Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 4, 2015

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Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document

P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Respiratory Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- For a diagnosis of allergic rhinitis, the patient must also have failed 30-day treatment trials with at least two prescribed antiallergic agents, to include oral antihistamines or intranasal corticosteroids either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- For all other diagnoses, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred respiratory agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- Requests for Pulmicort Respules® or Singulair® will not require failed therapy for children under age five with a diagnosis of asthma.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Respiratory agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Intranasal Corticosteroids

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred intranasal corticosteroids in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Intranasal corticosteroid agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

EENT Antiallergic Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- For ophthalmic products, the patient must also have failed 14-day treatment trials with at least two prescribed and preferred ophthalmic agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- For nasal products, the patient must have also failed 14-day treatment trials with at least two prescribed antiallergic agents, to include oral antihistamines, intranasal corticosteroids or intranasal cromolyn, either generic, OTC or brand within the past 6 months or have a documented allergy or contraindication to all preferred or acceptable agents.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- EENT antiallergic agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

EENT Antibacterial Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 3-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 30 days or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Not Applicable

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

EENT Vasoconstrictor Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 3-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- EENT vasoconstrictors are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

November 4, 2015
9:00 a.m. – 12:00 p.m.

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1. Opening remarks…….……..……Chair
2. Approval of August 19, 2015 P&T Committee Meeting minutes……Chair
3. Pharmacy program update.....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews…….…….University of Massachusetts Clinical Pharmacy Services
    - Inhaled Antimuscarinics – AHFS 120808
    - Respiratory β-adrenergic agonists – AHFS 121208
    - Leukotriene Modifiers – AHFS 481024
    - Inhaled Mast-cell Stabilizers – AHFS 481032
    - Respiratory Agents-Corticosteroids – AHFS 481008
    - Respiratory Smooth Muscle Relaxants – AHFS 861600
    - Intranasal Corticosteroids – AHFS 520808
    - Eye, Ear, Nose and Throat Preparations-Antiallergic Agents – AHFS 520200
    - Eye, Ear, Nose and Throat Preparations -Antibacterials – AHFS 520404
    - Eye, Ear, Nose and Throat Preparations -Vasoconstrictors – AHFS 523200
    - Androgens – AHFS 680800
6. New drug reviews
    - Afrezza®
    - Jardiance®
7. Results of voting announced…….....……...……..Chair
8. New business
9. Next meeting date
    - February 10, 2016
    - May 11, 2016
    - August 10, 2016
    - November 9, 2016
10. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Inhaled Antimuscarinics
AHFS Class 120808
November 4, 2015

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.[1-8] Tiotropium is also approved to reduce exacerbations in patients with COPD.[6] 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.[1-8]

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.[2] Aclidinium was Food and Drug Administration (FDA)-approved in July 2012. Similar to tiotropium, aclidinium is a long-acting inhaled antimuscarinic but requires twice daily dosing.[3] In April 2014 umeclidinium became the most recently FDA-approved inhaled antimuscarinic. It is also a long-acting agent approved for once-daily use.[8]

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 August 2013.

Table 1. Inhaled Antimuscarinics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aclidinium	dry powder inhaler	Tudorza Pressair®	none
Ipratropium	aerosol inhaler, inhalation solution*	Atrovent HFA®	ipratropium, Atrovent HFA®
Tiotropium	dry powder inhaler, solution inhaler	Spiriva Handihaler®, Spiriva Respimat®	Spiriva Handihaler®
Umeclidinium	dry powder inhaler	Incruse Ellipta®	none

*Generic is available in at least one dosage form or strength.
HFA=hydrofluoroalkane, 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.

Table 2. Treatment Guidelines Using the Inhaled Antimuscarinics

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2015)**[9]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking and occupational exposure to dusts/chemicals. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible. • A detailed medical history should be obtained for all patients suspected of developing COPD.

Clinical Guidelines	Recommendations

	• Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
	• Bronchodilator reversibility testing should be performed to rule out the possibility of asthma.
	• Chest radiograph may be useful to rule out other diagnoses.
	• Arterial blood gas measurements should be performed in advanced COPD.
	• Screening for α_1-antitrypsin deficiency should be performed in patients who are from areas with a particularly high prevalence of the deficiency. Typical patients develop COPD at 45 years of age or younger and have lower lobe emphysema.
	• Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis.
	
	<u>Therapeutic options</u>
	• In patients who smoke, smoking cessation is the intervention with the greatest capacity to influence COPD. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
	• The management of COPD should be individualized to address symptoms and improve the patient's quality of life.
	• None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications.
	• COPD patients should receive an annual influenza vaccine.
	• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value.
	• Patients who get short of breath while walking at their own pace on level ground should be offered rehabilitation.
	
	<u>Pharmacologic therapy for stable COPD</u>
	• Bronchodilators
	  o Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations.
	  o Principle bronchodilators include β_2-agonists, anticholinergics, and theophylline used as monotherapy or in combination.
	  o The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.
	  o For single-dose, as needed use, there is no advantage in using levalbuterol over conventional bronchodilators.
	  o Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable.
	• Corticosteroids
	  o Inhaled corticosteroids (ICSs) should be used in patients with an FEV_1 <60% of the predicted value.
	  o Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio.
	• Combination inhaled corticosteroid/ bronchodilator
	  o An inhaled corticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD.
	• Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended.

Clinical Guidelines	Recommendations
	Management of stable COPD • Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quite. • The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients and individualized assessment of symptoms and risk of exacerbation should also be considered. • Pharmacologic therapy is used to reduce symptoms, reduce frequency of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function. • For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators. • Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations. • Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD. • The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 <50% predicted, chronic bronchitis, and frequent exacerbations. • Influenza vaccines can reduce the risk of serious illness and death in COPD patients. • Currently, the use of antibiotics is not indicated in COPD, other than for treating infectious exacerbations of COPD and other bacterial infections. Management of exacerbations • The most common causes of an exacerbation are viral upper respiratory tract infections and infection of the tracheobronchial tree. • Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation. • Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function, and reduce the risk of early relapse, treatment failure, and length of hospital stay.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[10] **Reviewed July 2014**	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist.

Clinical Guidelines	Recommendations
	o FEV_1 ≥50% predicted: long acting beta agonist (LABA) or long-acting anticholinergic antagonist. o FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist. • In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined. • Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs. • In most cases, inhaled bronchodilator therapy is preferred. • Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. <u>Management of exacerbations</u> • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians,**	<u>Diagnosis</u> • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. <u>Treatment</u> • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with

Clinical Guidelines	Recommendations
American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)[11]	an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
International Primary Care Respiratory Group: **Management of Chronic Obstructive Pulmonary Disease (2006)** [12]	• 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/European Respiratory Society: **Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease (2004)**[13]	<u>Diagnosis</u>
	• 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:
	  o Mild COPD: FEV_1/FVC ≤0.70 and FEV_1 ≥80% predicted.
	  o Moderate COPD: FEV_1/FVC ≤0.70; FEV_1 ≥50% and <80% predicted.
	  o Severe COPD: FEV_1/FVC ≤0.70; FEV_1 ≥30% and <50% predicted.
	  o Very Severe COPD: FEV_1/FVC ≤0.70 and FEV_1 <30% predicted.
	
	<u>Treatment</u>
	• 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:
	  o Intermittent symptoms: Short-acting bronchodilator as needed for symptom control.
	  o Persistent symptoms (e.g., dyspnea, night waking):
	  ▪ Long- or short-acting bronchodilators given four times daily.

Clinical Guidelines	Recommendations
	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 three months than either agent alone. • Anticholinergics given four times a day can improve health status over a three-month period compared with placebo. • LABA 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 LABA and ipratropium leads to fewer exacerbations than either drug alone. • No good comparative data between different LABA are presently available although it is likely that their effects will be similar. • Combining LABA 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 LABA in its effect and in one clinical trial appeared to be superior to salmeterol in some measures over six 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 three-year 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 chromones (mast-cell stabilizers) in COPD.

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[3-8]

Indication	Aclidinium	Ipratropium	Tiotropium	Umeclidinium
Maintenance treatment of airflow obstruction associated with COPD, including chronic bronchitis and emphysema				✔
Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	✔	✔	✔	
Reduce exacerbations in COPD patients			✔	

COPD=chronic obstructive pulmonary disease.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Inhaled Antimuscarinics[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aclidinium	6	Not reported	Not reported	Feces (20 to 33) Renal (0.09)	5 to 8
Ipratropium	2 to 7	0 to 9	Liver	Feces (48) Renal (3.7 to 5.6)	1.6
Tiotropium	20	72	Liver (25)	Renal (14) Feces (% not reported)	120 to 144
Umeclidinium	Not reported	89	Not reported	Renal (<1) Feces (92)	11

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 Food and Drug Administration (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.[14] 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.[15]

Table 5. Adverse Drug Events (%) Reported with the Inhaled Antimuscarinics[3-8]

Adverse Events	Aclidinium	Ipratropium	Tiotropium	Umeclidinium
Cardiovascular				
Arrhythmia	-	<1	<1	<1
Chest pain	-	3	1 to 7	-
Edema	-	-	5	-
Hypotension	-	<1	-	-
Palpitation	-	✔	<1	-
Tachycardia	-	<1	<1	1
Central Nervous System				
Depression	-	-	1 to 4	-
Dizziness	-	1 to 3	<1	-
Headache	6.6	5 to 9	6	-

Adverse Events	Aclidinium	Ipratropium	Tiotropium	Umeclidinium
Insomnia	-	<1	4	-
Nervousness	-	<1	-	-
Paresthesia	-	-	1 to 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 to 5	-
Hypercholesterolemia	-	-	1 to 3	-
Hyperglycemia	-	-	1 to 3	-
Gastrointestinal				
Abdominal pain	-	-	5	1
Bitter taste	-	<1	-	-
Constipation	-	<1	1 to 5	-
Diarrhea	2.7	<1	-	-
Dyspepsia	-	1 to 5	1 to 6	-
Dysphagia	-	-	<1	-
Gastrointestinal pain	-	-	3 to 6	-
Gastrointestinal reflux	-	-	1 to 3	-
Gingivitis	-	-	<1	-
Intestinal obstruction	-	-	<1	-
Nausea	-	1 to 4	-	-
Stomatitis	-	-	1 to 3	-
Throat irritation	-	-	<1	-
Vomiting	1.1	-	1 to 4	-
Xerostomia	-	2 to 4	5 to 16	-
Genitourinary				
Urinary retention	-	<1	<1	-
Urinary tract infection	-	2 to 10	4 to 7	-
Musculoskeletal				
Arthralgia	-	-	4	2
Arthritis	-	<1	≥3	-
Back pain	-	2 to 7	-	-
Joint swelling	-	-	<1	-
Leg cramps	-	-	1 to 3	-
Myalgia	-	-	3 to 4	1
Skeletal pain	-	-	1 to 3	-
Respiratory				
Bronchitis	-	10 to 23	-	-
Bronchospasm	-	2	✔	-
COPD exacerbation	-	8 to 23	-	-
Cough	3	3 to 6	3	3
Dyspnea	-	7 to 10	-	-
Epistaxis	-	-	1 to 4	-
Laryngitis	-	-	1 to 3	-
Laryngospasm	-	<1	-	-
Nasopharyngitis	5.5	-	-	8
Pharyngitis	-	4	7 to 13	1
Rhinitis	1.6	2 to 6	3 to 6	-

Adverse Events	Aclidinium	Ipratropium	Tiotropium	Umeclidinium
Sinusitis	1.7	1 to 11	3 to 11	-
Sputum increased	-	1	-	-
Upper respiratory tract infection	-	9 to 34	41 to 43	1 to 5
Ocular				
Blurred vision	-	-	<1	-
Cataract	-	-	1 to 3	-
Eye pain	-	<1	-	-
Glaucoma	-	<1	<1	-
Intraocular pressure increased	-	-	<1	-
Mydriasis	-	<1	-	-
Narrow-angle glaucoma, worsening	-	-	✔	-
Pupil dilation	-	-	<1	-
Other				
Accidents	-	-	5 to 13	-
Allergic skin reactions	-	✔	2 to 4	-
Anaphylactic reactions	-	<1	-	-
Angioedema	-	<1	<1	-
Candidiasis	-	-	<1	-
Dehydration	-	-	<1	-
Dysphonia	-	-	1 to 3	-
Fall	1.1	-	-	-
Herpes zoster	-	-	1 to 3	-
Hypersensitivity reaction	-	<1	1 to 3	-
Infection	-	-	1 to 4	-
Influenza-like symptoms	-	2 to 8	3	-
Moniliasis	-	-	3 to 4	-
Toothache	1.1	-	-	1

✔ Percent not specified.
- Event not reported.
COPD=chronic obstructive pulmonary disease.

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[3-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aclidinium	COPD: Dry powder inhaler: 1 inhalation twice daily	Safety and efficacy in children have not been established.	Dry powder inhaler: 400 µg
Ipratropium	COPD: Aerosol inhaler: initial, 2 inhalations four times daily; maintenance, additional inhalations may be required; maximum, 12 inhalations in 24 hours Inhalation solution: 500 µg (1 unit dose vial) administered three to four times daily by oral nebulization, with doses 6 to 8 hours apart	Safety and efficacy in children have not been established.	Aerosol inhaler: 17 µg Inhalation solution: 0.2 mg/mL
Tiotropium	COPD: Dry powder inhaler: 2 inhalations of the powder contents of a single capsule once daily	Safety and efficacy in children have not been established.	Dry powder inhaler: 18 µg Solution inhaler:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Solution inhaler: 2 inhalations once daily		2.5 µg
Umeclidinium	COPD: Dry powder inhaler: 1 inhalation once daily	Safety and efficacy in children have not been established.	Dry powder inhaler: 62.5 µg

COPD=chronic obstructive pulmonary disease.

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.[16] (2010) Tiotropium 18 µg QD and beclomethasone 80 µg BID vs beclomethasone 160 µg BID vs beclomethasone 80 µg and salmeterol 50 µg BID	DB, RCT, XO Patients ≥18 years of age with asthma, FEV_1 >40% predicted, and non-smoking status (<10 pack-years)	N=210 52 weeks	Primary: Morning PEF 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, results of validated questionnaires	Primary: Patients receiving tiotropium had a morning PEF that was 25.8 L/min higher than that of patients receiving beclomethasone 160 µg 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 µg twice daily, the addition of tiotropium to beclomethasone improved most secondary outcomes, including evening PEF (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 pre bronchodilator FEV_1 more than the addition of salmeterol (P=0.003).
COPD				
Jones et al.[17] (2012) ATTAIN Aclidinium 200 µg BID vs aclidinium 400 µg BID	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD and an FEV_1/FVC <70% and FEV_1 <80% who were current or former smokers with a ≥10 pack-years history	N=828 24 weeks	Primary: Change from baseline in trough FEV_1 at 24 weeks Secondary: Change from baseline in peak FEV_1 at 24 weeks, proportion of patients	Primary: After 24 weeks of treatment, the mean trough FEV_1 was significantly higher in patients treated with aclidinium 200 µg (99±22 mL; P<0.0001) or 400 µg (128±22 mL; P<0.0001) when compared to patients treated with placebo. Secondary: At 24 weeks, the mean change from baseline in peak FEV_1 was significantly higher in patients treated with aclidinium 200 µg (185±23 mL) or 400 µg (209±24 mL) compared to patients receiving placebo (P<0.0001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			experiencing clinically significant improvements in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) scores at 24 weeks	A significantly higher proportion of patients treated with aclidinium 200 or 400 µg experienced a clinically significant improvement in SGRQ score when compared to patients treated with placebo at 24 weeks (56.0 and 57.3 vs 41.0%; P<0.001 for both). A significantly greater proportion of patients treated with aclidinium 200 or 400 µg achieved a clinical improvement in TDI score when compared to patients treated with placebo at 24 weeks (53.3 and 56.9 vs 45.5%; P≤0.05 for both). After 24 weeks, the mean total daily use of relief medication was significantly lower with aclidinium 200 (0.61 inhalations/day; P=0.0002) or 400 µg (0.95 inhalations/day; P<0.0001) compared to placebo; however, this was not a pre-specified endpoint. The rates of COPD exacerbations of any severity were decreased with both aclidinium 200 and 400 µg compared to placebo; however, this was not statistically significant and was not a pre-specified endpoint.
Kerwin et al.[18] (2012) ACCORD COPD I Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, PC, PG, RCT Patients ≥40 years of age diagnosed with moderate to severe stable COPD and a post-bronchodilator FVC <70% and FEV_1 ≥30% and <80% predicted and who were current or former smokers with a ≥10 pack-years history	N=561 12 Weeks	Primary: Change from baseline in trough FEV_1 at week 12 Secondary: Change from baseline in peak FEV_1 at week 12, FEV_1 on day one, trough and peak FEV_1 at weeks one, four and eight, $AUC_{0-3/3h}$ FEV_1, trough, peak and $AUC_{0-3/3h}$ FVC and trough IC at 12 weeks, changes in	Primary: Treatment with aclidinium 200 or 400 µg significantly increased trough FEV_1 from baseline compared to patients receiving placebo (86 and 124 mL, respectively; P<0.0001 for both). Secondary: Treatment with aclidinium 200 or 400 µg significantly increased the peak FEV_1 from baseline compared to patients receiving placebo (146 and 192 mL, respectively; P<0.0001 for both). There was a statistically significant improvement from baseline in peak FEV_1 at week 12 for patients receiving aclidinium 200 or 400 µg compared to patients receiving placebo (P<0.0001 for both). The changes from baseline in trough and peak FEV_1 were significantly higher in all aclidinium treatment groups at all-time points evaluated compared to the placebo group (P<0.0001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) at weeks four, eight and 12, nighttime symptoms, COPD exacerbations and safety	Patients randomized to receive aclidinium 200 or 400 µg experienced statistically significant increases in $AUC_{0\text{-}3/3h}$ FEV_1 compared to the placebo group (144 and 192 mL, respectively; P<0.0001 for both). At 12 weeks, a statistically significant improvements in peak FVC within three hours after dosing occurred for the aclidinium 200 (312 mL; P<0.0001) and 400 µg (359 mL; P<0.0001) groups compared to those randomized to placebo. Compared to the placebo group, there was a significant improvement from baseline in trough IC in both the aclidinium 200 (48 mL; P<0.001) and 400 µg (67 mL; P<0.0001) groups. At week four, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ score compared to treatment with placebo (-3.2 and -3.6, respectively; P<0.001 for both). At study end, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ scores compared to treatment with placebo (- 2.7 and -2.5, respectively; P=0.013 and P=0.019, respectively). At 12 weeks, a higher proportion of patients receiving aclidinium 200 µg experienced a decrease ≥4 units in SGRQ compared to patients receiving placebo (P<0.05); however, there was no difference in responder rates between patients receiving aclidinium 400 µg or placebo. At 12 weeks, a higher proportion of patients receiving aclidinium 200 or 400 µg achieved a clinically meaningful improvement (≥1 unit) in TDI scores compared to the placebo group (P<0.05 for both). Compared to placebo, patients receiving either dose of aclidinium experienced significantly improved nighttime COPD symptoms (P<0.05 for both). At week 12, there was a statistically significant decrease in the number of nighttime awakenings in the aclidinium 400 µg group compared to the placebo group (P<0.05). A reduction in the rate of moderate to severe COPD exacerbations per-patient per-year was observed with aclidinium 200 and 400 µg compared to placebo (33 and 34%, respectively; P>0.05 for both); however, these

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				results were not statistically significant. The incidence of adverse events was similar between the aclidinium and placebo groups. Treatment-emergent adverse events occurred in 44.7% of patients receiving aclidinium 400 µg, 50.5% of those receiving aclidinium 200 µg and 52.2% of the placebo group. A COPD exacerbation was the only adverse effect that was reported in >5% of patients in all groups, with a lower incidence in the aclidinium 400 µg group compared to the aclidinium 200 µg and placebo groups.
Rennard et al.[19] (2013) ACCORD COPD II Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, PG, RCT Patients ≥40 years old, current or former smokers (i.e., smoking history ≥10 pack-years), and diagnosed with stable moderate-to-severe COPD	N=542 12 weeks	Primary: Change from baseline to week 12 in morning pre-dose (trough) FEV_1 Secondary: Change from baseline to week 12 in peak FEV_1	Primary: Changes from baseline in trough FEV_1 at week 12 were significantly greater for aclidinium 200 and 400 µg versus placebo, with LSM treatment differences (95% CI) over placebo of 51 (8 to 94) mL and 72 (29 to 115) mL, respectively (both P<0.05). Secondary: Aclidinium-treated patients showed greater improvements over placebo in peak FEV_1 change from baseline at week 12 (both P<0.0001). Aclidinium 400 µg consistently provided greater improvements in all lung function outcomes versus aclidinium 200 µg throughout the study. Improvements from baseline were observed with aclidinium in SGRQ total score (200 µg, -6.0; 400 µg, -5.4) and Transition Dyspnea Index (TDI) focal score (200 µg, 1.0; 400 µg, 1.3). Clinically important improvements in SGRQ total and TDI focal scores were achieved by 45 and 51% of patients, respectively, who received aclidinium 400 µg, with a significant difference vs placebo for TDI (P<0.05). Anticholinergic-related adverse events (e.g., dry mouth) were infrequent, occurring <2% for any event in any treatment group. Both aclidinium doses were well tolerated.
Gelb et al.[20] (2013) Aclidinium 200 µg BID vs	DB, PG, RCT Patients ≥40 years old, current or former smokers (i.e., smoking history ≥10 pack-years), and	N=602 52 weeks	Primary: Safety (adverse events, laboratory tests, vital signs, and 12-lead electrocardiograms Secondary:	Primary: The percentage of patients reporting adverse events was similar for 200 µg (62.4%) and 400 µg (66.0%) groups, with most being mild to moderate in severity. Commonly reported adverse events (≥3% in total patient population) included nasopharyngitis, cough, sinusitis, headache, nausea, and upper respiratory infection. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aclidinium 400 µg BID	diagnosed with stable moderate-to-severe COPD		Efficacy (spirometry, SGRQ, rescue medication use)	Mean improvements from baseline in trough FEV_1 were observed during the first assessed time point at Week One (200 µg, 64 mL; 400 µg, 91 mL), with maximum improvements of 64 mL (Week One) and 101 mL (Week 24) for the 200 µg and 400 µg doses, respectively. Clinically important improvements in SGRQ total scores (≥4-point improvement from baseline) were observed at all study visits throughout the 52-week treatment period with aclidinium 200 µg and 400 µg.
Singh et al.[21] (2012) Aclidinium 100 µg BID vs aclidinium 200 µg BID vs aclidinium 400 µg BID vs formoterol 12 µg BID vs placebo	AC, DB, DD, MC, PC, XO Patients ≥40 years of age with a diagnosis of stable moderate to severe COPD and a FEV_1/FVC ratio <70%, a post-salbutamol FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history	N=79 7 days (each treatment arm had a 5 to 9 day washout period)	Primary: Mean change from baseline in FEV_1 $AUC_{0–12}$ on day seven Secondary: Change from baseline in FEV_1 $AUC_{12–24}$, FEV_1 $AUC_{0–24}$, trough FEV_1 on day seven, FVC AUC_{0-12}, AUC_{12-24} and AUC_{0-24} at day seven, morning peak FEV_1 on day one and seven, morning trough FVC on day seven, use of relief medication after seven days and safety	Primary: The change from baseline in FEV_1 $AUC_{0–12}$ on day seven compared to placebo was 154 mL for the aclidinium 100 µg group, 176 mL for the aclidinium 200 µg group, 208 mL for the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group (P<0.0001 for all compared to placebo). Aclidinium 400 µg was associated with statistically significant improvements in FEV_1 $AUC_{0–12}$ compared to the 100 µg dose (P<0.01) while the difference between patients receiving aclidinium 400 µg or formoterol 12 µg was not significantly different. Secondary: Improvements in FEV_1 $AUC_{12–24}$ and FEV_1 $AUC_{0–24}$ at day seven were significantly greater for all doses of aclidinium and formoterol compared to the placebo group (P<0.0001 for all). There was no difference between treatment with aclidinium 400 µg and formoterol with regard to changes in FEV_1 $AUC_{0–24}$. Patients treated with aclidinium 400 µg experienced a statistically significant improvement in FEV_1 $AUC_{12–24}$ compared to treatment with formoterol (56 mL; P<0.01). Compared to placebo the mean change from baseline in trough FEV_1 was 106, 114 and 154 and 148 mL with aclidinium 100, 200 and 400 µg, and formoterol, respectively (P<0.0001 for all compared to placebo). Patients treated with aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in FVC AUC_{0-12} compared to patients treated with placebo (243, 254, 274, and 301 mL, respectively; P<0.001 for all) on day seven. Following seven days of treatment, patients receiving aclidinium 100, 200,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 400 µg or formoterol demonstrated a statistically significant increase in FVC $AUC_{12–24}$ compared to patients receiving placebo (260, 255, 302, and 383 mL, respectively; P<0.001 for all). Patients treated with aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in FVC $AUC_{0–24}$ compared to patients treated with placebo (251, 255, 283, and 338 mL, respectively; P<0.001 for all) on day seven. After seven days of treatment, patients receiving aclidinium 100 µg, 200 µg, and 400 µg or formoterol demonstrated a statistically significant increase in morning peak FEV_1 on day one (140, 176, 223, and 221 mL, respectively; P<0.0001 for all) and day seven (189, 201, 242, and 246 mL, respectively; P<0.0001 for all) compared to placebo. Patients treated with aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in morning trough FVC (147, 191, 218, and 213 mL, respectively; P<0.001 for all) on day seven compared to patients treated with placebo. Patients treated with aclidinium 100, 200, and 400 µg or formoterol required significantly fewer daily inhalations of rescue medication compared to patients treated with placebo (-0.27, -0.39, -0.48, and -0.67, respectively; P<0.05 for all). The majority of adverse events were mild or moderate in severity and more prevalent in the placebo group (P value not reported). Four serious adverse events were reported, but none was treatment-related. There were no clinically relevant changes in laboratory parameters, and the incidence of ECG abnormalities was similar between placebo and active treatments.
Beier et al.[22] (2013) Aclidinium 400 µg BID vs	DB, DD, RCT Patients ≥40 years of age with a diagnosis of stable moderate to severe COPD and a	N=414 6 weeks	Primary: Change from baseline in normalized FEV_1 AUC over the 24-hour period post-morning dose	Primary: In the primary endpoint analysis, FEV_1 $AUC_{0–24}$ was significantly improved with aclidinium compared with placebo at week 6 (P<0.0001). Compared with placebo, tiotropium also significantly increased FEV_1 $AUC_{0–24}$ from baseline to week 6 (P<0.0001); the effects of aclidinium and tiotropium over six weeks were similar.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tiotropium 18 µg QD vs placebo	FEV_1/FVC ratio <70%, a post-salbutamol FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history		($AUC_{0–24}$) Secondary: Change from baseline in normalized FEV_1 AUC over the nighttime period ($AUC_{12–24}$), additional changes in FEV_1 and FVC, inhaler preference, safety	Secondary: FEV_1 $AUC_{12–24}$ and FEV1 $AUC_{0–12}$ were also significantly increased from baseline with both aclidinium and tiotropium vs placebo (P<0.0001). There were no differences between active treatment groups. When asked 'which device do you prefer?' at week six, significantly more patients overall preferred Genuair to HandiHaler (80.1 vs 10.7%; P<0.0001). Inhaler preference appeared to be independent of whether active medication or placebo was administered via the inhalers. Adverse event incidence was similar in the placebo (25.9%), aclidinium (27.5%), and tiotropium (29.7%) groups.
Ikeda et al.[23] (1995) Ipratropium 40 µg via MDI vs ipratropium 80 µg via MDI vs ipratropium 40 µg via MDI and albuterol 200 µg via MDI vs ipratropium 80 µg via MDI and albuterol 400 µg via MDI	DB, PC, RCT, XO Adult male patients with stable COPD with a history of >20 pack-years of cigarette smoking, and FEV_1 <60% and a FEV_1/FVC <70%, and chest radiographic findings compatible with pulmonary emphysema	N=26 5 separate visits over a period of 1 month	Primary: Change from baseline in FEV_1, FVC and the difference in adverse reactions reported Secondary: Not reported	Primary: All treatment groups showed a significant improvement in FEV_1 and FVC when compared to the placebo group at all-time points evaluated (P<0.01). Compared to all other regimens at every time point evaluated, 80 µg of ipratropium and 400 µg of albuterol showed significantly greater improvements in FEV_1 (P<0.05 and P<0.01). The lower dose combination was significantly different in FVC response from the low-dose monotherapy (P<0.01), but not high-dose monotherapy. No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and adverse effects (no P value reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Matera et al.[24] (1996) Ipratropium 40 µg QID and salmeterol 50 µg BID vs ipratropium 40 µg QID vs salmeterol 50 µg BID vs placebo	RCT, SB, XO Male patients ≥40 years of age with COPD and an FEV_1 between 16 and 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 Secondary: Changes in FEV_1 AUC	Primary: The peak response (28.8±5.0%) for salmeterol was greater than that for ipratropium (26.0±9.1%), but equivalent peak bronchodilation occurred with salmeterol and ipratropium plus salmeterol (28.0±4.2). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes, when compared to placebo ($P<0.05$), but only salmeterol and ipratropium plus salmeterol induced a significant ($P<0.05$) spirometric increase over the 12 hour monitoring period. Secondary: The AUC for active treatments were significantly increased compared to placebo ($P<0.05$), and salmeterol and ipratropium plus salmeterol significantly increased FEV_1 compared to ipratropium alone ($P<0.05$). There was no significant difference ($P>0.05$) between the salmeterol and ipratropium plus salmeterol AUC.
Van Noord et al.[25] (2000) Ipratropium 40 µg QID and salmeterol 50 µg BID vs salmeterol 50 µg BID	DB, MC, PG, RCT Patients 40 to 75 years of age with COPD, a FEV_1 ≤75% of predicted value	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication use, PEF, clinic lung function, adverse events and exacerbations	Primary: After inhalation of salmeterol, there was a mean±SEM peak increase in FEV_1 7.0±0.7% predicted after two hours. After 12 hours, the improvement was 2.0±1.0% of predicted value. Ipratropium plus salmeterol produced a peak increase in FEV_1 11.0±0.8% of predicted after two hours. After 12 hours, the improvement was 3.0±0.8% of predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Throughout the treatment period there was a mean±SEM decrease in the daytime symptom score from 1.9±0.1 to 1.7±0.1 in the placebo group (P value not significant), from 2.0±0.1 to 1.4±0.1 (P<0.001) in the salmeterol group and from 2.0±0.1 to 1.3±0.1 (P<0.001) in the ipratropium plus salmeterol group. Compared to placebo, salmeterol and ipratropium plus salmeterol 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 greater in both active treatment groups compared to the placebo group (P<0.001), while there was no difference between the salmeterol and the ipratropium plus salmeterol treatment groups with regard to morning PEF. The improvements in evening PEF were greater in both active treatment arms compared to the placebo arm (P<0.001), whereas the improvement was better in the ipratropium plus salmeterol group compared to the salmeterol group (P<0.01). During the 12-week treatment period, the mean±SEM increase in FEV_1 was 1.0±0.9% of predicted for placebo, 5.0±0.9% of predicted for salmeterol, and 8.0±0.8% for ipratropium plus salmeterol. All differences were statistically significant (P<0.01). The change in FVC was 4.0±1.2% of predicted with placebo, 7.0±1.2% of predicted with salmeterol and 12.0±1.2% with ipratropium plus salmeterol. The differences between ipratropium plus salmeterol and salmeterol alone and between ipratropium plus salmeterol and 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 adverse events were similar among the three groups. During the 12-week treatment period, 35 patients experienced a COPD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				exacerbation, 18 (36%) patients in the placebo group, 11 (23%) patients in the salmeterol group, and six (13%) patients in the ipratropium plus salmeterol group. The only significant difference was between the ipratropium plus salmeterol group and the placebo group (P<0.01).
Bone et al.[26] (1994) Ipratropium 21 µg QID via MDI vs albuterol 100 µg QID via MDI vs ipratropium and albuterol 21-100 µg QID via MDI (fixed-dose combination product)	DB, MC, PG, PRO, RCT Patients ≥40 years of age diagnosed with COPD with stable disease, relative stable, moderately severe airway obstruction with an FEV_1 ≤65% and FEV_1/FVC ratio ≤0.70, and a smoking history >10 pack-years, using at least two prescribed therapeutic agents for COPD control	N=534 85 days	Primary: Peak change from baseline in FEV_1, response AUC, symptom score and safety Secondary: Not reported	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 (P value not reported). Compared to 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 in terms of adverse effects or safety (P value not reported). Secondary: Not reported
Dorinsky et al.[27] (1999) Ipratropium 36 µg QID via MDI vs albuterol 180 µg QID via MDI vs equivalent dose of	DB, MC, PG, RETRO, RCT Patients ≥40 years of age with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, FEV_1 ≤65%	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as an 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 ipratropium and albuterol 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 one and two (P<0.05). The overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from two to eight percent (P value not reported). A significantly greater percentage of patients demonstrated a 12 or 15% increase in FEV_1 on three or more test days in the ipratropium and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ipratropium and albuterol via MDI (fixed-dose combination product)	predicted, FEV_1/FVC ratio ≤70%		Secondary: Not reported	albuterol group compared to the individual treatment groups (P<0.05). Secondary: Not reported
Friedman et al.[28] (1999) Ipratropium 36 µg QID via MDI vs albuterol 180 µg QID via MDI vs equivalent dose of ipratropium and albuterol via MDI (fixed-dose combination product)	DB, MC, PG, RETRO, RCT Patients ≥40 years of age diagnosed with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during three months prior to the trials, FEV_1 ≤65% predicted, FEV_1/FVC ratio ≤70%	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC_{0-4h} Secondary: Not reported	Primary: A statistically significant improvement in FEV_1 in the ipratropium and albuterol group was observed compared to other treatment groups on all test days (P<0.01). A significantly higher FEV_1 AUC_{0-4} in the ipratropium and albuterol group compared to the other treatment groups was observed on all test days (P≤0.008). Secondary: Not reported
Zuwallack et al.[29] (2010) Ipratropium and albuterol 20-100 µg QID, administered via Respimat® inhaler (fixed-dose combination product) vs	AC, DB, DD, MC, NI, PG, RCT Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack- years	N=1,480 12 weeks	Primary: FEV_1 change from test-day to baseline at day 85 for ipratropium and albuterol via Respimat® inhaler vs aerosol MDI and ipratropium and albuterol via Respimat® inhaler vs ipratropium via Respimat® inhaler	Primary: On day 85, ipratropium and albuterol Respimat® inhaler was NI to ipratropium and albuterol aerosol MDI at zero to six hours, and was significantly more effective to ipratropium Respimat® inhaler with a difference of 0.047 L (P<0.001) at zero to four hours. At four to six hours, ipratropium and albuterol Respimat® inhaler was non inferior to ipratropium Respimat® inhaler. Ipratropium and albuterol Respimat® inhaler significantly improved FEV_1 compared to ipratropium Respimat® inhaler at zero to four and four to six hours on all tests days. Secondary:

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ipratropium and albuterol 36-206 µg QID, administered via aerosol MDI (Combivent®) (fixed-dose combination product) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a 2 week run-in phase with ipratropium aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.			Secondary: FEV_1 at day one, 29 and 57; peak FEV_1; peak FEV_1 response; time to peak FEV_1 response; median time to onset of a therapeutic response; median duration of therapeutic response; FVC AUC_{0-6}, $_{0-4}$ and $_{4-6}$; peak FVC response on day one, 29, 57 and 85 and safety	Peak FEV_1, peak FEV_1 response and peak FVC response were comparable between ipratropium and albuterol Respimat® inhaler and ipratropium and albuterol aerosol MDI, and "superior" to ipratropium Respimat® inhaler (P<0.0001) on all test days. The median time to onset of therapeutic response occurred 13 days after treatment initiation with both ipratropium and albuterol Respimat® inhaler and ipratropium and albuterol aerosol MDI. The overall median time to a peak response was comparable across all treatments; 60 minutes for ipratropium and albuterol Respimat® inhaler and ipratropium and albuterol aerosol MDI on all test days, and 120 minutes on days one and 20, and 60 minutes on days 57 and 85 with ipratropium Respimat® inhaler. Medium duration of a therapeutic response was comparable between ipratropium and albuterol Respimat® inhaler (165 to 189 minutes) and ipratropium and albuterol aerosol MDI (172 to 219 minutes) overall. Median duration with ipratropium Respimat® inhaler was shorter (70 to 122 minutes). Seventy six (N=358), 74 (N=357) and 63% (N=295) of patients receiving ipratropium and albuterol Respimat® inhaler, ipratropium and albuterol aerosol MDI and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration. Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event

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				was lower with ipratropium/albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower respiratory system disorders were the most frequent event to lead to discontinuation (3.9%) and occurred with the lowest frequency with ipratropium/albuterol Respimat® inhaler (2.5 vs 4.3 vs 5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorders leading to treatment discontinuation. Serious adverse events occurred more frequently with ipratropium/albuterol aerosol MDI (6.7%) compared to ipratropium/albuterol Respimat® inhaler (3.5 and 2.9%). COPD exacerbations accounted for the majority of serious adverse events.
McCrory et al.[30] (2002) Ipratropium vs β-agonists, combination of β-agonists and ipratropium, or placebo	MA (9 RCTs) Adult patients with a diagnosis of COPD, symptoms consistent with an acute exacerbation	N=525 Duration ranged from 1 hour to 14 days	Primary: Short-term changes in FEV_1, WMD of long-term effects on FEV_1 Secondary: Not reported	Primary: There was no significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported). The change in FEV_1 was not significant when ipratropium was added to a β_2-adrenergic 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_2-adrenergic agonist groups (WMD, 0.05 L; 95% CI, -0.14 to 0.05). Secondary: Not reported
Casaburi et al.[31] (2005) Tiotropium 18 µg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with COPD and a FEV_1 ≤60% of predicted normal and a FEV_1/FVC ≤70% participating in 8 weeks of PR	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: TDI, SGRQ and rescue albuterol use	Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time compared to patients receiving placebo. The difference between the treatments was 1.65 minutes (P=0.183). Patients receiving tiotropium experienced significantly longer exercise endurance times compared to patients receiving placebo after 13 weeks of treatment (including eight weeks of PR) and following the termination of the PR program after 25 weeks of treatment. The mean differences were 5.35 (P=0.025) and 6.60 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 (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: On day 92, the mean TDI focal score for tiotropium was 1.75 and 0.91 for 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; differences exceeding one unit were considered clinically meaningful). 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 to 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant (P value not reported). On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication/day when compared to patients receiving placebo over 25 weeks of treatment (P<0.05).
Tashkin et al.[32] (2008) UPLIFT Tiotropium 18 µg QD vs placebo	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less	N=5,993 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from	Primary: The rate of decline in the mean post bronchodilator FEV_1 was greater in patients who prematurely discontinued a study drug as compared to those who completed the study period. There were no significant differences between the tiotropium group and the placebo group in the rate of decline in the mean value for FEV_1 either pre bronchodilator (P=0.95) or post bronchodilator (P=0.21) from day 30 to the end of study-drug treatment. Secondary: There were no significant differences between the treatment groups in the rate of decline in the mean value for FVC either pre bronchodilator (P=0.30) or post bronchodilator (P=0.84). The rate of decline in the mean value for SVC was not reported. Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (P<0.0001), although these differences on average were below what is considered to have clinical significance. The overall mean between-group difference in SGRQ total score at any time point was 2.7 (95% CI, 2.0 to 3.3) in favor of tiotropium (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			lower respiratory conditions	Tiotropium was associated with a significant delay in the time to first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. In addition, tiotropium was associated with a significant delay in the time to the first hospitalization for an exacerbation (P value not reported). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two treatment groups (P value not reported). During the four year study, among patients for whom vital-status information was available, 921 patients died; 14.4% in the tiotropium group and 16.3% in the placebo group (HR, 0.87; 95% CI, 0.76 to 0.99). During the four year study period plus 30 days included 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 to 1.02).
Decramer et al.[33] (2009) UPLIFT Tiotropium 18 µg QD vs placebo Subgroup analysis of patients in the UPLIFT trial with GOLD stage II COPD.	Subgroup analysis of UPLIFT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less	N=2,739 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory	Primary: Rate of decline of mean post-bronchodilator FEV_1 was lower in the tiotropium group compared to the placebo group (P=0.024). Rate of decline of mean pre-bronchodilator FEV_1 did not differ between groups. Secondary: Mean values for pre- and post-bronchodilator FEV_1 were higher in the tiotropium group at all time points (P<0.0001). Mean pre-bronchodilator FVC and SVC were higher in the tiotropium group at all time points (P<0.001). Mean post-bronchodilator FVC was significantly higher in the tiotropium group at all time points (P<0.01). No significant difference in mean post-bronchodilator SVC was observed between groups. Health status was better in the tiotropium group compared to the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			conditions	group for all time points (P≤0.006). Time to first exacerbation and time to exacerbation resulting in hospital admission were longer in the tiotropium group (HR, 0.82; 95% CI, 0.75 to 0.90 and 0.74; 95% CI, 0.62 to 0.88 respectively). Risk of mortality from lower respiratory tract conditions and from all causes were lower for the tiotropium group though differences between groups were not significant.
Troosters et al.[34] (2010) UPLIFT Tiotropium 18 µg QD vs placebo Subgroup analysis of patients in the UPLIFT trial who were not on other maintenance treatment at randomization.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less	N=810 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Primary: After 30 days of treatment, pre-bronchodilator FEV_1 was significantly larger in the tiotropium group compared to the placebo group (P<0.0001). Trough FEV_1 remained significantly larger in the tiotropium group compared to the placebo group at all time points throughout the trial (P<0.05). Secondary: No significant differences between groups were observed in pre- or post-FVC (P≥0.81). Pre- and post-SVC was significantly higher in the tiotropium group (P≤0.046). The improvement in the SGRQ scores was significantly higher in the tiotropium group compared to the placebo group in the first six months of treatment (P=0.0065). SGRQ total score declined more slowly in the tiotropium group compared to the placebo group (P=0.002). No statistically significant difference in exacerbation rate was observed between groups (P=0.08). No statistically significant difference in time to first exacerbation was observed between groups (P=0.24).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No statistically significant difference in exacerbations leading to hospitalizations was observed between groups.
Burgel et al.[35] (2014) UPLIFT Tiotropium 18 µg QD vs placebo Cluster analysis of patients in the UPLIFT trial based on age, BMI, FEV_1, smoking, and SGRQ score.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less	N=5706 4 years	Primary: Exacerbations, hospitalizations, mortality Secondary: Not reported	Cluster 1 (low-risk) (N=820) contained GOLD Stage 2 or 3 patients, who were heavy smokers and had relatively preserved HRQoL, but high rates of comorbidities. Cluster 2 (N=2339) contained mostly GOLD Stage 2 patients with moderate HRQoL impairment and very low rates of comorbidities. Cluster 3 (high-risk) (N=1022) contained 81% of GOLD Stage 3 and 4 patients, with severe HRQoL impairment, high pack-years, and high rates of comorbidities. Compared with cluster 3, cluster 4 (N=1525) contained patients with less severe airflow limitation, slightly less severe HRQoL impairment, and fewer pack-years and comorbidities. Primary: Tiotropium significantly reduced exacerbations rates and also increased time to first exacerbation in each cluster. Rates of severe exacerbations (leading to hospitalization) were significantly reduced in cluster 3 (P<0.05), which had the highest rate of exacerbations leading to hospitalization, but not in other clusters. The beneficial effect of tiotropium on all-cause mortality in the overall population (HR, 0.87; 95% CI, 0.75 to 1.00; P=0.054) was explained by a 21% reduction in cluster 3 (P=0.07), with no effect in other clusters. Secondary: Not reported
Halpin et al.[36] (2009) Tiotropium 18 µg QD vs placebo	Pooled analysis of 9 RCTs 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 ≥24 weeks	Primary: Proportion of patients with COPD exacerbation, proportion of patients with hospitalization due to COPD 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			time to first COPD exacerbation, time to first hospitalization for exacerbation Secondary: Not reported	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. Secondary: Not reported
Wise et al.[37] (2013) TIOSPIR Tiotropium handihaler 18 µg QD vs tiotropium respimat 2.5 µg QD vs tiotropium respimat 5 µg QD	DB, PG, RCT Patients ≥40 years of age with COPD, FEV_1 ≤70% predicted, FEV_1/FVC ≤70%, and smoking history ≥10 pack-years	N=17,183 Mean follow-up of 2.3 years	Primary: Time to death from any cause, risk of first COPD exacerbation Secondary: Number of COPD exacerbations, time to first moderate or severe exacerbation, time to and number of severe exacerbations, time to first major cardiovascular event	Primary: For the risk of death from any cause, the HR for Respimat 5 µg vs HandiHaler was 0.96 (95% CI, 0.84 to 1.09); for Respimat 2.5 µg vs HandiHaler, the HR was 1.00 (95% CI, 0.87 to 1.14). For the risk of the first exacerbation, the HR for Respimat 5 µg vs HandiHaler was 0.98 (95% CI, 0.93 to 1.03; P=0.42). Secondary: Rates of exacerbations, moderate or severe exacerbations, and severe exacerbations were similar in the three study groups. The overall incidence of major adverse cardiovascular events was 3.9, 3.9, and 3.6% in the Respimat 2.5-µg, Respimat 5-µg, and HandiHaler groups, respectively.
Troosters et al.[38] (2014) Tiotropium 18 µg QD vs placebo	DB, MC, PC, PG, RCT Patients with moderate (GOLD stage II) COPD previously naive to maintenance therapy	N=457 24 weeks	Primary: FEV_1 AUC from 0 to 3 hours (AUC_{0-3h}) post-dose response at week 24 Secondary: FEV_1 and FVC	Primary: For the primary endpoint at week 24, tiotropium was superior to placebo (0.19±0.27 vs −0.03±0.22 l; least-squares (LS) mean difference 0.23 l; 95% CI, 0.18 to 0.27; P<0.001). Secondary: The corresponding mean change from baseline to week 24 values for FVC AUC_{0-3h} were 0.23±0.47 l for tiotropium and −0.06±0.37 l for placebo (LS mean difference tiotropium vs placebo 0.31 l; 95% CI, 0.24 to 0.38;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received p.r.n. albuterol			parameters, physical activity, patient and physician assessments	P<0.001). At week 24 the mean increase from baseline in peak FEV_1 and FVC were significantly higher with tiotropium than with placebo (P<0.001). While physical activity levels were higher numerically in the tiotropium group than in the placebo group, they were not statistically significantly different. At week 24, patients treated with tiotropium were more frequently classified by their physician as 'excellent' than those in the placebo group (18.1 vs 10.9%) and were less frequently classified as 'poor/fair' compared with the placebo group (19.0 vs 25.4%), signifying improved health status with tiotropium vs placebo (P=0.045 at week 24).
Kerstjens et al.[39] (2012) Tiotropium 2.5 µg 2 inhalations QD via Respimat® inhaler vs placebo Individual pretrial maintenance therapy consisting of high dose glucocorticoids and LABAs was maintained throughout the study. Trial looked at two separate replicate	DB, PC, PG, RCT Patients 18 and 75 years of age and at least a 5 year history of asthma that was diagnosed before the age of 40 years, with a score of 1.5 on Asthma Control Questionnaire 7, FEV_1 ≤80% than predicted value and FVC ≤70% 30 minutes after inhalation of a short acting beta agonist, despite daily therapy with inhaled glucocorticoids and LABAs	N-912 48 weeks	Primary: Peak and trough FEV_1 at 24 weeks, time to first severe asthma exacerbation Secondary: Peak and trough FEV_1 at each treatment visit, AUC (for three hours after administration of study drug), time to first worsening of asthma, Asthma Control Questionnaire 7	Primary: At 24 weeks, the mean±SE change in peak FEV_1 was significantly greater in the tiotropium group compared to placebo in each trial with a difference of 86±34 mL in trial 1 (P=0.01) and 154±32 mL in trial 2 (P<0.001). The predose trough FEV_1 also significantly improved in each trial in the tiotropium group compared to placebo with a difference of 88±31 mL in trial 1 (P=0.01) and 111±30 mL in trial 2 (P<0.001), respectively. The average time to first severe asthma exacerbation was increased by 56 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 21% (HR, 0.79; P=0.03). Secondary: Improvements in peak FEV_1 were maintained over 48 weeks (P≤0.05 and P≤0.001 in trials 1 and 2, respectively). The mean difference in trough FEV_1 change from 24 to 48 weeks between tiotropium and placebo was 42 (95% CI, -21 to 104) and 92 (95% CI, 32 to 151) in trials 1 and 2, respectively. The median time to first worsening of asthma was increased by 134 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 31% (HR, 0.69; P<0.001). A minimally important difference for the Asthma Control Questionnaire 7 was not achieved in either trial.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
trials (trial 1 and trial 2).				
Canto et al.[40] (2012) Tiotropium 18 µg QD via Handihaler® vs placebo All patients were receiving formoterol 12 µg BID.	DB, PC, PRO, RCT, XO Patients with stable COPD (defined by GOLD) with a long history of smoking (>20 pack-years); patients were randomized to each treatment group for a 2 week treatment period, followed by a 7 day washout period and then patients XO for a second 2 week period of the alternative regimen	N=38 5 weeks	Primary: Pulmonary function tests (FEV_1, FVC, IC, EELV), inspiratory muscle strength, constant work exercise test Secondary: Not reported	Primary: Treatment with formoterol and tiotropium resulted in a greater numeric improvement in FEV_1 (1.07±0.25 to 1.25±0.32) compared to treatment with formoterol and placebo (1.09±0.21 to 1.21±0.29), although both groups achieved a statistically significant improvement (P<0.05). Similarly, patients treated with formoterol and tiotropium achieved a numerically greater increase in FVC (2.51±0.57 to 2.75±0.91) compared to patients treatment with formoterol and placebo (2.55±0.66 to 2.66±0.98), although a statistically significant improvement was observed in both groups (P<0.05). The increase in IC was greater in the formoterol and tiotropium group (1.68±0.41 to 2.16±0.77) compared to the formoterol and placebo group (1.66±0.45 to 2.02±0.49), although both groups achieved a statistically significant improvement (P<0.05). Patients treated with formoterol and tiotropium achieved a greater numeric improvement in EELV (4.35±0.77 to 3.98±0.67) compared to patients treated with formoterol and placebo (4.34±0.59 to 3.85±0.77), although both groups achieved a statistically significant improvement (P<0.05). Treatment with formoterol and tiotropium resulted in a statistically significant improvement in the maximal inspiratory pressure at rest, immediately after exercise and during recovery, while formoterol and placebo improved the maximal inspiratory pressure only at the 10 minute time point during recovery. Treatment with formoterol and tiotropium resulted in significantly larger increments in the maximal inspiratory pressure at all points of comparison. The time to the limit of tolerance was improved following two weeks of intervention in both groups, however, treatment with formoterol and tiotropium resulted in a greater increase compared to treatment with formoterol and placebo (40.7±7.6% vs 84.5±8.2%; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Van Noord et al.[41] (2000) Tiotropium 18 µg QD vs ipratropium 40 µg QID	DB, DD, MC, PG Patients with stable COPD with mean age of 65 years and average FEV_1 41% of predicted values	N=288 15 weeks	Primary: Changes in FEV_1 and FVC Secondary: Daily records of PEF, use of albuterol	Primary: The FEV_1 response, at all time points on days eight, 50 and 92, was significantly greater following tiotropium compared to ipratropium (differences of 0.09, 0.11, and 0.08 L; P<0.05). The results for FVC closely reflect those obtained for FEV_1. Tiotropium performed consistently better than 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.[42] (2002) Tiotropium 18 µg QD vs ipratropium 40 µg QID	DB, DD, MC, PG, RCT Patients with COPD ≥40 years of age with an FEV_1 ≤65% of predicted normal value and ≤70% of FVC	N=535 12 months	Primary: Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life	Primary: By the end of day eight, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared to 20 mL for the ipratropium group. Tiotropium was more effective compared to ipratropium at all time points on all test days except for the first two hours following the first dose and up to one hour after the dose, one week later (P<0.05). At the end of one year, trough FEV_1 was 120 mL above the day one 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 one baseline for patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				tiotropium and 110 mL for those receiving ipratropium (mean difference of 210 mL between groups). Secondary: Throughout the one-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). On average, patients receiving tiotropium self-administered approximately four fewer inhalations of albuterol/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 ≥1 unit) at one year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%; P=0.004). During the one-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). Quality of life, 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 two test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and generally not significant.
Yohannes et al.[43] (2011) Tiotropium	MA (16 RCTs) Trials lasting ≥12 weeks that compared	N=16,301 Up to 52 months	Primary: SGRQ and TDI scores, exacerbations, exacerbation-	Primary: The proportion of patients achieving a clinically important improvement in SGRQ scores was greater with tiotropium compared to placebo (OR, 1.61; 95% CI, 1.38 to 1.88; P<0.001). Patients receiving tiotropium were also more likely to experience improvements in SGRQ scores compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ipratropium vs LABA (salmeterol or formoterol)	tiotropium to placebo, ipratropium, or LABAs in patients ≥40 years of age with a diagnosis of COPD		related hospitalizations and adverse events Secondary: Not reported	patients receiving ipratropium (OR, 2.03; 95% CI, 1.34 to 3.07; P<0.001). There was no significant difference when tiotropium was compared to salmeterol (OR, 1.26; 95% CI, 0.93 to 1.69; P=0.13). There were statistically greater odds of achieving a clinically significant change in TDI score with tiotropium compared to placebo (OR, 1.96; 95% CI, 1.58 to 2.44; P<0.001). In addition, there were significantly greater odds of improving TDI scores associated with tiotropium compared to ipratropium (OR, 2.10; 95% CI, 1.28 to 3.44; P=0.003); however, there was no significant difference when tiotropium was compared to salmeterol (OR, 1.08; 95% CI, 0.80 to 1.45; P=0.61). Tiotropium significantly reduced the risk of exacerbations compared to placebo (OR, 0.83; 95% CI, 0.72 to 0.94; P=0.004) and ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92; P=0.02). A reduction in exacerbations was observed in the two studies that compared tiotropium to salmeterol; however, the difference was not statistically significant (OR, 0.86; 95% CI, 0.67 to 1.11; P=0.25). Patients receiving tiotropium were less likely to have an exacerbation-related hospitalization compared to patients receiving placebo (OR, 0.89; 95% CI, 0.80 to 0.98; P=0.02). There was a nonsignificant reduction in the odds of an exacerbation-related hospitalization with tiotropium compared to ipratropium (OR, 0.59; 95% CI, 0.32 to 1.09; P=0.09), salmeterol (OR, 0.54; 95% CI, 0.29 to 1.00; P=0.051) and formoterol (OR, 4.98; 95% CI, 0.58 to 42.96; P=0.15). The number of patients who experienced a serious adverse event was not statistically significant when tiotropium was compared to placebo (OR, 1.06; 95% CI, 0.97 to 1.17; P=0.19) Only one study compared tiotropium to salmeterol, reporting a significantly lower risk of a serious adverse event with tiotropium (OR, 0.39; 95% CI, 0.16 to 0.95; P=0.04). Secondary: Not reported
Donohue et al.[44] INHANCE	DB, PC, RCT	N=1,683	Primary: Trough FEV_1 at 12	Primary: The difference between both doses of indacaterol and placebo in trough

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Tiotropium 18 µg QD vs indacaterol 150 µg QD vs indacaterol 300 µg QD vs placebo Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.	Patients ≥40 years of age with moderate to severe COPD and a smoking history of ≥20 pack-years	26 weeks	weeks Secondary: Trough FEV_1 at 12 weeks, FEV_1 at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and safety	FEV_1 was 180 mL, which exceeded the prespecified minimum clinically important difference of 120 mL (P value not reported). Secondary: The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough FEV_1 were significant when tested for superiority (P≤0.01) and non-inferior (P<0.001). FEV_1 at five minutes post dose on day one was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium (P<0.001 for all vs placebo and for indacaterol vs tiotropium). TDI total scores significantly increased relative to placebo (P<0.001 for all) at all assessments with both doses of indacaterol and after four, 12 and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks (P<0.05 for all). Over 26 weeks, the change from baseline in mean daily number of inhalations of as-needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (P<0.001 for both). Significantly fewer inhalations of as-needed albuterol were required with either indacaterol dose compared to tiotropium (P≤0.001 for both). The proportion of days with no use of as-needed albuterol was significantly lower with both doses of indacaterol compared to placebo (P<0.001 for both) and tiotropium (P≤0.001). The change from baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (P<0.001 for all) and tiotropium (morning; P≤0.001 for both, evening; P<0.05 and P<0.01). The proportion of nights with no awakenings (P<0.01 for both), days with no daytime symptoms (P<0.05 for both) and days able to perform usual activities (P<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo. SGRQ total scores improved with both doses of indacaterol at all assessments compared to the placebo treatment group (P<0.01 for all) but

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				not compared to tiotropium (P value not reported). Analysis of time to first COPD exacerbation showed a reduced risk with indacaterol 150 µg compared to placebo (HR, 0.69; 95% CI, 0.51 to 0.94; P=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; P=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; P=0.08) compared to placebo. The rate of cough as an adverse event did not differ across treatments.
Decramer et al.[45] (2013) INVIGORATE Tiotropium 18 µg QD vs indacaterol 150 µg QD	MC, PG, RCT Patients aged ≥40 years with severe COPD and a history of at least one moderate to severe exacerbation in the previous 12 months	N=3444 52 weeks	Primary: To investigate whether indacaterol was non-inferior to tiotropium for trough FEV_1 at week 12 Secondary: Rate of exacerbations at week 52	Primary: The estimated least squares mean trough FEV_1 difference between the groups was −0.011 L (least squares mean with indacaterol 1.134 L [SE 0.008] vs tiotropium 1.145 L [0.008]; one-sided 97.5% CI lower limit −0.026 L; P<0.0001). The lower limit of the 97.5% CI was above the prespecified non-inferiority margin of −0.055 L, suggesting that indacaterol was non-inferior to tiotropium. Secondary: Indacaterol did not show non-inferiority in terms of exacerbation rates: 0.79 (indacaterol) versus 0.61 (tiotropium); ratio 1.29 (one-sided 97.5% CI upper limit 1.44). In the safety set, we recorded no between-group difference in the number of patients who had adverse events.
Niewoehner et al.[46] (2009) Tiotropium 18 µg QD vs ipratropium and albuterol MDI QID (fixed-dose combination product) Concomitant	Pooled analysis of 2 RCTs Patients ≥40 years of age with COPD, current or former cigarette smoker with lifetime consumption of ≥10 pack-years, postbronchodilator FEV_1 ≤70% of predicted, pre bronchodilator FEV_1 ≤65% of	N=676 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 and 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 and 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). Differences in FVC responses were similar to those observed with the FEV_1. Mean FVC trough for the tiotropium group was significantly larger

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medications allowed throughout the trial included ICSs, theophylline, and stable doses of prednisone (not to exceed 10 mg daily or its equivalent)	predicted, and FEV1/FVC ≤70% who were receiving ipratropium and albuterol (18-103 µg) MDI for ≥1 month			on study days 42 and 84 (P<0.01) compared with the ipratropium and albuterol group, but the AUC_{0-6} was not (P>0.5). Secondary: Weekly mean morning PEF and FEV_1 were both significantly larger in the tiotropium arm compared with the ipratropium and 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.[47] (2009) Tiotropium 18 µg QD vs arformoterol 15 µg BID vs arformoterol 15 µg BID and tiotropium 18 µg QD	MC, PG, RCT Patients ≥45 years of age with COPD, smoking history ≥15 pack-years, breathless severity ≥2 on Medical Council Dyspnea Score, pre bronchodilator FEV_1 >0.7, FEV_1/FVC ≤70%, FEV_1 ≤65% predicted	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-hour trough FEV_1, and IC 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: 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				arformoterol (25.0%), tiotropium (27.5%) and combination (30.8%).
Van Noord et al.[48] (2005) Tiotropium 18 µg QD for 6 weeks vs formoterol 12 µg BID for 6 weeks vs tiotropium 18 µg QD and formoterol 12 µg BID for 6 weeks	DB, RCT, XO Patients with COPD	N=71 18 weeks	Primary: FEV_1, FVC, rescue medication use Secondary: Not reported	Primary: Tiotropium produced a significantly greater improvement in average daytime FEV_1 (0-12 h) than formoterol (127 vs 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). Secondary: Not reported
Rabe et al.[49] (2008) Tiotropium 18 µg QD and formoterol 12 µg BID vs salmeterol 50 µg BID and fluticasone 500 µg 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 pre bronchodilator 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 and formoterol compared to those receiving salmeterol and fluticasone (P=0.0006). The difference in peak FEV_1 was 103 mL in favor of tiotropium and formoterol (P=0.0001). Secondary: The 12-h FVC profile and peak FVC were significantly higher with tiotropium and formoterol compared to salmeterol and fluticasone (P=0.0001). There was no significant difference in predose FEV_1, however the difference in predose FVC favored tiotropium and formoterol (P=0.05).
Brusasco et al.[50] (2003) Tiotropium 18 µg QD	DB, DD, PC, RCT Patients ≥40 years of age with COPD, a FEV_1 ≤65% of	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared to placebo (P<0.01). 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). The time to first hospital admission

