RCT, SB, MC, PG Patients ≥1 year of age with a clinical diagnosis of mild,	N=468 18 days	Primary: Clinical cure rates at the Day 18 (TOC) visit, microbiologic	Primary: The clinical cure rate at the Day 18 (TOC) visit was significantly higher with CIP/DEX than with N/P/H (90.9% vs 83.9%; P=0.0375). The microbiologic eradication rate in the culture positive patient

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dexamethasone 0.1% (CIP/DEX) otic suspension administered twice daily for 7 days vs neomycin, polymyxin B and hydrocortisone (P/N/H) 3.5 mg-10,000 units-1% otic suspension administered 3 times daily for 7 days	moderate, or severe acute otitis externa (AOE) and intact tympanic membranes		eradication rates at the Day 18 (TOC) visit in patients with positive baseline ear cultures Secondary: Investigators' assessments of clinical responses and of individual signs and symptoms of AOE at each study visit	population was significantly higher with CIP/DEX treatment than with N/P/H treatment at the Day 18 (TOC) visit (94.7% vs 86.0%; P=0.0057). Secondary: The investigators' assessment of the clinical response at each study visit showed CIP/DEX to be significantly more effective than N/P/H in achieving a clinical cure at the Day 3 and Day 18 visits (P=0.0279 and P=0.0321, respectively). The two treatments were equally effective at Day 8. Analyses of the individual signs and symptoms of AOE showed that CIP/DEX treatment was significantly more effective in reducing inflammation than N/P/H treatment at Day 18 (P=0.0268). Other signs and symptoms showed no significant differences between the two treatments at Day 18. Adverse events reported during the study were generally mild-to-moderate and usually resolved with or without treatment. Otic adverse events considered therapy-related included pruritus in 3 patients (1.3%) receiving CIP/DEX and 9 patients (3.8%) receiving N/P/H.
Roland et al.[44] (2007) Ciprofloxacin 0.3% and dexamethasone 0.1% (CIP/DEX) otic suspension administered twice daily for 7 days vs neomycin, polymyxin B and hydrocortisone (NPH) 3.5 mg-	RCT, SB, MC, PG Patients ≥1 year of age with a clinical diagnosis of moderate (constant but tolerable pain) or severe (intense and unrelenting pain) acute otitis externa (AOE) of <4 weeks duration in one or both ears and intact tympanic membranes	N=524 18 days	Primary: Patient assessment of ear pain and analgesic use; investigator-assessed inflammation, edema, tenderness, and discharge on study days 3, 8, and 18	Primary: Patient-reported results revealed a greater percentage of CIP/DEX-treated patients experienced relief of severe pain across time (P=0.0013) and relief of significant pain (moderate or severe) across time (P=0.0456) compared with NPH-treated patients. CIP/DEX-treated patients had significantly less pain than NPH-treated patients on day 2 (P=0.0204) and day 3 (P=0.0364). Evaluation of analgesic use showed no difference between treatment groups in the percentage of patients who used no analgesics, nonnarcotic analgesics, or narcotic analgesics (P>0.05). Significantly less inflammation (P=0.0043) and edema (P=0.0148) were reported with CIP/DEX at the investigator assessment on day 3. No difference in tenderness or discharge was observed between treatments. No differences were noted between treatments in terms of reported incidence or types of adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10,000 units-1% otic suspension administered 3 times daily for 7 days				No patients in either treatment group discontinued the study because of treatment-related adverse events.
Rahman et al.[78] (2007) Ciprofloxacin 0.3% and dexamethasone 0.1% (CD) otic suspension administered twice daily for 7 days vs neomycin, polymyxin B and hydrocortisone (PNH) 3.5 mg-10,000 units-1% otic suspension administered 3 times daily for 7 days	RCT, MC, SB, PG (Pooled analysis of 2 RCT) Patients ≥1 year of age diagnosed with acute otitis externa (AOE)	N=1,072 18 days	Primary: Clinical cure rates and time to cure	Primary: Following 7 days of therapy, 98.1% of CD-treated patients and 95.7% of PNH-treated patients were clinically cured. The mean time to cure was 9.7 days in the CD group compared to 10.3 days in the PNH group. The proportion of patients cured at the day-3, -8, and -18 assessments between the CD and PNH treatment groups were 0.14 and 0.10; 0.75 and 0.72; and 0.98 and 0.97. Treatment-related adverse event rates were similar between the 2 groups and occurred in 3.8% of the patients. The most common adverse events included otic pruritus (2.1%), otic congestion (0.6%), otic debris (0.5%), otic pain (0.3%), superimposed ear infection (0.3%), and erythema (0.1%).
Dohar et al.[103] (2009) Ciprofloxacin 0.3% and dexamethasone 0.1% (CD) otic suspension 3-4 drops administered twice daily for 7 days (CDex)	RCT, SB, MC, PG (pooled analysis[44,78]) Patients >1 year of age with acute otitis externa and intact tympanic membranes who were positive for *P. aeruginosa* and *S. aureus* at	N=789 18 days	Primary: Treatment failure rates, MIC_{50}, and MIC_{90} values for *P. aeruginosa* and *S. aureus*	Primary: Treatment with CDex was associated with a significantly lower treatment failure rate against *P. aeruginosa* (5.1%) than Cort (13.0%; P=0.0044). For *P. aeruginosa*, the MIC_{50} values were lowest for ciprofloxacin (0.13 mg/mL), followed by polymyxin B (0.5 mg/mL), neomycin (8 mg/mL), and polymyxin B: neomycin combined (1.0: 3.2 mg/mL). MIC_{90} values of each antibiotic preparation were 2- to 4-fold higher than MIC_{50} except for polymyxin B, which had identical MIC_{50} and MIC_{90} values. The overall treatment failure rates for *S. aureus* were similar between CDex and Cort (7.3 vs. 6.9%; P=0.9463).

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vs neomycin, polymyxin B and hydrocortisone (PNH) 3.5 mg-10,000 units-1% otic suspension administered 2-3 times daily for 7 days (Cort)	baseline			For *S. aureus*, the ciprofloxacin MIC_{50} was 0.25 mg/mL; the polymyxin B MIC_{50} was 65 mg/mL, the neomycin MIC_{50} was 0.5 mg/mL, and the polymyxin B: neomycin MIC_{50} was 0.25: 0.80 mg/mL. MIC_{90} were 2- to 4-fold higher than MIC_{50} values.
Pistorius et al.[86] (1999) Ciprofloxacin 0.2% (CIP Soln) otic solution or ciprofloxacin 0.2% and hydrocortisone 1% otic suspension (CIP/HC Susp) administered twice daily for 7 days vs neomycin, polymyxin B and hydrocortisone 3.5 mg-10,000 units-1% (PNH) otic suspension administered 3 times daily for 7 days	RCT Patients ≥2 years of age with acute diffuse bacterial otitis externa of less than 3 weeks' duration	N=842 14-28 days posttreatment	Primary: Clinical success (resolution or improvement), bacteriological eradication, and adverse events	Primary: For the per-protocol population, clinical success at the end of therapy was reported in 93% of CRP Soln-treated patients, 90% of CRP/HC Susp-treated patients, and 87% of PNH-treated patients. CRP Soln and CRP/HC Susp were found to be statistically equivalent to PNH therapy (95% CI, -0.0 to 10.5 for CIP Soln vs PNH; 95% CI, -3.3 to 8.0 for CIP/HC Susp vs PNH). For the intent-to-treat population, the clinical response was also statistically equivalent between CIP Soln or CIP/HC Susp and PNH. At the end of therapy, clinical success was reported in 91%, 91%, and 89% of the intent-to-treat patients in the CIP Soln, CIP/HC Susp, and PNH treatment groups, respectively. At the follow-up evaluation, continued resolution was observed in 97% of CIP Soln-, 98% of CIP/HC Susp-, and 95% of PNH-treated patients. Estimated median time-to-end of ear pain in the population valid for efficacy was 4.7 days for the CIP Soln group, 3.8 days for the CIP/HC Susp group, and 4.1 days for the PNH group. Treatment with CIP/HC Susp resulted in a statistically significantly shorter time-to-end of ear pain when compared with CIP Soln (P=0.039). The percentage of patients who took pain medications was similar across the treatment groups. Fifty percent of the CIP Soln patients, 51% of the CIP/HC Susp patients, and 53% of the PNH patients used analgesics for

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				ear pain. The median time to a 50% reduction in ear pain was 2.47 days for CIP Soln, 2.08 days for CIP/HC Susp, and 2.03 days for PNH. Bacteriologic eradication at the end of therapy was 92% in the CIP Soln-, 95% in the CIP/HC Susp-, and 87% in the PNH-treatment groups (95% CI, -2.0 to 12.4 for CIP Soln vs PNH; 95% CI, 0.3 to 13.7 for CIP/HC Susp vs PNH). At least one treatment- emergent event was reported in 23% of CIP Soln-, 25% of CIP/HC Susp-, and 20% of PNH-treated patients. Drug-related events were similar among the three treatment groups (6% CIP Soln, 5% CIP/HC Susp, 5% PNH). Headache, ear pain, and pruritus were the most common events reported in all three treatment groups. Most adverse events were mild to moderate in severity (94% CIP Soln, 94% CIP/HC Susp, 95% PNH) and improved or resolved with sufficient follow- up.
Jones et al.[73] (1997) Ofloxacin 0.3% otic solution administered twice daily for 10 days vs neomycin, polymyxin B and hydrocortisone 3.5 mg-10,000 units-1% (Cortisporin) otic solution administered 4 times daily for 10 days	2 RCT, SB, Adults (≥12 years of age) and children (≥1 and ≤11 years of age) with clinically diagnosed, unilateral or bilateral, stable or exacerbating otitis externa (OE) of 2 weeks' duration or less with purulent or mucopurulent otorrhea	N=314 17-20 days	Primary: Overall clinical efficacy in the clinically evaluable population	Primary: The overall clinical response was cure in 97% of ofloxacin-treated children and 95% of Cortisporin-treated children (P=0.48). The overall clinical response was cure in 82% of ofloxacin-treated adults and 84% of Cortisporin-treated adults (P=0.56). The rates of success in the overall clinical and microbiological responses were also comparable between treatment groups in both populations. Ofloxacin and Cortisporin demonstrated comparable efficacy (≥98%) in eradicating all pathogens. Compliance in adults was comparable in both treatment groups (91% for ofloxacin-treated and 86% for Cortisporin-treated patients). Compliance in children was also comparable in both treatment groups (94% for ofloxacin-treated and 84% for Cortisporin-treated patients). No significant differences between treatment groups were observed with respect to subject or patient or guardian satisfaction at during-therapy and post-therapy visits. There were no significant differences in the incidence of any individual treatment related adverse event between treatment arms. The most

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				common treatment-related adverse events reported in adults were pruritus (6.3% and 3.8% of ofloxacin- and Cortisporin-treated adults, respectively) and application site reactions (3.8% in each treatment group). The most common treatment-related adverse events reported in children were application site disorders in 2.1% of Cortisporin-treated children and no ofloxacin-treated children.
Schwartz et al.[74] (2006) Ofloxacin 0.3% otic suspension administered once daily for 7-10 days vs neomycin, polymyxin B and hydrocortisone 3.5 mg-10,000 units-1% otic suspension administered 4 times daily for 7-10 days	RCT, SB, MC, PG Pediatric patients aged ≥6 months and ≤12 years with stable or exacerbating symptoms of otitis externa (OE) of less than 2 weeks' duration	N=278 17-20 days	Primary: Overall clinical response (defined as cure in the clinically evaluable patients demonstrated by resolution of OE signs and symptoms at the test of cure visit) Secondary: Compliance, signs and symptoms, microbiological eradication, adverse events	Primary: The clinical response at the test of cure visit (7-10 days posttreatment) was cure (sustained clinical cure and subsequent clinical cure) in 96.5% and 95.8% of patients receiving ofloxacin otic solution and neomycin sulfate/polymyxin B sulfate/hydrocortisone otic suspension, respectively (P=0.097). The clinical cure rates in the overall clinical response were equivalent between the treatment groups. The clinical cure rates were 93.8% and 94.7% in the ofloxacin-treated and neomycin sulfate/polymyxin B sulfate/hydrocortisone treated patients, respectively (P=0.763). The clinical response at the end of therapy visit (days 7-9) was cure in 77.9% and 64.2% of patients receiving ofloxacin otic solution and neomycin sulfate/ polymyxin B sulfate/hydrocortisone otic suspension, respectively (P=0.045). Secondary: Mean subject compliance (P<0.001) and mean overall percent patient compliance (P=0.008) were significantly higher in the ofloxacin otic solution group than in the neomycin sulfate/polymyxin B sulfate/hydrocortisone group. The mean overall percent compliance for ofloxacin patients was 93.2% versus 84.1% for patients taking neomycin sulfate/ polymyxin B sulfate/hydrocortisone otic suspension (P<0.001). Mean scores for all signs and symptoms were similar between the two treatment groups. At the end of therapy visit, 69.6% (39/56) of the ofloxacin-treated patients and 67.6% (23/34) of the neomycin sulfate/polymyxin B sulfate/hydrocortisone-treated patients with a microbiological assessment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of eradication were clinically cured. At the test of cure visit, 100.0% (54/54) of the ofloxacin-treated patients and 97.0% (33/34) of the neomycin sulfate/polymyxin B sulfate/ hydrocortisone-treated patients with a microbiological assessment of eradication were clinically cured (combined sustained clinical cure and subsequent clinical cure). Treatment-related adverse events (AEs) were similar in both treatment groups and were mild to moderate in severity. The AEs reported with highest frequency were application-site reaction (22.3% and 20.3% of the ofloxacin-treated and neomycin sulfate/polymyxin B sulfate/hydrocortisone-treated patients, respectively) and earache (7.2% and 4.3% of the ofloxacin treated and neomycin sulfate/polymyxin B sulfate/ hydrocortisone- treated patients, respectively).
Rosenfeld et al.[85] (2006) Various topical antimicrobials with or without corticosteroids	MA Patients with diffuse acute otitis externa (AOE)	N=3,289 (20 RCT) Variable duration	Primary: Clinical cure rates (defined as absence of all presenting signs and symptoms of diffuse AOE) or improvement (defined as partial or complete relief of presenting signs and symptoms), bacteriological cure rates	Primary: <u>Antimicrobial vs Placebo</u> Topical antimicrobial increased absolute clinical cure rates of AOE by 46% and bacteriologic cure rates by 61% compared with placebo. The 95% CI for the clinical cure rate is consistent with a number needed to treat (NNT) of 1.5 to 3.5 patients. Treatment with topical neomycin/colistin/hydrocortisone was associated with less severe edema and itching at day 3 compared to placebo ($P<0.05$), and less severe edema, itching, redness, scaling, and weeping at day 7 ($P<0.05$). <u>Antiseptic vs Antibiotic</u> Topical antiseptic and topical antibiotic achieved comparable clinical cure rates at 7 to 14 days. <u>Quinolone Antibiotic vs Non-quinolone Antibiotic</u> Topical quinolone antibiotic and topical non-quinolone antibiotic achieved comparable clinical cure rates at 3 to 4 days, 7 to 10 days, and 14 to 28 days and comparable clinical improvement rates at 7 to 10 days. Quinolones used in the meta-analyses were ofloxacin, ciprofloxacin alone, or ciprofloxacin combined with dexamethasone or hydrocortisone. The antibiotic comparators used were gentamicin, tobramycin, or polymyxin/hydrocortisone combined with neomycin or oxytetracycline. None of the comparisons were statistically significant.

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				Topical quinolone therapy increased absolute bacteriologic cure rates by 8.0% over non-quinolone antibiotic therapy. This result was highly influenced by one study with a small sample size. When this study is excluded from the meta-analysis, the results were no longer statistically significant (P=0.079). Three studies that compared adverse events showed no overall combined difference between a quinolone preparation and neomycin/polymyxin B/hydrocortisone. The most common events reported were pruritus (about 7%) and site reaction (5%); other events with an incidence less than 2% included rash, discomfort, otalgia, dizziness, vertigo, superinfection, and reduced hearing. <u>Antimicrobial/steroid vs Antimicrobial Alone</u> Topical antimicrobial/steroid and topic antimicrobial alone achieved comparable clinical and bacteriologic cure rates at 7 days. Antimicrobial/steroid combinations used in the meta-analyses were ciprofloxacin/hydrocortisone, ciprofloxacin/ dexamethasone, and acetic acid/triamcinolone. The antibiotic comparator in all studies was the same antimicrobial without the steroid. <u>Steroid/antibiotic vs Steroid Alone</u> Topical steroid alone increased absolute clinical cure rates by 20% at 7 to 11 days compared with topical steroid/antibiotic combination therapy. Steroids used in the meta-analyses were betamethasone and hydrocortisone butyrate. The antibiotic/steroid comparator was oxytetracycline/polymyxin B/hydrocortisone in both studies. Although the overall effect is statistically significant, the 95% CI is broad and the lower limit approaches zero (0.03). Similarly, the 95% CI for the NNT (5 to 33 patients) cannot exclude a trivial effect.
Otitis Media				
Miro et al.[45] (2000) Ciprofloxacin 0.2% otic solution (CIP) administered twice	RCT, OL, MC Patients 14-71 years of age with chronic suppurative otitis	N=232 1 month following the end of therapy	Primary: Clinical response at visit 2 Secondary: Clinical response	Primary: In the per protocol population, 91% of patients in the CIP group and 87% of patients in the PNH group were cured at visit 2 (90% CI, -8.86 to 4.8; P=NS). In the evaluable patients and the randomized patients, the percentages of

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daily for 10 days vs neomycin, polymyxin B and hydrocortisone 3.5 mg-10,000 units-1% otic suspension (PNH) administered 4 times daily for 10 days	media (defined as serous, mucous, mucopurulent, or purulent otorrhea), a history of persistent tympanic perforation or the presence of a tympanostomy tube along with the current episode lasting for at least 6 weeks, and bacteriologic confirmation of ear infection		at visit 3 and bacteriologic outcome at visits 2 and 3	patients classified as cured at visit 2 were 90% and 87%, respectively in the CIP group and 81% and 76%, respectively in the PNH group (P=NS). Secondary: At visit 3 (1 month after the end of treatment), 78% of patients in both the CIP and PNH groups had sustained cure and 5% of patients (4% in the CIP group and 6% in the PNH group) showed a relapse of otorrhea. The rate of bacterial eradication was 79% in the CIP group and 76% in the PNH group. The most frequently reported adverse events were pruritus, stinging, earache, passage of the medication into the mouth, vertigo, and cephalea.
Dohar et al.[101] (2006) Ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension 4 drops twice daily for 7 days (CIP/DEX) vs amoxicillin-clavulanic acid 600/42.9 mg every 12 hours for 10 days (AMOX/CLAV)	RCT, SB, PG, MC Children 6 months to 12 years of age with acute otitis media with otorrhea through tympanostomy tubes of ≤3 weeks' duration and visible otorrhea	N=80 18 days	Primary: Time to cessation of otorrhea and clinical cure at test-of-cure (TOC) Secondary: Microbiologic response	Primary: The median time to cessation of otorrhea for CIP/DEX was 4.0 days (ITT and MITT) compared with 7.0 days (ITT) and 9.5 days (MITT) for AMOX/CLAV (ITT, P=0.006; MITT, P=0.0011). Clinical cure at TOC occurred in 84.6% and 80.7% of patients receiving CIP/DEX (ITT and MITT, respectively) compared to 58.5% and 55.2% of patients receiving AMOX/CLAV (ITT and MITT, respectively; P=0.0100 and P=0.0340, respectively). Secondary: The difference in the microbiologic response between the 2 treatment groups in the modified per-protocol data set was not statistically significant (83% vs 63%).
Roland et al.[102] (2003)	RCT, SB, MC, PG	N=201	Primary: Time to	Primary: The mean time to cessation of otorrhea in the culture-positive population

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Ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension 3 drops administered twice daily for 7 days vs ciprofloxacin 0.3% ophthalmic solution 3 drops administered twice daily for 7 days	Children 6 months to 12 years of age with acute otitis media with tympanostomy tubes (AOMT) and otorrhea for ≤3 weeks' duration	17 days	cessation of otorrhea Secondary: Physicians' assessment of the clinical response, reduction of granulation tissue, antimicrobial response	was 4.22 days in patients receiving ciprofloxacin/dexamethasone compared to 5.31 days in those receiving ciprofloxacin alone (P=0.004). Secondary: Patients receiving ciprofloxacin/dexamethasone showed significantly improved clinical responses at the day 3 (P<0.0001) and day 8 (P<0.0499) visits in comparison with those receiving ciprofloxacin alone. There were no statistically significant differences in reduction of granulation tissue between the two treatment groups at any visit. There were no significant differences between the two treatments in continued tympanostomy tube patency (97% in both groups). Of the 75 clinically and microbiologically evaluable patients in the ciprofloxacin/dexamethasone-treated group, 68 patients were microbiological successes, with all pretherapy pathogens eradicated. There were 7 microbiological failures in this treatment group, giving an overall ciprofloxacin/dexamethasone success rate of 90.7%. Of the 64 evaluable patients in the ciprofloxacin-treated group, 51 patients were microbiological successes, with all pretherapy pathogens eradicated. There were 14 microbiological failures in this treatment group, giving an overall ciprofloxacin success rate of 79.7%. There was no significant difference between the treatment groups (P=0.0660).
Roland et al.[83] (2004) Ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension administered twice daily for 7 days vs	RCT, SB, PG Children who were aged 6 months to 12 years and had patent tympanostomy tubes and a clinical diagnosis of uncomplicated acute otitis media (AOM) with otorrhea of less	N=599 21 days	Primary: Clinical response to therapy at the test-of-cure (TOC) visit (21 days), microbiological response, and treatment failure rate Secondary: Time to cessation of otorrhea, and	Primary: Ciprofloxacin/dexamethasone treatment was more effective than ofloxacin treatment for the primary efficacy variable of clinical cure at the TOC visit (90% vs 78%, respectively; P=0.0025). Microbiologic eradication was greater with ciprofloxacin/dexamethasone than ofloxacin at the TOC visit (92% and 82%, respectively; P=0.0061). There were significantly fewer treatment failures in patients who were treated with ciprofloxacin/dexamethasone (4%) compared with ofloxacin (14%; P=0.0017). Secondary:

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ofloxacin 0.3% otic solution administered twice daily for 10 days	than 3 weeks' duration in one or both ears		physicians' assessment of clinical response at each visit	There was a significant difference in the median time to cessation of otorrhea with ciprofloxacin/dexamethasone (4 days) compared to ofloxacin (6 days; P=0.0209). The physicians' assessment of clinical response at each visit showed significantly greater cure rates with ciprofloxacin/dexamethasone at day 3 (P=0.0001), day 11 (P=0.0001), and day 18 (P=0.0023). The adverse-event profiles of ciprofloxacin/dexamethasone and ofloxacin are similar. No serious treatment-related adverse events were reported during the study. Adverse events were generally mild to moderate, usually resolved with or without treatment, and generally did not interrupt patient continuation in the study. Similar types of adverse events were noted in pediatric patients who were treated in both treatment groups.
Goldblatt et al.[104] (1998) Ofloxacin 0.3% otic solution twice daily for 10 days vs amoxicillin-clavulanic acid oral suspension 40 mg/kg/day (AUG)	RCT, MC, PG, SB Patients 1–12 years of age with tympanostomy tubes and acute purulent otorrhea of presumed bacterial origin for <3 weeks	N=474 10 days	Primary: Overall clinical response (cure or failure, defined as the absence or presence of otorrhea), microbiologic outcomes, safety	Primary: There was no significant difference in the overall clinical cure rates among patients receiving ofloxacin (76%) compared to patients receiving AUG (69%; P=0.169). Within the microbiologically evaluable population, a significantly higher percentage of ofloxacin-treated patients (96%) had an overall microbiologic response than did AUG-treated patients (67%; P<0.001). Pathogen persistence occurred in one ofloxacin-treated patient (1%) and 26 AUG-treated patients (28%). There was recurrence in two ofloxacin-treated patients (2%) and four AUG treated patients (4%). Reinfection was noted in only one subject, in the AUG treatment arm (1%). There were significantly higher eradication rates in the ofloxacin-treated group than in the AUG-treated group for *S. aureus* and for *P. aeruginosa*. Equivalent eradication rates occurred in the two treatment groups for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Overall clinical:microbiologic success (both clinical cure and microbiologic eradication) was 77% (64:83) for the ofloxacin-treated