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs salmeterol 50 µg BID vs placebo	predicted and an FVC ≤70%		Secondary: SGRQ, TDI, spirometry and adverse events	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 (P value not reported). 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 to 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 six-month trial for the tiotropium, salmeterol and placebo groups, respectively. A significant difference was observed for tiotropium compared to placebo (P<0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared to the placebo group (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 AUC from 0 to three 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%; P value not reported).
Donohue et al.[51] (2002) Tiotropium 18 µg QD vs	DB, MC, PC, PG, RCT Patients ≥40 years of age with stable COPD, FEV_1 ≤60% of predicted normal	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 had improved significantly over placebo by 137 mL in the tiotropium group 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 µg BID vs placebo	and FEV_1/FVC ≤70%			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, 21.4, 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 six 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 six 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 (P value not reported).
Briggs et al.[52] (2005) Tiotropium 10 µg QD vs salmeterol 50 µg BID	DB, PG, RCT Patients with COPD	N=653 12 weeks	Primary: Lung function Secondary: Not reported	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). 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Tiotropium demonstrated a significantly higher pre-dose FVC than salmeterol (P<0.05). Secondary: Not reported
van Noord et al.[53] (2010) Tiotropium 18 µg QD vs salmeterol 50 µg BID vs tiotropium 18 µg QD and salmeterol 50 µg QD vs tiotropium 18 µg QD and salmeterol 50 µg BID	DB, RCT, 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 Secondary: Not reported	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. Secondary: Not reported
Aaron et al.[54] (2007) Tiotropium 18 µg QD vs tiotropium 18 µg QD and	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	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 who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics in the tiotropium and placebo group (62.8%) did not differ from the tiotropium and salmeterol group (64.8%; 95% CI, -12.8 to 8.8) or from the tiotropium plus fluticasone and salmeterol group (60.0%; 95% CI, -8.2 to 13.8). Secondary: COPD exacerbations did not significantly differ between the tiotropium and placebo and the other two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 µg BID vs tiotropium 18 µg QD plus fluticasone and salmeterol 500-50 µg BID (fixed-dose combination product)	of cigarette smoking; documented chronic airflow obstruction with FEV_1/FVC <0.70 and a postbronchodilator FEV_1 ≤65% of the predicted value		Secondary: Number of COPD exacerbations per patient-year; number of hospitalizations for COPD and all causes; changes in health-related quality of life, dyspnea, lung function	Patients treated with tiotropium plus fluticasone and salmeterol had lower rates of severe exacerbations of COPD requiring hospitalization than did patients treated with tiotropium and placebo (P=0.01). Tiotropium and salmeterol did not statistically affect hospitalization rates compared with tiotropium and placebo. All-cause hospitalizations were reduced in patients treated with tiotropium plus fluticasone and salmeterol compared with patients treated with tiotropium and placebo (P=0.04). Treatment with tiotropium and salmeterol or tiotropium plus fluticasone and salmeterol improved health-related quality of life significantly more than did therapy with tiotropium and placebo. Dyspnea scores did not significantly differ among the treatment groups. Tiotropium plus fluticasone and salmeterol improved lung function compared with tiotropium and placebo (P=0.049). Tiotropium and salmeterol did not statistically improve lung function compared with tiotropium and placebo.
Welte et al.[55] (2009) Tiotropium 18 µg QD plus budesonide and formoterol 320-9 µg BID (fixed-dose combination product) vs tiotropium 18 µg QD	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 steroids and/or antibiotics, smoking history of ≥10 pack-years, FEV_1 ≤50% predicted and FEV_1/FVC <70% predose	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 60 minutes, IC at 60 minutes plus SGRQ	Primary: Treatment with budesonide and 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) vs 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 (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 and formoterol plus 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 and formoterol plus tiotropium and tiotropium alone, respectively (P=0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Puhan et al.[56] (2009) Tiotropium vs LABA monotherapy vs ICS monotherapy vs ICS and LABA combination therapy	MA (35 trials) Patients with stable COPD	N=26,786 ≥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 to 0.80), ICS (OR, 0.78; 95% CI, 0.70 to 0.86), LABA (OR, 0.77; 95% CI, 0.64 to 0.84), and ICS and LABA (OR, 0.72; 95% CI, 0.64 to 0.80). Neither tiotropium nor combination therapy reduced exacerbations more than LABA monotherapy (OR, 1.02; 95% CI, 0.90 to 1.16 and OR, 0.93; 95% CI, 0.84 to 1.04, respectively). Combined treatment was not more effective than LABA or tiotropium monotherapy (OR, 0.93; 95% CI, 0.84 to 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 and LABA significantly reduced exacerbations compared to LABA monotherapy (OR, 0.83; 95% CI, 0.71 to 0.98; OR, 0.75; 95% CI, 0.57 to 1.00, and OR, 0.79; 95% CI, 0.67 to 0.93, respectively). In patients with FEV_1 >40% predicted, there was no difference in COPD exacerbations between treatments.
Triverdi et al.[57] (2014) Umeclidinium 125 µg vs umeclidinium 62.5 µg	PC, PG, RCT Current or former smokers of ≥40 years of age, with a smoking history of ≥10 pack-years, an established clinical history of COPD, FEV_1 ≤70%	N=206 12 weeks	Primary: Change from baseline in FEV_1 at day 85 Secondary: Weighted mean FEV_1 0 to 6 hours post dose on days 1, 28, and 84,	Primary: Change from baseline in FEV_1 was observed for umeclidinium 62.5 µg (127 mL; 95% CI, 52 to 202 mL) and 125 µg (152 mL; 95% CI, 76 to 229 mL) compared with placebo (P<0.001 for both). Secondary: Statistically significant (P<0.001) improvements were observed in LSM change from baseline in 0 to 6-hour weighted mean FEV_1 for both umeclidinium groups compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	predicted and $FEV_1/FVC \leq 70\%$		transitional dyspnea index (TDI) score, rescue salbutamol use, SGRQ, safety	The umeclidinium 62.5 and 125 µg treatment groups exhibited an LSM TDI focal score of 0.7 and 1.0 units, respectively, which is approximate to the clinically meaningful improvement 1 unit, whereas the placebo group had an LSM TDI focal score of -0.3, reflecting a worsening compared to baseline. The differences in rescue-treatment use from placebo were statistically significant for 62.5 µg (mean -0.7 puffs per day (95% CI, -1.3 to -0.1), P=0.025), but not 125 µg (mean -0.6 puffs per day (95% CI, -1.2 to 0.0), P=0.069). On day 84, the LSM change from baseline in SGRQ total score was -6.12 (125 µg), -3.14 (62.5 µg) and +4.75 (placebo). Overall incidence of adverse events was similar across treatment groups (62.5 µg, 39%; 125 µg, 41%; and placebo, 35%).
Donohue et al.[58] (2014) Umeclidinium 125 µg vs umeclidinium-vilanterol 125-25 µg vs placebo	DB, MC, PC, PG, RCT Current or former smokers of ≥40 years of age, with a smoking history of ≥10 pack-years and an established clinical history of COPD	N=562 52 weeks	Primary: Safety, trough FEV_1, trough FVC Secondary: Not reported	Primary: The incidence of on-treatment adverse events (AEs), serious AEs (SAEs) and drug-related AEs was similar across active treatment groups and placebo. Greater mean changes from baseline in trough FEV_1 and FVC were demonstrated for umeclidinium-vilanterol and umeclidinium compared with placebo at all visits. At 12 months, umeclidinium-vilanterol and umeclidinium had improved trough FEV_1 in comparison with placebo by 0.231 L (95% CI, 0.153 to 0.310) and 0.178 L (95% CI, 0.098 to 0.258), respectively, and trough FVC by 0.252 L (95% CI, 0.135 to 0.368) and 0.194 L (95% CI, 0.076 to 0.312), respectively. There were fewer patients reporting COPD exacerbations with umeclidinium-vilanterol and umeclidinium (13 and 15%) compared with placebo (24%). Secondary: Not reported
Exercise-Induced Bronchoconstriction				
Spooner et al.[59] (2003)	MA (24 trials)	N=518	Primary: Pulmonary	Primary: On average, the maximum percent decrease in FEV_1 after a single dose of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	Patients $\geq$6 years of age with exercise-induced bronchoconstriction with a fall in FEV_1 of $\geq$10% after an exercise challenge test	Variable duration	function Secondary: Complete protection from exercise-induced broncho-constriction, clinical protection, adverse events, symptom score or preference measure	either mast-cell stabilizer was 7.1%, compared to a 13.8% fall observed in the anticholinergic group (95% CI, 3.3 to 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 to 9.2). Secondary: Mast cell stabilizers provided a greater number of patients with complete protection (73 vs 56%; 95% CI, 1.3 to 3.7) and clinical protection from exercise-induced bronchoconstriction, 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 to 0.5) and clinical protection from exercise-induced bronchoconstriction, compared with β_2-adrenergic agonists (55 vs 77%; 95% CI, 0.2 to 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 to 1.4).
Safety				
Singh et al.[60] (2011) Any inhaled anticholinergics for treatment of COPD	MA (17 RCTs) Patients receiving inhaled anticholinergics with more than 30 days of follow up, study participants with a diagnosis of COPD of any severity, an inhaled anticholinergic as the intervention	N=14,783 6 to 26 weeks	Primary: Composite of cardiovascular death, MI, or stroke Secondary: All-cause mortality	Primary: In a MA of 17 trials of 14,783 participants, cardiovascular death, MI, or stroke occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR, 1.58; 95% CI, 1.21 to 2.06; P<0.001). Among the individual components of the composite primary endpoint, inhaled anticholinergics significantly increased the risk of MI (1.2 vs 0.8% for control; RR, 1.53; 95% CI, 1.05 to 2.23; P=0.03) and cardiovascular death (0.9 vs 0.5% for control; RR, 1.80; 95% CI, 1.17 to 2.77; P=0.008), but did not significantly increase the risk of stroke (0.5 vs 0.4% for control; RR, 1.46; 95% CI, 0.81 to 2.62; P=0.20).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	drug vs a control, and reported data on the incidence of serious cardiovascular adverse events, including MI, stroke, or cardiovascular death			Secondary: Inhaled anticholinergics did not significantly increased the risk of all-cause mortality (2.0 vs 1.6% for control; RR, 1.26; 95% CI, 0.99 to 1.61; P=0.06).
Ogale et al.[61] (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 during the period of interest (acute coronary syndrome, heart failure, or cardiac dysrhythmia) Secondary: Not reported	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 cardiovascular events, for a rate of 2.2 cardiovascular events per 100 patient-years. Nearly 75% of the patients followed had at least one cardiovascular risk factor at study entry. There were 6,234 cardiovascular events (44% heart failure, 28% acute coronary syndrome, 28% dysrhythmia). Compared with subjects not exposed to ipratropium within the past year, any exposure to ipratropium within the past six months was associated with an increased risk of cardiovascular event: ≤4 and ≥4 30-day equivalents (HR, 1.40; 95% CI, 1.30 to 1.51 and HR, 1.23; 95% CI, 1.13 to 1.36, respectively). Overall, exposure to anticholinergics was associated with a 29% higher risk of cardiovascular events relative to no exposure in the past year. Among subjects who received anticholinergics more than six months prior, there did not appear to be an elevated risk of a cardiovascular event. Effect modification by the presence of cardiovascular disease at baseline was statistically significant (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lee et al.[62] (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, COPD hospitalizations Secondary: Not reported	Primary: Treatment with tiotropium+ICS+LABA was associated with a 40% reduction in death compared with ICS+LABA (95% CI, 0.45 to 0.79). Treatment with tiotropium+ICS+LABA was associated with a 16% reduction of COPD exacerbations compared with other regimens (95% CI, 0.73 to 0.97). There was no significant difference in exacerbations with tiotropium+ICS+LABA compared with ICS+LABA (HR, 1.03; 95% CI, 0.88 to 1.21). Treatment with tiotropium+ICS+LABA was associated with a 22% reduction of COPD hospitalizations compared with other regimens (95% CI 0.62 to 0.98). There was no significant difference in hospitalizations with tiotropium+ICS+LABA compared with ICS+LABA (HR, 1.15; 95% CI, 0.90 to 1.46). Other three drug combination regimens that included tiotropium and the four drug combination regimens that included tiotropium+ICS+LABA+ ipratropium were associated with increased mortality risk (HR, 1.38; 95% CI, 1.06 to 1.81 and HR, 1.36; 95% CI, 1.05 to 1.76, respectively). Secondary: Not reported
Celli et al.[63] (2009) UPLIFT Tiotropium 18 µg QD vs placebo	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	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 to 0.97; P=0.016). For the full four 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 to 0.99; P=0.034). For the period of four years plus 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 to 1.02; P=0.086). Between Days 1,440 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			medications	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 HRs for lower respiratory and cardiac mortality during treatment were 0.86 (95% CI, 0.68 to 1.09) and 0.86 (95% CI, 0.75 to 0.99), respectively.
Singh et al.[64] (2008) Tiotropium 5 to 10 µg vs placebo	MA (5 RCTs) Patients using tiotropium solution using a mist inhaler (Respimat® Soft Mist Inhaler) vs placebo for COPD that evaluated mortality as an outcome and had a trial duration of more than 30 days	N=6,522 Up to 52 weeks	Primary: Mortality from any cause Secondary: Deaths from cardiovascular causes (MI, stroke, cardiac death, and sudden death)	Primary: The tiotropium mist inhaler was associated with a significantly increased risk of mortality compared to placebo (RR, 1.52; 95% CI, 1.06 to 2.16; P=0.02). Secondary: Although the numbers for cardiovascular death were low, tiotropium was associated with a significantly increased RR in the five trials evaluating this outcome (RR, 2.05; 95% CI, 1.06 to 3.99; P=0.03).
Celli et al.[65] (2010) Tiotropium 18 µg QD vs placebo	MA (30 trials) 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 ≥4 weeks	Primary: All-cause mortality and selected cardiovascular events (composite of cardiovascular deaths, nonfatal MI, nonfatal stroke, and the terms sudden death, sudden cardiac death, and	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 to 0.999). The incidence rate for the cardiovascular endpoint was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years (RR, 0.83; 95% CI 0.71 to 0.98). The incidence rate for cardiovascular 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 to 0.98). The RRs of total MI, cardiac failure, and stroke were 0.78 (95% CI, 0.59

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cardiac death) Secondary: Not reported	to 1.02), 0.82 (95% CI, 0.69 to 0.98), and 1.03 (95% CI, 0.79 to 1.35), respectively. Secondary: Not reported
Lee et al.[66] (2008) Exposure to ICS, ipratropium, LABA, theophylline, and short-acting β_2-agonist	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABA were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABA was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABA (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00), however this did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABA (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABA. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Barr et al.[67] (2005) Tiotropium vs placebo, ipratropium, LABA	MA (9 RCTs) Patients diagnosed with COPD, whose disease was stable	N=6,584 1 month or greater	Primary: Exacerbations, hospitalizations, mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use and adverse events	Primary: Reduced exacerbations were seen with tiotropium compared to placebo (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 with tiotropium compared to placebo (OR, 0.65; 95% CI, 0.50 to 0.85) and compared to ipratropium or salmeterol but these differences were not statistically significant (OR, 0.59; 95% CI, 0.32 to 1.09 and 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 (P value not reported). Secondary: In the tiotropium group, there was a greater mean change in trough FEV_1 from baseline that was statistically significant compared to the placebo group (140 mL; 95% CI, 118 to 162), the ipratropium group (150 mL; 95% CI, 106 to 193) and the salmeterol group (40 mL; 95% CI, 12 to 68). In the tiotropium group, there was a greater mean change in trough FVC from baseline that was statistically significant compared to the placebo group (278 mL; 95% CI, 208 to 348), the ipratropium group (210 mL; 95% CI, 112 to 308), and the salmeterol group (90 mL; 95% CI, 35 to 145). In the tiotropium group, there was a greater mean change in morning peak flow from baseline that was statistically significant compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo group (21 mL; 95% CI, 15 to 28) and the ipratropium group (16 mL; 95% CI, 7 to 25). There was no difference between the tiotropium and salmeterol treatment groups (0 mL; 95% CI, -8 to 9). In the tiotropium group, dry mouth was significantly increased compared to the placebo group (OR, 5.4; 95% CI, 3.3 to 8.8), the ipratropium group (OR, 2.1; 95% CI, 1.05 to 4.2) and the salmeterol group (OR, 5.1; 95% CI, 2.2 to 12.0).
Rodrigo et al.[68] (2009) Tiotropium vs placebo, LABA, or ICS and LABA	MA (19 trials) Patients >35 years of age with stable COPD	N=18,111 ≥4weeks	Primary: Major cardiovascular events (composite of nonfatal MI, stroke, and cardiovascular death), cardiovascular mortality (includes sudden death), nonfatal MI, and nonfatal stroke (includes transient ischemic attack) Secondary: All-cause mortality	Primary: There was no difference in the incidence of major cardiovascular events among the treatment groups (RR, 0.96; 95% CI, 0.82 to 1.12). There was no difference in cardiovascular deaths among the treatment groups (RR, 0.93; 95% CI, 0.73 to 1.20). There was no difference in nonfatal MI among the treatment groups (RR, 0.84; 95% CI, 0.6 to 1.09). There was no difference in nonfatal stroke among the treatment groups (RR, 1.04; 95% CI, 0.78 to 1.39). Secondary: Tiotropium did not significantly increase the risk of all-cause mortality (RR, 0.97; 95% CI, 0.86 to 1.09).
Dong et al.[69] (2013) Tiotropium vs LABA vs	MA (42 trials) Patients with COPD	N=52,516 ≥6 months	Primary: Mortality Secondary: Not reported	Primary: Results indicated that tiotropium Soft Mist Inhaler® was associated with an increased risk of overall death compared to placebo (OR, 1.51; 95% CI, 1.06 to 2.19), tiotropium Handihaler® (OR, 1.65; 95% CI, 1.13 to 2.43), LABA (OR, 1.63; 95% CI, 1.10 to 2.44), and LABA and ICS combination therapy (OR, 1.90; 95% CI, 1.28 to 2.86). The risk with tiotropium Soft Mist Inhaler® was more evident for cardiovascular death, severe COPD, and at higher daily doses. Among all treatments LABA and ICS combination therapy was associated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ICS vs LABA and ICS combination therapy vs placebo				with the lowest risk of death, while no excess risk was noted for tiotropium Handihaler® or LABA therapy. Secondary: Not reported
Baker et al.[70] (2009) Tiotropium vs ICS vs LABAs vs combination therapy	MA (43 trials) Patients with COPD	N=31,020 4 to 60 weeks	Primary: COPD exacerbations, all-cause mortality Secondary: Withdrawal from trial based on drug class	Primary: LABAs, tiotropium, ICSs, and combination ICS and LABA therapy each decreased the odds of having an exacerbation by 16, 31, 15, and 24%, respectively, compared to placebo. Tiotropium reduced the odds of having at least one exacerbation by 18% compared with LABAs and by 19% compared with ICSs alone. Compared to 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 LABAs alone. Compared to 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 to 41%) compared with placebo. Both tiotropium and combination therapy significantly reduced patient withdrawals compared with LABAs or ICSs alone.
Karner et al.[71] (2011) Tiotropium and ICS/LABA vs	MA (3 RCTs) Patients 62 to 68 years with severity of COPD varied from moderate to very severe	N=1,051 Up to 52 weeks	Primary: All cause mortality, hospital admissions, exacerbations, pneumonia, SGRQ scores	Primary: There was no significant difference in mortality rates between patients receiving therapy with ICS/LABA plus tiotropium and tiotropium alone (OR, 1.88; 95% CI, 0.57 to 6.23; P=0.30). There were fewer patients admitted to the hospital who received ICS/LABA plus tiotropium (41/474) compared to the tiotropium plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tiotropium vs ICS/LABA	according to GOLD guideline definitions of COPD		Secondary: Symptoms, FEV_1, non-fatal serious adverse events, adverse events and withdrawals	placebo group (50/487); however, the difference between groups was not significant (OR, 0.84; 95% CI, 0.53 to 1.33). The number of patients admitted to hospital with exacerbations was higher in the tiotropium plus placebo group (38/487) compared to the ICS/LABA plus tiotropium group (25/ 474); however, this difference was not significant (OR, 0.66; 95% CI, 0.39 to 1.13). Two studies examined the effect of ICS/LABA plus tiotropium on exacerbation rates compared to tiotropium alone. One study reported no difference in exacerbations between the treatment groups (OR, 0.89; 95% CI, 0.56 to 1.41), while the other study reported a significant reduction with the triple therapy compared to tiotropium monotherapy (OR, 0.36; 95% CI, 0.22 to 0.60). The risk of developing pneumonia was low, and there was no statistically significant difference between treatment with ICS/LABA plus tiotropium and tiotropium plus placebo (OR, 1.35; 95% CI, 0.31 to 5.99). Changes in SGRQ scores significantly favored ICS/LABA plus ipratropium treatment compared to ipratropium plus placebo after five months (P=0.002) and one year (P=0.01). Secondary: The addition of tiotropium to ICS/LABA significantly increased FEV_1 (difference, 0.06 L; 95% CI, 0.04 to 0.08 L), although this was below the threshold of 100 to 140 mL which is considered to be a clinically important increase. There were fewer patients suffering non-fatal serious adverse events in the tiotropium plus ICS/LABA group (12/504) compared to patients taking tiotropium plus placebo (20/517), although the difference was not statistically significant (OR, 0.60; 95% CI, 0.29 to 1.25). A higher number of patients suffered adverse events while treated with tiotropium plus ICS/LABA (140/504) compared to patients tiotropium plus placebo (132/517), although the difference was not significant (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.12; 95% CI, 0.85 to 1.49). The difference between the number of patients who withdrew from the studies due to adverse events was not significantly different between patients taking tiotropium plus ICS/LABA and tiotropium plus placebo (OR, 0.92; 95% CI, 0.46 to 1.83).

Drug regimen abbreviations: QD=once daily, BID=twice daily, QID=four times daily
Study abbreviations: AC=active controlled, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, BDI=Baseline Dyspnea Index , BMI=body mass index, CI=confidence interval, COPD=chronic obstructive pulmonary disease, ECG=electrocardiogram, EELV=end-expiratory lung volume, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, GOLD=Global Initiative for Chronic Obstructive Lung Disease , HR=hazard ratio, IC=inspiratory capacity, ICS=inhaled corticosteroids, LABA=long-acting beta agonists, LSM=least square mean, MDI=metered dose inhaler, MI=myocardial infarction, OR=odds ratio, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PR=pulmonary rehabilitation, RR=relative risk, SE=standard error, SEM=standard error of the mean, SF-36= 36-item short form health survey, SGRQ=St. George Respiratory Questionnaire, SVC=slow vital capacity, TDI=Transition Dyspnea Index , WMD=weighted mean difference

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. However, it should be noted that devices studied are only equally effective in patients who can use them appropriately. It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[72] 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.[52] Adherence to inhaled therapy is often poor, with rates of 40 to 72% being reported.[73] Patient preference should be considered when selecting an inhalation delivery device. Barta et al. mailed a survey to 82 patients (most with chronic obstructive pulmonary disease [COPD]) using a home nebulizer treatment. 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.[74] 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.[72]

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
Aclidinium	aerosol inhaler	Tudorza Pressair®	$$$$$	N/A
Ipratropium	aerosol inhaler, inhalation solution*	Atrovent HFA®	$$$$$	$$$$
Tiotropium	dry powder inhaler, solution inhaler	Spiriva Handihaler®, Spiriva Respimat®	$$$$$	N/A
Umeclidinium	dry powder inhaler	Incruse Ellipta®	$$$$$	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 chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-8] Tiotropium is also approved to reduce exacerbations in patients with COPD.[6] Tiotropium has a longer duration of action than ipratropium, which distinguishes tiotropium and ipratropium as long- and short-acting antimuscarinics, respectively.[2] Aclidinium and umeclidinium are both newly available long-acting inhaled antimuscarinics, similar to tiotropium.[3,8] Ipratropium inhalation solution is the only product that is available in a generic formulation.

Most trials have indicated that the existing medications to treat COPD do not modify the long-term decline in lung function.[9] 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.[9,10,13] For patients who require daily maintenance therapy to control symptoms, an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic).[9-13] Treatment guidelines do not indicate a preference as there is insufficient evidence to favor one long-acting bronchodilator over another.[9,11,13] When selecting an inhaled antimuscarinic, a long-acting agent is preferred over a short-acting agent due to differences in efficacy.[9,10,12]

Clinical trials have demonstrated that the regular use of a short- or long-acting antimuscarinic improves health status.[17-56] Tiotropium has been shown to significantly reduce COPD exacerbations, improve spirometric indices, and lead to improvements in quality of life and symptom scales compared to treatment with ipratropium.[42,43] Similar results were observed in a meta-analysis of 16 trials comparing tiotropium, ipratropium, and long-acting β_2-agonist therapy.[43] In addition, tiotropium may provide a greater clinical benefit than long-acting β_2-agonists.[48,50-53,75] Treatment with aclidinium, a new long-acting inhaled antimuscarinic, has demonstrated statistically significant improvements in pulmonary function, COPD symptoms, and quality of life in patients with COPD compared to placebo.[17-21] A trial comparing aclidinium to tiotropium found the effects of the medications to be similar over six weeks of treatment.[22] Treatment with umeclidinium has also demonstrated statistically significant improvements in pulmonary function, COPD symptoms, and quality of life in patients with COPD compared to placebo; however, head to head trials with other inhaled antimuscarinics have not been conducted.[57,58]

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.[35,60,61,64,65,68] In 2008, the Food and Drug Administration (FDA) released several communications describing a potential increased risk of stroke, myocardial infarction, or death from cardiovascular causes with tiotropium.[14] However, the results of the UPLIFT trial did not support these findings.[32,63] 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.[15]

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. 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. However, it should be noted that devices studied are only equally effective in patients who can use them appropriately. 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.[72]

Therefore, all brand short-acting inhaled antimuscarinics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Aclidinium, tiotropium, and umeclidinium offer 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.

At least one long-acting inhaled antimuscarinic is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting antimuscarinic is selected as a preferred agent.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Respiratory Beta-Adrenergic Agonists
AHFS Class 121208
November 4, 2015

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.[1-19] 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, and terbutaline. These agents increase airflow within 30 minutes and the effects may last up to four to five 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. Indacaterol (Arcapta®), a LABA, was Food and Drug Administration (FDA) approved in July 2011 for the long term, once-daily maintenance bronchodilator treatment of airflow obstruction in people with COPD including chronic bronchitis and emphysema. Additional once-daily LABAs have been recently approved, including olodaterol in 2014 and a umeclidinium-vilanterol combination inhaler in 2013.[1-19]

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 August 2013.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Albuterol	aerosol inhaler, dry powder inhaler, extended-release tablet, inhalation solution, syrup, tablet	ProAir HFA®, Proventil HFA®, ProAir Respiclick®, Ventolin HFA®, Vospire ER®*	albuterol, ProAir HFA®, Proventil HFA®
Arformoterol	inhalation solution	Brovana®	none
Formoterol	inhalation solution, dry powder inhaler	Foradil®, Perforomist®	none
Indacaterol	dry powder inhaler	Arcapta®	none
Levalbuterol	aerosol inhaler, inhalation solution	Xopenex®*, Xopenex HFA®	levalbuterol
Metaproterenol	syrup, tablet	N/A	metaproterenol
Olodaterol	solution inhaler	Striverdi Respimat®	none
Salmeterol	dry powder inhaler	Serevent Diskus®	Serevent Diskus®
Terbutaline	injection, tablet	N/A	terbutaline
Combination Products			
Ipratropium and albuterol	inhalation solution, solution inhaler	Combivent Respimat®	albuterol and ipratropium, Combivent Respimat®
Umeclidinium and vilanterol	dry powder inhaler	Anoro Ellipta®	none

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

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.

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

Clinical Guidelines	Recommendations

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2015)**[20]	Diagnosis
	• A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking and occupational exposure to dusts/chemicals.
	• A diagnosis of COPD should be confirmed by spirometry.
	• COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio.
	• The presence of a post-bronchodilator FEV_1/FVC <0.70 and FEV_1 <80% predicted confirms the presence of airflow limitation that is not fully reversible.
	• A detailed medical history should be obtained for all patients suspected of developing COPD.
	• Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
	• Bronchodilator reversibility testing should be performed to rule out the possibility of asthma.
	• Chest radiograph may be useful to rule out other diagnoses.
	• Arterial blood gas measurements should be performed in advanced COPD.
	• Screening for α_1-antitrypsin deficiency should be performed in patients who are from areas with a particularly high prevalence of the deficiency. Typical patients develop COPD at 45 years of age or younger and have lower lobe emphysema.
	• Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis.
	
	Therapeutic options
	• In patients who smoke, smoking cessation is the intervention with the greatest capacity to influence COPD. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
	• The management of COPD should be individualized to address symptoms and improve the patient's quality of life.
	• None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications.
	• COPD patients should receive an annual influenza vaccine.
	• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value.
	• Patients who get short of breath while walking at their own pace on level ground should be offered rehabilitation.
	
	Pharmacologic therapy for stable COPD
	• Bronchodilators
	  o Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations.
	  o Principle bronchodilators include β_2-agonists, anticholinergics, and theophylline used as monotherapy or in combination.
	  o The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.

Clinical Guidelines	Recommendations
	o For single-dose, as needed use, there is no advantage in using levalbuterol over conventional bronchodilators. o Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable. • Corticosteroids o Inhaled corticosteroids (ICSs) should be used in patients with an FEV_1 <60% of the predicted value. o Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • Combination inhaled corticosteroid/ bronchodilator o An inhaled corticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD. • Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended. <u>Management of stable COPD</u> • Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quite. • The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients and individualized assessment of symptoms and risk of exacerbation should also be considered. • Pharmacologic therapy is used to reduce symptoms, reduce frequency of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function. • For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators. • Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations. • Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD. • The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 <50% predicted, chronic bronchitis, and frequent exacerbations. • Influenza vaccines can reduce the risk of serious illness and death in COPD patients. • Currently, the use of antibiotics is not indicated in COPD, other than for treating infectious exacerbations of COPD and other bacterial infections. <u>Management of exacerbations</u> • The most common causes of an exacerbation are viral upper respiratory tract infections and infection of the tracheobronchial tree. • Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation. • Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function, and reduce the risk of early relapse, treatment failure, and length of hospital stay.
National Institute for Health and Clinical Excellence:	<u>Diagnosis</u> • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional

Clinical Guidelines	Recommendations

Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)[21]
 	
Reviewed July 2014
	breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze.
	• The primary risk factor is smoking.
	• Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%.
	
	<u>Treatment</u>
	• Smoking cessation should be encouraged for all patients with COPD.
	• Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.
	• Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.
	• Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist.
	  o FEV_1 ≥50% predicted: long acting beta agonist (LABA) or long-acting anticholinergic antagonist.
	  o FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist.
	• In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined.
	• Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa.
	• Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs.
	• In most cases, inhaled bronchodilator therapy is preferred.
	• Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation.
	• Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy.
	• Pulmonary rehabilitation should be made available to patients.
	• Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure.
	
	<u>Management of exacerbations</u>
	• Patients with exacerbations should be evaluated for hospital admission.
	• Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial.
	• Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days.
	• Oxygen should be given to maintain oxygen saturation above 90%.
	• Patients should receive invasive and noninvasive ventilation as necessary.
	• Respiratory physiotherapy may be used to help remove sputum.
	• Before discharge, patients should be evaluated by spirometry.
	• Patients should be properly educated on their inhaler technique and the necessity

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	of usage and should schedule a follow up appointment with a health care professional.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)**[22]	Diagnosis • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
International Primary Care Respiratory Group: **Management of Chronic Obstructive Pulmonary Disease (2006)**[23]	• 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/European Respiratory Society:	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

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Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease (2004)[24]	disease. • COPD is classified with the use of spirometry as follows: o Mild COPD: $FEV_1/FVC \leq 0.70$ and $FEV_1 \geq 80\%$ predicted. o Moderate COPD: $FEV_1/FVC \leq 0.70$; $FEV_1 \geq 50\%$ and $<80\%$ predicted. o Severe COPD: $FEV_1/FVC \leq 0.70$; $FEV_1 \geq 30\%$ and $<50\%$ predicted. o Very Severe COPD: $FEV_1/FVC \leq 0.70$ and $FEV_1 <30\%$ predicted. <u>Treatment</u> • 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: o Intermittent symptoms: Short-acting bronchodilator as needed for symptom control. o 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 three months than either agent alone. • Anticholinergics given four times a day can improve health status over a three-month period compared with placebo. • LABA 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 LABA and ipratropium leads to fewer exacerbations than either drug alone. • No good comparative data between different LABA are presently available although it is likely that their effects will be similar. • Combining LABA 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 LABA in its effect and in one clinical trial appeared to be superior to salmeterol in some measures over six 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

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	COPD. • Evidence from four large prospective three-year 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 chromones (mast-cell stabilizers) in COPD.

Global Initiative for Asthma:
Global Strategy for Asthma Management and Prevention (2015)[25]
	General principles of asthma management
	• The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.
	• Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers.
	• Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources.
	• Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects.
	• For population-level decisions about asthma management, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness, and safety from randomized controlled trials, meta-analyses, and observational studies, and net cost.
	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	Treatment overview
	• At present, step 1 treatment is with as-needed short-acting $beta_2$ agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a lack of studies of inhaled corticosteroids (ICS) in such populations.
	• Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	• For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities.
	  o For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting $beta_2$ agonist (LABA).
	  o For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller plus as-needed SABA.
	  o For children six to 11 years, increasing the ICS dose is preferred over combination ICS/LABA.
	• Consider step down once good asthma control has been achieved and maintained for about three months to find the patient's lowest treatment that controls both symptoms and exacerbations.
	  o Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.
	  o Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
	• For all patients with asthma:
	  o Provide inhaler skills training.
	  o Encourage adherence with controller medication, even when symptoms are

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infrequent.
- o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations and need for healthcare utilization.

- For patients with one or more risk factors for exacerbations:
  - o Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients.
  - o Identify and address modifiable risk factors (e.g., smoking, low lung function).
  - o Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction.

Categories of asthma medications

- *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
- *Reliever (rescue medications)*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
- *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.

Stepwise approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years old

- Initial controller treatment: For best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.
- Once treatment has been commenced (see table below), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - o Incorrect inhaler technique.
  - o Poor adherence.
  - o Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - o Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - o Incorrect diagnosis.

Stepwise approach to control symptoms and minimize future risk					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller choice		Low dose ICS	Low dose ICS/LABA*	Med/high ICS/LABA	Refer for add-on treatment (e.g., anti-IgE)
Other	Consider	Leukotriene receptor	Med/high dose	High dose	Add low

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controller options	low dose ICS	antagonist (LTRA) or low dose theophylline*	ICS or low dose ICS+LTRA (or + theoph*)	ICS + LTRA (or + theoph*)	dose oral corticoste-roids
Reliever	As-needed SABA		As-needed SABA or low dose ICS/formoterol**		

*For children six to 11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium-dose ICS.
**Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy.

Management of worsening asthma and exacerbations

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
- Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
- The management of worsening asthma and exacerbations is part of a continuum, from self-management by the patient with a written asthma action plan, though to management of more severe symptoms in primary care, the emergency department, and the hospital.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (in adults) peak expiratory flow.
- For patients presenting with an exacerbation to a primary care or acute care facility:
  - Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy.
  - Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA therapy, controlled oxygen, and systemic corticosteroids should be given.
  - Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Response should be reviewed after one hour.
  - Ipratropium bromide treatment is recommended only for severe exacerbations not responding to initial treatment.
  - Chest X-ray is not routinely recommended.
  - Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.
  - Before the patient goes home, ongoing treatment should be arranged. This should include starting controller treatment or stepping up the dose of existing controller treatment for two to four weeks, and reducing reliever medication to as-needed use.
- Antibiotics should not be routinely prescribed for asthma exacerbations.
- Arrange early follow-up after any exacerbation, regardless of where it was managed.

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- Review the patient's symptom control and risk factors for further exacerbations.
- For most patients, prescribe regular controller therapy to reduce the risk of further exacerbations. Continue increased controller doses for two to four weeks.
- Check inhaler technique and adherence.

Children five years and younger: assessment and management

- The goals of asthma management in young children are similar to those in older patients:
  - To achieve good control of symptoms and maintain normal activity levels.
  - To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects.
- Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made.
- A trial of controller therapy should be given if the symptom pattern suggests asthma and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <4 years and mouthpiece for most four to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

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

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

Management of worsening asthma and exacerbations in children five and younger

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is

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	worsening, especially in children less than one year of age. o Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours. o There is only weak evidence to support patient-initiated oral corticosteroids. • In children presenting to primary care or an acute care facility with an asthma exacerbation: o Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94-98%). o Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air. o Give oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years. • Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one week of an exacerbation to plan ongoing asthma management.
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[26]	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids. Long-term control medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages.

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- Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma.
- When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton.
- Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens.
- Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy.
- Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.
- LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.
- LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
- Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
- Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma.

Quick-relief medications

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

Assessment, treatment and monitoring

- A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
- Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
- The stepwise approach for managing asthma is outlined below:

Inter-mittent Asthma	Persistent Asthma: Daily Medication				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred SABA as needed	Preferred Low-dose ICS Alternative Cromolyn, leukotriene receptor	Preferred Low-dose ICS+LABA or medium-dose ICS Alternative	Preferred Medium-dose ICS+LABA Alternative Medium-dose ICS+either a	Preferred High-dose ICS+ LABA and consider omalizu-mab for patients who	Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab for patients

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	<table><tr><td></td><td>antagonists, nedocromil, or theophylline</td><td>Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>leukotriene receptor antagonists, theophylline, or zileuton</td><td>have allergies</td><td>who have allergies</td></tr></table> Management of exacerbations • Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. Special populations • For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. • The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm. • Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. • Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. • ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2014)**[27]	Diagnosis in children • The diagnosis is based on recognizing a characteristic pattern of episodic respiratory symptoms and signs in the absence of an alternative explanation for them. • Presence of the following factors increases the probability that a child with respiratory symptoms will have asthma: age at presentation, sex, severity and frequency of previous wheezing episodes, coexistence of atopic disease, family history of atopy, and abnormal lung function. • Focus the initial assessment in children suspected of having asthma on presence of key features in the history and examination and careful consideration of alternative diagnoses. Diagnosis in adults • The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them. • Confirmation of airflow obstruction is vital for diagnosis of asthma. Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction. Pharmacological management • The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication. • Lung function measurements cannot be reliably used to guide asthma management in children under five years of age. • Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors. • Step 1: Mild intermittent asthma: o For all patients, prescribe an inhaled SABA as short term reliever

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	therapy for all patients with symptomatic asthma. • Step 2: Introduction of regular preventer therapy: o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma. o ICS should be considered for patients with any of the following asthma-related features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o In patients >12 years of age, health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Step 3: Initial add-on therapy: o In adults and children five to 12 years of age, the first choice for add-on therapy to ICS is an inhaled LABA, which should be considered before going above a dose of 400 µg beclomethasone or equivalent per day and certainly before going >800 µg beclomethasone or equivalent. o In adults and children five to 12 years of age, if asthma control remains suboptimal after the addition of an inhaled LABA then the dose of ICS should be increased to 800 µg/day in adults or 400 µg/day in children five to 12 years of age if not already receiving these doses. o In children <5 years of age, the first choice for add-on therapy to ICS is leukotriene receptor antagonists. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence. • Step 4: Poor control on moderate dose of ICS plus add-on therapy (addition of fourth drug): o If control remains inadequate on ICS 800 µg beclomethasone daily in adults and 400 µg beclomethasone daily in children plus LABA, consider the following interventions: ▪ Increasing ICS to 2,000 (adults) or 800 (children five to 12 years of age) µg BDP daily. ▪ Leukotriene receptor antagonists. ▪ Theophyllines. ▪ Slow-release β_2-agonist tablets, though caution needs to be used in patients already on LABAs. • Step 5: Continuous or frequent use of oral steroids: o In adults, the recommended method of eliminating or reducing the dose of steroid tablets is ICS, at doses of up to 2,000 µg/day, if required. o In children 5 to 12 years of age, consider very carefully before going above 800 µg/day of ICS. o For all patients, there is a role for a trial of treatment with LABAs, leukotriene receptor antagonists, and theophylline for about six weeks. They should be stopped if no improvement in steroid dose, symptoms, or lung function is detected. o The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children. • A summary of the stepwise management of asthma is outlined below:

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Children <5 Years Old	Children 5 to 12 Years Old	Adults and Children >12 Years Old
Step 1: Mild Intermittent Asthma		
• Inhaled SABA as required	• Inhaled SABA as required	• Inhaled SABA as required
Step 2: Regular Preventer Therapy		
• Add ICS 200 to 400 µg/day*† or leukotriene antagonist if ICS cannot be used • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 400 µg/day* (other preventer drug if ICS cannot be used) • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 800 µg/day* • Start at dose of ICS appropriate to severity of disease
Step 3: Initial Add-on Therapy		
• In those taking ICS 200 to 400 µg/day, consider addition of leukotriene receptor antagonist • In those taking a leukotriene receptor antagonist alone, reconsider addition of an ICS 200 to 400 µg/day • In children under 2 years, consider proceeding to step 4	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 400 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 400 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 800 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 800 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline
Step 4: Persistent Poor Control		
• Refer to a respiratory pediatrician	• Increase ICS up to 800 µg/day*	Consider trials of: • Increase ICS up to 2,000 µg/day* • Add a fourth drug (leukotriene receptor antagonist, sustained-release 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 ICS at 800 µg/day* • Refer to respiratory pediatrician	• Use daily corticosteroid tablet in lowest dose providing adequate control • Maintain high-dose ICS at 2,000 µg/day* • Consider other treatments to minimize use of corticosteroid tablets • Refer patient for specialist care

*Beclomethasone or equivalent.
†Higher nominal doses may be required if drug delivery is difficult.

Specific management issues

- For adults and children 5 to 12 years of age, if exercise is a specific problem in patients taking ICS who are otherwise well controlled, consider adding one of the following: leukotriene receptor antagonists, LABAs, chromones, oral β_2-agonists, or theophyllines.
- For adults and children 5 to 12 years of age, immediately prior to exercise inhaled SABAs are the drug of choice.

International Primary Care Respiratory Group:	Diagnosis • Diagnosis of asthma is based on signs and symptoms of airway obstruction. • Treatment requires a stepwise approach based on asthma classification.

Clinical Guidelines	Recommendations

Management of Asthma (2006)[28]	<u>Treatment</u>
	• Step 1: intermittent asthma:
	  o Short-acting β_2-agonists as needed for symptoms and for exercise-induced bronchospasm.
	  o In patients >60 years of age, consider an anticholinergics agent.
	• Step 2: mild persistent asthma:
	  o Low-dose ICS.
	• Step 3: moderate persistent asthma:
	  o Combination therapy with an ISC and a LABA.
	  o An alternative treatment option includes using the combination of an ICS and a leukotriene modifier or sustained-release theophylline.
	• Step 4: severe persistent asthma:
	  o Combination therapy with a high-dose ICS and LABA.
	  o An alternative treatment option includes high-dose ICS and sustained-release theophylline.
	  o An alternative treatment option includes high-dose ICS and a leukotriene modifier.
	  o Oral corticosteroids can be used over the short-term.
	
	<u>General treatment consideration</u>
	• 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 ICS.
	• For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of ICS and a LABA. Alternatives are combinations of ICS with sustained-release theophylline or with leukotriene receptor antagonists.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory beta-adrenergic agonists are noted in Tables 3 and 4. 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 Single Entity Respiratory Beta-Adrenergic Agonists[1-17]

Indication	Albuterol	Arformoterol	Formoterol	Indacaterol	Levalbuterol	Metaproterenol	Olodaterol	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		✔	✔ †§					✔	
Long term, once-daily maintenance bronchodilator treatment of airflow obstruction in COPD patients, including chronic bronchitis and/or emphysema				✔			✔		
Exercised-Induced Bronchospasm									
Prevention of exercise-induced bronchospasm	✔ ‡§		✔ §					✔	

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

Table 4. FDA-Approved Indications for the Combination Respiratory Beta-Adrenergic Agonists[1-2,18-19]

Indication	Ipratropium and albuterol	Umeclidinium and vilanterol
COPD		
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema		✔
Patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator	✔ (Combivent Respimat®)	
Treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator	✔ (inhalation solution)	

COPD=chronic obstructive pulmonary disease.

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory beta-adrenergic agonists are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Respiratory Beta-Adrenergic Agonists[1-19]

Generic Name(s)	Onset (minutes)	Duration (hours)	Bio-availability (%)	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents						
Albuterol	Oral: within 30 Inhalation: within 5	Oral: 6 to 12 Inhalation: 3 to 6	INH: <20 IR/ER: 100	10	Renal (76 to 100)	ER: 9.3 HFA: 4.6 to 6.0 Neb: 5 Tab: 5.0 to 7.2 Syrup: 5.0 to 7.2
Arformoterol	<7	Not reported	Not reported	52 to 65	Renal (67)	26
Formoterol	Within 5	12	Not reported	31 to 64	DPI: Renal (59 to 62) Neb: Renal (1.1 to 1.7)	DPI: 10 Neb: 7
Indacaterol	Not reported	24	43 to 45	94.1 to 96.2	<2	40 to 56
Levalbuterol	5 to 17	3 to 6	Not reported	Not reported	Not reported	4
Metaproterenol	30	4	<10	Not reported	Not reported	Not reported
Olodaterol	Not reported	7.5	30	60	Renal (38) Feces (53)	45
Salmeterol	5 to 45	12	Not reported	96	Renal (25)	5.5
Terbutaline	30	4 to 8	100	Not reported	Renal (30 to50)	3.4
Combination Products						
Ipratropium and albuterol	15 to 45	3 to 6	A: <20 I: 2 to 7	A: 10 I: 0 to 9	A: Renal (76 to 100) I: Renal (3.7.to 5.6)	A: 5 I: 1.6
Umeclidinium and vilanterol	27	Not reported	Not reported	U: 89 V: 94	U: Renal (<1), Feces	U: 11 V: 11

					(92) V: Renal (70), Feces (30)	

A=albuterol, ER=extended-release oral formulation, HFA=hydrofluoroalkane, I=ipratropium, INH=inhalation, IR=immediate-release oral formulation, Neb=nebulizer, U=umeclidinium, V=vilanterol

V. Drug Interactions

Significant drug interactions with the respiratory beta-adrenergic agonists are listed in Table 6.

Table 6. Significant Drug Interactions with the Respiratory Beta-Adrenergic Agonists[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Albuterol, arformoterol, formoterol, levalbuterol, salmeterol, terbutaline	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.

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 7 to 9. The boxed warnings for the long-acting respiratory beta-adrenergic agonists are listed in Tables 10 to 16. A meta-analysis of all clinical trial data for the long-acting β_2-agonists (LABAs) was presented at an Food and Drug Administration (FDA) Advisory Committee meeting in December 2008.[29] 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% confidence interval [CI], 1.51 to 5.75) per 1,000 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 7. Adverse Drug Events (%) Reported with the Single Entity Respiratory Beta-Adrenergic Agonists (Drugs A – I)[1-11]

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

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Indacaterol
Headache	7	0.9 to 1.7	7	✔	✔	✔	5.1
Hypokinesia	-	-	-	<2	-	-	-
Insomnia	2	-	-	<2	1.5	2.4	-
Irritable behavior	✔	✔	✔	-	-	-	-
Nervousness	20	-	7	<2	✔	✔	-
Nightmares	✔	✔	✔	-	-	-	-
Paresthesia	-	-	-	<2	-	-	-
Restlessness	<1	✔	<1	-	-	-	-
Somnolence	2	-	-	<2	-	-	-
Sweating	-	-	-	-	-	-	-
Seizure	✔	✔	✔	-	-	-	-
Tremor	20	✔	✔	<2	1.9	✔	-
Vertigo	-	-	✔	-	-	-	-
Weakness	2	-	-	-	-	-	-
Dermatological							
Angioedema	✔	-	✔	-	-	-	-
Dry skin	-	-	-	<2	-	-	-
Flushing	<1	-	-	-	-	-	-
Herpes simplex/zoster	-	-	-	<2	-	-	-
Photodermatitis	-	-	-	-	-	-	-
Pruritus	-	-	-	-	1.5	-	-
Rash	✔	✔	✔	4	1.1	-	-
Skin discoloration	-	-	-	<2	-	-	-
Skin hypertrophy	-	-	-	<2	-	-	-
Urticaria	✔	0.9 to 1.7	✔	✔	-	-	-
Endocrine and Metabolic							
Diabetes	-	-	-	-	-	-	>2
Hyperglycemia	✔	-	-	✔	✔	✔	>2
Hypokalemia	✔	✔	✔	<2	✔	✔	-
Lactic acidosis	✔	✔	✔	-	✔	✔	-
Gastrointestinal							
Constipation	-	-	-	<2	-	-	-
Diarrhea	✔	✔	✔	6	-	4.9	-
Dry mouth	✔	✔	✔	-	1.2	1.3 to 3.3	-
Dyspepsia	✔	✔	✔	-	-	3.3	-
Gastrointestinal distress	-	-	-	-	-	-	-
Gastroenteritis	✔	0.9 to 3.4	✔	<2	-	-	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Indacaterol
Heartburn	-	-	-	-	-	-	-
Nausea	2	0.9 to 1.7	-	-	-	4.9	2.4
Oral candidiasis	-	-	-	<2	-	-	-
Oral moniliasis	-	-	-	<2	-	-	-
Periodontal abscess	-	-	-	<2	-	-	-
Rectal hemorrhage/melena	-	-	-	<2	-	-	-
Sore throat	-	-	-	-	-	-	-
Taste changes	✔	✔	✔	-	-	-	-
Vomiting	-	-	7	-	-	2.4	-
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	-	-	✔	-	-	-	-
Hematologic							
Liver enzyme elevation	-	-	-	-	-	-	-
Musculoskeletal							
Arthralgia	✔	✔	✔	<2	-	-	-
Arthritis	-	-	-	<2	-	-	-
Back pain	-	-	-	-	4.2	-	-
Bone disorder	-	-	-	<2	-	-	-
Leg cramps	-	-	-	4	1.7	-	-
Muscle cramps	✔	✔	✔	<2	1.7	✔	>2
Pain	<1	-	3 to 5	8	-	-	>2
Rheumatoid arthritis	-	-	-	<2	-	-	-
Tendinous contracture	-	-	-	<2	-	-	-
Respiratory							
Asthma exacerbation	✔	11 to 13	✔	-	✔	✔	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Indacaterol
Bronchitis	-	0.9 to 1.7	-	✔	4.6	-	-
Bronchospasm	✔	✔	✔	-	-	-	-
Chest infection	-	-	-	-	2.7	-	-
Chronic obstructive pulmonary disease exacerbation	-	-	-	-	-	4.1	-
Cough	✔	✔	5	-	-	-	6.5
Cold symptoms	-	3.4	-	-	-	-	-
Drying of oropharynx	✔	✔	✔	-	-	-	-
Drying of secretions	-	-	-	-	-	-	-
Dysphonia	-	-	-	<2	1	-	-
Dyspnea	-	-	✔	4	2.1	-	-
Epistaxis	✔	✔	✔	-	-	-	-
Hoarseness	✔	✔	✔	-	-	-	-
Increased sputum	-	-	-	-	1.5	-	-
Irritation	-	-	-	-	-	-	-
Laryngospasm	-	-	-	-	-	-	-
Lung disease	-	-	-	-	-	-	-
Lung carcinoma	-	-	-	<2	-	-	-
Lymphadenopathy	-	0.9 to 2.6	-	-	-	-	-
Nasal congestion	-	1	-	-	-	-	-
Nasopharyngitis	-	-	-	-	-	-	5.3
Oral mucosal abnormality	-	-	-	<2	-	-	-
Oropharyngeal pain	-	-	-	-	-	-	2.2
Pharyngitis	✔	<1	14	-	3.5	3.3	-
Pneumonia	-	-	-	-	-	-	-
Pulmonary edema	✔	✔	✔	-	-	-	-
Respiratory disorder	-	-	-	2	-	-	-
Rhinitis	✔	✔	5 to 16	-	-	-	-
Sinusitis	-	-	-	5	2.7	-	>2
Skin/appendage infection	-	0 to 1.7	-	-	-	-	-
Throat irritation	✔	✔	1	-	-	-	-
Upper respiratory tract infection	-	-	21	-	7.4	-	>2
Viral respiratory infection	✔	2.6	7	-	-	-	-
Voice alterations	-	-	-	<2	-	-	-
Wheezing	-	-	-	-	-	-	-
Other							
Acute eye pain	-	-	-	-	-	-	-
Alopecia	-	-	-	-	-	-	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡	Formoterol§	Indacaterol
Anaphylactic reaction	✔	0.9 to 3.4	6	✔	-	-	-
Back pain	-	-	-	6	-	-	-
Blurred vision	-	-	-	<2	-	-	-
Edema	-	-	✔	3	-	-	-
Fever	-	-	6	-	2.2	-	-
Glossitis	✔	✔	✔	-	-	-	-
Glaucoma	-	-	-	<2	-	-	-
Influenza	-	-	3	-	-	-	-
Otitis media	✔	0.9 to 4.3	✔	-	-	-	-
Peripheral edema	-	-	-	-	-	-	>2
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 8. Adverse Drug Events (%) Reported with the Single Entity Respiratory Beta-Adrenergic Agonists (Drugs L – T)[1-2,12-17]

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Cardiovascular						
Angina	-	-	✔	-	-	-
Arrhythmias	-	✔	✔	-	1 to 3	1.5
Chest pain	<2	-	<1	-	-	-
Electrocardiogram abnormal	<2	-	-	-	-	-
Hypertension	<2	<2	0.4	-	-	-
Hypotension	<2	-	-	-	-	-
Palpitations	-	-	3.8	-	✔	5
Syncope	<2	-	<1	-	✔	-
Tachycardia	2.7	✔	17.1	-	✔	3.5
Vasodilations	-	-	-	-	-	1
Central Nervous System						
Anxiety	2.7	-	-	-	1 to 3	1
Asthenia	3	-	-	-	-	-
Dizziness	1.4 to 2.7	2.7	2.4	2.3	4	3.5

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Fatigue	-	-	<1	-	-	-
Hallucinations	-	-	-	-	-	<1
Headache	-	-	7	-	13 to 17	7.5
Hypertonia	-	-	-	-	-	<1
Hypesthesia of the hand	<2	-	-	-	-	-
Insomnia	<2	-	1.8	-	-	1.5
Migraine	2.7	-	-	-	-	-
Nervousness	2.8 to 9.6	✔	20.2	-	✔	35
Paresthesia	<2	-	-	-	1 to 3	<1
Sensory disturbances	-	-	<1	-	1 to 3	-
Somnolence	-	-	-	-	-	5.5
Sweating	<2	-	-	-	-	1
Tremor	6.8	✔	1 to 17	-	✔	15
Weakness	-	-	<1	-	-	-
Dermatological						
Angioedema	-	✔	-	-	✔	-
Contact dermatitis	-	-	-	-	1 to 3	-
Diaphoresis	-	-	<1	-	-	-
Eczema	-	-	-	-	1 to 3	-
Hives	-	-	<1	-	-	-
Photodermatitis	-	-	-	-	1 to 2	-
Pruritus	-	-	2	-	-	-
Rash	7.5	✔	-	2.2	1 to 3	<1
Skin reaction	-	-	-	-	4	-
Urticaria	3	✔	-	-	3	-
Endocrine and Metabolic						
Hyperglycemia	-	-	-	-	1 to 3	-
Gastrointestinal						
Constipation	-	<2	-	-	-	-
Dental discomfort	-	-	-	-	1 to 3	-
Diarrhea	1.5 to 6.0	-	1.2	2.9	-	-
Dry mouth	<2	-	<1	-	-	1.5
Dyspepsia	1.4 to 2.7	-	-	-	-	-
Dyspeptic symptoms	-	-	-	-	1 to 3	-
Gastroenteritis	<2	<2	-	-	-	-
Gastrointestinal infections	-	-	-	-	1 to 3	-
Gastrointestinal distress	-	-	-	-	1 to 3	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Hyposalivation	-	-	-	-	1 to 3	-
Nausea	<2	-	3.6	-	1 to 3	3
Oral candidiasis	-	-	-	-	1 to 3	-
Taste changes	-	-	<1	-	-	-
Vomiting	<2	10.5	<1	-	3	<1
Genitourinary						
Vaginal moniliasis	-	<2	-	-	-	-
Hematuria	-	<2	-	-	-	-
Urinary tract infection	-	-	-	2.5	-	-
Musculoskeletal						
Arthralgia	-	-	-	2.1	1 to 2	-
Articular rheumatism	-	-	-	-	1 to 2	-
Leg cramps	2.7	-	-	-	-	-
Muscle cramps	-	-	-	-	3	-
Muscle spasm	-	-	-	-	3	<1
Muscle stiffness	-	-	-	-	1 to 3	-
Muscle tightness	-	-	-	-	1 to 3	-
Muscle rigidity	-	-	-	-	1 to 3	-
Musculoskeletal inflammation	-	-	-	-	1 to 3	-
Myalgia	1.5	<2	-	-	12	-
Pain	1.4 to 3.0	4	<1	3.5	1 to 3	-
Respiratory						
Asthma	9.0 to 9.1	9.4	2	-	3 to 4	-
Bronchitis	-	2.6	-	4.7	7	-
Bronchospasm	-	-	-	-	✔	-
Cough	1.4 to 4.1	-	<1	4.2	4	-
Dyspnea	-	✔	-	-	-	-
Epistaxis	-	<2	-	-	-	-
Influenza	-	-	-	-	5	-
Laryngeal irritation/swelling	-	-	<1	-	1 to 3	-
Laryngeal spasm	-	-	-	-	1 to 3	-
Lung Disorder	-	<2	-	-	-	-
Nasopharyngitis	-	-	-	11.3	-	-
Oral mucosal abnormality	-	-	-	-	1 to 3	-
Pharyngitis	3.0 to 10.4	6.6 to 7.9	-	-	6	-
Rhinitis	2.7 to 11.1	7.4	-	-	2	-
Sinus headache	-	-	-	-	1 to 3	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Sinusitis	1.4 to 4.2	-	-	-	-	-
Upper respiratory tract infection	-	-	-	8.2	-	-
Viral respiratory infection	-	-	-	-	4	-
Wheezing	<2	-	-	-	-	-
Other						
Accidental injury	4.5 to 6.1	9.2	-	-	-	-
Acne	-	<2	-	-	-	-
Anaphylaxis	-	-	-	-	1 to 3	-
Conjunctivitis	-	<2	-	-	1 to 3	-
Cyst	-	<2	-	-	-	-
Chills	<2	-	<1	-	-	-
Chatty	-	-	<1	-	-	-
Clonus on flexed foot	-	-	<1	-	-	-
Dysmenorrhea	-	<2	-	-	-	-
Ear pain	-	<2	-	-	-	-
Ear signs	-	-	-	-	4	-
Edema	-	-	<1	-	1 to 3	-
Eye itch	<2	-	-	-	-	-
Fever	3.0 to 9.1	-	<1	-	1 to 3	-
Flu syndrome	-	<2	<1	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	<1
Herpes Simplex	-	<2	-	-	-	-
Lymphadenopathy	3	-	-	-	-	-
Turbinate edema	1.4 to 2.8	-	-	-	-	-
Viral infection	6.9 to 12.3	<2	-	-	-	-

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

Table 9. Adverse Drug Events (%) Reported with the Combination Respiratory Beta-Adrenergic Agonists[1-2,18-19]

Adverse Events	Ipratropium and Albuterol‡	Ipratropium and Albuterol*	Umeclidinium and Vilanterol
Cardiovascular			
Arrhythmias	-	-	-
Chest pain/discomfort	2.6	-	<1
Palpitations	✔	-	-
Tachycardia	✔	-	-

Adverse Events	Ipratropium and Albuterol‡	Ipratropium and Albuterol*	Umeclidinium and Vilanterol
Central Nervous System			
Drowsiness	✔	-	-
Headache	-	2 to 3	-
Dermatological			
Flushing	✔	-	-
Pruritus	<1	-	<1
Rash	<1	-	<1
Urticaria	<1	-	-
Gastrointestinal			
Abdominal pain	1	1	<1
Constipation	✔	-	1
Diarrhea	1.8	-	2
Dry mouth	-	-	<1
Dyspepsia	1.3	-	<1
Nausea	1.4	-	-
Sore throat	✔	-	-
Taste changes	✔	-	-
Vomiting	-	-	<1
Genitourinary			
Urinary tract infection	1.6	-	-
Musculoskeletal			
Arthralgia	✔	-	-
Back pain	✔	-	-
Leg cramps	1.4	-	-
Muscle spasms	1	1	<1
Pain	1.3	-	1
Respiratory			
Bronchitis	1.7	3	-
Bronchospasm	✔	-	-
Chronic obstructive pulmonary disease exacerbation	✔	-	-
Cough	-	2 to 3	<1
Dyspnea	-	2	-
Lower respiratory tract infection	-	-	1
Lung disease	6.4	-	-
Nasopharyngitis	-	3 to 4	-
Pharyngitis	4.4	-	2
Pneumonia	1.3	-	-

Adverse Events	Ipratropium and Albuterol‡	Ipratropium and Albuterol*	Umeclidinium and Vilanterol
Sinusitis	✔	-	1
Upper respiratory tract infection	✔	3 to 4	-
Voice alterations	✔	-	-
Wheezing	✔	-	-
Other			
Acute eye pain	✔	-	-
Blurred vision	✔	-	-
Conjunctivitis	-	-	<1
Worsening glaucoma	✔	-	-

✔ Percent not specified.
- Event not reported.
‡Inhalation solution formulation.
*Solution inhaler.