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				patients and 67% (62:93) for the AUG-treated group. There was no significant difference among the treatment groups. A significantly lower percentage of adverse events occurred in ofloxacin-treated patients (42%) than in AUG-treated patients (52%; P=0.043). The most commonly reported adverse events were rhinitis, fever, diarrhea, coughing and upper respiratory tract infection. Most of these were mild or moderate in severity. A significantly lower percentage of ofloxacin-treated patients (6%) experienced adverse events that were considered possibly or probably related to study medication than AUG-treated patients (31%; P<0.001). A significantly higher percentage of AUG-treated patients than of ofloxacin-treated patients experienced treatment-related diarrhea (27% vs. 1%; P<0.001), treatment-related rash (5% vs. 1%; P=0.022), or treatment-related moniliasis (3% vs. 0%; P=0.015).
Periodontitis				
Caton et al.[42] (2000) Doxycycline hyclate (SDD) 20 mg BID for 9 months vs placebo At the baseline visit, scaling and root planing (SRP) was performed on the qualifying quadrants until the tooth and root surfaces were free from deposits as determined by visual or tactile examination.	RCT, DB, PC Patients aged 30 to 75 years with evidence of periodontitis (at least 2 tooth sites within each of 2 qualifying quadrants with probing depth and clinical attachment level between 5 and 9 mm, inclusive, that bled on probing)	N=190 9 months	Primary: Change in clinical attachment level (CAL) and probing depth (PD), microbial outcomes	Primary: In tooth sites with mild-to-moderate disease, improvements in attachment from baseline were demonstrated in both groups at all post-baseline time points. The per-patient attachment gains were significantly greater with adjunctive SDD at months 3, 6, and 9 than with adjunctive placebo (P<0.05). After 9 months of treatment, the mean attachment gains were 1.03 mm and 0.86 mm for the SDD and the placebo groups, respectively (P<0.05). In tooth sites with severe disease (baseline PD ≥7 mm), improvements in attachment were demonstrated for both treatment groups at all time points. The per-patient attachment gains were significantly greater with SDD than placebo (P<0.05). In tooth sites with mild-to-moderate disease, reductions in PD from baseline were demonstrated for both treatment groups. The per-patient reductions in PD were significantly greater for the SDD group at every post-baseline time point than for placebo (P<0.005). In tooth sites with severe disease (baseline PD ≥7 mm), treatment with SDD significantly reduced PD compared to treatment with placebo at all time points (P<0.01). Treatment with SDD also significantly reduced PD

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				in tooth sites with no disease compared to placebo (P<0.01). Small (<6%) but significant differences in the proportions of spirochetes present at months 3, 6, and 9 of the treatment period were demonstrated between the SDD and placebo groups (P<0.05), with lower proportions of small, intermediate, and large spirochetes present in the SDD group than in the placebo group. There were no significant differences between the treatment groups in the proportions of other cellular morphotypes. There were no significant differences between treatment groups in total cultivable anaerobic flora or periodontal pathogens.
Caton et al.[40] (2001) Doxycycline hyclate (SDD) 20 mg BID for 9 months vs placebo At the baseline visit, scaling and root planing (SRP) was performed on the qualifying quadrants until the tooth and root surfaces were free from deposits as determined by visual or tactile examination.	RCT, DB, PC Patients aged 30 to 75 years with evidence of periodontitis (at least 2 tooth sites within each of 2 qualifying quadrants with probing depth and clinical attachment level between 5 and 9 mm, inclusive, that bled on probing)	N=151 12 months	Primary: Probing depth (PD), clinical attachment level (CAL), adverse events, microbial outcomes	Primary: During active treatment (months 3, 6, and 9), per-patient reductions in PD from baseline were significantly greater for the SDD group than for the placebo group (P<0.05). The incremental reductions in PD demonstrated in the SDD group over 9 months of active treatment were maintained through 3 additional months of no treatment (month 12). For tooth sites with mild to- moderate disease, reductions in PD from baseline were significantly greater for the SDD group than for the placebo group at months 3 and 9 of active treatment, and at the end of the no-treatment follow-up (month 12; P<0.05). Statistically significant treatment differences favoring SDD over placebo were demonstrated between the treatment groups at months 3 and 6 of active treatment (P<0.05). Improvements in CAL demonstrated in the SDD group during active treatment were maintained 3 months posttreatment (month 12); however, this difference was not statistically significant. During the 3-month follow-up, the most frequent adverse events reported by more than one patient in a treatment group were headache, backache, toothache, sinus congestion and periodontal abscess. The incidence of adverse events was similar between the treatment groups. No deaths, serious adverse events, or discontinuations owing to adverse events were reported in either treatment group. Examination of microbial samples by darkfield microscopy revealed no

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				differences in the proportions of selected bacterial morphotypes between the treatment groups in samples taken from the SRP quadrants at month 9 (end of active treatment) and month 12 (end of no-treatment followup). No significant differences were demonstrated between the SDD group and the placebo group in the posttreatment composition of the normal flora (P>0.05). No differences were detected in the recovery of either periodontal pathogens (P>0.05) or opportunistic pathogens (P>0.05).
Deo et al.[99] (2010) Doxycycline 20 mg twice daily vs placebo All patients underwent scaling and root planing (SRP) prior to receiving study treatment.	RCT, PC, PG Patients with periodontitis and type 2 diabetes mellitus	N=20 6 months	Primary: Probing pocket depth (PPD), clinical attachment level (CAL), and gingival recession (GR)	Primary: The mean PPD reduction was 3.06 mm with doxycycline and 2.54 mm with placebo (P<0.05). The mean CAL gain was 2.25 mm with doxycycline and 1.58 mm with placebo (P<0.05). The mean increase in gingival recession was 0.80 mm in the doxycycline group and 0.93 mm in the placebo group (P<0.05).
Gapski et al.[105] (2010) Doxycycline 20 mg BID vs placebo Patients received full mouth scaling and root planing (SRP) within 90 days	RCT, MC, PC, DB Patients with chronic severe periodontitis with at least three teeth in the same sextant demonstrating both PD and CAL ≥5 to ≤12 mm and bleeding on probing (BOP) with at least 10 teeth in the	N=70 12 months	Primary: Clinical attachment levels (CAL), probing depth (PD), bleeding on probing (BOP), gingival crevicular fluid bone marker assessment	Primary: <u>Pooled Surgical Sites</u> Both placebo and doxycycline groups demonstrated a significant reduction in PD compared to baseline; however, there were no significant differences between the groups. Surgical therapy resulted in mean CAL gains in both groups (P<0.05). Doxycycline-treated patients demonstrated a significant reduction in GCF ICTP levels compared with placebo immediately after the surgery (2 months, P=0.03). <u>Moderate Sites (Baseline PD 5–6 mm)</u> There were significant reductions in PD and gains in CAL compared with baseline for the doxycycline and placebo groups. The doxycycline group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
before randomization. They also received access flap surgery in a minimum of one sextant.	functional dentition			demonstrated a significant decrease in the expression of GCF ICTP levels compared with placebo immediately after the surgery (2 months, P=0.001). There was a significant reduction in percentage of BOP sites at 3 months between doxycycline and placebo (P=0.02). Both doxycycline and placebo showed comparable levels in percentage of sites BOP after the patients discontinued drug therapy (P>0.05). <u>Deep Sites (Baseline PD ≥7 mm)</u> Greater reductions in PD were noted for both doxycycline and placebo. Doxycycline resulted in greater reductions in PD compared with controls at 3 months (P=0.004). Doxycycline-treated patients demonstrated a significant increase in CAL compared with placebo during the drug administration (3 months, P=0.02; 6 months, P=0.005).
Preshaw et al.[41] (2004) Doxycycline hyclate (SDD) 20 mg BID with scaling and root planing (SRP) vs placebo with scaling and root planing (SRP)	DB, MC, RCT Patients with moderate to severe chronic periodontitis	N=209 9 months	Primary: Changes in clinical attachment level (CAL) and probing depth (PD) from baseline, and the total number of sites with attachment gains and probing depth reductions ≥2 mm and ≥3 mm from baseline	Primary: Improvements in CAL and PD were greater following SRP with adjunctive SDD than SRP with placebo, achieving statistical significance in all baseline disease categories at month 9 (P<0.05). At month 9, 42.3% of sites in the SDD group demonstrated CAL gain ≥2 mm compared to 32.0% of sites in the placebo group (P<0.01). CAL gain ±3 mm was seen in 15.4% of sites in the SDD group compared to 10.6% of sites in the placebo group (P<0.05). When considering the same thresholds of change in PD, 42.9% of sites in the SDD group compared to 31.1% of sites in the placebo group demonstrated PD reduction ±2 mm (P<0.01), and 15.4% of sites in the SDD group compared to 9.1% of sites in the placebo group demonstrated PD reduction ±3 mm (P<0.01).
Haffajee et al.[39] (2007) Doxycycline 20 mg twice daily for 12 weeks vs	RCT, SB Patients with chronic periodontitis	N=92 1 year	Primary: Clinical parameters	Primary: There were statistically significant improvements over time for most parameters, irrespective of treatment group, with the greatest improvements between baseline and 3 months post-therapy. All groups showed clinical improvements at 12 months, with patients receiving adjunctive agents showing a somewhat better response. All treatment groups showed statistically significant reductions in mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
azithromycin 500 mg once daily for 3 days (AZ) vs metronidazole 250 mg three times daily for 14 days (MET) vs scaling and root planing (SRP)				pocket depth (PD) reduction and attachment-level (AL) gain over time. Patients receiving either systemically administered AZ or MET showed greater mean PD reduction post-therapy compared with patients in the doxycycline- and SRP-only groups. The differences among treatment groups were statistically significant at 6 and 12 months. After adjusting for multiple comparisons, MET was significantly different from SDD at 12 months (P<0.05) and the MET group was also significantly different from the SRP group at 6 months (P<0.05) and 12 months (P<0.01). The greatest improvement in mean AL post-therapy at initially deeper sites was observed for the MET group, and the antibiotic groups showed greater improvement than the doxycycline and SRP groups. Differences among treatment groups were significant at 12 months and approached significance at 6 months. MET was significantly different from SRP (P<0.05) at 12 months after adjusting for multiple comparisons. Patients showed attachment loss at 12 months ranging from 15% to 39% of patients in the doxycycline and SRP only groups respectively.

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective cohort study, RR=relative risk, SB=single-blind, SC=single center

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 16. Relative Cost of the EENT Antibacterials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Azithromycin	solution†	AzaSite®	$$$	N/A
Bacitracin	ointment†	N/A	N/A	$$$
Bacitracin and polymyxin B	ointment†	N/A	N/A	$
Besifloxacin	suspension†	Besivance®	$$$	N/A
Ciprofloxacin	ointment†, solution†§	Cetraxal®, Ciloxan®*	$$-$$$	$
Ciprofloxacin and dexamethasone	suspension§	Ciprodex®	$$$$	N/A
Ciprofloxacin and hydrocortisone	suspension§	Cipro HC®	$$$$	N/A
Doxycycline	oral tablet	Periostat®*	$$$	$$
Erythromycin base	ointment†	Ilotycin®*	$	$
Gatifloxacin	solution†	Zymar®, Zymaxid®	$$$	N/A
Gentamicin	ointment†, solution†	Garamycin®*‡	$$	$
Gentamicin and prednisolone	ointment†, suspension†	Pred-G®	$-$$	N/A
Levofloxacin	solution†	Iquix®, Quixin®*	$$$	$$$
Moxifloxacin	solution†	Vigamox®	$$$	N/A
Mupirocin	nasal ointment	Bactroban Nasal®	$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Neomycin, bacitracin and polymyxin B	ointment†	N/A	N/A	$$
Neomycin, bacitracin, polymyxin B and hydrocortisone	ointment†	N/A	N/A	$
Neomycin, colistin, hydrocortisone and thonzonium	suspension§	Coly-Mycin S®, Cortisporin-TC®	$$$	N/A
Neomycin, polymyxin B and dexamethasone	ointment†, suspension†	Maxitrol®*	$$$	$
Neomycin, polymyxin B and gramicidin	solution†	Neosporin®*	$	$
Neomycin, polymyxin B and hydrocortisone	solution§, suspension†§	Cortisporin®*	$	$-$$$
Neomycin, polymyxin B and prednisolone	suspension†	Poly-Pred®	$$	N/A
Ofloxacin	solution†§	Ocuflox®*	$	$
Polymyxin B and trimethoprim	solution†	Polytrim®*	$	$
Sulfacetamide	solution†	Bleph-10®*	$	$
Sulfacetamide and prednisolone	ointment†, solution†*, suspension†	Blephamide®, Blephamide S.O.P.®	$$$	$
Tobramycin	ointment†, solution†	Tobrex®*	$-$$$	$
Tobramycin and dexamethasone	ointment†, suspension†	TobraDex®*, TobraDex ST®	$$$-$$$$	$$$
Tobramycin and loteprednol	suspension†	Zylet®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
‡Product was added to Medicaid's drug file after the meeting's drug list was approved.
†Ophthalmic formulation
§Otic formulation
N/A=Not available

X. Conclusions

The eye, ear, nose, and throat (EENT) antibacterials effectively treat a variety of infections. There is at least one single entity ophthalmic aminoglycoside, macrolide, quinolone, sulfonamide and miscellaneous antibacterial available in a generic formulation. For the single entity otic products, ofloxacin is also available generically. There are several ophthalmic and otic antibacterial/corticosteroid combination products that are available in a generic formulation.

For the treatment of blepharitis, guidelines recommend the initial use of bacitracin or erythromycin ointment.[24] Corticosteroids may also be used to control inflammation and maintain patient comfort; however, adverse effects (increased intraocular pressure and cataracts) should be considered.[24] Bacterial conjunctivitis is often a self-limiting condition and resolves spontaneously without specific treatment.[25,32] The use of topical antibacterial therapy may lead to earlier clinical and microbiological remission. The choice of antibiotic is usually empirical and guidelines do not give preference to one ophthalmic antibacterial agent over another.[25,96] However, soft contact lens wearers with conjunctivitis have a high incidence of infection with *Pseudomonas* and quinolones are the preferred treatment option in this patient population.[32] For the empiric treatment of bacterial keratitis, topical broad-spectrum antibacterials are used initially.[26] Guidelines recommend the use of a quinolone if the organism is unknown or if multiple types of organisms are identified.[26] Numerous clinical trials have demonstrated similar clinical cure rates with the ophthalmic antibacterial agents.[43,46,49,58-59,63,65,67,69,71-72,76,80-82,84,106-107]

For the treatment of acute otitis externa, guidelines recommend the use of a topical antibacterial agent; however, they do not give preference to agent over another as there is minimal or no difference in clinical or bacteriologic cure rates among the agents.[27] Topical preparations that contain alcohol or have a low pH, as well as aminoglycosides, should be avoided in patients with tympanostomy tubes or perforated tympanic membranes due to the risk of ototoxicity.[27,95] Guidelines recommend the use of an oral antibacterial agent for the treatment of acute otitis media.[27-28,98,108-110] Topical antibacterials may be used as an alternative treatment option in patients with perforated tympanic membranes, tympanostomy tubes, or chronic suppurative otitis media.[35-36] Several clinical trials have demonstrated similar cure rates with the otic antibacterials.[45,57,73-74,78,85-86] Relatively few studies have demonstrated greater efficacy with one agent over another.[64,83,102]

Mupirocin is indicated for the eradication of nasal colonization with MRSA in adult patients and health care workers during institutional outbreaks.[16] Several clinical trials have demonstrated that mupirocin eradicates *S. aureus* and MRSA nasal colonization in a variety of patient populations immediately following therapy.[56,61,66,68,70,79,88] However, these studies do not consistently document a long-term benefit on nasal decolonization, nor do they consistently show a reduction in the incidence of *S. aureus* or MRSA infections.[51,53,56,68,79,89] There is insufficient evidence that mupirocin prevents autoinfection of patients from their own nasal colonization with *S. aureus*.[16] The majority of the published trials using mupirocin were compared to placebo or no treatment.[51,53,56,61,66,68,70,79,89] Mupirocin nasal ointment is not available in a generic formulation.

Doxycycline is approved for use as an adjunct to scaling and root planing (SRP) to promote attachment level gain and reduce pocket depth in adult patients with periodontitis.[9] Studies have shown that the adjunctive use of doxycycline with SRP was more effective than SRP alone.[39-42] Doxycycline (subantimicrobial dose) is available in a generic formulation.

There is insufficient evidence to support that one brand EENT antibacterial is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand EENT antibacterials within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand EENT antibacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2009. Available from Wolters Kluwer Health, Inc. Accessed December 2010.
2. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed December 2010.
3. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2009; December 2010.
4. Azasite® [package insert]. Durham, NC: Inspire Pharmacueticals, Inc; November 2008.
5. Besivance® [package insert]. Tampa, FL: Bausch & Lomb, Inc.; April 2009.
6. Ciloxan® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; February 2006.
7. Cetraxal® [package insert]. Ridgeland, MS: WraSer Pharmaceuticals; April 2009.
8. CiproDex® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; July 2003.
9. Periostat® [package insert]. Newtown, PA: CollaGenex Pharmaceuticals, Inc.; November 2004.
10. Zymar® [package insert]. Irvine, CA: Allergan, Inc.; August 2004.
11. Zymaxid® [package insert]. Irvine, CA: Allergan, Inc.; May 2010.
12. Pred-G® [package insert]. Irvine, CA: Allergan, Inc.; June 2004.
13. Iquix® [package insert]. Jacksonville, FL: Vistakon Pharmaceuticals, LLC; April 2007.
14. Quixin® [package insert]. Jacksonville, FL: Vistakon Pharmaceuticals, LLC; April 2006.
15. Vigamox® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; June 2004.
16. Bactroban Nasal® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; April 2009.
17. Coly-Mycin® S [package insert]. Rochester, MN: JHP Pharmaceuticals, LLC; June 2009.
18. Cortisporin-TC® [package insert]. Rochester, MN: JHP Pharmaceuticals, LLC; February 2008.
19. Maxitrol® suspension [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; December 2007.
20. Neosporin® [package insert]. Bristol, TN: Monarch Pharmaceuticals, Inc.; July 2004.
21. Cortisporin® [package insert]. Bristol, TN: Monarch Pharmaceuticals, Inc.; April 2003.
22. TobraDex® suspension [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; April 2010.
23. Zylet® [package insert]. Tampa, FL: Bausch & Lomb, Inc.; May 2010.
24. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Blepharitis (September 2008) Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=080ac46b-ea4d-4556-893a-2a63ba87ffcd. Accessed December 2010.
25. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Conjunctivitis (September 2008). Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=9d9650fb-39a3-439c-9225-5fbb013cf472. Accessed December 2010.
26. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Bacterial Keratitis (September 2008) Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=1d56d934-c309-4072-b6b5-0698559a3b47. Accessed December 2010.
27. Rosenfeld R, Brown L, Cannon C, et al. American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF). Clinical practice guideline: Acute otitis externa. Otolaryngology–Head and Neck Surgery 2006;134:S4-S23.
28. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatr. 2004 May;113(5):1451-65.
29. Wilder RS. Gingivitis and periodontitis in adults: Classification and dental treatment. In: UpToDate, Sokol HN (Ed), UpToDate, Waltham, MA, 2010.
30. Jacobs D. Corenal abrasions and corneal foereign bodies. In: UpToDate, Sokol HN (Ed), UpToDate, Waltham, MA, 2010.
31. Shtein RM. Blepharitis. In: UpToDate, Sokol HN (Ed), UpToDate, Waltham, MA, 2010.
32. Jacobs DS. Conjunctivitis. In: UpToDate, Sokol HN (Ed), UpToDate, Waltham, MA, 2010.
33. Jacobs DS. Evaluation of red eye. In: UpToDate, Sokol HN (Ed), UpToDate, Waltham, MA, 2010.
34. Goguen LA. External otitis. In: UpToDate, Sokol HN (Ed), UpToDate, Waltham, MA, 2010.
35. Isaacson GC. Prevention and management of tympanostomy tube otorrhea in children. In: UpToDate, Torchia MM (Ed), UpToDate, Waltham, MA, 2010.
36. Klein JO. Acute otitis media in children: treatment. In: UpToDate, Torchia MM (Ed), UpToDate, Waltham, MA, 2010.

37. Harris A. Prevention and control of methicillin-resistant *Staphylococcus aureus* in adults. In: UpToDate, Baron EL (Ed), UpToDate, Waltham, MA, 2010.
38. Durand ML. Bacterial endophthalmitis. In: UpToDate, Thorner AR (Ed), UpToDate, Waltham, MA, 2010.
39. Haffajee A, Torresyap G, Socransky S, et al. Clinical changes following four different periodontal therapies for the treatment of chronic periodontitis: 1-year results. J Clin Periodontol 2007;34:243-53.
40. Caton J, Ciancio S, Blieden T, et al. Subantimicrobial dose doxycycline as an adjunct to scaling and root planing: post-treatment effects.J Clin Periodontol 2001;28:782-9.
41. Preshaw P, Hefti A, Novak M, et al. Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: a multicenter trial. J Periodontol 2004;75:1068-76.
42. Caton J, Ciancio S, Blieden T, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. J Periodontol 2000;71:521-32.
43. Laibson P, Michaud R, Smolin G, et al. A clinical comparison of tobramycin and gentamicin sulfate in the treatment of ocular infections. Am J Ophthalmol 1981;92:836-41.
44. Roland P, Younis R, Wall G, et al. A comparison of ciprofloxacin/dexamethasone with neomycin/polymyxin/hydrocortisone for otitis externa pain. Adv Ther 2007;24:671-5.
45. Miro N. Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymyxin B, neomycin, and hydrocortisone suspension. Otolaryngol Head Neck Surg 2000;123:617-23.
46. Schwab I, Friedlaender M, McCulley J, et al. A phase III clinical trial of 0.5% levofloxacin ophthalmic solution versus 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Ophthalmology 2003;110:457-65.
47. Hwang D, Schanzlin D, Rotberg M, et al. A phase III, placebo controlled clinical trial of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Br J Ophthalmol 2003;87:1004-9.
48. Yee R, Tepedino M, Bernstein P, et al. A randomized, investigator- masked clinical trial comparing the efficacy and safety of gatifloxacin 0.3% administered BID versus QID for the treatment BID versus QID for the treatment of acute bacterial conjunctivitis of acute bacterial conjunctivitis. Curr Med Res Opin 2005;21:425-31.
49. Prajna N, George C, Selvaraj S, et al. Bacteriologic and clinical efficacy of ofloxacin 0.3% versus ciprofloxacin 0.3% ophthalmic solutions in the treatment of patients with culture-positive bacterial keratitis. Cornea 2001;20:175-8.
50. Karpecki P, Depaolis M, Hunter J, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: A multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. Clin Ther 2009;31:514-26.
51. Harbarth S, Dharan S, Liassine N, et al. Randomized-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus* Antimicrob Agents Chemother 1999;43(6):1412-1416.
52. Foulks G, Austin R, Knowlton G, et al. Clinical comparison of topical solutions containing trimethoprim in treating ocular surface bacterial infections. J Ocul Pharmacol 1988;4:111-5.
53. Wertheim HFL, Vos M, Ott A, et al. Mupirocin prophylaxis against *Staphylococcus aureus* infections in nonsurgical patients. Ann Intern Med 2004; 140:419-425.
54. Leibowitz H. Clinical evaluation of ciprofloxacin 0.3% ophthalmic solution for treatment of bacterial keratitis. Am J Ophthalmol 1991;112:34S-47S.
55. Lamberts D, Buka T, Knowlton G, et al. Clinical evaluation of trimethoprim-containing ophthalmic solutions in humans. Am J Ophthalmol 1984;98:11-6.
56. Mody L, Kauffman CA, McNeil SA, et al. Mupirocin-based decolonization of *Staphylococcus aureus* carriers in residents of 2 long-term care facilities: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2003;37:1467-1474.
57. Drehobl M, Guerrero J, Lacarte P, et al. Comparison of efficacy and safety of ciprofloxacin otic solution 0.2% versus polymyxin B-neomycin-hydrocortisone in the treatment of acute diffuse otitis externa. Curr Med Res Opin 2008;24:3531-42.
58. White E, Macy J, Bateman K, et al. Comparison of the safety and efficacy of loteprednol 0.5%/tobramycin 0.3% with dexamethasone 0.1%/tobramycin 0.3% in the treatment of blepharokeratoconjunctivitis. Curr Med Res Opin 2008;24:287-96.
59. Lohr J, Austin R, Grossman M, et al. Comparison of three topical antimicrobials for acute bacterial conjunctivitis. Pediatr Infect Dis J 1988;7:626-9.
60. Rhee S, Mah F. Comparison of tobramycin 0.3%/dexamethasone 0.1% and tobramycin 0.3%/loteprednol 0.5% in the management of blepharo-keratoconjunctivitis. Adv Ther 2007;24:60-7.

61. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. N Engl J Med 2002; 346(24):1871-1877.
62. Szaflik J, Szaflick JP, Kamin S, et al. Clinical and microbiological efficacy of levofloxacin administered three times a day for the treatment of bacterial conjunctivitis. Eur J Ophthalmol 2009;19:1-9.
63. Lichtenstein S, Rinehart M. Efficacy and safety of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis in pediatric patients. J AAPOS 2003;7:317-24.
64. Roland P, Pien F, Schultz C, et al. Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. Curr Med Res Opin 2004;20:1175-83.
65. Gross R, Hoffman R, Lindsay R, et al. A comparison of ciprofloxacin and tobramycin in bacterial conjunctivitis in children Clin Pediatr (Phil) 1997;36:435-444.
66. Ammerlaan H, Kluytmans J, Wertheim H, et al. Eradication of methicillin-resistant Staphylococcus aureus carriage: a systematic review. Clin Infect Dis 2009;48:922-30.
67. Gibson J. Trimethoprim-polymyxin B ophthalmic solution in the treatment of presumptive bacterial conjunctivitis--a multicentre trial of its efficacy versus neomycin-polymyxin B-gramicidin and chloramphenicol ophthalmic solutions. J Antimicrob Chemother 1983;11:217-21.
68. van Rijen M, Bonten M, Wenzel R, et al. Intranasal mupirocin for reduction of Staphylococcus aureus infections in surgical patients with nasal carriage: a systematic review. J Antimicrob Chemother 2008;61:254.
69. Cagle G, Davis S, Rosenthal A, et al. Topical tobramycin and gentamicin sulfate in the treatment of ocular infections: multicenter study. Curr Eye Res 1981;1:523-34.
70. van Rijen M, Bonten M, Wenzel R, et al. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database Syst Rev 2008; (4); Cochrane AN: CD006216.
71. Abelson M, Protzko E, Shapiro A, et al. A randomized trial assessing the clinical efficacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric patients with bacterial conjunctivitis. Clin Ophthalmol 2007;1:177-182.
72. Genée E, Schlechtweg C, Bauerreiss P, et al. Trimethoprim-polymyxin eye drops versus neomycin-polymyxin-gramicidin eye drops in the treatment of presumptive bacterial conjunctivitis - a double-blind study. Ophthalmologica 1982;184:92-6.
73. Jones RN, Milazzo J, Seidlin M. Ofloxacin otic solution for treatment of otitis externa in children and adults. Arch Otolaryngol Head Neck Surg 1997;123:1193-200.
74. Schwartz R. Once-daily ofloxacin otic solution versus neomycin sulfate/polymyxin B sulfate/hydrocortisone otic suspension four times a day: a multicenter, randomized, evaluator-blinded trial to compare the efficacy, safety, and pain relief in pediatric patients with otitis externa. Curr Med Res Opin 2006;22:1725-36.
75. John T, Shah A. Use of azithromycin ophthalmic solution in the treatment of chronic mixed anterior blepharitis. Ann Ophthalmol 2008;40:68-74.
76. Protzko E, Bowman L, Abelson M, et al. Phase 3 safety comparisons for 1.0% azithromycin in polymeric mucoadhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis. Invest Ophthalmol Vis Sci 2007;48:3425-9.
77. Tepedino M, Heller W, Usner D. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. Curr Med Res Opin 2009;25:1159-69.
78. Rahman A, Rizwan S, Waycaster C, et al. Pooled analysis of two clinical trials comparing the clinical outcomes of topical ciprofloxacin/dexamethasone otic suspension and polymyxin B/neomycin/hydrocortisone otic suspension for the treatment of acute otitis externa in adults and children. Clin Ther 2007;29:1950-6.
79. Sit D, Kadiroglu A, Kayabasi H, et al. Prophylactic intranasal mupirocin ointment in the treatment of peritonitis in continuous ambulatory peritoneal dialysis patients. Adv Ther 2007;24:387-93.
80. Leibowitz H, Hyndiuk R, Smolin G, et al. Tobramycin in external eye disease: a double-masked study vs gentamicin. Curr Eye Res 1981;1:259-66.
81. Granet B, Dorfman M, Stroman D, et al. A multicenter comparison of polymyxin B sulfate/trimethoprim ophthalmic solution and moxifloxacin in the speed of clinical efficacy for the treatment of bacterial conjunctivitis. J Pediatr Ophthalmol Strabismus 2008;45:340-349.
82. Bloom P, Leeming J, Power W, et al. Topical ciprofloxacin in the treatment of blepharitis and blepharoconjunctivitis. Eur J Ophthalmol 1994;4:6-12.
83. Roland PS, Kreisler LS, Reese B, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2004;113:e40-6.
84. Gwon A. Topical ofloxacin compared with gentamicin in the treatment of external ocular infection. Ofloxacin Study Group. Br J Ophthalmol 1992;76:714-8.

85. Rosenfeld RM, Singer M, Wasserman JM, et al. System review of topical antimicrobial therapy for acute otitis externa. Otolaryngol Head Neck Surg 2006;134(Suppl 4):S24 –S48.
86. Pistorius B, Westberry K, Drehobl M, et al. Prospective, randomized comparative trials of ciprofloxacin otic drops with or without hydrocortisone vs polymyxin B-neomycin-hydrocortisone otic suspension in the treatment of acute diffuse otitis externa. Infec Dis Clin Pract 1999;8:387-95.
87. Coates T, Bax R, Coates A. Nasal decolonization of *Staphylococcus aureus* with mupirocin: strengths, weaknesses and future prospects. J Antimicrob Chemother 2009;64:9-15.
88. Soto N, Vaghjimal A, Stahl-Avicolli A, et al. Bacitracin versus mupirocin for *Staphylococcus aureus* nasal colonization. Infect Control Hosp Epidemiol 1999;20:351-353.
89. Loeb M, Main C, Walker-Dilks C, Eady A. Antimicrobial drugs for treating methicillin-resistant Staphylococcus aureus colonization. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD003340. DOI: 10.1002/14651858.CD003340.
90. Parmar P, Salman A, Kalavathy C, et al. Comparison of topical gatifloxacin 0.3% and ciprofloxacin 0.3% for the treatment of bacterial keratitis. Am J Ophthalmol 2006;141:282-6.
91. Fiscella R, Lewis C, Jensen M. Topical ophthalmic fourth-generation fluoroquinolones: Appropriate use and cost considerations. Am J Health-Syst Pharm 2007;64:2069-73.
92. Maxitrol® ointment [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; July 2004.
93. TobraDex® ointment [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; October 2003.
94. TobraDex ST® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; February 2009.
95. Roland PS, Stewart MG, Hannley M, Friedman R, Manolides S, Matz G, Rybak L, Weber P, Owens F. Consensus panel on role of potentially ototoxic antibiotics for topical middle ear use: Introduction, methodology, and recommendations. Otolaryngol Head Neck Surg 2004;130:S51-S56.
96. American Optometric Association. Care of the patient with conjunctivitis. 2nd ed. St. Louis (MO): American Optometric Association; 2002 Nov 8. 55 p. [80 references]. Available at: http://www.aoa.org/documents/CPG-11.pdf. Accessed December 2010.
97. American Optometric Association. Care of the patient with ocular surface disorders. 2nd ed. St. Louis (MO): American Optometric Association; 2002 Nov 8. [117 references]. Available at: http://www.aoa.org/documents/CPG-10.pdf. Accessed December 2010.
98. Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of otitis media in children. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Jan. 25 p. [49 references]. Available at: http://www.icsi.org/otitis_media/diagnosis_and_treatment_of_otitis_media_in_children_2304.html. Accessed December 2010.
99. Deo V, Gupta S, Bhongade ML, et al. Evaluation of subantimicrobial dose doxycycline as an adjunct to scaling and root planing in chronic periodontitis patients with diabetes: a randomized, placebo-controlled clinical trial. J Contemp Dent Pract 2010;11:9-16.
100. Calfee DP, Salgado CD, Classen D, et al. Strategies to prevent transmission of methicillin-resistant *Staphylococcus aureus* in acute care hospitals. Infect Control Hosp Epidemiol 2008;29 Suppl 1:S62-80.
101. Dohar J, Giles W, Roland P, Bikhazi N, Carroll S, Moe R, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in otitis media with otorrhea through tympanostomy tubes. Pediatrics 2006;118:e561-9. Epub 2006 Jul 31.
102. Roland P, Anon J, Moe R, et al. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tubes. Laryngoscope 2003;113:2116-2122.
103. Dohar J, Roland P, Wall G, et al. Differences in bacteriologic treatment failures in acute otitis externa between ciprofloxacin/dexamethasone and neomycin/polymyxin B/hydrocortisone: results of a combined analysis. Curr Med Res Opin 2009;25:287-291.
104. Goldblatt EL, Dohar J, Nozza RJ, et al. Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes. Int J Pediatr Otorhinolaryngol 1998;46:91-101.
105. Gapski R, Hasturk H, Van Dyke TE, et al. Systemic MMP inhibition for periodontal wound repair: results of a multi-centre randomized-controlled clinical trial. J Clin Periodontol 2009;36:149-56.
106. McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology 2009;116:1615-1623.
107. Comstock TL, Paterno MR, Usner DW, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% in children and adolescents with bacterial conjunctivitis: a post hoc, subgroup analysis of three randomized, double-masked, parallel-group, multicenter clinical trials. Paediatr Drugs 2010;12:105-12.

108. American Academy of Pediatrics. Principles of Appropriate Use for Upper Respiratory Tract Infections. In: Pickering LK, ed. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:740-742. Available at: http://aapredbook.aappublications.org/cgi/content/full/2009/1/4.2.1. Accessed December 2010.
109. Kerschner JE. Otitis Media. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. 18th ed. Philadelphia, PA: Saunders Elsevier; 2007. Available at: http://www.mdconsult.com/das/book/body/178224860-2/0/1608/0.html. Accessed December 2010.
110. Gilbert D, Moellering R, Eliopoulos G, Chambers, H, Saag M, eds. The Sanford Guide to Antimicrobial Therapy 2010. 40th ed. Sperryville, VA: Antimicrobial Therapy, Inc., 2010:10-11.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Vasoconstrictors
AHFS Class 523200
February 9, 2011

I. Overview

The eye, ear, nose, and throat (EENT) vasoconstrictors include both ophthalmic and nasal formulations. They constrict the arterioles and reduce blood flow, and are approved for use in a variety of ophthalmic conditions/procedures and to treat nasal congestion.[1-3] The nasal formulations are often used for the short-term treatment of congestion due to rhinitis, the common cold and sinusitis. The ocular formulations are frequently used for the temporary relief of redness due to minor eye irritation, protection against further irritation, and temporary relief of burning and irritation due to dryness of the eye. They are also used as a mydriatic in ophthalmic conditions and procedures.

Rhinitis medicamentosa (rebound congestion) can occur following the use of a nasal vasoconstrictor for several days.[1-3] It is characterized by chronic swelling of the nasal mucosa resulting in redness, swelling and rhinitis. The rebound congestion prompts patients to administer the medication more frequently to obtain relief, which may lead to dependency. Treatment includes withdrawal of the medication and the use of an intranasal or oral glucocorticosteroid.

The EENT vasoconstrictors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Naphazoline and phenylephrine are available in a generic formulation. This class was last reviewed in December 2008.

Table 1. EENT Vasoconstrictors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Epinephrine	solution†	Adrenalin Chloride®	none
Naphazoline	solution§	N/A	naphazoline
Phenylephrine	solution§	Mydfrin®*	phenylephrine
Tetrahydrozoline	solution†	Tyzine®	Tyzine®

*Generic is available in at least one dosage form or strength.
†Nasal formulation.
§Ophthalmic formulation.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the EENT vasoconstrictors are summarized in Table 2. For a comprehensive overview of the treatment of allergic rhinitis, please refer to the Appendix.

Table 2. Treatment Guidelines Using the EENT Vasoconstrictors

Clinical Guideline	Recommendation(s)
American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter**[5]	Allergic Conjunctivitis • Allergic rhinitis is often accompanied by symptoms of allergic conjunctivitis. Many treatments used for allergic rhinitis can benefit associated symptoms of allergic conjunctivitis, and a variety of topical ophthalmic agents is useful for specific treatment of associated ocular symptoms. • Intranasal corticosteroids, oral antihistamines, and intranasal antihistamines have similar effectiveness in relieving ocular eye symptoms associated with rhinitis. • Oral antihistamines, intranasal antihistamines, oral anti-leukotriene

Clinical Guideline	Recommendation(s)
(2008)	agents, intranasal corticosteroids, and allergen immunotherapy are treatments for allergic rhinitis that have been reported to relieve associated ocular allergy symptoms in controlled trials. • Use of cold compresses and irrigation with saline solution or artificial tears has been advocated to relieve mild symptoms of allergic conjunctivitis. • Topical ophthalmic agents are indicated for specific treatment of itching or symptoms of allergic conjunctivitis. • Vasoconstrictors are indicated for relief of ocular redness, although they do not reduce the allergic response. Prolonged use of ocular decongestants may lead to rebound hyperemia. Use limited to 10 days does not appear to induce this condition. • The combination of an ocular antihistamine and a vasoconstrictor works better than either agent alone. • Mast cell stabilizers have a slow onset of action and may require several days of treatment before optimal symptom relief is achieved, making them more suitable for prophylactic or longer-term treatment of chronic ocular allergies than for acute symptom relief. • Topical NSAIDs reduce prostaglandin production involved in mediating ocular allergy. • Multiple-action agents possess both antihistamine and mast cell stabilizer activities, generally have onset of action within 30 minutes, and are suitable for acute and long-term treatment of allergic conjunctivitis symptoms. • Ocular corticosteroids should be reserved for more severe symptoms of allergic conjunctivitis considering that the ocular side effects from their use can threaten vision because of the increased risk of cataract formation, elevated intraocular pressure (IOP), and secondary infections. <u>Allergic Rhinitis</u> • Oral decongestants are effective at treating nasal congestion associated with allergic rhinitis, but may cause insomnia, irritability, and palpitations. • Topical decongestants are also effective for the short-term and intermittent treatment of nasal congestion. Continuous use of topical decongestants has been associated with rhinitis medicamentosa and should be avoided. • Caution should be exercised when using oral and topical decongestants in young children, older adults, and those individuals with a history of cardiac arrhythmia, angina, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism.
World Health Organization (WHO)/Global Allergy and Asthma European Network (GA^2LEN)/AllerGen: **Allergic Rhinitis and its Impact on Asthma (ARIA)**[6] **(2008)**	<u>Pharmacotherapy of Allergic Rhinitis and Conjunctivitis</u> • Second-generation oral or intranasal H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First-generation oral H_1-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Topical H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis. • Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for the treatment of allergic rhinitis. • Intramuscular glucocorticosteroids and the long-term use of oral glucocorticosteroids are not recommended due to safety concerns. • Topical cromones are recommended in the treatment of allergic rhinitis

Clinical Guideline	Recommendation(s)
	and conjunctivitis, but they are only modestly effective. • Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age. • Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis. • In the treatment of nasal obstruction, in both allergic and nonallergic rhinitis, intranasal decongestants are effective in the short term. However, they do not improve nasal itching, sneezing or rhinorrhea. They may be used for a short period of time in patients with severe nasal obstruction. • Oral decongestants (and their combination with oral H_1-antihistamines) may be used in the treatment of allergic rhinitis in adults, but side effects are common. • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy and availability. • A stepwise approach depending on the severity and duration of rhinitis is proposed. Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. <u>Treatment Algorithm</u> • Patients with mild intermittent allergic rhinitis should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, or leukotriene receptor antagonist. • Patients with moderate/severe intermittent symptoms or mild persistent symptoms should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, intranasal corticosteroid, or leukotriene receptor antagonist. • Patients with moderate/severe persistent symptoms should initially be treated with the following (in preferred order): intranasal corticosteroid, antihistamine (oral or nasal), or leukotriene receptor antagonist.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults**[7] **(2008)**	• Decongestants reduce nasal congestion and oral preparations are useful in combination with antihistamines. • Topical decongestants should only be used for short-term relief of symptoms and should be discontinued after 3 days due to rebound congestion.
International Primary Care Respiratory Group (IPCRG): **Management of Allergic Rhinitis**[8] **(2006)**	• Treatment recommendations are consistent with the ARIA guidelines. • Mild intermittent allergic rhinitis may be treated with an antihistamine, decongestant, and intranasal saline. • Mild persistent and moderate/severe intermittent allergic rhinitis may be treated with antihistamines, decongestants, intranasal corticosteroids, intranasal saline, a mast-cell stabilizer, or a leukotriene receptor antagonist. • Moderate/severe persistent allergic rhinitis may be treated with intranasal corticosteroids, antihistamines, decongestants, intranasal saline, or a leukotriene receptor antagonist.
American Academy of Ophthalmology (AAO): **Preferred Practice Pattern Guidelines: Conjunctivitis**[4] **(2008)**	<u>Seasonal Allergic Conjunctivitis</u> • Mild allergic conjunctivitis can be treated with an OTC antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • If the condition is frequently recurrent or persistent, mast-cell stabilizers can be utilized. • If the symptoms are not adequately controlled, a brief course of low-potency topical corticosteroid can be added to the regimen.

Clinical Guideline	Recommendation(s)
	• A nonsteroidal anti-inflammatory agent (ketorolac) has also been FDA-approved for the treatment of allergic conjunctivitis. • Additional measures include using artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the EENT vasoconstrictors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the EENT Vasoconstrictors[1-3]

Indication	Epinephrine	Naphazoline	Phenylephrine	Tetrahydrozoline
Nasal Decongestant				
For use as a nasal decongestant	✔			
For decongestion of nasal and nasopharyngeal mucosa				✔
Ocular Vasoconstrictor				
For use as a topical ocular vasoconstrictor		✔		
For the temporary relief of redness due to minor eye irritation, protection against further irritation, and temporary relief of burning and irritation due to dryness of the eye		✔		
For use as a vasoconstrictor, decongestant, and mydriatic in a variety of ophthalmic conditions and procedures (pupillary dilation in uveitis, ophthalmic surgical procedures, refraction without cycloplegia, funduscopy and other diagnostic procedures)			✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the EENT vasoconstrictors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the EENT Vasoconstrictors[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Epinephrine	Not reported	Not reported	Not reported	Not reported	Not reported
Naphazoline	Not reported	Not reported	Not reported	Not reported	Not reported
Phenylephrine	Variable	Not reported	Intestinal wall, Liver	Renal (80-86)	2-3
Tetrahydrozoline	Good	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Significant drug interactions with the EENT vasoconstrictors are listed in Table 5.

Table 5. Significant Drug Interactions with the EENT Vasoconstrictors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
EENT Vasoconstrictors (Epinephrine, naphazoline, phenylephrine, tetrahydrozoline)	1	Furazolidone	The alpha-adrenergic effects of epinephrine may be increased. Headache, hyperpyrexia and hypertension (possibly hypertensive crisis and intracranial hemorrhage) could occur.
EENT Vasoconstrictors (Naphazoline, phenylephrine, tetrahydrozoline)	1	MAO Inhibitors	MAO Inhibitors may increase the pharmacologic effects of naphazoline. Headache, hyperpyrexia and hypertension (possibly hypertensive crisis and intracranial hemorrhage) may occur.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the EENT vasoconstrictors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the EENT Vasoconstrictors[1-3]

Adverse Events	Epinephrine	Naphazoline	Phenylephrine	Tetrahydrozoline
Cardiovascular				
Angina	✔	-	-	-
Arrhythmia	✔	✔	✔	-
Chest pain	✔	-	-	-
Flushing	✔	-	-	-
Hypertension	✔	✔	✔	-
Myocardial infarction	-	-	✔	-
Pallor	✔	-	-	-
Palpitation	✔	-	-	✔
Subarachnoid hemorrhage	-	-	✔	-
Sudden death	✔	-	-	-
Syncope	-	-	✔	-
Vasoconstriction	✔	-	-	-
Ventricular ectopy	✔	-	-	-
Central Nervous System				
Anxiety (transient)	✔	-	-	-
Apprehensiveness	✔	-	-	-
Cerebral hemorrhage	✔	-	-	-
Dizziness	✔	✔	-	-
Drowsiness	-	-	-	✔
Headache	✔	✔	-	✔
Insomnia	✔	-	-	✔
Lightheadedness	✔	-	-	✔
Nervousness	✔	✔	-	-
Restlessness	✔	-	-	-
Gastrointestinal				

Adverse Events	Epinephrine	Naphazoline	Phenylephrine	Tetrahydrozoline
Dry throat	✔	-	-	-
Loss of appetite	✔	-	-	-
Nausea	✔	✔	-	-
Vomiting	✔	-	-	-
Xerostomia	✔	-	-	-
Genitourinary				
Urinary retention	✔	-	-	-
Musculoskeletal				
Tremor	✔	-	-	✔
Weakness	-	✔	-	✔
Ocular				
Allergic lid reaction	✔	-	-	-
Blurred vision	-	✔	-	-
Burning/stinging	✔	-	✔	-
Diaphoresis	✔	-	-	-
Discomfort	-	✔	-	-
Eye pain	✔	-	-	-
Floaters	-	-	✔	-
Intraocular pressure increased	-	✔	-	-
Irritation	✔	✔	✔	-
Keratitis	-	✔	-	-
Mydriasis	-	✔	-	-
Rebound miosis	-	-	✔	-
Redness increased	-	✔	-	-
Tearing	-	✔	-	-
Visual disturbances	-	-	✔	-
Respiratory				
Dyspnea	✔	-	-	-
Nasal burning/stinging	-	-	-	✔
Nasal congestion (rebound)	-	-	-	✔
Nasal dryness	-	-	-	✔
Pulmonary edema	✔	-	-	-
Sneezing	-	-	-	✔
Other				
Hyperglycemia	-	✔	-	-
Sweating	-	✔	-	-

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the EENT vasoconstrictors are listed in Table 7.