Table 10. Boxed Warning for Arformoterol[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 United States study that compared the safety of another long-acting beta-2 adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of long-acting beta-2 agonists, including arformoterol. The safety and efficacy of arformoterol in patients with asthma have not been established. All long-acting beta-2 agonists, including arformoterol, are contraindicated in patients with asthma without use of a long-term asthma control medication.

Table 11. Boxed Warning for Formoterol[1]

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

Table 12. Boxed Warning for Indacaterol[1]

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

Table 13. Boxed Warning for Olodaterol[1]

WARNING
Asthma-related death: Long-acting beta-2 adrenergic agonists increase the risk of asthma-related death. Data from a large, placebo-controlled United States study that compared the safety of another long-acting beta-2

WARNING
adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of long-acting beta-2 adrenergic agonists, including olodaterol. The safety and efficacy of olodaterol in patients with asthma have not been established. Olodaterol is not indicated for the treatment of asthma.

Table 14. Boxed Warning for Salmeterol[1]

WARNING
Long-acting beta-2 adrenergic agonists, such as salmeterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol vs 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from long-acting beta-2 adrenergic agonists. Because of this risk, use of salmeterol for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use salmeterol only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue salmeterol) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use salmeterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. Children and adolescents: Available data from controlled clinical trials suggest that long-acting beta-2 adrenergic agonists increase the risk of asthma-related hospitalization in children and adolescents. For children and adolescents with asthma who require addition of a long-acting beta-2 adrenergic agonist to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 adrenergic agonist should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a long-acting beta-2 adrenergic agonist is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be ensured, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 adrenergic agonist is recommended.

Table 15. Boxed Warning for Terbutaline[1]

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

Table 16. Boxed Warning for Umeclidinium-Vilanterol[1]

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

VII. Dosing and Administration

The usual dosing regimens for the respiratory beta-adrenergic agonists are listed in Table 17.

Table 17. Usual Dosing Regimens for the Respiratory Beta-Adrenergic Agonists[1-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Albuterol	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler, dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily Inhalation solution: 2.5 mg 3 to 4 times daily Syrup: 2 to 4 mg 3 to 4 times daily; maximum, 8 mg 4 times daily Tablet (IR): 2 to 4 mg 3 to 4 times daily Tablet (SR): 4 to 8 mg every 12 hours; maximum, 32 mg daily Exercise-induced bronchospasm: Aerosol inhaler, dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler (≥4 years of age), dry powder inhaler (≥12 years of age): 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily Inhalation solution: 2 to 12 years of age: 0.63 to 1.25 mg 3 to 4 times daily; maximum, 2.5 mg 3 to 4 times daily Syrup: 2 to 5 years of age: 0.1 mg/kg of body weight 3 times daily; maximum, 4 mg 3 times daily; 6 to 14 years of age: 2 mg 3 to 4 times daily; maximum, 24 mg daily Tablet (IR): 6 to 12 years of age: 2 mg 3 to 4 times daily Tablet (SR): 6 to 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), dry powder inhaler (≥12 years of age): 2 inhalations 15 to 30 minutes before exercise	Aerosol inhaler: 90 µg Dry powder inhaler: 90 µg 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 Syrup: 2 mg /5 mL Tablet (IR): 2 mg 4 mg Tablet (SR): 4 mg 8 mg
Arformoterol	COPD: Inhalation solution: 15 µg every 12 hours; maximum 2 doses per 24 hours	Safety and efficacy in children has not been established.	Inhalation solution: 15 µg/2 mL
Formoterol	Asthma, nocturnal asthma, reversible bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 µg) inhaled every 12 hours COPD: Inhalation solution: 20 µg	Asthma, nocturnal asthma, reversible bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 µg) inhaled every 12 hours Exercise-induced bronchospasm:	Inhalation solution: 20 µg/2 mL Dry powder inhaler: 12 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	every 12 hours Dry powder inhaler: the contents of 1 capsule (12 µg) inhaled every 12 hours Exercise-induced bronchospasm: Dry powder inhaler: the contents of 1 capsule (12 µg) inhaled at least 15 minutes before exercise	Dry powder inhaler: the contents of 1 capsule (12 µg) inhaled at least 15 minutes before exercise	
Indacaterol	COPD: Inhaler: initial, maintenance and maximum, the contents of 1 capsule inhaled once daily	Safety and efficacy in children have not been established.	Capsules for inhalation: 75 µg
Levalbuterol	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily Inhalation solution: 0.63 mg 3 times daily every 6 to 8 hours; maximum, 1.25 mg 3 times daily	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler: ≥4 years of age: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily Inhalation solution: 6 to 11 years of age: 0.31 mg 3 times daily; maximum:0.63 mg 3 times daily	Aerosol inhaler: 45 µg 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 to 4 times daily; maximum, titrated to patient's response Tablet: 20 mg 3 to 4 times daily; maximum, titrated to patient's response	Asthma, nocturnal asthma, reversible bronchospasm: Syrup: 6 to 9 years of age (<60 lb): 1 teaspoonful 3 to 4 times daily >9 years of age (>60 lb): 2 teaspoonfuls 3 to 4 times daily; maximum, titrated to patient's response Tablet: 6 to 9 years of age (<60 lb): 10 mg 3 to 4 times daily >9 years of age (>60 lb): 20 mg 3 to 4 times daily; maximum, titrated to patient's response	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg
Olodaterol	COPD: Solution inhaler: 2 inhalations once daily	Safety and efficacy in children have not been established.	Solution inhaler: 2.5 µg
Salmeterol	Asthma, nocturnal asthma, reversible bronchospasm: Dry powder inhaler: 1 inhalation (50 µg) 2 times daily COPD: Dry powder inhaler: 1 inhalation (50 µg) 2 times daily	Asthma, nocturnal asthma, reversible bronchospasm: Dry powder inhaler (≥4 years of age): 1 inhalation (50 µg) 2 times daily Exercise-induced bronchospasm: Dry powder inhaler (≥4 years	Dry powder inhaler: 50 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation (50 µg) at least 30 minutes before exercise	of age): 1 inhalation (50 µg) at least 30 minutes before exercise	
Terbutaline	Asthma, nocturnal asthma, reversible bronchospasm: Tablet: 2.5 to 5 mg repeated every 6 hours 3 times daily; maximum, 15 mg daily	Asthma, nocturnal asthma, reversible bronchospasm: Tablet (12 to 15 years of age): 2.5 mg repeated every 6 hours 3 times daily; maximum, 7.5 mg daily	Injection: 1 mg/mL Tablet: 2.5 mg 5 mg
Combination Products			
Ipratropium and albuterol	COPD: Inhalation solution: 1 vial four times daily; maximum, 6 vials daily Solution inhaler: one inhalation (20-100 µg) four times daily; maximum, six inhalations a day	Safety and efficacy in children has not been established.	Inhalation solution: 0.5-3 mg/3 mL Solution inhaler: 20-100 µg
Umeclidinium and vilanterol	COPD: Dry powder inhaler: 1 inhalation once daily	Safety and efficacy in children has not been established.	Dry powder inhaler: 62.5-25 µg

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 18.

Table 18. 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				
Nelson et al.[30] (2006) SMART Salmeterol 42 µg BID vs placebo	DB, MC, OS, PC, PG, RCT 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 three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol (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).
Salpeter et al.[31] (2006) Long-acting beta-adrenergic agonists vs	MA Patients diagnosed with asthma	N=33,826 (19 trials) ≥3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			exacerbations, asthma-related deaths Secondary: Not reported	Not reported
Von Berg et al.[32] (1998) Salmeterol 50 µg BID vs placebo	DB, PC, PG, RCT Patients 6 to 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 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 six 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 six 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 six months of the study (P=0.05). Secondary: Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the 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). 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).
Casaburi et al.[33] (1991) Albuterol 5 mg via compressed air	RCT Individuals presenting for routine pulmonary function testing	N=180 Clinic visit	Primary: FEV_1 and FVC Secondary: Not reported	Primary: There was no statistical difference in FEV_1 or FVC at five and 10 minutes post-administration between the two groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs isoproterenol 5 mg via compressed air				
Carl et al.[34] (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)	DB, PRO, RCT Individuals 1 to 18 years of age with diagnosed with asthma presenting to the ED (1 patient had been using levalbuterol the remainder albuterol as rescue prior to presenting to the ED)	N=547 Varying duration of hospitali-zations	Primary: Hospital admission rate Secondary: LOS, ED LOS, intensification, number of aerosols, requirement for oxygen, and adverse effects	Primary: Compared with the albuterol group (45%), the levalbuterol group (36%) had a significantly lower hospitalization rate (P=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse effects (P=0.26 to P=0.94). No significant adverse events occurred in either group.
Schreck et al.[35] (2005) Albuterol 2.5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25 mg via nebulization (plus standard treatment)	CR, OS, RETRO Individuals 1 year of age or older with a diagnosis of acute asthma presenting to the ED requiring nebulization with a SABA	N=736 9 months	Primary: Patient disposition, ED LOS, and objective measures of patient upon arrival Secondary: Not reported	Primary: There was a significantly lower hospitalization rate in the levalbuterol group compared 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 concerning ED LOS and other objective measures upon patient presentation (P=0.762). Due to a decrease in hospitalizations, treatment costs were lower in the levalbuterol treatment group (no P value reported). Secondary: Not reported
Qureshi et al.[36] (2005) Albuterol 2.5-5 mg	DB, PRO, RCT Children 2 to 14 years of age with a	N=129 Study was complete after	Primary: Changes from baseline in clinical asthma score and	Primary: No significant differences between the treatment groups were found (no P value reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
via nebulization (plus standard treatment) vs levalbuterol 1.25-2.5 mg via nebulization (plus standard treatment)	known history of asthma presenting to a pediatric ED with an acute moderate or severe asthma exacerbation	patient received 5 doses, was admitted, or discharged	the percent of predicted FEV_1 after the 1st, 3rd, and 5th treatment Secondary: Number of treatments, length of ED care, rate of hospitalizations, changes in pulse rate, and oxygen saturation	Secondary: No significant differences between the treatment groups were found (no P value reported). No significant differences between the treatment groups concerning adverse effects (no P value reported).
Nowak et al.[37] (2006) Albuterol 2.5 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg vs levalbuterol 1.25 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg	DB, MC, PG, PRO, RCT Individuals ≥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 plasma concentration of (S)-albuterol at presentation on FEV_1 response and on hospitalization	Primary: For the levalbuterol and albuterol groups the median time to discharge (76.0 and 78.5 minutes) was not statistically different (P=0.74). Secondary: There was no significant difference (P=0.28) in the admission rate between the albuterol (9.3%) and the levalbuterol (7.0%) groups. After dose one 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 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 (no P value reported).
Nelson et al.[38] (1998) Albuterol 1.25 mg via nebulization TID	DB, PC, PG, RCT Patients ≥12 years of age that do not smoke and had at least a 6-month	N=362 4 weeks	Primary: Peak change in FEV_1 after four weeks Secondary:	Primary: Change in peak FEV_1 in the combined levalbuterol group was not significantly greater than combined albuterol (0.84 and 0.74; no P value reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	history of chronic and stable asthma, demonstrating at least a 15% improvement in FEV_1 to a single dose of albuterol 2.5 mg via nebulization		AUC, use of rescue racemic albuterol meter dose inhaler	A similar trend was noticed when evaluating the AUC; after the first dose, levalbuterol treatment was significantly better (P=0.02) compared to albuterol. However, at week four, even though the AUC values were higher in the levalbuterol groups, the difference was not significant. There was a significant improvement (P=0.006) in predose FEV_1 in the combined levalbuterol arm compared to the combined albuterol arm in the subset of patients not taking corticosteroids. There was significantly less rescue medication used in the active treatment groups compared to placebo. Compared to baseline there was a significant decrease in rescue-medication use in both the levalbuterol 1.25 mg arm (P<0.001) and the albuterol 2.5 mg arm (P=0.056). All active treatments were well tolerated with the percent of patients reporting nervousness or tremor in the low dose groups being statistically significantly lower (P=0.003) compared to the high dose groups.
Gawchik et al.[39] (1999) Albuterol 1.25 mg via nebulization (1 dose) vs albuterol 2.5 mg via nebulization (1 dose) vs	DB, PC, RCT, XO Patients 3 to 11 years of age with a history of asthma for at least 6 months and reversibility of 12% or more 30 minutes after 2.5 mg of albuterol administered by nebulization	N=43 4 treatment visits (2 to 8 days apart)	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC Secondary: Not reported	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC was significantly improved in all treatment arms (with the exception of albuterol 1.25 mg in AUC) compared 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 (no P values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levalbuterol 0.16 mg via nebulization (1 dose) vs levalbuterol 0.31 mg via nebulization (1 dose) vs levalbuterol 0.63 mg via nebulization (1 dose) vs levalbuterol 1.25 mg via nebulization (1 dose) vs placebo (1 dose)				
Milgrom et al.[40] (2001) Albuterol 1.25 mg via nebulization vs	DB, MC, PC, PG, RCT Patients 4 to 11 years of age with documented diagnosis of at least mild asthma with a	N=338 3 weeks	Primary: Peak percent change in FEV_1 from baseline Secondary: Change in pulmonary	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 ($P<0.02$) and, with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	reversibility of at least 15% to albuterol		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	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 (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.[41] (2004) Albuterol 2.5 mg via nebulization (3 doses) vs albuterol 5 mg via nebulization (3 doses) vs levalbuterol 0.63 mg via nebulization	OL, PRO Adult asthmatics presenting to the ED with an acute asthma exacerbation	N=93 2 hours	Primary: FEV_1 percent change from baseline following the 3rd nebulization 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	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 (no P value reported). Secondary: Compared to baseline at 60 minutes post treatment, levalbuterol 1.25, 2.5, and 5.0 mg improved the median percent predicted FEV_1 by 33 to 38% compared to 12 to 24% with 2.5 and 5.0 mg doses of albuterol and 0.63 and 3.75 mg doses of levalbuterol (no P value reported). (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
(3 doses) vs levalbuterol 1.25 mg via nebulization (3 doses) vs levalbuterol 2.5 mg via nebulization (3 doses) vs levalbuterol 3.75 mg via nebulization (3 doses) vs levalbuterol 5 mg via nebulization (3 doses)				
Skoner et al.[42] (2005) Albuterol 1.25 to 5 mg TID via nebulizer vs	DB, MC, PC, PG, RCT Children 2 to 5 years of age who have been diagnosed with asthma for at least 30 days and had no	N=211 4 weeks	Primary: Change from baseline in the total score on the PAQ Secondary: PEF, rescue medication use, and the Child	Primary: Decrease in the PAQ scores was demonstrated in all treatment groups (no P value reported). Secondary: All treatment groups demonstrated an improvement in PEF compared to placebo (P<0.01 for all treatment groups). All treatment groups, including the placebo group, demonstrated a

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levalbuterol 0.31 mg to 0.63 mg TID via nebulizer vs placebo	other underlying medical condition		Health Status Questionnaire	decrease in rescue medication use. There were no significant differences between the treatment groups (No P value reported). All treatment groups demonstrated and improvement from baseline in the Child Health Status Questionnaire (no P value reported). Overall, the incidence of adverse events was similar for each treatment group during the study period. Adverse events were mild (68.0%) to moderate (28.1%) in severity. Among all patients, significant increases in ventricular heart rate were demonstrated in the levalbuterol 0.63 mg and racemic albuterol 2.5 mg groups compared to placebo (no P value reported).
Berger et al.[43] (2006) Albuterol HFA 180 µg QID vs levalbuterol HFA 90 µg QID vs placebo	DB, MC, RCT Patients 4 to 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 percent 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. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared with placebo; P<0.01, and levalbuterol compared with albuterol; P>0.05).
Hamilos et al.[44] (2007) Albuterol HFA 180 µg QID vs levalbuterol HFA 90 µg 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 ED 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.[45] (2008) Albuterol HFA 90 µg per dose (1x, 2x, 4x, 8x, and 16x) administered over a 2-hour period vs levalbuterol HFA 45 µg per dose (1x, 2x, 4x, 8x, and 16x) administered over	AC, MC, RCT, XO Patients with asthma	N=49 Single-day	Primary: Safety and efficacy Secondary: Not reported	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 to 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 to 6.4). (R)-albuterol plasma levels ranged from 10 to 18% higher after racemic albuterol HFA dosing vs after levalbuterol HFA. FEV_1 improvements were similar for both treatments. The relative potencies of the two therapies (based on FEV_1) were similar (ratio, 1.1; 90% CI, 0.9 to 1.2). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
a 2-hour period				
Wolfe et al.[46] (1991) Albuterol syrup 2 mg TID vs metaproterenol syrup 10 mg TID	IB, MC, PG, RCT Patients 6 to 9 years of age with chronic asthma	N=65 4 weeks	Primary: Time to maximal response, maximum percent increase from baseline, peak flow measurements, heart rate, blood pressure, adverse effects Secondary: Not reported	Primary: There was a greater degree of bronchodilation with albuterol compared to metaproterenol from two to eight hours post dose (P<0.05). The peak percent improvement in FEV_1 from baseline was significantly greater for albuterol compared to metaproterenol (29.3 vs 20.6%; P<0.05). There were no significant differences in the mean change from baseline in systolic blood pressure in either group, however with metaproterenol the chronotropic effect was significantly greater (P<0.05) at one hour on day one and 28 and 1.5 hour on day 28 compared to albuterol. There was no significant difference in the frequency of adverse effects between the two groups. Secondary: Not reported
Habib et al.[47] (1987) Albuterol 5 mg via nebulizer vs metaproterenol 15 mg via nebulizer	DB, RCT Patients reversible airway obstruction utilizing intermittent positive pressure ventilation	N=20 7 days	Primary: Lung function and adverse events Secondary: Not reported	Primary: There were no significant differences observed between the spirometric responses or the adverse effects of the two groups to either agent. Secondary: Not reported
Papi et al.[48] (2007) Albuterol 100 µg as needed (as needed albuterol) vs	DB, DD, MC, PG, RCT Patients 18 to 65 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 ≥75% of	N=455 6 months	Primary: Mean rate of morning PEFR Secondary: Lung function, symptom scores, and number/severity of	Primary: The morning PEF rate at six 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 PEF rate did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
beclomethasone-albuterol 250/100 µg in a single inhaler as needed (as needed combination) vs beclomethasone 250 µg BID and albuterol 100 µg as needed (regular beclomethasone) vs beclomethasone-albuterol 250/100 µg BID in a single inhaler and albuterol 100 µg as needed (regular combination)	predicted value, associated with either an increase in FEV_1 ≥12% of predicted value after inhalation of 200 µg of albuterol or a positive methacholine challenge		exacerbations	The evening PEF 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 pre bronchodilator FEV_1 and 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 PEF rate increased significantly in the regular combination group. The evening PEF 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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[49] (2006) Budesonide-formoterol 160/4.5 µg BID and terbutaline MDI 0.4 mg as needed vs budesonide-formoterol 160/4.5 µg BID and formoterol MDI 4.5 µg as needed vs budesonide-	DB, MC, PG, RCT 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 to 100% of predicted normal (pre bronchodilator) with 12% reversibility or more after inhalation of terbutaline 1 mg	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 exacerbations; FEV_1; morning and evening PEF; and reliever medication	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 vs terbutaline (P=0.0051). Secondary: As-needed budesonide-formoterol reduced the risk of a severe exacerbation by 27% (95% CI, 10 to 41) vs formoterol and by 45% (95% CI, 32 to 55) vs terbutaline. The risk reduction with as-needed formoterol vs terbutaline was 24% (95% CI, 8 to 37). The yearly rate of severe exacerbations per patient was reduced with as-needed budesonide-formoterol by 33% vs formoterol (P<0.0001), by 48% vs terbutaline (P<0.0001), and by 22% with as-needed formoterol vs terbutaline (P=0.012; table 2). Rates of exacerbations needing emergency room treatment or hospitalization were reduced with as-needed budesonide-formoterol by 27% (P=0.046) vs formoterol and by 39% (P=0.0010) vs terbutaline, respectively. There was no significant difference between formoterol and terbutaline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
formoterol 160/4.5 µg BID and budesonide-formoterol 160/4.5 µg as needed			use	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 to 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 vs 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 vs maintenance therapy plus formoterol (P=0.0002) or terbutaline (P=0.0007). Night-time awakenings were reduced by 2% (seven nights per year) with as-needed budesonide-formoterol vs formoterol (P=0.018) and by 3% vs 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 vs terbutaline. 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 vs formoterol (P=0.0001) and terbutaline (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean morning PEF increased from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol vs 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.[50] (2006) Budesonide-formoterol 80/4.5µg BID (fixed-dose inhaler) vs budesonide 100 µg 2 puffs BID vs budesonide 100 µg 2 puffs BID and	AC, DB, MC, PG, RCT Patients 4 to 11 years of age with PEF >50% of predicted normal who had 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	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; use of reliever medication; reliever-free days; symptom-free days; change in FEV_1, change 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). Secondary: 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
formoterol 4.5 µg 2 puffs BID (separate inhalers)	to the study		health-related quality of life (PAQLQ)	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.[51] (2007) LOCSS Fluticasone 100µg BID vs montelukast 5 to 10 mg QD vs fluticasone-salmeterol 100-50µg 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 µg 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 pre bronchodilator 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

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				similar across groups, ranging from 78.6 to 85.8%.
Boonsawat et al.[52] (2003) Formoterol 18 µg administered at 0, 30, and 60 minutes vs albuterol 100 µg administered at 0, 30, and 60 minutes	DB, DD, PG, RCT Patients 18 to 67 years of age with asthma presenting to the ED with acute bronchoconstriction	N=88 1 day	Primary: FEV_1, asthma symptoms Secondary: Not reported	Primary: A non-significant increase in FEV_1 at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group; P=0.18). There was a significant increase in the maximum FEV_1 between 75 to 240 and 15 to 45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51 vs 36%; P<0.05). Subjective symptom score assessments decreased during the course of the study. Secondary: Not reported
Lee-Wong et al.[53] (2008) Formoterol 12 µg every 30 minutes, up to 2 treatments vs albuterol 2.5 µg via nebulization every 30 minutes, up to 2 treatments	RCT Patients 18 to 65 years of age who presented to the ED with mild to moderate asthma exacerbation (PEFR 40 to 60% of predicted)	N=34 1 treatment period	Primary: Symptom scores and PEFR Secondary: Not reported	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 two 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 two groups was not significantly different at 30 and 60 minutes (P=0.61 and 0.76, respectively). Secondary: Not reported
Pauwels et al.[54] (2003) Formoterol 4.5 µg as needed	MC, OL, RCT Patients ≥6 years of age with asthma requiring the use of	N=18,124 6 month	Primary: Asthma-related and non-asthma-related SAE, discontinuation	Primary: The number of adverse effects was not statistically significant between the two groups. There was a significantly higher number of asthma-related due to adverse

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vs albuterol 200 µg administered as needed	beta-adrenergic agonists as reliever medication		due to adverse effects, and time to first exacerbation Secondary: Rescue reliever mediation	event with formoterol compared to albuterol (1 vs 0.5%; P<0.001). 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.[55] (2001) Formoterol 12 µg and albuterol aerosol inhaler to use as needed vs albuterol 100 µg per inhalation to be used throughout the day on demand (ODS)	MC, OL, PG, RCT 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 SGRQ	Primary: There was a higher mean increase in the morning PEF in the formoterol group than in the ODS group (25.7 and 4.5 L/min (P<0.0001). Secondary: At visits three and five 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.[56] (2003) Formoterol 12 µg BID vs formoterol 24 µg BID	DB, DD, MC, PC, PG, RCT Patients 12 to 75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: FEV_1 at the 12-hour evaluation time point Secondary: AUC of FEV_1, and percent of predicted FEV_1	Primary: 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 µg at time 0. Both groups also showed significant improvement compared to

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vs albuterol 180 µg QID vs placebo				albuterol at time 0, 2 to 6 hours, and 10 to 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 to 6 and 10 to 12 hours (P<0.013). The AUC of FEV_1 was significantly different in favor of both formoterol groups compared to placebo (P<0.001), formoterol 24 µg compared to albuterol (P<0.001) and albuterol compared to placebo (P<0.008) at all visits. Both medications were well tolerated with no significant difference between them.
Wolfe et al.[57] (2006) Formoterol 24 µg BID vs formoterol 12 µg BID, with up to 2 additional 12 µg daily doses of formoterol as needed for worsening symptoms (12 µg bid plus on demand) vs formoterol 12 µg BID vs	DB, MC, PC, RCT 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: SAE Secondary: Not reported	Primary: Nine patients had SAEs requiring hospitalization: two patients (0.4%) in the 24 µg BID group; one patient (0.2%) in the 12 µg BID plus on demand group; five patients (0.9%) in the 12 µg BID group; one patient (0.2%) in the placebo group. All events were asthma-related, except for two SAE in the 12 µg 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 µg BID group (6.3%), 12 µg BID group (5.9%) and placebo group (8.8%) and lower in the 12 µg 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). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Bouros et al.[58] (1999) Formoterol 12 µg BID and beclomethasone 500 µg daily vs beclomethasone 1,000 µg daily	MC, OL, PG, RCT, PG Patients ≥18 years of age with asthma who were symptomatic on 500 µg daily of inhaled beclomethasone	N=132 12 weeks	Primary: Mean PEF during final seven days of treatment Secondary: Overall PEF, asthma symptoms, rescue medication, and safety	Primary: There was a treatment effect of 20.36 L/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.[59] (2005) Levalbuterol 1.25 mg via nebulization (≤6 doses) vs albuterol 5 mg and ipratropium 0.25 mg via nebulization (≤3 doses) followed by	DB, PRO, RCT Patients 6 to 18 years of age with a history of asthma (any severity), ability to use a peak flow meter, and PEF <80% predicted upon presentation to the ED	N=154 1 day	Primary: ED LOS Secondary: Percent change in PEF, percent change in heart rate, number of nebulized treatments until disposition, frequency of adjunctive treatment in ED, frequency of unplanned return to	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
albuterol 5 mg via nebulization (≤3 doses)			medical facility within 72 hours of discharge	
Tinkelman et al.[60] (1990) Metaproterenol via inhalation vs pirbuterol via inhalation	DB, MC, PG Asthmatic patients	N=133 12 weeks	Primary: Onset of action, peak effect, side effects, and tolerance Secondary: Not reported	Primary: There was no clinical difference between the two treatment groups in the outcomes. Secondary: Not reported
Boulet et al.[61] (1997) Salmeterol 50 µg BID vs albuterol 200 µg QID	DB, MC, PG, RCT 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 to 6 (P<0.001) and 10 to 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 vs 6 L/min; P<0.001). The average percent increase of symptom free days in the salmeterol 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.[62] (1996) Salmeterol 100 µg BID and on-demand albuterol vs albuterol 400 µg	DB, DD, MC, PG, RCT Patients ≥18 years of age with asthma currently receiving ICS	N=190 6 weeks	Primary: PEFR Secondary: Symptom scores, use of rescue inhaler, FEV_1, and patient and physician assessment of	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 to 22 L/min) compared to the albuterol group (34 to 37 L/min; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and on demand albuterol			efficacy	Salmeterol increased FEV_1 after three and six weeks compared to baseline significantly more than albuterol (P<0.05 for both weeks). There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group (P<0.001); however, there was no significant difference in symptom-free days. There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol-treated group (P<0.04).
Martin et al.[63] (1999) Salmeterol 84 µg BID vs albuterol extended-release tablets 4 mg in the morning and 8 mg in the evening	DB, DD, MC, 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 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.[64] (1999) Salmeterol Accuhaler (SM DPI) or pressurized MDI	OL, RCT, XO Patients ≥12 years of age with mild to moderate persistent asthma who were not adequately	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 (percent 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(SM MDI) 50 µg BID for 8 weeks, then cross-over to eformoterol* for 4 weeks vs eformoterol* Turbuhaler (eFM) 12 µg BID for 8 weeks, then cross-over to salmeterol for 4 weeks	controlled on ICS		Secondary: Not reported	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 ED (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 Turbuhaler was preferred by patients given both Turbuhaler and a 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. Secondary: Not reported
Everden et al.[65] (2004) Salmeterol DPI (SM DPI) 50 µg BID vs	OL, PG, RCT Patients 6 to 17 years of age with moderate persistent asthma who were not adequately controlled on ICS	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-	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eformoterol* Turbuhaler (eFM) 12 µg BID			related quality of life Secondary: Not reported	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 eight 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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). Secondary: Not reported
Vervloet et al.[66] (1998) Salmeterol 50 µg BID vs formoterol 12 µg BID	MC, OL, PG, RCT Patients ≥18 years of age with moderate to severe asthma and currently using regular ICS	N=482 6 months	Primary: Asthma symptoms, rescue medication use, quality of life, missed days of work, emergency room visits, and inpatient hospitalization days Secondary: Not reported	Primary: There was no significant difference in asthma symptoms. The number of episode-free days per patient per six 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 six 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 six 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 six months): 0.027 (formoterol) compared with 0.095 (salmeterol; P=0.188). There was no significant difference in the number of inpatient hospitalization days (mean number of days per patient per six months): 0.58 (formoterol) compared with 0.43 (salmeterol); P=0.996). Secondary: Not reported
Condemi et al.[67] (2001)	MC, OL, PG	N=528	Primary: Mean morning	Primary: There was a significant increase in mean PEF values measured five

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Salmeterol 50 µg BID vs formoterol 12 µg BID	Patients 18 to 75 years of age with moderate to moderately severe asthma and currently on ICS	6 months	PEF measured five minutes after dosing Secondary: Mean morning and evening predose PEF, number of episode-free days, use and time of rescue medications, symptom score, overall mean morning predose PEF, and safety	minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 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.[68] (2004) Salmeterol 50 µg BID vs formoterol 12 µg BID vs placebo	DB, MC, PC, RCT, XO Patients with moderate persistent asthma	N=35 2 weeks	Primary: FEV_1 and VAS scores, PEFR, and use of rescue medications Secondary: Not reported	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 three minutes post-dose, more patients demonstrated an onset of action (≥15% increase in FEV_1) with formoterol than salmeterol (36 vs 13%; P=0.063), as well as at six 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 two weeks treatment. There was no difference between formoterol and salmeterol with regards to PEFR values or the use of rescue medication. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Nightingale et al.[69] (2002) Salmeterol 50 µg BID vs formoterol 12 µg BID vs placebo	PC, RCT, XO Patients with severe asthma whose symptoms were not being controlled by high doses of ICS (≥1,500 µg/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 Secondary: Not reported	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. Secondary: Not reported
Brambilla et al.[70] (2003) Salmeterol 50 µg BID and on-demand albuterol vs formoterol 12 µg BID and on-demand albuterol vs on-demand albuterol	MC, OL, PG, RCT Patients ≥18 years of age with moderate to severe persistent asthma suboptimally controlled on ICS 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.
Brambilla et al.[71] (1994)	DB, DD, MC, PG, RC	N=159 2 weeks	Primary: Number of awakening-free	Primary: In the salmeterol group, the mean number of awakening-free nights over the last week of treatment was significantly higher than with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Salmeterol 50 µg BID vs terbutaline 5 mg SR tablets BID	Patients 18 to 67 years of age with asthma and >15% reversibility after inhaled albuterol		nights over the last week of treatment Secondary: Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake	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.[72] (1997) Salmeterol 50 µg BID vs beclomethasone 200 µg BID vs placebo	DB, PC, PG, RCT Patients 6 to 14 years of age with stable asthma	N=241 56 weeks	Primary: Airway hyper-responsiveness Secondary: PEF, rescue inhaler use, and adverse effects	Primary: During months one to two of the study, there was significantly less airway hyperresponsiveness with beclomethasone compared to salmeterol (P=0.003) or placebo (P<0.001); however, this difference was lost two weeks after discontinuation of treatment. Secondary: In the beclomethasone group, the PEF varied significantly less when compared to the salmeterol and placebo groups (P=0.002 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 one to 12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; P=0.018) and the salmeterol-treated children (5.40 cm; P=0.004).
Lemanske et al.[73] (2010)	DB, RCT, XO	N=165	Primary: Differential	Primary: A differential response occurred in 161 of 165 patients (98%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BADGER Salmeterol 50 µg BID+fluticasone 100 µg BID (LABA step-up therapy) vs fluticasone 250µg BID (ICS step-up therapy) vs fluticasone 100 µg BID+montelukast 5 to 10 mg QD (LTRA step-up therapy)	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 µg BID	48 weeks	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) Secondary: Not reported	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). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gappa et al.[74] (2009) Salmeterol-fluticasone 50-100 µg BID (SFC) vs fluticasone 200 µg BID	DB, MC, PG, RCT Patients 6 to 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 Secondary: Not reported	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 to 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 three and six patients receiving SFC and fluticasone, respectively. Both treatments were generally well tolerated. Serious adverse events were reported in two and one patients in the SFC and fluticasone groups, respectively. Secondary: Not reported
Lazarus et al.[75] (2001) Salmeterol 42 µg BID vs triamcinolone 400 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 to 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.[76]	DB, PG, RCT	N=362	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Terbutaline 0.5 mg inhaled as needed vs formoterol 4.5 µg inhaled as needed	Patients ≥18 years of age with asthma for at least six months who were treated with a constant dose of inhaled corticosteroid for at least 4 weeks	12 weeks	Time to first severe exacerbation Secondary: Morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of relief medication, and safety data Secondary: Not reported	In the formoterol group, patients experienced a longer time to the first severe exacerbation than in the terbutaline group (P=0.013) with the relative risk ratio for having an exacerbation first in the formoterol group compared 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 pre bronchodilator 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. Secondary: Not reported
Hermansson et al.[77] (1995) Terbutaline 500 µg QID vs salmeterol 50 µg BID	MC, OL, PG, RCT Patients ≥18 years of age with mild to moderate asthma	N=243 4 weeks	Primary: Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler, FEV_1 Secondary: Not reported	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 four 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 four weeks, there were no significant differences in FEV_1 or FVC between the two groups (P=0.598 and P=0.916, respectively). Secondary: Not reported
Hancox et al.[78] (1999)	PC, RCT, XO Individuals aged 9	N=61 24 weeks	Primary: Construct a rank order of treatment	Primary: Combined treatment was ranked significantly higher than each individual treatment and placebo (P<0.0001, P<0.0001, and P<0.01), budesonide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Terbutaline 1,000 µg QID vs budesonide 400 µg BID vs terbutaline 1,000 µg QID and budesonide 400 µg BID vs placebo	to 64 years of age with mild to moderate asthma with documented hyper-responsiveness		from worst [1] to best [4], period of asthma control for each subject Secondary: PEF, nocturnal and daytime symptoms, use of rescue medication, and compliance	ranked higher than placebo (P=0.025), and there was no significant difference between budesonide and terbutaline or terbutaline and placebo. Secondary: Mean morning peak flow was higher during combined treatment than budesonide alone (P<0.02), and both the combined treatment and budesonide were higher than either placebo or terbutaline (P<0.01). Mean evening peak flow was higher with all treatments (P<0.0003) and was higher with the combined treatment than either active medication alone (P<0.0002), 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.
Chronic Obstructive Pulmonary Disease (COPD)				
Combivent Study Group[79] (1994) Albuterol 100 µg QID vs ipratropium 21 µg QID	DB, MC, PG, PRO, RCT Patients ≥40 years of age with stable COPD	N=534 12 weeks	Primary: FEV_1, AUC, symptom score, and safety Secondary: Not reported	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 in terms of adverse effects or safety.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs albuterol 100 µg and ipratropium 21 µg QID (fixed-dose combination MDI)				Secondary: Not reported
Dorinsky et al.[80] (1999) Albuterol 180 µg QID vs ipratropium bromide 36 µg QID vs albuterol-ipratropium 180-36 µg QID	DB, MC, PG, RCT, RETRO 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) Secondary: Not reported	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 to 8%. Significantly greater percentage of patients demonstrated a 12 or 15% increase in FEV_1 on three or more test days in albuterol/ipratropium group compared to the individual treatment groups (P<0.05). Secondary: Not reported
Friedman et al.[81] (1999) Albuterol 180 µg QID vs ipratropium bromide 36 µg QID vs	DB, MC, PG, RCT, RETRO 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,	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC from time 0 to four hours, total health care expenditures Secondary: Not reported	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≤0.008). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
albuterol-ipratropium 180-36 µg QID	FEV_1 ≤65% predicted value, FEV_1 ≤70% of FVC			
Tashkin et al.[82] (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)	MC, PG, SB Patients >50 years of age with COPD, history of >10 pack-years of cigarette smoking, FEV1 >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 six or 12 weeks. Patient symptom scores improved from baseline to week six 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.
Zuwallack et al.[83] (2010) Ipratropium-albuterol 20-100 µg QID, administered via Respimat® inhaler vs ipratropium-	AC, DB, DD, MC, NI, PG, RCT Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack years	N=1,480 12 weeks	Primary: FEV_1 change from test-day to baseline at day 85 for ipratropium-albuterol via Respimat® inhaler vs aerosol MDI and ipratropium-albuterol via Respimat® inhaler vs ipratropium via	Primary: On day 85, ipratropium-albuterol Respimat® inhaler was non inferior to ipratropium-albuterol aerosol MDI at zero to six hours, and was "superior" to ipratropium Respimat® inhaler with a difference of 0.047 L (P<0.001) at zero to four hours. At four to six hours, ipratropium/albuterol Respimat® inhaler was non inferior to ipratropium Respimat® inhaler. Ipratropium-albuterol Respimat® inhaler significantly improved FEV_1 compared to ipratropium Respimat® inhaler at zero to four and four to six hours on all tests days. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
albuterol 36-206 µg QID, administered via aerosol MDI (Combivent®) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a 2 week run-in phase with ipratropium aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.			Respimat® inhaler Secondary: FEV_1 at day one, 29 and 57; peak FEV_1; peak FEV_1 response; time to peak FEV_1 response; median time to onset of a therapeutic response; median duration of therapeutic response; FVC $AUC_{zero\ to\ six,\ zero\ to\ four}$ and $_{four\ to\ six}$; peak FVC response on day one, 29, 57 and 85; safety	Peak FEV_1, peak FEV_1 response and peak FVC response were comparable between ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI, and "superior" to ipratropium Respimat® inhaler (P<0.0001) on all test days. The median time to onset of therapeutic response occurred 13 days after treatment initiation with both ipratropium-albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI. The overall median time to a peak response was comparable across all treatments; 60 minutes for ipratropium-albuterol Respimat® inhaler and ipratropium-albuterol aerosol MDI on all test days, and 120 minutes on days one and 20, and 60 minutes on days 57 and 85 with ipratropium Respimat® inhaler. Medium duration of a therapeutic response was comparable between ipratropium-albuterol Respimat® inhaler (165 to 189 minutes) and ipratropium-albuterol aerosol MDI (172 to 219 minutes) overall. Median duration with ipratropium Respimat® inhaler was shorter (70 to 122 minutes). Seventy six (n=358), 74 (n=357) and 63% (n=295) of patients receiving ipratropium-albuterol Respimat® inhaler, ipratropium-albuterol aerosol MDI and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration. Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was lower with ipratropium-albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower respiratory system disorders were the most frequent event to lead to discontinuation (3.9%) and occurred with the lowest frequency with ipratropium-albuterol Respimat® inhaler (2.5 vs 4.3 vs 5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorders leading to treatment discontinuation. Serious adverse events occurred more frequently with ipratropium/albuterol aerosol MDI (6.7%) compared to ipratropium-albuterol Respimat® inhaler (3.5 and 2.9%). COPD exacerbations accounted for the majority of serious adverse events.
Baumgartner et al.[84] (2007) Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer vs salmeterol 42µg BID vs placebo	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 Questionnaire); adverse events; COPD exacerbations	Primary: Mean improvement in trough FEV_1 over 12 weeks was significantly greater with all three arformoterol doses (15 µg BID, 16.9%; 25 µg BID, 18.9%; 50 µg 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 µg BID, 12.7%; 25 µg BID, 13.9%; 50 µg QD, 18.9%; salmeterol, 9.8%) vs placebo (2.7%; P≤0.001). All doses of arformoterol were statistically different from salmeterol (P<0.024). Secondary: At week 12, TDI focal scores were significantly greater with all arformoterol doses compared with placebo (mean [95% CI]: 15 µg BID, 0.97 [0.25 to 1.69]; 25 µg BID, 1.08 [0.3 to 1.86]; 50 µg 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 µg BID and salmeterol groups. There was a similar frequency of AEs and COPD exacerbations across all groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hanrahan et al.[85] (2008) Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer vs salmeterol 42 µg BID vs placebo	DB, RCT (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 Secondary: Not reported	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 µg BID: 11.4%; 25 µg BID: 15.4%; 50 µg 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 to 24%; peak percent change: 20 to 25%) and at week 12 (trough FEV_1: 10 to 13%; FEV_1 $AUC_{(0 - 12 hrs)}$: 6 to 13%; peak percent change: 7 to 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 to 87% of arformoterol subjects had ≥10% increases in FEV_1 from pre-dose (56% salmeterol, 44% placebo); the median time to response was three to 13 minutes (142 minutes salmeterol). Secondary: Not reported
Donohue et al.[86] (2014) Arformoterol 15 µg BID vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with COPD, smoking history ≥15 pack-yearsFEV_1/FVC ≤70%, FEV_1 ≤65% predicted	N=841 1 year	Primary: Time from randomization to respiratory death or first COPD exacerbation-related hospitalization Secondary: COPD exacerbations,	Primary: Primary events were reported in 40 patients (9.5%) and 63 patients (15.0%) receiving arformoterol or placebo, respectively. Time to respiratory death or first COPD exacerbation-related hospitalization was 171.7 days and 155 days, respectively, for patients having a primary event. The point estimate for the primary event indicated an approximately 40% reduction in risk with arformoterol vs placebo (HR, 0.606; 90% repeated CI, 0.425 to 0.864). Secondary: Risks for first protocol-defined COPD exacerbation (HR, 0.801; P=0.078) and recurrent protocol-defined COPD exacerbation (HR, 0.768; P=0.043)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			mortality, adverse events	were lower with arformoterol than placebo. Patients receiving arformoterol or placebo had a similar incidence of adverse events (72.9 vs 68.2%, respectively). Twelve patients (2.9%) receiving arformoterol and 10 patients (2.4%) receiving placebo died postrandomization.
Donohue et al.[87] (2008) Arformoterol 50 µg QD vs salmeterol 42 µg BID	MC, OL, RCT Patients with COPD	N=793 12 months	Primary: Adverse events, COPD exacerbations, use of short-acting bronchodilators, and pulmonary function Secondary: Not reported	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 to 13: 15.7 and 11.7%, respectively; weeks 39 to 52: 10.0 and 9.4%, respectively). Supplemental ipratropium bromide and albuterol use decreased for both groups by 0.8 to 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. Secondary: Not reported
Tashkin et al.[88] (2009) Arformoterol 15 µg BID vs	MB, MC, PG, RCT Patients ≥45 years of age with COPD, smoking history ≥15 pack-years, breathless severity	N=234 2 weeks	Primary: Difference in mean FEV_1 AUC_{0-24} Secondary: Differences in rescue therapy use	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tiotropium 18 µg QD vs arformoterol 15 µg BID and tiotropium 18 µg QD	≥2 on Medical Council Dyspnea Score, pre bronchodilator FEV_1 >0.7, FEV_1/FVC ≤70%, FEV_1 ≤65% predicted		and occurrence of adverse events	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: 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.[89] (2001) Formoterol 24 µg inhaled via dry powder inhaler (1 dose) vs albuterol 400 µg inhaled via dry powder inhaler (1 dose) vs placebo	DB, PC, RCT, XO Patients 40 to 75 years of age with stable, reversible COPD	N=25 1 dose	Primary: AUC (0-30 min) of FEV_1 in one minute Secondary: AUC (0-1 hour) of FEV_1 in one minute, AUC (0-3 hours) of FEV_1 in one minute, maximal change in FEV_1 a percent of predicted value	Primary: There were no significant differences between formoterol (5.89) and salmeterol (6.06) in the primary endpoint, but both were statistically higher than placebo (-0.32; P<0.0001). Secondary: There were no statistical differences between the two active medication groups in secondary endpoints, and each had a similar onset (five minutes). No serious adverse effects or clinically relevant changes in vital sign were observed in any of the groups.
Cazzola et al.[90] (2002) Formoterol 12 µg, 12 µg, and 24 µg vs	RCT, SB, XO Patients 51 to 77 years of age with COPD who had an acute exacerbation (defined as	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary:	Primary: There was a significant increase in FEV_1, inspiratory capacity, and FVC in both the albuterol and formoterol groups compared to baseline after 48 µg of formoterol and 800 µg of albuterol (P<0.05). Secondary: There was no significant difference between FEV_1, inspiratory capacity,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
albuterol metered dose inhaler (MDI) 200 µg, 200 µg, and 400 µg Doses were administered on two consecutive days.	sustained worsening of the patient's condition from stable and beyond normal day-to-day variations, FEV_1 <70% of personal best that is acute in onset and necessitating a change in the medication regimen)		Spirometric data (inspiratory capacity and FVC), pulse rate, SpO_2 values	and FVC values in the formoterol group compared to the albuterol group after 48 µg of formoterol and 800 µg of albuterol. There was a significant increase in change in FEV_1 values after 24 µg of formoterol compared to 48 µg of formoterol (P=0.022). There was no significant difference in pulse rate or SpO_2 values compared to baseline after 48 µg of formoterol or 800 µg of albuterol (P>0.05). SpO_2 values decreased below 90% in two patients after the highest dose of formoterol and in 1 patient after the highest dose of albuterol. The clinical significance of was not reported.
Donohue et al.[91] (2008) Formoterol 20 µg BID via nebulizer (FFIS) vs formoterol 12 µg BID via dry powder inhaler (FA) vs placebo	AC, ES, OL Patients ≥40 years of age with COPD who were current or former smokers	N=569 12 months	Primary: Safety Secondary: Not reported	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. Secondary: Not reported
Bouros et al.[92] (2004) Formoterol 12 to 24 µg vs	MC, PC, RCT, XO Patients with stage II and III COPD who demonstrated an increase in FEV_1 of ≤12% from the	N=47 Single dose	Primary: Inspiratory capacity (IC) measured before dosing and at five, 10, 15 and 30 minutes and one,	Primary: Both formoterol and salmeterol increase inspiratory capacity in patients with COPD. Formoterol 12 µg was significantly more effective than salmeterol 50 µg 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
salmeterol 50 to 100 µg vs placebo	patient's predicted normal value after salbutamol inhalation		two, three and four hour post-dose Secondary: Not reported	Secondary: Not reported
Cote et al.[93] (2009) Formoterol 12 µg BID vs salmeterol 50 µg BID	MC, OL, PG, RCT 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 six minute walk test, rescue medication use, and safety assessments Secondary: Not reported	Primary: Change from baseline in FEV_1 at five 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). Secondary: Not reported
Berton et al.[94] (2010) Formoterol 12 µg BID plus tiotropium 18 µg QD (FOR-TIO)	DB, XO Patients with moderate to severe COPD	N=33 2 weeks	Primary: Change in inspiratory capacity, obtained on constant-speed treadmill tests to the limit of tolerance	Primary: FOR-TIO was more effective than FOR-PLA in increasing post-treatment FEV_1 and limit of tolerance (1.34 vs 1.25 L and 124 vs 68, respectively; P<0.05). FOR-TIO slowed the rate of decline in exercise inspiratory capacity compared to FOR-PLA (Δ isotime-res, -0.27 vs -0.45 L; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs formoterol 12 µg BID plus placebo (FOR-PLA)			Secondary: Not reported	End-expiratory lung volume (percent 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). Secondary: Not reported
Van Noord et al.[95] (2005) Formoterol 12 µg BID for 6 weeks vs tiotropium 18 µg QD for 6 weeks vs tiotropium 18 µg QD and formoterol 12 µg BID for 6 weeks	DB, RCT, XO Patients with COPD	N=71 18 weeks	Primary: FEV_1, FVC, rescue medication use Secondary: Not reported	Primary: Tiotropium produced a significantly greater improvement in average daytime FEV_1 (0 to 12 h) than formoterol (127 vs 86 mL). The average nighttime FEV_1 (12 to 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). Secondary: Not reported
O'Donnell et al.[96] (2011) Indacaterol 300 µg QD for 3 weeks followed by placebo for 3 weeks vs placebo for 3	DB, MC, PC, RCT, XO Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of at least 20 pack years, a post bronchodilator FEV1 ≥30% and <80% of predicted	N=90 9 weeks	Primary: Exercise endurance time after three weeks Secondary: End-exercise inspiratory capacity and Borg CR10, resting inspiratory capacity, FEV_1 and	Primary: After three weeks of treatment, exercise endurance time was significantly longer with patients treated with indacaterol compared to placebo with a least square mean difference of 111 seconds (95% CI, 27 to 195; P=0.011). In a subgroup analysis, patients with a FEV_1 <50% predicted had a significantly higher endurance time with indacaterol compared to placebo after three weeks (difference, 229 seconds; 95% CI, 31 to 426; P=0.024). For patients with FEV_1 ≥50%, the exercise endurance time was higher in the indacaterol group compared to placebo, but the difference was not statistically significant (difference, 85 seconds; 95% CI, -10 to 180;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks followed by indacaterol 300 µg QD for 3 weeks There was a 3 week washout period between treatments.	normal value and post-bronchodilator FEV1/FVC<70%		FVC 60 minutes predose and 75 minutes postdose, patient reported symptoms and use of rescue medications after three weeks	P=0.078). In another subgroup analysis, patients who were smokers had a significantly higher exercise endurance time when treated with indacaterol compared to placebo after three weeks (difference, 161 seconds; 95% CI, 22 to 229; P=0.023). In ex-smokers, the exercise endurance time was higher in the indacaterol group compared to placebo, but the difference was not statistically significant (difference, 81 seconds; 95% CI, -25 to 188; P=0.132). Secondary: End-exercise inspiratory capacity was significantly higher in the indacaterol group compared to placebo after three week with a least squares mean difference of 280 mL (P=0.002). There was no significant difference in Borg 10CR scale outcomes. The 75 minute postdose and 60 minute predose inspiratory capacities were significantly higher with indacaterol compared to placebo (P=0.004 and P≤0.001, respectively). The FEV_1 and FVC were significantly higher with the indacaterol group compared to placebo (P<0.001 for both). After three weeks there were significantly less use of rescue medication with the indacaterol group compared to placebo in number of puffs daily (P<0.001), number of puffs during the daytime (P<0.001) and number used at nighttime (P=0.003). There was also a significantly higher percentage of days that patients did not require rescue medications with indacaterol compared to placebo (P=0.001). There was a decrease in patient reported symptoms with patients treated with indacaterol (-0.49) compared to an increase with placebo (0.30). The incidence of adverse effects was 22.9% with indacaterol-treated patients and 27.4% with placebo.
Chapman et al.[97] (2011) INDORSE	DB, MC, RCT Patients in the extension had	N=415 52 weeks (26 week	Primary: Trough FEV_1 at 52 weeks and time to first COPD	Primary: Trough FEV_1 at week 52 was significantly higher for both indacaterol groups compared to placebo (170 mL; 95% CI, 110 to 230 and 180; 95% CI, 120 to 240, for the 150 and 300 µg doses, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Indacaterol 150 µg QD vs indacaterol 300 µg QD vs placebo	completed the 26-week core study for which they were required to have moderate to severe COPD with postbronchodilator FEV_1 <80% and ≥30% predicted and postbronchodilator FEV_1 /FVC <70% and were aged ≥40 years with a ≥20 pack-years smoking history	extension)	exacerbation Secondary: FEV_1 at other time points, albuterol use, rate of exacerbations, and SGRQ total score	The percent change from baseline in trough FEV_1 at week 52 was 120 mL (10%), 130 mL (10%), and -40 mL (-3%) with indacaterol 150 µg, indacaterol 300 µg and placebo, respectively. The differences between indacaterol and placebo in trough FEV_1 were maintained at a similar level from week two to the end of the study, with differences ≥160 mL with both doses compared to placebo at each time point (all P<0.001). There were not enough events in the study to evaluate the time to first exacerbation. The HR compared with placebo of 0.82 (95% CI, 0.51 to 1.34) and 0.86 (95% CI, 0.53 to 1.39) for indacaterol 150 and 300 µg, respectively, suggested a trend toward improvement associated with indacaterol treatment but this was not statistically significant. Secondary: At five minutes postdose on day one, FEV_1 increased relative to placebo by 90 mL (95% CI, 40 to 140) with indacaterol 150 µg, and by 100 mL (95% CI, 50 to 150) with indacaterol 300 µg (both P<0.001). This bronchodilation at five minutes post-dosing was maintained at all subsequent assessments, with differences compared with placebo of 150 to 290 mL with indacaterol 150 µg, and 180 to 240 mL with indacaterol 300 µg (P value not reported). At 52 weeks, the use of daily albuterol decreased from baseline by 1.2 puffs with indacaterol 150 µg, and 1.4 puffs with indacaterol 300 µg, compared with to placebo (P<0.001 for both comparisons). The proportions of days without albuterol use were 56 and 59% with 150, and 300 µg of indacaterol, respectively, (P<0.05) compared to placebo (46% of days without albuterol). The mean SGRQ total scores with both indacaterol doses were numerically higher at all assessments, and significantly higher at week 26 (150 µg; P=0.002, 300 µg; P=0.025) and week 44 (P=0.002 for both doses) compared to placebo.
Dahl et al.[98] (2010) INVOLVE	DB, PC, RCT Patients ≥40 years	N=129 1 year	Primary: Trough FEV_1 after 12 weeks	Primary: Trough FEV_1 at week 12 with both indacaterol doses was 170 mL higher than placebo (P<0.001) and 100 mL higher than formoterol (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Indacaterol 300 µg QD vs indacaterol 600 µg QD vs formoterol 12 µg BID vs placebo Fixed-dose combinations of ICS plus long-acting beta$_2$ agonist were replaced by monotherapy ICS at an equivalent dose and regimen plus salbutamol† as needed.	of age with moderate-to-severe COPD, a smoking history of at least 20 pack years, and a post bronchodilator FEV_1 ≥30% and <80% of predicted normal value and post-bronchodilator FEV_1/FVC<70% at screening		Secondary: Days of poor COPD control, SGRQ score, time to first exacerbation, spirometry based outcomes, TDI score, response rate and safety outcomes.	Over the remainder of the study (one year), improvement compared to placebo was maintained at a similar level for indacaterol, while the difference between formoterol and placebo diminished. Secondary: Secondary endpoints generally favored indacaterol and formoterol compared to placebo. Cough occurring within five min of drug administration was observed in an average of 19.1% of patients in both indacaterol groups, 0.8% of the formoterol group and 1.8% of the placebo group. Otherwise, there were no significant differences in the rate or severity of adverse events between treatment groups.
Korn et al.[99] (2011) INSIST indacaterol 150 mg QD vs	AC, MC, PG, RCT Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of at least 10 pack	N=1,123 12 weeks	Primary: AUC of FEV_1 values between five minutes and 11 hours, 45 minutes after the morning dose at week 12.	Primary: There was a significantly greater FEV_1 AUC at week 12 was for indacaterol compared to salmeterol (57 mL difference; 95% CI, 35 to 79; P<0.001). Secondary: Trough FEV_1 results favored indacaterol compared to salmeterol at week 12 (60 mL; 95% CI, 37 to 83; P<0.001) Indacaterol maintained statistical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 µg BID Permitted concomitant ICS was allowed if the dose and regimen were stable for 1 month prior to screening. The dose and regimen was maintained stable throughout the study.	years, and a post bronchodilator FEV_1 ≥30% and <80% of predicted normal value and post-bronchodilator FEV_1/FVC<70% at screening		Secondary: Trough FEV_1‡ determined after the first day and on days 28, 29, 84, and 85, standardized AUC FEV_1 at week 12 (between five minutes to four hours, five minutes to eight hours and eight hours to 11 hours, 45 minutes) individual time point FEV_1 on day 1/2 and at week 12, individual time point FVC measured at week 12, BDI/TDI, use of rescue medication and safety evaluations.	improvement over salmeterol at all visits (P<0.001) except day two in which there was no significant difference). Other FEV_1 measures favored indacaterol as well (P<0.001 for all measurements). On day 1/2, indacaterol provided higher FEV_1 than salmeterol at most time points, with statistical significance at six of the eleven assessments. Similarly at week 12, the FVC measurements for indacaterol were significantly greater than salmeterol at all time points. TDI total score for indacaterol was significantly improved compared to salmeterol at week 12 (0.63 difference; 95% CI, 0.30 to 0.97; P<0.001). The proportion of patients with a clinically important improvement from baseline (≥1 point) in TDI total score was significantly greater with indacaterol compared to salmeterol (69.4 vs 62.7%, respectively; OR, 1.41; 95% CI, 1.07 to 1.85; P<0.05). Over the 12-week study, the use of rescue salbutamol was lower with indacaterol than salmeterol (-0.18 puffs/day; 95% CI, -0.36 to 0.00; P<0.05) and had a greater percentage of days with no rescue medication use (4.4 days; 95% CI, 0.6 to 8.2; P<0.05). Overall incidences of adverse events were similar between the treatment groups.
Kornmann et al.[100] (2011) INLIGHT-2 indacaterol 150 µg QD vs salmeterol 50 µg BID	DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of ≥20 pack-years, a post-bronchodilator FEV_1 value <80% and ≥30% of the	N=1,002 26 weeks	Primary: Change from baseline in trough FEV_1 at week 12 Secondary: Trough FEV_1 at week 26, FEV_1 at five minutes after first dose, percent of patients achieving MCID in	Primary: Indacaterol increased trough FEV_1 at week 12 by 170 mL over placebo (P<0.001) and by 60 mL over salmeterol (P<0.001). Secondary: Indacaterol was associated with an increased trough FEV_1 at week 26 by 70 mL over salmeterol (P<0.001). Both active treatments improved SGRQ and TDI compared with placebo, with differences between them favoring indacaterol. The mean percentage of days of poor COPD control over 26 weeks was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	predicted normal value, and a post-bronchodilator FEV_1/FVC ratio <70% at screening		SGRQ score (≥4-point increase), % of days of poor COPD control after 26 weeks, change from baseline in as needed albuterol use, puffs/day, days with no as-needed albuterol use, change from baseline in morning PEF, change from baseline in evening PEF, nights with no awakenings, days with no daytime symptoms, days able to perform usual activities and safety evaluations.	34.1+/-1.82% with both indacaterol and salmeterol, compared with 38.1+/-1.85% with placebo; however these differences were not significant. Compared with salmeterol, indacaterol-treated patients used less as-needed salbutamol, had higher morning PEF and experienced more days when they were able to undertake usual activities. Safety profiles were similar across the treatment groups and both indacaterol and salmeterol were well tolerated.
Magnussen et al.[101] (2010) INPUT indacaterol 300 µg QAM vs indacaterol 300 µg QPM vs	DB, DD, PC RCT, XO Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of at least 20 pack years, and a post bronchodilator FEV_1 ≥30% and <80% of predicted normal value and post-bronchodilator	N=96 12 weeks	Primary: Trough FEV_1 after 14 days of treatment Secondary: FEV_1 post day 14 dose between AM indacaterol and placebo and PM indacaterol and AM indacaterol, percent of nights with no	Primary: After 14 days, the difference compared to placebo in trough FEV_1 for PM indacaterol was 200 mL (P<0.001) and for AM indacaterol was 200 mL (P<0.001). Compared with salmeterol, trough FEV_1 for PM indacaterol was 110 mL higher (P<0.001), and for AM indacaterol was 50 mL higher, however this difference was not significant (P>0.05). Secondary: For individual time point FEV_1 values on day 1, all active treatments were significantly greater to placebo at all post-exposure time points. In addition, other secondary endpoints generally favored active treatment compared to placebo and favored indacaterol compared to salmeterol. Over 14 days vs placebo, both PM and AM indacaterol improved the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 50 µg BID vs placebo Patients received 3 of the above 4 treatments QD for 14 days followed by a 14 day washout period. Allowable concurrent COPD therapies included the use of ICS, provided the regimen had been stabilized for at least 1 month prior to the screening visit	FEV_1/FVC<70% at screening		awakenings, percent of days with no daytime symptoms, percent of days able to perform usual activities and safety evaluations.	percent of nights with no awakenings (by 11.9 and 8.1 points; P<0.01); the percent of days with no daytime symptoms (by 6.7 and 5.5 points; P<0.05); and the percent of days able to perform usual activities (by 6.7 and 7.8 points; P<0.05). Improvements in these endpoints generally favored indacaterol compared to salmeterol, however not all comparisons reached statistical significance. The overall incidence of adverse events was comparable between treatments and most were mild or moderate in severity. Cough was the most frequently reported drug-related adverse event and was reported more frequently with indacaterol (7.7 and 5.9% with PM and AM indacaterol, compared with 1.5% with salmeterol and 0% with placebo).
Balint et al.[102] (2010) INSURE indacaterol 150 µg QD vs indacaterol 300 µg QD vs	DB, MC, RCT, XO Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of at least 20 pack years, and a post bronchodilator FEV_1 ≥30% and <80% of predicted normal value and post-bronchodilator FEV_1/FVC<70% at	N=89 5 single dose treatment periods followed by 4 to 7 day washouts	Primary: FEV_1 at five minutes post-dose comparing both doses of indacaterol to placebo Secondary: FEV_1 at five minutes postdose comparing indacaterol to other	Primary: At five minutes postdose, both indacaterol doses were statistically greater than placebo (P<0.001), with treatment–placebo differences in FEV_1 of 100 mL (95% CI, 70 to 130) and 120 mL (95% CI, 90 to 150) for indacaterol 150 µg and 300 µg, respectively. Secondary: FEV_1 at five minutes postdose with both indacaterol doses (150 µg and 300 µg) was non-significantly higher than for salbutamol (10 and 30 mL, respectively) and significantly higher than salmeterol-fluticasone (50 mL; P=0.003, 70 mL; P<0.001, respectively). Both indacaterol doses showed significantly higher FEV_1 than placebo (P<0.001) at all postdose time points. In addition, both Indacaterol doses