Table 7. Usual Dosing Regimens for the EENT Vasoconstrictors[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Epinephrine	Nasal Congestion: Apply locally as drops or spray or with a sterile swab, as required	Nasal Congestion: ≥6 years of age: apply locally as drops or spray or with a sterile swab, as required	Nasal solution: 1:1000
Naphazoline	Ocular Vasoconstrictor/ Decongestant: 1 to 2 drops every 3 to 4 hours, up to 4 times daily	Safety and efficacy have not been established in pediatric patients.	Ophthalmic drops: 0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Phenylephrine	Blanching Test: 2.5%: 1 or 2 drops into the injected eye Glaucoma: 2.5% and 10% ophthalmic solutions may be used with miotics in patients with open-angle glaucoma Ophthalmoscopic Examination: 2.5%: 1 drop in each eye Posterior Synechiae: 2.5% and 10%: 1 drop in each eye; repeat as necessary, not to exceed 3 times Provocative Test for Angle Closure Glaucoma: 2.5%: may be used cautiously as a provocative test when intermittent narrow-angle closure glaucoma is suspected Refraction: 2.5%: 1 drop in each eye Retinoscopy: 2.5%: use when dilation of the pupil without cycloplegic action is desired Surgery: 2.5% and 10%: apply topically 30 to 60 minutes before the operation Vasoconstriction and Pupil Dilation: 2.5% and 10%: 1 drop in each eye; may repeat after 1 hour	Refraction: 2.5%: 1 drop in each eye	Ophthalmic drops: 2.5% 10%
Tetrahydrozoline	Nasal Congestion: 2 to 4 drops or 3 to 4 sprays instilled in each nostril as needed, never more often than every 3 hours	Nasal Congestion: ≥6 years of age (0.1%): 2 to 4 drops or 3 to 4 sprays instilled in each nostril as needed, never more often than every 3 hours 2-5 years of age (0.05%): 2 to 3 drops instilled in each nostril as needed, and never more often than every 3 hours	Nasal drops: 0.05% 0.1% Nasal spray: 0.1%

VIII. Effectiveness

There were no studies found in the medical literature that directly compared the safety and efficacy of the ophthalmic or nasal EENT vasoconstrictors.

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Vasoconstrictors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Epinephrine	solution†	Adrenalin Chloride®	$	N/A
Naphazoline	solution§	N/A	N/A	$
Phenylephrine	solution§	Mydfrin®*	$	$
Tetrahydrozoline	solution†	Tyzine®	$$$	N/A

*Generic is available in at least one dosage form or strength.
†Nasal formulation.
§Ophthalmic formulation.
N/A=Not available

X. Conclusions

The EENT vasoconstrictors are approved for use in a variety of ophthalmic conditions/procedures and to treat nasal congestion.[1-3] The ophthalmic products that are available in a generic formulation include naphazoline and phenylephrine. There are no nasal products that are currently available in a generic formulation.

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists and mast cell stabilizers.[5-6,8] The selection of therapy should be individualized and take into consideration the severity and duration of the disease, patient preference, efficacy and safety.[6] The intranasal corticosteroids are the most effective agents for the treatment of allergic rhinitis. Antihistamines treat rhinorrhea, sneezing, itching, and allergic conjunctivitis but have little effect on nasal congestion. They are also less effective than intranasal corticosteroids.[5-6] Oral decongestants effectively treat nasal congestion; however, they may cause insomnia, irritability and palpitations. Topical decongestants are also effective for the short-term treatment of nasal congestion. Chronic use of topical decongestants may cause rhinitis medicamentosa and should be avoided.

The scientific evidence regarding the efficacy of the EENT vasoconstrictors is extremely limited. There were no studies found in the medical literature that directly compared the safety and efficacy of the ophthalmic or nasal EENT vasoconstrictors.

There is insufficient evidence to support that one brand EENT vasoconstrictor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand EENT vasoconstrictors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand EENT vasoconstrictor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed October 2010.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; October 2010.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 2010.
4. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Conjunctivitis; September 2008. Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=9d9650fb-39a3-439c-9225-5fbb013cf472. Accessed October 2010.
5. Wallace DV, Dykewicz MS, Bernstein DI, et al., Joint Task Force on Practice, American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1-84.
6. Bousquet J, Khaltaev N, Cruz A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). Allergy 2008:63(S86):8–160.
7. Institute for Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Respiratory Illness in Children and Adults. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); January 2008. Available at: http://www.icsi.org/respiratory_illness_in_children_and_adults__guideline_/respiratory_illness_in_children_and_adults__guideline__13116.html. Accessed October 2010.
8. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of allergic rhinitis. Primary Care Respiratory Journal 2006;15:58-70.

Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Allergic Rhinitis
February 9, 2011

I. Overview

Allergic rhinitis is an inflammatory condition involving the nasal passages in response to an allergen. The condition occurs because of interplay between epithelial cells and infiltrating inflammatory cells, which include inflammatory mediators and cytokines. This leads to sensory nerve activation, plasma leakage and congestion of venous sinusoids. The severity of symptoms range from mild and intermittent to seriously debilitating.[1] Nasal symptoms include congestion, rhinorrhea (anterior and posterior), sneezing and itching. Patients may also experience symptoms of allergic conjunctivitis. These symptoms may decrease quality of life by causing headache, cognitive impairment and fatigue.

Risk factors for the development of allergic rhinitis include a family history of atopic disease, a serum immunoglobulin E (IgE) >100 units/mL before the age of 6 years, higher socioeconomic class, and presence of a positive allergy skin prick test.[1] Diagnosis of allergic rhinitis involves ruling out rhinitis from other causes. This includes vasomotor rhinitis, rhinitis from foods and alcohol, infectious rhinitis, non-allergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, hormonal rhinitis, drug-induced rhinitis and atrophic rhinitis.[1]

Proper treatment of allergic rhinitis can reduce morbidity and improve quality of life. Nonpharmacologic treatment options include environmental control measures. Pharmacologic treatment options include antihistamines, decongestants, corticosteroids, mast-cell stabilizers, anticholinergics, leukotriene receptor antagonists, omalizumab and nasal saline.[1]

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of allergic rhinitis are summarized in Table 1.

Table 1. Current Treatment Guidelines for Allergic Rhinitis

American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): Diagnosis and Management of Rhinitis: An Updated Practice Parameter[1] (2008)
Diagnosis • Diagnosis of allergic rhinitis involves ruling out rhinitis from other causes. This includes vasomotor rhinitis, rhinitis from foods and alcohol, infectious rhinitis, non-allergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, and atrophic rhinitis.[1] • Ann effective evaluation of the patient should be conducted to determine pattern, chronicity, and seasonality of symptoms; response to medications; coexisting conditions; environmental / occupational exposures; precipitating factors; and quality of life. • Physical examination of all organ systems affected by allergies should be conducted before diagnosis. • Testing for specific IgE antibodies (preferably by skin testing) is indicated to provide evidence of an allergic component to the patient's symptoms and to assess the sensitivity to a specific antigen. • Fiberoptic nasal endoscopy, acoustic rhinometry, nasal provocation testing, and rhinomanometry may be indicated in certain patient populations. **Treatment**

- Nonpharmacologic treatment of allergic rhinitis involves environmental control measures. This includes limiting /avoiding exposure to indoor and outdoor allergens.
- Pharmacologic treatment options include oral and intranasal antihistamines, oral and topical decongestants, oral and intranasal corticosteroids, over-the-counter cough and cold medications for young children, intranasal cromolyn sodium, intranasal anticholinergics, leukotriene receptor antagonists, omalizumab, and nasal saline.
- Oral and intranasal antihistamines effectively treat rhinorrhea, sneezing, itching, and allergic conjunctivitis, but have little effect on nasal congestion. Intranasal antihistamines may be considered as first-line therapy for the treatment of allergic rhinitis and are equal to or superior in efficacy to oral second-generation antihistamines. However, intranasal antihistamines are less effective than intranasal corticosteroids. Second-generation antihistamines are preferred over first-generation antihistamines due to fewer adverse events. Antihistamines are more effective when used continuously for seasonal and perennial allergic rhinitis than intermittent use.
- Oral decongestants are effective at treating nasal congestion associated with allergic rhinitis, but may cause insomnia, irritability, and palpitations. Topical decongestants are also effective for the short-term and intermittent treatment of nasal congestion. Continuous use of topical decongestants has been associated with rhinitis medicamentosa and should be avoided. Caution should be exercised when using oral and topical decongestants in young children, older adults, and those individuals with a history of cardiac arrhythmia, angina, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism.
- Intranasal corticosteroids are the most effective class of medications for the treatment of allergic rhinitis. These agents can be used continuously or intermittently, however continuous use is generally more effective for allergic rhinitis. Intranasal corticosteroids have minor systemic absorption but can be associated with local side effects. Intranasal corticosteroids should be used before oral corticosteroids. A 5 to 7 day course of oral corticosteroids may be indicated in severe or intractable allergic rhinitis. Parenteral corticosteroid use is discouraged.
- Over-the-counter cough and cold medications should generally be avoided in all children below 6 years of age because of the potential toxicity in this age group.
- Intranasal cromolyn may be effective in some groups for controlling allergic rhinitis and is associated with minimal adverse events. However, this agent is less effective than intranasal corticosteroids.
- Intranasal anticholinergics primary reduce rhinorrhea, however are ineffective at treating other symptoms of rhinitis. Anticholinergics may cause excessive drying of mucus membranes.
- Leukotriene receptor antagonists (LTRA) have been proven to be useful in the treatment of allergic rhinitis, either alone or in combination with antihistamines. There is no significant difference in efficacy between LTRA and antihistamines. LTRA are less effective than intranasal corticosteroids.
- Omalizumab is only approved by the FDA for the treatment of allergic asthma. However, this therapy has demonstrated efficacy in allergic rhinitis.
- Nasal saline is an effective treatment, either as monotherapy or as an adjunctive therapy, in individuals with chronic rhinorrhea.
- Allergen immunotherapy may be indicated in patients who have not responded to other agents, have comorbidities, and have severe symptoms.

World Health Organization (WHO)/Global Allergy and Asthma European Network (GA^{2}LEN)/AllerGen: Allergic Rhinitis and its Impact on Asthma (ARIA)[2] (2008)

Diagnosis

- Several nonallergic conditions can cause similar symptoms. Therefore, rhinitis is classified as infectious (viral, bacterial, or other); allergic (intermittent or persistent); occupational (intermittent or persistent); drug-induced (aspirin or other medications); hormonal; other causes (NARES, irritants, food, emotional, atrophic); and idiopathic.
- The diagnosis of allergic rhinitis is based upon allergic symptoms and diagnostic tests. Typical symptoms include rhinorrhea, sneezing, nasal obstruction, pruritus, and ocular symptoms. Diagnostic tests include identifying the allergen-specific IgE in the skin or the blood.

- Allergic rhinitis is subdivided into intermittent or persistent disease. Intermittent allergic rhinitis is defined by symptoms occurring less often than 4 days per week or with a total duration of less than 4 weeks. Persistent allergic rhinitis is defined by symptoms occurring more often than 4 days per week and lasting longer than 4 weeks in duration.
- The severity of the disease is classified as 'mild' or 'moderate/severe'. Mild allergic rhinitis means that none of the following are present: sleep disturbance, impairment of daily living, impairment of school or work, or troublesome symptoms. Moderate/severe allergic rhinitis means that one or more of the following are present: sleep disturbance, impairment of daily living, impairment of school or work, or presence of troublesome symptoms.

Treatment

- The management of allergic rhinitis should take into account the following: severity and duration of disease; patient preference; efficacy, safety and cost of medications. Treatment options include allergen avoidance, patient education, pharmacotherapy, and immunotherapy.
- Patients with mild intermittent allergic rhinitis should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, or leukotriene receptor antagonist.
- Patients with moderate/severe intermittent symptoms or mild persistent symptoms should initially be treated with the following (in no particular order): antihistamine (oral or intranasal), and/or decongestant, intranasal corticosteroid, or leukotriene receptor antagonist.
- Patients with moderate/severe persistent symptoms should initially be treated with the following (in preferred order): intranasal corticosteroid, antihistamine (oral or nasal), or leukotriene receptor antagonist.
- Topical antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis. Second-generation antihistamines are preferred due to safety concerns.
- Intranasal glucocorticosteroids are the most effective treatment. Oral/systemic use of glucocorticosteroids is not recommended due to safety concerns.
- Topical mast-cell stabilizers are recommended in the treatment of allergic rhinitis and conjunctivitis, but they are only modestly effective.
- Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age.
- Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis.
- Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction. Oral decongestants may be used in the treatment of allergic rhinitis in adults, however adverse events are common.
- If the patient is refractory to the above treatments consider referral to a specialist and consider specific immunotherapy.

Institute for Clinical Systems Improvement (ICSI): Diagnosis and Treatment of Respiratory Illness in Children and Adults[3]
(2008)

Diagnosis

- Diagnosis should be based on the history and physical examination.
- Personal and family history should be obtained concerning allergic conditions. Social and environmental history should also be obtained.
- Diagnostic tests including skin testing, radioallergosorbent tests and nasal smear for eosinophils may be performed.

Treatment

- Treatment should consist of patient education on avoidance and pharmacologic therapies. These include corticosteroids, antihistamines, decongestants, cromolyn, anticholinergics, and leukotriene receptor antagonists.
- Intranasal corticosteroids are considered the most effective treatment option. Therefore, they are recommended as first-line therapy in patients with moderate to severe symptoms of allergic rhinitis. Oral corticosteroids should only be used in refractory patients and injectable corticosteroids should be avoided.

- Antihistamines are effective for the treatment of allergic rhinitis, however are somewhat less effective than intranasal corticosteroids. Antihistamines can be used in patients who are not candidates for intranasal corticosteroids. Second-generation antihistamines are preferred due to safety concerns. Antihistamines or antihistamine/decongestant combinations can be used initially in patients with mild or episodic allergic rhinitis for rapid relief of symptoms. They can be used on a daily basis or as needed.
- Decongestants reduce nasal congestion and oral preparations are useful in combination with antihistamines. Topical decongestants should only be used for short-term relief of symptoms and should be discontinued after 3 days due to rebound congestion.
- Topical cromolyn is not considered as effective as intranasal corticosteroids; however it is an alternative in patients who are not candidates for intranasal corticosteroids.
- Intranasal anticholinergic agents primarily relieve symptoms of rhinorrhea, but have no effect on congestion, sneezing, or itching.
- Leukotriene receptor antagonists are as effective as antihistamines, however are not as effective as intranasal corticosteroids.
- Referral to a specialist may be necessary if treatment measures are inadequate. Immunotherapy may be indicated in patients fail to respond to other treatment options.
- Patients should receive proper education and follow up concerning their condition and treatment.

International Primary Care Respiratory Group (IPCRG): Management of Allergic Rhinitis[4] (2006)

Diagnosis

- Diagnosis is consistent with the ARIA guidelines.
- Patients with asthma should be evaluated for allergic rhinitis and patients with allergic rhinitis should be evaluated for asthma.
- Classification should be based on the duration of symptoms and their severity.

Treatment

- Treatment goals consist of the maintenance of activities of normal daily living and the maintenance of an uninterrupted sleep pattern.
- The primary treatment should be allergen avoidance.
- Pharmacologic treatment should be individualized for each patient.
- Mild intermittent allergic rhinitis may be treated with an antihistamine, decongestant, and intranasal saline.
- Mild persistent and moderate/severe intermittent allergic rhinitis may be treated with antihistamines, decongestants, intranasal corticosteroids, intranasal saline, a mast-cell stabilizer, or a leukotriene receptor antagonist.
- Moderate/severe persistent allergic rhinitis may be treated with intranasal corticosteroids, antihistamines, decongestants, intranasal saline, or a leukotriene receptor antagonist.

III. References

1. Wallace DV, Dykewicz MS, Bernstein DI, et al., Joint Task Force on Practice, American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1-84.
2. Bousquet J, Khaltaev N, Cruz A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA^2LEN and AllerGen). Allergy 2008:63(S86):8–160.
3. Institute for Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Respiratory Illness in Children and Adults. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); January 2008. Available at: http://www.icsi.org/respiratory_illness_in_children_and_adults__guideline_/respiratory_illness_in_children_and_adults__guideline__13116.html. Accessed October 2010.
4. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of allergic rhinitis. Primary Care Respiratory Journal 2006;15:58-70.

Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Asthma
February 9, 2011

I. Overview

Asthma is a chronic inflammatory condition caused by a variety of changes in the airway, including bronchoconstriction, edema, hyperresponsiveness and remodeling.[1] Mast cells, eosinophils, T lymphocytes, neutrophils and epithelial cells may all play a role in its pathogenesis. IgE antibodies have been shown to have a relationship with the airway response to allergens. IgE is synthesized in response to environmental stimuli and can bind to mast cells and basophils, resulting in the release of mediators, including histamine and leukotrienes. These mediators lead to constriction of airway smooth muscle. Mast cells also release proinflammatory proteins. There is a lack of consensus as to the role lymphocytes play in the progression of asthma. These mediators also contribute to the bronchoconstriction present in asthma.

Certain risk factors are associated with the development of asthma. A family history of asthma or allergic rhinitis is a risk factor for late childhood-onset asthma. Coexistence of other allergic diseases appears to increase the risk of asthma. Males appear to be at a higher risk of childhood-onset asthma, while females are more prone to adult-onset asthma. Viral infections as an infant appear to increase the risk of childhood-onset asthma. Maternal smoking and premature birth are also risk factors for childhood asthma. Children who present with asthma symptoms before the age of 2 may outgrow the condition. However, increasing severity of childhood episodes is often predictive of a continuation of asthma into adulthood.

Asthma is diagnosed based on symptoms and evaluation of lung function. Lung function can be evaluated using pulmonary function tests. The forced expiratory volume in one second (FEV_1) and the peak expiratory flow (PEF) are usually decreased in patients with asthma. Patients with asthma typically have recurring intermittent episodes. Acute symptoms are generally associated with bronchospasm involving breathlessness, chest tightness, cough, and wheezing. These episodes occur more often at night or in the early morning and are associated with diminished airflow that is reversible and susceptible to treatment. Patients with asthma display a hyperresponsiveness to a variety of stimuli that trigger these events. Diagnosis of asthma in children may be more difficult than in adults. It is often not possible to measure airway function in children. Diagnosis is typically made via auscultation of the lungs by a healthcare professional. Diagnosis should be confirmed by bronchodilator responsiveness and peak flow meter variability when possible.

Nonpharmacologic treatment options for asthma include allergen avoidance, elevation of the head while in a resting position, smoking cessation, as well as the treatment of other comorbid conditions which may exacerbate asthma. Pharmacologic therapies include long-term controller medications (corticosteroids, mast-cell stabilizers, methylxanthines, leukotriene modifiers, and long-acting β_2-agonists) and quick relief medications (short-acting β_2-agonists and anticholinergic agents). Asthma treatments can be administered by either inhaled or systemic routes (oral and parenteral). Inhaled products are delivered directly into the airways and result in less systemic toxicity than systemic formulations. They are available as pressurized metered-dose inhalers (MDIs), breath-actuated MDIs, dry powder inhalers (DPIs) and nebulized aerosols. Several factors may influence the delivery of mediation to the lower airways, including device selection, formulation of medication, particle size and ease of use by patients.[3] The use of a spacer with pressurized MDIs may improve drug delivery, increase lung disposition, reduce oral and gastrointestinal absorption, and reduce adverse events.[3] Breath-actuated MDIs may be beneficial in patients who have difficulty coordinating a pressurized MDI. Although DPIs may be easier to use, they require a minimal inspiratory flow rate for use.[3] Nebulized aerosols are rarely indicated for the chronic treatment of asthma in adults.[3] Nebulizers are generally reserved for children who cannot use other inhaler devices.[1,3]

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of asthma are summarized in Table 1.

Table 1. Current Treatment Guidelines for Asthma

Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS): British Guideline on the Management of Asthma[2] (2009)
Diagnosis • Suspect asthma in children if they present with the following: 1) recurring symptoms (wheezing, cough, difficulty breathing, and/or chest tightness); 2) personal history of atopic disease; 3) family history of atopic disease or asthma; 4) widespread wheeze on auscultation; 5) history of improvement in symptoms or lung function with treatment. • Suspect asthma in adults if they present with the following: 1) recurring symptoms (wheezing, cough, difficulty breathing, and/or chest tightness); 2) personal history of atopic disease; 3) family history of atopic disease or asthma; 4) widespread wheeze on auscultation; 5) low FEV_1 or PEF; 6) unexplained peripheral blood eosinophilia. **Treatment** • The goal of therapy is to control the disease with minimal adverse events. This includes: 1) no daytime symptoms; 2) no nighttime awakening due to asthma; 3) no need for rescue medication; 4) no exacerbations; 5) no limitations on activity including exercise; 6) normal lung function (FEV_1 and/or PEF >80% predicted). • Inhaled corticosteroids are the recommended preventer drug for adults and children for achieving overall treatment goals. They should be considered for adults, children aged 5-12 and children <5 years of age with any of the following features: 1) using inhaled β_2-agonists ≥3 times/week; 2) symptomatic ≥3 times/week; or 3) waking ≥1 night/week. They should also be considered in adults and children aged 5-12 who have had an exacerbation of asthma requiring oral corticosteroids in the last two years. • Alternative preventer therapies in patients taking short-acting β_2-agonists alone are mast-cell stabilizers, leukotriene receptor antagonists and theophylline. In children <5 years of age who are unable to take inhaled corticosteroids, leukotriene receptor antagonists are an effective first-line preventer. • The first choice as add-on therapy to inhaled corticosteroids in adults and children (5-12 years of age) is an inhaled long-acting β_2-agonist. In children <5 years of age, the first choice as add-on therapy to inhaled corticosteroids is leukotriene receptor antagonists. Long-acting inhaled β_2-agonists should not be used without inhaled corticosteroids. • If control remains inadequate on an inhaled corticosteroid plus a long-acting β_2-agonist, consider the following interventions: leukotriene receptor antagonists, theophylline, slow release β_2-agonist tablets (adults). There are no controlled trials indicating which treatment option is best; however, the potential for adverse events is greater with theophylline and β_2-agonist tablets. Addition of short-acting anticholinergics is of no value and the addition of nedocromil is of marginal benefit. • In selected adult patients at step 3 who are poorly controlled or in selected adult patients at step 2, the use of budesonide/formoterol in a single inhaler as rescue medication instead of a short-acting β_2-agonist, in addition to its regular use as controller therapy has been shown to be an effective treatment regimen. When this management option is introduced the total regular dose of daily inhaled corticosteroids should not be decreased. The regular maintenance dose of inhaled corticosteroids may be budesonide 200 mcg twice daily or budesonide 400 mcg twice daily. Patients taking rescue budesonide/formoterol once a day or more should have their treatment reviewed. Careful education of patients about the specific issues around this management strategy is required. • There is no difference in efficacy in giving inhaled corticosteroid and long-acting β_2-agonist in combination or in separate inhalers. Once a patient is stable, the combination inhalers might be advantageous as they may prevent the accidental use of the long-acting β_2-agonist without the inhaled corticosteroid.

Children <5 Years Old	Children 5-12 Years Old	Adults/Children >12 Years Old
Step 1: Mild Intermittent Asthma		
• Inhaled short-acting β_2-agonist as required	• Inhaled short-acting β_2-agonist as required	• Inhaled short-acting β_2-agonist as requir d
Step 2: Regular Preventer Therapy		
• Add inhaled corticosteroid 200-400 mcg/day*† or leukotriene antagonist if inhaled corticosteroid cannot be used	• Add inhaled corticosteroid 200-400 mcg/day* (other preventer drug if inhaled corticosteroid cannot be used) • Start at dose of inhaled corticosteroid appropriate to severity of disease	• Add inhaled corticosteroid 200-800 mcg/day* • Start at dose of inhaled corticosteroid appropriate to severity of disease
Step 3: Initial Add-on Therapy		
• In those children taking inhaled corticosteroids 200-400 mcg/day, consider addition of leukotriene receptor antagonist • In those children taking a leukotriene receptor antagonist alone, reconsider addition of an inhaled corticosteroid 200-400 mcg/day • In children under 2 years, consider proceeding to step 4	• Add inhaled long-acting β_2-agonist (LABA) • If good response to LABA, continue LABA • If benefit from LABA, but control still inadequate, continue LABA and increase inhaled corticosteroid dose to 400 mcg/day* (if not already on this dose) • If no response to LABA, stop LABA and increase inhaled corticosteroid to 400 mcg/day* • If control still inadequate, consider leukotriene receptor antagonist or SR theophylline	• Add inhaled long-acting β_2-agonist (LABA) • If good response to LABA, continue LABA • If benefit from LABA, but control still inadequate, continue LABA and increase inhaled corticosteroid dose to 800 mcg/day* (if not already on this dose) • If no response to LABA, stop LABA and increase inhaled corticosteroid to 800 mcg/day* • If control still inadequate, consider leukotriene receptor antagonist or SR theophylline
Step 4: Persistent Poor Control		
• Refer to a respiratory pediatrician	• Increase inhaled corticosteroid up to 800 mcg/day*	Consider trials of: • Increase inhaled corticosteroid up to 2,000 mcg/day* • Add a fourth drug (leukotriene receptor antagonist, SR theophylline, β_2-agonist tablet)
Step 5: Continuous or Frequent Use of Oral corticosteroids		
	• Use daily corticosteroid tablet in lowest dose providing adequate control • Maintain high-dose inhaled corticosteroid at 800 mcg/day*	• Use daily corticosteroid tablet in lowest dose providing adequate control • Maintain high-dose inhaled corticosteroid at 2,000 mcg/day* • Consider other treatments to minimize use of corticosteroid tablets

Abbreviations: SABA=short-acting β_2-agonist; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LTRA=leukotriene receptor antagonist
*beclomethasone or equivalent
†Higher nominal doses may be required if drug delivery is difficult

Exacerbations of Asthma

- Doubling the dose of an inhaled corticosteroid at the time of an exacerbation is of unproven value.
- In adult patients on a low dose of an inhaled corticosteroid, a fivefold increase in dose at the time of exacerbation leads to a decrease in the severity of exacerbations. This data should not be extrapolated to patients already taking higher doses of inhaled corticosteroids.
- There is limited evidence that leukotriene antagonists may be used intermittently in children with episodic asthma. Treatment is started at the onset of either asthma symptoms or of coryzal symptoms and continued for seven days.
- The benefit of parent-initiated oral steroids at the start of an exacerbation has not been established.

Exercise-Induced Asthma

- The following treatments provide protection against exercise-induced asthma: inhaled corticosteroids, short-acting β_2-agonists, long-acting β_2-agonists, theophyllines, leukotriene receptor antagonists, chromones, and β_2-agonist tablets.
- Long-acting β_2-agonists (LABAs) and leukotriene antagonists provide more prolonged protection than short-acting β_2-agonists, but some tolerance may develop with LABAs. No tolerance has been demonstrated with leukotriene receptor antagonists.
- If exercise is a specific problem in patients who are well controlled on inhaled corticosteroids, consider the following therapies: leukotriene receptor antagonists, long-acting β_2-agonists, chromones, oral β_2-agonists, or theophyllines.
- Inhaled short-acting β_2-agonists are the drug of choice immediately prior to exercise.

Inhaler Devices

β_2-agonist delivery:

- For acute asthma, the use of a pressurized metered dose inhaler (pMDI) + spacer is at least as good as a nebulizer at treating mild and moderate exacerbations of asthma in children and adults.
- For stable asthma in children aged 0-5, there is no evidence comparing nebulizer and other inhalers, and there is insufficient evidence to draw conclusions regarding pMDI compared to a dry powder inhaler (DPI). A pMDI + spacer are the preferred method of delivery of β_2-agonists. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. Where this is ineffective, a nebulizer may be required.
- For stable asthma in children aged 5-12, there is no significant difference between pMDI + spacer and DPI.
- For stable asthma in adults, there is no significant difference between pMDI ± spacer and DPI. Patients have been shown to prefer Turbohaler to pMDI.
- The choice of a reliever inhaler for stable asthma should be based on patient preference and the assessment of correct use. Many patients will not be prepared to carry a spacer.

Inhaled corticosteroid delivery:

- In children aged 5-12 years, pMDI + spacer is as effective as any DPI. No recommendation can be given for nebulized therapy.
- In adults, a pMDI ± spacer is as effective as any DPI.
- There is no evidence relating to children aged <5 years. A pMDI + spacer are the preferred method of delivery of inhaled steroids. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. Where this is ineffective, a nebulizer may be required.

Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention[3] (2009)

Diagnosis

- Diagnosis is made following a detailed medical history, physical exam, and spirometry to demonstrate obstruction and assess reversibility (in adults and children ≥5 years of age).

Treatment

- The goal of treatment is to achieve and maintain control. Asthma control is defined as: 1) no daytime

symptoms (twice or less/week); 2) no limitations of daily activities (including exercise); 3) no nocturnal symptoms or awakening because of asthma; 4) no need for reliever treatment (twice or less/week); 5) normal or near-normal lung function results; and 6) no exacerbations.

Controller Medications – Adults

- Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. To achieve control, add-on therapy with another type of controller medication is preferred over increasing the dose of the inhaled glucocorticosteroid.
- Leukotriene modifiers are considered an alternative treatment option for adults with mild persistent asthma. Some patients with aspirin-sensitive asthma may also respond favorably to leukotriene modifiers.
- Leukotriene modifiers are generally less effective than low doses of inhaled glucocorticosteroids when used as monotherapy.
- When used as add-on therapy, leukotriene modifiers may reduce the dose of inhaled glucocorticosteroids in patients with moderate to severe asthma. They may improve asthma control in patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. However, leukotriene modifiers are less effective as add-on therapy than long-acting inhaled β_2-agonists.
- Long-acting β_2-agonists (LABAs) should not be used as monotherapy in asthma as they do not affect airway inflammation. They are most effective when combined with inhaled glucocorticosteroids. This combination is preferred when a medium dose of an inhaled glucocorticosteroid alone fails to achieve control of asthma.
- Studies have shown that delivering an inhaled glucocorticosteroid and a LABA in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers may increase compliance and ensure that the LABA is always accompanied by a glucocorticosteroid.
- LABAs, when used in combination with an inhaled glucocorticosteroid, can be used to prevent exercise-induced bronchospasm. They may also provide longer protection than rapid-acting inhaled β_2-agonists.
- Sustained-release theophylline has little effect as a first-line controller. It may provide benefit as add-on therapy in patients who do not achieve control on inhaled glucocorticosteroids alone. As add-on therapy, theophylline is less effective than LABAs.
- The role of mast-cell stabilizers in the long-term treatment of asthma in adults is limited. Efficacy has been reported in patients with mild persistent asthma and exercise-induced bronchospasm. Their anti-inflammatory effect is weak and they are less effective than a low dose of inhaled glucocorticosteroid.

Controller Medications - Children

- Inhaled glucocorticosteroids are the most effective controller therapy and are the recommended treatment for children of all ages.
- In children, leukotriene modifiers provide clinical benefit at all levels of asthma severity, but generally less than that of low-dose inhaled glucocorticosteroids. They also provide partial protection against exercise-induced bronchoconstriction. When used as add-on therapy in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers may provide moderate clinical improvements (including a reduction in exacerbations). Combination therapy is less effective than increasing to moderate doses of inhaled glucocorticosteroids in children with moderate persistent asthma.
- Inhaled LABAs should not be used as monotherapy in children with asthma. They are primarily used as add-on therapy in children >5 years of age whose asthma is insufficiently controlled by inhaled glucocorticosteroids, or as single-dose therapy for exercise-induced bronchoconstriction. Inhaled LABAs have not been adequately studied in children ≤5 years of age.
- Combination products containing an inhaled glucocorticosteroid and a LABA are preferred to the coadministration of each component as separate inhalers. Fixed combination inhalers ensure that the LABA is always accompanied by a glucocorticosteroid. The combination of budesonide and formoterol has been shown to reduce asthma exacerbations in children ≥4 years of age with moderate to serve asthma.
- Theophylline has been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids in children >5 years of age. Sustained-release products with reliable absorption profiles and complete bioavailability (with and without concomitant food intake) are preferable for maintenance therapy.
- Mast-cell stabilizers have a limited role in the management of asthma in children.
- The use of oral LABAs is not recommended due to potential adverse events.

Reliever Medications – Adults

- Rapid-acting inhaled β_2-agonists are the mediations of choice for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction, in both adults and children of all ages. They should be used only on an as needed basis at the lowest dose and frequency required. Increased use is a warning of deterioration of asthma control.
- Systemic glucocorticosteroids are an important treatment option for severe acute exacerbations because they prevent progression of the asthma exacerbation, reduce the need for hospitalization, prevent early relapse after emergency treatment, and reduce the morbidity of the illness. The main effects are seen after 4 to 6 hours and oral therapy is preferred over other routes of administration.
- Inhaled ipratropium is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. The benefits of ipratropium bromide in the long-term management of asthma have not been established, although it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from rapid-acting β_2-agonists.
- Short-acting theophylline may be considered for relief of asthma symptoms; however, its role in the treatment of exacerbations is unclear. Short-acting theophylline may provide no additional bronchodilator effect over rapid-acting β_2-agonists, but it may benefit respiratory drive.
- Short-acting oral β_2-agonists are appropriate for use in patients who are unable to use inhaled medications.

Reliever Medications - Children

- Rapid-acting inhaled β_2-agonists are the most effective bronchodilators and are the preferred treatment for acute asthma in children of all ages. Oral therapy is rarely needed and should be reserved for young children who cannot use inhaled therapy.
- Inhaled anticholinergics are not recommended for the long-term management of asthma in children.

Treating to Achieve Control

- Treatment requires a stepwise approach and should be adjusted based on asthma control.
- Step 1 treatment with an as needed reliever medication is reserved for untreated patients with occasional daytime symptoms (cough, wheeze, dyspnea occurring twice or less per week, or less frequently if nocturnal) of short duration (lasting only a few hours) comparable with controlled asthma.
- For steps 2 – 5, combine an as needed reliever treatment with regular controller treatment.

	Children >5 Years Old/Adolescents/Adults
Step 1	• As needed rapid-acting β_2-agonist
Step 2	• Select one: o Low-dose inhaled glucocorticosteroid o Leukotriene modifier • The low-dose inhaled glucocorticosteroid is recommended as the initial controller treatment for patients of all ages. • Leukotriene modifiers are considered an alternative treatment option. They may be appropriate for patients who are unable or unwilling to use an inhaled glucocorticosteroid, those who experience adverse events with an inhaled glucocorticosteroid, and those with concomitant allergic rhinitis.
Step 3	• Select one: o Low-dose inhaled glucocorticosteroid plus inhaled long-acting β_2-agonist o Medium-or high-dose inhaled glucocorticosteroid o Low-dose inhaled glucocorticosteroid plus leukotriene modifier o Low-dose inhaled glucocorticosteroid plus sustained-release theophylline • For adolescents and adults, the recommended treatment option is to combine a low-dose of an inhaled glucocorticosteroid with an inhaled long-acting β_2-agonist, either in a combination inhaler device or as separate components. • For all children, combination therapy has been less well studied and the addition of an inhaled long-acting β_2-agonist may not be as effective as increasing the dose of inhaled glucocorticosteroids in reducing exacerbations. • For children, it is recommended to increase to a medium-dose of inhaled glucocorticosteroids. • If a combination inhaler containing formoterol and budesonide is selected, it

	may be used for both rescue and maintenance. Whether this approach can be employed with other combinations of controller and reliever requires further study.
Step 4	• Select one or more and add to step 3 treatment: o Medium-or high-dose inhaled glucocorticosteroid plus inhaled long-acting β_2-agonist o Leukotriene modifier o Sustained-release theophylline • The preferred treatment is to combine a medium- or high-dose of inhaled glucocorticosteroid with an inhaled long-acting β_2-agonist. However, an increase from medium- to a high-dose of inhaled glucocorticosteroid provides relatively little additional benefit.
Step 5	• Add either to step 4 treatment: o Oral corticosteroid (lowest dose) o Anti-IgE treatment

Exacerbations of Asthma

- Severe asthma exacerbations should be treated in an acute care facility. Milder exacerbations (reduction in peak flow <20%, nocturnal awakening, or increased use of short-acting β_2-agonists) can usually be treated in a community setting.
- The repeated administration of rapid-acting inhaled β_2-agonists (2 to 4 puffs every 20 minutes for the first hour) achieves rapid reversal of airflow limitation for patients with mild to moderate exacerbations. Additional treatment should be titrated depending upon the patient's response.
- Bronchodilator therapy delivered via a MDI (ideally with a spacer) produces at least an equivalent improvement in lung function at the same dose delivered via nebulizer.
- No additional medication is necessary if the rapid-acting inhaled β_2-agonist produces a complete response (PEF returns to >80% of predicted or personal best) and the response lasts for 3 to 4 hours.
- Oral glucocorticosteroids should be used to treat exacerbations.

Device Selection – Children

- Children <4 years of age
  - Preferred: pressurized MDI plus spacer with face mask
  - Alternate: nebulizer with face mask
- Children 4 – 6 years of age
  - Preferred: pressurized MDI plus spacer with mouthpiece
  - Alternate: nebulizer with mouthpiece
- Children >6 years of age
  - Preferred: DPI, or breath-actuated MDI, or pressurized MDI plus spacer with mouthpiece
  - Alternate: nebulizer with mouthpiece

Global Initiative for Asthma (GINA): Global Strategy for the Diagnosis and Management of Asthma in Children 5 years and Younger[6]
(2009)

Diagnosis

- Diagnosis of asthma in children <5 years of age can be difficult.
- Asthma should be suspected if the child experiences any of the following: 1) frequent episodes of wheeze (>1/month); 2) activity-induced cough or wheeze; 3) nocturnal cough without viral infection; 4) absence of seasonal variation in wheeze; or 5) symptoms that persist after age 3.

Treatment

- The goal of treatment is to achieve control of the clinical manifestations of the disease and maintain this control for prolonged periods.
- Inhaled therapy constitutes the cornerstone of asthma treatment in children ≤5 years of age.

- A pressurized metered-dose inhaler (MDI) with a valved spacer (with or without a face mask, depending on the child's age) is the preferred delivery system.
- Nebulizers should be reserved for children who cannot be taught effective use of a spacer device.

Device Selection

- Children <4 years of age
  - Preferred: pressurized MDI plus spacer with face mask
  - Alternate: nebulizer with face mask
- Children 4 – 5 years of age
  - Preferred: pressurized MDI plus spacer with mouthpiece
  - Alternate: pressurized MDI plus spacer with face mask or nebulizer with mouthpiece or face mask

Controller Medications

- A low-dose inhaled glucocorticosteroid is the recommended initial treatment option in children ≤5 years of age. Inhaled glucocorticosteroids have been shown to be more effective than other controller treatment for asthma.
- The role of leukotriene modifiers as add-on therapy in children ≤5 years of age whose asthma is uncontrolled on inhaled glucocorticosteroids has not been specifically evaluated.
- The efficacy of theophylline is less than that of low-dose inhaled glucocorticosteroids and adverse events are more common.
- The effect of long-acting inhaled β_2-agonists (LABAs) or combination products (LABA plus glucocorticosteroid) has not been adequately studied in children ≤5 years of age. Therefore, LABAs cannot be recommended in this age group.
- Mast-cell stabilizers are not recommended in this age group.
- Oral glucocorticosteroids should be restricted to the treatment of acute severe exacerbations.

Reliever Medications

- Rapid-acting inhaled β_2-agonists are the most effective bronchodilators and are the preferred reliever treatment for asthma in children ≤5 years of age.
- An MDI with spacer is an effective way for delivering reliever therapy. Nebulizer therapy is also an option when delivery is not optimal because of lack of cooperation or distress, or when the child is hypoxic.
- Oral therapy is not recommended due to its slower onset of action and adverse events.
- Inhaled ipratropium is not recommended for the daily management of asthma in children ≤5 years of age.

Treating to Achieve Control

- If the child is controlled on as needed rapid-acting β_2-agonists, then continue this therapy.
- If the child is partly controlled on as needed rapid-acting β_2-agonists, then the addition of a low-dose inhaled glucocorticosteroid (beclomethasone 100 mcg, budesonide MDI + spacer 200 mcg, budesonide nebulized 500 mcg, fluticasone 100 mcg) is recommended. Ciclesonide, mometasone and triamcinolone have not been studied in this age group. Leukotriene modifiers are considered an alternative treatment option.
- If the child is uncontrolled or only partly controlled on low-dose inhaled glucocorticosteroid, then the initial dose of the inhaled glucocorticosteroid should be doubled. The addition of a leukotriene modifier to the low-dose inhaled glucocorticosteroid may also be considered; however, this has not been studied in this age group.
- The best treatment for children whose asthma is not controlled on twice the initial dose of inhaled glucocorticosteroids has not been established. If the above steps fail to achieve control, additional treatment options include: 1) further increase the dose of the inhaled glucocorticosteroid; 2) add a leukotriene modifier; 3) add theophylline; or 4) add a low dose of oral glucocorticosteroid for a few weeks until the child's asthma improves.

Exacerbations of Asthma

- Initial home management includes 2 puffs of a rapid-acting β_2-agonist administered via a mask or spacer device. Medical attention should be sought the same day if the inhaled bronchodilator is required for symptom relief more than every 3 hours or for more than 24 hours.

- The evidence to support the initiation of oral glucocorticosteroids in the home management of asthma exacerbations in children is weak, and should be considered only where the physician is confident that they will be used appropriately.

National Heart, Lung, and Blood Institute (NHLBI): Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma[1]
(2007)

Diagnosis

- Diagnosis is made following a detailed medical history, physical exam, and spirometry to demonstrate obstruction and assess reversibility (in adults and children ≥5 years of age).
- Reversibility is determined by either an increase in FEV_1 of ≥12% from baseline or by an increase of ≥10% of predicted FEV_1 following bronchodilator treatment.

Treatment

- The first goal of therapy is to reduce impairment, which includes: 1) preventing chronic and troublesome symptoms (coughing and breathlessness); 2) reduce the use of short-acting bronchodilators for symptoms (≤2 days per week); 3) maintain near normal pulmonary function; and 4) maintain normal activity levels.
- The second goal of therapy is to reduce risk, which includes: 1) prevent recurrent exacerbations; 2) minimize the need for emergency department visits or hospitalizations; 3) prevent loss of lung function; and 4) provide optimal treatment with minimal adverse effects.

Long-Term Control Medications

- Inhaled corticosteroids (ICSs) are the most effective long-term therapy for mild, moderate, or severe persistent asthma. Most benefit is achieved with relatively low doses, whereas the risk of adverse effects increases with dose.
- LABAs are not recommended for use as monotherapy for long-term control of persistent asthma or to treat acute symptoms or exacerbations of asthma; however, they are used as an adjunct to ICS therapy. LABAs are the preferred treatment to combine with ICS in children ≥12 years of age and adults. For children ≥5 years of age, LABAs should be considered an adjunctive therapy in those who have asthma that requires more than low-dose ICS. LABAs may be used before exercise to prevent EIB, but frequent and chronic use of LABAs for EIB may indicate poorly controlled asthma.
- LTRAs are an alternative (not preferred) treatment option for mild persistent asthma. LTRAs can also be used as an adjunctive treatment with ICS; however, for children ≥12 years of age and adults, they are not the preferred adjunct therapy (compared to the addition of long-acting bronchodilators). Zileuton is an alternative treatment option; however it is less desirable than LTRAs due to more limited efficacy data and the need for liver function monitoring.
- Sustained-release theophylline is an alternative (not preferred) treatment for mild persistent asthma. It may also be used as alternative (not preferred) adjunctive therapy with ICS**.**
- Mast-cell stabilizers are alternative (not preferred) medications for the treatment of mild persistent asthma. They can also be used as preventive treatment before exercise or unavoidable exposure to known allergens.
- Tiotropium and ipratropium have not demonstrated effectiveness in the long-term management of asthma.
- Chronic administration of oral corticosteroids as a long-term-control medication should only be used for the most severe, difficult-to-control asthma because of well-documented risk for side effects.
- Omalizumab is considered an adjunctive treatment in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA.

Quick-Relief Medications

- Short-acting bronchodilators (SABAs) are the preferred treatment for the relief of acute symptoms and prevention of EIB. Scheduled daily use of short-acting bronchodilators is not recommended.
- Ipratropium bromide, administered in multiple doses along with SABA in moderate or severe asthma exacerbations in the ED, provides additive benefit.
- The use of oral systemic corticosteroids is recommended for patients with moderate or severe exacerbations.

Device Selection

- Metered-dose inhaler (MDI):
  - ≥5 years of age
  - <5 years of age with a spacer or valved holding chamber (VHC) with face mask
- Breath-actuated MDI:
  - ≥5 years of age
- Dry powder inhaler (DPI):
  - ≥4 years of age
- Spacer or VHC
  - ≥4 years of age
  - <4 years of age with VHC with face mask
- Nebulizer:
  - Patients of any age who cannot use MDI with VHC and face mask

Long-Term Management of Asthma

- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains.
- Quick-relief medications must be available for every level of care.