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salbutamol 200 µg QD† vs salmeterol 50 µg/ fluticasone 500 µg QD vs placebo	screening		active treatments, FEV_1 at other scheduled time points, proportion of patients with at least 10, 12, and 15% increase in FEV_1 from baseline to each scheduled time point, proportion of patients with at least a 12% and 200 mL increase in FEV_1 from baseline to each scheduled time point and safety evaluations.	demonstrated either comparable or greater increases in FEV_1 than salmeterol-fluticasone and salbutamol at all postdose time points. The proportion of patients with at least a 10, 12 or 15% increase in FEV_1 from baseline at five minutes postdose was higher in both indacaterol groups compared with salmeterol-fluticasone (P<0.01), and similar to salbutamol (P value not significant). However, comparisons at later points did not consistently favor both doses of indacaterol compared to placebo. The proportions of patients with at least a 12% and 200 mL increase in FEV_1 from baseline at five minutes postdose in the indacaterol 150 µg, indacaterol 300 µg, and salbutamol 200 µg groups were higher than that in the salmeterol/fluticasone 50/500 µg and placebo groups (P<0.05 for all comparisons). All reported adverse events were mild or moderate in severity, and none were suspected of being related to study drug.
Donohue et al.[103] (2010) INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs	DB, PC, RCT Patients ≥40 years of age with moderate-to-severe COPD and a smoking history of at least 20 pack years	N=391 26 weeks	Primary: Trough FEV_1‡ at 12 weeks compared to placebo Secondary: Non-inferiority and superiority of indacaterol compared to tiotropium in trough FEV_1 at 12 weeks, TDI score, use of rescue medication and safety evaluations	Primary: At week 12, the differences in trough FEV_1 vs placebo were 180 mL for both indacaterol doses and 140 mL for tiotropium (P<0.001 for all measurements). Secondary: The 40 mL difference between indacaterol and tiotropium was considered significantly greater in tests for non-inferiority and superiority (P<0.001 and P≤0.01, respectively). The TDI total score increased relative to placebo (P<0.001) at all assessments with indacaterol and at weeks four, 12, and 16 with tiotropium, with significant differences between indacaterol 300 mg and tiotropium (P<0.05) at weeks four, eight, and 12. Over the 26-week study, the use of as-needed albuterol was lower during active treatments than placebo (P<0.001), and lower with indacaterol than with tiotropium (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				SGRQ total scores were improved relative to placebo with both doses of indacaterol at all assessments (P<0.01) but not with tiotropium (P value not reported). Analysis of time to first COPD exacerbation showed a reduced risk relative to placebo for indacaterol 150 µg (HR, 0.69; 95% CI, 0.51 to 0.94] P=0.019). Nonsignificant reductions were observed for indacaterol 300 mg (HR, 0.74; 95% CI, 0.55 to 1.01; P=0.05) and tiotropium (0.76; 95% CI, 0.56 to 1.03; P=0.08) compared to placebo. Cough within 5 minutes post-dose was observed in an average of 16.6 and 21.3% of patients per visit in the indacaterol 150 and 300 mg groups, in 0.8% of the tiotropium group, and in 2.4% of the placebo group. This cough typically had a median duration of 6 seconds and was not associated with bronchospasm or with increased study discontinuation rates. Otherwise, adverse events were similar across treatment groups
Vogelmeir et al.[104] (2010) INTIME Indacaterol 150 mg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo	DB, CO, RCT Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of at least 10 pack years, and a post bronchodilator FEV_1 ≥30% and <80% of predicted normal value and post-bronchodilator FEV_1/FVC<70% at screening	N=153 12 weeks	Primary: Trough FEV_1‡ after 14 days of treatment Secondary: Non-inferiority comparison of trough FEV_1 after 14 days of treatment, trough FEV_1* after first dose, FEV_1 measurements at individual time points after first dose and safety evaluations	Primary: Treatment with both doses (150 and 300 µg) of indacaterol resulted in significant improvement in trough FEV_1 14 days after treatment compared with placebo (170 and 150 mL difference, respectively; P<0.001 for both comparisons). Both doses were also associated with significantly greater improvement compared to tiotropium (40 and 30 mL difference; respectively; P<0.05 for both comparisons). Secondary: Both doses of indacaterol had greater improvements in trough FEV_1 after the first dose compared to placebo (P<0.001). The mean trough FEV_1 values after treatment with both indacaterol 150 and 300 µg were higher than with tiotropium, by 10 and 30 mL, respectively although this was not considered statistically different (P>0.05 for both comparisons). At all time points on both the first day and after 14 days of treatment, all active treatments resulted in statistically significantly greater FEV_1 results compared with placebo (P<0.05 for all comparisons). Indacaterol was associated with greater FEV_1 measurements than for tiotropium at all time points for the 300 µg dose and at a majority of time points for the 150 µg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received 3 of the above 4 treatments QD for 14 days followed by a 14 day washout period. Allowable concurrent COPD therapies included the use of ICS, provided the regimen had been stabilized for at least 1 month prior to the screening visit.				dose. Both indacaterol (150 and 300 µg) doses had a fast onset of action on Day 1, providing treatment differences in FEV_1 at five minutes post-dose compared to placebo (120 and 130 mL, respectively; P<0.001 for both comparisons) and tiotropium (50 mL; P<0.004). The overall incidence of adverse events was similar across all treatments, and were predominantly mild or moderate in severity including cough COPD worsening, and nasopharyngitis.
Buhl et al.[105] (2011) INTENSITY Indacaterol 150 µg QD vs tiotropium 18 µg QD	DB, DD, MC, RCT Patients ≥40 years of age with moderate-to-severe COPD, a smoking history of at least 10 pack years, and a post bronchodilator FEV_1 ≥30% and <80% of predicted normal value and post-bronchodilator FEV_1/FVC<70% at screening	N=1,593 12 weeks	Primary: Change in Trough FEV_1 from baseline Secondary: TDI score, SGRQ score, change from baseline in use of rescue medication and safety evaluations.	Primary: There was a greater FEV_1 at 12 weeks with indacaterol compared to tiotropium (1.44 vs 1.43 L, respectively; P<0.001). Secondary: Secondary endpoints including changes in TDI score (2.01 vs 1.43, respectively; P<0.001), SGRQ score (37.1 vs 39.2; P<0.001) and use of rescue medications (-1.40 vs -0.85, respectively; P<0.001) generally favored indacaterol compared to tiotropium. Overall incidences of adverse events were similar between the treatment groups.
Decramer et al.[106] (2013) INVIGORATE	MC, PG, RCT Patients aged ≥40 years with severe	N=3444 52 weeks	Primary: To investigate whether indacaterol was	Primary: The estimated least squares mean trough FEV_1 difference between the groups was −0.011 L (least squares mean with indacaterol 1.134 L [SE 0.008] vs tiotropium 1.145 L [0.008]; one-sided 97.5% CI lower limit

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Indacaterol 150 µg QD vs tiotropium 18 µg QD	COPD and a history of at least one moderate to severe exacerbation in the previous 12 months		non-inferior to tiotropium for trough FEV_1 at week 12 Secondary: Rate of exacerbations at week 52	−0.026 L; P<0.0001). The lower limit of the 97.5% CI was above the prespecified non-inferiority margin of −0.055 L, suggesting that indacaterol was non-inferior to tiotropium. Secondary: Indacaterol did not show non-inferiority in terms of exacerbation rates: 0.79 (indacaterol) versus 0.61 (tiotropium); ratio 1.29 (one-sided 97.5% CI upper limit 1.44). In the safety set, we recorded no between-group difference in the number of patients who had adverse events.
Ikeda et al.[107] (1995) Ipratropium 40 µg plus albuterol 200 µg vs ipratropium 80 µg plus albuterol 400 µg vs ipratropium 40 µg vs ipratropium 80 µg vs placebo	DB, PC, RCT, XO Adult male patients with stable COPD	N=26 1 month	Primary: FEV_1, FVC, and adverse reactions Secondary: Not reported	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 µg 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 adverse effects. Secondary: Not reported
Datta et al.[108] (2003) Levalbuterol 1.25	DB, RCT, XO Patients with COPD (mean age of 69	N=30 4 days	Primary: FEV_1 Secondary:	Primary: Mean change in FEV_1 from baseline increased significantly in all three active treatment groups compared to placebo at 0.5 hours and persisted at one hour (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	years), FEV_1 45 to 75% of predicted value, FEV_1/FVC ratio of <0.70, stable disease (absence of clinical exacerbation and no change in COPD medications in previous month)		FVC, pulse rate, oxygen saturation (measured by pulse oximetry), hand tremor (rating scale 0 to 7, rated by same blinded investigator for all patients) Secondary: Not reported	At two 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 three 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 three active treatment groups compared to placebo at 0.5 hours ($P \leq 0.03$) and this persisted at one hour ($P \leq 0.03$). The percentage of patients in exhibiting a positive bronchodilator response at two and three hours was only significant compared to placebo in the combined albuterol and ipratropium group (P=0.03 at two hours and P=0.003 at three hours). Between-group comparisons were not reported. Secondary: All three active treatment groups led to significant improvements in FVC compared to placebo at 0.5 hours (P<0.05) and remained significant at one hour only for the combined albuterol and ipratropium group (P<0.05). No significant differences between active treatment groups and placebo were noted from two 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 one hour and beyond. 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.[109] (2006) Levalbuterol	DB, MC, PG, RCT Adults with COPD	N=209 6 weeks	Primary: Average FEV_1 $AUC_{(0\text{-}8\ hrs)}$ over weeks 0, two and	Primary: All active treatments demonstrated improvements in the percent change in FEV_1 $AUC_{(0\text{-}8\ hrs)}$ during the DB period and at each visit compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(LEV) 0.63 mg or 1.25 mg TID via nebulizer vs albuterol (RAC) 2.5 mg TID via nebulizer vs placebo			six, rescue medication use, safety parameters, COPD exacerbations, and global evaluations Secondary: Not reported	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). Secondary: Not reported
Koch et al.[110] (2014) Olodaterol 5 µg QD vs olodaterol 10 µg QD vs formoterol 12 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤80% predicted and FEV_1/FVC ≤70%	N=1,838 48 weeks	Primary: FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1 response after 24 weeks of treatment, TDI all at 24 weeks Secondary: SGRQ, additional FEV_1 and FVC parameters	Primary: After 24 weeks, statistically significant improvements in FEV_1 AUC_{0-3} response (P<0.0001) and trough FEV_1 response (P<0.01) were demonstrated with olodaterol 5 µg, olodaterol 10 µg, and formoterol vs placebo. After 24 weeks' treatment, the analysis revealed no statistically significant differences in TDI focal score for any of the active therapies vs placebo. Secondary: Secondary lung-function responses over 48 weeks of treatment were in line with the primary end points. Combined analysis of SGRQ after 24 weeks illustrated an improvement in total score for olodaterol 5 µg (−2.8 difference from placebo; P<0.005) and olodaterol 10 µg (−3.4 difference from placebo; P<0.0005), but not formoterol (−1.2; P= not significant) compared to placebo.
Ferguson et al.[111]	DB, MC, PC, PG,	N=1,266	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2014) Olodaterol 5 µg QD vs olodaterol 10 µg QD vs placebo	RCT Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤80% predicted and FEV_1/FVC ≤70%	48 weeks	FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1 response after 24 weeks of treatment, rescue medication use, all at 12 weeks Secondary: Additional FEV_1 and FVC parameters, safety	After 12 weeks, statistically significant improvements compared with placebo were demonstrated in the end point of FEV_1 AUC_{0-3} response for both olodaterol 5 µg and 10 µg once daily (P<0.0001). Statistically significant improvements vs placebo in trough FEV_1 response was also observed. Weekly mean daytime and nighttime rescue medication use with olodaterol was significantly reduced vs placebo over the 48 weeks of treatment; at week 48, daytime rescue medication use was reduced for olodaterol 5 µg by 0.46 actuations/day (P<0.0001) and for 10 µg by 0.57 actuations/day (P<0.0001); night-time rescue medication use was reduced for olodaterol 5 µg by 0.50 actuations/day (P<0.0001) and for 10 µg by 0.78 actuations/day (P<0.0001). Secondary: Over the 48-week treatment period, the FEV_1 AUC_{0-3} response with olodaterol 5 µg and 10 µg once daily was significantly improved compared with placebo at all time points (P<0.0001). In both studies, the incidences of adverse events, serious adverse events, deaths, and adverse events leading to discontinuations with olodaterol 5 µg and 10 µg once daily were similar to those for placebo.
Hanania et al.[112] (2003) Salmeterol 50 µg BID vs fluticasone 250 µg BID vs fluticasone-salmeterol	DB, MC, PC, RCT Patients 40 to 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 two-hour post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, chronic respiratory disease questionnaire, chronic bronchitis symptom questionnaire,	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 seen from baseline in salmeterol and fluticasone monotherapy groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
250-50 µg BID vs placebo			exacerbations, and supplemental albuterol use	(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 chronic respiratory disease questionnaire scores in the fluticasone-salmeterol group compared to placebo (P=0.006). There was a significant increase in chronic respiratory disease questionnaire scores in fluticasone monotherapy group compared to placebo (P=0.002). There was a significant increase in chronic bronchitis symptom questionnaire scores in fluticasone-salmeterol group and fluticasone monotherapy group compared to placebo (P≤0.017).
Matera et al.[113] (1996) Salmeterol 50 µg BID and ipratropium 40 µg QID vs ipratropium 40 µg QID vs	SB, RCT, XO Male patients ≥40 years of age with COPD and FEV_1 between 16 and 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) Secondary: Not reported	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 µg BID vs placebo				Secondary: Not reported
Van Noord et al.[114] (2000) Salmeterol 50 µg BID and ipratropium 40 µg QID vs salmeterol 50 µg BID vs placebo	DB, MC, PG, RCT Patients 40 to 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 two 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 two 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.[115] (2010) Salmeterol 50 µg BID vs tiotropium 18 µg QD vs tiotropium 18 µg QD and salmeterol 50 µg QD vs tiotropium 18 µg QD and salmeterol	DB, RCT, 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 Secondary: Not reported	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 to 12h: 12mL; P=0.38) as tiotropium plus salmeterol QD, but significantly more bronchodilation during the night-time (12 to 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 µg BID				
Donohue et al.[116] (2002) Salmeterol 50 µg BID vs tiotropium 18 µg QD vs placebo	DB, MC, PC, RCT 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, 21.4, 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.[117] (2003) Salmeterol 50 µg BID vs tiotropium 18 µg QD	DB, DD, PC, RCT 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),	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			spirometry, adverse events	(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 six 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 AUC from 0 to three 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.[118] (2005) Salmeterol 50 µg	DB, PG, RCT Patients with COPD	N=653 12 weeks	Primary: Lung function Secondary:	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
BID vs tiotropium 10 µg QD			Not reported	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 to six hours and six to 12 hours 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). Secondary: Not reported
Rabe et al.[119] (2008) Salmeterol 50µg BID and fluticasone 500 µg BID vs tiotropium 18 µg QD and formoterol 12 µg 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 pre bronchodilator FEV_1 ≤65% predicted at visit 2	N=605 6 weeks	Primary: FEV_1 AUC 0 to 12 h and peak FEV_1 Secondary: Peak FVC and FVC AUC 0 to 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).
Ohar et al.[120] (2014) Salmeterol 50µg BID (SAL)	AC, DB, PG, RCT Patients with COPD aged ≥40 years with recent (≤14 days)	N=639 26 weeks	Primary: Estimated annualized rate of exacerbations requiring	Primary: There was no statistically significant treatment difference in rates of recurrent severe exacerbations (treatment ratio 0.92 [95% CI, 0.58 to 1.45]) and moderate/severe exacerbations (0.82 [0.64 to 1.06]) between FP/SAL and SAL in the intent-to-treat population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone propionate-salmeterol 250-50 µg BID (FP/SAL)	history of exacerbation requiring: hospitalization for ≤10 days, emergency room observation of duration ≥24 hours during which oral steroids ±antibiotics treatment was administered, or physician's office or emergency room visit of <24 hours duration with steroids ±antibiotics treatment plus 6-month history of exacerbation-related hospitalization		hospitalization Secondary: Rate of exacerbations requiring treatment with oral steroids, antibiotics, and/or hospitalization	Secondary: Pre-dose morning FEV_1 change from baseline was greater (0.10 L [0.04 to 0.16]) with FP/SAL than SAL. No treatment difference was seen for other endpoints including patient-reported health outcomes and biomarker levels for the full cohort.
Donohue et al.[121] (2013) Umeclidinium-vilanterol (UMEC/VI) 62.5-25 µg vs UMEC 62.5 µg monotherapy vs VI 25 µg	DB, PC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <70% and FEV_1/FVC ≤70% predicted, score ≥2 on the modified Medical Research Council Dyspnoea Scale	N=1532 24 weeks	Primary: Pre-dose trough FEV_1 on treatment Day 169 Secondary: Additional FEV_1 and FVC parameters at specified time points, quality of life	Primary: Statistically significant improvements in trough FEV_1 at Day 169 were observed for UMEC/VI 62.5-25 µg, UMEC 62.5 µg, and VI 25 µg compared with placebo (all P<0.001). Increases with UMEC/VI were significantly greater than monotherapies (P≤0.004). Secondary: Greater increases from baseline in 0–6 hour weighted mean FEV_1 were observed with UMEC/VI 62.5-25 µg, UMEC 62.5 µg, and VI 25 µg compared with placebo (0.242 L, 0.150 L and 0.122 L; all P<0.001). Similarly, greater increases were observed for UMEC/VI 62.5-25 µg compared with UMEC 62.5 µg (0.092 L; P<0.001) and VI 25 µg (0.120 L; P<0.001). All active treatment groups increased TDI focal score at Day 168 and throughout the study compared with placebo. Over the 24-week study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
monotherapy vs placebo				period, all active treatments resulted in less rescue salbutamol use compared with placebo. On-treatment COPD exacerbations were reported in 13% of patients in the placebo group and 7 to 9% in active treatment groups. The incidence of treatment-emergent adverse events was similar across treatment groups.
Donohue et al.[122] (2014) Umeclidinium 125 µg vs umeclidinium-vilanterol 125-25 µg vs placebo	DB, MC, PC, PG, RCT Current or former smokers of ≥40 years of age, with a smoking history of ≥10 pack-years and an established clinical history of COPD	N=562 52 weeks	Primary: Safety, trough FEV_1, trough FVC Secondary: Not reported	Primary: The incidence of on-treatment adverse events (AEs), serious AEs (SAEs) and drug-related AEs was similar across active treatment groups and placebo. Greater mean changes from baseline in trough FEV_1 and FVC were demonstrated for umeclidinium-vilanterol and umeclidinium compared with placebo at all visits. At 12 months, umeclidinium-vilanterol and umeclidinium had improved trough FEV_1 in comparison with placebo by 0.231 L (95% CI, 0.153 to 0.310) and 0.178 L (95% CI, 0.098 to 0.258), respectively, and trough FVC by 0.252 L (95% CI, 0.135 to 0.368) and 0.194 L (95% CI, 0.076 to 0.312), respectively. There were fewer patients reporting COPD exacerbations with umeclidinium-vilanterol and umeclidinium (13 and 15%) compared with placebo (24%). Secondary: Not reported
Exercise-Induced Bronchospasm				
Berkowitz et al.[123] (1986) Albuterol MDI 0.18 mg 15 minutes prior to exercise vs metaproterenol MDI 1.3 mg 15	RCT, SB, XO Patients 12 to 17 years of age with asthma and exercised-induced bronchospasm (FEV_1 >20% of pre-exercise level) following a treadmill exercise test	N=18 4 days	Primary: Mean percent increase in FEV_1 five minutes after medication, mean workload for exercise challenges, mean decrease in FEV_1 from baseline, and the number of patients in whom	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 medications, the mean workloads were not found to be significantly different. Following the initial post-medication exercise test, a majority of patients in the placebo group experienced exercise-induced spasm compared to both active ingredient groups. This was a significant difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
minutes prior to exercise vs placebo			broncho-constriction was blocked over time Secondary: Not reported	(P<0.0005) between the placebo and active ingredient groups, but not between the active ingredient groups themselves. Following the two-hour exercise challenge, the remainder of the placebo group experienced exercise-induced spasm and a greater number in the remaining metaproterenol group compared to the albuterol group experienced exercise-induced spasm. There was a greater decrease in mean maximum decrease in FEV_1 in the placebo group compared to the active ingredient groups, which was found to be statistically significant (P<0.001). Albuterol prevented exercise-induced bronchospasm in more patients and for a significantly longer time than metaproterenol did (P<0.05).
Shapiro et al.[124] (2002) Albuterol 180 µg prior to exercise challenge vs formoterol 12 µg prior to exercise challenge vs formoterol 24 µg prior to exercise challenge vs placebo	DD, XO Patients 12 to 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 to 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. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pearlman et al.[125] (2006) Formoterol 12 to 24 µg vs albuterol 180 µg vs placebo	DB, RCT, XO Patients 4 to 11 years of age with exercise-induced bronchoconstriction	N=23 4 treatment periods	Primary: Maximum percent decrease in FEV_1 from the pre-exercise value after exercise challenge tests (six minute treadmill) conducted 15 minutes and four, eight, and 12 hours after give the dose Secondary: Not reported	Primary: The maximum percentage decrease in FEV_1 after the four hour exercise test was significantly less for formoterol, 12 and 24 µg, 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 µg, differed from placebo at eight 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 µg, respectively, compared with 35% with albuterol and 27% with placebo. Secondary: Not reported
Richter et al.[126] (2002) Formoterol 12 µg prior to exercise challenge vs salmeterol 50 µg prior to exercise challenge vs terbutaline 500 µg prior to exercise challenge vs	DB, DD, PC, RCT, XO Patients 25 to 48 years of age with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled methacholine	N=25 13 visits	Primary: Percent increase in FEV_1 between the inhalation of the study medication and the initiation of exercise (five, 30, or 60 minutes), AUC of percent change in FEV_1 from end of exercise to 90 minutes Secondary: Not reported	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 five-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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Edelman et al.[127] (2000) Salmeterol 100 µg BID vs montelukast 10 mg QD	DB, PG, RCT Patients 15 to 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 eight weeks of treatment Secondary: Change from baseline for maximal percent decrease in FEV_1 at days one to three and week four, the time required after maximal decrease to return to within 5% of pre-challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of exercise test, and the number and percent of patients whose decrease in FEV_1 from pre-exercise levels was <10%, 10 to 20%,	Primary: By day three, similar reductions in maximal percentage decrease in FEV_1 were seen with both therapies. Sustained improvement occurred in the montelukast group at weeks four and eight; however, at these time points, the bronchoprotective effect of salmeterol decreased significantly. At week eight, 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 eight, 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 one to three, and was maintained at week four in the montelukast group but not in the salmeterol group (P=0.015). A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre-challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (P<0.001, P<0.001, P=0.010, P<0.001). 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
			20 to 40% and >40%	
Storms et al.[128] (2004) Salmeterol 50 µg QD vs montelukast 10 mg QD vs placebo	DB, MC, PG, RCT Patients 15 to 45 years of age with asthma, documentation of exercise-induced bronchospasm, and uncontrolled on ICS 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	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 one and four; P=0.010). In addition, there was no difference between the montelukast and placebo groups. Montelukast significantly decreased exercise-induced bronchospasm at week four compared to placebo (P=0.008), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups. Compared to both placebo and salmeterol, after four weeks of treatment montelukast permitted significantly faster rescue with beta-adrenergic agonists (P=0.036, P=0.005). After four weeks, there was a significant difference in the clinic exercise-assessment questionnaire 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, ICS=inhaled corticosteroid, LOS=length of stay, LTRA=leukotriene receptor antagonist, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, SAE=serious asthma exacerbations, SGRQ=St. George's respiratory questionnaire, TDI=transition dyspnea index score

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.[129] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[129] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[129] 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.[130] Adherence to inhaled therapy is often poor, with rates of 40 to 72% being reported.[131] 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 chronic obstructive pulmonary disease (COPD).[132] 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.[133] 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.[129]

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 19. Relative Cost of the Respiratory Beta-Adrenergic Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Albuterol	aerosol inhaler, dry powder inhaler, extended-release tablet, inhalation solution, syrup, tablet	ProAir HFA®, Proventil HFA®, ProAir Respiclick®, Ventolin HFA®, Vospire ER®*	$$$$	$$
Arformoterol	inhalation solution	Brovana®	$$$$$	N/A
Formoterol	inhalation solution, dry powder inhaler	Foradil®, Perforomist®	$$$$$	N/A
Indacaterol	dry powder inhalation	Arcapta®	$$$$$	N/A
Levalbuterol	aerosol inhaler, inhalation solution	Xopenex®*, Xopenex HFA®	$$$$$	$$$
Metaproterenol	syrup, tablet	N/A	N/A	$
Olodaterol	solution inhaler	Striverdi Respimat®	$$$$	N/A
Salmeterol	dry powder inhaler	Serevent Diskus®	$$$$$	N/A
Terbutaline	injection, tablet	N/A	N/A	$$$$$
Combination Products				
Ipratropium and albuterol	inhalation solution, solution inhaler	Combivent Respimat®	$$$$$	$$$
Umeclidinium and vilanterol	dry powder inhaler	Anoro Ellipta®	$$$$$	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.[1-19] 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, 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, indacaterol, olodaterol, salmeterol, and umeclidinium-vilanterol. 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.[25-28] 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.[25] For the long-term maintenance treatment of asthma, the inhaled corticosteroids are recommended as first-line therapy.[25-28] When additional therapy is needed, guidelines recommend the addition of an inhaled LABA in children five to 12 years of age and adults. The use of an oral LABA is not recommended due to potential adverse events.[25] 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.[1-2,8-11,15,16,19] 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.[1-2, 8-11,15,16,19] 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.[1-2, 8-11,15,16,19] The available data also suggest that the inhaled LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.[1-2,8-11,15,16,19 ,134] 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.[1-2,8-11,15,16,19 ,134]

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. 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. 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. There does not appear to be a difference in adverse events with the LABAs.[135-137]

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[20-24] 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.[20-24] 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). Treatment guidelines do not indicate a preference as there is insufficient evidence to favor one long-acting bronchodilator over another.[20-24] Regular treatment with long-acting bronchodilators are more effective than treatment with short-acting bronchodilators.[20-24] Studies directly comparing the LABAs have demonstrated similar improvements in some, but not all, respiratory endpoints. Some studies suggest that formoterol may have a faster onset of action than salmeterol. Tiotropium may provide a greater clinical benefit than LABAs with regards to spirometric endpoints, dyspnea, exacerbations, quality of life, and health care resource utilization. Combining an inhaled antimuscarinic with a β_2-agonist has also been shown to be more effective than monotherapy.

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. 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.[129] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[129] 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.[129]

Therefore, all brand short-acting respiratory beta-adrenergic agonists within the class reviewed are comparable to each other and to the generic 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 and are comparable to each other and to the generic products (if available). 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Leukotriene Modifiers
AHFS Class 481024
November 4, 2015

I. Overview

The leukotriene modifiers are approved for the long-term management of patients with asthma.[1-6] 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.[3] 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. Blocking the action of cysteinyl leukotrienes has been shown to reduce or prevent airway obstruction and decrease the activation of inflammatory cells.[7]

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.[3,4] Zileuton is the only 5-lipoxygenase inhibitor currently available. It inhibits the actions of the 5-lipoxygenase enzyme, thereby preventing the formation of leukotrienes.[5,6] All of the leukotriene modifiers elicit a similar biologic response, but differ in their dosing requirements, adverse events, drug interactions, and pharmacokinetic parameters.[1-6]

The leukotriene modifiers that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Montelukast and zafirlukast are available in a generic formulation. This class was last reviewed in August 2013.

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®*	montelukast
Zafirlukast	tablet	Accolate®*	zafirlukast
Zileuton	sustained-release tablet, tablet	Zyflo®, Zyflo CR®	none

*Generic available in at least one dosage form and/or strength.
‡Generic product requires prior authorization.
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.

Table 2. Treatment Guidelines Using the Leukotriene Modifiers

Clinical Guideline	Recommendation(s)
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2015)**[8]	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. • Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. • Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. • Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects. • For population-level decisions about asthma management, the 'preferred option'

Clinical Guideline	Recommendation(s)

	at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness, and safety from randomized controlled trials, meta-analyses, and observational studies, and net cost.
	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	Treatment overview
	• At present, step 1 treatment is with as-needed short-acting beta$_2$ agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a lack of studies of inhaled corticosteroids (ICS) in such populations.
	• Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	• For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities.
	  o For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta$_2$ agonist (LABA).
	  o For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller plus as-needed SABA.
	  o For children six to 11 years, increasing the ICS dose is preferred over combination ICS/LABA.
	• Consider step down once good asthma control has been achieved and maintained for about three months to find the patient's lowest treatment that controls both symptoms and exacerbations.
	  o Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.
	  o Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
	• For all patients with asthma:
	  o Provide inhaler skills training.
	  o Encourage adherence with controller medication, even when symptoms are infrequent.
	  o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations and need for healthcare utilization.
	• For patients with one or more risk factors for exacerbations:
	  o Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients.
	  o Identify and address modifiable risk factors (e.g., smoking, low lung function).
	  o Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction.
	
	Categories of asthma medications
	• *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
	• *Reliever (rescue medications)*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a

Clinical Guideline	Recommendation(s)

measure of the success of asthma treatment.

- *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.

Stepwise approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years old

- Initial controller treatment: For best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.
- Once treatment has been commenced (see table below), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - Incorrect inhaler technique.
  - Poor adherence.
  - Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - Incorrect diagnosis.

Stepwise approach to control symptoms and minimize future risk					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller choice		Low dose ICS	Low dose ICS/LABA*	Med/high ICS/LABA	Refer for add-on treatment (e.g., anti-IgE)
Other controller options	Consider low dose ICS	Leukotriene receptor antagonist (LTRA) or low dose theophylline*	Med/high dose ICS or low dose ICS+LTRA (or + theoph*)	High dose ICS + LTRA (or + theoph*)	Add low dose oral corticoste-roids
Reliever	As-needed SABA		As-needed SABA or low dose ICS/formoterol**		

*For children six to 11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium-dose ICS.
**Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy.

Management of worsening asthma and exacerbations

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

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

Clinical Guideline	Recommendation(s)
	The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <4 years and mouthpiece for most four to five year olds. • Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

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

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

Management of worsening asthma and exacerbations in children five and younger

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

The National Heart, Lung, and Blood	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of

Clinical Guideline	Recommendation(s)
Institute/ National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[9]	episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include SABAs, anticholinergics and systemic corticosteroids. <u>Long-term control medications</u> • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an

Clinical Guideline	Recommendation(s)

alternative treatment for mild persistent asthma.

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

Quick-relief medications

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

Assessment, treatment and monitoring

- A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
- Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
- The stepwise approach for managing asthma is outlined below:

Inter-mittent Asthma	Persistent Asthma: Daily Medication				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred SABA as needed	Preferred Low-dose ICS Alternative Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline	Preferred Low-dose ICS+LABA or medium-dose ICS Alternative Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred Medium-dose ICS+LABA Alternative Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies	Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies

Management of exacerbations

- Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

Special populations

- For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs.
- The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm.
- Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
- Albuterol is the preferred SABA in pregnant women because of an excellent

Clinical Guideline	Recommendation(s)
	safety profile. • ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.

British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2014)**[10]	Diagnosis in children
	• The diagnosis is based on recognizing a characteristic pattern of episodic respiratory symptoms and signs in the absence of an alternative explanation for them.
	• Presence of the following factors increases the probability that a child with respiratory symptoms will have asthma: age at presentation, sex, severity and frequency of previous wheezing episodes, coexistence of atopic disease, family history of atopy, and abnormal lung function.
	• Focus the initial assessment in children suspected of having asthma on presence of key features in the history and examination and careful consideration of alternative diagnoses.
	
	Diagnosis in adults
	• The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them.
	• Confirmation of airflow obstruction is vital for diagnosis of asthma. Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction.
	
	Pharmacological management
	• The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication.
	• Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.
	• Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors.
	• Step 1: Mild intermittent asthma:
	  o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma.
	• Step 2: Introduction of regular preventer therapy:
	  o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma.
	  o ICS should be considered for patients with any of the following asthma-related features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 who have had an asthma attack requiring oral corticosteroids in the last two years.
	  o ICS should initially be administered twice daily, except ciclesonide which is administered once daily.
	  o Once a day ICS at the same total daily dose can be considered if good control is established.
	  o In patients >12 years of age, health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers.
	• Step 3: Initial add-on therapy:
	  o In adults and children five to 12 years of age, the first choice for add-on therapy to ICS is an inhaled LABA, which should be considered before

Clinical Guideline	Recommendation(s)

going above a dose of 400 µg beclomethasone or equivalent per day and certainly before going >800 µg beclomethasone or equivalent.
  - In adults and children five to 12 years of age, if asthma control remains suboptimal after the addition of an inhaled LABA then the dose of ICS should be increased to 800 µg/day in adults or 400 µg/day in children five to 12 years of age if not already receiving these doses.
  - In children <5 years of age, the first choice for add-on therapy to ICS is leukotriene receptor antagonists.
  - LABAs should only be started in patients who are already on ICS, and the ICS should be continued.
  - Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence.
- Step 4: Poor control on moderate dose of ICS plus add-on therapy (addition of fourth drug):
  - If control remains inadequate on ICS 800 µg beclomethasone daily in adults and 400 µg beclomethasone daily in children plus LABA, consider the following interventions:
    - Increasing ICS to 2,000 (adults) or 800 (children five to 12 years of age) µg BDP daily.
    - Leukotriene receptor antagonists.
    - Theophyllines.
    - Slow-release β_2-agonist tablets, though caution needs to be used in patients already on LABAs.
- Step 5: Continuous or frequent use of oral steroids:
  - In adults, the recommended method of eliminating or reducing the dose of steroid tablets is ICS, at doses of up to 2,000 µg/day, if required.
  - In children 5 to 12 years of age, consider very carefully before going above 800 µg/day of ICS.
  - For all patients, there is a role for a trial of treatment with LABAs, leukotriene receptor antagonists, and theophylline for about six weeks. They should be stopped if no improvement in steroid dose, symptoms, or lung function is detected.
  - The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children.
- A summary of the stepwise management of asthma is outlined below:

Children <5 Years Old	Children 5 to 12 Years Old	Adults and Children >12 Years Old
Step 1: Mild Intermittent Asthma		
• Inhaled SABA as required	• Inhaled SABA as required	• Inhaled SABA as required
Step 2: Regular Preventer Therapy		
• Add ICS 200 to 400 µg/day*† or leukotriene antagonist if ICS cannot be used • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 400 µg/day* (other preventer drug if ICS cannot be used) • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 800 µg/day* • Start at dose of ICS appropriate to severity of disease
Step 3: Initial Add-on Therapy		
• In those taking ICS 200 to 400 µg/day, consider addition of leukotriene receptor antagonist • In those taking a leukotriene receptor antagonist alone, reconsider addition of an ICS 200 to 400 µg/day • In children under 2 years, consider proceeding to step 4	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 400 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 400 µg/ day.* If	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 800 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 800 µg/ day.* If

Clinical Guideline	Recommendation(s)
	control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline **Step 4: Persistent Poor Control** • Refer to a respiratory pediatrician • Increase ICS up to 800 µg/day* Consider trials of: • Increase ICS up to 2,000 µg/day* • Add a fourth drug (leukotriene receptor antagonist, sustained-release 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 ICS at 800 µg/day* • Refer to respiratory pediatrician • Use daily corticosteroid tablet in lowest dose providing adequate control • Maintain high-dose ICS at 2,000 µg/day* • Consider other treatments to minimize use of corticosteroid tablets • Refer patient for specialist care *Beclomethasone or equivalent. †Higher nominal doses may be required if drug delivery is difficult. Specific management issues • For adults and children 5 to 12 years of age, if exercise is a specific problem in patients taking ICS who are otherwise well controlled, consider adding one of the following: leukotriene receptor antagonists, LABAs, chromones, oral β_2-agonists, or theophyllines. • For adults and children 5 to 12 years of age, immediately prior to exercise inhaled SABAs are the drug of choice.
International Primary Care Respiratory Group: **Management of Asthma (2006)**[11]	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: o Short-acting β_2-agonists as needed for symptoms and for exercise-induced bronchospasm. o In patients >60 years of age, consider an anticholinergics agent. • Step 2: mild persistent asthma: o Low-dose ICS. • Step 3: moderate persistent asthma: o Combination therapy with an ISC and a LABA. o An alternative treatment option includes using the combination of an ICS and a leukotriene modifier or sustained-release theophylline. • Step 4: severe persistent asthma: o Combination therapy with a high-dose ICS and LABA. o An alternative treatment option includes high-dose ICS and sustained-release theophylline. o An alternative treatment option includes high-dose ICS and a leukotriene modifier. o Oral corticosteroids can be used over the short-term. General treatment consideration

Clinical Guideline	Recommendation(s)
	• 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 ICS. • For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of ICS and a LABA. Alternatives are combinations of ICS with sustained-release theophylline or with leukotriene receptor antagonists.
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)**[12]	<u>Pharmacologic treatment of allergic rhinitis</u> • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma, and Immunology/	<u>Pharmacologic therapy</u> • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most

Clinical Guideline	Recommendation(s)
American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[13]	prominent symptoms, severity, and patient age. <u>Oral antihistamines</u> • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. <u>Intranasal antihistamines</u> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone.

Clinical Guideline	Recommendation(s)
	• Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • 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 in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <u>Oral corticosteroids</u> • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <u>Intranasal cromolyn</u> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines.

Clinical Guideline	Recommendation(s)
	Intranasal anticholinergics • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. Oral antileukotriene agents • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. Omalizumab • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)**[14]	Strep pharyngitis • Penicillin is the drug of choice for treatment of culture positive cases of group A beta streptococcal pharyngitis. In children and patients unable to swallow pills, amoxicillin is an acceptable alternative due to the poor palatability of the penicillin suspension. • In penicillin-allergic patients, options include cephalosporins (for some types of allergies), macrolides, and clindamycin. Consider reevaluating patient for carrier status. Although macrolides may be an acceptable alternative, clinicians should check their local resistance patterns. • Alternative medication recommendations include macrolides, cephalexin, clindamycin, amoxicillin-clavulanate, and rocephin. Non-infectious rhinitis • With the exception of systemic steroids, intranasal corticosteroids are the most effective single agents for controlling allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. Systemic corticosteroid use should be reserved for refractory or severe cases only and given as a short burst. Injectable corticosteroids are generally not recommended as they are invasive and tend to have a longer course of action than typical courses of corticosteroids. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They are less than intranasal corticosteroids, but can be used either on a daily basis or on an as-needed basis. • Second-generation antihistamines are less sedating than first-generation antihistamines, and cause less central nervous system impairment. Adverse events commonly associated with first-generation antihistamines include somnolence, decreased alertness, and anticholinergic effects. These agents may cause central nervous system impairment and impair driving performance. • Oral decongestants can reduce nasal congestion but can result in side effects such

Clinical Guideline	Recommendation(s)
	as irritability, insomnia, and palpitations. Topical decongestants are used for short-term or intermittent/episodic therapy. Routine daily use is not recommended because of the risk for the development of rhinitis medicamentosa. Both oral and topical decongestants should be used with caution in older adults, children under the age of six, and patients of any age who have a history of the following: arrhythmia, angina, cerebrovascular disease, high blood pressure, bladder neck obstruction, glaucoma, or hyperthyroidism. • Cromolyn is less effective than intranasal corticosteroids, and is most effective when used regularly prior to the onset of allergic symptoms. Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in patients with allergic and non-allergic rhinitis. They have no effect on congestion, sneezing, or itching. • Montelukast is a leukotriene receptor antagonist that is as effective as loratadine and less effective than nasal steroids. It is generally well tolerated and may be considered as a third-line option to add after the failure of a nasal corticosteroid and an oral antihistamine. • Ophthalmic preparations contain antihistamines, decongestants, corticosteroids, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers. Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. <u>Non-allergic rhinitis</u> • Treatment of symptomatic nasal obstruction due to non-allergic rhinitis includes the use of azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants, nasal strips, and topical antihistamines. • Intranasal corticosteroids can be used to treat chronic nasal congestion secondary to non-allergic rhinitis. Intranasal corticosteroids have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic symptoms. • Intranasal cromolyn may improve sneezing and congestion scores, and it can be safely used in children two years of age and older. • Some patients find oral decongestants helpful at relieving symptomatic nasal obstruction secondary to non-allergic rhinitis. Oral decongestants have a relatively rapid onset of action and therefore are particularly useful for sporadic symptoms. Patients using oral decongestants should be monitored for hypertension. • Nasal strips may be effective for patients with nocturnal symptoms. They are more effective for patients with narrow noses or with anterior septal deviations. Daytime use of nasal strips is not usually practical. • Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis. • Conservative treatment of symptomatic non-purulent chronic posterior nasal drainage includes increased water intake, decreased caffeine and alcohol intake, nasal saline irrigation, use of petroleum jelly or antibiotic ointment for nasal crusting, and the addition of humidity in bedroom, if significantly less than 50%. In addition, it should be determined if the patient is using any medications that may cause oral or nasal dryness. • Medical treatment of symptomatic non-purulent chronic posterior nasal drainage includes intranasal corticosteroids. • Treatment of symptomatic bilateral chronic anterior rhinorrhea due to non-allergic rhinitis includes avoidance of triggers, intranasal corticosteroids, intranasal ipratropium bromide, and nasal saline. <u>Bacterial sinusitis</u>

Clinical Guideline	Recommendation(s)
	• Intranasal corticosteroids may be rational but is an unproved adjunctive therapy for acute sinusitis. This therapy may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology. • Antibiotics should be reserved for those patients who failed decongestant therapy, those we present with symptoms and signs of a more severe illness, and those who have complications of acute sinusitis.
International Primary Care Respiratory Group: **Management of Allergic Rhinitis (2006)**[15]	<u>Mild intermittent allergic rhinitis</u> • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. o Decongestant. AND/OR o Intranasal saline. • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe intermittent allergic rhinitis treatment options). <u>Moderate/severe intermittent allergic rhinitis</u> • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal saline. o Intranasal glucocorticosteroid. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis and compliance, query infections and other causes, then consider trial of different treatment option or specialist referral. <u>Mild persistent allergic rhinitis</u> • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal glucocorticosteroid. o Intranasal saline. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe persistent allergic rhinitis treatment options). <u>Moderate/severe persistent allergic rhinitis</u> • Recommended therapy: o Intranasal glucocorticosteroid. o Decongestant.

Clinical Guideline	Recommendation(s)
	o Oral H_1-blocker. o Intranasal saline. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then choose one or more of the following options: o Increase nasal steroid dose, consider trial of different treatment option, or consider referral to specialist. o If sneeze/itch: add H_1-blocker. o If rhinorrhea: add ipratropium. o If blockage: add decongestant or short course of oral steroids. <u>General treatment considerations</u> • First generation H_1-antihistamines cause sedation and central nervous system impairment. These side effects may adversely affect cognition, learning and driving. These side effects may be potentiated by alcohol and other sedatives. Adverse events may not always be perceived by patients. • Second generation H_1-antihistamines are associated with less sedation and impairment than first generation antihistamines. • Intranasal and intraocular H_1-antihistamines are as effective as oral antihistamines at the site of their administration. • Intranasal glucocorticosteroids are the most effective class of medications available for the treatment of allergic and nonallergic rhinitis. Oral glucocorticosteroids are rarely needed to control severe symptoms of allergic rhinitis. • Mast cell stabilizers reduce symptoms of allergic rhinitis, but are generally less effective than other treatments and require frequent administration. Ocular mast cell stabilizers are effective and have a role in the treatment of allergic conjunctivitis. • Anticholinergic agents can reduce rhinorrhea, but have little effect on other symptoms of allergic rhinitis. • Antileukotriene agents are effective for the treatment of allergic rhinitis and asthma. They have been shown to be as effective as oral antihistamines, but have a greater effect on nasal obstruction. They may have an additive effect with antihistamines.

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[3-6]

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 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			
Acute prevention of exercise-induced bronchoconstriction in patients 6 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[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Montelukast	60 to 78	>99	Liver, extensive (% not reported)	Feces (86)	2.7 to 5.0
Zafirlukast	Not reported	99	Liver, extensive (% not reported)	Renal (10) Feces (90)	13.3
Zileuton	Not reported	93	Liver (% not reported)	Renal (95)	2.5*/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
Leukotriene modifiers (zileuton)	1	Pimozide	Zileuton may inhibit the metabolism of pimozide (possibly via cytochrome P450 3A4 enzyme), potentially causing fatal cardiac arrhythmias.
Leukotriene modifiers (zileuton)	2	Theophyllines	Zileuton may decrease the metabolism of theophylline compounds, and thereby increase theophylline levels.

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. 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.[5,6] 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.[4] 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.[3-6]

Table 6. Adverse Drug Events (%) Reported with the Leukotriene Modifiers[3-6]

Adverse Events	Montelukast	Zafirlukast	Zileuton
Cardiovascular			
Chest pain	-	-	>1

Adverse Events	Montelukast	Zafirlukast	Zileuton
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			
Alanine transaminase elevations	2.1	1.5	1.9
Aspartate aminotransferase elevations	1.6	-	-
Cholestatic hepatitis	✔	-	-

Adverse Events	Montelukast	Zafirlukast	Zileuton
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[3-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Montelukast	Allergic rhinitis: Tablet: 10 mg daily at any time of day Asthma: Tablet: 10 mg daily in evening Exercise-induced bronchospasm: Tablet: 10 mg at least 2 hours before exercise; maximum, an additional dose should not be taken within 24 hours of a previous dose	Allergic rhinitis in patients 6 to 23 months of age: Granules: 4 mg once daily Allergic rhinitis in patients 2 to 5 years of age: Chewable tablet, granules: 4 mg once daily Allergic rhinitis in patients 6 to 14 years of age: Chewable tablet: 5 mg once daily Allergic rhinitis in patients ≥15 years of age: Tablet: 10 mg once daily Asthma in patients 12 to 23 months: Granules: 4 mg once daily in the evening Asthma in patients 2 to 5 years of age: Chewable tablet, granules: 4 mg once daily in the evening Asthma in patients 6 to 14 years of age: Chewable tablet: 5 mg once daily in the evening Asthma in patients ≥15 years of age: Tablet: 10 mg once daily in the evening Exercise-induced bronchospasm in patients 6 to 14 years of age: Chewable tablet: 5 mg at least 2 hour before exercise; maximum, an additional dose should not be taken within 24 hours of a previous dose Exercise-induced bronchospasm in patients ≥15 years of age: Tablet: 10 mg tablet as least 2	Chewable tablet: 4 mg 5 mg Granules: 4 mg Tablet: 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		hours before exercise; maximum, an additional dose should not be taken within 24 hours of a previous dose	
Zafirlukast	Asthma: Tablet: 20 mg two times daily	Asthma in patients 5 to 11 years of age: Tablet: 10 mg two times daily	Tablet: 10 mg 20 mg
Zileuton	Asthma: Sustained-release tablet: 1,200 mg twice daily Tablet: 600 mg four times daily	Asthma in patients ≥12 years of age: Sustained-release tablet: 1,200 mg twice daily Tablet: 600 mg four times daily	Sustained-release tablet: 600 mg Tablet: 600 mg

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				
Cingi et al.[16] (2010) Montelukast 10 mg QD vs placebo	DB, PC, RCT Patients with persistent allergic rhinitis	N=78 1 month	Primary: RQLQ Secondary: Not reported	Primary: A significant improvement in the RQLQ was observed in the montelukast group compared to the placebo group (P<0.001). A significant improvement in the RQLQ compared to baseline was observed in both the montelukast group and the placebo group (P<0.001). The difference in change from baseline to the end of the first month was significant in favor of the montelukast group for sleep, practical problems, nasal problems and activities that had been limited by nose or eye symptoms and for overall score (P<0.001). Secondary: Not reported
Li et al.[17] (2009) Montelukast 5 or 10 mg QD vs placebo All patients were also administered fexofenadine 60 or 120 mg QD.	DB, PC, RCT Patients 6 to 18 years of age with persistent allergic rhinitis for at least two years not previously treated with LTRAs	N=44 26 weeks (2 week run-in, 16 week treatment phase and 8 weeks of follow-up)	Primary: Composite nasal symptom score Secondary: Adenoidal size, nasal and blood cytokine levels	Primary: Significant between-group differences were observed in daytime sneezing score, nighttime sneezing score and daytime composite score at week four of treatment (P≤0.013) (level of significance adjusted to P<0.016). Eventually patients in the placebo group would experience symptom relief but this took a longer time when compared to the montelukast group. No significant differences were observed between groups during the follow-up period. Secondary: No significant differences were observed between groups.
Esteitie et al.[18] (2010)	DB, PC, RCT Patients 18 to 55	N=54 4 weeks	Primary: RQLQ, nasal symptoms	Primary: No significant differences were observed between groups in RQLQ or nasal symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Montelukast 10 mg QD vs placebo All patients were also administered fluticasone nasal spray 200 µg daily.	years of age with symptoms of perennial allergic rhinitis		Secondary: Not reported	Secondary: Not reported
Pullerits et al.[19] (2002) Montelukast 10 mg QD vs fluticasone nasal spray 200 µg QD vs montelukast 10 mg QD and loratadine 10 mg QD vs placebo	DB, DD, PC, PG, RCT Patients 15 to 50 years with a diagnosis of allergic rhinitis during the grass pollen season for at least the two previous years	N=62 50 days	Primary: Daytime and nighttime nasal symptom score as reported by patient (analysis divided into three periods: weeks one to two [period 1], weeks three to five [period 2] and week six to end of study [period 3]) Secondary: EG^{2+} eosinophilic inflammation	Primary: No statistically significant differences were noted in any of the primary endpoints between montelukast monotherapy and placebo. A significant decrease in the development of nasal allergy symptoms in both the fluticasone and the montelukast and loratadine groups compared to the placebo group during all three treatment periods for daytime symptoms was reported for period 1 (fluticasone; P=0.003, montelukast and loratadine; P=0.04), period 2 (fluticasone; P=0.001, montelukast and loratadine; P=0.04) and period 3 (fluticasone; P<0.001, montelukast and loratadine; P<0.001). No statistically significant differences in the fluticasone group and the montelukast and loratadine group in daytime nasal symptom scores were reported. A statistically significant decrease in development of nasal symptoms in the fluticasone group was reported compared to the montelukast monotherapy group (P=0.046). A statistically significant decrease in the development of nasal symptoms in the montelukast monotherapy group was observed compared to the placebo group (P=0.03). Significantly lower symptom scores in the fluticasone group was observed compared to the placebo group in all periods (P=0.02, P=0.002, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.001 respectively). Significantly lower symptom scores in the fluticasone group were reported compared to the montelukast plus loratadine group during peak season in period 2 (P=0.04). Significantly lower symptom scores in the fluticasone group compared to the montelukast monotherapy group during periods 2 and 3 were observed (P=0.01). Significantly lower symptom scores in the montelukast plus loratadine group compared to the placebo group during period 3 were reported (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).
Baena-Cagnani et al.[20] (2003) Montelukast 10 mg QD vs desloratadine 5 mg QD vs placebo	DB, PC, RCT Patients 15 to 75 years of age diagnosed with seasonal allergic rhinitis for at least two years, clinical symptoms of seasonal allergic rhinitis at screening, $FEV_1 \geq 70\%$ predicted value, asthma controlled with as-needed bronchodilators	N=924 4 weeks	Primary: Total asthma symptom score, individual asthma symptom scores, FEV_1, PEF values and use of β_2-agonists Secondary: Not reported	Primary: A statistically significant reduction in the total asthma symptom scores in both the montelukast and desloratadine groups compared to the placebo group was observed ($P \leq 0.05$). No statistically significant differences between montelukast and desloratadine groups were noted at any time during the study for total asthma symptom scores. A statistically significant reduction in individual symptom scores in both the montelukast and desloratadine groups compared to the placebo group was reported (P<0.05). No statistically significant differences between montelukast and desloratadine groups were noted at any time during the study for individual asthma symptom scores.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	only, increase in FEV_1 of at least 12% following bronchodilator use, greater than weekly but no daily asthma symptoms and/or bronchodilator use and positive skin test for seasonal allergen			A statistically significant increase in FEV_1 in both the montelukast and desloratadine groups was reported compared to the placebo group (P<0.01 and P<0.05 respectively). There was no statistically significant difference between the montelukast and desloratadine groups at any time. Secondary: Not reported
Saengpanich et al.[21] (2003) Montelukast 10 mg QD and loratadine 10 mg QD vs fluticasone nasal spray 200 µg QD	DB, DD, PG, RCT Patients 21 to 54 years of age with history of sensitivity to ragweed pollen for last two years, and had a positive skin test to ragweed pollen	N=63 2 weeks	Primary: RQLQ, daily nasal symptom scores, number of eosinophils, and level of ECP found in nasal lavage fluids Secondary: Not reported	Primary: A statistically significant improvement in questionnaire answers in both the fluticasone and montelukast and loratadine groups was observed (P<0.01). A statistically significant reduction in nasal symptoms on the questionnaire in the fluticasone group compared to montelukast and loratadine group was observed (P=0.05). There was no statistically significant decrease in daily nasal symptom scores in either the fluticasone or montelukast and loratadine groups, though both did decrease from baseline. There was a statistically significant decrease in number of eosinophils in nasal lavage in the fluticasone group compared to baseline (P=0.05), though no significant decrease in the montelukast and loratadine group compared to baseline. When compared between groups, this was not statistically significant. A statistically significant decrease in ECP from baseline (P=0.009) and between groups (P=0.04) favoring fluticasone was observed. Secondary: Not reported
Meltzer et al.[22] (2000)	DB, MC, PC, PG, RCT	N=460	Primary: Daytime nasal	Primary: A statistically 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 to 75 years of age diagnosed with spring seasonal allergic rhinitis for two years, positive skin test for at least one of eight allergens including oak, grass, elm, olive, walnut and sycamore	2 weeks	symptoms score Secondary: Eye symptoms, nighttime symptoms, individual daytime symptoms, global evaluations and rhinoconjunctivitis quality of life scores	in the montelukast and loratadine group compared to placebo and to either agent alone was observed (P<0.001). A statistically significant improvement in all secondary endpoints in the montelukast plus loratadine group was reported compared to the placebo group (P<0.05). There was no statistically significant difference in the primary endpoint between montelukast or loratadine monotherapy groups compared to the placebo group. Secondary: A statistically significant improvement in rhinoconjunctivitis quality of life was reported in the montelukast 10 mg and loratadine group compared to the placebo group (P<0.05). A statistically significant improvement in daytime eye symptom score, nighttime symptom score, and composite daytime and nighttime symptom score was reported in the montelukast 10 mg monotherapy group compared to the placebo group (P<0.05).
Mucha et al.[23] (2006) Montelukast 10 mg QD vs pseudoephedrine 240 mg QD	DB, PG, RCT Patients 18 to 45 years of age with a diagnosis of allergic rhinitis during the ragweed season and a positive skin test to ragweed antigen extract	N=58 2 weeks	Primary: Nasal symptoms, NPIF, quality of life scores and tolerability profiles Secondary: Not reported	Primary: A statistically significant improvement in all primary outcome measures in both groups compared to baseline values (P<0.05) was observed. A statistically significant improvement was reported in nasal congestion in the pseudoephedrine group compared to the montelukast group (P=0.01). Secondary: Not reported
Sardana et al.[24] (2010) Montelukast 10 mg QD for 2 weeks	DB, PC, RCT, XO Patients 18 to 55 years of age with perennial allergic rhinitis	N=56 8 weeks	Primary: Changes in RSS Secondary: Not reported	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 28 µg 2 sprays BID for 2 weeks vs azelastine 137 µg 2 sprays BID for 2 weeks				improvement in rhinorrhea compared to montelukast (P=0.0044) and budesonide (P=0.0033). Secondary: Not reported
Jiang et al.[25] (2006) Zafirlukast 20 mg 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				
Virchow et al.[26] (2010) MONICA Montelukast 10 mg QD Therapy added to	OL, OS, PRO Patients ≥18 years of age with mild or moderate persistent asthma insufficiently controlled with ICS	N=1,681 6 months	Primary: ACT scores Secondary: Mini-AQLQ	Primary: Mean ACT score significantly improved compared to baseline (P<0.0001). The percentage of patients with uncontrolled or poorly controlled asthma at baseline decreased. The percentage of patients with well-controlled or completely controlled asthma increased.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
current therapy with ICS or ICS and LABA.	or ICS and LABA			Secondary: Significant improvement in the Mini-AQLQ was observed from baseline (P<0.0001). Significant improvements in FEV_1 were observed from baseline (P<0.0001).
Virchow et al.[27] (2010) MONICA Montelukast 10 mg QD Therapy added to current therapy with ICS or ICS and LABA.	Subgroup analysis Patients ≥18 years of age with mild or moderate persistent asthma insufficiently controlled with ICS or ICS and LABA	N=1,681 12 months (additional 6 month follow-up after original MONICA)	Primary: ACT scores Secondary: Mini-AQLQ	Primary: Mean ACT score significantly improved at 12 months compared to baseline (P<0.0001). Secondary: Mean total Mini-AQLQ score increased significantly at 12 months compared to baseline (P<0.0001). Asthma control improved in all patient subgroups (gender, age [<30, 30 to 50, >50 years old], duration of asthma [<5 years, ≥5 years], presence of allergic rhinitis, prior therapy with ICS or LABA and ICS). Comorbid allergic rhinitis, younger age, shorter duration of asthma and prior treatment with only ICS were indicators of better control with add-on montelukast.
Knorr et al.[28] (1998) Montelukast 5 mg QD vs placebo	DB, MC, PC, RCT Patients 6 to 14 years of age with asthma, FEV_1 between 50%-85% of predicted value, ≥15% reversibility after inhaled β-agonist therapy, daytime asthma symptoms, and reported daily β-agonist use	N=336 8 weeks	Primary: Improvements in morning FEV_1 Secondary: Daytime asthma symptoms, morning and evening PEF, daily use of inhaled short-acting β-agonists, nocturnal awakenings, pediatric asthma-specific quality of	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 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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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	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.[29] (1998) Montelukast 10 mg QD vs placebo Patients could also use ICS.	DB, MC, PC, RCT Patients 15 to 79 years with chronic stable asthma, FEV_1 50 to 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-specific quality of life, global assessment, blood eosinophil count, percentage of days with asthma exacerbation, use	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of oral corticosteroids, discontinuation because of worsening of asthma, and asthma control days	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.
Visitsunthorn et al.[30] (2011) Montelukast 5 mg QD vs placebo The use of ICS during study was permitted.	DB, PC, RCT, XO Patients 6 to 13 years of age with mild to moderate, persistent asthma	N=29 14 weeks (6 weeks with each treatment phase separated by a 2-week wash-out period)	Primary: Changes in FEV_1, FEV_1/FVC, PEFR and results of methacholine challenge test Secondary: Not reported	Primary: At six weeks, patients treated with montelukast had an increase in FEV_1 by 6.68 L/min, compared to a decrease by 2.74 L/min in patients treated with placebo (P=0.042). Similarly, FEV_1/FVC increased by 2.18% with montelukast and decreased by 3.18% with placebo (P=0.018). Improvement in PEFR was 25.05 L/min with montelukast and 0.12 L/min with placebo (P=0.63). The mean provocative concentration of methacholine that causes a 20% decline in FEV_1 was 6.8±1.74 and 5.7±1.41 mg/mL after six weeks of treatment with montelukast and placebo, respectively (P=0.79). Secondary: Not reported
Bozek et al.[31] (2012) Montelukast 10 mg QD vs placebo All patients were receiving budesonide 1,400 to 2,800 µg/day and salmeterol 50	OL, PRO, RCT Patients >60 years of age with severe asthma	N=512 24 months	Primary: Percentage of days without asthma symptoms Secondary: Compliance with therapy, average percentage of days with β_2-agonist use, change from baseline in pre-bronchodilator percent predicted FEV_1 and asthma	Primary: Patients in the montelukast group had a higher percentage of days without asthma symptoms compared to those in the placebo group (78.4 vs 66.2%; P<0.05). Secondary: Mean compliance was 80.1% in the montelukast group and 73.1% in the placebo group. Percentage of days with β_2-agonist use was 39.5 and 44.1% in the montelukast and placebo groups, respectively (P<0.05). FEV_1 percent predicted was similar in the montelukast and placebo groups (72.1 vs 71.5%; P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg BID.			exacerbations per year	One or more asthma exacerbations per year were observed in 30.2 and 38.4% of patients in the montelukast and placebo groups, respectively (P value not reported). The median number of asthma exacerbations per patient was 1.2 and 1.4, respectively (P value not reported).
Riccioni et al.[32] (2004) Montelukast 10 mg QD vs zafirlukast 40 mg/day	PG, RCT Adults with mild persistent asthma	N=40 12 weeks	Primary: FEV_1, FVC, PEF, use of rescue medications, AQLQ Secondary: Not reported	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 value not reported). There was no difference in quality of life between montelukast and zafirlukast: overall AQLQ (5.5 vs 5.7, P value not reported); symptoms (5.7 vs 5.6; P value not reported); environment (5.3 vs 5.6; P value not reported), emotions (5.3 vs 5.8; P value not reported), and activities (5.9 compared with 5.7; P value not reported). Secondary: Not reported
Kubavat et al.[33] (2013) Montelukast 10 mg QD vs zileuton ER 1200 mg BID	AC, MC, OL, RCT Patients 18 to 65 years of age with an established diagnosis of mild to moderate chronic persistent bronchial asthma	N=227 12 weeks	Primary: Improvement in PEFR Secondary: Improvement in respiratory symptom scores	Primary: Improvement in PEFR was significantly better in the zileuton group at the time points of 8 and 12 weeks as compared with the montelukast group (P<0.01 for both). The mean percent increase in PEFR at the end of 12 weeks' treatment was 27.0 ± 23.6% (22.6 to 31.5%) with zileuton and 18.4 ± 22.0% (14.1 to 22.7%) with montelukast (P=0.006). Secondary: Improvements occurred in all the assessed symptoms during the initial four weeks of therapy and further decreased in severity during the rest of the treatment period. A decline in rescue medication usage was noted in both the groups at the end of study as compared with the baseline; with no significant difference between the treatment groups. At the end of the study (week 12), as per the investigators' assessment of global efficacy of the study medication in the zileuton group, 95/109