Children 0-4 Years Old	Children 5-11 Years Old	Adults/Children ≥12 Years Old
Step 1 Care		
Preferred: • SABA as needed	Preferred: • SABA as needed	Preferred: • SABA as needed
Step 2 Care		
Preferred: • Low-dose ICS Alternative (alphabetical): • Cromolyn • Montelukast	Preferred: • Low-dose ICS Alternative (alphabetical): • Cromolyn • LTRA • Nedocromil • Theophylline	Preferred: • Low-dose ICS Alternative (alphabetical): • Cromolyn • LTRA • Nedocromil • Theophylline
Step 3 Care		
Preferred: • Medium-dose ICS	Preferred (either): • Low-dose ICS and either LABA, LTRA, or theophylline (listed alphabetically) • Medium-dose ICS	Preferred (either): • Low-dose ICS and LABA • Medium-dose ICS Alternative: • Low-dose ICS and either LTRA, theophylline, or zileuton
Step 4 Care		
Preferred: • Medium-dose ICS and either LABA or montelukast	Preferred: • Medium-dose ICS and LABA Alternative: • Medium-dose ICS and either LTRA or theophylline	Preferred • Medium-dose ICS and LABA Alternative: • Medium-dose ICS and either LTRA, theophylline, or zileuton
Step 5 Care		
Preferred: • High-dose ICS and either LABA or montelukast	Preferred: • High-dose ICS and LABA Alternative: • High-dose ICS and either LTRA or theophylline	Preferred: • High-dose ICS and LABA • Consider adding omalizumab for patients who have allergies

Step 6 Care		
Preferred: • High-dose ICS and LABA or montelukast and oral corticosteroids	Preferred: • High-dose ICS and LABA and oral corticosteroids Alternative: • High-dose ICS and either LTRA or theophylline and oral corticosteroids	Preferred: • High-dose ICS and LABA and oral corticosteroids • Consider adding omalizumab for patients who have allergies

Abbreviations: SABA=short-acting β_2-agonist; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LTRA=leukotriene receptor antagonist

Exercise-Induced Bronchospasm (EIB):

- Appropriate long-term control of asthma with anti-inflammatory medication will reduce airway responsiveness, which is associated with a reduction in the frequency and severity of EIB.
- Pretreatment before exercise with inhaled β_2-agonists will prevent EIB in >80% of patients.
- SABAs used shortly before exercise (or as close to exercise as possible) may be helpful for 2–3 hours. LABAs can be protective up to 12 hours.
- LTRAs can attenuate EIB in up to 50% of patients. The onset of action is generally hours after administration.
- Cromolyn or nedocromil taken shortly before exercise is an alternative treatment to prevent EIB, but it is not as effective as SABAs.

Management of Asthma Exacerbations at Home

- Increase the frequency of SABA treatment.
- Initiate oral systemic corticosteroid treatment under certain circumstances.
- Doubling the ICS dose is not sufficient.
- Continue more intensive treatment for several days.

International Primary Care Respiratory Group (IPCRG): Management of Asthma[4-5] (2006)

Diagnosis

- Diagnosis of asthma is based on signs and symptoms of airway obstruction.
- Treatment requires a stepwise approach based on asthma classification.

Treatment

Step 1: Intermittent Asthma

- Short-acting β_2-agonists as needed for symptoms and for exercise-induced bronchospasm.
- In patients >60 years of age, consider an anticholinergics agent.

Step 2: Mild Persistent Asthma

- Low-dose inhaled corticosteroid.

Step 3: Moderate Persistent Asthma

- Combination therapy with an inhaled corticosteroids and a long-acting β_2-agonist.
- An alternative treatment option includes using the combination of an inhaled corticosteroid and a leukotriene modifier or sustained-release theophylline.

Step 4: Severe Persistent Asthma

- Combination therapy with a high-dose inhaled corticosteroid and long-acting β_2-agonist.
- An alternative treatment option includes high-dose inhaled corticosteroids and sustained-release theophylline.
- An alternative treatment option includes high-dose inhaled corticosteroids and a leukotriene modifier.
- Oral corticosteroids can be used over the short-term.

General Treatment Considerations

- When patients present with infrequent symptoms, prescribe rapid-acting β_2-agonists.
- Prescribe a rapid-acting β_2-agonist for patients with exercise-induced asthma.
- The most effective preventative therapy is inhaled corticosteroids.
- For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting β_2-agonist. Alternatives are combinations of inhaled corticosteroids with sustained-release theophylline or with leukotriene receptor antagonists.

III. References

1. Education for a partnership in asthma care. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 93-164. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 2010.
2. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2009 Jun. 125 p. Available at: http://www.sign.ac.uk/pdf/sign101.pdf. Accessed October 2010.
3. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 112 p. Available at: http://www.ginasthma.com. Accessed October 2010.
4. Van der Molen T, Ostrem A, Stallberg B, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of asthma. Prim Care Respir J 2006;15:5-47.
5. Levy ML, Fletcher M, Price DB, et al. International Primary Care Respiratory Group (IPCRG) guidelines: diagnosis of respiratory diseases in primary care. Prim Care Respir J 2006;15:20-34.
6. Global Initiative for Asthma (GINA). Global strategy for the diagnosis and management of asthma in children 5 years and younger. Bethesda (MD): Global Initiative for Asthma (GINA); 2009. 28 p. Available at: http://www.ginasthma.org. Accessed October 2010.

Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Chronic Obstructive Pulmonary Disease
February 9, 2011

I. Overview

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible.[1-5] It is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Pathological changes include chronic inflammation and structural changes in the proximal and peripheral airways, lung parenchyma, and pulmonary vasculature. Cigarette smoking is the most common risk factor for the development of COPD. Additional inhalational exposures that increase the risk of developing COPD include occupational dust/chemicals and air pollution. Other risk factors for the development of COPD include genetics, lung growth and development, history of severe childhood respiratory infections and lower socioeconomic status.

A diagnosis of COPD should be considered in individuals presenting with dyspnea, cough, sputum production, or history of exposure to risk factors for the disease.[1-2] The diagnosis should be confirmed with spirometry as it provides meaningful information on the severity and stage of COPD. Spirometry should include an assessment of the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Post-bronchodilator FEV_1 <80% and FEV_1/FVC <0.70 predicted confirms the presence of airflow limitation that is not fully reversible.[1-2]

Pharmacologic treatments for COPD include long- and short-acting β_2-agonists, anticholinergics, methylxanthines and glucocorticosteroids. Smoking cessation programs should also be incorporated into all treatment plans. Proper treatment is aimed at: 1) decreasing symptoms, exacerbations, and complications; 2) improving exercise capacity; and 3) improving quality of life.[1-2] Most studies have demonstrated that the available treatments do not modify the long-term decline in lung function associated with COPD.[1-5]

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of chronic obstructive pulmonary disease are summarized in Table 1.

Table 1. Current Treatment Guidelines for Chronic Obstructive Pulmonary Disease

National Institute for Clinical Excellence (NICE): Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care[3] (2010)

Diagnosis
• COPD should be considered in patients >35 years of age who have at least one risk factor (especially smoking) and in those who present with one or more of the following symptoms: dyspnea, chronic cough, sputum production, wheeze, or frequent winter "bronchitis".
• Assessment of COPD severity is based on spirometry:
  o Mild airflow obstruction: FEV_1/FVC <0.70 and FEV_1 50-80% predicted
  o Moderate airflow obstruction: FEV_1/FVC <0.70 and FEV_1 30-49% predicted
  o Severe airflow obstruction: FEV_1/FVC <0.70 and FEV_1 <30% predicted
 	
Treatment
• Inhaled agents are preferred over oral treatments because of the reduction in systemic side effects.
• As needed short-acting bronchodilators should be the initial empirical treatment for the relief of

breathlessness and exercise limitation.

- A once-daily, long-acting muscarinic antagonist (LAMA) is preferred to a four-times-daily, short-acting muscarinic antagonist (SAMA) in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, as well as in those whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist.
- In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the following treatments are recommended as maintenance therapy:
  - If FEV_1 ≥50% predicted: either long-acting β_2-agonist (LABA) or LAMA
  - If FEV_1 <50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler or LAMA
- In people with stable COPD and an FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
  - Consider LABA+ICS in a combination inhaler
  - Consider LAMA in addition to LABA where ICS is declined or not tolerated
- Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1.
- Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA, irrespective of their FEV_1.
- If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include:
  - β_2-agonist and theophylline
  - Anticholinergic and theophylline
- Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions.
- Maintenance use of oral corticosteroid therapy in COPD is not normally recommended. Some patients with advanced COPD may require maintenance oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible.

Delivery Systems

- In most cases, bronchodilator therapy is best administered using a hand-held inhaler device (including a spacer device if appropriate).
- Patients with distressing or disabling breathlessness despite maximal therapy using inhalers should be considered for nebulizer therapy.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[1]
(2009)

Diagnosis

- COPD should be suspected in any patient with cough, excess sputum production, dyspnea, or history of exposure to risk factors including smoking. The diagnosis should be confirmed using spirometry.
- Assessment of COPD severity is based on spirometry and symptoms as follows:
  - Stage 1 (Mild): FEV_1/FVC <0.70 and FEV_1 ≥80% predicted. Symptoms may include chronic cough and sputum production.
  - Stage 2 (Moderate): FEV_1/FVC <0.70; FEV_1 ≥50% and <80% predicted. Symptoms may include shortness of breath with exertion, cough, and sputum production.
  - Stage III (Severe): FEV_1/FVC <0.70; FEV_1 ≥30% and <50% predicted. Symptoms may include shortness of breath, reduced exercise capacity, fatigue, and exacerbations that affect quality of life.
  - Stage IV (Very Severe): FEV_1/FVC <0.70; FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure. QOL is significantly impacted and exacerbations may be life threatening.

Treatment

- Most studies have indicated that the existing medications for COPD do not modify the long-term decline in lung function. Therefore, pharmacotherapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance.

Therapy at Each Stage of COPD

- Stage I (Mild COPD):
  - Use a short-acting bronchodilator when needed.
- Stage II (Moderate COPD):
  - Use a short-acting bronchodilator when needed
  - Add regular treatment with one or more long-acting bronchodilators when needed
  - Add rehabilitation
- Stage III (Severe COPD):
  - Use a short-acting bronchodilator when needed
  - Add regular treatment with one or more long-acting bronchodilators when needed
  - Add rehabilitation
  - Add inhaled corticosteroids if repeated exacerbations
- Stage IV (Very Severe COPD):
  - Use a short-acting bronchodilator when needed
  - Add regular treatment with one or more long-acting bronchodilators when needed
  - Add rehabilitation
  - Add inhaled corticosteroids if repeated exacerbations
  - Add long-term oxygen if chronic respiratory failure
  - Consider surgical treatments

General Treatment Considerations

- Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis or on a regular basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination.
- Regular treatment with long-acting bronchodilators, including nebulized formulations, are more effective than treatment with short-acting bronchodilators.
- Regular use of a long-acting β_2-agonist or a short-or long-acting anticholinergic improves health status.
- Treatment with a long-acting inhaled anticholinergic drug reduces the rate of COPD exacerbations and improves the effectiveness of pulmonary rehabilitation.
- Theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
- Most studies have demonstrated that regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD. However, one study in patients with an FEV_1 <60% predicted demonstrated that inhaled glucocorticosteroids decreased the rate of decline of lung function. Regular treatment with inhaled glucocorticosteroids has been shown to reduce the frequency of exacerbations and improve health status for symptomatic COPD patients with an FEV_1 <50% predicted, as well as repeated exacerbations. Treatment with inhaled glucocorticosteroids increases the likelihood of pneumonia and does not reduce overall mortality. Treatment with inhaled glucocorticosteroids can be recommended for patients with more advanced COPD and repeated exacerbations.
- An inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status.
- There is insufficient evidence to recommend a therapeutic trial with oral glucocorticosteroids in patients with Stage II-IV COPD and a poor response to an inhaled bronchodilator. Long-term treatment with oral glucocorticosteroids is not recommended in COPD.

Device Systems

- COPD patients may have more problems in effective coordination and find it harder to use a metered-dose inhaler (MDI) than do healthy volunteers or younger asthmatics.
- Alternative breath-activated or spacer devices are available.
- Dry powder inhalers (DPIs) may possibly provide improved drug deposition; however, this has not been established in COPD.
- Nebulizers are not recommended for regular treatment because they require appropriate maintenance.

American College of Physicians (ACP): Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease[5]
(2007)

Diagnosis

- Spirometry should be performed to diagnose airflow obstruction in patients with respiratory symptoms, particularly dyspnea.
- Spirometry should not be used to screen for airflow obstruction in asymptomatic individuals.
- Treatment for stable COPD should be reserved for patients who have respiratory symptoms and FEV_1 <60% predicted, as documented by spirometry.

Treatment

- Clinicians should prescribe one of the following maintenance monotherapies for symptomatic patients with COPD and FEV_1 <60% predicted: long-acting inhaled β_2-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids.
- Monotherapy with a long-acting inhaled β_2-agonist, a long-acting inhaled anticholinergic, or an inhaled corticosteroid is beneficial in reducing exacerbations.
- Inhaled corticosteroids and long-acting inhaled bronchodilators have similar effectiveness, but differ in adverse effects, reductions in deaths, and hospitalizations.
- Evidence is insufficient to recommend one monotherapy agent over another.
- Clinicians may consider combination inhaled therapies for symptomatic patients with COPD and FEV_1 <60% predicted. However, when to use combination therapy instead of monotherapy has not been clearly established. Studies of combination therapies do not consistently demonstrate benefits of combination therapy over monotherapy.

International Primary Care Respiratory Group (IPCRG): Management of Chronic Obstructive Pulmonary Disease[4]
(2006)

Diagnosis

- COPD should be suspected in any patient with cough, excess sputum production, dyspnea, or history of exposure to risk factors including smoking. The diagnosis should be confirmed using spirometry.
- Assessment of COPD severity is based on spirometry and symptoms as follows:
  - Stage 1 (Mild): FEV_1/FVC <0.70 and FEV_1 ≥80% predicted (with or without chronic symptoms). Stage 2 (Moderate): FEV_1/FVC <0.70; FEV_1 ≥50% and <80% predicted (with or without chronic symptoms).
  - Stage III (Severe): FEV_1/FVC <0.70; FEV_1 ≥30% and <50% predicted (with or without chronic symptoms).
  - Stage IV (Very Severe): FEV_1/FVC <0.70; FEV_1 <30% predicted *or* FEV_1 <50% predicted plus chronic respiratory failure. QoL is significantly impacted and exacerbations may be life threatening.

Treatment

- None of the current pharmacologic treatments for COPD have been shown to modify the long-term decline

in lung function. Treatment should be focused on reducing symptoms and complications.

- Stage I (Mild):
  - Use a short-acting bronchodilator when needed
- Stage II (Moderate):
  - Use a short-acting bronchodilator when needed
  - Add regular treatment with one or more long-acting bronchodilators when needed
  - Add rehabilitation
- Stage III (Severe):
  - Use a short-acting bronchodilator when needed
  - Add regular treatment with one or more long-acting bronchodilators when needed
  - Add rehabilitation
  - Add medium –to high dose inhaled corticosteroids if repeated exacerbations
- Stage IV (Very Severe):
  - Use a short-acting bronchodilator when needed
  - Add regular treatment with one or more long-acting bronchodilators when needed
  - Add rehabilitation
  - Add medium – to high dose inhaled corticosteroids if repeated exacerbations
  - Add long-term oxygen if chronic respiratory failure
- Bronchodilators (anticholinergics and β_2-agonists) are central to symptom management in COPD.
- For regular treatment, long-acting bronchodilators are more effective than short-acting bronchodilators.
- Inhaled glucocorticosteroids are recommended in patients with 'Severe' (Stage III) and 'Very Severe' (Stage IV) COPD who have repeated exacerbations (three or more in the last three years) requiring oral corticosteroids or antibiotics.
- Regular treatment with inhaled glucocorticosteroids reduces the frequency of exacerbations and improves health status in this group of patients.

American Thoracic Society (ATS)/European Respiratory Society (ERS): Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease[2]
(2004)

Diagnosis

- A diagnosis of COPD should be considered in individuals presenting with dyspnea, cough, sputum production, or history of exposure to risk factors for the disease.
- COPD is classified with the use of spirometry as follows:
  - Mild COPD: $FEV_1/FVC \leq 0.70$ and $FEV_1 \geq 80\%$ predicted.
  - Moderate COPD: $FEV_1/FVC \leq 0.70$; $FEV_1 \geq 50\%$ and $<80\%$ predicted.
  - Severe COPD: $FEV_1/FVC \leq 0.70$; $FEV_1 \geq 30\%$ and $<50\%$ predicted.
  - Very Severe COPD: $FEV_1/FVC \leq 0.70$ and $FEV_1 < 30\%$ predicted.

Treatment

- Medications for COPD can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status.
- At present, no treatment has been shown to modify the rate of decline in lung function.
- A general algorithm for the treatment of COPD includes the following:
  - Intermittent symptoms: Short-acting bronchodilator as needed for symptom control.
  - Persistent symptoms (e.g., dyspnea, night waking):
    - Long- or short-acting bronchodilators given four times daily. Use additional short-acting bronchodilators as needed for additional symptom control.
    - If symptoms are not controlled with the above measures, consider using alternate classes or combine classes.
    - If symptoms are not controlled with the above measures, consider adding/substituting oral theophylline.
- The inhaled route is preferred when both inhaled and oral formulations are available. Smaller doses of active treatment can be delivered directly with equal or greater efficacy and with fewer side-effects when

administered by inhalation.

- The initial trial data show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its components. The largest effects in terms of exacerbations and health status are seen in patients with an FEV_1<50% predicted, where combining treatment is clearly better than either component drug used by itself.
- Three types of bronchodilators are in common clinical use: β-agonists, anticholinergic drugs and methylxanthines.
- Short-acting bronchodilators can increase exercise tolerance acutely in COPD. Combining short-acting agents produces a greater change in spirometry over 3 months than either agent alone.
- Anticholinergics given q.i.d. can improve health status over a 3-month period compared with placebo.
- Long-acting inhaled β-agonists improve health status, possibly to a greater degree than using regular ipratropium. Additionally, these drugs reduce symptoms, rescue medication use and increase the time between exacerbations compared with placebo.
- Combining long-acting inhaled β_2-agonists and ipratropium leads to fewer exacerbations than either drug alone.
- No good comparative data between different long-acting inhaled β-agonists are presently available although it is likely that their effects will be similar.
- Combining long-acting β_2-agonists and theophylline appears to produce a greater spirometric change than either drug alone.
- Tiotropium improves health status and reduces exacerbations and hospitalizations compared with both placebo and regular ipratropium. It is at least equivalent to long-acting β_2-agonists in its effect and in one clinical trial appeared to be superior to salmeterol in some measures over 6 months.
- In patients with more advanced disease (usually classified as an FEV_1 <50% predicted) there is evidence that the number of exacerbations per year and the rate of deterioration in health status can be reduced by inhaled corticosteroids in COPD.
- Evidence from four large prospective 3-yr studies has shown no effect of inhaled corticosteroids on rate of change of FEV_1 in any severity of COPD.
- There are no data to support the use of leukotriene receptor antagonists or cromones (mast-cell stabilizers) in COPD.

III. References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009. 93 p. Available at: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed October 2010.
2. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
3. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease: national guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 June. 61 p. Available at: http://guidance.nice.org.uk/CG101. Accessed October 2010.
4. Bellamy D, Bouchard J, Henrichsen S, et al. International Primary Care Respiratory Group (IPCRG) guidelines: management of chronic obstructive pulmonary disease (COPD). Prim Care Respir J 2006;15:48-57.
5. Qaseem A, Snow V, Shekelle P, et al., Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians (ACP). Ann Intern Med 2007;147:633-8.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review – Victoza® (liraglutide)
Incretin Mimetics, AHFS Class 682006
February 9, 2011

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into 4 main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States, which can be associated with physical inactivity and other lifestyle characteristics. A diagnosis of type 2 diabetes is not dependent on plasma insulin levels, which may be decreased, increased, or normal. Glucose-stimulated secretion of endogenous insulin is frequently reduced, and decreased peripheral sensitivity to insulin is almost always associated with glucose intolerance. Obesity is often a confounder as it contributes to insulin resistance. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat this devastating disease.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, which was approved by the FDA in January 2010. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] GLP-1 is a human incretin hormone that is secreted from the small intestine in response to food intake. It has multiple effects on the stomach, liver, pancreas and brain to control glucose concentrations. Human GLP-1 is inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. Liraglutide is a synthetic peptide with approximately 97% homology to human GLP-1, but is more resistant to inactivation by DPP-4. It enhances glucose-dependent insulin secretion by pancreatic beta cells, suppresses glucagon secretion and delays gastric emptying.[1]

The liraglutide products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Liraglutide is not currently available in a generic formulation. The incretin mimetics were last reviewed May 2010.

Table 1. Liraglutide Products Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Liraglutide	injection	Victoza®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the incretin mimetics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Incretin Mimetics

Clinical Guideline	Recommendation(s)
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[6] (2010)**	Treatment of Type 2 Diabetes • Refer to the ADA/EASD consensus statement on the management of individuals with type 2 diabetes for specific treatment recommendations.[7]
American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation**	• There is insufficient data to support recommending one class of agents or a combination of medications over other classes or combinations with regards to effects on complications. • The effects on long-term complications of diabetes are likely due to the level of glycemic control rather than the specific intervention. • Tier 1 interventions represent the best established and most effective therapeutic strategy for achieving glycemic goals. In selected clinical

Clinical Guideline	Recommendation(s)
and Adjustment of Therapy[7] (2009)	settings, the tier 2 algorithm may be considered. Tier 1 Interventions • Lifestyle intervention and metformin should be initiated as the first step in treating patients with type 2 diabetes mellitus. • If lifestyle intervention and metformin fail to achieve glycemic goals within 2-3 months, insulin or a sulfonylurea should be added. • If lifestyle, metformin, and either a sulfonylurea or basal insulin do not achieve glycemic goals, insulin therapy should be started or intensified. • The addition of a third oral agent can be considered, especially if the A1C is <8.0%; however, this is not preferred as it is no more effective in lowering glucose than initiating or intensifying insulin. Tier 2 Interventions • Lifestyle intervention and metformin should be initiated as the first step in treating patients with type 2 diabetes mellitus. • If lifestyle intervention and metformin fail to achieve glycemic goals within 2-3 months, the addition of exenatide or pioglitazone may be considered if hypoglycemia is a concern. Rosiglitazone is not recommended. • If promotion of weight loss is a major consideration and the A1C is <8.0%, exenatide is an option. • If the above interventions are not effective in achieving target A1C, addition of a sulfonylurea (other than glyburide or chlorpropamide) could be considered. • If further adjustments are needed, the above tier 2 interventions should be stopped and basal insulin should be added to metformin.

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **An Algorithm for Glycemic Control[8] (2009)**	Management of Patients With A1C Levels of 6.5% to 7.5%
	• Monotherapy:
	  o Metformin, TZDs, DPP-4 inhibitors, and α-glucosidase inhibitors (AGIs) are all appropriate for use as monotherapy. These agents have a minimal risk of hypoglycemia.
	  o Metformin is the cornerstone of monotherapy because of its safety and efficacy.
	• Dual therapy:
	  o Metformin is the cornerstone of dual therapy because of its safety and efficacy.
	  o The second component of the dual therapy regimen includes the agents in the following order: incretin mimetic, DPP-4 inhibitor, or an insulin secretagogue (glinide and sulfonylurea).
	  o The combination of a TZD with metformin is recommended with a higher priority than a glinide or sulfonylurea because of a lower risk of hypoglycemia and greater flexibility in timing of administration.
	  o Additional dual therapy regimens include (1) metformin combined with colesevelam, and (2) metformin combined with an AGI.
	• Triple therapy:
	  o The following combinations are considered for triple therapy in the following order:
	  1. Metformin + GLP-1 agonist + TZD
	  2. Metformin + GLP-1 agonist + glinide
	  3. Metformin + GLP-1 agonist + sulfonylurea
	  4. Metformin + DPP-4 inhibitor + TZD
	  5. Metformin + DPP-4 inhibitor + glinide

Clinical Guideline	Recommendation(s)
	6. Metformin + DPP-4 inhibitor + sulfonylurea o Metformin is the cornerstone of triple therapy because of its safety and efficacy. o Exenatide is the second preferred component because of the low risk of hypoglycemia, potential for inducing weight loss, as well as the ability to increase satiety and delay gastric emptying. • Insulin therapy: o Metformin is the most commonly used and safest medication to combine with insulin. o Exenatide has not been approved by the FDA for concomitant use with insulin. <u>Management of Patients With A1C Levels of 7.6% to 9.0%</u> • Dual therapy should be started initially if the patient has an A1C of 7.6% to 9.0% because no single agent is likely to achieve the A1C goal. • Dual therapy: o The following combinations are recommended for dual therapy in the following order: 1. Metformin + GLP-1 agonist 2. Metformin + DPP-4 inhibitor 3. Metformin + TZD 4. Metformin + sulfonylurea 5. Metformin + glinide o Metformin is the cornerstone of dual therapy because of its safety, mechanism of action, and insulin sensitization. o A GLP-1 agonist or a DPP-4 inhibitor is the preferred second component due to the safety and efficacy of these agents in combination with metformin. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor due to the greater effect on reducing postprandial glucose and potential for weight loss. • Triple therapy: o The following combinations are recommended for triple therapy in the following order: 1. Metformin + GLP-1 agonist + TZD 2. Metformin + DPP-4 inhibitor + TZD 3. Metformin + GLP-1 agonist + sulfonylurea 4. Metformin + DPP-4 inhibitor + sulfonylurea 5. Metformin + TZD + sulfonylurea o Metformin is the cornerstone of triple therapy because of its safety and efficacy. o A GLP-1 agonist or a DPP-4 inhibitor is the preferred second component due to the lower risk of hypoglycemia with these agents. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor due to its greater effect on reducing postprandial glucose and potential for weight loss. • Insulin therapy: o Insulin therapy for patients with an A1C of 7.6% to 9.0% follows the same principles as outlined previously for patients with an A1C level of 6.5% to 7.5%. <u>Management of Patients With A1C Levels of >9.0%</u> • If the A1C is >9.0%, then the probability of reaching an A1C ≤6.5% is low. If the patient is asymptomatic, initiating a triple therapy regimen may be appropriate. If the patient is symptomatic, or therapy with medications has failed, it is appropriate to initiate insulin therapy,

Clinical Guideline	Recommendation(s)

	either with or without additional oral agents. Metformin is the most commonly used and safest medication to combine with insulin.
	• Combination therapy:
	  o The following 8 combinations are considered:
	  1. Metformin + GLP-1 agonist
	  2. Metformin + GLP-1 agonist + sulfonylurea
	  3. Metformin + DPP-4 inhibitor
	  4. Metformin + DPP-4 inhibitor + sulfonylurea
	  5. Metformin + TZD
	  6. Metformin + TZD + sulfonylurea
	  7. Metformin + GLP-1 + TZD
	  8. Metformin + DPP-4 inhibitor + TZD
	  o Metformin is the cornerstone of combination therapy because of its safety and efficacy.
	  o A GLP-1 agonist or DPP-4 inhibitor may be added to metformin. It may be preferable to use a GLP-1 agonist due to its greater effect on reducing postprandial glucose and potential for weight loss.
	Insulin Therapy
	• Insulin therapy for patients with A1C levels exceeding 9.0% follows the same principles as outlined previously for patients with A1C values of ≤9.0%.

American Association of Clinical Endocrinologists (AACE): **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus**[9] **(2007)**	Patients With Type 2 Diabetes Mellitus • Refer to the updated AACE/ACE consensus statement on the management of individuals with type 2 diabetes for specific treatment recommendations.[8]

National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents**[10] **(2009)**	• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate (A1C ≥7.5%) and the person has:
	  o A body mass index ≥35 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups), or
	  o A BMI <35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
	• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in A1C and weight loss >3% of initial body weight at 6 months).

National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)**[12] **(2008)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes. • Refer to the updated NICE recommendations for specific treatment recommendations using the GLP-1 mimetics.[10]
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults**[11] **(2009)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes due to the low risk of hypoglycemia, side effects, and lack of weight gain. • Sulfonylureas and thiazolidinediones are acceptable secondary choices if metformin is contraindicated. • Combination therapy may be required to achieve goals. • If treatment goals are not met on oral agents, or if oral agents are contraindicated, then it is necessary to begin insulin either alone or as an adjunct to oral therapy.

Clinical Guideline	Recommendation(s)
	• Exenatide may be used as an additional agent in combination with metformin, sulfonylurea, or metformin/sulfonylurea in patients who have not achieved glycemic control. • Exenatide may be offered as an alternative option before starting insulin for patients on oral medications who are not achieving adequate glucose control. • Metformin, acarbose, exenatide, sitagliptin and human amylin are more often associated with weight loss or weight maintenance.
International Diabetes Federation (IDF) Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes[5] (2005)	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes. • Exenatide was approved by the FDA in April 2005. • This guideline does not discuss the role of exenatide in the treatment of type 2 diabetes mellitus.

III. Indications

The Food and Drug Administration (FDA)-approved indications for liraglutide are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for Liraglutide[1-4]

Indication	Liraglutide†§
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔

†The concurrent use of liraglutide with insulin has not been studied.
§Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.

IV. Pharmacokinetics

The pharmacokinetic parameters of liraglutide are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Liraglutide[1-4]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Elimination (%)	Half-Life (hours)
Liraglutide	55	>98	Not significant	Renal (6) Feces (5)	13

V. Drug Interactions

There are no significant drug interactions reported with liraglutide.[2] However, liraglutide slows gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications.[1] Caution should be exercised when oral medications are concomitantly administered with liraglutide.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with liraglutide are listed in Table 5 and the boxed warning is listed in Table 6.

Table 5. Adverse Drug Events (%) Reported with Liraglutide[1-4]

Adverse Events	Liraglutide
Cardiovascular	
Hypertension	3
Central Nervous System	
Dizziness	6
Headache	3
Gastrointestinal	
Constipation	10
Diarrhea	17
Nausea	28
Pancreatitis	<1
Vomiting	11
Laboratory Test Abnormalities	
Hyperbilirubinemia	4
Hypoglycemia	<1
Respiratory	
Nasopharyngitis	5
Sinusitis	6
Upper respiratory tract infection	10
Other	
Anti-liraglutide antibodies	7-9
Back pain	5
Influenza	7
Injection site reaction	2
Papillary thyroid carcinoma	<1
Thyroid C-cell hyperplasia	<1
Urinary tract infection	6

Table 6. Boxed Warning for Liraglutide[1]

WARNING: RISK OF THYROID C-CELL TUMOR
Liraglutide causes dose-dependent and treatment-duration–dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2 (MEN2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Counsel patients regarding the risk and symptoms of thyroid tumors.

VII. Dosing and Administration

The usual dosing regimens for liraglutide are listed in Table 7.

Table 7. Usual Dosing Regimens for Liraglutide[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Liraglutide	Initial: 0.6 mg once daily for one week, then 1.2 to 1.8 mg once daily	Safety and efficacy have not been established in children.	Injection: 0.6 mg/0.1 ml

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of liraglutide are summarized in Table 8.

Table 8. Comparative Clinical Trials with Liraglutide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes Mellitus - Monotherapy				
Garber et al.[15] (2009) LEAD-3 MONO Liraglutide 1.2 to 1.8 mg once daily vs glimepiride 8 mg once daily	RCT, DB, MC, AC Patients 18 to 80 years of age with type 2 diabetes mellitus and BMI <45 kg/m^2 who had been treated with diet/exercise or up to half the highest dose of oral antidiabetic drug monotherapy for at least 2 months	N=746 52 weeks	Primary: Change in A1C Secondary: Body weight, FPG, self-measured eight-point plasma-glucose profiles, blood pressure, β-cell function (proinsulin to insulin ratio, HOMA-B and HOMA-IR), and patients' reported assessment of quality-of-life	Primary: After 52 weeks, the mean A1C decreased by 0.51% with glimepiride, 0.84% with liraglutide 1.2 mg (–0.33% vs glimepiride; P=0.0014), and 1.14% with liraglutide 1.8 mg (–0.62% vs glimepiride; P<0.0001). The reduction in A1C with liraglutide 1.8 mg was greater than with liraglutide 1.2 mg (–0.29%; P=0.0046). After 52 weeks, 28% of patients receiving liraglutide 1.2 mg and 38% of patients receiving liraglutide 1.8 mg achieved an A1C <6.5%, compared to 16% receiving glimepiride (P=0.0025 and P<0.0001 for liraglutide 1.2 mg and 1.8 mg, respectively). Likewise, 43% of patients receiving liraglutide 1.2 mg and 51% of patients receiving liraglutide 1.8 mg achieved an A1C <7%, compared to 28% receiving glimepiride (P=0.0007 and P<0.0001 for liraglutide 1.2 mg and 1.8 mg, respectively).The proportion of patients achieving these targets with liraglutide 1.8 mg was significantly higher than with liraglutide 1.2 mg (P value not reported). Secondary: After 52 weeks, FPG values were 8.65 mmol/l, 8.25 mmol/l, and 9.27 mmol/l in the liraglutide 1.2 mg, liraglutide 1.8 mg, and glimepiride groups, respectively. Changes in FPG were significantly greater with liraglutide 1.2 mg and 1.8 mg than with glimepiride (P=0.027 and P=0.001, respectively). Postprandial glucose concentrations were significantly lower with liraglutide 1.8 mg compared to glimepiride (P=0.0038). There were no other significant differences among the treatment groups. Insulin resistance decreased by 0.65% with liraglutide 1.2 mg and 1.35% with liraglutide 1.8 mg, but increased 0.85% with glimepiride (P=0.0249 and P=0.0011, respectively). There was no significant difference in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				proinsulin:insulin ratio or HOMA-B among the treatment groups. Those receiving liraglutide lost weight and those taking glimepiride gained weight. The weight loss in the first 16 weeks was sustained throughout the study. Patients who had nausea for >7 days had a mean weight change of –3.24 kg, –3.39 kg, and –1.43 kg (liraglutide 1.2 mg, liraglutide 1.8 mg and glimepiride, respectively). Patients who had no nausea or <7 days of nausea had a mean weight change of –1.85 kg, –2.26 kg, and +1.22 kg (liraglutide 1.2 mg, liraglutide 1.8 mg and glimepiride, respectively). There was no significant difference among the treatment groups (P=NS). Patients receiving liraglutide 1.8 mg reported improved quality of life scoring for physical and emotional domains compared with those assigned to glimepiride (P=0.02), which were the result of improvements in weight image and weight concern (P<0.01). There were no events of major hypoglycemia reported during the study. Minor hypoglycemia occurred in 12% and 8% of patients receiving liraglutide 1.2 mg and 1.8 mg, respectively compared with 24% in the glimepiride group (P<0.0001). Nausea was reported in 27.5% and 29.3% of patients in the liraglutide 1.2 mg and 1.8 mg groups, respectively compared to 8.5% in the glimepiride group (P<0.0001). Vomiting was reported in 9.3%, 12.4%, and 3.6% of patients receiving liraglutide 1.2 mg, liraglutide 1.8 mg and glimepiride, respectively (P<0.0001). Diarrhea was reported in 8.9% of patients receiving glimepiride compared with 15.5% and in the liraglutide 1.2 mg group (P=0.0283) and 18.7% in the liraglutide 1.8 mg group (P=0.0017).
Madsbad et al.[16] (2004) Liraglutide 0.045 mg, 0.225 mg, 0.45 mg, 0.60 mg, or 0.75 mg once daily (double-blind vs placebo)	RCT, MC, DB, OL Patients ≥30 years of age with type 2 diabetes, BMI ≤40 kg/m^2, who were being treated with diet or an oral hypoglycemic agent (OHA) and who had	N=193 12 weeks	Primary: Change in A1C Secondary: Fasting serum glucose, fasting C-peptide, glucagon, insulin, HOMA, proinsulin-to-insulin ratio, and	Primary: After 12 weeks, compared to placebo, the A1C decreased -0.34% (liraglutide 0.225 mg; P=0.0877), -0.30% (liraglutide 0.45 mg; P=0.1131), -0.70% (liraglutide 0.60 mg; P=0.0002), -0.75% (liraglutide 0.75 mg; P<0.0001), and -0.74% (glimepiride; P<0.0001). In the liraglutide 0.045 mg group, A1C increased 0.25% (P=0.1905). Secondary: After 12 weeks, compared to placebo, fasting serum glucose levels decreased -1.37 mmol/l (liraglutide 0.225 mg; P=0.0090), -0.35 mmol/l