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				[87.2% (80.9 to 93.4%)] patients were rated to have an ''excellent'' or a ''good'' efficacy as compared with 64 of 101 [63.4% (54.0 to 72.8%)] patients in the montelukast group (P<0.001).
Szefler et al.[34] (2005) Montelukast 5 to 10 mg QD vs fluticasone 100 µg BID	MC, RCT, XO Patients 6 to17 years of age with mild to moderate persistent asthma, asthma symptoms or rescue bronchodilator use on average ≥3 days/week for past 4 weeks, reversibility defined as ≥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 or greater	N=144 16 weeks	Primary: Percent change in pre-bronchodilator FEV_1 from baseline Secondary: Not reported	Primary: A significantly greater percent change in FEV_1 from baseline in the fluticasone group was reported compared to the montelukast group (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 associated with allergic inflammation responded better to the ICS than to montelukast. Secondary: Not reported
Zeiger et al.[35] (2006) Montelukast 5 to 10 mg QD vs fluticasone 100 µg BID	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	N=144 16 weeks	Primary: Asthma control days Secondary: Pulmonary function as measured by eNO, FEV_1 and FEV_1/FVC,	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	20% improvement in FEV_1 after methacholine dose of ≤12.5 mg/ml, and FEV_1 ≥70% of predicted value		resistance of the respiratory system at 5 Hz and area of reactance	favoring fluticasone (P=0.028). Significant improvements were noted in both groups in FEV_1, FEV_1/FVC, resistance of the respiratory system at 5 Hz, and area of reactance compared to baseline.
Garcia et al.[36] (2005) Montelukast 5 mg QD vs fluticasone 100 µg BID	DB, NI, RCT Patients 6 to 14 years of age with mild persistent asthma, FEV_1 ≥80% predicted value with β_2-agonist withheld ≥6 hours at least twice in run in period and FEV_1 or PEF ≥70% predicted value at visit 3	N=994 12 months	Primary: Percent of asthma rescue-free days measured as change from baseline Secondary: Percentage change from baseline in predicted FEV_1, percentage of patients requiring anti-asthma medications other than β_2-agonists, percentage of patients with an asthma attack, average percentage of days with β_2-agonist use, change in blood eosinophil count, patient reports of asthma control, patient lost school days and parental lost work days	Primary: Montelukast was shown to be equivalent to fluticasone in percentage of asthma rescue-free days. 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 the fluticasone group and montelukast group was observed. There was a significant difference in percentage of β_2-agonist use from baseline in both groups (P≤0.001). A significant decrease in percentage of β_2-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_2-agonists compared to the montelukast group (P value not reported). Significantly fewer patients in the fluticasone group experienced an asthma attack compared to the montelukast group (P value not reported). 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 (P value not reported). A significant improvement in overall quality of life from baseline in both fluticasone and montelukast groups was reported (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A significant decrease in blood eosinophil count was reported in both fluticasone and montelukast groups from baseline (P≤0.001). 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 (P value not reported). The proportion of patients with at least one lost school day during the four 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 at least one lost work day was reported in parents of 2.9% of montelukast patients and 2.0% of fluticasone patients during the four 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.
Busse et al.[37] (2001) Montelukast 10 mg QD vs fluticasone 44 µg BID	DB, DD, PG, RCT Patients 15 to 83 years of age diagnosed with asthma for at least six months, pre-bronchodilator FEV_1 between 50 to 80% of predicted value, increase in FEV_1 of 15% or greater after β_2-agonist use, regular or as-needed use of inhaled or oral β_2-agonist in the three months prior to screening	N=533 24 weeks	Primary: Mean percentage change from baseline in morning pre-medication FEV_1 Secondary: Mean change in FVC, $FEF_{25\%-75\%}$, morning and evening PEF, percentage of symptom-free days, asthma symptom scores, nighttime awakenings, daily rescue albuterol use, percentage of	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 the 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			rescue-free days, physicians' global assessment of effectiveness, asthma quality of life questionnaire and patient-rated satisfaction with treatment	The physician's global assessment significantly favored fluticasone compared to montelukast (P<0.001). Significantly greater improvements was 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.[38] (2007) LOCSS Montelukast 5 to 10 mg QD vs fluticasone 100 µg BID vs fluticasone-salmeterol 100-50 µg QD (fixed-dose combination product)	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 µg 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 and 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 pre bronchodilator FEV_1 values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone and 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 ACQ, was better in the fluticasone group and in the fluticasone and 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 and 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 and 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%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sorkness et al.[39] (2007) Montelukast 5 mg QD vs fluticasone 100 µg BID vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product)	DB, RCT Patients ages 6 to 14 years of age with mild-moderate persistent asthma, with an FEV_1 of ≥80% predicted normal at screening and ≥70% predicted normal at randomization	N=285 48 weeks	Primary: The percent of asthma control days Secondary: Percent of episode-free days, time to first exacerbation requiring prednisone, time to treatment failure, number of treatment failures, ACQ score, FEV_1%, FEV_1/FVC, morning and evening PEF and growth	Primary: The percent of asthma control days were 64.2% for the fluticasone monotherapy group, 59.6% for the fluticasone and salmeterol group and 52.5% for the montelukast group. The difference between the fluticasone monotherapy and the montelukast group was significant (P=0.004). The difference between the fluticasone and salmeterol group and montelukast was not significant (P=0.08). Secondary: The percent of episode-free days were 26.4% in the fluticasone group, 26.8% in the fluticasone and salmeterol group, and 17.8% in the montelukast group. The differences were significant between the fluticasone group and the montelukast group (P=0.040) and between the fluticasone and salmeterol and montelukast groups (P=0.032). Kaplan-Meier survival curves showed significant "superiority" of fluticasone compared to montelukast monotherapy in favor of fluticasone in both time to first exacerbation requiring prednisone (P=0.002) and time to treatment failure (P=0.015). Twenty-eight total treatment failures occurred, five with fluticasone, eight with fluticasone and salmeterol and 15 with montelukast. The difference between fluticasone monotherapy and montelukast was significant (P=0.04). ACQ score improved by -0.69 in the fluticasone monotherapy group, -0.55 in the fluticasone and salmeterol group and by -0.45 in the montelukast group. There was no significant difference between the fluticasone monotherapy and fluticasone plus salmeterol therapy in ACQ score improvement; however, the difference between fluticasone monotherapy and montelukast was significant (P=0.018). The mean change in FEV_1 was 6.32% with fluticasone monotherapy, 3.62% with fluticasone and salmeterol and -0.58% with montelukast. The differences were significant between both the fluticasone monotherapy (P<0.001) and fluticasone and salmeterol (P=0.010) therapy when compared to montelukast.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean change for FEV_1/FVC was 3.95% for the fluticasone monotherapy group, 1.76% for the fluticasone and salmeterol group and 0.07% for the montelukast group. The difference was significant between the fluticasone monotherapy group and montelukast (P<0.001). Morning PEF values improved by 5.18% in the fluticasone monotherapy group, 5.33% in the fluticasone and salmeterol group and by 0.65% in the montelukast group. The differences were significant between both the fluticasone monotherapy (P=0.002) and fluticasone and salmeterol (P=0.001) therapy when compared to montelukast. Evening PEF values improved by 2.95% in the fluticasone monotherapy group, 4.31% in the fluticasone and salmeterol group and worsened by -0.57% in the montelukast group. The differences were significant between both the fluticasone monotherapy (P=0.017) and fluticasone and salmeterol (P<0.001) therapy when compared to montelukast. The mean increase height from baseline was 5.3 cm with fluticasone monotherapy and fluticasone and salmeterol. The increase in height was 5.7 cm in the montelukast group; however, the differences did not reach significance (P<0.001) for both groups compared to montelukast.
Calhoun et al.[40] (2001) Montelukast 10 mg QD vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product)	DB, DD, MC, RCT Patients 15 to 72 years of age diagnosed with asthma for at least six months and had been treated with oral or inhaled β_2-agonists for at least six weeks prior to study, FEV_1 values of between 50 to 80% of predicted value and an	N=423 12 weeks	Primary: Change from baseline in pre-dose FEV_1 values Secondary: Morning and evening PEF values, asthma symptom score, percentage of symptom-free days, β_2-agonist use, percentage of rescue-free days,	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
	increase in FEV_1 of at least 12% within 30 minutes of inhaled albuterol		percent of nights with no asthma-related awakenings, percentage of nights with no asthma-related awakenings in patients with ≥2 awakenings/week at baseline and nights/week with no awakenings	
Maspero et al.[41] (2008) Montelukast 5 mg QD vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product)	DB, DD, MC, PG, RCT Patients 6 to 14 years of age with a diagnosis of asthma for ≥6 months, a FEV_1 between 55 to 80% of predicated normal with ≥12% FEV_1 reversibility and were not on any asthma control medications except for a SABA	N=548 12 weeks	Primary: Morning PEF values Secondary: FEV_1, evening PEF values, levels of symptoms and rescue medications, assessment of asthma control, asthma exacerbations, and safety	Primary: The mean change from baseline in morning PEF was 45.8 L/min in the fluticasone and salmeterol group, and 28.7 L/min in the montelukast group (P<0.001). Secondary: The mean change from baseline in evening PEF was 46.2 L/min in the fluticasone and salmeterol group, and 28.0 L/min in the montelukast group (P<0.001). The mean change from baseline in FEV_1 was 0.47 L in the fluticasone and salmeterol group, and 0.30 L in the montelukast group (P<0.001). The fluticasone and salmeterol group had significantly greater improvements in percentage of symptom free (P=0.025) and rescue free (P<0.001) 24-hour periods compared to the montelukast group. Asthma control was higher in the fluticasone and salmeterol group (88.3%) than in the montelukast group (66.7%; P<0.001). Twice as many patients in the montelukast group (23.2%) had asthma exacerbations than in the fluticasone and salmeterol group (10.3%). Fifty five percent of patients in the fluticasone and salmeterol group and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				57% in the montelukast group reported an adverse event during treatment. The most common adverse event reported in both groups was headache (23% in the fluticasone and salmeterol group and 27% in the montelukast group).
Katial et al.[42] (2010) Montelukast 10 mg QD (MON) vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product) (FSC) vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product) plus montelukast 10 mg QD (FSC+MON) vs fluticasone and salmeterol 100-50 µg BID and fluticasone nasal spray 200 µg QD (FSC+FPANS)	DB, MC, PC, RCT 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	N=1,081 4 weeks	Primary: Mean change from 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 D/N-TNSS	Primary: There was no significant difference in AM PEF between FSC and FSC+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 (percent symptom free days, percent 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).
Fish et al.[43]	DB, DD, MC, PG,	N=948	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Montelukast 10 mg QD vs salmeterol 50 µg BID	RCT Patients ≥15 years of age diagnosed with asthma remaining symptomatic despite therapy with a stable dose of ICS for the previous 30 days	12 weeks	Morning PEF values Secondary: Evening PEF, daytime asthma symptom score, supplemental albuterol use and nighttime awakenings	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).
Yildirim et al.[44] (2004) Montelukast 10 mg QD and budesonide 400 µg/day vs budesonide 800 µg/day	PG, RCT Patients with moderate persistent asthma for minimum of six months who were admitted into the Department of Chest Diseases in Trabzon, Turkey	N=30 6 weeks	Primary: Morning, daytime and evening asthma symptoms, morning and evening PEF, FEV_1, blood eosinophil counts, frequency of SABA use and frequency of asthma exacerbations Secondary: Not reported	Primary: A significant decrease in morning and daytime symptom scores was reported in both groups compared to baseline scores (P<0.05), but no significant differences between the two groups were noted. No significant difference in evening symptom scores was reported in either group compared to baseline. No significant differences in FEV_1 or PEF values from baseline or between groups were reported. A significant decrease in blood eosinophil counts in both groups when compared to baseline (P<0.05) was reported, but there was no significant difference between the two groups. There was a significant decrease in β_2-agonist use in the budesonide plus montelukast group compared to baseline (P<0.05), but there was no significant difference in β_2-agonist use in the budesonide group compared to baseline. No patients in either group experienced an asthma exacerbation during the study period. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Price et al.[45] (2003) Montelukast 10 mg QD and budesonide 800 µg/day vs budesonide 1,600 µg/day	DB, NI, PG, RCT Patients 15 to 75 years of age diagnosed with asthma not optimally controlled on regular ICS	N=889 12 weeks	Primary: Morning PEF values Secondary: Initial treatment effect on PEF (days one to three), daily self-reported β_2-agonist use, daytime symptoms, nocturnal awakenings, asthma exacerbations, asthma-free days, blood eosinophil counts and 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 insignificant at the end of the study. Secondary: The change from baseline in PEF during the first three 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.[46] (2003) Montelukast 10 mg QD and fluticasone 100 µg BID vs fluticasone 100 µg BID and salmeterol 50 µg BID	DB, DD, MC, PG, RCT Patients 15 to 72 years of age with chronic asthma ≥1 year, baseline FEV_1 50 to 90% predicted value, improvement of 12% or more in FEV_1 or in morning PEF after β_2-agonist use, regular use of ICS for at least 8 weeks prior to study and average β_2-agonist use of at	N=1,490 52 weeks	Primary: Percentage of patients with at least one asthma exacerbation Secondary: Asthma specific quality of life, nocturnal awakenings, mean FEV_1 before and after β_2-agonist use, mean morning PEF, time to first asthma exacerbation and	Primary: No significant difference between the two groups in percentage of patients with at least one asthma attack was reported. 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 two 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 two groups. A significant improvement in FEV_1 before β_2-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_2-agonist use was similar between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	least one puff/day		blood eosinophil counts	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.[47] (2010) BADGER Montelukast 5 to 10 mg QD and fluticasone 100 µg BID (LTRA step-up therapy) vs salmeterol 50 µg BID and fluticasone 100 µg BID (LABA step-up therapy) vs fluticasone 250 µg BID (ICS step-up therapy)	DB, RCT, XO Patients 6 to 17 years of age with mild to moderate asthma uncontrolled while receiving fluticasone 100 µg BID	N=182 48 weeks (three 16 week periods)	Primary: Differential response to each of the three step-up therapies based on control measures including requirement of oral prednisone for acute exacerbations, number of asthma control days and FEV_1 Secondary: Not reported	Primary: The response to LABA step-up therapy was significantly more likely to be the best response as compared to the response to LTRA step-up and ICS step-up therapy (P=0.004 and P=0.002 respectively). Secondary: Not reported
Suissa et al.[48] (1997)	DB, MC, PC, RCT	N=146	Primary: Days without	Primary: Significantly more days without asthma symptoms was observed in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zafirlukast 20 mg BID vs placebo	Patients ≥12 years of age, non-smokers in the last six months, smoking history of less than 10 pack-years, FEV_1 at least 55% of predicted value, with bronchial hyper-responsiveness and who were symptomatic during the seven-day run-in period of the study	13 weeks	limitation of activity, days without use of β_2-agonists, days without episodes of asthma and days without sleep disturbance Secondary: Unscheduled health care visits and contacts, total number of β_2-agonist inhalers used, number of prescriptions for non-asthma medications consumed and number of days absent from work or school	zafirlukast group (P=0.03). Significantly more days without β_2-agonist use were observed in the zafirlukast group (P=0.001). Significantly more days without episodes of asthma were reported in the zafirlukast group (P=0.003). More days without sleep disturbances were reported in the zafirlukast group (P>0.2). Secondary: A significant decrease in health care contacts was reported in the zafirlukast group (P=0.007). A significant decrease in asthma-related absenteeism was reported in zafirlukast group (P=0.04). A decrease in canisters of β_2-agonists used was observed in the zafirlukast group (P=0.17). A decrease in the use of non-asthma medications was observed in the zafirlukast group (P>0.2).
Busse et al.[49] (1999) Zafirlukast 20 mg BID vs salmeterol 42 µg BID	DB, DD, MC, PG, RCT Patients 12 to 73 years of age with a diagnosis of asthma for ≥6 months; after the run-in period, patients were required to have FEV_1 values of 50 to 70% predicted value with or without symptoms	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	or FEV_1 values of 70.1 to 80.0% predicted value with one or more of the following criteria: average of ≥4 puffs/ day of albuterol, symptom score ≥2 in any asthma symptom category on ≥2 days, ≥1 nighttime awakening due to asthma, or ≥2 days when evening to morning PEF values differed by ≥20%			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 two 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). Seven patients in the salmeterol group and nine patients in the zafirlukast group experienced asthma exacerbations during the treatment period (P values not reported).
Israel et al.[50] (1993) Zileuton 600 mg QID vs zileuton 800 mg BID vs placebo	DB, PC, RCT Patients 18 to 65 years of age with FEV_1 40 to 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_2-agonist use Secondary: Not reported	Primary: There was a significant (14.6%) increase in FEV_1 within one 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 four weeks compared to the placebo group (P=0.02). There was a significant decrease in asthma symptoms in all three groups (P<0.01), but the change was the greatest in the zileuton 600 mg group compared to the placebo group (P=0.02). There was a significant decrease in β_2-agonist use in the zileuton 600 and 800 mg group (P<0.001 and P=0.005 respectively) from baseline. Compared to the placebo group, the change was only significant in the 600 mg group (P=0.03). Secondary: Not reported
Israel et al.[51]	DB, PG, RCT	N=401	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1996) Zileuton 600 mg QID vs zileuton 400 mg QID vs placebo	Patients with mild to moderate asthma, FEV_1 40 to 80% of predicted value, only being treated with inhaled β_2-agonists	13 weeks	Frequency of asthma exacerbations requiring corticosteroid treatment, use of inhaled β_2-agonists, FEV_1, asthma symptoms and quality of life evaluations Secondary: Not reported	There was a significantly lower percentage of patients requiring corticosteroid treatment in the zileuton 600 mg group compared to the placebo group (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). Secondary: Not reported
Wenzel et al.[52] (2007) Zileuton CR 1200 mg BID vs placebo	DB, MC, PC, RCT Patients ≥12 years of age and non-smoking for at least 6 months; ex-smokers with ≤10-pack year history of cigarette smoking; FEV_1 ≥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%	N=926 6 months	Primary: Mean change in PEFs Secondary: Improvement in trough FEV1; change in number of daily doses of SABA; change from baseline in total score of Asthma quality of life questionnaire measured at three and six months	Primary: Sustained improvements in PEF were observed in the zileuton group compared to placebo. Secondary: Improvement in trough FEV_1 was similar between zileuton and placebo 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 quality of life than did treatment with placebo at six for the symptoms domain (0.74 vs 0.56, P=0.040) and the emotions domain (0.63 vs 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	reversibility documented within 1 year			
Nelson et al.[53] (2007) Zileuton CR 1,200 mg BID vs zileuton IR 600 mg QID vs placebo CR or placebo IR	AC, DB, MC, PC, RCT Patients ≥12 years with moderate persistent asthma with an FEV_1 of 40 to 75% of predicted when taken ≥48 hours after the last theophylline use and at least six hours after SABA use or 24 hours after LABA use who had not been hospitalized for asthma within six months	N=591 16 weeks	Primary: Change from baseline in morning trough FEV_1 Secondary: Percentage of patients with clinically significant improvement in lung function (≥12% in FEV_1), change from baseline in morning PEFR and reduction in the number of daily puffs of SABA, safety	Primary: At week 12, compared to the placebo CR group, the zileuton CR group demonstrated a significant mean improvement in FEV_1 (0.39 L [20.8%] vs 0.27 L [12.7%]; P=0.02). Compared to the placebo IR group, the zileuton IR group reported a non-significant improvement (0.38 L [19.3%] vs 0.28 L [14.1%]; P=0.19). Secondary: At week 12, 63.2% of the zileuton CR patients showed a 12.0% or greater improvement in FEV_1, compared to 50.0% in the placebo CR group. In the zileuton IR group 45.5% of patients had a 12.0% or great FEV_1 improvement, compared to 27.8% in the placebo IR group (P=0.02). However, this was only seen in the IR group at week four. The zileuton CR group reported an increasing mean improvement from baseline morning PEFR from 19.42 L/min for days two to 22 to 58.45 L/min for days 72 to 92. The difference between the zileuton CR group and the placebo CR group were not significant (P value not reported). Similar improvements were reported in the zileuton IR treatment group; however, the values were also not statistically significant. There was a 15.14% reduction from baseline of SABA use in the zileuton CR treatment grouped compared to a 2.29% reduction in the zileuton IR treatment group. The difference between the two groups was significant (P=0.009). The overall incidence of adverse events in the study was similar between all treatment groups (78.4% with zileuton CR, 76.8% with zileuton IR and 77.3% with placebo IR). The most common adverse events in the zileuton CR group were exacerbation of asthma, headache, sinusitis, nausea, nasopharyngitis and pharyngolaryngeal pain. Eight percent more patients in the placebo CR treatment group experienced asthma exacerbation that the zileuton CR

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group. Five out of 199 patients (2.5%) in the zileuton CR group and one out of 198 patients (0.5%) in the placebo CR group developed ALT level elevations of three times the upper limit of normal or greater. The investigators did not attribute the adverse events to the treatment medication. Two of the 97 patients (2.1%) in the zileuton IR group and one of the 97 patients (1.0%) in the placebo IR group developed ALT levels of three times the upper limit of normal or greater.
Exercise-Induced Bronchoconstriction				
Wasfi et al.[54] (2011) Montelukast 4 or 5 mg for a single dose vs placebo Two exercise challenges were administered at two and 24 hours post-dose.	DB, PC, RCT, XO Patients 4 to 14 years of age with a history of exercised-induced bronchoconstriction or wheeze or shortness of breath with exercise as well as a preexercise FEV_1 ≥70% predicted and a maximum percent fall in postexercise FEV_1 ≥20% within 60 minutes	N=66 24 hours	Primary: Maximum percent fall from preexercise baseline in FEV_1 after exercise challenge at two hours post-dose Secondary: Maximum percent fall from preexercise FEV_1 after exercise challenge at 24 hours post-dose, AUC over the first 60 minutes for the percent fall from preexercise FEV_1, time to recovery of FEV_1 to within 5% of baseline, need for rescue medication,	Primary: The mean maximum percent fall in FEV_1 at two hours post-dose was smaller in the montelukast group compared to the placebo group (15.35 vs 20.00%; P=0.02). Secondary: At 24 hours post-dose, the maximum percent fall in FEV_1 was significantly smaller with montelukast compared to placebo (12.92 vs 17.25%; P=0.005). The AUC over the first 60 minutes for the percent fall in FEV_1 was also significantly smaller with montelukast compared to placebo at two hours (294.50 vs 415.37 %*minute; P=0.022) and 24 hours post-dose (227.98 vs 350.80 %*minute; P=0.013). Time to recovery of FEV_1 to within 5% of baseline in the montelukast and placebo groups were 16.21 and 24.48 minutes, respectively, at two hours post-dose (P=0.064) and 11.49 and 18.55 minutes, respectively (P=0.054) 24 hours post-dose. The differences were not statistically significant. At two hours post-dose 1.6% of patients in the montelukast group and 3.1% in the placebo group required rescue medications after the exercise challenges (P=1.0). At 24 hours, 3.2% of patients in the placebo group and no one in the montelukast group required rescue medication (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			proportion of patients achieving maximum percent fall in FEV_1 ≤20% and safety	At two hours post-dose, the proportion of patients who had a maximum percent fall in FEV_1 ≤20% was 76.6 and 56.3% in the montelukast and placebo groups, respectively (P=0.015). At 24 hours, the proportion was 80.6 and 67.7%, respectively (P=0.077). In the montelukast group, proportion of patients who had a maximum percent fall in FEV_1 <10%, 10 to 20% and >20% at two hours was 26.6, 50.0 and 23.4%, respectively, at two hours and 45.2, 35.5 and 19.4%, respectively, at 24 hours. In the placebo group, the corresponding numbers were 25.0, 31.3 and 43.8%, respectively, at two hours (P=0.034) and 30.6, 37.1 and 32.3%, respectively, at 24 hours (P=0.061). Adverse events were reported in 6.2 and 7.6% of patients in the montelukast and place groups, respectively (P value not reported). No serious or drug-related adverse events were reported.
Philip et al.[55] (2007) Montelukast 10 mg vs salmeterol 50 µg vs placebo	DB, PC, RCT, XO Men and women who demonstrated a fall in FEV_1 following exercise (ΔFEV_1) of ≥20%	N=47 9 to 21 days	Primary: Maximum ΔFEV_1 observed after exercise challenge at two 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 2.0, 8.5, and 24.0 hours were significantly smaller after montelukast administration than after placebo administration (least squares mean, 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 2.0 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 two 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.
Fogel et al.[56] (2010) Montelukast 5 mg QD	DB, MC, RCT, XO Patients 6 to 14 years of age with exercise-induced	N=154 8 weeks	Primary: Percent change in FEV_1 after exercise and before SABA administration	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs salmeterol 50 µg BID All patients received OL fluticasone 50 µg 2 puffs BID throughout the study.	bronchoconstriction, $FEV_1 \geq 70\%$, who were receiving treatment with an ICS		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	Montelukast provided significantly more effective broncho-protection 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: BID=twice daily, CR=controlled-release, IR=immediate-release, QD=once daily, QID=four times daily
Study design abbreviations: AC=active comparator, DB=double blind, DD=double dummy, OL=open label, OS=observational, MC=multicenter, NI=non inferiority, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=cross over
Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, ACT=asthma control test, ALT=alanine aminotransferase, AUC=area under the curve, CI=confidence interval, D/N-TNNS=daytime and nighttime total nasal symptom score, ECP=eosinophil cationic protein, eNO=exhaled nitric oxide, FEV_1= forced expiratory volume in 1 second, FVC=forced vital capacity, HR=hazard ratio, ICS=intranasal corticosteroid, LABA=long-acting β_2-agonist, LTRA=leukotriene receptor antagonist, Mini-AQLQ=Mini Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, RQLQ=rhinoconjunctivitis quality of life questionnaire, SABA=short-acting β_2-agonist

Additional Evidence

Dose Simplification
Dorais et al. analyzed pharmacy claims to assess adherence with leukotriene modifiers and inhaled corticosteroids. 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 (relative risk, 0.46; 95% confidence interval, 0.85 to 0.98), and were more likely to be on treatment longer during the first year of therapy (38 vs 19%; P<0.001).[57]

Bukstein et al. evaluated preference with montelukast or inhaled cromolyn sodium in children with asthma. 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).[58]

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.[48] Price et al. found no difference in health care resource utilization with montelukast compared to budesonide in patients with asthma.[45]

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®*	$$$$	$$$
Zafirlukast	tablet	Accolate®*	$$$$$	$$$$$
Zileuton	sustained-release tablet, tablet	Zyflo®, Zyflo CR®	$$$$$	N/A

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

X. Conclusions

For the treatment of asthma, guidelines recommend the use of an inhaled corticosteroid as initial therapy.[8-11] Due to the fact they the leukotriene modifiers are generally less effective compared to inhaled corticosteroids, they may be considered as an alternative treatment in patients with mild persistent asthma.[8-11] In addition, leukotriene modifiers may be used first line in patients less than five years of age who cannot receive inhaled corticosteroids.[10] Add-on leukotriene modifier therapy may reduce the dose of inhaled corticosteroids required in patients with moderate to severe asthma and improve asthma control. However, add-on leukotriene modifier therapy is not as effective as long-acting β_2-agonist add-on therapy; therefore, when a medium dose inhaled corticosteroid fails to achieve asthma control, the addition of a long-acting β_2-agonist is the preferred treatment.[8] However, in children less than five years of age, leukotriene modifiers are recommended first-line as add-on therapy to inhaled corticosteroids.[10] Guidelines do not give preference to one leukotriene modifier over another for the treatment of asthma.[8-11]

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists, and mast cell stabilizers. 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.[12-15] Intranasal corticosteroids are considered the most effective treatment for controlling symptoms of allergic rhinitis and should be considered first-line therapy in patients with moderate to severe symptoms.[13,14] Leukotriene modifiers are less effective compared to intranasal corticosteroids and may be as effective as second generation oral antihistamines for the treatment of allergic rhinitis.[14] Montelukast is recommended for adults and children with seasonal allergic rhinitis, and in pre-school children with persistent allergic rhinitis; however, montelukast has limited efficacy in adults with persistent allergic rhinitis.[12] Currently, montelukast is the only leukotriene modifier Food and Drug Administration (FDA)-approved for the treatment of allergic rhinitis and guidelines do not give preference to one leukotriene modifier over another.[3,12-15]

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. However, they have generally been shown to be less effective than inhaled corticosteroids and long-acting β_2-agonists.[26-53] There are limited head-to-head trials comparing the leukotriene modifiers for the treatment of asthma.[32,33]

Clinical trials have demonstrated that the leukotriene modifiers improve quality of life and symptom scores in patients with 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.[16-25]

Few clinical trials have demonstrated that montelukast is effective in the treatment of exercised-induced bronchocontstriction.[54-56] Currently, montelukast is the only leukotriene modifier FDA-approved for acute prevention of exercise-induced bronchoconstriction.[3]

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 generic 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Inhaled Mast-Cell Stabilizers
AHFS Class 481032
November 4, 2015

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. Cromolyn sodium has no intrinsic bronchodilator or antihistaminic activity; however, it inhibits mast cell degranulation after exposure to antigens. 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.[1-3]

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 August 2013.

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.
N/A=Not available.
PDL=Preferred Drug List.

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.

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

Clinical Guideline	Recommendations
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2015)**[4]	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. • Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. • Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. • Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects. • For population-level decisions about asthma management, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness, and safety from randomized controlled trials, meta-analyses, and observational studies, and net cost. • For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.

Clinical Guideline	Recommendations

	Treatment overview
	• At present, step 1 treatment is with as-needed short-acting beta$_2$ agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a lack of studies of inhaled corticosteroids (ICS) in such populations.
	• Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	• For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities.
	  o For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta$_2$ agonist (LABA).
	  o For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller plus as-needed SABA.
	  o For children six to 11 years, increasing the ICS dose is preferred over combination ICS/LABA.
	• Consider step down once good asthma control has been achieved and maintained for about three months to find the patient's lowest treatment that controls both symptoms and exacerbations.
	  o Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.
	  o Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
	• For all patients with asthma:
	  o Provide inhaler skills training.
	  o Encourage adherence with controller medication, even when symptoms are infrequent.
	  o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations and need for healthcare utilization.
	• For patients with one or more risk factors for exacerbations:
	  o Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients.
	  o Identify and address modifiable risk factors (e.g., smoking, low lung function).
	  o Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction.
	
	Categories of asthma medications
	• *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
	• *Reliever (rescue medications)*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
	• *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.
	
	Stepwise approach for adjusting asthma treatment in adults, adolescents, and children

Clinical Guideline	Recommendations

six to 11 years old

- Initial controller treatment: For best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.
- Once treatment has been commenced (see table below), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - Incorrect inhaler technique.
  - Poor adherence.
  - Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - Incorrect diagnosis.

Stepwise approach to control symptoms and minimize future risk					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller choice		Low dose ICS	Low dose ICS/LABA*	Med/high ICS/LABA	Refer for add-on treatment (e.g., anti-IgE)
Other controller options	Consider low dose ICS	Leukotriene receptor antagonist (LTRA) or low dose theophylline*	Med/high dose ICS or low dose ICS+LTRA (or + theoph*)	High dose ICS + LTRA (or + theoph*)	Add low dose oral corticoste-roids
Reliever	As-needed SABA		As-needed SABA or low dose ICS/formoterol**		

*For children six to 11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium-dose ICS.
**Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy.

Management of worsening asthma and exacerbations

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
- Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
- The management of worsening asthma and exacerbations is part of a continuum, from self-management by the patient with a written asthma action plan, though to management of more severe symptoms in primary care, the emergency department, and the hospital.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (in adults) peak

Clinical Guideline	Recommendations
	expiratory flow. • For patients presenting with an exacerbation to a primary care or acute care facility: o Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy. o Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA therapy, controlled oxygen, and systemic corticosteroids should be given. o Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Response should be reviewed after one hour. o Ipratropium bromide treatment is recommended only for severe exacerbations not responding to initial treatment. o Chest X-ray is not routinely recommended. o Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home. o Before the patient goes home, ongoing treatment should be arranged. This should include starting controller treatment or stepping up the dose of existing controller treatment for two to four weeks, and reducing reliever medication to as-needed use. • Antibiotics should not be routinely prescribed for asthma exacerbations. • Arrange early follow-up after any exacerbation, regardless of where it was managed. o Review the patient's symptom control and risk factors for further exacerbations. o For most patients, prescribe regular controller therapy to reduce the risk of further exacerbations. Continue increased controller doses for two to four weeks. o Check inhaler technique and adherence. <u>Children five years and younger: assessment and management</u> • The goals of asthma management in young children are similar to those in older patients: o To achieve good control of symptoms and maintain normal activity levels. o To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects. • Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. • A trial of controller therapy should be given if the symptom pattern suggests asthma and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe. • Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis. • The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <4 years and mouthpiece for most four to five year olds. • Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children. **Stepwise approach to long-term management of asthma in children 5 years and younger** **Step 1** / **Step 2** / **Step 3** / **Step 4**

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td>Preferred controller choice</td><td></td><td>Daily low dose ICS</td><td>Double ‘low dose’ ICS</td><td>Continue controller & refer for to specialist</td></tr>
<tr><td>Other controller options</td><td></td><td>Leukotriene receptor antagonist (LTRA)
Intermittent ICS</td><td>Low dose ICS + LTRA</td><td>Add LTRA
↑ ICS frequency
Add intermitt ICS</td></tr>
<tr><td>Reliever</td><td colspan="4">As-needed SABA (all children)</td></tr>
</table>
<table>
<tr><td rowspan="2">Consider this step for children with:</td><td rowspan="2">Infrequent viral wheezing and no or few interval symptoms</td><td>Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year</td><td>Asthma diagnosis, and not controlled on low dose ICS</td><td>Not controlled on double ICS</td></tr>
<tr><td>Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6 to 8 weeks. Give diagnostic trial for 3 months</td><td colspan="2">First check diagnosis, inhaler skills, adherence, exposures</td></tr>
</table>
<u>Management of worsening asthma and exacerbations in children five and younger</u>

Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.

Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
There is only weak evidence to support patient-initiated oral corticosteroids.

In children presenting to primary care or an acute care facility with an asthma exacerbation:

Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94-98%).
Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
Give oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years.

Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one week of an exacerbation to plan ongoing asthma management.

</td></tr>
<tr><td>The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: Guidelines for the Diagnosis and Management of Asthma</td><td><u>Diagnosis</u>

To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded.
The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses.
A diagnosis of asthma should be considered if any of the following indicators are
</td></tr>
</table>

Clinical Guideline	Recommendations
(2007)[5]	present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include SABAs, anticholinergics and systemic corticosteroids. <u>Long-term control medications</u> • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma. <u>Quick-relief medications</u> • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>

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

<u>Assessment, treatment and monitoring</u>

A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
The stepwise approach for managing asthma is outlined below:

<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

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

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

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

Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special populations</u>

For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs.
The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm.
Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.
ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.

</td></tr>
<tr><td>British Thoracic Society/ Scottish Intercollegiate</td><td><u>Diagnosis in children</u>

The diagnosis is based on recognizing a characteristic pattern of episodic respiratory symptoms and signs in the absence of an alternative explanation for
</td></tr>
</table>

Clinical Guideline	Recommendations

Guidelines Network: **British Guideline on the Management of Asthma (2014)**[6]	them.
	• Presence of the following factors increases the probability that a child with respiratory symptoms will have asthma: age at presentation, sex, severity and frequency of previous wheezing episodes, coexistence of atopic disease, family history of atopy, and abnormal lung function.
	• Focus the initial assessment in children suspected of having asthma on presence of key features in the history and examination and careful consideration of alternative diagnoses.
	
	<u>Diagnosis in adults</u>
	• The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them.
	• Confirmation of airflow obstruction is vital for diagnosis of asthma. Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction.
	
	<u>Pharmacological management</u>
	• The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication.
	• Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.
	• Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors.
	• Step 1: Mild intermittent asthma:
	  o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma.
	• Step 2: Introduction of regular preventer therapy:
	  o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma.
	  o ICS should be considered for patients with any of the following asthma-related features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 who have had an asthma attack requiring oral corticosteroids in the last two years.
	  o ICS should initially be administered twice daily, except ciclesonide which is administered once daily.
	  o Once a day ICS at the same total daily dose can be considered if good control is established.
	  o In patients >12 years of age, health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers.
	• Step 3: Initial add-on therapy:
	  o In adults and children five to 12 years of age, the first choice for add-on therapy to ICS is an inhaled LABA, which should be considered before going above a dose of 400 µg beclomethasone or equivalent per day and certainly before going >800 µg beclomethasone or equivalent.
	  o In adults and children five to 12 years of age, if asthma control remains suboptimal after the addition of an inhaled LABA then the dose of ICS should be increased to 800 µg/day in adults or 400 µg/day in children five to 12 years of age if not already receiving these doses.
	  o In children <5 years of age, the first choice for add-on therapy to ICS is leukotriene receptor antagonists.

Clinical Guideline	Recommendations

- LABAs should only be started in patients who are already on ICS, and the ICS should be continued.
- Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence.

- Step 4: Poor control on moderate dose of ICS plus add-on therapy (addition of fourth drug):
  - If control remains inadequate on ICS 800 µg beclomethasone daily in adults and 400 µg beclomethasone daily in children plus LABA, consider the following interventions:
    - Increasing ICS to 2,000 (adults) or 800 (children five to 12 years of age) µg BDP daily.
    - Leukotriene receptor antagonists.
    - Theophyllines.
    - Slow-release β_2-agonist tablets, though caution needs to be used in patients already on LABAs.
- Step 5: Continuous or frequent use of oral steroids:
  - In adults, the recommended method of eliminating or reducing the dose of steroid tablets is ICS, at doses of up to 2,000 µg/day, if required.
  - In children 5 to 12 years of age, consider very carefully before going above 800 µg/day of ICS.
  - For all patients, there is a role for a trial of treatment with LABAs, leukotriene receptor antagonists, and theophylline for about six weeks. They should be stopped if no improvement in steroid dose, symptoms, or lung function is detected.
  - The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children.
- A summary of the stepwise management of asthma is outlined below:

Children <5 Years Old	Children 5 to 12 Years Old	Adults and Children >12 Years Old
Step 1: Mild Intermittent Asthma		
• Inhaled SABA as required	• Inhaled SABA as required	• Inhaled SABA as required
Step 2: Regular Preventer Therapy		
• Add ICS 200 to 400 µg/day*† or leukotriene antagonist if ICS cannot be used • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 400 µg/day* (other preventer drug if ICS cannot be used) • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 800 µg/day* • Start at dose of ICS appropriate to severity of disease
Step 3: Initial Add-on Therapy		
• In those taking ICS 200 to 400 µg/day, consider addition of leukotriene receptor antagonist • In those taking a leukotriene receptor antagonist alone, reconsider addition of an ICS 200 to 400 µg/day • In children under 2 years, consider proceeding to step 4	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 400 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 400 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 800 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 800 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline
Step 4: Persistent Poor Control		
• Refer to a respiratory pediatrician	• Increase ICS up to 800 µg/day*	Consider trials of: • Increase ICS up to 2,000 µg/day*

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>• Add a fourth drug (leukotriene receptor antagonist, sustained-release theophylline, β_2-agonist tablet)</td></tr>
<tr><td colspan="3">Step 5: Continuous or Frequent Use of Oral corticosteroids</td></tr>
<tr><td></td><td>• Use daily corticosteroid tablet in lowest dose providing adequate control
• Maintain high-dose ICS at 800 µg/day*
• Refer to respiratory pediatrician</td><td>• Use daily corticosteroid tablet in lowest dose providing adequate control
• Maintain high-dose ICS at 2,000 µg/day*
• Consider other treatments to minimize use of corticosteroid tablets
• Refer patient for specialist care</td></tr>
</table>
*Beclomethasone or equivalent.
†Higher nominal doses may be required if drug delivery is difficult.

<u>Specific management issues</u>
• For adults and children 5 to 12 years of age, if exercise is a specific problem in patients taking ICS who are otherwise well controlled, consider adding one of the following: leukotriene receptor antagonists, LABAs, chromones, oral β_2-agonists, or theophyllines.
• For adults and children 5 to 12 years of age, immediately prior to exercise inhaled SABAs are the drug of choice.
</td></tr>
<tr><td>International Primary Care Respiratory Group:
Management of Asthma (2006)[7]</td><td>
<u>Diagnosis</u>
• Diagnosis of asthma is based on signs and symptoms of airway obstruction.
• Treatment requires a stepwise approach based on asthma classification.

<u>Treatment</u>
• Step 1: intermittent asthma:
  o Short-acting β_2-agonists as needed for symptoms and for exercise-induced bronchospasm.
  o In patients >60 years of age, consider an anticholinergics agent.
• Step 2: mild persistent asthma:
  o Low-dose ICS.
• Step 3: moderate persistent asthma:
  o Combination therapy with an ISC and a LABA.
  o An alternative treatment option includes using the combination of an ICS and a leukotriene modifier or sustained-release theophylline.
• Step 4: severe persistent asthma:
  o Combination therapy with a high-dose ICS and LABA.
  o An alternative treatment option includes high-dose ICS and sustained-release theophylline.
  o An alternative treatment option includes high-dose ICS and a leukotriene modifier.
  o Oral corticosteroids can be used over the short-term.

<u>General treatment consideration</u>
• 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 ICS.
• For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of ICS and a LABA. Alternatives are combinations of ICS with sustained-release theophylline or leukotriene receptor antagonists.
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</table>

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[3]

Indication	Cromolyn Sodium
Asthma	
Management of patients with bronchial asthma	✔
Exercised-Induced Bronchospasm	
Prophylaxis of acute bronchoconstriction in response to exercise, toluene diisocyanate, and environmental pollutants	✔

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[2]

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

Adverse Events	Cromolyn Sodium
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	✔
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[3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cromolyn sodium	Asthma: Inhalation solution: 20 mg four times daily Bronchospasm prophylaxis: Inhalation solution: 20 mg administered shortly before exposure to the precipitating factor	Asthma in patients ≥2 years of age: Inhalation solution: 20 mg four times daily Bronchospasm prophylaxis in patients ≥2 years of age: Inhalation solution: 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/day via nebulization for 8 weeks, followed by dose titration	MC, OL, PG, RCT Children 2 to 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/day via nebulization for 8 weeks, followed by dose titration	MC, OL, PG, RCT Children 2 to 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 (PACQLQ), caregiver satisfaction, treatment convenience, ease of use, compliance, child health status (FS-II and CHQ-PF50) Secondary: Not reported	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). Secondary: Not reported
Hoshino et al.[10] (1998) Disodium cromoglycate* (DSCG) 2 mg QID vs ketotifen 1 mg tablet BID vs beclomethasone 100 µg† QID	PG, RCT Patients with mild-moderate atopic asthma, no anti-inflammatory drugs within 4 months of study onset, and no respiratory tract infection 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 Secondary: Not reported	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 beclomethasone 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 were significantly decreased in all three treatment groups (P<0.01). Mast-cell count significantly decreased in the DSCG and beclomethasone groups (P<0.05), but not in the ketotifen group. Secondary: Not reported
Furusho et al.[11]	MC, OL, PRO,	N=257	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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	RCT, XO Patients <20 years of age with moderate-severe, allergic or non-allergic perennial asthma, not on maintenance treatment with cromolyn, albuterol, or injected steroids	12 weeks	Change in asthma severity, measured by the mean asthma score Secondary: Patients' opinion of treatment effectiveness	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.[12] (2001) Sodium cromoglycate* (SCG) 4 to 10 mg/day vs nedocromil sodium† 4 to 8 mg/day	MA (8 trials) Patients ≥6 years of age with EIB, with a fall in FEV_1 of >10% after an exercise challenge test	N=117 Variable duration	Primary: Pulmonary function Secondary: Complete protection from exercise-induced broncho-constriction, 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 to 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). There was no significant difference between SCG and nedocromil sodium with respect to clinical protection from EIB (OR, 0.71; 95% CI 0.36 to 1.39). There was no significant difference between SCG and nedocromil sodium with respect to unpleasant taste (OR, 6.85; 95% CI, 0.77 to 60.73) or sore

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				throat (OR, 3.46; 95% CI, 0.32 to 37.48).
Spooner et al.[13] (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 (24 trials) Patients $\geq$6 years of age with EIB with a fall in FEV_1 of $\geq$10% after an exercise challenge test	N=518 Variable duration	Primary: Pulmonary function Secondary: Complete protection from exercise-induced broncho-constriction, 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 to 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 to 9.2). Secondary: Mast cell stabilizers provided a greater number of patients with complete protection (73 vs 56%; 95% CI, 1.3 to 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 to 0.5) and clinical protection from EIB, compared with β_2-adrenergic agonists (55 vs 77%; 95% CI, 0.2 to 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 to 1.4).

*Synonym for cromolyn.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QID=four times daily
Study design abbreviations: MA=meta-analysis, MC=multi-center, OL=open-label, PG=parallel-group, PRO=prospective, RCT=randomized trial, XO=crossover
Miscellaneous abbreviations: CHQ-PF50=Modified Child Health Questionnaire-Parent Form 50, CI=confidence interval, EIB=exercise-induced bronchoconstriction, FEV_1=forced expiratory volume in 1 second, FS-II=Functional Status II Questioner, OR=odds ratio, PACQLQ=pediatric asthma caregiver's quality of life questionnaire, PEF=peak expiratory flow

Additional Evidence

Dose Simplification
Sherman et al. evaluated adherence rates with asthma medications in children with persistent asthma who were Medicaid recipients. Maximum potential adherence was found to be 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn.[14] 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. 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 ($P \leq 0.001$).[9]

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] Inhaled mast-cell stabilizers are less effective compared to inhaled corticosteroids; therefore, may be used as an alternative for the treatment of mild persistent asthma.[4-6] Guidelines also recognized inhaled mast-cell stabilizers as preventive treatment prior to exercise or unavoidable exposure to known allergens.[5]

Clinical trials have demonstrated that inhaled corticosteroids are more effective than mast-cell stabilizers in patients with persistent asthma.[8-11] Few clinical trials have demonstrated that inhaled mast-cell stabilizers are effective for the prevention of exercise-induced bronchospasm as they are not as effective as short-acting bronchodilators.[12-14]

Therefore, all brand inhaled mast-cell stabilizers within the class reviewed are comparable to each other and to the generic 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Respiratory Agents-Corticosteroids
AHFS Class 481008
November 4, 2015

I. Overview

The respiratory agents-corticosteroids (inhaled corticosteroids) are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-17] 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.[18]

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, salmeterol, or vilanterol). Inhaled β_2-agonists dilate the airways by relaxing bronchial smooth muscle.

Fluticasone furoate (Arnuity Ellipta®) was approved in 2014 for the maintenance treatment of asthma.[9] Fluticasone furoate and fluticasone propionate are distinct drugs with differing pharmacokinetic and pharmacodynamic properties. Fluticasone furoate has enhanced affinity for the target receptors in both nasal and lung tissues and therefore is approved for use at a lower daily dose as compared with fluticasone propionate.[19]

The respiratory agents-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 August 2013. Flunisolide was last reviewed in February 2015 as a new drug.

Table 1. Respiratory Agents-Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Beclomethasone	aerosol inhaler	QVAR®	QVAR®
Budesonide	dry powder inhaler, inhalation suspension	Pulmicort Flexhaler®, Pulmicort Respules®*	Pulmicort Respules®*
Ciclesonide	aerosol inhaler	Alvesco®	none
Flunisolide	aerosol inhaler	Aerospan®	Aerospan®
Fluticasone furoate	dry powder inhaler	Arnuity Ellipta®	none
Fluticasone propionate	aerosol inhaler, dry powder inhaler	Flovent Diskus®, Flovent HFA®	none
Mometasone	aerosol inhaler, dry powder inhaler	Asmanex HFA®, Asmanex Twisthaler®	Asmanex Twisthaler ®
Combination Products			
Budesonide and formoterol	aerosol inhaler	Symbicort®	none
Fluticasone propionate and salmeterol	aerosol inhaler, dry powder inhaler	Advair Diskus®, Advair HFA®	none
Fluticasone furoate and vilanterol	dry powder inhaler	Breo Ellipta®	none
Mometasone and formoterol	aerosol inhaler	Dulera®	Dulera®

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the respiratory agents-corticosteroids are summarized in Table 2.

Table 2. Treatment Guidelines Using the Respiratory Agents-Corticosteroids

Clinical Guidelines	Recommendations

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2015)**[20]	Diagnosis
	• A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking and occupational exposure to dusts/chemicals.
	• A diagnosis of COPD should be confirmed by spirometry.
	• COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio.
	• The presence of a post-bronchodilator FEV_1/FVC <0.70 and FEV_1 <80% predicted confirms the presence of airflow limitation that is not fully reversible.
	• A detailed medical history should be obtained for all patients suspected of developing COPD.
	• Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
	• Bronchodilator reversibility testing should be performed to rule out the possibility of asthma.
	• Chest radiograph may be useful to rule out other diagnoses.
	• Arterial blood gas measurements should be performed in advanced COPD.
	• Screening for α_1-antitrypsin deficiency should be performed in patients who are from areas with a particularly high prevalence of the deficiency. Typical patients develop COPD at 45 years of age or younger and have lower lobe emphysema.
	• Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis.
	
	Therapeutic options
	• In patients who smoke, smoking cessation is the intervention with the greatest capacity to influence COPD. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
	• The management of COPD should be individualized to address symptoms and improve the patient's quality of life.
	• None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications.
	• COPD patients should receive an annual influenza vaccine.
	• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value.
	• Patients who get short of breath while walking at their own pace on level ground should be offered rehabilitation.
	
	Pharmacologic therapy for stable COPD
	• Bronchodilators
	  o Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations.
	  o Principle bronchodilators include β_2-agonists, anticholinergics, and theophylline used as monotherapy or in combination.
	  o The use of long-acting bronchodilators is more effective and convenient than

Clinical Guidelines	Recommendations
	short-acting bronchodilators. o For single-dose, as needed use, there is no advantage in using levalbuterol over conventional bronchodilators. o Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable. • Corticosteroids o Inhaled corticosteroids (ICSs) should be used in patients with an FEV_1 <60% of the predicted value. o Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • Combination inhaled corticosteroid/ bronchodilator o An inhaled corticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD. • Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended. <u>Management of stable COPD</u> • Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quite. • The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients and individualized assessment of symptoms and risk of exacerbation should also be considered. • Pharmacologic therapy is used to reduce symptoms, reduce frequency of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function. • For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators. • Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations. • Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD. • The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 <50% predicted, chronic bronchitis, and frequent exacerbations. • Influenza vaccines can reduce the risk of serious illness and death in COPD patients. • Currently, the use of antibiotics is not indicated in COPD, other than for treating infectious exacerbations of COPD and other bacterial infections. <u>Management of exacerbations</u> • The most common causes of an exacerbation are viral upper respiratory tract infections and infection of the tracheobronchial tree. • Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation. • Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function, and reduce the risk of early relapse, treatment failure, and length of hospital stay.
National Institute for Health and Clinical	<u>Diagnosis</u> • Diagnosis should be considered in patients >35 years of age who have a risk factor

Clinical Guidelines	Recommendations

Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[21]
 	
Reviewed July 2014
	for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze.
	• The primary risk factor is smoking.
	• Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%.
	
	Treatment
	• Smoking cessation should be encouraged for all patients with COPD.
	• Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.
	• Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.
	• Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist.
	  o FEV_1 ≥50% predicted: long acting beta agonist (LABA) or long-acting anticholinergic antagonist.
	  o FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist.
	• In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined.
	• Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa.
	• Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs.
	• In most cases, inhaled bronchodilator therapy is preferred.
	• Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation.
	• Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy.
	• Pulmonary rehabilitation should be made available to patients.
	• Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure.
	
	Management of exacerbations
	• Patients with exacerbations should be evaluated for hospital admission.
	• Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial.
	• Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days.
	• Oxygen should be given to maintain oxygen saturation above 90%.
	• Patients should receive invasive and noninvasive ventilation as necessary.
	• Respiratory physiotherapy may be used to help remove sputum.
	• Before discharge, patients should be evaluated by spirometry.
	• Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Clinical Guidelines	Recommendations
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)**[22]	Diagnosis • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
International Primary Care Respiratory Group: **Management of Chronic Obstructive Pulmonary Disease (2006)**[23]	• 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/European Respiratory Society: **Standards for the Diagnosis and**	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:

Clinical Guidelines	Recommendations
Treatment of Patients with Chronic Obstructive Pulmonary Disease (2004)[24]	o Mild COPD: $FEV_1/FVC \leq 0.70$ and $FEV_1 \geq 80\%$ predicted. o Moderate COPD: $FEV_1/FVC \leq 0.70$; $FEV_1 \geq 50\%$ and <80% predicted. o Severe COPD: $FEV_1/FVC \leq 0.70$; $FEV_1 \geq 30\%$ and <50% predicted. o Very Severe COPD: $FEV_1/FVC \leq 0.70$ and FEV_1 <30% predicted. <u>Treatment</u> • 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: o Intermittent symptoms: Short-acting bronchodilator as needed for symptom control. o 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 three months than either agent alone. • Anticholinergics given four times a day can improve health status over a three-month period compared with placebo. • LABA 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 LABA and ipratropium leads to fewer exacerbations than either drug alone. • No good comparative data between different LABA are presently available although it is likely that their effects will be similar. • Combining LABA 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 LABA in its effect and in one clinical trial appeared to be superior to salmeterol in some measures over six 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 three-year studies has shown no effect of

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	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 chromones (mast-cell stabilizers) in COPD.

Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2015)**[25]	General principles of asthma management
	• The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.
	• Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers.
	• Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources.
	• Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects.
	• For population-level decisions about asthma management, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness, and safety from randomized controlled trials, meta-analyses, and observational studies, and net cost.
	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	Treatment overview
	• At present, step 1 treatment is with as-needed short-acting $beta_2$ agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a lack of studies of inhaled corticosteroids (ICS) in such populations.
	• Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	• For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities.
	  o For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting $beta_2$ agonist (LABA).
	  o For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller plus as-needed SABA.
	  o For children six to 11 years, increasing the ICS dose is preferred over combination ICS/LABA.
	• Consider step down once good asthma control has been achieved and maintained for about three months to find the patient's lowest treatment that controls both symptoms and exacerbations.
	  o Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.
	  o Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
	• For all patients with asthma:
	  o Provide inhaler skills training.
	  o Encourage adherence with controller medication, even when symptoms are infrequent.
	  o Provide training in asthma self-management to control symptoms and

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minimize the risk of exacerbations and need for healthcare utilization.

- For patients with one or more risk factors for exacerbations:
  - Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients.
  - Identify and address modifiable risk factors (e.g., smoking, low lung function).
  - Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction.

Categories of asthma medications

- *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
- *Reliever (rescue medications)*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
- *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.

Stepwise approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years old

- Initial controller treatment: For best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.
- Once treatment has been commenced (see table below), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - Incorrect inhaler technique.
  - Poor adherence.
  - Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - Incorrect diagnosis.

Stepwise approach to control symptoms and minimize future risk					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller choice		Low dose ICS	Low dose ICS/LABA*	Med/high ICS/LABA	Refer for add-on treatment (e.g., anti-IgE)
Other controller options	Consider low dose ICS	Leukotriene receptor antagonist (LTRA) or low dose theophylline*	Med/high dose ICS or low dose ICS+LTRA (or + theoph*)	High dose ICS + LTRA (or + theoph*)	Add low dose oral corticoste-roids
Reliever	As-needed SABA		As-needed SABA or low dose		

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		ICS/formoterol**

*For children six to 11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium-dose ICS.
**Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy.

Management of worsening asthma and exacerbations

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
- Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
- The management of worsening asthma and exacerbations is part of a continuum, from self-management by the patient with a written asthma action plan, though to management of more severe symptoms in primary care, the emergency department, and the hospital.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use oral corticosteroids, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (in adults) peak expiratory flow.
- For patients presenting with an exacerbation to a primary care or acute care facility:
  - Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy.
  - Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA therapy, controlled oxygen, and systemic corticosteroids should be given.
  - Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of oral corticosteroids, and controlled flow oxygen if available. Response should be reviewed after one hour.
  - Ipratropium bromide treatment is recommended only for severe exacerbations not responding to initial treatment.
  - Chest X-ray is not routinely recommended.
  - Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.
  - Before the patient goes home, ongoing treatment should be arranged. This should include starting controller treatment or stepping up the dose of existing controller treatment for two to four weeks, and reducing reliever medication to as-needed use.
- Antibiotics should not be routinely prescribed for asthma exacerbations.
- Arrange early follow-up after any exacerbation, regardless of where it was managed.
  - Review the patient's symptom control and risk factors for further exacerbations.
  - For most patients, prescribe regular controller therapy to reduce the risk of further exacerbations. Continue increased controller doses for two to four

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weeks.
- o Check inhaler technique and adherence.

Children five years and younger: assessment and management

- The goals of asthma management in young children are similar to those in older patients:
  - o To achieve good control of symptoms and maintain normal activity levels.
  - o To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects.
- Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made.
- A trial of controller therapy should be given if the symptom pattern suggests asthma and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <4 years and mouthpiece for most four to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

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

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

Management of worsening asthma and exacerbations in children five and younger

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - o Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - o Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  - o Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  - o There is only weak evidence to support patient-initiated oral corticosteroids.

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	• In children presenting to primary care or an acute care facility with an asthma exacerbation: o Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94-98%). o Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air. o Give oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years. • Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one week of an exacerbation to plan ongoing asthma management.
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[18]	<u>Diagnosis</u> • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include SABAs, anticholinergics and systemic corticosteroids. <u>Long-term control medications</u> • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton.

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- Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens.
- Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy.
- Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.
- LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.
- LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
- Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
- Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma.