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glimepiride 1 to 4 mg once daily (open-label treatment) vs placebo	an A1C ≤9.5% (OHA) or 7.5% to 10.0% (diet)		weight	(liraglutide 0.45 mg; P=0.4976), -2.14 mmol/l (liraglutide 0.60 mg; P<0.0001), -1.82 mmol/l (liraglutide 0.75 mg; P=0.0003), and -2.60 mmol/l (glimepiride; P<0.0001). In the liraglutide 0.045 mg group, fasting serum glucose increased 0.74 mmol/l (P=0.1499). Mean β-cell function increased 23.56% with liraglutide 0.75 mg compared to placebo (P=0.0002) and by 24.57% with glimepiride compared to placebo (P=0.0002). There were no other significant differences among the treatment groups. There were significant differences in insulin resistance among any of the treatment groups. The proinsulin-to-insulin ratio decreased significantly with liraglutide 0.75 mg compared with placebo (P=0.0244). There was no change in the proinsulin-to-insulin with glimepiride. There were no significant differences between the liraglutide groups and placebo for fasting insulin, C-peptide, and glucagon. Treatment with liraglutide did not increase body weight. In the 0.45 mg liraglutide group, a significant decrease in body weight was observed compared to placebo (-1.2 kg). There were no other significant differences among the treatment groups. The number of patients with adverse events was comparable across the liraglutide groups and the placebo group (60% vs. 55%, respectively) and was lower in the open-label group (35%). Nausea was reported by 10 of 135 patients exposed to liraglutide compared with 1 of 29 patients in the placebo group. Other gastrointestinal events included diarrhea (5 of 135 liraglutide-treated patients), vomiting (3 of 135 patients), and constipation (3 of 135 patients). None of these events were reported in the placebo or glimepiride groups. No antibody formation against liraglutide was detected in this trial.
Seino et al.[17] (2010) Liraglutide 0.9 mg once daily	RCT, DB, MC, PG Japanese patients ≥20 years of age with type 2 diabetes mellitus, BMI <35	N=411 24 weeks	Primary: Change in A1C Secondary: FPG, SMPG, PPG, weight, percentage	Primary: The mean change in A1C was significantly greater with liraglutide compared to glibenclamide (-1.88% vs -1.38%; P<0.001). Secondary: More patients achieved an A1C <7.0% with liraglutide (49.0%) compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glibenclamide* 2.5 mg once or twice daily	kg/m^2, A1C 7-10% who were inadequately controlled with diet therapy or oral antidiabetic drug monotherapy		of patients achieving A1C <7% and <6.5%	to glibenclamide (30.8%; P<0.0001). Similarly, more patients achieved A1C <6.5% with liraglutide (27.8%) compared to glibenclamide (10.8%; P<0.0001). Mean FPG levels were significantly lower with liraglutide (7.6 mmol/l) than with glibenclamide (8.3 mmol/l; P<0.0001). The mean AUC was significantly lower in the liraglutide group (32.1 mmol/l*h) than in the glibenclamide group (37.3 mmol/l*h; P<0.0001). Improvement in glycemic control with liraglutide was apparent in the 7-point SMPG profile at 24 weeks, with significant reductions in mean PG levels and PPG increment with liraglutide compared with glibenclamide (P<0.0001 for both). Mean body weight was reduced with liraglutide (-0.92 kg) compared to an increase with glibenclamide (0.99 kg; P<0.0001). The most common AEs were nasopharyngitis, diarrhea, constipation and upper respiratory tract infection. More patients reported gastrointestinal AEs in the liraglutide group compared with glibenclamide. The most common were diarrhea (6.3% with liraglutide and 3.8% with glibenclamide) and constipation (5.6% with liraglutide and 3.8% with glibenclamide). Nausea was reported infrequently (4.5% with liraglutide, 1.5% with glibenclamide). The overall rate of minor hypoglycemic episodes was significantly lower in the liraglutide group compared with the glibenclamide group (P<0.0001).
Feinglos et al.[19] (2005) Liraglutide 0.045 mg, 0.225 mg, 0.45 mg, 0.6 mg or 0.75 mg once daily vs	RCT, DB, MC, PG Patients 18 to 75 years of age with type 2 diabetes who received at least 3 months of previous treatment with oral antidiabetic drug monotherapy, BMI	N=210 12 weeks	Primary: Change in body weight, glycemic control, serum insulin and C-peptide levels, body composition, safety	Primary: After 12 weeks, patients receiving metformin experienced a weight loss of −0.61% compared to baseline (P=0.124). Patients receiving liraglutide experienced a weight loss ranging from −0.05% (0.045 mg; P=0.825) to −1.87% (0.225 mg; P=0.006) compared to baseline. There were no significant differences detected for body weight change when each of the liraglutide treatment groups was compared with metformin. The baseline A1C levels were 6% to 7% after the 4 week metformin run-in period. At 12 weeks, mean A1C changes from baseline for liraglutide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 1,000 mg twice daily	27 to 42 kg/m^2 and A1C ≤10%			0.045 mg, 0.225 mg, 0.45 mg, 0.6 mg, 0.75 mg and metformin were +1.28%, +0.86%, +0.22%, +0.16%, +0.30% and +0.09%, respectively. There were no significant differences in A1C between the liraglutide (0.45 mg, 0.6 mg and 0.75 mg) and metformin treatment groups. Liraglutide 0.045 mg and 0.225 mg dosing groups had increasing A1C values over time and the differences were significant compared to metformin (P values not reported). FPG increased in the liraglutide 0.45 mg (0.56 mmol/l; P=0.136 vs metformin), 0.6 mg (0.015 mmol/l; P=0.696 vs metformin), and 0.75 mg (0.87 mmol/l; P=0.050 vs metformin) groups. FPG decreased by -0.22 mmol/l with metformin. The two lowest liraglutide doses (0.045 mg and 0.225 mg) did not maintain adequate glycemic control compared to metformin (P<0.001). After 12 weeks, liraglutide increased fasting serum insulin levels. The greatest increases in serum insulin levels were observed at the 0.75 mg dose of liraglutide. Increases in C-peptide levels were significantly different from metformin for 0.75 mg liraglutide (0.24 nm vs. 0 nm for metformin, P=0.002). All treatment groups (except for liraglutide 0.045 mg) showed a decrease in total body mass and total fat mass. All groups were significantly different from the liraglutide 0.045 mg group in changes in total body mass. Changes in total fat mass were significantly greater with liraglutide 0.225 mg and metformin than liraglutide 0.045 mg (P=0.016 and P=0.015, respectively). The percentage of patients reporting treatment-emergent adverse events (TEAE) with liraglutide was 52% to 68% compared to 56% with metformin. The most frequently reported TEAEs were injection site bruising, constipation and diarrhea among the liraglutide groups, and coughing, diarrhea and abdominal pain for the metformin treatment group. No major hypoglycemic events were reported during the trial. In the liraglutide group, 2.8% of patients and 5.9% of patients in the metformin group reported minor hypoglycemic events. There was no increase in the frequency of hypoglycemia as compared with metformin. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients who showed a positive test for antibodies against liraglutide during the trial.
Type 2 Diabetes Mellitus – Add-on Studies				
Nauck et al.[18] (2009) LEAD-2 Liraglutide 0.6 to 1.8 mg once daily vs glimepiride 4 mg once daily vs placebo All patients continued to receive metformin 1 g twice daily in addition to study medication.	RCT, DB, PC, AC, PG Patients 25-79 years of age with type 2 diabetes mellitus, A1C 7-11% (previous OAD monotherapy for ≥3 months) or 7-10% (previous OAD combination therapy for ≥3 months), and BMI ≤40 kg/m^2	N=1,091 26 weeks	Primary: Change in A1C Secondary: Changes in body weight, fasting plasma glucose (FPG), 7-point plasma glucose profiles, and β-cell function, fasting C-peptide, fasting proinsulin-to-insulin ratio, and the homeostasis model assessment index of β-cell function (HOMA-B)	Primary: The mean A1C decreased by 0.7% with liraglutide 0.6 mg (95% CI -1.0 to -0.6 vs placebo), 1.0% with liraglutide 1.2 mg and 1.8 mg (95% CI, -1.3 to -0.9 vs placebo), 1.0% with glimepiride, and increased by 0.1% with placebo. Analysis of the estimated treatment difference in A1C between liraglutide and glimepiride demonstrated that liraglutide 1.2 mg and 1.8 mg liraglutide were non-inferior to treatment with glimepiride (95% CI, -0.2 to 0.2). A significantly greater percentage of patients in all of the liraglutide groups achieved the ADA and AACE A1C goals than in the placebo group (P<0.02 for all comparisons of liraglutide to placebo for both A1C goals). The percentages of patients in the 1.2 and 1.8 mg liraglutide treatment groups achieving the ADA and AACE A1C goals were comparable to the percentage achieving goals in the glimepiride group. Secondary: The decreases in FPG for all of the liraglutide groups were significantly greater than the increase observed for the placebo group (P<0.0001), but were similar to the decrease observed for the glimepiride group. Mean postprandial glucose values decreased in all treatment groups (P<0.001 for comparisons of all liraglutide groups to placebo; the decreases in the 1.2 and 1.8 mg liraglutide groups were comparable to those with glimepiride). Weight loss was dose dependent in the liraglutide treatment groups (1.8 kg, 2.6 kg, and 2.8 kg for liraglutide 0.6 mg, 1.2 mg, and 1.8 mg, respectively) and was significantly different (P<0.0001) from the weight gain in the glimepiride group (1.0 kg). The weight losses in the 1.2 and 1.8 mg liraglutide groups were also significantly greater (P<0.01) than the weight loss in the placebo group (1.5 kg). The decreases in the proinsulin-to-insulin ratio for the three liraglutide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups were comparable to those in the glimepiride group and were significantly different (P<0.0001) than those in the placebo group. No significant differences in fasting insulin and fasting C-peptide values were observed between the liraglutide groups compared with either the glimepiride or placebo groups. The liraglutide treatment groups had improvements in HOMA-B of 63%, 70%, and 71% for the 0.6 mg, 1.2 mg, and 1.8 mg doses. The glimepiride group had an improvement in the mean HOMA-B value of 68%. No improvement in HOMA-B was observed in the placebo group. No significant differences were observed between treatments for the homeostasis model assessment index of insulin resistance. Gastrointestinal disorders (nausea, vomiting, and diarrhea) were the most frequently reported adverse events in the liraglutide groups and were reported during the course of the study by 35%, 40%, and 44% of the patients in the 0.6, 1.2, and 1.8 mg liraglutide groups, respectively, and by 17% in the placebo and glimepiride groups. Minor hypoglycemia occurred in 3% of patients in the placebo and liraglutide groups and 17% in the glimepiride group.
Marre et al.[20] (2009) LEAD-1 SU Liraglutide 0.6 to 1.8 mg once daily vs rosiglitazone 4 mg once daily vs placebo	RCT, DB, AC, PG Patients 18 to 80 years of age with type 2 diabetes mellitus who were receiving oral glucose-lowering agents (OGLAs) for ≥3 months, A1C 7% to 11% (monotherapy) or 7% to 10% (combination therapy), and BMI ≤45.0 kg/m^2	N=1,040 26 weeks	Primary: Change in A1C Secondary: Percentages of patients reaching A1C goal (<7.0% or ≤6.5%), FPG goal (≤7.2 mmol/l) and postprandial plasma glucose goal (PPG ≤10.0 mmol/l); changes in body weight, FPG, mean PPG,	Primary: After 26 weeks, A1C increased 0.2% with placebo and decreased -1.1% with liraglutide 1.2 mg (P<0.0001), -1.1% with liraglutide 1.8 mg (P<0.0001), -0.4% with rosiglitazone (P<0.0001). Treatment with liraglutide 1.2 mg and 1.8 mg led to a greater reduction in A1C than rosiglitazone (P<0.0001). There was no significant difference between liraglutide 0.6 mg and rosiglitazone. Secondary: After 26 weeks, 42% and 21% of patients treated with liraglutide 1.8 mg reached an A1C <7% and ≤6.5%, respectively, compared with 8% and 4% for placebo (P<0.0001). More patients receiving liraglutide 1.8 mg achieved A1C <7% compared to liraglutide 1.2 mg (P=0.018). In the rosiglitazone group, 22% and 10% of patients achieved an A1C <7% and ≤6.5%, respectively. The proportion of patients achieving A1C goals was higher with liraglutide than rosiglitazone (P≤0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All groups also received glimepiride 2 to 4 mg once daily.				At week 26, all doses of liraglutide decreased FPG more than did placebo (P<0.0001). Only liraglutide 1.2 and 1.8 mg produced greater reductions in FPG than rosiglitazone (P≤ 0.006). The percentage of patients achieving FPG goals was 19% with liraglutide 0.6 mg (P=0.002), 37% with liraglutide 1.2 mg (P<0.001); and 38% with liraglutide 1.8 mg (P<0.001) compared to placebo (7%). The liraglutide 1.2 and 1.8 mg treatment groups also had more patients achieving the same FPG goal compared rosiglitazone (26%; P=0.007 and P= 0.01, respectively). Treatment differences for PPG were greater with all doses of liraglutide compared with placebo (P< 0.0001) and greater with liraglutide 1.2 mg (P=0.043) and 1.8 mg (P=0.0022) compared with rosiglitazone. Mean reductions in weight were 0.2 kg with liraglutide 1.8 mg and 0.1 kg with placebo. Increases occurred with liraglutide 0.6 mg (0.7 kg), liraglutide 1.2 mg (0.3 kg) and rosiglitazone (2.1 kg).The differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no significant differences compared with placebo. The most common adverse events were gastrointestinal (diarrhea, nausea, dyspepsia and constipation) and nervous system disorders (headache and dizziness). Nausea was highest with liraglutide 1.2 mg (10.5%) and lowest with placebo (1.8%). Vomiting (4.4%) and diarrhea (7.9%) were higher with liraglutide 1.2 mg. The proportion of patients experiencing minor hypoglycemia was lowest with placebo (2.6%), comparable with liraglutide 0.6 mg (5.2%) and rosiglitazone (4.3%) groups, and similar between the liraglutide 1.2 mg (9.2%) and liraglutide 1.8 mg (8.1%) treatment groups. The incidence was higher with liraglutide 1.2 mg (P=0.0024) and 1.8 mg (P=0.0065) compared with rosiglitazone.
Pratley et al.[22] (2010) Liraglutide 1.2 to 1.8 mg once daily	RCT, OL, PG, MC Patients 18-80 years of age with type 2 diabetes mellitus	N=665 26 weeks	Primary: Change in A1C Secondary: Proportion of	Primary: Mean decreases in A1C were –1.50% with liraglutide 1.8 mg (95% CI, –1.63 to –1.37), –1.24% with liraglutide 1.2 mg (95% CI, –1.37 to –1.11), and –0.90% with sitagliptin (95% CI, –1.03 to –0.77). Estimated mean treatment differences were –0.60% with liraglutide 1.8 mg compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sitagliptin 100 mg once daily Patients continued to receive metformin therapy.	who had inadequate glycemic control (A1C 7.5-10%), BMI ≤45 kg/m^2 who were on metformin (≥1,500 mg daily for ≥3 months)		patients achieving A1C goals, FPG, PPG, body weight, β-cell function, fasting lipid profile, cardiovascular risk markers, treatment satisfaction	sitagliptin (95% CI, –0.77 to –0.43; P<0.0001), and –0.34% with liraglutide 1.2 mg compared to sitagliptin (95% CI, –0.51 to –0.16; P<0.0001). Secondary: Significantly more patients achieved A1C <7.0% with liraglutide 1.8 mg (OR 4.50; 95% CI, 2.90–6.97) and liraglutide 1.2 mg (OR 2.75; 95% CI, 1.78–4.25) than sitagliptin. Significantly more patients achieved A1C ≤6.5% with liraglutide 1.8 mg (OR 4.25; 95% CI, 2.55-7.08) and liraglutide 1.2 mg (OR 2.11; 95% CI, 1.24-3.59) than sitagliptin. Mean decreases in fasting plasma glucose were significantly greater with liraglutide than with sitagliptin: –2.14 mmol/l for liraglutide 1.8 mg (95% CI, –2.43 to –1.84); –187 mmol/l for liraglutide 1.2 mg (95% CI, –2.16 to –1.57), and –0.83 mmol/l for sitagliptin (95% CI, –1.13 to –0.54). Estimated least squares mean treatment differences were –1.31 mmol/l for liraglutide 1.8 mg versus sitagliptin (95% CI, –1.70 to –0.91), and –1.04 mmol/l for liraglutide 1.2 mg versus sitagliptin (95% CI, –1.43 to –0.64). Mean weight loss was significantly greater with liraglutide than with sitagliptin: –3.38 kg for liraglutide 1.8 mg (95% CI, –3.91 to –2.84); –2.86 kg for liraglutide 1.2 mg (95% CI, –3.39 to –2.32), and –0.96 kg for sitagliptin (95% CI, –1.50 to –0.42). Estimated mean treatment differences were –2.42 kg for liraglutide 1.8 mg versus sitagliptin (95% CI, –3.14 to –1.70), and –1.90 kg for liraglutide 1.2 mg (95% CI, –2.61 to –1.18). Liraglutide was associated with significant improvements in β-cell function, C-peptide concentration, and proinsulin-to-insulin ratio compared with sitagliptin, but no treatment-related differences were recorded for insulin resistance, or fasting insulin concentration. Improvements were seen in all DTSQ items for all treatment groups. The increase in patients' treatment satisfaction from baseline was significantly higher with liraglutide 1.8 mg than with sitagliptin (95% CI, 0.13–2.64), but the increase with liraglutide 1.2 mg versus sitagliptin was not significant. There was no difference in perceived convenience of treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(oral vs injection) between sitagliptin and liraglutide. The most common adverse events were gastrointestinal symptoms. Minor hypoglycemia was reported by similar proportions of patients treated with liraglutide 1.8 mg (5%), liraglutide 1.2 mg (5%), and sitagliptin (5%).
Russell-Jones et al.[23] (2009) LEAD-5 MET+SU Liraglutide 1.8 mg once daily vs insulin glargine (open-label) titrated and administered once daily vs placebo Patients also received metformin 2 g/day and glimepiride 4 mg/day.	RCT, PG, PC Patients 18-80 years of age with type 2 diabetes mellitus who were treated with oral glucose lowering drugs for ≥3 months, A1C 7.5-10% (monotherapy) or 7-10% (combination therapy), and BMI ≤45 kg/m^2	N=581 26 weeks	Primary: Change in A1C Secondary: Body weight, waist circumference, FPG, eight point plasma glucose profiles, β-cell function	Primary: After 26 weeks, the A1C reduction from baseline with liraglutide was 1.33%, with placebo was 0.24% and with insulin glargine was 1.09%. The reduction in A1C with liraglutide was significantly greater than the reductions observed in both the placebo and insulin glargine groups (treatment differences for liraglutide vs placebo −1.09%; 95% CI, −1.28 to −0.90; P<0.0001 and liraglutide vs insulin glargine −0.24%; 95% CI, −0.39 to −0.08; P=0.0015). The A1C reduction in the insulin glargine group was also significantly greater than in the placebo group (treatment difference −0.85%; 95% CI, −1.04 to −0.66; P<0.0001). Significantly more patients reached A1C ≤6.5% and <7% with liraglutide than with either placebo or insulin glargine. Secondary: The mean weight loss from baseline of 1.8 kg achieved in the liraglutide group was significantly greater than the reduction in the placebo group (0.42 kg; weight difference of −1.39 kg; 95% CI, −2.10 to −0.69; P=0.0001). Weight increased by 1.6 kg with insulin glargine, resulting in a mean treatment difference of −3.43 kg (95% CI, −4.00 to −2.86; P<0.0001). The reduction in waist circumference for the liraglutide group (1.50 cm) was significant compared with the insulin glargine group (0.89 cm increase; treatment difference −2.40 cm; 95% CI, −3.14 to −1.65; P<0.0001), but not compared with the placebo group (0.62 cm reduction; treatment difference −0.88 cm; 95% CI, −1.81 to 0.04; P=0.0608). The reduction in mean FPG in the liraglutide group was significantly greater compared with the placebo group (treatment difference for FPG −2.08 mmol/l; P<0.0001), but not compared to the insulin glargine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A reduction in postprandial plasma glucose was observed in the liraglutide (1.81 mmol/l) and insulin glargine (1.61 mmol/l) groups, with the reduction with liraglutide being significantly greater than with placebo (P<0.0001) but not vs insulin glargine. The proinsulin to C-peptide ratio showed a significant improvement in the liraglutide group compared with the insulin glargine group (P=0.0019) and the placebo group (P<0.0001). The proportion of patients experiencing minor hypoglycemia in the liraglutide group (27.4% patients) was not different from the insulin glargine group (28.9%), but higher compared with the placebo group (16.7%). The most common AEs in the liraglutide group were gastrointestinal and of mild or moderate severity (mainly nausea).
Zinman et al.[21] (2009) LEAD-4 MET+TZD Liraglutide 1.2 to 1.8 mg once daily vs placebo Patients also received metformin 1 g twice daily and rosiglitazone 4 mg twice daily.	RCT, DB, PC, PG Patients 18 to 80 years of age with type 2 diabetes, A1C 7-11% (previous oral antidiabetic monotherapy for ≥3 months) or 7-10% (previous combination therapy for ≥3 months), and BMI ≤45 kg/m^2	N=533 26 weeks	Primary: Change in A1C Secondary: Change in weight, FPG, 7-point SMPG, percentage of patients achieving A1C goals	Primary: The mean A1C values decreased by 1.5% for liraglutide 1.2 mg and 1.8 mg compared to 0.5% for placebo (liraglutide 1.2 mg vs. placebo: -0.9%; 95% CI, -1.1 to -0.8; liraglutide 1.8 mg vs. placebo: -1.1%; 95% CI, -1.1 to -0.8). Secondary: A total of 57.5% and 53.7% of patients in the liraglutide 1.2 mg and liraglutide 1.8 mg groups, respectively, achieved an A1C <7%, compared with 28.1% in the placebo group (P<0.0001). A total of 37.3% and 36.2% of patients receiving liraglutide 1.2 mg and liraglutide 1.8 mg, respectively, achieved an A1C <6.5% compared with 14.4% of patients receiving placebo (P<0.0001). The decreases in FPG were significantly greater with liraglutide 1.2 mg (-40 mg/dl) and liraglutide 1.8 mg (-44 mg/dl) than placebo (-8 mg/dl; P<0.0001). Mean 90-min PPG decreased in all treatment groups by -47 mg/dl for liraglutide 1.2 mg, -49 mg/dl for liraglutide 1.8 mg, and -14 mg/dl for placebo (all, P<0.001 vs placebo). Weight loss was observed in the liraglutide-treated groups (-1.0 kg and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				-2.0 kg for liraglutide 1.2 and liraglutide 1.8 mg, respectively) and was significantly different from the weight gain in the placebo group (+0.6 kg; P<0.0001). The weight loss in the liraglutide 1.8 mg group was significantly greater than the liraglutide 1.2 mg group (P=0.011). Gastrointestinal disorders were the most frequently reported adverse events in the liraglutide groups and were reported by 45%, 56%, and 19% of the patients in the liraglutide 1.2 mg, liraglutide 1.8 mg, and placebo groups, respectively. Minor hypoglycemia occurred at low incidence (9.0%, 7.9%, and 5.1%) for the liraglutide 1.2 mg, liraglutide 1.8 mg, and placebo groups, respectively. The rate of minor hypoglycemia for the 1.8 mg liraglutide group was significantly higher than placebo (P<0.004).
Type 2 Diabetes Mellitus – Liraglutide vs Exenatide				
Buse et al.[13] (2009) LEAD-6 Liraglutide 1.8 mg once daily vs exenatide 10 mcg twice daily	RCT, OL, AC, MC Patients 18-80 years of age with inadequately controlled type 2 diabetes (A1C 7-11%), BMI ≤45 kg/m^2 who were on maximally tolerated doses of metformin, sulfonylurea, or both for ≥3months	N=464 26 weeks	Primary: Change in A1C Secondary: Proportion of patients achieving A1C <7.0% and ≤6.5%, changes in fasting plasma glucose, self-measured 7-point plasma glucose profiles, bodyweight, β-cell function	Primary: The mean change in A1C was significantly greater with liraglutide than with exenatide (–1.12% vs –0.79%, respectively; 95% CI, –0.47 to –0.18). Secondary: The proportion of patients achieving A1C <7% was 54% with liraglutide vs 43% with exenatide (OR 2.02; 95% CI, 1.31 to 3.11). The proportion of patients achieving A1C ≤6.5% was 35% with liraglutide vs 21% with exenatide (OR 2.73; 95% CI, 1.68 to 4.43). Liraglutide reduced fasting plasma glucose significantly more than did exenatide (–1.61 mmol/l vs –0.60 mmol/l; 95% CI, –1.37 to –0.65; P<0.0001). Exenatide reduced postprandial plasma glucose more than liraglutide after breakfast (P<00001) and dinner (P=0.0005). Liraglutide and exenatide were associated with similar weight loss (liraglutide –3.24 kg vs exenatide –2.87 kg; P=0.2235). A similar proportion of patients lost weight with liraglutide (78%) compared to exenatide (76%). Increases in fasting insulin and β-cell function (HOMA-B) were significantly greater with liraglutide than with exenatide. Treatment differences for fasting C-peptide or proinsulin-to-insulin ratio were not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall treatment satisfaction was significantly better in the liraglutide group than in the exenatide group (P=0.0004). Adverse events were reported in 74.9% of patients receiving liraglutide and 78.9% of patients receiving exenatide. The most frequent severe adverse events were dyspepsia in the liraglutide group and nausea in the exenatide group. No major hypoglycemia occurred with liraglutide, but there were two episodes in patients receiving exenatide and a sulfonylurea. The proportion of patients who had minor hypoglycemia was lower with liraglutide (26%) compared to exenatide (34%).
Buse et al.[14] (2010) Liraglutide 1.8 mg	ES (LEAD-6) Patients 18-80 years of age with inadequately controlled type 2 diabetes (A1C 7-11%), BMI ≤45 kg/m^2 who were on maximally tolerated doses of metformin, sulfonylurea, or both for ≥3months. After 26 weeks, all patients previously receiving exenatide were switched to liraglutide 1.8 mg.	N=389 14 weeks	Primary: Efficacy and safety	Primary: Mean A1C decreased from 7.2% at week 26 to 6.9% at week 40 (P<0.0001) after switching from exenatide to liraglutide, but remained similar in patients who continued liraglutide (7.0% to 6.9%; P=0.1222). Additional patients reached A1C targets after switching from exenatide to liraglutide. After switching from exenatide to liraglutide, further reductions in FPG (P<0.0001), bodyweight (P<0.0001), and SBP (P<0.0001) occurred. In those continuing liraglutide, reductions in FPG (P=0.0973), bodyweight (P=0.0089) and SBP (P=0.0128) occurred. No significant changes in postprandial glucose, DBP, fasting insulin, fasting C-peptide, proinsulin:insulin ratio, or HOMA-IR occurred in either group. Similar numbers of patients reported ≥1 AE during the extension study (exenatide switched to liraglutide: 37.4% and liraglutide continued: 37.6%). Nausea and diarrhea occurred in 3.2% of patients switching from exenatide to liraglutide and 1.5% for continuing liraglutide. Vomiting was reported in 0.5% of patients switched from exenatide to liraglutide and in 2.0% of patients who continued liraglutide.
Obesity				
Astrup et al.[24] (2009)	RCT, DB, PC Patients 18-65 years	N=564 20 weeks	Primary: Change in bodyweight	Primary: Mean weight loss was 2.8 kg with placebo and 4.1 kg with orlistat. Mean weight loss was 4.8 kg with liraglutide 1.2 (P=0.003 vs placebo), 5.5 kg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Liraglutide 1.2 to 3 mg once daily vs orlistat 120 mg three times daily vs placebo	of age with BMI of 30-40 kg/m^2, stable bodyweight, and fasting plasma glucose <7 mmol/l		Secondary: Change in waist circumference, blood pressure, prevalence of metabolic syndrome, prediabetes status, fasting lipids, cardiovascular biomarkers, glucose metabolism parameters, and homoeostasis model assessment (HOMA) of β-cell function and insulin resistance	with liraglutide 1.8 mg was (P<0.001 vs placebo), 6.3 kg with liraglutide 2.4 mg (P<0.0001 vs placebo; P=0.003 vs orlistat), and 7.2 kg with liraglutide 3.0 mg (P<0.001 vs placebo; P<0.0001 vs orlistat). Secondary: Mean waist circumference was lower with liraglutide 2.4 mg and 3.0 mg than with placebo for women but not for men. Mean systolic and diastolic blood pressure decreased in all the treatment groups. The proportion of patients with metabolic syndrome decreased by >60% in those treated with liraglutide 2.4 mg and 3.0 mg. The reduction in the placebo group was 38% and in the orlistat group was 13%. The prevalence of prediabetes decreased by 84–96% with liraglutide 1.8 mg, 2.4 mg, and 3.0 mg. There was no significant effect of liraglutide on lipids or cardiovascular biomarkers. Mean fasting plasma glucose decreased by 7–8% with liraglutide in addition to the diet and exercise program. Placebo or orlistat treatment had no effect on mean fasting plasma glucose. Mean fasting insulin decreased with liraglutide 3.0 mg, placebo, and orlistat compared to baseline. Mean A1C decreased from 0.14% with liraglutide 1.2 mg to 0.24% with liraglutide 3.0 mg. Mean change in plasma glucose during OGTT decreased for all liraglutide groups compared with placebo and orlistat. Plasma insulin and C-peptide during OGTT did not change with liraglutide. Median β-cell function decreased with placebo and orlistat by 17% and 21%, respectively, but increased with liraglutide by 5–24%. Liraglutide treatment did not have any effect on insulin resistance.

*Synonym for glyburide
Study abbreviations: DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: A1C=glycosylated hemoglobin A1c, AEs=adverse events, BMI=body mass index, CRP=C-reactive protein, FFA=free fatty acids, FPG=fasting plasma glucose, FPI=fasting plasma insulin, HDL=high-density lipoprotein, HOMA=homeostasis model assessment, HOMA-B=homeostasis model assessment of β-cell function, HOMA-S=homeostasis model assessment of insulin sensitivity, LDL=low-density lipoprotein, PPG=postprandial glucose, PPI=postprandial insulin, SMPG=self-measured plasma glucose, TC=total cholesterol, TG=triglycerides

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of Liraglutide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Liraglutide	injection	Victoza®	$$$$$	N/A

N/A=Not available

X. Conclusions

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, which was approved by the FDA in January 2010. It is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] Liraglutide is not currently available in a generic formulation.

There are several guidelines that provide recommendations on the treatment of type 2 diabetes. According to the ADA/EASD treatment algorithm, metformin is recommended as first-line therapy, followed by the addition of insulin or a sulfonylurea.[7] However, the addition of exenatide or pioglitazone to metformin may be considered if hypoglycemia is a concern.[7] According to the AACE/ACE algorithm, metformin is recommended as first-line therapy.[8] An incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin; however, the incretin mimetics are given a higher priority than DPP-4 inhibitors due to the greater effect on reducing postprandial glucose and potential for weight loss.[8] The incretin mimetics are recommend as a second- or third-line treatment option in other guidelines.[10-11] Since liraglutide was approved by the FDA in January 2010, it is not mentioned in the available guidelines.

Liraglutide has been evaluated in several clinical trials as monotherapy, as well as in combination with metformin, sulfonylureas and thiazolidinediones. As monotherapy, liraglutide improved glycemic parameters to a greater extent than placebo or a sulfonylurea.[15-17] As add-on to metformin therapy, liraglutide was found to be as effective as glimepiride and more effective than sitagliptin.[18,22] As add-on to glimepiride therapy, liraglutide was found to be more effective than rosiglitazone.[20] As add-on to the combination of metformin and glimepiride, liraglutide was found to be more effective than insulin glargine.[23] In a 26-week open-label trial sponsored by the manufacturer, liraglutide was found to be more effective than exenatide in reducing A1C and other glycemic endpoints in patients who were not adequately controlled on oral antidiabetic drugs.[13] There have been no studies establishing conclusive evidence of macrovascular risk reduction with liraglutide or any other antidiabetic drug.[1]

Nausea is the most common adverse event with liraglutide. In clinical trials, there were more cases of pancreatitis reported with liraglutide than with comparators.[1] Liraglutide has also been shown to cause thyroid C-cell tumors in rats and mice; however, it is unknown if it causes thyroid C-cell tumors in humans.[1] According to the prescribing information, liraglutide should only be prescribed in patients for whom the benefits are considered to outweigh the risks because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans.[1] Liraglutide is not recommended as first-line therapy for patients inadequately controlled on diet and exercise, and it is not approved for use with insulin.[1] Patients may develop antibodies to liraglutide consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals.[1]

At this time, there is insufficient evidence to conclude that liraglutide offers a significant clinical advantage over other alternatives in general use. Since liraglutide is not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, it should be managed through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand liraglutide product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Victoza® [package insert]. Princeton, NJ: Novo Nordisk, Inc.; January 2010.
2. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2010. Available from Wolters Kluwer Health, Inc. Accessed September 2010.
3. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2010; September 2010.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 2010.
5. IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation, 2005. Available at: http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf. Accessed September 2010.
6. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33:S11-S61.
7. Nathan D, Buse J, Davidson M, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203.
8. Rodbard, H, Jellinger, P, Davidson, J, et al. American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocrine Pract 2009;15:540-559.
9. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus: Endocr Pract 2007;13(Suppl 1):1-68.
10. National Institute for Health and Clinical Excellence (2009) Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. Available at: www.nice.org.uk/CG87ShortGuideline. Accessed September 2010.
11. Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of type 2 diabetes mellitus in adults (2009). Available at: http://www.icsi.org/diabetes_mellitus__type_2/management_of_type_2_diabetes_mellitus__9.html. Accessed September 2010.
12. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008. Available at: http://www.nice.org.uk/nicemedia/pdf/CG66FullGuideline0509.pdf. Accessed September 2010.
13. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.
14. Buse JB, Sesti G, Schmidt WE, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care 2010;33:1300-3.
15. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473-81.
16. Madsbad S, Schmitz O, Ranstam J, et al. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care 2004;27:1335-42.
17. Seino Y, Rasmussen MF, Nishida T, et al. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. Curr Med Res Opin 2010;26:1013-22.
18. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90.
19. Feinglos MN, Saad MF, Pi-Sunyer FX, et al. Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in patients with Type 2 diabetes. Diabet Med 2005; 22:1016-23.
20. Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in patients with Type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268-78.
21. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 2009;32:1224-30.
22. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010;375:1447-56.

23. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia 2009;52:2046-55.
24. Astrup A, Rössner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374:1606-16.