Quick-relief medications

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

Assessment, treatment and monitoring

- A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
- Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
- The stepwise approach for managing asthma is outlined below:

Inter-mittent Asthma	Persistent Asthma: Daily Medication				
Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
Preferred SABA as needed	Preferred Low-dose ICS Alternative Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline	Preferred Low-dose ICS+LABA or medium-dose ICS Alternative Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred Medium-dose ICS+LABA Alternative Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies	Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies

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	Management of exacerbations • Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. Special populations • For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. • The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm. • Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. • Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. • ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.

British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2014)**[26]	Diagnosis in children
	• The diagnosis is based on recognizing a characteristic pattern of episodic respiratory symptoms and signs in the absence of an alternative explanation for them.
	• Presence of the following factors increases the probability that a child with respiratory symptoms will have asthma: age at presentation, sex, severity and frequency of previous wheezing episodes, coexistence of atopic disease, family history of atopy, and abnormal lung function.
	• Focus the initial assessment in children suspected of having asthma on presence of key features in the history and examination and careful consideration of alternative diagnoses.
	
	Diagnosis in adults
	• The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them.
	• Confirmation of airflow obstruction is vital for diagnosis of asthma. Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction.
	
	Pharmacological management
	• The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication.
	• Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.
	• Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors.
	• Step 1: Mild intermittent asthma:
	  o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma.
	• Step 2: Introduction of regular preventer therapy:
	  o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma.
	  o ICS should be considered for patients with any of the following asthma-

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	related features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o In patients >12 years of age, health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Step 3: Initial add-on therapy: o In adults and children five to 12 years of age, the first choice for add-on therapy to ICS is an inhaled LABA, which should be considered before going above a dose of 400 µg beclomethasone or equivalent per day and certainly before going >800 µg beclomethasone or equivalent. o In adults and children five to 12 years of age, if asthma control remains suboptimal after the addition of an inhaled LABA then the dose of ICS should be increased to 800 µg/day in adults or 400 µg/day in children five to 12 years of age if not already receiving these doses. o In children <5 years of age, the first choice for add-on therapy to ICS is leukotriene receptor antagonists. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence. • Step 4: Poor control on moderate dose of ICS plus add-on therapy (addition of fourth drug): o If control remains inadequate on ICS 800 µg beclomethasone daily in adults and 400 µg beclomethasone daily in children plus LABA, consider the following interventions: ▪ Increasing ICS to 2,000 (adults) or 800 (children five to 12 years of age) µg BDP daily. ▪ Leukotriene receptor antagonists. ▪ Theophyllines. ▪ Slow-release β_2-agonist tablets, though caution needs to be used in patients already on LABAs. • Step 5: Continuous or frequent use of oral steroids: o In adults, the recommended method of eliminating or reducing the dose of steroid tablets is ICS, at doses of up to 2,000 µg/day, if required. o In children 5 to 12 years of age, consider very carefully before going above 800 µg/day of ICS. o For all patients, there is a role for a trial of treatment with LABAs, leukotriene receptor antagonists, and theophylline for about six weeks. They should be stopped if no improvement in steroid dose, symptoms, or lung function is detected. o The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children. • A summary of the stepwise management of asthma is outlined below:

Children <5 Years Old	Children 5 to 12 Years Old	Adults and Children >12 Years Old
Step 1: Mild Intermittent Asthma		
• Inhaled SABA as required	• Inhaled SABA as required	• Inhaled SABA as required
Step 2: Regular Preventer Therapy		
• Add ICS 200 to 400 µg/day*† or leukotriene	• Add ICS 200 to 400 µg/day* (other preventer	• Add ICS 200 to 800 µg/day*

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	antagonist if ICS cannot be used • Start at dose of ICS appropriate to severity of disease drug if ICS cannot be used) • Start at dose of ICS appropriate to severity of disease • Start at dose of ICS appropriate to severity of disease
	Step 3: Initial Add-on Therapy
	• In those taking ICS 200 to 400 µg/day, consider addition of leukotriene receptor antagonist • In those taking a leukotriene receptor antagonist alone, reconsider addition of an ICS 200 to 400 µg/day • In children under 2 years, consider proceeding to step 4 • Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 400 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 400 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline • Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 800 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 800 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline
	Step 4: Persistent Poor Control
	• Refer to a respiratory pediatrician • Increase ICS up to 800 µg/day* Consider trials of: • Increase ICS up to 2,000 µg/day* • Add a fourth drug (leukotriene receptor antagonist, sustained-release 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 ICS at 800 µg/day* • Refer to respiratory pediatrician • Use daily corticosteroid tablet in lowest dose providing adequate control • Maintain high-dose ICS at 2,000 µg/day* • Consider other treatments to minimize use of corticosteroid tablets • Refer patient for specialist care
	*Beclomethasone or equivalent. †Higher nominal doses may be required if drug delivery is difficult. Specific management issues • For adults and children 5 to 12 years of age, if exercise is a specific problem in patients taking ICS who are otherwise well controlled, consider adding one of the following: leukotriene receptor antagonists, LABAs, chromones, oral β_2-agonists, or theophyllines. • For adults and children 5 to 12 years of age, immediately prior to exercise inhaled SABAs are the drug of choice.
International Primary Care Respiratory Group: **Management of Asthma (2006)**[27]	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: o SABAs as needed for symptoms and for exercise-induced bronchospasm. o In patients >60 years of age, consider an anticholinergics agent. • Step 2: mild persistent asthma:

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	o Low-dose ICS. • Step 3: moderate persistent asthma: o Combination therapy with an ISC and a LABA. o An alternative treatment option includes using the combination of an ICS and a leukotriene modifier or sustained-release theophylline. • Step 4: severe persistent asthma: o Combination therapy with a high-dose ICS and LABA. o An alternative treatment option includes high-dose ICS and sustained-release theophylline. o An alternative treatment option includes high-dose ICS and a leukotriene modifier. o Oral corticosteroids can be used over the short-term. <u>General treatment consideration</u> • 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 ICS. • For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of ICS and a LABA. Alternatives are combinations of ICS with sustained-release theophylline or with leukotriene receptor antagonists.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory agents-corticosteroids are noted in Tables 3 and 4. 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 Single Entity Respiratory Agents-Corticosteroids[1-17]

Indication	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
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	✔			✔		✔	

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

Table 4. FDA-Approved Indications for the Combination Respiratory Agents-Corticosteroids[1-17]

Indication	Budesonide and Formoterol	Fluticasone Propionate and Salmeterol	Fluticasone Furoate and Vilanterol	Mometasone and Formoterol
Asthma				
Maintenance treatment of asthma as prophylactic therapy in patients ≥4 years of age		✔ †		
Maintenance treatment of asthma as prophylactic therapy in patients ≥12 years of age		✔ §		
Treatment of asthma in patients 12 years of age and older	✔			✔

Indication	Budesonide and Formoterol	Fluticasone Propionate and Salmeterol	Fluticasone Furoate and Vilanterol	Mometasone and Formoterol
Treatment of asthma in patients aged ≥18 years			✔	
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.
#Symbicort® 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
*Advair® 250/50 µg is the only strength FDA-approved for this indication.
COPD=chronic obstructive pulmonary disease.

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory agents-corticosteroids are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Respiratory Agents-Corticosteroids[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Beclomethasone	Not available	Not reported	Hepatic and respiratory	Renal (<10) Feces (main, percent not specified)	2.8
Budesonide	39	85 to 90	Hepatic extensive	Renal (60) Feces (15.1 to 29.6)	2.0 to 3.6
Ciclesonide	<1	≥99	Hepatic predominantly, respiratory	Renal (<20) Feces (66)	6 to 7
Flunisolide	39 to 40	Not reported	Hepatic, extensive	Renal (50) Feces (50)	1 to 2
Fluticasone furoate	13.9	>99	Hepatic, extensive	Renal (1) Feces (100)	24
Fluticasone propionate	18	91	Hepatic	Renal (<5) Feces (95)	3.2 to 11.2
Mometasone	<1	98 to 99	Hepatic, extensive	Renal (8) Feces (74)	5.0 to 5.8
Combination Products					
Budesonide and formoterol	B: 39 F: Not reported	B: 85 to 90 F: 31 to 64	Hepatic extensive	B: Renal (60) Feces (15.1 to 29.6) F: Renal (59 to 62) Feces (32 to 34)	B: 2.0 to 3.6 F: 7 to 10
Fluticasone propionate and salmeterol	F: 18 S: Not reported	F: 91 S: 96	Hepatic	F: Renal (<5) Feces (95) S: Renal (25) Feces (60)	F: 3.2 to 11.2 S: 5.5
Fluticasone furoate and vilanterol	F: 15.3 V: 27.3	F: >99 V: >93	F: Hepatic, extensive V: Hepatic, unknown	F: Renal (1) Feces (100) V: Renal (70) Feces (30)	F: 24 V: 16 to 21.3
Mometasone and formoterol	M: <1 F: Not reported	M: 98 to 99 F: 31 to 64	Hepatic, extensive	M: Renal (8) Feces (74) F: Renal (59 to 62) Feces (32 to 34)	M:5.0 to 5.8 F: 7 to 10

V. Drug Interactions

Significant drug interactions with the respiratory agents-corticosteroids are listed in Table 6.

Table 6. Significant Drug Interactions with the Respiratory Agents-Corticosteroids[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Budesonide, fluticasone	1	Human immunodeficiency virus (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

Generic Name(s)	Significance Level	Interaction	Mechanism
			HIV protease inhibitors may decrease the metabolic elimination of specific inhaled steroids. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur.
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.
Budesonide, 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.
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	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	Mifepristone	The pharmacologic effects of budesonide may be reduced. Mifepristone antagonizes the pharmacologic effects of budesonide. Coadministration of budesonide with mifepristone is contraindicated.
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 budesonide. Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of budesonide.

Significance level 1=major severity, significance level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the respiratory agents-corticosteroids are listed in Tables 7 to 8. The boxed warnings for the respiratory agents-corticosteroids containing a long-acting β_2-agonist are summarized in Tables 9 to 12.

Table 7. Adverse Drug Events (%) Reported with the Single Entity Respiratory Agents-Corticosteroids[1-17]

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Cardiovascular							
Arrhythmias	-	-	-	-	-	-	-
Chest pain	-	1 to 3†	<1	1 to 3	-	✔ §; 1 to 3†	-
Hypertension	-	-	-	-	-	-	-
Palpitations	-	-	<1	-	-	-	-
Syncope	-	1 to 3§	-	-	-	-	-
Central Nervous System							
Anxiety	-	-	-	-	-	✔ §†	-
Depression	-	-	-	-	-	✔ §†	-
Dizziness	-	-	≥3	1 to 3	-	✔ §; 1 to 3†	-
Drowsiness	-	-	-	-	-	-	-
Emotional lability	-	1 to 3†	-	-	-	✔ §†	-
Headache	12 to 15	13 to 14§	4.9 to 11	8.8 to 13.8	6 to 13	2 to 14§; 5 to 11†	17 to 22
Hyperkinesia	-	1 to 3†	-	-	-	✔ §†	-
Hypertonia	-	1 to 3§	-	-	-	-	-
Insomnia	-	1 to 3§	-	1 to 3	-	-	1 to 3
Migraine	-	1 to 3§	-	1 to 3	-	✔ §; 1 to 3†	-
Dermatological							
Angioedema	-	-	-	-	-	✔ §†	-
Ecchymosis	-	1 to 3§	<1	-	-	✔ §†	-
Eczema	-	1 to3†	-	-	-	-	-
Erythema multiforme	-	-	-	1 to 3	-	-	-
Pruritus	-	1 to 3†	-	-	-	✔ §†	-
Purpura	-	1 to 3†	-	-	-	-	-
Pustular rash	-	1 to 3†	-	-	-	-	-
Rash	-	1 to 4†	<1	-	-	-	-
Skin infection	-	-	-	-	-	✔ §; 1 to3†	-
Urticaria	-	-	-	-	-	-	-
Vasculitis	-	-	-	-	-	✔ §†	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Endocrine and Metabolic							
Cushingoid features	-	-	-	-	-	✔ §†	-
Edema	-	-	-	1 to 3	-	✔ §†	-
Hyperglycemia	-	-	-	-	-	✔ §†	-
Hypothyroidism	-	-	-	-	-	-	-
Osteoporosis	-	-	-	-	-	✔ §†	-
Gastrointestinal							
Anorexia	-	1 to 3†	-	-	-	-	1 to 3
Constipation	-	-	-	-	-	-	-
Diarrhea	-	2 to 4†	-	1 to 3	-	✔ §; 1 to 3†	-
Dry mouth	-	1 to 3§	<1	-	-	-	-
Dyspepsia	-	1 to 4§	<1	2.1 to 3.5	-	✔ §; 1 to 3†	3 to 5
Epigastric fullness	-	-	-	-	-	-	-
Flatulence	-	-	-	-	-	-	1 to 3
Gastroenteritis	-	1 to 3§; 4 to 5†	≥3	1 to 3	3	-	1 to 3
Gastrointestinal pain	-	1 to 3§; 2 to 3†	-	-	0 to 3	✔ §; 1 to 3†	2 to 3
Nausea	1 to 3	1 to 3§	<1	1 to 3	-	-	1 to 3
Oral candidiasis	-	2 to 4§	≥3	-	<1 to 3	1 to 9§; 2 to 5†	4 to 6
Taste alteration	-	1 to 3§	-	1 to 3	-	-	-
Vomiting	-	2 to 4†	-	0 to 4.6	-	-	1 to 3
Genitourinary							
Dysuria	-	-	-	-	-	<1§†	-
Polyuria	-	-	-	-	-	✔ §; <3†	-
Urinary tract infection	-	-	-	0.9 to 3.5	-	-	1 to 3
Vaginitis	-	-	-	1 to 3	-	-	-
Hematologic							
Enlarged lymph nodes	-	-	-	-	-	-	-
Musculoskeletal							
Arthralgia	-	-	≤4	-	≥3	-	-
Fracture	-	1 to 3§†	-	-	-	-	-
Myalgia	-	1 to 3§†	-	1 to 3	-	2 to 3	-
Respiratory							
Bronchitis	-	-	-	1 to 3	7 to 12	0 to 8§; 2 to 6†	-
Cold symptoms	-	-	-	-	-	-	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Coughing	1 to 3	5 to 8†	<1	1.8 to 8.5	0 to 3	1 to 5§; 4 to 6†	-
Dyspnea	-	✔ †	-	2.1 to 3.5	-	✔ §†	-
Hoarseness	-	-	-	-	-	✔ §; 2 to 6†	-
Increased asthma symptoms	3 to 8	-	-	-	-	✔ §†	-
Influenza	-	-	-	-	-	-	-
Lower respiratory infections	-	-	-	-	-	-	-
Nasal congestion	-	-	2 to 6	-	≥3	-	-
Nasopharyngitis				-	8 to 13	-	-
Pharyngitis	8 to 10	5 to 10§	7 to 11	16.6 to 17.5	3 to 6	✔ §†	11 to 13
Pneumonia	-	-	≥3	-	-	-	-
Rhinitis	6 to 11	7 to 12†	-	3.5 to 15.7	<1 to 3	✔ §†	11 to 15
Rhinorrhea	-	-	<1	-	-	-	-
Sinusitis	-	2 to 11§	≤6	4.1 to 8.8	4 to 7	6 to 10§; 4 to 7†	-
Stridor	-	1 to 3†	3 to 5	-	-	-	-
Throat irritation	-	-	<1	-	<1 to 3	-	-
Upper respiratory tract infection	9 to 12	19 to 24§; 34 to 38†	4 to 7	-	2 to 6	14 to 20§; 16 to 18†	8 to 15
Wheezing	-	✔ †	-	-	-	✔ §†	-
Other							
Back pain	1 to 4	2 to 6§	1 to 3	-	3	-	3 to 6
Blurred vision	-	-	-	-	-	-	-
Cataract	-	-	<1	-	-	-	-
Conjunctivitis	-	1 to 2†	≥3	1 to 3	-	-	-
Dysmenorrhea	1 to 3	-	-	1 to 3	-	-	4 to 9
Dysphonia	2 to 4	1 to 6§; 1 to 3†	<1	-	2 to 3	-	1 to 3
Ear pain	-	1 to 3†	≤2	1 to 3	-	-	1 to 3
Ear infection	-	2 to 5†	-	-	-	-	-
Epistaxis	-	2 to 4†	-	-	-	-	1 to 3
Eye infection	-	1 to 3†	-	-	-	-	-
Fever	-	2 to 4§	-	-	-	1 to 7§; 1 to 3†	-
Flu syndrome	-	6 to 14§; 1 to 3†	-	-	4 to 7	-	-
Hypersensitivity reaction	-	1 to 3†	-	4.2 to 4.6	-	-	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Infection	-	1 to 3§†	-	0.9 to 3.7	-	-	1 to 3
Intraocular pressure increased	-	-	<1	-	-	-	-
Moniliasis	-	3 to 4†	-	-	-	-	-
Neck pain	-	1 to 3§	-	1 to 3	-	-	-
Otitis media	-	9 to 12†	-	-	-	-	-
Pain	2 to 3	5§	0 to 3	-	-	✔ §; 1 to 3†	1 to 3
Poisoning/toxicity	-	-	-	-	-	-	-
Throat Pain	-	-	2 to 5	-	3 to 4	✔ §†	-
Toothache	-	-	-	-	<1 to 3	-	-
Viral infection	-	3 to 5†	-	-	-	-	-
Weight gain	-	1 to 3§	<1	-	-	✔ §†	-

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

Table 8. Adverse Drug Events (%) Reported with the Combination Respiratory Agents-Corticosteroids[1-17]

Adverse Event	Budesonide and Formoterol	Fluticasone Proprionate and Salmeterol	Fluticasone Furoate and Vilanterol	Mometasone and Formoterol
Ear, Nose, and Throat				
Candidiasis, oral	1.4 to 3.2	1 to 4	5	-
Hoarseness/dysphonia	<3	2 to 5	-	-
Nasal congestion	2.5 to 3.2	-	-	-
Nasopharyngitis	9.7 to 10.5	-	9	4.7
Pharyngitis	<3	10 to 13	≥3	-
Pharyngolaryngeal pain	6.1 to 8.9	-	≥3	-
Sinusitis	4.8 to 5.8	4 to 5	≥3	2.0 to 3.3
Upper respiratory infection	7.6 to 10.5	21 to 27	7	-
Upper respiratory inflammation	-	6 to 7	-	-
Lower Respiratory				
Bronchitis	<4	2 to 8	≥3	-
Cough	<4	3 to 6	≥3	-
Pneumonia	-	-	6	-
Viral respiratory infections	-	4	-	-
Neurology				
Headache	6.5 to 11.3	12 to 13	7	2.0 to 4.5
Gastrointestinal				
Gastrointestinal discomfort	1.1 to 6.5	1 to 4	-	-
Diarrhea	-	2 to 4	≥3	-
Influenza	2.4 to 3.2	-	≥3	-
Nausea/vomiting	1.4 to 3.2	4 to 6	-	-
Viral gastrointestinal infections	-	<3	-	-
Other				
Arthralgia	-	-	≥3	-
Back pain	1.6 to 3.2	-	≥3	-
Candidiasis, unspecified site	-	<3	-	-
Fever	-	-	≥3	-
Hypertension	-	-	≥3	-
Musculoskeletal pain	-	2 to 4	-	-
Peripheral edema	-	-	≥3	-

- Event not reported or incidence <1%.

Table 9. Boxed Warning for Budesonide and Formoterol[1]

WARNING
Long-acting beta-2 adrenergic agonists (LABAs) such as formoterol, one of the active ingredients in budesonide/formoterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of another LABA (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 the LABAs, including formoterol. 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 asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, only use budesonide/formoterol for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or for patients whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue budesonide/formoterol) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication such as an inhaled corticosteroid. Do not use budesonide/formoterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Table 10. Boxed Warning for Fluticasone Propionate and Salmeterol[1]

WARNING
Long-acting beta-2 adrenergic agonists such as salmeterol may increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths of 13,176 patients treated for 28 weeks on salmeterol vs 3 deaths of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma-control drugs mitigates the increased risk of asthma-related death from long-acting beta-2 adrenergic agonists. Available data from controlled clinical trials suggest that long-acting beta-2 adrenergic agonists increase the risk of hospitalization in children and adolescents. Therefore, when treating patients with asthma, only prescribe fluticasone propionate-salmeterol 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 long-acting beta-2 adrenergic agonist. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue fluticasone propionate -salmeterol) if possible without loss of asthma control, and maintain the patient on a long-term asthma-control medication, such as an inhaled corticosteroid. Do not use fluticasone propionate -salmeterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Table 11. Boxed Warning for Mometasone and Formoterol[1]

WARNING
Long-acting beta$_2$-adrenergic agonists (LABAs), such as formoterol, one of the active ingredients in mometasone/formoterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of another LABA (salmeterol) with 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 the LABAs, including formoterol. 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 asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, use mometasone/formoterol only in patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or in patients whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals, step down therapy (e.g., discontinue mometasone/formoterol) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication such as an inhaled corticosteroid. Do not use mometasone/formoterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Table 12. Boxed Warning for Fluticasone Furoate and Vilanterol[1]

WARNING
Long-acting beta$_2$-adrenergic agonists (LABAs), such as vilanterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of another LABA (salmeterol) with 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 the LABAs, including vilanterol. 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 asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, use fluticasone furoate-vilanterol only in patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or in patients whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once

WARNING

asthma control is achieved and maintained, assess the patient at regular intervals, step down therapy (e.g., discontinue fluticasone furoate-vilanterol) 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 fluticasone furoate-vilanterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

VII. Dosing and Administration

The usual dosing regimens for the respiratory agents-corticosteroids are listed in Table 13. The estimated comparative daily doses for the available products are listed in Table 14.

Table 13. Usual Dosing Regimens for the Respiratory Agents-Corticosteroids[1-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Beclomethasone	Asthma: Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators: initial, 40 to 80 µg BID; maximum, 320 µg BID; patients treated previously with an inhaled corticosteroid; initial, 40 to 160 µg BID; maximum, 320 µg BID	Asthma: Meter dose aerosol inhaler (HFA): 5 to 11 years of age: 40 µg BID; maximum, 80 µg BID	Meter dose aerosol inhaler (HFA): 40 µg 80 µg
Budesonide	Asthma: Dry powder inhaler: initial, 360 µg BID (selected patients can be initiated at 180 µg BID); maximum, 720 µg BID	Asthma: Dry powder inhaler: children six to 17 years of age; initial, 180 µg BID (selected patients can be initiated at 360 µg BID); maximum, 360 µg BID Suspension for nebulization: children 12 months to eight years of age treated previously with only bronchodilators; initial, 0.5 mg total daily dose administered either QD or in divided doses; maximum, 0.5 mg total daily dose; children 12 months to eight years of age treated previously with an inhaled corticosteroid; initial, 0.5 mg total daily dose administered either QD or BID in divided doses; maximum, 1 mg total daily dose; children 12 months to eight years of age treated previously with an oral corticosteroid; initial, 1 mg total daily dose administered either as 0.5 mg BID or 1 mg QD; maximum, 1 mg total daily dose	Dry powder inhaler: 90 µg 180 µg Suspension for nebulization: 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL
Ciclesonide	Asthma:	Not indicated for children <12	Meter dose aerosol

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 80 µg BID; maximum, 160 µg BID; patients treated previously with an inhaled corticosteroid; initial, 80 µg BID; maximum, 320 µg BID; patients treated previously with oral corticosteroids; initial, 320 µg BID; maximum, 320 µg BID	years of age.	inhaler (HFA): 80 µg 160 µg
Flunisolide	Asthma: Meter dose aerosol inhaler (HFA): patients 12 years of age and older; initial 160 µg BID; maximum, 320 µg BID	Asthma: Meter dose aerosol inhaler (HFA): children six to 11 years of age; initial 80 µg BID; maximum, 160 µg BID	Aerosol inhaler: 80 µg
Fluticasone furoate	Asthma: Dry powder inhaler: 1 inhalation once daily, beginning with 100 or 200 µg based on previous therapy; maximum, 200 µg daily	Safety and efficacy in children <12 years of age have not been established.	Dry powder inhaler: 100 µg 200 µg
Fluticasone propionate	Asthma: Dry powder inhaler: patients treated previously with only bronchodilators; initial, 100 µg BID; maximum, 500 µg BID; patients treated previously with an inhaled corticosteroid; initial, 100 to 250 µg BID; maximum, 500 µg BID; patients treated previously with oral corticosteroids; initial, 500 to 1,000 µg BID; maximum, 1,000 µg BID Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 88 µg BID; maximum, 440 µg BID; patients treated previously with an inhaled corticosteroid; initial, 88 to 220 µg BID; maximum, 440 µg BID; patients treated previously with oral corticosteroids; initial, 440 µg BID; maximum, 880 µg BID	Asthma: Dry powder inhaler: children four to 11 years of age treated previously with only bronchodilators or with inhaled corticosteroids; initial, 50 µg BID; maximum, 100 µg BID Meter dose aerosol inhaler (HFA): children four to 11 years of age; initial 88 µg BID; maximum, 88 µg BID	Dry powder inhaler (Diskus®): 50 µg 100 µg 250 µg Meter dose aerosol inhaler (HFA): 44 µg 110 µg 220 µg
Mometasone	Asthma: Dry powder inhaler: patients treated previously with only bronchodilators or inhaled	Asthma: Dry powder inhaler: children four to 11 years of age; initial, 110 µg QD in the evening;	Dry powder inhaler (Twisthaler®): 110 µg 220 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	corticosteroids; initial, 220 µg QD in the evening; maximum, 440 µg administered as QD in the evening or as 220 µg BID; patients treated previously with oral corticosteroids; initial, 440 µg BID; maximum, 880 µg daily Meter dose aerosol inhaler (HFA): patients treated previously with inhaled medium-dose corticosteroids; initial, 100 µg 2 inhalations BID; patients treated previously with high-dose oral corticosteroids; initial, 200 µg 2 inhalations BID; maximum, 2 inhalations of 200 µg BID	maximum, 110 µg QD in the evening Safety and efficacy of meter dose aerosol inhaler (HFA) in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA): 100 µg 200 µg
Combination Products			
Budesonide and formoterol	Asthma: Meter dose aerosol inhaler (HFA): initial, two inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, for patients who do not respond adequately to the starting dose after one to two weeks with 80-4.5 µg, consideration to using 160-4.5 µg can be made to provide additional asthma control; maximum, 160-4.5 µg BID COPD*†: Meter dose aerosol inhaler (HFA): 160/4.5 µg, two inhalations BID	Safety and efficacy in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA): 80-4.5 µg 160-4.5 µg
Fluticasone propionate and salmeterol	Asthma: Dry powder inhaler: initial, one inhalation BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 500-50 µg BID	Asthma in children >4 years of age: Dry powder inhaler: 100-50 µg one inhalation BID (initial dose is indicated for patients not currently on an inhaled corticosteroid and whose treatment warrants the initiation of two maintenance therapies) Safety and efficacy in children <4 years of age have not been established for the dry powder	Dry powder inhaler: 100-50 µg 250-50 µg 500-50 µg Meter dose aerosol inhaler (HFA): 45-21 µg 115-21 µg 230-21 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Meter dose aerosol inhaler (HFA): initial, two inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 230-21 µg two inhalations BID COPD*‡: Dry powder inhaler: 250-50 µg one inhalation BID	inhaler. Safety and efficacy in children <12 years of age have not been established for the meter dose aerosol inhaler (HFA).	
Fluticasone furoate and vilanterol	Asthma: Dry powder inhaler: one 100-25 µg or 200-25 µg inhalation once daily; maximum, 200-25 µg inhalation once daily COPD: Dry powder inhaler: one 100-25 µg inhalation once daily	Safety and efficacy in children <18 years of age have not been established.	Dry powder inhaler: 100-25 µg 200-25 µg
Mometasone and formoterol	Asthma: Meter dose aerosol inhaler (HFA): initial, 100-5 µg two inhalations BID if previous therapy with medium dose inhaled corticosteroid or 200-5 µg two inhalations BID if previous therapy with high dose inhaled corticosteroid; maintenance, two inhalations BID; maximum, 200-5 µg two inhalations BID	Safety and efficacy in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA): 100-5 µg 200-5 µg

*Including bronchitis and/or emphysema.
†Symbicort® 160-4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
‡Advair® 250-50 µg is the only strength FDA-approved for this indication.
BID=twice daily, COPD=chronic obstructive pulmonary disease, HFA=hydrofluoroalkane, QD=once daily

Table 14. Estimated Comparative Daily Doses for the Respiratory Agents-Corticosteroids[18]

Adolescents ≥12 Years of Age and Adults*			
Generic Name	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)**
Beclomethasone HFA	80 to 240	>240 to 480	>480
Budesonide DPI	180 to 600	>600 to 1,200	>1,200
Flunisolide HFA	320	>320 to 640	>640
Fluticasone propionate HFA	88 to 264	>264 to 440	>440
Fluticasone propionate DPI	100 to 300	>300 to 500	>500
Mometasone DPI	200	400	>400

Adolescents ≥12 Years of Age and Adults*			
Triamcinolone	300 to 750	>750 to 1,500	>1,500
Children 5 to 11 Years of Age*			
Generic Name	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)**
Beclomethasone HFA	80 to 160	>160 to 320	>320
Budesonide DPI	180 to 400	>400 to 800	>800
Budesonide neb	0.5 mg	1.0 mg	2.0 mg
Flunisolide HFA	160	320	≥640
Fluticasone propionate HFA	88 to 176	176 to 352	>352
Fluticasone propionate DPI	100 to 200	>200 to 400	>400
Mometasone	NA	NA	NA
Triamcinolone	300 to 600	>600 to 900	>900
Children 0 to 4 Years of Age*			
Generic Name	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)**
Beclomethasone HFA	NA	NA	NA
Budesonide DPI	NA	NA	NA
Budesonide neb	0.25 to 0.5 mg	>0.5 to 1.0 mg	>1.0 mg
Flunisolide HFA	NA	NA	NA
Fluticasone propionate HFA	176	>176 to 352	>352
Fluticasone propionate DPI	NA	NA	NA
Mometasone	NA	NA	NA
Triamcinolone	NA	NA	NA

*Comparative dosages are based on published comparative clinical trials.[16]
DPI=dry powder inhaler, HFA=hydrofluoroalkane, NA=not approved

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory agents-corticosteroids are summarized in Table 15.

Table 15. Comparative Clinical Trials with the Respiratory Agents-Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Tinkelman et al.[28] (2003) Budesonide 100 to 800 µg QD via DPI	OL for 52 weeks following two weeks to five months of treatment in one of four DB, PC studies Adults with persistent asthma not receiving corticosteroids, adults and children previously maintained on ICS, and adults previously maintained on oral corticosteroids	N=1,133 52 weeks	Primary: FEV_1 and oral corticosteroid use Secondary: Plasma cortisol levels and adverse events	Primary: The mean FEV_1 values continued to improve in all patient populations through week six of OL treatment and were sustained for the remainder of the 52-week study. Patients who had not received prior ICS treatment demonstrated the greatest improvement in FEV_1 (67.1±18.0 to 81.2±14.8%). Of the 144 oral corticosteroid-dependent patients, 64 entered the OL 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 µg of budesonide BID. Basal and stimulated cortisol levels increased by 20.7±183.3 and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 µg of budesonide BID. Thirty-three patients discontinued treatment due to adverse events. Of these patients, the relationship between budesonide therapy and the adverse events was none in 18 patients, unlikely in four patients, possible in eight patients, likely in one patient, and highly likely in two 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.
Rowe et al.[29] (1999) Budesonide 1,600	DB, PC, RCT Patients 16 to 60 years of age	N=1,006 21 days	Primary: Rates of relapse Secondary:	Primary: The budesonide group experienced fewer relapses (12 patients, 12.8%; 95% CI, 7 to 21) compared to the placebo group (23 patients, 24.5%; 95% CI, 16 to 34) by 21 days (P=0.049). This represents a 48% relapse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/day via DPI vs placebo	presenting to the emergency department with acute asthma who were discharged with a course of oral prednisone (50 mg/day) for seven days		Quality of life, rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects and compliance	reduction and suggests as few as nine patients would require treatment with budesonide to prevent one relapse. Secondary: Quality of life scores were higher in the budesonide group compared to the placebo group (P=0.001). The budesonide group used fewer mean albuterol inhalations/day compared to the placebo group (2.4 vs 4.2; P=0.01). The mean and percent predicted peak flow and spirometry findings revealed no differences between the groups. At the conclusion of the study, patients in 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 to patients receiving placebo. Patients in the budesonide group assessed their asthma as more improved than those in the placebo group at the 21-day follow-up (6.2 vs 5.2; P=0.001). Adverse events were more frequent in the placebo group for both hoarseness and sore throat (P=0.02). The overall incidence of adverse events 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 seven (100% for both groups) and 21 days (92% for budesonide vs 93% for placebo; P=0.95).
Sheffer et al.[30] (2005) START Budesonide 200 to 400 µg QD via	DB, PC, RCT (first three years); OL (following two years) Patients five to 66	N=7,241 5 years	Primary: Time to the first severe asthma-related event, change in post-bronchodilator	Primary: Budesonide reduced the risk of a first severe asthma-related event in patients with mild persistent asthma by 44% (HR, 0.56; 95% CI, 0.45 to 0.71; P<0.001). A significant improvement in both pre bronchodilator and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DPI vs placebo Treatment was added to existing asthma therapy.	years of age with mild persistent asthma for less than two years and with no previous regular corticosteroid treatment		FEV_1 percent predicted Secondary: Number of asthma-related events during the DB period, time to first addition of a steroid treatment (systemic or inhaled) during the DB period, symptom-free days, data on healthcare utilization, days off work, and lost school days	postbronchodilator FEV_1 percent values was observed after years one and three of the study for the budesonide treatment group compared to the placebo group. After one year, the differences were 2.24% pre bronchodilator and 1.48% postbronchodilator (P<0.0001 for both) and after three years were 1.71%, (P<0.0001) and 0.88% (P=0.0005), respectively. 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 corticosteroids over time compared to the placebo group (31 vs 45%, respectively; P<0.001). An improvement from baseline in symptom-free days occurred for both the budesonide and placebo groups over time. Patients receiving budesonide had significantly more symptom-free days over the three-year study period compared to patients receiving placebo (P<0.001).
Busse et al.31 (2008) START Budesonide 200 to 400 µg QD via DPI vs placebo Treatment was added to existing asthma therapy. Randomization was for 3 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 >15% after exercise challenge, or variation >15% between the 2	N=7,221 5 years	Primary: Change from baseline in postbronchodilator percent predicted FEV_1 Secondary : Change in pre bronchodilator percent predicted FEV_1;the number of SAE; change in asthma-related symptoms; use of concomitant asthma medication to achieve asthma	Primary: During the full five-year study period, the postbronchodilator percent predicted FEV_1 decreased, irrespective of randomized treatment during the DB 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 five-year study period, pre bronchodilator percent predicted FEV_1 increased, irrespective of randomized treatment during the DB 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 five-year treatment period. During the three-year DB phase, 315 patients (117 in the budesonide group and 198 in the reference group) experienced one or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by OL treatment for 2 years.	highest and 2 lowest PEF rates in 14 days		control	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 one or more SAE during the two-year OL phase, with the risk being similar in the two treatment groups (OR, 1.12; P=0.76). The cumulative risk of having one or more SAE during the full five 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 DB treatment phase were maintained or further improved during the subsequent two years of OL budesonide treatment. Between-group differences, which existed during the DB phase, were, however, no longer statistically significant during the OL phase. The percentage of symptom-free days increased among patients in both treatment groups throughout the five-year study period, and the differences between groups were no longer significant during the OL phase. Patients who received budesonide during the DB treatment phase used significantly less additional asthma medication during the OL treatment phase. Significantly fewer patients in the budesonide group required additional ICS (10.4 vs 14.6%; P<0.001) or LABA (6.3 vs 9.3%; P<0.001) in addition to their budesonide treatment by year five.
Agertoft et al.[32] (2000) Budesonide vs control group Patients were enrolled in a one to two year run-in period where their	PRO Children with asthma	N=332 10 years	Primary: Measured adult height in relation to the target adult height Secondary: Difference between measured height and target adult height in relation to mean cumulative	Primary: The measured and target adult height was 173.2 and 172.9 cm, respectively, in the budesonide group and 173.9 and 174.1 cm, respectively, in the control group. The mean differences between the measured and target adult heights were 0.3 cm (95% CI, -0.6 to 1.2) for the budesonide group, and -0.2 cm (95% CI, -2.4 to 2.1) for the control group. Secondary: Twenty children in the budesonide group did not achieve their adult height. Their mean cumulative dose of 1.25 g was not significantly different from that of children who had attained their adult height, which was 1.35 g (P=0.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
asthma medication was adjusted according to Danish guidelines. Patients considered controlled without continuous ICS use, were then asked to change treatment to budesonide.			budesonide dose, duration of treatment, patient gender, age at beginning of budesonide treatment, age at which adult height was obtained, duration of asthma before budesonide start growth rate of budesonide treatment compared to the run-in period	There was no significant correlation between the duration of treatment and the differences between the measured and target adult heights (P=0.16). The difference between measured and target adult heights was not associated with gender (P=0.30), age at the beginning of budesonide treatment (P=0.13), age at which adult height was attained (P=0.82) or duration of asthma before the start of budesonide treatment (P=0.37). Budesonide was associated with a significant change in growth rate during the first years of treatment compared to the run-in period. The mean growth rate was 6.1 cm/year (95% CI, 5.7 to 6.5) during the run-in period, 5.1 cm/year (95% CI, 4.7 to 5.5; P<0.001) during the first year of treatment, 5.5 cm/year (95% CI, 5.1 to 5.9; P=0.02) during the second year of treatment and 5.9 cm/year (95% CI, 5.5 to 6.3; P=0.53) during the third year of treatment. Changes in growth rate during this period were not correlated with the differences between measured and target adult heights (P=0.44). The initial growth retardation was correlated with age, with a more pronounce reduction in younger children (P=0.04). Children with a low SD score for height before budesonide treatment had a smaller adult height than expected (P<0.001).
Baker et al.[33] (1999) Budesonide 0.25 mg BID via nebulizer vs budesonide 0.5 mg BID via nebulizer vs budesonide 1mg AM and placebo	DB, MC, PC, PG, RCT Children, six months to eight years of age, with a diagnosis of asthma	N=480 12 weeks	Primary: Changes in asthma symptom improvement score from baseline, PEF and improvements in FEV_1 Secondary: Not reported	Primary: When symptom scores for all active treatment groups were combined, a statistically significant difference between budesonide and placebo was seen as early as day two for nighttime asthma symptoms, and day five for daytime asthma symptoms (P<0.05). There were statistically significant improvements in morning PEF in the budesonide 0.25 mg BID (10.9 L/minute), 0.5 mg BID (24.8 L/minute) and 1 mg QAM (17.1 L/minute) treatment groups compared to placebo (P<0.030 for all) and in evening PEF for each active treatment group (16.8 L/minute for 0.25 mg QAM; P<0.05, 19.2 L/minute for 0.25 mg BID, P<0.05; and 21.0 L/minute for 0.5 mg BID; P<0.010) except 1 mg QAM (14.1 L/minute; P value not reported). All treatment groups experienced a numerical improvement in FEV_1; however, only the improvement with budesonide 0.5 mg BID dose was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PM via nebulizer vs placebo				statistically significant compared to placebo (P=0.031). Secondary: Not reported
Kerwin et al.[34] (2008) (Abstract) Budesonide 400 µg BID (dry powder inhaler [DPI-A]) vs budesonide 360 µg BID (redesigned dry powder inhaler [DPI-B]) vs budesonide 200 µg BID (dry powder inhaler [DPI-A]) vs budesonide 180 µg QD (redesigned dry powder inhaler [DPI-B]) vs placebo	DB, MC, PG, RCT Adult patients with mild to moderate asthma and patients 6 to 17 years of age with mild asthma.	N=1,137 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Change is asthma symptoms, β-agonist use, PEF and worsening asthma	Primary: There were significant improvements in FEV_1 for all treatment groups compared to placebo (P<0.05), except DPI-B 180 µg. Secondary: For the adult patients, there were significant greater improvements in all secondary endpoints for all treatment groups compared to placebo (P<0.05). For the pediatric patients, there were significant improvements in PEF in the DPI-B 360 µg BID group compared to placebo (P≤0.011). There were no other significant differences reported. Adverse event profiles were similar for the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sheikh et al.[35] (1999) Flunisolide 1,500 µg/day for a period of one year then crossed over to fluticasone propionate 880 µg/day for one year	AC, OL, XO Children with moderate to severe asthma with a mean age of 12.7 years	N=30 2 years	Primary: Mean percent predicted values for FVC, FEV_1, $FEF_{25\ to\ 75\%}$ and PEFR Secondary: Not reported	Primary: There were significant improvements in all clinical parameters in patients treated with fluticasone propionate compared to patients treated with flunisolide. There was a significant improvement in FVC during the two to six and seven to 12-month periods after switching to fluticasone propionate. Significant improvements were noted in FEV_1 and $FEF_{25\ to\ 75\%}$ at all time points evaluated after switching to fluticasone propionate. There was no significant difference in PEFR between groups at any time period. Secondary: Not reported
Chiu et al.[36] (2014) Budesonide two 200 µg inhalations BID vs ciclesonide two 160 µg inhalations QD	MC, OL, PG, RCT Patients with mild-to-moderate asthma well controlled by a combination of ICS and long-acting β_2-agonist changing to step-down therapy	N=150 12 weeks	Primary: improvement in FEV_1 Secondary: FVC, maximum mid-expiratory flow (MMEF), ACT score, adherence	Primary: The FEV_1 in the ciclesonide group remained stable throughout the treatment period. The FEV_1 (before bronchodilators) of the ciclesonide group (2.2 l; 95% CI, 2.0 to 2.4) was significantly higher than that of the budesonide group (1.9 l; 95% CI, 1.7 to 2.1; P=0.02) at four weeks and at the end of 12 weeks (2.0 l; 95% CI, 1.8 to 2.3; P=0.03) of step-down therapy. Secondary: Patients in the ciclesonide group maintained a stable FVC throughout the 12-week treatment, whereas that of patients receiving budesonide decreased after four weeks of treatment (2.8 l; 95% CI, 2.5 to 3.0 l) compared with baseline (2.9 l; 95% CI, 2.7 to 3.1). However, there was no significant difference between the two groups throughout the 12 weeks of treatment. Patients in the ciclesonide group had a higher rate of treatment adherence (76%) than those in the budesonide group (59%; P=0.03). In the ciclesonide group, patients maintained MMEF, a measurement of the small airway function, during the step-down therapy. The MMEF in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the ciclesonide group was higher than that of the budesonide group (P=0.02). The ACT scores were not significantly different between the two groups at baseline, but improved in the ciclesonide group after four and eight weeks of treatment compared with baseline (P=0.02 and 0.04, respectively).
Vogelmeier et al.[37] (2011) Ciclesonide 160 µg QD All treatment decisions were left to the discretion of the investigator (dose and concomitant rescue medication).	3 MC, OL, OS, PRO Patients 12 years of age and older with persistent, mild to moderate asthma who newly started or switched to treatment with ciclesonide	N=24,037 3 months	Primary: Change from baseline in FEV_1 and symptomatic improvements Secondary: Adverse events and changes in rescue medication use	Primary: The mean FEV_1 was increased from 2.66 L (95% CI, 2.65 to 2.67) at baseline to 3.00 L (95% CI, 2.99 to 3.01) following three months treatment with ciclesonide. This represents an increased from 80.7% (95% CI, 80.5 to 80.9) to 90.1% (96% CI, 89.9 to 90.2) of predicted values. Ciclesonide treatment was associated with a significant increase in PEF of 14% from baseline (from 338 L/min [95% CI, 335 to 340] to 392 L/min [95% CI, 390 to 395]). The concentration of NO significantly decreased from 53.6 PPB (95% CI, 51.8 to 55.4) to 26.2 PPB (95% CI, 25.2 to 27.1), representing a 51% reduction with ciclesonide treatment. The proportion of patients with daily daytime symptoms was reduced from 24.3 to 1.9% after three months of ciclesonide treatment. The proportion of patients with symptoms that occurred >1 day per week was reduced from 59.4 to 24.4% with ciclesonide treatment (P values not reported). The proportion of patients reporting less frequent symptoms (<1 day per week) increased from 14.1 to 68.9% with ciclesonide treatment. A similar improvement was observed for night-time symptoms. The number of nights of the preceding month with nocturnal symptoms decreased from 5.4±5.1 days at baseline to 2.5±2.8 days with ciclesonide treatment. The proportion of patients with impaired sleep quality was reduced from 39.8% at baseline to 8.2% after three months of ciclesonide treatment. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported in 0.2% of patients receiving ciclesonide treatment. Most adverse events were mild or moderate in severity. The most commonly reported adverse events were dysphonia (n=11) and cough (n=10). The proportion of patients with daily use of β_2-agonists decreased from 26.9% at baseline to 8.8% after three months of ciclesonide treatment.
Bateman et al.[38] (2006) Ciclesonide 320 µg BID vs ciclesonide 640 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for at least one year prior to screening, were corticosteroid dependant with severe asthma and use of oral prednisone at least every other day for five to six months prior to screening, a history of ICS during the six months prior to screening, use of a β_2-agonist for asthma control the two weeks prior to screening, an FEV_1 between 40 to 80% of predicted normal following a six-hour β_2-agonist treatment withholding period	N=141 12 weeks	Primary: Percent change from baseline in oral prednisone dose Secondary: Percentage of patients who were able to completely discontinue prednisone, change in morning pre-dose FEV_1, change in morning PEF, change in albuterol utilization, change in asthma symptom score, assessment of HPA-axis suppression and adverse events	Primary: The percent reduction in oral prednisone dose was statistically significant in both treatment groups (-47.39% for the 320 µg BID group; P=0.0001, -62.54% for the 640 µg BID group; P=0.0001 and 4.21% for the placebo group). Secondary: The percent of patients who were able to eliminate their prednisone usage was statistically significant in both treatment groups when compared to the placebo group (29.8% in the 320 µg BID group; P=0.0386, 31.3% in the 640 µg BID group; P=0.0233 and 11.1% in the placebo group). Both treatment groups demonstrated statistically significant improvements in FEV_1 compared to the placebo group (0.17 L for the 320 µg BID group; P=0.0237, 0.17 L for the 640 µg BID group; P=0.0277). Neither treatment group experienced a statistically significant improvement in PEF compared to the placebo group (5.02 L/min for the 320 µg BID group; P=0.5803, 16.67 L/min for the 640 µg BID group; P=0.0736). Neither treatment group experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (P>0.05 for both). The total asthma symptom score (zero to five scale) was not statistically significant compared to the placebo group for either treatment group (change for the 320 µg BID group, 0.33; P=0.2669, change for the 640 µg BID group, -0.07; P=0.8197).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At baseline the percentage of patients with suppressed HPA-axis was 66.0, 60.4 and 62.2% and at week 12 it was 46.8, 43.8 and 53.3% in the 320 µg BID group, 640 µg BID and placebo groups, respectively. The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (320 µg BID, 85.1%; 640 µg BID, 79.6%; placebo, 88.9%). The most common adverse event that occurred in at least 5% of patients for the treatment groups were aggravated asthma, upper respiratory infection, headache, sinusitis and nasopharyngitis.
Erin et al.[39] (2008) Ciclesonide 320 µg, 1 inhalation QD vs ciclesonide 640 µg, 1 inhalation BID vs placebo	DB, PC, RCT, XO 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: NO exhalation (two hours after inhalation), pulmonary function test (two to five minutes after inhalation), adenosine monophosphate challenge five hours after inhalation) and sputum induction Secondary: Not reported	Primary: Ciclesonide 320 and 640 µg produced significantly greater improvements in FEV_1 compared with placebo on days one, three, and seven (all P<0.0001). Compared with placebo, ciclesonide 320 and 640 µg improved median exhaled NO levels by -22.6 and -20.7 PPB after seven days, respectively (P<0.001 for both). Although not statistically significant, sputum eosinophils decreased after seven days of ciclesonide treatment. Secondary: Not reported
Brenner et al.[40] (2000) Flunisolide 2 mg/day vs placebo	PC, RCT Patients 18 to 50 years of age with a diagnosis of asthma presenting to the emergency department with an acute asthma	N=104 24 days	Primary: 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 to 27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
At discharge, all patients were given prednisone 40 mg/d x 5 days and inhaled β-agonists as needed.	exacerbation			
Lee-Wong et al.[41] (2002) Flunisolide 2,000 µg BID via spacer vs placebo Patients were also randomized to receive oral prednisone or placebo.	DB, PC, RCT Patients 18 to 55 years of age admitted to the emergency department for an acute asthma exacerbation	N=40 7 days	Primary: PEFR, FEV_1 Secondary: Change in asthma symptom scores	Primary: From day one to day seven, mean PEFR increased from 190 to 379 L/min in the ICS group, and from 207 to 347 L/min in the prednisone group (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).
O'Byrne et al.[42] (2014) Fluticasone furoate 50 µg inhaled QPM vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and treatment with non-ICS, FEV_1 ≥60% predicted, and reversibility with albuterol or salbutamol	N=248 12 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily morning and evening PEF averaged, percentage of symptom-free 24-hour periods, number of	Primary: Pre-dose FEV_1 at week 12 for the fluticasone furoate group was 157 mL as compared to 38 mL in the placebo group, resulting in a treatment difference of 120 mL (P=0.012). The per protocol population was similar, with a treatment difference in favor of fluticasone furoate 50 mcg of 131 mL; 95% CI, 38 to 224; P=0.006). Secondary: There was a significant improvement in the percentage of rescue-free 24-hour periods in patients treated with fluticasone furoate (28.7%) compared to placebo (17.1%), resulting in a treatment difference of 11.6% (P=0.004). This equated to an additional 0.8 rescue-free 24-hour periods per week with fluticasone 50 µg treatment. Change from baseline in evening PEF over the 12-week treatment period

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			withdrawals due to lack of efficacy, ACT test score, percentage of patients controlled, AQLQ total score, ease of use of the ELLIPTA® dry powder inhaler	was increased with treatment with fluticasone furoate 50 µg (22.8 L/min) and placebo (19.5 L/min), but the treatment difference (3.3 L/min) was not statistically significant (P=0.536). Due to this, significance could not be inferred for the remaining endpoints. Morning PEF was numerically increased and greater for fluticasone furoate 50 µg (34.5 L/min) compared with placebo treatment (22.9 L/min; treatment difference of 11.6 L/min). Increase from baseline in the percentage of symptom-free 24-hour periods was also numerically greater for fluticasone furoate 50 µg (22.6%) compared with placebo treatment (14.0%; treatment difference of 8.6%), which equates to an additional 0.6 symptom-free 24-hour periods per week with fluticasone furoate treatment. A numerically greater proportion of patients in the placebo group withdrew due to lack of efficacy (14%) compared with patients in the fluticasone furoate 50 µg group (6%) Numerically greater increases in ACT scores, proportion of patients with an ACT score ≥20 and change from baseline in total AQLQ scores were observed for fluticasone furoate 50 µg compared with placebo. At baseline, most patients were able to use the ELLIPTA® inhaler correctly after being instructed once (98% fluticasone furoate; 96% placebo). At week four, most patients rated the ELLIPTA® inhaler as 'easy/very easy' to use (97%) and 'easy/very easy' to see how many doses of medication were left in the inhaler (95%).
Woodcock et al.[43] (2011) Fluticasone furoate 200 µg inhaled QAM vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma, FEV_1 50 to 80% predicted, and reversibility with	N=545 8 weeks	Primary: Pre-dose FEV_1 Secondary: Safety	Primary: Pre-dose FEV_1 was significantly improved for each of the fluticasone furoate treatment arms compared to placebo at week eight (P=0.033 for 200 µg once-daily arms, P<0.001 for 400 µg once daily and 200 µg twice daily arms). Fluticasone furoate 400 µg once daily in the evening resulted in similar placebo-adjusted improvements in evening pre-dose FEV_1 at week eight compared with 200 µg twice daily (240 mL compared with 235 mL).

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fluticasone furoate 400 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone furoate 200 µg inhaled BID vs placebo	inhaled salbutamol			Fluticasone furoate 200 µg twice daily resulted in greater improvements in placebo-adjusted morning pre-dose FEV_1 than 400 µg once daily in the morning at week eight (315 mL compared with 202 mL). A ≥200 mL increase in placebo-adjusted pre-dose FEV_1 was observed for the 400 µg once daily in the morning or evening groups and for 200 µg twice daily group but not for either of the 200 µg once daily groups. However, the increase from baseline was ≥200 mL with both 200 µg once daily groups. Results for the per protocol population were consistent with those of the intention to treat population; although, the relative treatment effect of all active treatment groups was generally lower. The effect of fluticasone furoate 200 µg once daily in the evening FEV_1 was not significantly different from placebo (P=0.264). Secondary: The proportion of patients who reported any adverse event during the treatment period was 28% in the placebo group and 31 to 39% in the active treatment groups. The most frequently reported adverse events during treatment were headache (6 to 9%), nasopharyngitis (3 to 8%), bronchitis (0 to 4%), pharyngolaryngeal pain (<1 to 3%), and upper respiratory tract infection (<1 to 3%). The incidence and type of adverse events were generally similar to placebo and the frequency of adverse events did not appear to be related to the dose of fluticasone furoate. A total of four serious adverse events were reported, with angioedema the only one considered to be possibly related to the study drug. A total of 11 patients reported 13 adverse events that resulted in study withdrawal: three patients in the 200 µg once-daily morning group, one in the 200 µg once-daily evening group, three in the 400 µg once-daily morning group, three in the 400 µg once-daily evening group and one in the 200 µg twice-daily group. There was no safety concerns related to vital signs, or laboratory safety tests. No treatment-related changes were apparent. The incidence of oral

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				candidiasis was low in the active treatment groups (0%to 4% compared with <1% for placebo) as was the incidence of asthma exacerbations (<1 to 4% compared with 14% for placebo).
Medley et al.[44] (2012) Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs placebo BID (QAM and QPM)	DB, DD, MC, PC, PG, RCT Patients 16 to 55 years of age with a diagnosis of persistent asthma and PEF 50 to 90% predicted; reversibility with inhaled salbutamol	N=578 28 days	Primary: Change from baseline in pre-treatment daily trough PEF between morning and evening doses Secondary: FEV1, PEF, percentage of symptom-free 24-hour periods, symptom-free days and nights, nights with no awakenings, rescue medication-free 24-hour periods, and withdrawals due to lack of efficacy, adverse events	Primary: The mean difference in trough PEF between fluticasone furoate 100 µg once daily in the morning compared with 100 µg once daily in the evening was 13.4 L/min (95% CI, 2.3 to 24.4). However, the placebo response was greater in the morning than in the evening (18.8 L/min compared with 8.8 L/min. All fluticasone furoate groups were associated with a statistically significant improvement in trough PEF compared to placebo (P<0.001 for 100 µg QAM and 250 µg QPM, P=0.005 for 100 µg QPM). There was an indication that the 250 µg once daily in the evening produced greater increases in PEF than 100 µg once daily in the evening (by 6.7 L/min), but the difference was not statistically significant. Secondary: Analyses of change from baseline in pre-dose FEV_1 found substantial improvements from baseline in FEV_1 that were greater with fluticasone furoate (203 to 317 mL) than with placebo (99 mL). However, statistical superiority of any dose was not demonstrated. When compared to placebo, fluticasone propionate was associated with a significant reduction in symptoms, rescue medication taken, and night-time awakenings (all P<0.001; except: P=0.001 for percent symptom-free days with 100 µg evening; P=0.006 for percent symptom-free nights with 100 µg in the morning, and P=0.002 for percent rescue medication-free days with 100 µg in the evening). Analysis of the effect of fluticasone furoate 250 µg once daily in the evening compared to 100 µg once daily in the evening indicated a greater improvement with 250 µg once daily in the evening in 24-hour symptom-free periods, rescue medication-free 24-hour periods, and night-time awakenings, but the differences were not significant. Three patients withdrew from the study due to lack of efficacy (other than exacerbations); two on placebo and one on fluticasone furoate 100 µg once daily in the morning. The number of withdrawals with fluticasone furoate

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				was not statistically significant compared to placebo. The proportion of patients reporting an adverse event during the treatment period was 26% in the placebo group and 23 to 26% with fluticasone furoate. Rates of occurrence of the most frequent adverse events (≥3% of patients in any treatment group) and treatment-related adverse events were low and similar across the treatment groups. The most frequently reported AEs during treatment were headache (4 to 9%) and nasopharyngitis (3 to 4%). None of the three serious adverse events were considered related to study treatment and all were resolved within three weeks after withdrawal. No clinically significant abnormalities or shifts from baseline were observed in any treatment group for hematological, clinical chemistry, vital signs, or ECG parameters. The incidence of oropharyngeal candidiasis was low (≤3% of patients in any treatment group), with slightly higher incidence (3% [4 patients]) in the 250 µg group than in any of the other three groups.
Wooodcock et al.[45] (2014) Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and stable use of any ICS dose for ≥12 weeks or for ≥ 4 weeks for mid-high dose, FEV_1 40 to 90% predicted and reversibility with albuterol	N=238 24 weeks	Primary: Pre-dose (trough) FEV_1 at week 24 Secondary: Percentage of rescue-free and symptom-free 24-hour periods, change in PEF average, ACT scores	Primary: Both strengths of fluticasone furoate were associated with improvements in trough FEV_1 of >200 mL from baseline at week 24. A numerically greater increase was observed with the fluticasone furoate 200 µg dose than with 100 µg dose (treatment difference, 77 mL; 95% CI, -39 to 192). Repeated-measures analysis of change from baseline in trough FEV_1 over 24 weeks of treatment showed that improvement in trough FEV_1 was apparent within two weeks of randomization and was maintained throughout the treatment period. Secondary: Improvements over 24 weeks in percentage of rescue-free and symptom-free 24-hour periods and PEF, as well as in ACT score at week 24, were observed in both treatment groups. No treatment differences were observed in incidence of severe asthma exacerbations or healthcare resource utilization. There were no asthma-related inpatient hospitalizations.
van den Berge et al.[46]	MC, DB, PC, PG, RCT, XO (six-way)	N=24	Primary: PC_{20} AMP, eNO	Primary: Fluticasone furoate significantly improved the PC_{20} AMP at all time points

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(2010) Fluticasone furoate 1,000 µg inhaled 2, 14, or 26 hours prior to measure of eNO and PC_{20} AMP vs fluticasone propionate 1,000 µg inhaled 14 or 26 hours prior to measure of eNO and PC_{20} AMP vs placebo Each treatment period was separated by at least five days and a maximum of 10 days.	Patients 18 to 55 years of age diagnosed with asthma, FEV_1 >70% predicted, PC_{20} AMP< 50 mg/mL, presence of atopy	8 weeks	Secondary: Adverse reactions	compared to placebo. The mean difference in doubling concentrations being 2.18 (95% CI, 1.13 to 3.23), 1.54 (95% CI, 0.48 to 2.59), and 1.30 (95% CI, 0.26 to 2.34) at two, 14, and 26 hours, respectively (P<0.05 for all time points). Fluticasone propionate significantly improved the PC_{20} AMP at 14 hours but not at 26 hours compared to placebo. The difference in doubling concentrations being 1.72 (95% CI, 0.70 to 2.75; P<0.05) and 0.33 (95% CI, −0.69 to 1.34; P value not reported) at 14 and 26 hours respectively. No significant changes in the concentration of eNO were observed after treatment with fluticasone furoate or propionate at any time point. Secondary: The most frequently occurring adverse event was bronchospasm (33%), followed by dyspnea, dizziness, headache, nausea, palpitations and fatigue. None of the adverse events occurred more frequently during treatment with fluticasone furoate when compared to fluticasone propionate or placebo.
Bleecker et al.[47] (2011) Fluticasone furoate 100 µg inhaled QPM vs	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with moderate persistent symptomatic asthma while receiving low-dose ICS	N=622 8 weeks	Primary: Pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF averaged, percentage symptom-free and	Primary: At week eight, all active treatment groups demonstrated significant placebo-adjusted improvements from baseline in predose FEV_1 (P<0.001) and achieved the predefined 200 mL difference from placebo. Improvements with fluticasone furoate were similar to or greater than those reported for twice-daily fluticasone propionate. The treatment interaction with each of the covariates modeled was not statistically significant. Similar results were obtained for the per-protocol population.

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fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 300 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo	therapy (for at least eight weeks); reversibility to albuterol, pre-bronchodilator FEV_1 of 40% to 90% predicted		rescue-free 24-hour periods, withdrawals due to lack of efficacy, safety	Secondary: Morning and evening predose PEF values over weeks one through eight were also significantly different from placebo, indicating greater improvement with therapy (morning PEF, P<0.001 for all doses; evening PEF, P=0.18 for fluticasone furoate and P<0.001 for all other active treatments). Mean symptom- and rescue-free 24-hour periods increased over eight weeks in all groups. Significant improvements in symptoms were observed with fluticasone furoate 400 µg once daily and fluticasone propionate 250 µg twice daily, and for rescue use with all treatments except fluticasone furoate 200 µg once daily (P values not reported). Withdrawals attributable to lack of efficacy were significantly greater with placebo (33%) compared with all fluticasone furoate treatment groups (10, 11, 8, and 7% for 100, 200, 300, and 400 µg, respectively; P<0.001) and twice-daily fluticasone propionate 250 µg (14%; P=0.002). On-treatment adverse events were reported in 33 to 41% of patients across the fluticasone furoate groups, 42% with fluticasone propionate and 30% with placebo. The most commonly reported on-treatment adverse events were headache (6 to 9% across treatment groups) and nasopharyngitis (4 to 9%). No dose-related increases in the frequency of the most common adverse events were observed. The incidence of oral/oropharyngeal candidiasis across the fluticasone furoate groups was less than 1 to 4%, 4% with fluticasone propionate 250 µg, and 0% with placebo.
Busse et al.[48] (2011) Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with persistent asthma not controlled using medium-dose ICS, FEV_1 of 40 to 90% predicted;	N=627 8 weeks	Primary: Pre-dose FEV_1 Secondary: Asthma symptom scores, rescue salbutamol use, morning and evening pre-dose PEF averaged, percentage	Primary: Pre-dose FEV_1 was significantly improved in all active treatment groups when compared with placebo at week eight (P<0.001). The predefined 200 mL difference relative to placebo was achieved in all fluticasone furoate groups. Secondary: All active treatments provided significant improvement from baseline in evening PEF over the eight-week treatment period (P<0.001). Similar improvements for all active treatments were also observed in morning PEF and were significantly improved when compared with placebo (P<0.001).

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QPM vs fluticasone furoate 600 µg inhaled QPM vs fluticasone furoate 800 µg inhaled QPM vs fluticasone propionate 500 µg inhaled BID vs placebo	reversibility of asthma with inhaled salbutamol		symptom-free and rescue-free 24-hour periods, withdrawals due to worsening asthma	Based on patient-reported data, the proportion of symptom-free 24-hour periods during weeks one to eight increased relative to baseline in all study groups and was greater with all active treatments than placebo (P<0.001, P<0.001, P=0.022, and P=0.002 for fluticasone furoate 200 µg, 400 µg, 600 µg, and 800 µg, respectively; P=0.017 for fluticasone propionate). Similar significant improvements were observed for rescue-free 24-hour periods in the treatment groups compared to placebo (P<0.001 for all). The proportion of patients with symptom-free and rescue-free days were also significantly greater in the all treatment groups than in the placebo group (comparisons with placebo P<0.001, except for P=0.006 with fluticasone furoate 600 µg for symptom-free days). Withdrawal rates due to lack of efficacy were significantly lower in all active treatment groups compared with the placebo group (6 to 12% compared with 33%; P<0.001 for all comparisons). The fewest withdrawals due to lack of efficacy occurred in the fluticasone furoate 400 µg and fluticasone propionate groups (6 and 7%, respectively). Overall, fluticasone furoate was well tolerated; 31% to 35% of patients in the fluticasone furoate groups and 22% in the placebo group experienced one or more adverse event during treatment. The most frequently reported adverse events were oral candidiasis (<1 to 12%), headache (3 to 11%), nasopharyngitis (2 to 7%) and dysphonia (<1 to 5%). The incidence of drug-related adverse events was 2% in the placebo group and 11, 11, 3, 17, and 9% of patients in the fluticasone furoate 200, 400, 600, and 800 µg groups and fluticasone propionate group, respectively; the most frequent of these were oropharyngeal candidiasis, oral candidiasis, and dysphonia. The frequency of these events was similar in all active treatment groups, with the exception of oral candidiasis, which occurred most frequently in the fluticasone furoate 800 µg group. The incidence of asthma exacerbations was lower in the active treatment groups (<1 to 6%) than in the placebo group (16%). Most exacerbations in the placebo group were attributed to lack of efficacy. Eight percent of patients in the placebo arm required oral corticosteroids compared with 0 to 2% in the fluticasone furoate groups and 3% in the fluticasone

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				propionate group. Three patients were hospitalized due to asthma exacerbation, one each in the placebo, fluticasone furoate 200 µg once daily and fluticasone propionate 500 µg twice daily arms.
Bateman et al.[49] (2012) Fluticasone furoate 25 µg inhaled QPM vs fluticasone furoate 50 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QPM fluticasone furoate 200 µg inhaled QPM vs fluticasone propionate 25 µg inhaled BID vs placebo	AC, DB, DD, MC PC, PG, RCT Patients ≥12 years of age with a diagnosis of persistent asthma, FEV_1 40 to 90% predicted, and not adequately controlled on SABAs (or other non-steroidal controllers) that they had been using for ≥3 months	N=598 8 weeks	Primary: Pre-dose evening FEV_1 Secondary: PEF average, percentage of symptom-free 24-hour periods, rescue-free 24-hour periods and number of withdrawals due to lack of efficacy, safety	Primary: A significant dose–response relationship for change in pre-dose evening FEV_1 (baseline to week eight) was achieved across once-daily fluticasone furoate (25 to 200 µg) both when placebo was included (P<0.001) and when placebo was not included (P=0.03). At week eight, all active treatment groups showed a >200 mL improvement in pre-dose FEV_1 from baseline; the fluticasone furoate 100 µg and 200 µg once daily doses achieved a >200 mL difference compared with placebo (P<0.001). Fluticasone furoate 50 µg once daily, although failing to reach the pre-defined 200 mL difference, was also significantly better than placebo (P<0.05). Fluticasone furoate 25 µg and fluticasone propionate failed to show superiority compared with placebo (P value not reported). Secondary: Evening PEF improvements from baseline were largest in the fluticasone furoate 50 µg and 200 µg once-daily groups (mean difference 20.7 and 21.7 L/min, respectively, compared with placebo; P<0.001). Significant but smaller differences were also achieved with fluticasone furoate 25 µg once daily (14.0 L/min, P=0.019) and 100 µg once daily (16.1 L/min, P=0.005) and were of a similar magnitude to the fluticasone propionate 100 µg twice daily group (14.9 L/min; P=0.011). Similarly, all active treatment groups improved morning PEF relative to baseline and these changes were significantly greater than with placebo (P values not reported). Fluticasone furoate 200 µg once daily exhibited the greatest difference in morning PEF (22.0 L/min; P<0.001). For symptom-free periods, fluticasone furoate 100 µg once daily demonstrated the greatest increase from baseline relative to placebo (20.2%). Fluticasone furoate 50 µg and 200 µg once daily showed numerically lower increases, similar in magnitude to the fluticasone propionate 100 µg twice-daily group. For all except the fluticasone furoate 25 µg once-daily group, the effect was significantly better than for placebo

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				(P values not reported). A similar pattern was evident for rescue-free periods (P values not reported). Withdrawal rates due to lack of efficacy were highest in the placebo and fluticasone propionate twice-daily groups (15% and 11%, respectively). Rates for fluticasone furoate once-daily ranged from 3 to 9%. The differences in the fluticasone furoate 50 µg (3%) and 100 µg (5%) once-daily groups were significantly lower than for placebo (P=0.004 and P=0.032, respectively). Overall, 26%, 34%, and 20% to 32% of patients in the placebo, fluticasone propionate twice-daily and fluticasone furoate once-daily groups, respectively, reported at least one on-treatment adverse events. Drug-related adverse events were low in all groups (0 to 6%), with no apparent dose-dependent events.
Woodcock et al.[50] (2011) Fluticasone furoate 200 µg QD for 28 days and fluticasone propionate 100 µg BID for 28 days and placebo vs Fluticasone furoate 200 µg QD for 28	AC, DB, MC, PC, RCT, XO Patients ≥12 years of age with moderate persistent asthma, FEV_1 40 to 80% predicted and reversibility to inhaled salbutamol	N=190 28 days (per period)	Primary: Pre-dose FEV_1 at day 28 of each treatment period Secondary: Safety	Primary: Pre-dose FEV_1 increased in all groups, but the mean increases in the four active treatment groups were approximately twice those in the placebo group. The differences compared to placebo were statistically significant in all four active treatment groups, as assessed in the ITT population (P<0.001 for fluticasone furoate 200 µg once daily, fluticasone furoate 100 µg twice daily and fluticasone propionate 100 µg twice daily; P=0.02 for the fluticasone propionate 200 µg once daily). In the ITT population, the lower 95% CI for the mean difference between fluticasone furoate 200 µg once daily and 100 µg twice daily in pre-dose FEV_1 on day 28 was -35 mL (LS mean difference of 11 mL). This difference was within the pre-defined limit of -110 mL, thus demonstrating non-inferiority of the fluticasone furoate 200 µg once-daily regimen. Similar results were obtained from the non-inferiority analysis in the PP population. Data from patients treated with fluticasone propionate indicated numerically reduced improvement in pre-dose FEV_1 with the 200 µg once-daily dose in comparison with 100 µg twice daily, although no statistical comparison of these groups was performed.

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days and fluticasone furoate 100 µg BID for 28 days and placebo Twelve sequences comprising three 28-day treatment periods. Patients received either a fluticasone furoate plus placebo regimen or a fluticasone propionate plus placebo regimen. The order of receiving different periods is varied by sequence.				Secondary: No serious adverse events were reported and no adverse events led to permanent discontinuation of drug or to patient withdrawal. The frequency of on-treatment adverse events was higher in the fluticasone furoate 200 µg once-daily, fluticasone furoate 100 µg twice-daily and dry powder inhaler placebo groups (16, 18, and 14%, respectively) than in the fluticasone propionate 200 µg once-daily, fluticasone propionate 100 µg twice-daily and diskus placebo groups (5, 7, and 12% respectively). Upper respiratory tract infections were the most commonly reported adverse event, occurring in 5% of patients in each of the fluticasone furoate groups and 1% in the placebo group; no other AEs were reported by more than 1% of patients in either of the fluticasone furoate groups or the placebo group during the treatment period. However, only three of the adverse events reported, headache, dry throat, and tachycardia, were considered to be potentially drug-related. One patient reported dysphonia in the fluticasone propionate 200 µg once daily group. There were no cases of oral candidiasis. Asthma exacerbations occurred in five (3%) patients on placebo, and one (<1%) patient on fluticasone furoate 200 µg once daily. None of the exacerbations were severe enough to require hospitalization.
Lötvall et al.[51] (2014) Fluticasone furoate 100 µg inhaled QPM vs fluticasone	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4	N=343 24 weeks	Primary: Pre-dose FEV_1 at 24 weeks Secondary: Mean change in percentage of rescue-free 24-hour periods, PEF and percentage of	Primary: Pre-dose evening FEV_1 was significantly improved at week 24 with fluticasone furoate 100 µg QPM and fluticasone propionate 250 µg BID when compared to placebo (P=0.009 and P=0.011, respectively); both active treatments resulted in similar effects compared with placebo. Secondary: The percentage of rescue-free 24-hour periods was significantly increased compared with placebo for both fluticasone furoate µg QPM and fluticasone propionate 250 µg BID (P<0.001).

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propionate 250 µg inhaled BID vs placebo QPM or BID	weeks, FEV_1 40 to 90% predicted; reversible on inhalation of albuterol or salbutamol		symptom-free 24-hour periods over the 24 weeks, change in AQLQ score at weeks 12 and 24, Asthma Control Test score at weeks 12 and 24 and withdrawal due to lack of efficacy	Initial analysis of evening PEF found no significant difference between placebo and active therapy. Because of the step-down closed testing procedure employed, significance could not be inferred for all subsequent efficacy comparisons regardless of P value. Morning PEF, percentage of symptom-free 24-h periods over the course of the study and AQLQ at weeks 12 and 24 were numerically improved by both active treatments compared with placebo (P value not reported).
Busse et al.[52] (2014) Fluticasone furoate 50 µg inhaled QPM vs fluticasone propionate 100 µg inhaled BID vs placebo	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma for ≥12 weeks, treatment with non-ICS controllers or short-acting beta agonists, FEV_1 ≥60% predicted, and reversibility with salbutamol	N=222 24 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily AM and PM PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients with ACT score ≥20, change in total AQAQ score, and unscheduled asthma-related healthcare resource utilization	Primary: Improvement in change from baseline of FEV_1 at week 24 for fluticasone furoate was not statistically significant when compared to placebo (37 mL, P=0.430). When fluticasone propionate was compared to placebo, there was a significant improvement in favor of the active treatment (102 mL, P=0.030). Because of the lack of statistical significance on the primary endpoint, all subsequent endpoints were interpreted as descriptive only for the fluticasone furoate group when compared to placebo treatment. Secondary: The percentage of rescue-free 24-hour periods increased from baseline over weeks 0 to 24 in all treatment groups; mean improvements compared to placebo, were not statistically significant for fluticasone furoate (7.8%; 95% CI, −1.0 to 16.7), but were significant for fluticasone propionate (10.6%; 95% CI, 1.7 to 19.6). The number of additional rescue-free days per week compared to placebo was similar for fluticasone furoate (0.5) and fluticasone propionate (0.7). Mean change from baseline in evening PEF over the 24-week study for fluticasone furoate compared to placebo was 17.2 L/min (95% CI, 5.9 to 28.6) and 4.3 L/min (95% CI, −7.0 to 15.7) for fluticasone propionate compared to placebo. Change in morning PEF compared to placebo was 19.2 L/min (95% CI, 8.5 to 29.9) for and 10.6 L/min (95% CI, −0.2 to 21.3) for fluticasone propionate. Changes from baseline in percentage of symptom-free 24-hour periods for

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				fluticasone furoate and fluticasone propionate when compared to placebo were 8.3 (95% CI, 0.3 to 16.3) and 7.5 (95% CI, −0.5 to 15.5), respectively. The equivalent number of additional symptom-free days per week compared to placebo was similar for fluticasone furoate (0.6) and fluticasone propionate (0.5). There were more withdrawals due to lack of efficacy with placebo (20%) than with fluticasone furoate (12%) or fluticasone propionate (8%).
Bleecker et al.[53] (abstract) (2014) Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate/vilanterol 100/25 µg inhaled QPM vs placebo QPM	DB, PC, PG, RCT Patients ≥12 years of age with a diagnosis of persistent asthma	N=609 12 weeks	Primary: Pre-dose (trough) FEV_1, and serial (0 to 24 hours) $wmFEV_1$ Secondary: Rescue-free 24-hour periods, safety	Primary: When compared with placebo, trough FEV_1 was significantly improved in both the fluticasone furoate and fluticasone furoate/vilanterol groups (placebo, 196 mL; fluticasone furoate, 136 mL; P=0.002; fluticasone furoate/vilanterol, 172 mL; P<0.001). There was also a significant difference in serial (0 to 24 hours) $wmFEV_1$ for both treatment groups when compared to placebo. The serial (0 to 24 hour) $wmFEV_1$ for the placebo group was 212 mL as compared to 186 mL in the fluticasone furoate group (P=0.003) and 302 mL in the fluticasone furoate/vilanterol (P=<0.001). When fluticasone furoate/vilanterol was compared to fluticasone furoate, treatment differences approached significance for serial wmFEV1 (116 mL; P=0.060), but not for trough FEV1 (36 mL; P=0.405). Secondary: The percentage of rescue-free 24-hour periods with fluticasone furoate/vilanterol was 10.6% greater than fluticasone furoate and 19.3% greater than placebo. Urinary cortisol suppression was observed with fluticasone furoate/vilanterol (ratio, 0.82) relative to placebo (P=0.032), but not with fluticasone furoate (no P value reported). Adverse event and safety profiles were similar across treatment groups.
O'Byrne et al.[54] (2014)	AC, DB, DD, MC, PG, RCT	N=586 24 weeks	Primary: Pre-dose FEV_1 and $wmFEV_1$ (0 to 24	Primary: Trough FEV_1 at week 24 was improved from baseline with all active therapies. The differences between fluticasone furoate-vilanterol and

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Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate-vilanterol 200-25 µg inhaled QPM vs fluticasone propionate 500 µg inhaled BID	Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40% to 90% predicted; reversible on inhalation of albuterol or salbutamol		hours post-dose) Secondary: Mean change in percentage of rescue-free 24-hour periods, percentage of symptom-free 24-hour periods and total AQLQ score after 12 and 24 weeks	fluticasone furoate, and fluticasone furoate-vilanterol and fluticasone propionate were both significant (P<0.001 for both), while fluticasone furoate was noninferior to fluticasone propionate. Change from baseline in trough FEV_1 by treatment showed sustained benefit with fluticasone furoate/vilanterol over fluticasone furoate and fluticasone propionate at all study time-points. The $wmFEV_1$ from 0 to 24 hours post-dose at week 24 compared with baseline was improved in all treatment arms. When compared to the single entity fluticasone furoate and fluticasone propionate, fluticasone furoate-vilanterol significantly improved $wmFEV_1$ 0 to 24 hours post-dose (P=0.048 and P=0.003, respectively). Secondary: The percentage of rescue-free 24-hour periods increased over the study with all therapies. The difference in improvement was significant for the comparison of fluticasone furoate-vilanterol with fluticasone furoate, but not for fluticasone furoate-vilanterol compared with fluticasone propionate (P<0.001 and P=0.067, respectively). The percentage of symptom-free 24-hour periods increased over the course of the study. Fluticasone furoate-vilanterol provided a significant improvement when compared to fluticasone furoate but not fluticasone propionate (P=0.010 and P=0.137, respectively). Improvements from baseline in the AQLQ score were seen in all treatment groups at week 24. The improvements were similar in each arm and were not statistically significant. Over the 24-week treatment period, fewer patients withdrew due to lack of efficacy in the fluticasone furoate-vilanterol group (3%) compared with the fluticasone furoate (11%) or fluticasone propionate (9%) groups.
Bateman et al.[55] (2014) Fluticasone furoate- vilanterol	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma	N=2019 24 to 78 weeks	Primary: Time to first severe asthma exacerbation	Primary: Fluticasone furoate-vilanterol significantly delayed the time to first severe exacerbation relative to fluticasone furoate. The adjusted probability of experiencing a severe asthma exacerbation by 52 weeks was 15.9% (95% CI, 13.5 to 18.2%) in the single agent group and 12.8% (95% CI, 10.7 to

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100-25 µg QD vs fluticasone furoate 100 µg QD Patients replaced their current short-acting bronchodilator and used albuterol/salbutamol as-needed for symptoms	for ≥1 year and documented use of ICS or ICS/LABA for ≥12 weeks with a stable dose for ≥ 4 weeks, ≥1 asthma exacerbation in the previous year, FEV_1 of 50 to 90% predicted		Secondary: Rate of severe asthma exacerbations per patient per year and change from baseline at week 36 in evening trough FEV_1	14.9%) in the combination group. The HR for combination vs fluticasone furoate alone was 0.795 (95% CI, 0.642 to 0.98; P=0.036, adjusted for the interim analysis). Secondary: The rate of severe asthma exacerbations per patient per year was significantly lower in the combination group than in the fluticasone furoate group (0.14 vs 0.19). Trough FEV_1 increased over the treatment period in both treatment groups. Fluticasone furoate- vilanterol demonstrated statistically significant improvements over fluticasone furoate in trough FEV_1, with adjusted mean changes of 83 to 95 mL (P<0.001).
Woodcock et al.[56] (2013) Fluticasone furoate- vilanterol 100-25 µg QD vs fluticasone propionate-salmeterol 250-50 µg BID	DB, DD, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40% to 85% predicted; reversible on inhalation of albuterol	N=806 24 weeks	Primary: Change from baseline in $wmFEV_1$ after 24 weeks Secondary: FEV_1 assessments, time to onset of bronchodilator effect, AQLQ	Primary: Improvements from baseline in 0- to 24-hour $wmFEV_1$ were seen in both groups; however, the adjusted mean treatment difference was not statistically significant. Secondary: There were no differences in key secondary end points.
Qaqundah et al.[57] (2006) Fluticasone propionate HFA 88 µg BID	RCT Children 1 to <4 years of age with a history of symptomatic asthma and ≥2 episodes of	N=359 12 weeks	Primary: Mean percent change from baseline to endpoint in 24-hour daily asthma symptom scores	Primary: Fluticasone propionate group had a significantly greater mean percent (P=0.036) reduction in 24-hour daily asthma symptom scores vs placebo. Secondary: Fluticasone propionate group had significantly greater (P<0.05) reduction in nighttime asthma symptom scores over the treatment period vs placebo;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	increased asthma symptoms requiring medical attention/asthma treatment within the year before screening		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.	mean change in 24-hour daily asthma symptom scores was also significantly increased in fluticasone propionate group. Fluticasone propionate 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 propionate 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.
Nelson et al.[58] (1999) Fluticasone propionate 500 µg BID vs fluticasone propionate 1,000 µg BID vs placebo	DB, PC, PG, RCT Patients 12 years of age or older with chronic asthma diagnosed according to the American Thoracic Society criteria who were receiving oral corticosteroid treatment over the preceding six months	N=111 16 weeks	Primary: Percentage of patients with a change in maintenance prednisone dose and mean change from baseline in maintenance dose of prednisone Secondary: Changes in FEV_1, patient-measured morning and evening PEF, patient-rated asthma symptoms and number of nighttime awakenings requiring albuterol	Primary: At 16 weeks, oral prednisone use was discontinued in 75 and 89% of patients treated with fluticasone propionate 500 or 1,000 µg BID, respectively, compared to 9% of placebo-treated patients. The mean maintenance dose of oral prednisone decreased significantly in both fluticasone propionate groups compared to the placebo group ($P<0.001$). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone propionate 500 µg BID group (8.37 ± 3.84) and 1,000 µg BID group (24.21 ± 5.67) compared to the placebo group (0.56 ± 5.56; $P \leq 0.05$ for all). Both morning and evening PEF improved in the fluticasone propionate 500 µg BID group (23+10 morning and 3 ± 7 evening) and 1,000 µg group (67 ± 12 morning and 48 ± 10 evening) compared to the placebo group (-23 ± 11 morning and -9 ± 12 evening; $P \leq 0.05$ for all). Asthma symptom scores improved in both the fluticasone propionate 500 µg BID (-0.26 ± 0.08) and 1,000 µg BID groups (-0.47 ± 0.13; $P \leq 0.05$), while symptom scores worsened in the placebo group (0.26 ± 0.12; $P \leq 0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Nighttime awakenings requiring albuterol decreased in both the fluticasone propionate 500 µg BID (-0.19±0.11) and 1,000 µg BID groups (-0.42±0.13), while nighttime awakenings increased in the placebo group (0.26±0.15; P≤0.05 for all).
Fish et al.[59] (2000) Mometasone 400 to 800 µg BID vs placebo	MC, PC, RCT Patients with severe, persistent, oral corticosteroid-dependent asthma	N=132 12 weeks, followed by 9 month OL phase	Primary: Percentage change in daily oral corticosteroid prednisone requirement Secondary: Spirometric measurements (FEV_1, FVC, FEF, midexpiratory phase), morning and evening 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	Primary: Oral corticosteroid requirements were reduced by 46.0% in the mometasone 400 µg BID group and by 23.9% in the mometasone 800 µg BID group compared to the placebo group (164.4%; P<0.01). Oral corticosteroids were discontinued in 40, 37 and 0% of patients after 12 weeks and 71, 62 and 58% of patients at the end of the nine month OL phase in the mometasone 400 and 800 µg BID and placebo groups, respectively. Secondary: Nocturnal awakenings were reduced by 57 and 66% in the mometasone 400 and 800 µg BID groups, respectively, and increased by 62% in the placebo group (P<0.01). Daily rescue medication use was significantly reduced in the mometasone 400 µg BID group (P<0.01), but not in the mometasone 800 µg BID group compared to the placebo group. There were no statistically significant differences between the treatment groups with regard to all other secondary endpoints.
Schmier et al.[60] (2003) Mometasone 400 to 800 µg BID vs	DB, MC, PC, RCT Patients with severe persistent asthma previously maintained on oral steroids	N=132 12 weeks, followed by a 9 month OL extension	Primary: Corticosteroid use, AQLQ-M Secondary: Not reported	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: Not reported
Krouse et al. (abstract)[61] (2009) Mometasone 400 µg QPM vs placebo	DB, PC, RCT Patients 18 to 60 years of age with mild to moderate asthma and a history of nocturnal asthma	N=20 14 days	Primary: Nocturnal decline in evening to morning FEV_1 values Secondary: Nocturnal decline in evening to morning PEFR values, polysomnographic indices of sleep, NRQLQ, SF-36 and AQLQ	Primary: No significant differences were observed between groups with regard to nocturnal decline in FEV_1. Secondary: No significant differences were observed between groups with regard to polysomnographic indices of sleep, NRQLQ, SF-36 or AQLQ. A trend toward improvement in the activity scale of the AQLQ was observed in the mometasone group.
Price et al.[62] (2010) Mometasone 400 µg QPM vs mometasone 200 µg BID	MC, OL Patients 12 years of age and older with mild to moderate persistent asthma for at least one year	N=1,233 12 weeks	Primary: Adherence, measured by automatic dose counter Secondary: Self-reported adherence, physician's assessment of therapeutic response, HRQOL, healthcare resource utilization and days missed from work or school	Primary: Adherence, as measured by the automatic dose counter was significantly higher in the QPM group compared to the BID group ($P<0.001$). Secondary: Adherence, as measured by self-report was significantly higher in the QPM group compared to the BID group ($P<0.001$). No significant differences between groups were observed in physician's assessment of therapeutic response, HRQOL, healthcare resource utilization, or days missed from work or school ($P\geq0.08$ for all).
Busse et al.[63] (1999)	DB, MC, PG, RCT	N=323	Primary: Change from	Primary: For each treatment group, the FEV_1 percent predicted increased over the

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Beclomethasone HFA 100 µg/day vs beclomethasone HFA 400 µg/day vs beclomethasone HFA 800 µg/day vs beclomethasone CFC 100 µg/day vs beclomethasone CFC 400 µg/day vs beclomethasone CFC 800 µg/day	Asthmatic patients who had deteriorated in their asthma control following discontinuation of ICS	6 weeks	baseline in FEV_1 percent predicted Secondary: Percent change from baseline in $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings and daily albuterol use	first four weeks of treatment and plateaued by week six. The change from baseline in FEV_1 percent predicted was greater with beclomethasone 800 µg/day HFA (-32.7%; P=0.049) compared to beclomethasone 400 µg/day HFA (-25.1%) and numerically, but not significantly greater (P=0.09) with beclomethasone CFC 800 µg/day (-31.3%) compared to beclomethasone CFC 400 µg/day (-22.6%). Secondary: ANOVA showed significant dose effects across both products for $FEF_{25\ to\ 75\%}$, FVC and morning PEF. Evening PEF, asthma symptom scores, nighttime sleep disturbances, and daily albuterol use were similar among all treatment groups.
Papi et al.[64] (2007) Beclomethasone 250 µg BID and albuterol 100 µg as needed (regular beclomethasone)	DB, DD, MC, PG, RCT Patients 18 to 65 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 ≥75% of	N=455 6 months	Primary: Mean rate of morning PEFR Secondary: Lung function, symptom scores, and number/ severity of	Primary: The morning PEFR at six 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 PEFR did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy. Secondary:

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vs beclomethasone-albuterol 250-100 µg in a single inhaler as needed (as needed combination) vs beclomethasone-albuterol 250-100 µg BID in a single inhaler and albuterol 100 µg as needed (regular combination) vs albuterol 100 µg as needed (as needed albuterol)	predicted value, associated with either an increase in FEV_1 ≥12% of predicted value after inhalation of 200 µg of albuterol or a positive methacholine challenge		exacerbations	The evening PEFR 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 pre bronchodilator FEV_1 and 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 PEFR increased significantly in the regular combination group. The evening PEFR 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. 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; $P<0.001$).

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				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).
Sharek et al.[65] (2000) Beclomethasone 328 to 400 µg/day vs fluticasone propionate 200 µg/day	MA 1966 to 1998, DB, RCT studies that evaluated linear growth in children six to 16 years of age with asthma and concomitant ICS therapy	N=855 (5 studies)	Primary: Linear growth velocity in cm/year Secondary: Not reported	Primary: There was a significant decrease in linear growth in children using beclomethasone for mild-to-moderate asthma. The WMD between 231 patients using beclomethasone compared to 209 patients using a non-steroid medication was -1.51 cm/year (95% CI, -1.15 to -1.87). For the fluticasone propionate study the mean difference between 96 children treated with fluticasone propionate and 87 patients treated with placebo was -0.43 cm/year (95% CI, -0.01 to -0.85; P value not reported). Secondary: Not reported
van Aalderen et al.[66] (2007) Beclomethasone 200 µg/day via HFA MDI vs fluticasone propionate 200	AC, DB, DD, PG, RCT Patients five to 12 years of age with asthma for at least three months, a PEF ≥60% of predicted normal, and currently using a SABA on an as-needed basis	N=139 18 weeks	Primary: Morning PEF percent predicted Secondary: Evening PEF percent predicted, FEV_1 percent predicted, FVC percent predicted, symptom-free days, nights	Primary: The mean change from baseline in morning PEF percent predicted was 5.7% in the beclomethasone group and 7.3% in the fluticasone propionate group. The treatment difference was -1.9 (90% CI, -4.9 to 1.0; P value not reported). Secondary: The mean change from baseline in evening PEF percent predicted was 5.9% in the beclomethasone group and 7.3% in the fluticasone propionate group. The treatment difference was -1.5 (90% CI, -4.6 to 1.6; P=0.415). The mean change from baseline in FEV_1 percent predicted was 3.0% in

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µg/day via CFC MDI During weeks seven to 12 and 13 to 18 patients were stepped down to 100 and 50 µg/day respectively if they were achieving good control. Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.			without sleep disturbances, use of a β_2-agonist, asthma control, quality of life and adverse events	the beclomethasone group and 0.6% in the fluticasone propionate group. The treatment difference was 1.6 (P=0.335). The mean change from baseline in FVC percent predicted was 5.3% in the beclomethasone group and 0.4% in the fluticasone propionate group. The treatment difference was 4.6 (P=0.084). The percent change from baseline in symptom-free days was 35.2% in both treatment groups (P=0.897). The percent change in nights without sleep disturbances was 17.5 and 20.8% in the beclomethasone and fluticasone propionate groups, respectively (P=0.561). The mean use of a β_2-agonist decreased from 1.59 to 0.73 puffs/day in the beclomethasone group, and from 1.40 to 0.69 puffs/day in the fluticasone propionate group (P=0.505). At six weeks, 36% of patients in the beclomethasone group and 42% in the fluticasone propionate group had good asthma control and were able to step down in their respective doses to 100 µg/day. At 12 weeks, another step down therapy to 50 µg/day was possible in 66 and 61% of the patients in the beclomethasone and fluticasone propionate groups, respectively. The proportion of patients with a clinically significant improvement in asthma quality of life was similar in both groups (P=0.369). There were no statistically significant differences in the proportion of patients experiencing adverse events in the beclomethasone (47%) and fluticasone propionate (49%) groups.
Berkowitz et al.[67] (1998) Beclomethasone 336 µg/day vs	AC, DB, DD, PC, RCT Patients 18 to 65 years of age with a documented history of bronchial asthma	N=339 56 days	Primary: Change from baseline in FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, PEFR and FVC	Primary: For both active treatment groups, patients experienced statistically significant increases from baseline in FEV_1 compared to the placebo group at all time points (P<0.05 for all). Over the course of the study, the FEV_1 was significantly increased by 10.3% in the beclomethasone group and by 11.2% in the triamcinolone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triamcinolone 800 µg/day vs placebo				group compared to the placebo group ($P \leq 0.05$ for both). Secondary: The mean increases in $FEF_{25 \text{ to } 75\%}$ FVC and PEFR were among the beclomethasone and triamcinolone treatment groups. All results were numerically and statistically significant compared to the placebo group ($P<0.05$).
Bronsky et al.[68] (1998) Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs placebo	AC, DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe asthma maintained on an ICS	N=328 56 days	Primary: Mean changes from baseline in FEV_1 Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25 \text{ to } 75\%}$, and FVC	Primary: The mean change from baseline in FEV_1 for both active treatments was significantly greater compared to placebo (0.27 and 0.16 vs -0.10 L for beclomethasone and triamcinolone compared to placebo; $P \leq 0.01$ for both). Secondary: At each visit, the mean improvements in total symptom severity scores were significantly greater in the beclomethasone group compared to the triamcinolone group ($P=0.028$) and at endpoint in both active treatment groups compared to the placebo group (-1.37, -0.58, and 0.83; $P<0.001$ for all). The mean average daily use of albuterol calculated weekly was lowest in the beclomethasone group (2.86) followed by the triamcinolone group (3.61) and the placebo group (4.43; P values not reported). Nighttime awakenings were not significantly different among the treatment groups. The mean change from baseline in $FEF_{25 \text{ to } 75\%}$, and FVC demonstrated both active treatment groups to be more effective compared to the placebo group, and beclomethasone being more effective than triamcinolone throughout the study.
Ferguson et al.[69] (2007) Budesonide 200 µg BID via DPI vs	AC, DB, DD, MC, PG, RCT Children six to nine years of age with persistent asthma for at least six	N=400 12 months	Primary: Growth velocity Secondary: PEFR, FEV_1, exacerbations, symptoms-free	Primary: Mean growth velocity from baseline was 5.5 cm/year in the fluticasone propionate group and 4.6 cm/year in the budesonide group. This difference of 0.9 cm/year was statistically significant ($P<0.001$).The difference in growth velocities increased over the 12 months. The majority of patients in the fluticasone propionate group grew 5.0 to 7.0 cm/year whereas patients in the budesonide group grew 3.0 to 5.0 cm/year.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate 100 µg BID via DPI	months, and an FEV ≥60% predicted, height between the 5th and 95th percentiles for the patients' age and run-in growth velocity between the 20th and 95th percentiles		days and nights, salbutamol-free nights and adverse events	Secondary: Change in morning PEFR was 29.7 and 26.2 L/minute for the fluticasone propionate and budesonide groups, respectively (P=0.460). Change in FEV_1 was 0.19 and 0.25 L for the fluticasone propionate and budesonide groups, respectively (P=0.154). The proportions of patients with no exacerbations were 75 and 68% in the fluticasone propionate and budesonide groups, respectively (P=0.131). The proportion of patients who were 100% symptom-free was 49 and 48% in the fluticasone propionate and budesonide groups respectively (P=0.799). The proportion of patients who had 100% symptom-free nights was 50 and 58% in the fluticasone propionate and budesonide groups respectively (P=0.232). The proportion of patients who had 100% salbutamol-free nights was 57 and 52% in the fluticasone propionate and budesonide groups respectively (P=0.180). Adverse events were reported in 81 and 71% of the fluticasone propionate and budesonide groups, respectively. Less than 3% of these events were considered to be treatment-related.
Weiss et al.[70] (2004) Budesonide 200 to 1,600 µg/day vs triamcinolone 1,200 to 1,600 µg/day	AC, OL, RCT Adult patients with persistent asthma enrolled in 25 United States health plans	N=945 52 weeks	Primary: Mean change from baseline in symptom-free days Secondary: Changes from baseline in number episode-free days, FEV_1, FVC, asthma symptom	Primary: Increases from baseline in mean estimated symptom- and episode-free days occurred in both groups by month one and were maintained throughout the treatment period. These increases were consistently greater with budesonide than with triamcinolone (7.74 and 5.73 for the budesonide group compared to 3.78 and 2.12 for the triamcinolone group; P<0.001 for both). Secondary: The adjusted mean increase in symptom- and episode-free days from baseline to month 12 and the estimated mean number of symptom- and

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			scores, breakthrough bronchodilator use and HRQOL	episode-free days over the 52-week treatment period were significantly greater in the budesonide group compared to the triamcinolone group (P<0.001). The mean FEV_1 and FVC improved from baseline in both groups. Patients receiving budesonide experienced a greater improvement in FEV_1 compared to patients receiving triamcinolone (0.35 vs 0.25 L; P=0.005). The difference between the two groups in FVC was not statistically significant. The mean daytime and nighttime asthma symptom scores improved from baseline in both groups. Improvements were significantly greater in patients receiving budesonide at month 12 compared to patients receiving triamcinolone (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 to 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).
Niphadkar et al.[71] (2005) Ciclesonide 160 µg QAM or QPM vs budesonide 200 µg BID	DB, MC, OL, RCT Patients 18 to 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 µg QAM vs budesonide, 95% CI, -0.051 to 0.123 for ciclesonide 160 µg QPM vs budesonide). No significant differences were found among the three treatment groups with regard to the change in FEV_1 at the end of treatment. Similar results were obtained in the ITT analysis. Secondary: Ciclesonide was found to be non-inferior to budesonide with regard to

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				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 µg PM group, compared with -5.7 L/min in the ciclesonide 160 µg 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 three treatment groups for the secondary endpoints FVC, PEF by spirometry, and morning and evening PEF by diary. Ciclesonide 160 µg QAM, ciclesonide 160 µg 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 µg QAM, ciclesonide 160 µg 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 vs baseline, and no significant differences were found between the treatment groups. Both treatments were well tolerated.
von Berg et al.[72] (2007) Ciclesonide 160 µg QPM vs budesonide 400 µg QPM	AC, DB, DD, MC, PG, RCT Patients six to 11 years of age with persistent asthma for at least six months	N=621 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Change in morning PEF, asthma symptom score, rescue medication utilization,	Primary: Significant increases from baseline in FEV_1 occurred in both the ciclesonide (0.232 L; P<0.0001) and budesonide (0.250 L; P<0.0001) treatment groups. Ciclesonide proved to be non-inferior to budesonide with no significant differences between treatment groups (P=0.8158). Secondary: Both treatment groups experienced a statistically significant increase in morning PEF compared to baseline (ciclesonide, 22.5 L/minute; P<0.0001, budesonide, 26.3 L/minute; P<0.0001).There were no significant

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			percentage of days without asthma symptoms and without need for rescue medication, percentage of patients with asthma exacerbations, PAQLQS and PACQLQ score, adverse events, body height increase at week 12, and change in 24-hour urinary cortisol	differences between treatment groups (P=0.8531). Both treatment groups experienced a statistically significant improvement in asthma symptom score (zero to five scale) after 12 weeks of treatment (ciclesonide, -1.21; P<0.0001, budesonide, -1.21; P<0.0001). There were no significant differences between treatment groups (P=0.8379). Both treatment groups experienced a statistically significant reduction in the need for rescue medication (puffs/day) after 12 weeks of treatment compared to baseline (ciclesonide, -1.58; P<0.0001, budesonide, -1.64; P<0.0001). There were no significant differences between treatment groups (P=0.8593). The percentage of days without asthma symptoms and without need for rescue medication was 73% in the ciclesonide treatment group, and 70% in the budesonide treatment group (P value not reported). The percentage of patients with asthma exacerbations was 2.6% in the ciclesonide treatment group and 1.0% in the budesonide treatment group (P value not reported). Both treatment groups experienced a statistically significant improvement in overall PAQLQS (one to seven scale) and PACQLQ scores compared to baseline (0.69, 0.88 and 0.70, 0.96 for the ciclesonide and budesonide treatment groups respectively (P<0.0001 for all). The percentage of patients who experienced treatment-emergent adverse events was 38% among both treatment groups. The most common adverse events that occurred in at least 5% of patients in the ciclesonide and budesonide treatment groups, respectively, were pharyngitis (5.9 vs 3.8%), nasopharyngitis (4.1 vs 5.4%), upper respiratory tract infection (3.6 vs 6.3%) and oropharyngeal infection (0.2 vs 1.5%). At week 12 the body height increased by 1.18 cm in the ciclesonide treatment group and by 0.70 cm in the budesonide treatment group (P<0.0001 for both). The increase in height was significantly greater in the ciclesonide treatment group than in the budesonide treatment group

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				(P=0.0025). Treatment with ciclesonide and budesonide resulted in significant decreases of urinary cortisol (nmol/mmol creatinine) (ciclesonide, -2.17; P<0.0001, budesonide, -5.16; P<0.0001). The difference between treatment groups was significant (P<0.0001).
Boulet et al.[73] (2006) Ciclesonide 320 µg QD vs budesonide 320 µg QD	DB, MC, RCT Patients 12 to 75 years of age with persistent asthma for ≥6 months, FEV_1 65 to 95% of predicted value, receiving treatment with budesonide 320 to 640 µg, fluticasone propionate 175 to -440 µg/day or equivalent. patients entering the treatment period had to fulfill inclusion criteria and demonstrate improvement in FEV_1 during the pretreatment period of either ≥7% or 0.15 L following the increase in their daily ICS dose from budesonide 320 to 640 mg (or the equivalent) to	N=359 12 weeks	Primary: Change in FEV_1, FVC, PEF, asthma symptom scores, rescue medication use Secondary: Not reported	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 QD, 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 vs 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 vs 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

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	budesonide 1,280 mg.			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% vs 53.6% for ciclesonide and budesonide group, respectively). 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. Secondary: Not reported
Ukena et al.[74] (2007) Ciclesonide 320 µg QPM vs budesonide 400 µg QPM	DB, MC, PG, RCT Patients 12 to 75 years of age with asthma for ≥6 months, FEV_1 50 to 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 vs 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 vs 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.

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				Ciclesonide treatment achieved a significant improvement in morning PEF by day two (P=0.039 vs baseline) compared with day seven for budesonide (P=0.047 vs baseline). Adverse events occurred with a similar incidence in both treatment groups.
Vermeulen et al.[75] (2007) Ciclesonide 320 µg QPM vs budesonide 800 µg QPM	AC, DB, DD, MC, PG, RCT Patients 12 to 17 years of age with severe asthma for six months with an FEV_1 50 to <80% who were not controlled with budesonide 400 µg/day for at least four weeks prior to study	N=403 12 weeks	Primary: Change from baseline in evening pre-dose FEV_1, percentage of days without asthma symptoms and without use of rescue medication Secondary: Change from baseline in FEV_1, percentage of patients experiencing an asthma exacerbation, morning PEF, asthma symptom score, albuterol utilization, PAQLQS score and adverse events	Primary: At 12 weeks, significant increases from baseline in FEV_1 were reported in both the ciclesonide (0.505 L; P<0.0001) and budesonide (0.536 L; P<0.0001) treatment groups. There were no significant differences between treatment groups (P=0.076). The percentage of days without asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group (P value not reported). Secondary: FEV_1 percent predicted increased in the ciclesonide group from 73.1 percent at baseline to 89.4% at the end of the study. In the budesonide group FEV_1 percent predicted was 73.0% at baseline and 90.7% at the end of the study. There was no significant difference between the two study groups (P value not reported). The change from baseline in FVC was significant in both the ciclesonide and budesonide treatment groups (0.433 and 0.472 L, respectively). The difference between the treatment groups was not significant (P=0.080). Asthma exacerbations were reported in 2.6% of patients in the ciclesonide group and 1.5% of patients in the budesonide group. There was no significant difference between the two treatment groups (P value not reported). Morning PEF increased from baseline by 8.0 L/minute in the ciclesonide group (P=0.0424) and 4.9 L/minute in the budesonide group, which was not statistically significant (P value not reported). Asthma symptom scores (zero to five scale) were significantly improved from baseline in both the ciclesonide and budesonide treatment groups (-

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				0.07 and -0.14, respectively; P<0.05 for both). There were no significant differences between treatment groups (P value not reported). The median use of rescue medication was reduced to zero puffs/day in both the ciclesonide (P<0.0001) and budesonide groups (P=0.0003). Overall PAQLQS scores (one to seven scale) were improved in both treatment groups (ciclesonide, 0.19; P=0.0001 and budesonide, 0.18; P=0.0056). The percentage of patients who experienced treatment emergent adverse events was comparable among the ciclesonide and budesonide treatment groups (26.5 vs 18.3%, respectively). The most common adverse event that occurred in at least 5% of patients for either treatment groups was pharyngitis (5.9 vs 3.8%, respectively).
Hansel et al.[76] (2006) Ciclesonide 80 µg QD vs ciclesonide 320 µg QD vs budesonide 200 µg BID	DB, MC, OL, RCT Patients 12 to 75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: Change in FEV_1 Secondary: Changes from baseline in morning PEF, asthma symptom scores, and rescue medication use	Primary: Significant increases from baseline in FEV_1 were achieved in all three 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 µg vs budesonide; 97.5% CI, -0.200 to 0.001for ciclesonide 320 µg vs budesonide). Similar findings were seen in the PP population. There was no significant difference between the two ciclesonide groups. Secondary: Morning PEF was improved significantly in the ciclesonide 80 and 320 µg groups, as well as the budesonide group (all; P<0.008). Ciclesonide was found to be non-inferior to budesonide. No significant differences in morning PEF were found between the two ciclesonide groups. Significant improvements were found in median daily asthma symptom scores in all three treatment groups (all; P<0.001). Significant improvements were found in median daytime and nighttime asthma symptom scores in all three groups (all; P<0.001). Comparisons between treatments for daily, daytime, and nighttime asthma symptom scores did not demonstrate any significant differences throughout the

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				study. Overall, the percentages of patients without any asthma symptoms (score, 0) increased from -20 to -40% after three days of treatment; these percentages were similar across all three 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 µg BID (four patients), the mean onset of action was 4 weeks, whereas in smokers treated with ciclesonide 80 µg QD (23 patients) or 320 µg QD (15 patients), onset was within one week. There were significant decreases in rescue medication use in all three groups by day one of treatment (all; P<0.001). These decreases remained significant throughout the study in all three treatment groups (all; P<0.001). AEs were reported in 36.8% of patients receiving ciclesonide 80 µg QD, 80 (40.8%) patients receiving ciclesonide 320 µg QD, and 60 (33.9%) patients receiving budesonide 200 µg BID.
Buhl et al.[77] (2006) Ciclesonide 160 µg QD vs fluticasone propionate 88 µg BID	DB, MC, RCT Patients 12 to 75 years of age with asthma for ≥6 months, FEV_1 50 to 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 to 400 µg of salbutamol or	N=529 12 weeks	Primary: Changes in FEV_1, FVC, PEF, $FEF_{25-75\%}$, asthma symptom scores, rescue mediation use Secondary: Not reported	Primary: Ciclesonide produced similar improvements in FEV_1 as fluticasone propionate (0.489 and 0.499 L for ciclesonide and fluticasone propionate, 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 propionate, 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 propionate. $FEF_{25-75\%}$ increased in both the ciclesonide and fluticasone propionate treatment groups by 0.519 and 0.601 L/s, respectively (P<0.0001 for both), and no significant differences were observed between treatment

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	have shown a diurnal PEF fluctuation ≥15%			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 propionate groups. Ciclesonide and fluticasone propionate also significantly reduced rescue medication use with no significant differences between the groups. There was no significant difference between ciclesonide and fluticasone propionate with regards to rescue medication-free days, asthma symptom-free days, and nights without awakenings due to asthma. 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 propionate group). Secondary: Not reported
Boulet et al.[78] (2007) Ciclesonide 320 µg QPM vs fluticasone propionate 200 µg BID	MC, OL, RCT Patients 12 to 75 years of age with moderate asthma for ≥6 months and FEV_1 60 to 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, HRQOL Secondary: Not reported	Primary: FEV_1 increased significantly from baseline with ciclesonide and fluticasone propionate 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 propionate (-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 propionate -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

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				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 propionate 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 propionate groups, 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 propionate 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 propionate group. The improvement with ciclesonide was significantly greater than with fluticasone propionate (P=0.005). Both ciclesonide and fluticasone propionate produced significant increases in all of the individual AQLQ(S) domain scores. Non-inferiority of ciclesonide to fluticasone propionate 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 vs fluticasone propionate (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 propionate group).
Magnussen et al.[79]	DB, PG, RCT	N=808	Primary:	Primary:

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(2007) Ciclesonide 80 µg QPM vs ciclesonide 160 µg QPM vs fluticasone propionate 88 µg BID	Patients 12 to 75 years of age with persistent asthma for ≥6 months	12 weeks	Change in FEV_1 and change in nighttime asthma symptoms score Secondary: PEF, FVC, asthma symptoms, rescue medication use, and days with asthma control	Ciclesonide 80 µg, ciclesonide 160 µg and fluticasone propionate achieved similar improvements in FEV_1 (P<0.0001 for all groups and time points vs baseline; ITT). PP analysis revealed similar results. Both doses of ciclesonide were found to be non-inferior to fluticasone propionate and led to similar improvements in FEV_1 from baseline. Non-inferiority of both ciclesonide 80 and 160 µg vs fluticasone propionate was achieved for PEF and FVC, as well as evening PEF. For morning PEF, the within-treatment improvements were statistically significant for all three treatment groups (P<0.0001). Non-inferiority was demonstrated for ciclesonide 160 µg vs fluticasone propionate, but not for ciclesonide 80 µg. Treatment with ciclesonide 80 µg, ciclesonide 160 µg and fluticasone propionate 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 vs baseline). There were no significant differences among groups for asthma symptom scores. Similar results were obtained in the PP analysis. All three treatment groups significantly reduced rescue medication use (all P<0.0001 vs 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 two patients in each of the ciclesonide 80 and 160 µg groups and one patient in the fluticasone propionate group experienced an asthma exacerbation that required treatment with oral steroids. A total of 25% of patients in the ciclesonide 80 µg group, 24% of patients in the ciclesonide 160 µg group and 27% of patients in the fluticasone propionate group experienced AEs.
Pedersen et al.[80] (2009)	DB, PG, RCT	N=744	Primary: Change in FEV_1,	Primary: FEV_1 increased significantly in all treatment groups (P<0.0001). Non-

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Ciclesonide 80 µg QD vs ciclesonide 160 µg QD vs fluticasone propionate 88 µg BID	Patients 6 to 11 years of age with persistent asthma for ≥6 months, FEV_1 50 to 90% of predicted and FEV_1 reversibility of ≥12% predicted after salbutamol 200 to 400 µg	12 weeks	PEF, exacerbations, asthma symptom scores, rescue medication use, quality of life Secondary: Not reported	inferiority was demonstrated for ciclesonide 160 µg vs fluticasone propionate (95% CI, -0.079 to 0.027; P=0.0030, whereas ciclesonide 80 µg was not shown to be non-inferior to fluticasone propionate. Morning PEF increased significantly in all treatment groups (all P<0.0001). Both ciclesonide doses were non-inferior to fluticasone propionate (P<0.0063 for both doses). Asthma exacerbations occurred in 7.1% of patients receiving ciclesonide 80 µg, 2.9% of patients receiving ciclesonide 160 µg, and 2.0% of patients receiving fluticasone propionate. 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 propionate 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 µg and ciclesonide 160 µg to fluticasone propionate (P<0.0001 for all). The percentage of patients experiencing AEs was comparable across all treatment groups (ciclesonide 80 µg, 46.4%; ciclesonide 160 µg, 41.7%; fluticasone propionate 176 µg, 47.6%).
Bateman et al.[81] (2008)	MC, MG, OL, RCT	N=528	Primary: Change in FEV_1	Primary: FEV_1 was maintained from baseline to study end in both groups (mean

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Ciclesonide 160 µg, 2 inhalations BID vs fluticasone propionate 110 µg, 3 inhalations BID Patients using LABAs, oral β_2-agonists, theophylline, leukotriene antagonists or lipoxygenase inhibitors could continue treatment provided the dose was kept constant throughout the trial.	Patients 12 to 75 years of age with ≥6 month history of asthma, FEV_1 ≥80% of predicted, reversibility of FEV_1 ≥12% after 200 to 400 µg salbutamol, and ≥1 day without asthma symptoms during the last 7 days; patients were receiving fluticasone propionate 500 to 1,000 µg/day	6 months	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 with asthma control; and AQLQ(S)	increase, ciclesonide 11 mL, fluticasone propionate 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 propionate. Six patients in the ciclesonide group and seven in the fluticasone propionate 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 propionate were not statistically significant for any of the asthma symptom scores or rescue medication use. 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 propionate group. There was no significant difference between the treatment groups. There were significant improvements in HRQOL (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.
Newhouse et al.[82] (2000) Flunisolide 750 µg BID (administered	AC, MC, PG, RCT Patients with moderate asthma (FEV_1 40 to 85% of	N=176 6 weeks	Primary: Change from baseline in pre bronchodilator FEV_1 and albuterol	Primary: There were no statistically significant differences between the two 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).

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via AeroChamber®) vs budesonide 600 µg BID (administered via Turbuhaler®)	predicted)		usage Secondary: Changes in PEF, asthma scores and nocturnal awakenings	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 groups in the changes in PEF, asthma symptoms scores or nocturnal awakenings during the treatment period.
Berend et al.[83] (2001) Fluticasone propionate (at ~50% of the ICS dose during the run-in phase) vs beclomethasone or budesonide (at the same dose used during the run-in phase)	MC, OL, PG, RCT Patients 18 years of age or older with a history of severe asthma, currently receiving at least 1,750 µg/day of inhaled beclomethasone or budesonide	N=133 6 months	Primary: Changes from baseline in morning PEF and FEV_1 Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations and quality of life	Primary: Patients in the fluticasone propionate group experienced a significant improvement in morning PEF compared to patients continuing the same dose of their ICS (adjusted difference between two groups, 26±32 L/minute; 95% CI, 8 to 45; P=0.006). The changes from baseline in FEV_1 measured at clinic visits paralleled those values of the morning PEF (1.87±0.70 L with fluticasone propionate and 2.03±0.86 L with beclomethasone/budesonide; P values not reported). Secondary: Serum osteocalcin levels increased significantly in the fluticasone propionate group (adjusted mean [SD], 2.6 [4.0] µg/L; 95% CI, 0.2 to 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 groups. There was a low incidence of oropharyngeal candidiasis during the study in both groups. Four patients (6%) in the fluticasone propionate group and one patient (2%) in the beclomethasone or budesonide group had evidence of candidiasis. There was no significant difference between the two groups. Thirty-four patients (51%) in the fluticasone propionate group and 36 patients (55%) in the beclomethasone/budesonide group reported one or

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				more exacerbations during the course of the trial. There was a significant increase in the overall asthma quality of life score in the fluticasone propionate group (P<0.001); however, there was no significant difference in the beclomethasone or budesonide group (P=0.13).
Raphael et al.[84] (1999) Fluticasone propionate 88 µg BID vs fluticasone propionate 220 µg BID vs beclomethasone 168 µg BID vs beclomethasone 336 µg BID	AC, DB, PG, RCT Nonsmoking patients 12 years of age or older with a diagnosis of chronic asthma requiring daily ICS therapy for at least six months prior to the study	N=399 14 weeks	Primary: Changes in morning predose FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings and asthma symptoms	Primary: The FEV_1 was significantly improved from baseline in both treatment groups; however, greater improvements occurred with fluticasone propionate compared to beclomethasone (0.05 vs 0.03 L; P=0.006). At endpoint, mean FEV_1 values in the low-and medium-dose fluticasone propionate treatment groups improved by 0.31 (14%) and 0.36 L (15%) respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively. Secondary: The $FEF_{25\ to\ 75\%}$ and FVC were significantly improved from baseline in all treatment groups; however, patients receiving fluticasone propionate experienced greater improvements compared to patients receiving beclomethasone ($P \leq 0.034$ for all). Fluticasone propionate treatment provided a significantly greater improvement in morning PEF compared to beclomethasone treatment at all time points except week two (P<0.004 for all). There was a significant improvement in morning PEF relative to baseline in the fluticasone propionate group (15.8 to 22.8 L), but not in the beclomethasone groups (0.7 to 7.2 L; P values not reported). A similar trend was seen in evening PEF, but the differences between treatments was not statistically significant. There were no significant differences noted in the analysis of the probability of remaining in the study. The percentage of albuterol-free days was significantly higher in the fluticasone propionate group compared to the beclomethasone group (P=0.01 at 14 weeks). Albuterol use declined by 0.9 (26%) and 0.5 (16%)

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				puffs/day in the low and moderate fluticasone propionate 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 improvements in asthma symptom scores (P=0.024) and in the percentage of days in which no symptoms were recorded (P=0.027) occurred with fluticasone propionate treatment compared to beclomethasone treatment.
Ferguson et al.[85] (1999) Fluticasone propionate 200 µg BID via DPI vs budesonide 400 µg BID via DPI	AC, DB, DD, PG, RCT Children four to 12 years of age with a history of moderate to severe asthma who required moderate to high doses of an ICS to control symptoms for at least one month preceding the study	N=442 22 weeks	Primary: Mean morning PEF during the last seven treatment days Secondary: Adverse events	Primary: The adjusted mean morning PEF, measured over the last seven treatment days, were 271±82 and 259±75 L/minute, for the fluticasone propionate and budesonide treatment groups, respectively. The difference in means was 12 L/minute (90% CI, 6 to 19; 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 seven days of the 20-week treatment period were within ±15 L/minute. The 90% upper and lower confidence limits for the treatment difference were 6 and 9 L/minute, respectively, indicating that the treatments were not equivalent, with fluticasone propionate demonstrating improved outcomes. Secondary: There was no significant difference in the number of children who experienced an adverse event in the two treatment groups.
Fitzgerald et al.[86] (1998) Fluticasone propionate 375 µg BID vs	AC, DB, RCT, XO Children five to 16 years of age with persistent severe asthma requiring 1,000 to 2,000 µg/day of inhaled	N=30 12 weeks	Primary: The daily mean morning and evening PEF and day and night symptom scores Secondary:	Primary: There was no statistically significant difference between the treatment groups in PEF or symptoms scores. Secondary: There was no difference in physician/patient/parent assessment of efficacy with 90% rating both fluticasone propionate and budesonide effective or very effective.

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budesonide 750 µg BID	beclomethasone or budesonide continuously for symptom control over the previous 12 months		Physician/patient/parent assessment of efficacy, total number of exacerbations requiring systemic steroids, adrenal function, growth and adverse events	The total number of exacerbations (33 in the fluticasone propionate group and 35 in the budesonide group) and those exacerbations requiring systemic steroids (nine in the fluticasone propionate group and 11 in the budesonide group) suggested no difference between the treatment groups. There were no significant differences in adjusted means for urinary free cortisol levels, adrenocorticotropic hormone 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 adverse events were related to exacerbations of asthma or upper respiratory tract infections. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to ICSs between the treatment groups.
Harnest et al.[87] (2008) Fluticasone propionate 500 µg BID vs mometasone 500 µg BID	AC, RCT Patients 18 years of age and older with moderate to severe persistent asthma who were previously using an ICS for daily maintenance therapy for ≥30 days	N=203 12 weeks	Primary: Change from baseline in weekly average PEF Secondary: FEV_1, asthma symptom scores, rescue medication use, response to therapy and adverse events	Primary: The change from baseline in PEF was 7.8% in the mometasone group and 7.7% in the fluticasone propionate group (P=0.815). Secondary: At week 12, the change from baseline in FEV_1 was 0.4 L in both the mometasone and fluticasone propionate groups (P=0.988). The morning and evening asthma symptom scores were not significantly different between the mometasone and fluticasone propionate groups (P=0.251). Rescue albuterol use decreased from baseline in patients receiving either treatment; however, there was no significant difference between the groups (P=0.890). Treatment-emergent adverse events occurred in 51% of the patients in the mometasone group and 43% of the patients in the fluticasone propionate group. The difference between the two groups was not significant (P value not reported).

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Condemi et al.[88] (1997) Fluticasone propionate 250 µg BID vs triamcinolone 200 µg QID vs placebo	AC, DB, DD, PC, PG, RCT Patients 12 years of age and older with asthma (FEV_1 50 to 80% 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 PEF, albuterol use, number of nighttime awakenings requiring albuterol and asthma symptom scores Secondary: Adverse events and morning plasma cortisol levels	Primary: Patients in both the fluticasone propionate and triamcinolone groups experienced statistically significant improvements in FEV_1 compared to the placebo group (0.27 and 0.07 vs -0.18 L for fluticasone propionate and triamcinolone compared to placebo, respectively; $P \leq 0.001$ for both). Only 27% of patients in the placebo group remained in the study over time compared to 66% of patients in the fluticasone propionate group and 55% of patients in the triamcinolone group. Patients in either active treatment group had a significantly greater probability of remaining in the study over time compared to patients in the placebo group ($P<0.001$). There was no significant difference between the two active treatment groups. The mean PEF was significantly improved in patients who received fluticasone propionate (21 L/minute) compared to mean decreases of six and 28 L/minute in the triamcinolone and placebo groups, respectively ($P<0.001$). Albuterol use was reduced by 30% in the fluticasone propionate group and by 6% in the triamcinolone group. Patients in the placebo group increased their albuterol use by 50% ($P<0.05$). The number of nighttime awakenings requiring albuterol was significantly decreased with either fluticasone propionate or triamcinolone compared to placebo ($P \leq 0.001$ for both). The frequency of nighttime awakenings significantly increased after treatment with placebo ($P<0.05$). There were no significant differences between the treatment groups with respect to symptom scores. Secondary: Thirteen percent of patients in the placebo group, 15% of patients in the fluticasone propionate group and 8% of patients in the triamcinolone group experienced at least one adverse event that was considered to be potentially treatment-related. One percent of patients in the placebo group, 3% of patient in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				triamcinolone group and 1% of patients in the fluticasone propionate group had morning plasma cortisol concentrations <5 µg/mL.
Noonan et al.[89] (2009) Mometasone 200 µg QD vs mometasone 100 µg BID vs beclomethasone 168 µg BID	AC, MC, OL, PRO Patients four to 11 years of age with mild to moderate persistent asthma using an ICS within 30 days prior to the study and on a stable regimen at least two weeks before screening	N=233 52 weeks	Primary: Incidence of adverse events Secondary: Laboratory tests including cortisol concentrations, vital signs and physical examinations	Primary: The incidence of adverse events was similar in all three groups. Secondary: No significant differences between groups were observed in any secondary end points.
Nathan et al.[90] (2001) Mometasone 100 µg BID vs mometasone 200 µg BID vs beclomethasone 168 µg BID vs placebo	AC, DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously maintained on an ICS	N=227 12 weeks	Primary: Changes in FEV_1 Secondary: PEFR, asthma symptoms, nocturnal awakenings and albuterol use	Primary: The FEV_1 was significantly improved in all three active treatment groups compared to the placebo group (P<0.01). There was no statistically significant difference in FEV_1 between the mometasone 200 µg and beclomethasone groups (P=0.07) or the mometasone 200 µg and mometasone 100 µg groups (P=0.08). Secondary: The improvements in FEV_1, PEFR, asthma symptoms, nocturnal awakenings, and albuterol use were approximately twice as large for the mometasone 200 µg group as for the mometasone 100 µg and beclomethasone groups; however, the difference was not significant.
Bernstein et al.[91]	AC, DB, DD, MC,	N=365	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1999) Mometasone 100 µg BID vs mometasone 200 µg BID vs mometasone 400 µg BID vs beclomethasone 168 µg BID vs placebo	RCT Patients with asthma previously treated with an ICS	12 weeks	Mean change from baseline in FEV_1 Secondary: FVC, $FEF_{25\ to\ 75\%}$, PEFR, patient evaluation of asthma symptoms and physician evaluation of asthma symptoms	The changes from baseline in FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and PEFR were significantly greater in all the active treatment groups compared to the placebo group (P<0.01 for all). The mometasone 200 µg BID group demonstrated a greater improvement compared to the mometasone 100 µg BID group, with the mometasone 400 µg BID group showing no additional benefit. Secondary: Changes in lung function were similar between the mometasone 100 µg BID group and the beclomethasone group. Improvements in asthma symptoms as evaluated subjectively by patients and physicians were similar for the mometasone 200 (P<0.01) and 400 (P=0.05) µg BID groups, which were also significantly better than the mometasone 100 µg BID (P=0.01) and beclomethasone (P=0.02) treatment groups.
Bousquet et al.[92] (2000) Mometasone 100 to 400 µg BID vs budesonide 400 µg BID	AC, DB, MC, RCT Patients with moderate persistent asthma previously maintained on a daily ICS	N=730 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: Self-rated asthma symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use and physician	Primary: The FEV_1 was significantly improved from baseline in the mometasone 200 and 400 µg BID treatment groups compared to the budesonide treatment group (P<0.05 for both). Secondary: Morning wheezing scores were significantly improved in the mometasone 400 µg BID group compared to the budesonide group and mometasone 100 µg BID group (P value not reported). Patients treated with mometasone 200 or 400 µg BID required significantly less albuterol compared to patients treated with budesonide. Physicians reported a significant improvement in asthma symptom scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			evaluation of response to therapy	in the mometasone 200 and 400 µg BID groups compared to the budesonide group (65 and 63 vs 50%; P value not reported).
Corren et al.[93] (2003) Mometasone 440 µg QD vs budesonide 400 µg QD vs placebo	AC, DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously using ICSs	N=262 8 weeks	Primary: Percent change from baseline in FEV_1 Secondary: Morning and evening PEFR, FVC, $FEF_{25\ to\ 75\%}$, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy and asthma symptom scores	Primary: The percent change in FEV_1 was significantly greater in the mometasone group compared to the budesonide ($P<0.01$) and placebo groups ($P<0.001$). Secondary: Pulmonary function ($FEF_{25\ to\ 75\%}$, 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 to both the budesonide and placebo groups ($P<0.05$ for both).
Wardlaw et al.[94] (2004) Mometasone 400 µg QPM vs fluticasone propionate 250 µg BID	AC, OL, PG, RCT Patients with moderate, persistent asthma previously using fluticasone propionate	N=167 8 weeks	Primary: Percent change from baseline in FEV_1 Secondary: FVC, PEFR, asthma symptom scores, albuterol use and device evaluation	Primary: There were no significant differences in the percent change in FEV_1 between the groups at any point in the study ($P\geq0.14$ for all). Secondary: There were no significant differences in the percent change in FVC ($P\geq0.24$), PEFR ($P=0.60$), albuterol use or asthma symptom scores ($P\geq0.06$) between the groups at any point in the study. A greater proportion of patients in the mometasone group experienced an improvement in asthma symptoms compared to the fluticasone propionate group ($P=0.007$) as reported by physicians' evaluations of response to therapy. A significantly greater proportion of patients reported having "liked the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				inhaler a lot" in the mometasone group compared to the fluticasone propionate group (P=0.01).
O'Connor et al.[95] (2001) Mometasone 100 to 400 µg BID vs fluticasone propionate 250 µg BID	AC, DB, MC, PG, RCT Patients with moderate, persistent asthma previously treated with an ICS	N=733 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Mean changes from baseline in PEFR, $FEF_{25\ to\ 75\%}$, FVC, asthma symptom scores, albuterol use, nocturnal awakenings due to asthma and physician-evaluation of response to therapy	Primary: Patients in either group experienced an improvement from baseline in FEV_1. There was no statistically significant difference between the groups. Patients in the mometasone 400 µg BID group experienced a significant improvement in FEV_1 compared to patients in the mometasone 100 µg BID group (P=0.02). Patients in the mometasone 200 µg BID and fluticasone propionate groups experienced similar improvements in FEV_1. Secondary: The $FEF_{25\ to\ 75\%}$ and PEFR were significantly improved in the mometasone 200 µg BID, 400 µg BID and fluticasone propionate groups compared to the mometasone 100 µg BID group. There were no statistically significant differences in the other outcomes between groups.
Kramer et al.[96] (2013) Ciclesonide vs budesonide vs fluticasone propionate	MA (6 RCTs) Patients <18 years of age with chronic asthma	N=3,256 ≥4 weeks	Primary: Asthma symptoms, asthma exacerbations, adverse effects Secondary: Quality of life, compliance, change in lung function and airway inflammation	Primary: There were two studies included that evaluated ciclesonide for non-inferiority to budesonide. There were no significant differences in asthma symptoms or exacerbations. Rates of adverse effects were similar between the two treatments. Four studies compared ciclesonide to fluticasone propionate. There were no significant differences in asthma symptoms, asthma exacerbations and adverse effects. However, in the one study that compared ciclesonide and fluticasone propionate in a 1:2 dose ratio, the number of asthma exacerbations was significantly higher in the ciclesonide group (RR, 3.57; 95% CI, 1.35 to 9.47). Secondary: When ciclesonide was compared to budesonide, there were no significant differences in quality of life measures and FEV_1. No other secondary endpoints were reported.

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				For the studies comparing ciclesonide and fluticasone propionate, non-inferiority of ciclesonide was confirmed for quality of life measures (P<0.0001). There were no significant differences in FEV_1. No other secondary endpoints were reported.
Szefler et al.[97] (2007) Budesonide 500 µg QD (BIS group) vs montelukast 4 to 5 mg QD	MC, OL, 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 two 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 and PM PEF, for which improvements were

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				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 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 and 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.
Nakanishi et al.[98] (2003)	PC, PG, RCT, Masked	N=58 7 days	Primary: Percentage of predicted FEV_1	Primary: The FEV_1 percentage of predicted for the ICS group was lower on day three (65 vs 78% for oral corticosteroids; P=0.03) and on day seven (77 vs

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Flunisolide 1 mg BID via valved holding chamber vs prednisone 2 mg/kg	Children 6 to 16 years of age seeking emergent care for an acute exacerbation of asthma		Secondary: Symptom score, initial vital signs and oximetry, side effects, recurrence rate for acute asthma symptoms, and daily PEF Secondary: Not reported	95%; P=0.002). Both groups continued to improve over the seven-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 ICS group required additional corticosteroids after the seven-day study period to control symptoms. One 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.
Pohl et al.[99] (2006) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (AMD) vs budesonide 320 µg, 2 inhalations BID (AMD)	DB, PG, RCT Patients >19 years of age with asthma, FEV_1 reversibility ≥15% (or 200 mL) within 1 month prior to enrollment, FEV_1 40 to 85% of predicted normal, requirement with an ICS or ICS/LABA combination within given starting dose range	N=133 20 weeks	Primary: Number of patients/ treatment group with ≥1 treatment failure (defined as hospitalization, oral steroids, nebulized β_2-agonists, withdrawal due to lack of efficacy or life-threatening condition) Secondary: HRQOL measured by the SF-36, dose of study	Primary: The rate of treatment failures were comparable between the two treatment groups with five out of the 63 patients in the budesonide/formoterol group and two out of the 63 patients in the budesonide group experiencing treatment failure throughout the duration of the study. Secondary: Patients in the budesonide/formoterol group had a statistically significant improvement in HRQOL and treatment satisfaction (for patients and physicians) vs 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 vs budesonide (P=0.024). Both groups had minimal use of reliever medications.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			medication, days of reliever medication use, and treatment satisfaction	
Tal et al.[100] (2002) Budesonide-formoterol 80-4.5 µg, 2 inhalations BID vs budesonide 100 µg, 2 inhalations BID	DB, DD, MC, PG, RCT Children 4 to 17 years of age with a diagnosis of asthma for ≥6 months, FEV_1 40 to 90% of predicted value at visit 1, >15% reversibility of FEV_1 within 15 minutes of inhalation of a SABA, 6 weeks constant dosing with an ICS (budesonide, fluticasone propionate or beclomethasone)	N=286 12 weeks	Primary: Morning PEF Secondary: FEV_1, FEV_1 over a 12 hour time period, rescue inhaler use, comparison of nocturnal asthma symptoms, and safety	Primary: Combination therapy resulted in a significantly greater increase in morning PEF than monotherapy (P<0.001). Results were similar for evening PEF (P value not reported). Secondary: FEV_1 scoring (P<0.05), mean improvement of FEV_1 over 12 hours after one dose (P<0.05) and mean improvement of FEV_1 ten minutes after first dose (P<0.05) favored combination therapy. A decrease in rescue inhaler use from 0.71 to 0.60 inhalations/day was seen in the combination therapy group, and a change of 0.50 to 0.41 inhalations was seen with the monotherapy group. There was no statistical significance between the groups (P value not reported). A decrease in the number of nights awakening with asthma symptoms was seen in both groups with no significant difference (combination therapy decreased from 7.2 to 5.5% and monotherapy decreased from 8.5 to 6.6%; P value not reported). Reported adverse events between the two groups were comparable and reported as combination vs monotherapy. 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 combination therapy group, 4.7% of patients had serious adverse side effects.
Lalloo et al.[101] (2003) Budesonide-formoterol 80-4.5 µg BID	DB, MC, PG, RCT Patients >18 years of age with a diagnosis of asthma assessed by the	N=467 12 weeks	Primary: Morning and evening PEF values Secondary:	Primary: Morning and evening PEF values increased for both treatment groups; however, significantly larger increases were seen with combination therapy than with monotherapy (P=0.002 and P<0.001, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 200 µg BID Inhaled terbutaline or salbutamol was used as a reliever medication depending on patient preference.	following: FEV_1 60 to 90% of predicted normal value and >12% reversibility of basal FEV_1 within 15 minutes of terbutaline or salbutamol inhalation; all patients received ICSs of any brand at a constant dose of 200 to 500 µg/day for ≥1 month prior to study entry		FEV_1/FVC measurements, symptom free days, reliever free days, nighttime awakenings, time to first mild and severe exacerbation, and safety	Mean FEV_1 scores increased in both groups but no significant difference was found, additionally, FVC showed no change from baseline. The incidence of asthma control days, symptom free days and reliever medication use (P=0.025) all favored combination therapy. Asthma control days favored combination therapy (17 vs 10%; P=0.002). Symptom free days were similar between groups (16 vs 10%; P=0.007). A reduction of 24 vs 6% and 23 vs 14% favored combination therapy for asthma symptom score and nighttime awakenings, respectively (P values not reported). Fewer patients experienced a mild exacerbation (110/230) in the combination group than the monotherapy group (136/237; P value not reported). Nighttime awakenings also favored combination therapy (75 vs 105; P value not reported). The monotherapy group showed a shorter time to first mild exacerbation compared to the combination group (P=0.02). The risk of having a mild exacerbation was estimated to be 26% lower in the combination group (P=0.02). The chance of having a severe exacerbation was six percent lower in the combination group (P=0.85). No between group differences were noted for the profile and frequency of adverse events. Both treatment groups commonly reported respiratory infection, pharyngitis, and rhinitis. Overall, there were seven severe adverse events, five occurred with combination therapy and two with monotherapy.
Berger et al.[102] (2010) Budesonide-formoterol 160-4.5 µg BID vs	MC, OL, RCT Patients 6 to 11years of age with asthma for ≥ 6 months who previously received daily ICS for ≥4	N=187 26 weeks	Primary: Safety analysis, urinary cortisol, EKG's Secondary: Pulmonary function, health	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

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budesonide 200 µg BID	weeks prior to randomization and had FEV_1 ≥50%		care resource utilization, HRQL	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 vs budesonide (0.15 vs 0.07 L; 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).
Zangrilli et al.[103] (2011) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg, 2 inhalations BID via MDI	AC, DB, MC, RCT Hispanic patients ≥12 years of age with asthma for ≥6 months and a pre-bronchodilator FEV_1 of 45 to 85% of predicted normal and reversibility of ≥12% with albuterol administration and a documented daytime or nighttime asthma symptom scores ≥0 on 3 or more days within 7 consecutive days during a 2-week run-in period on budesonide 160 µg	N=150 12 weeks	Primary: Mean change from baseline in morning (AM) PEF Secondary: Predefined asthma events (decreased FEV_1 ≥20% from randomization or FEV_1 <40% of predicted normal, ≥12 inhalations of albuterol per day, decreased morning PEF ≥20% from baseline on ≥3 of seven consecutive days after	Primary: The morning PEF value increased from baseline during randomized treatment, in both treatment groups but there was no significant difference between treatments (25.4 vs 19.9% in the combination and monotherapy groups, respectively; P≥0.428). Secondary: Patients who received combination therapy experienced fewer asthma events compared to patients receiving monotherapy, although the difference was not statistically significant (25.2 vs 31.7%; P value not reported). Similarly, 3.1 and 6.5% of patients in the combination and monotherapy treatment groups withdrew from the study due to asthma related events, although the differences in discontinuation rates were not significant (P value not reported). There was no significant difference between patients receiving combination treatment or monotherapy, in regard to the change in daily asthma symptom score, daytime symptom score or nighttime symptom score (P≥0.181 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	BID		randomization, ≥2 nocturnal asthma awakenings requiring rescue medication within seven days after randomization, or a clinical exacerbation requiring emergency treatment, hospitalization, or use of an excluded asthma medication) and withdrawals caused by these events, pulmonary function assessments and diary-based measures of asthma control	Rescue medication use decreased, and the percentage of symptom-free days, awakening-free nights, and rescue medication-free days increased in both treatment groups, but no differences in these outcomes were observed between the treatment groups (P values not reported).
Spector et al.[104] (2012) Budesonide-formoterol 320-9 µg BID vs budesonide 320 µg Each group had a two week run-in	DB, DD, RCT Self-reported black patients ≥12 years of age with an asthma diagnosis for ≥6 months, FEV_1 of 45 to 85% predicted normal, reversibility of FEV_1 ≥12% and ≥0.2 L, and consistent treatment	N=311 12 weeks	Primary: Change from baseline in predose FEV_1 at weeks two, six, 12 Secondary: Change from baseline in FVC, FVC in middle portion of expiration, diary-related assessments	Primary: Improvements in predose FEV_1 was significantly greater in the budesonide-formoterol group compared to the budesonide group (P=0.008) at 12 weeks. Significant differences in predose FEV_1 started at week two and continued throughout the time points (P≤0.032). Secondary: The improvement in predose FVC was significantly greater in the budesonide-formoterol group compared to the budesonide group (P<0.05). However the improvement in FVC in middle portion of expiration was not significantly different between the groups. Improvements in morning and evening PEF was significantly greater in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
period with single-blinded budesonide 180 µg BID.	with daily medium- to high-dose ICSs for ≥30 days		(morning and evening PEF, asthma symptoms, rescue medication use, nighttime awakenings, awakening fee nights, rescue medication free days, asthma control days) and asthma worsening	the budesonide-formoterol group compared to the budesonide group (P<0.001). The rate of asthma worsening was lower in the budesonide-formoterol group compared to the budesonide; however, the difference was not statistically significant. Compared to the budesonide group, reductions in daily asthma symptoms (P=0.039) and rescue medication use (P=0.029) were significantly greater in the budesonide-formoterol group. Improvements in awakening fee nights, rescue medication free days, and asthma control days were not significantly different between the groups. In the budesonide-formoterol group, 41.2% of patients experienced and adverse event compared to 30.3% in the budesonide group. The most comment adverse events in both groups were headache, nasopharyngitis and upper respiratory infection.
Brown et al.[105] (2012) Budesonide-formoterol 320-9 µg BID vs budesonide 320 µg BID Each group had a two week run-in period with single-blinded budesonide 180 µg BID.	DB, MC, PG, RCT Self-reported African American patients ≥12 years of age with stable asthma for ≥6 months, FEV_1 ≥50% predicted normal value at screening and randomization, reversibility of FEV_1 ≥12% and ≥0.2 L, and consistent treatment with daily medium- to high-dose ICSs for ≥30 days	N=752 52 weeks	Primary: Change in asthma exacerbations and adverse events Secondary: Changes in FEV_1, FVC, patient daily diary measure of asthma control (rescue medication usage, rescue medication free days, symptoms free days and asthma control days)	Primary: There percentage of patients with ≥1 asthma exacerbation was significantly lower in the budesonide-formoterol group compared to the budesonide group (P=0.006). The rate of asthma exacerbations was significantly reduced in the budesonide-formoterol group compared budesonide (P=0.002). The rate of prednisone usage was significantly reduced in the budesonide-formoterol group compared budesonide (P<0.001). In the budesonide-formoterol group, 51.2% experienced ≥1 adverse events compare to 47.8% in the budesonide group. Adverse events that were reported in ≥5% of patients included headache (8.6%), nasopharyngitis (7.4%), sinusitis (5.1%) and viral upper respiratory tract infection (5.1%). In the budesonide-formoterol group and budesonide, there were similar rates of discontinuation due to adverse events (2.7 and 2.2%), serious adverse events (3.2 and 4.1%) and nonfatal serious adverse events (2.9 and 3.8%). Secondary: Improvements in FEV_1, FVC and morning PEF were significantly greater with budesonide-formoterol group compared budesonide (P≤0.013). Additionally, there was significant improvements with budesonide-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				formoterol group compared budesonide in percentage of rescue medication-free days (P=0.003) and asthma control (0.006). There was no significant difference in symptom-days. Reductions in rescue albuterol metered dose inhaler usage was significantly higher in the budesonide-formoterol group compared budesonide (P=0.0030).
Remington et al.[106] (2002) Budesonide (range: 200, 400, and 800 µg) vs budesonide (range: 200, 400, and 800 µg) plus formoterol (range: 9 to 24 µg)	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 Secondary: Not reported	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 µg 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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Rosenhall et al.[107] (2002) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations BID (separate inhalers)	MC, OL, RCT Patients with moderate persistent asthma (average age, 45)	N=586 6 months	Primary: Safety and efficacy (FEV_1, Mini AQLQ, ACQ, exacerbations Secondary: Not reported	Primary: Patients in both treatment groups had a mean FEV_1 increase of five to six percent from baseline (P value not reported). There was no significant change in response using the Mini AQLQ and the ACQ from baseline in both treatment groups. Both treatment groups were well tolerated, with asthma exacerbations occurring at a low frequency (P value not reported). The withdrawal rate in both groups was also similar (P=0.085). Secondary: Not reported
Rosenhall et al.[108] (2003) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations BID (separate inhalers)	MC, OL, PG, RCT Adult patients with asthma of ≥6 months duration, predicted FEV_1 ≥50%, receiving constant ICS dose of ≥400 to 1,200 µg for ≥30 days, and daily use of inhaled short- and/or LABA	N=321 6 months	Primary: Lung function, asthma control, HRQOL 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 HRQOL 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).
Rosenhall et al.[109] (2006)	ES, MC, OL, PG, RCT	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations BID (separate inhalers)	Adult patients with asthma		Secondary: Not reported	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). Secondary: Not reported
Rabe et al.[110] (2006) Budesonide-formoterol 160-4.5 µg BID and terbutaline MDI 0.4 mg as needed vs budesonide-formoterol 160-4.5 µg BID and formoterol MDI 4.5 µg as needed vs budesonide-formoterol 160-4.5 µg BID	DB, MC, PG, RCT 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 to 100% of predicted normal (pre bronchodilator) with 12% reversibility or more after inhalation of terbutaline 1 mg	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 exacerbations; FEV_1; morning and evening PEF; and reliever medication use	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 vs terbutaline (P=0.0051). Secondary: As-needed budesonide-formoterol reduced the risk of a severe exacerbation by 27% (95% CI, 10 to –41) vs formoterol and by 45% (95% CI, 32 to 55) vs terbutaline. The risk reduction with as-needed formoterol vs terbutaline was 24% (95% CI, 8 to 37). The yearly rate of severe exacerbations per patient was reduced with as-needed budesonide-formoterol by 33% vs formoterol (P<0.0001), by 48% vs terbutaline (P<0.0001), and by 22% with as-needed formoterol vs terbutaline (P=0.012). Rates of exacerbations needing emergency room treatment or hospitalization were reduced with as-needed budesonide-formoterol by 27% (P=0.046) vs formoterol and by 39% (P=0.0010) vs terbutaline, respectively. There was no significant difference between formoterol and terbutaline. The proportion of patients with more than one exacerbation was lowest in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and budesonide-formoterol 160-4.5 µg as needed				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 to 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 vs 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 vs maintenance therapy plus formoterol (P=0.0002) or terbutaline (P=0.0007). Night-time awakenings were reduced by 2% (seven nights per year) with as-needed budesonide-formoterol vs formoterol (P=0.018) and by 3% vs 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 vs terbutaline. 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 and 0.08 L were seen with as-needed budesonide-formoterol vs formoterol (P=0.0001) and terbutaline (P<0.0001). Mean morning PEF increased from run-in in all groups, with a small

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				additional improvement observed with as-needed budesonide-formoterol vs 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.[111] (2004) CAST Budesonide-formoterol 80-4.5 µg, 2 inhalations BID (AMD) vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID (AMD) vs budesonide-formoterol 80-4.5	RCT Patients with persistent asthma	N=2,358 12 weeks	Primary: Frequency of asthma exacerbations and changes in asthma symptom severity Secondary: Asthma control, safety and health economics	Primary: Both FD and AMD 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 value not reported). Secondary: Both treatment groups had improved lung function, less asthma symptoms and fewer nighttime awakenings compared to the mean value of the run-in period (P value not reported). Patients in the AMD budesonide/formoterol dose group utilized 24% less of the study drug in comparison to those in the FD group (2.95 vs 3.86 daily inhalations, respectively; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg, 2 inhalations BID (FD) vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID (FD)				
Berger et al.[112] (2010) Budesonide-formoterol 80-4.5 µg, 2 inhalations BID via MDI vs budesonide-formoterol 160-4.5 µg, 2 inhalations QD via MDI vs budesonide-formoterol 80-4.5 µg, 2 inhalations QD via MDI vs budesonide 160 µg, 2 inhalations QD via MDI	AC, DB, DD, MC, PC, RCT Patients ≥16 years of age with a documented diagnosis of asthma for ≥6 months, mild to moderate persistent asthma based on ICS use and pulmonary function, previous use of low to medium dose ICS during the month prior to enrollment and a pre bronchodilator FEV_1 60 to 90%, with bronchodilator reversibility to albuterol of ≥12% and ≥0.20 L in FEV_1	N=752 12 weeks	Primary: Pulmonary function (evening PEF as primary outcome) Secondary: Daytime and nighttime symptom scores, nighttime awakenings, rescue medication use, events of and patient withdrawals from the trial because of predefined criteria for worsening asthma control, and AQLQ	Primary: For pulmonary function variables (evening PEF and evening pre-dose FEV_1) at the end of QD administration, all combination therapy groups were significantly (P<0.001) more effective than placebo. Compared to budesonide, results for evening PEF significantly favored combination therapy (P<0.001), whereas results for evening pre-dose FEV_1 significantly favored budesonide/formoterol BID (P<0.001). For both evening PEF and evening pre-dose FEV_1, significant differences were observed between the budesonide/formoterol BID and QD groups, favoring BID administration (P≤0.010). There were no significant differences in pulmonary function variables between the two combination therapy QD groups. Secondary: Changes from baseline in all rescue medication use and symptom-related variables were significantly better for all combination therapy groups vs placebo (P<0.001 for all). Compared to budesonide, significantly (P≤0.045) better results were observed for all rescue medication use and symptom-related variables with the combination therapy BID and QD (320-9 µg/day) groups. Over the 12 week period, the percentage of patients with a symptom-free day was greater in all combination therapy groups compared to budesonide and placebo. Nighttime asthma control variables were similar in the budesonide-formoterol QD and BID groups; however, BID administration showed significantly better results than QD (160-9 µg/day) administration for all other asthma control variables (P≤0.020).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients discontinued their current asthma therapy and received SB treatment with budesonide-formoterol 80-4.5 µg, 2 inhalations BID via MDI and rescue albuterol as needed during a 4 to 5 week run-in period.				For combination therapy, significant differences in favor of BID administration compared to QD administration (320-9 µg/day) were observed for asthma control days (P=0.030) and daytime rescue medication use (P=0.050). Significant differences in favor of the higher QD dose (320-9 µg/day) compared to the lower (160-9 µg/day) QD dose were observed for symptom-free days, asthma control days and rescue medication-free days (P≤0.040). The percentage of patient with events of or withdrawals due to worsening asthma control were significantly lower for all combination therapy groups compared to placebo (P<0.001 for all), and for budesonide-formoterol BID and QD (160-9 µg/day) compared to budesonide (P≤0.028). In addition, significantly fewer patients in the budesonide-formoterol BID, budesonide-formoterol QD (320-9 µg/day) and budesonide groups met the criterion of clinical asthma exacerbation compared to placebo (P<0.01). Results were not significantly different between the combination therapy groups for these variables. Mean changes from baseline in AQLQ overall and all domain scores were significantly more favorable (P≤0.010), and differences were clinically meaningful, for all combination therapy groups compared to placebo, with the exception of the environmental exposure domain, for which clinically meaningful differences between placebo were observed only for budesonide-formoterol BID.
Jenkins et al.[113] (2006) Budesonide-formoterol 320-9 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 400 µg	DB, DD, MC, RCT Outpatients >12 years of age with a diagnosis of asthma for ≥6 months, FEV_1 40 to 85% of predicted, >15% reversibility in increase from baseline FEV_1 after inhalation of a	N=456 24 weeks	Primary: Morning and evening PEF Secondary: Adherence to therapy, FEV_1, symptom free days and nights, total number of reliever inhalations recorded in diary,	Primary: Patients receiving combination therapy had greater increases from baseline PEF scoring in both the morning and evening with 37.4 and 4.5 L/minute respectively (P<0.001). There was no significant difference between either of the combination therapies (P value not reported). Secondary: FEV_1 increased over time for all three treatment groups. However, those receiving combination therapy compared to monotherapy showed significant improvement (0.30 vs 0.14 L, respectively; P<0.001). Combination therapy reduced asthma symptom scores significantly better

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plus formoterol 9 µg, 2 inhalations BID (separate inhalers) vs budesonide 400 µg, 2 inhalations BID for 12 weeks, followed by either budesonide-formoterol or budesonide plus formoterol via separate inhalers for 12 weeks Terbutaline 0.5 mg was used throughout the study for as-needed relief.	bronchodilator (for patients >18 years of age an increase of >200 mL, 15 to 30 minutes post bronchodilator); all patients used ICSs for >4 months before study entry at a daily dose >750 µg for >4 weeks, patients required an asthma symptoms score of >1 for ≥4 of 7 days of the run-in period		daytime/nighttime symptom scores via diary, and safety	than monotherapy alone (P=0.0051). Patients receiving combination therapy had 16% more symptom free days than budesonide alone (P<0.001), used 0.97 inhalations of reliever medication/day compared to 1.61 for budesonide alone (P<0.001), had 19% more reliever free days (P<0.001) compared to budesonide alone, and resulted in 16% more asthma-control days, which is approximately 58 more days a year with asthma control (P<0.001) compared to budesonide alone. Combination therapy reduced the risk for mild exacerbation by 36% (P=0.0032). Combining budesonide/formoterol in one inhaler reduced the risk of mild exacerbation by 17% compared to separate inhaler therapy (P=0.13).
Kuna et al.[114] (2006) Budesonide-formoterol 80-4.5 µg, 2 inhalations in the evening vs budesonide-formoterol 80-4.5 µg, 1 inhalation BID	AC, DB, DD, PG, RCT Adult patients with mild to moderate persistent asthma who were not optimally controlled on an ICS dose of 200 to 500 µg/day, mean predicted FEV_1 at baseline was 78.5%	N=617 12 weeks	Primary: Morning PEF Secondary: Evening PEF, symptom-free days, reliever-free days, asthma control days, and adverse events	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 asthma-control days compared to the budesonide regimen (P<0.05). Both budesonide/formoterol regimens were similar in all efficacy variables, except for evening PEF which was higher with the BID regimen (18.3 vs 9.6 L/minute; P<0.05). There were no between-group differences in nighttime awakenings due to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 200 µg, 1 inhalation in the evening				asthma, or in the number and nature of adverse events.
Morice et al.[115] (2007) Budesonide-formoterol pMDI 160-4.5 µg vs budesonide-formoterol DPI 160-4.5 µg vs budesonide pMDI 200 µg	DB, DD, MC, PG, RCT Outpatients ≥12 years of age with asthma for ≥6 months with inadequate control on an ICS alone, FEV_1 50 to 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 MDI groups had improved morning PEF compared to those in the budesonide group by 31.4 and 28.6 L/minute, respectively (P<0.001). Secondary: Patients in the budesonide/formoterol groups had greater improvements observed compared to those in the budesonide group. End points 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.
Zetterström et al.[116] (2001) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 200 µg plus formoterol 4.5	DB, DD, MC, PG, RCT Adult patients with moderate persistent asthma (mean ICS dose 960 µg/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,	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 vs 32.0 s 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
µg, 2 inhalations BID (separate inhalers) vs budesonide 200 µg, 2 inhalations BID			safety	
Pohunek et al.[117] (2006) Budesonide-formoterol 80-4.5µg BID (fixed-dose inhaler) vs budesonide 200 µg BID and formoterol 9 µg BID (separate inhalers) vs budesonide 200 µg BID	AC, DB, MC, PG, RCT Patients 4 to 11 years of age with PEF >50% of predicted normal who had received stable treatment with an ICS, and history of an average of ≥1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study	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; use of reliever medication; reliever-free days; symptom-free days; change in FEV_1, change in HRQOL (Pediatric AQLQ)	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. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pauwels et al.[118] (1997) FACET Budesonide 100 µg and formoterol 12 µg BID vs budesonide 400 µg and formoterol 12 µg BID vs budesonide 100 µg BID vs budesonide 400 µg BID	DB, MC, PC, PG, RCT Adult patients with persistent asthma (mean ICS dose, 829 µg/day, mean predicted FEV_1 76%, mean reversibility of 21%)	N=852 1 year	Primary: Frequency of asthma exacerbations, lung function, asthma symptoms Secondary: Adverse events	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 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.[119] (2009) Budesonide-formoterol 80-4.5 µg, 2 inhalations BID (320-18 µg/day) vs budesonide-formoterol 160-4.5 µg, 2 inhalations	AC, DB, PG, RCT Patients ≥12 years of age with asthma for ≥6 months, mild to moderate asthma based on pulmonary function and ICS use, received an ICS or ICS/LABA therapy for ≥4 weeks before screening, with a FEV_1 60 to 90%	N=619 12 weeks	Primary: Evening pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF, daytime and nighttime asthma symptom scores, daytime and nighttime rescue medication use, nighttime	Primary: Budesonide-formoterol QD (320-9 µg/day) was significantly more effective than budesonide for evening pre-dose FEV_1 and evening PEF (P≤0.004). For combination therapy, changes in evening pre-dose FEV_1 and evening PEF were significantly more favorable for BID administration vs QD administration (320-9 µg/day) (P<0.001). Mean morning PEF was maintained throughout the study with budesonide/formoterol QD (320-9 µg/day). Budesonide-formoterol QD (160-9 µg/day) was significantly more effective than budesonide in maintaining evening pre-dose FEV_1 and morning PEF during treatment (P≤0.016). For combination therapy, changes in evening pre-dose FEV_1 and evening PEF were significantly more favorable for BID administration vs QD administration (160/9

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QPM (320-9 µg/day) vs budesonide-formoterol 80-4.5 µg, 2 inhalations QPM (160-9 µg/day) vs budesonide 160 µg, 2 inhalations QD (320 µg-day) All patients discontinued their current asthma therapy and received SB budesonide/ formoterol 80-4.5 µg, 2 inhalations BID via MDI during a 4 to 5 week run-in period.	and demonstrated reversibility of FEV_1 ≥12% and ≥0.20 L from baseline within 15 to 30 minutes of SABA use		awakenings due to asthma, symptoms-free days, awakening-free nights, asthma control days, rescue medication-free days, patient withdrawals due to predefined criteria for worsening asthma, AQLQ, and safety	µg/day) (P<0.001). Across all efficacy variables, differences between the two combination therapy QD groups were small and of questionable clinical relevance. The only significant difference noted between the two groups was for evening pre-dose PEF (least squares mean difference, 0.05 L; 95% CI, 0.00 to 0.10) which favored the higher dose QD group (320-9 µg/day) (P=0.031). Secondary: Results for morning and evening pre-dose PEF are reported in the primary outcome section. Changes in rescue medication use and symptom-related variables significantly favored budesonide-formoterol QD (320-90 µg/day) vs budesonide (P≤0.045), except awakening-free nights, asthma control days and daytime rescue medication use. For combination therapy, QD administration (320-9 µg/day) and BID administration were similarly effective for diary variables reflective of the 12 hour period after evening dosing (nighttime asthma symptoms, awakening-free nights and nighttime rescue medication use), with significantly more favorable results for BID administration compared to QD administration (320-9 µg/day) for all other symptom-related and rescue medication use variables. Changes in symptom-related variables were significantly more favorable for budesonide-formoterol QD (160-9 µg/day) compared to budesonide (P≤0.023), except symptom-free days and daytime rescue medication use. For combination therapy, BID administration was significantly more effective than QD (160-9 µg/day) administration for all symptom-related and rescue medication use variables (P<0.01), except those that reflected the 12 hour period after evening dose. For combination therapy, results for asthma control days significantly favored BID administration compared to QD administration (320-9 and 160-9 µg/day) (P≤0.005). The percentages of patients withdrawing due to worsening asthma were as follows: 4.6, 6.6, 3.3 and 6.6% for budesonide-formoterol QD (320/9

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				µg/day), budesonide-formoterol QD (160-9 µg/day), budesonide/formoterol BID and budesonide (P values not reported). Mean changes in AQLQ overall and domain scores were small in all groups and less than the clinically meaningful difference. These changes were significantly more favorable for budesonide-formoterol BID vs budesonide (P≤0.018), but similar among the combination groups (except for the AQLQ symptoms domain, which significantly favored BID administration vs QD [160-9 µg/day] administration; P=0.034). All treatments were generally well tolerated, with most adverse events being of mild to moderate intensity.
Corren et al.[120] (2007) Budesonide-formoterol pMDI 80-4.5 µg, 2 inhalations BID vs budesonide pMDI* 80 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs placebo	DB, DD, MC, PC, RCT Patients ≥12 years of age with predominantly mild to moderate persistent asthma treated with an ICS for ≥4 weeks before screening and with a pre bronchodilator FEV_1 60 to 90% of predicted normal on ICS at screening	N=480 12 weeks	Primary: Changes from baseline in morning pre-dose FEV_1 and 12-hour mean FEV_1 after morning dose Secondary: Morning and evening pre-dose PEF, daytime and nighttime symptom scores, nighttime awakenings, daily rescue medication use, and worsening asthma	Primary: The mean change from baseline in pre-dose FEV_1 was greater in patients who received budesonide-formoterol compared to those who received budesonide, formoterol or placebo (P<0.005). Observed mean changes from baseline in 12-hour FEV_1 were greater in patients who received budesonide/formoterol compared to 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 pre-dose PEF compared to budesonide or formoterol (P<0.001). Mean decreases in symptom scores were greater with budesonide-formoterol compared to formoterol and placebo (P<0.046). Active treatments were associated with greater mean increases in awakening-free nights compared to placebo (P<0.012). Patients who received budesonide/formoterol had a greater mean reduction from baseline in daily rescue medication use compared to 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 to formoterol or placebo (P≤0.01).
Murphy et al.[121] (2008) Budesonide-formoterol pMDI 80-4.5 µg, 2 inhalations BID vs budesonide pMDI* 80 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs placebo	DB, DD, MC, PC, RCT Patients ≥18 years of age 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, percentage of asthma control days), and PSAM Secondary: Not reported	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). Significantly greater PSAM scores were reported in the budesonide-formoterol group compared to all other treatment arms (P<0.004). Secondary: Not reported
Noonan et al.[122] (2006) Budesonide-formoterol pMDI 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs	DB, DD, MC, PC, RCT Patients ≥12 years of age, documented diagnosis of asthma for ≥6 months, moderate to high ICS use for ≥4 weeks, pre bronchodilator FEV_1 45 to 85% of	N=596 12 weeks	Primary: Mean change from baseline in morning pre-dose FEV_1 and mean change from baseline in 12-hour FEV_1 after administration of morning dose Secondary:	Primary: Greater improvements in morning pre-dose FEV_1 were obtained in patients treated with budesonide-formoterol (0.19 L) than those treated with budesonide (0.10 L), formoterol (-0.12 L) or 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 two weeks and end of treatment (P≤0.001). Fewer patients receiving budesonide/formoterol than the individual products or placebo met worsening asthma criteria.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide pMDI* 160 µg, 2 inhalations plus formoterol DPI 4.5 µg, 2 inhalations, both BID (separate inhalers) vs budesonide pMDI* 160 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs placebo	predicted normal		PEF, asthma symptoms, rescue medications use, and worsening asthma	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 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 to 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. Similar results were obtained for treatment arms with combination budesonide-formoterol and concurrent administration of the individual components. 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.
Chervinsky et al.[123] (2008) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5	DB, MC, PC, 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 Secondary: Medical Outcomes Study 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg, 2 inhalations BID (separate inhalers) vs budesonide 160 µg, 2 inhalations BID vs formoterol 4.5 µg, 2 inhalations BID vs placebo				Secondary: No significant differences were observed among the treatment groups for the Medical Outcomes Study 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). 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.
Gappa et al.[124] (2009) Fluticasone propionate 200 µg BID	DB, MC, PG, RCT Patients 6 to 14 years of age with persistent asthma uncontrolled by	N=283 8 weeks	Primary: Change in mean morning PEF, asthma symptom scores, number of days without	Primary: Mean increase in morning PEF was 30.4 L/min in SFC group and 16.7 L/min in fluticasone propionate 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 propionate 50-100 µg BID (SFC)	standard ICS doses		asthma symptoms, use of rescue albuterol, asthma control, and exacerbations Secondary: Not reported	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 to 15.3) than patients receiving fluticasone propionate. Good asthma control was achieved for a longer period in SFC group (3.4 weeks) than in the fluticasone propionate group (2.7; P=0.02). Asthma exacerbations were recorded in three and six patients receiving SFC and fluticasone propionate, respectively. Both treatments were generally well tolerated. Serious adverse events were reported in two and one patients in the SFC and fluticasone propionate groups, respectively. Secondary: Not reported
Vaessen-Verberne et al.[125] (2010) Fluticasone propionate 200 µg, BID vs fluticasone propionate - salmeterol 100/50 µg, BID All patients received fluticasone propionate 100 µg BID during a 4	DB, MC, PG, RCT Patients 6 to 16 years of age with asthma who are still symptomatic on conventional doses of ICSs	N=158 26 weeks	Primary: Percentage of symptom-free days during the last 10 weeks of treatment Secondary: Not reported	Primary: The percentage of symptom-free days did not differ between the two treatment groups in any of the treatment periods (zero to six, six to 16 and 16 to 26 weeks). The mean adjusted difference in symptom-free days between fluticasone propionate and combination therapy during the last 10 weeks was 2.6% (95% CI, -8.1 to 13.4; P=0.63) in the per-protocol analysis and 0.4% (95% CI, -9.1 to 9.9; P=0.93) in the intent-to-treat analysis. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
week run-in period. A SABA was used for symptom relief during this period.				
Strand et al.[126] (2004) Fluticasone propionate -salmeterol 100-50 µg BID vs fluticasone propionate 100 µg BID	DB, MC, PG, RCT Patients 23 to 54 years of age with persistent asthma who were using short acting bronchodilators one or more times per week for asthma for symptom relief	N=150 24 weeks	Primary: Percentage of symptom free days and nights Secondary: Morning and evening PEF, daytime symptom score, nighttime symptom score, days and nights without symptoms, β-agonist use, episode free days and night, and asthma exacerbations	Primary: Statistically significant increase in percentage of symptom free days and nights in fluticasone propionate -salmeterol group compared to fluticasone propionate group (P=0.008). Secondary: Statistically significant improvement in morning PEF (P=0.0011) and evening PEF (P=0.011) in the fluticasone propionate -salmeterol group compared to fluticasone propionate group. Statistically significant improvement in percentage of episode-free days and nights in the fluticasone propionate -salmeterol group compared to fluticasone propionate group (P=0.015). Statistically significant increase in percentage of days and nights without β-agonist use in the fluticasone propionate -salmeterol group compared to fluticasone propionate group (P<0.05). No statistically significant difference observed in asthma exacerbations between groups.
Bateman et al.[127] (2004) Fluticasone propionate -salmeterol 100-50 µg BID vs fluticasone	DB, MC, PG, RCT Patients ≥12 years of age with asthma	N=3,421 12 months	Primary: Asthma control, symptoms, and rescue albuterol use Secondary: Dose of ICS, exacerbations	Primary: In the fluticasone propionate -salmeterol group, 71% of the patients achieved well-controlled asthma compared to 65% with the fluticasone propionate group. Compared to fluticasone propionate, individuals in the fluticasone propionate -salmeterol group were significantly faster to achieve asthma control (P≤0.002). Secondary: At a lower corticosteroid dose with fluticasone propionate -salmeterol, control was achieved more rapidly than fluticasone propionate alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propionate 100 µg BID NOTE: all patients were "stepped up" every 12 weeks until asthma totally controlled or highest dose reached (fluticasone propionate -salmeterol 500-50 µg BID or fluticasone propionate 500 µg BID)				There were a significantly lower amount of exacerbations requiring oral corticosteroids and or hospitalizations or emergency visits in the fluticasone propionate -salmeterol group in each stratum ($P \leq 0.009$).
Bateman et al.[128] (2006) Fluticasone propionate -salmeterol 100-50 µg BID vs fluticasone propionate 250 µg BID NOTE: all patients were stabilized on fluticasone propionate -salmeterol 250-50 µg BID during OL	DB, MC, PG, RCT Patients 12 to 80 years 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 to 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	N=484 12 weeks	Primary: Mean morning PEF Secondary: Asthma control, symptoms, and rescue albuterol use	Primary: Patients in the fluticasone propionate -salmeterol group maintained the improved PEF values achieved in the OL treatment period compared to those in the fluticasone propionate 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 propionate -salmeterol group compared with the fluticasone propionate group (no P value reported). The odds of a patient achieving total control of their asthma were 62% greater in fluticasone propionate -salmeterol group compared to the fluticasone propionate 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 propionate -salmeterol ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment for 12 weeks and were "stepping down" therapy	and no exacerbations in the run-in period; patients received 12 weeks of OL fluticasone propionate plus salmeterol 250-50 µg BID before being randomized to the other treatment groups			
de Blic et al.[129] (2009) Fluticasone propionate - salmeterol 100-50 µg BID vs fluticasone propionate 200 µg BID	DB, MC, RCT Patients 4 to 11years of age with asthma who were previously uncontrolled on a low dose inhaled ICS (equivalent to beclomethasone 400 µg/day)	N=321 12 weeks	Primary: Change in mean PEF, asthma control, percent rescue free days, percent symptom free days, nighttime awakenings Secondary: Not reported	Primary: Change from baseline in mean morning PEF increased following both treatments, but was significantly greater in the fluticasone propionate - salmeterol group compared with fluticasone propionate (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 and percentage rescue-free days showed significantly greater improvements in the fluticasone propionate -salmeterol group compared with fluticasone monotherapy. All other efficacy indices showed comparable improvements in each group. Secondary: Not reported
Bateman et al.[130] (2001) Fluticasone propionate - salmeterol 50-25 µg, 2 inhalations	DB, DD, PG, RCT Patients ≥12 years of age with diagnosis of reversible airway obstruction,	N=497 12 weeks	Primary: Mean morning PEF Secondary: Evening PEF, daytime and	Primary: Mean morning PEF values were equivalent between the fluticasone propionate - salmeterol HFA and Diskus groups (P value not reported). There was a significant improvement in mean morning PEF values in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC group (P<0.001). Comparisons were not made between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID (HFA) vs fluticasone propionate - salmeterol 100-50 µg, 1 inhalation BID (DPI) vs fluticasone propionate 50 µg, 2 inhalations BID (CFC)	smoking history of <10 pack-years, using ICSs (beclomethasone, budesonide or flunisolide at a dose of 400 to 500 µg/day or fluticasone propionate 200 to 250 µg/day) for ≥4 weeks prior to randomization, mean morning PEF 50 to 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, taking albuterol ≤800 µg/day and FEV_1 >50% of predicted value		nighttime symptom scores, albuterol use, and clinic FEV_1 values	the fluticasone propionate - salmeterol Diskus and the fluticasone propionate CFC groups. Secondary: Mean evening PEF improved in all three groups compared to baseline with the greatest improvements seen in the fluticasone propionate -salmeterol HFA and Diskus groups, and the difference was significant in the fluticasone propionate and salmeterol HFA group compared to the fluticasone propionate CFC group (P<0.001). The number of symptom free days and nights increased in all three treatment groups. The proportion of symptom free days and nights were similar in the fluticasone propionate -salmeterol HFA and Diskus groups. The fluticasone propionate -salmeterol HFA group reported significantly more symptom free days compared to the fluticasone propionate CFC group (P=0.001). The fluticasone propionate -salmeterol HFA group reported more symptom free nights compared to the fluticasone propionate CFC group, but this difference was not significant (P=0.063). The increase in albuterol free days and nights was similar in the fluticasone propionate -salmeterol HFA and Diskus groups. The increase in albuterol free days and nights was significantly higher in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC group (P<0.033) for every assessment period except for weeks five through eight (P=0.093). Clinic FEV_1 values improved in all three treatment groups and the differences between groups was not significant (P value not reported).
Nelson et al.[131] (2003) Fluticasone propionate -	DB, MC, PG, RCT Patients diagnosed with persistent asthma uncontrolled	N=283 12 weeks	Primary: Area under the FEV_1 curve relative to baseline, withdrawal due to	Primary: Morning pre-dose FEV_1 was significantly improved in the fluticasone propionate - salmeterol HFA group compared to the fluticasone propionate CFC and salmeterol CFC groups (P≤0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 88-42 µg (HFA) vs fluticasone propionate 88 µg (CFC) vs salmeterol 42 µg (CFC)	with an as-needed SABA alone		asthma exacerbation, and morning and evening PEF Secondary: Not reported	Fewer patients in the fluticasone propionate -salmeterol HFA group withdrew due to worsening of asthma compared to the fluticasone propionate CFC and salmeterol CFC groups (P=0.024). Morning and evening PEF values were significantly increased in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC and salmeterol CFC groups at endpoint (P≤0.002). Secondary: Not reported
Lundback et al.[132] (2006) Fluticasone propionate - salmeterol 250-50 µg BID vs fluticasone propionate 250 µg BID vs salmeterol 50 µg BID	DB, PG, RCT Patients 18 to 70 years of age with mild to moderate asthma, symptoms ≥2 times/week and ≥1 of the following: airway hyper-responsiveness, diurnal variability in PEF ≥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 ≥15% in FEV_1 or PEF after β_2-agonist administration	N=282 12 months	Primary: Number of patients requiring an 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, diary card data containing information on morning PEF, rescue medication use, and daytime and nighttime	Primary: Statistically significant lower percentage of patients in the fluticasone propionate - salmeterol group required an increase in study medication compared to fluticasone propionate and salmeterol monotherapy (P<0.001). Secondary: Statistically significant lower number of patients having ≥2 asthma exacerbations in the fluticasone propionate -salmeterol group compared to the fluticasone propionate monotherapy (P<0.01) and salmeterol monotherapy groups (P<0.001). Statistically significant improvement in morning PEF values in the fluticasone propionate -salmeterol group compared to the fluticasone propionate and salmeterol monotherapy groups (P<0.001). Statistically significant improvement in FEV_1 (P<0.001) and FVC (P<0.05) from baseline in the fluticasone propionate -salmeterol group compared to the salmeterol monotherapy group. No statistically significant difference in FEV_1 or FVC from baseline in the fluticasone propionate -salmeterol group compared to the fluticasone propionate monotherapy group (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			asthma symptom scores	Statistically significant improvement in airway hyper-responsiveness in the fluticasone propionate -salmeterol group compared to the fluticasone propionate monotherapy (P<0.05) and salmeterol monotherapy groups (P<0.001). Statistically significant increase in symptom-free days in the fluticasone propionate -salmeterol group and the fluticasone propionate monotherapy group than in the salmeterol monotherapy group (P<0.05). Statistically significant increase in symptom-free nights in the fluticasone propionate - salmeterol group and the fluticasone propionate monotherapy group than in the salmeterol monotherapy group (P<0.001). Statistically significant increase in rescue-medication-free days in the fluticasone propionate -salmeterol group and the fluticasone propionate monotherapy group compared to the salmeterol group (P<0.05). Rescue-medication-free nights was 100% for all treatment groups.
Nathan et al.[133] (2006) Fluticasone propionate - salmeterol 110-21 µg, 2 inhalations BID (HFA) vs fluticasone propionate 110 µg, 2 inhalations BID (CFC) vs salmeterol 21 µg, 2	DB, PC, PG, RCT Patients ≥12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40 to 85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration, history of an ICS ≥3 months with no change in regimen for ≥1 month prior	N=365 12 weeks	Primary: For fluticasone propionate - salmeterol HFA vs fluticasone propionate CFC: AUC of the 12-hour serial FEV_1 relative to baseline For fluticasone propionate - salmeterol HFA vs salmeterol CFC: morning pre-dose FEV_1 at endpoint and the probability of patients remaining in the	Primary: The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC and placebo groups (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 propionate -salmeterol HFA group compared to the improvements in the fluticasone propionate 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 propionate -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 the fluticasone propionate -salmeterol HFA group and the fluticasone propionate CFC group (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhalations BID (CFC) vs placebo	to screening at the following daily doses: beclomethasone 378 to 840 µg, triamcinolone 900 to 1,600 µg, flunisolide 1,250 to 2,000 µg, fluticasone propionate 440 to 660 µg of MDI or 400 to 600 µg of DPI or budesonide 800 to 1,200 µg		study without being withdrawn for worsening of asthma Secondary: Morning and evening PEF, asthma symptom scores, albuterol use, and nighttime awakenings requiring albuterol use	Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.001). There was a significant improvement in asthma symptom scores in the fluticasone propionate -salmeterol HFA group compared to the placebo group (P<0.001), but the difference when compared to the fluticasone propionate CFC and the salmeterol CFC groups was not significant (P value not reported). There was a significant increase in the proportion of days with no asthma symptoms in the fluticasone propionate -salmeterol HFA group compared to the placebo group (P<0.001), but the difference when compared to the fluticasone propionate CFC and the salmeterol CFC groups was not significant (P value not reported). The number of nighttime awakenings decreased in the fluticasone propionate -salmeterol HFA group and increased in the fluticasone propionate CFC, salmeterol CFC and placebo groups, but only the difference between the fluticasone propionate -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 propionate -salmeterol HFA group compared to the fluticasone propionate CFC and placebo groups (P≤0.005), but there was no significant difference when compared to the salmeterol CFC group (P value not reported).
Pearlman et al.[134] (2004) Fluticasone propionate - salmeterol 44-21 µg, 2 inhalations BID (HFA)	DB, PC, PG, RCT Patients ≥12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6	N=360 12 weeks	Primary: For fluticasone propionate - salmeterol HFA vs fluticasone propionate CFC: AUC of the 12-hour serial FEV_1	Primary: At week 12, the average percent change in serial FEV_1 compared to baseline was significantly greater for fluticasone propionate -salmeterol HFA compared to fluticasone propionate CFC, salmeterol CFC and placebo (P≤0.007). The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone propionate -salmeterol HFA

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone propionate 44 µg, 2 inhalations BID (CFC) vs salmeterol 21 µg, 2 inhalations BID (CFC) vs placebo Patients were stratified into 2 groups based on asthma therapy at baseline: Group 1-history of an ICS ≥3 months with no change in regimen for ≥1 month prior to screening at the following daily doses: beclomethasone 252 to 336 µg, triamcinolone 600 to 800 µg, flunisolide 1,000 µg, fluticasone	months, FEV_1 40 to 85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration		relative to baseline For fluticasone propionate -salmeterol HFA vs salmeterol CFC: 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 AQLQ scores	group compared to the fluticasone propionate CFC and placebo groups (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 propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.0112). There were significantly fewer patients withdrawn due to worsening of asthma in the fluticasone propionate -salmeterol group compared to the salmeterol CFC and placebo groups (P<0.001). The difference was not significant when comparing the fluticasone propionate -salmeterol HFA group and the fluticasone propionate 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 propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.006). There was a significantly greater percentage of days without asthma symptoms in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P<0.001). There was a significant decrease in nighttime awakenings in patients in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.007). There was a significant reduction in the need for albuterol in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.002). There were no results reported for AQLQ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propionate 176 µg of MDI or 200 µg of DPI or budesonide 400 to 600 µg. Group 2-β_2-agonist use for only for 1 week prior to screening (ineligible if treated with an ICS within last month).				
Chapman et al.[135] (1999) Fluticasone propionate - salmeterol 250-50 µg BID (fixed-dose inhaler) vs fluticasone propionate 250 µg and salmeterol 50 µg BID (separate inhalers)	DB, DD, RCT Individuals 13 to 75 years of age with symptomatic asthma	N=371 28 weeks	Primary: Change in PEFR Secondary: Mean daytime symptom score and FEV_1	Primary: Over weeks one to 12, PEFR was 43 L/minute for the combination therapy group and 36 L/minute for the concurrent therapy group respectively. The difference between the two treatment groups was 6 L/minute (CI, -13 to 0; P=0.114), which was within the predefined criteria for clinical equivalence. Secondary: Over weeks one to 12, 35% of the combination therapy group had a mean daytime symptom score of zero compared to 31% of the concurrent therapy group. No statistically significant difference in FEV_1 between the combination and concurrent therapy groups was noticed (P value not reported).
Nelson et al.[136] (2003) Fluticasone propionate - salmeterol 100-50 to 500-50 µg BID	MA (4 DB, DD, MC, RCTs) Individuals ≥4 years of age diagnosed with asthma	N=1,375 All trials were 12 weeks in duration	Primary: Change from baseline in mean PEF over 12 weeks Secondary: Mean change in evening PEF and	Primary: A significant advantage (5.4 L/minute) was seen for PEF in the combination therapy over the 12 week treatment period (P=0.006). Secondary: There was a difference in favor of the combination therapy in the mean difference in FEV_1 (0.04 L) compared to the concurrent therapy (P=0.054). The difference was statistically significant (6.11 L/minute) in the mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone propionate 100 to 500 µg BID and salmeterol 50 µg BID			clinic FEV_1, median percentage of symptom-free days, nights or both, and rescue inhaler free	evening PEF in favor of the combination therapy (P<0.001). There was no significant difference seen in the percentage of symptom-free and/or rescue inhaler free days and nights between treatment groups (P=0.165 and P=0.635).
You-Ning et al.[137] (2005) Fluticasone propionate - salmeterol 125-25 µg, 2 inhalations BID (HFA) vs fluticasone propionate-salmeterol 250-50 µg, 1 inhalation BID (DPI)	MC, OL, PG, RCT Patients 18 to 70 years of age with diagnosis of asthma, receiving stable doses of budesonide or beclomethasone up to 1,200 µg/day or fluticasone propionate up to 600 µg per/day for ≥1 month, or required therapy with ICSs, total score of ≥8 for daytime and nighttime symptoms and ≥15% reversibility and 200 mL elevation in FEV_1 following albuterol	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 propionate - salmeterol HFA and Diskus groups compared to baseline (P<0.05), but the differences between groups was not significant (P>0.05). Secondary: All secondary endpoints improved significantly compared to baseline in both the fluticasone propionate -salmeterol HFA and Diskus groups (P<0.05), but the difference between groups was not significant for any secondary endpoint (P>0.05) except patient self-evaluation of efficacy at visit three which was significantly higher in the Diskus group compared to the HFA group (P<0.05).
Weinstein et al.[138] (2010) Mometasone-formoterol 200-10 to 400-10 µg BID (MF/F)	DB, MC, PG, RCT Patients ≥12 years of age with asthma for ≥12 months uncontrolled on high dose ICSs	N=728 12 weeks	Primary: Mean change in FEV_1 $AUC_{0 \text{ to } 12h}$ for combination therapy (800-20 µg) vs mometasone	Primary: A significant improvement from baseline to week 12 for mean change in FEV_1 $AUC_{0 \text{ to } 12h}$ occurred with both doses of combination therapy compared to mometasone alone (4.19 and 3.59 L/hour vs 2.04 L/hour; for the combination therapy doses of 200-10 µg, 400-10 µg and mometasone 400 µg, respectively; P<0.001). Both doses of combination therapy resulted in rapid (five minutes) and sustained improvement in lung

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mometasone 400 µg BID (MF) All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 400 µg, BID.	(>1,000 mg beclomethasone equivalent) with or without LABA for 12 weeks before screening		Secondary: Change from baseline in ACQ, AQLQ, proportion on nocturnal awakenings requiring SABA rescue medication, trough FEV1, evening PEF and number of asthma deteriorations (any one of the following: ≤80% of baseline FEV_1, a ≤70% of baseline PEF for at least two consecutive days or a clinically judged deterioration resulting in emergency treatment, hospitalization, or treatment with additional asthma medication such as systemic glucocorticoid steroids	function throughout 12 weeks. Secondary: Both doses of combination therapy were associated with lower ACQ scores after 12 weeks of treatment compared to mometasone alone (P≤0.014), indicating an improvement in asthma control. The mean AQLQ scores increased in all three treatment groups indicating less impairment on activities; however, differences between the groups were not statistically significant. Both doses of combination therapy significantly reduced the number of nocturnal awakenings due to asthma that required SABA use compared to mometasone alone (P≤0.006). Mean changes from baseline to week 12 were 0.10, 0.14 and 0.19 L for mometasone 400 µg monotherapy, 200-10 µg combination therapy and 400-10 µg combination therapy, respectively. The 400-10 µg combination dose was significantly more effective at improving trough FEV_1 at week 12 (P=0.006) and at all other time points (P≤0.04) compared to monotherapy, whereas the 200-10 µg combination dose was more effective than monotherapy only at week 4 (P=0.027). The improvement from baseline in evening PEF was 11.8, 13.3, and 6.6% for the 200-10 µg and 400-10 µg combination doses, and 400 µg of monotherapy, respectively. Improvements from baseline in evening PEF were also significantly greater for both combination treatment groups compared to mometasone monotherapy at all time points (P≤0.004). Patients receiving the 200-10 µg dose of combination therapy had significantly fewer asthma deteriorations compared to the mometasone monotherapy group (P=0.038). The difference between the 400-10 µg combination treatment group and the mometasone monotherapy group was not significant (P=0.053). A combined analysis of both doses of (400-10 µg and 200-10 µg) showed that combination treatment was significantly better than mometasone monotherapy for reducing asthma deteriorations (P=0.029).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nathan et al.[139] (2010) Mometasone-formoterol 100-5 µg, 2 inhalations BID (MF/F) vs mometasone 100 µg, 2 inhalations BID (MF) vs formoterol 5 µg, 2 inhalations BID (F) vs placebo	DB, MC, PC, PG, RCTC 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 to 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 vs 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 AM 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 vs placebo (P<0.001). There was a significant improvement in asthma control for patients treated with MF/F vs F or vs 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 vs 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 vs F (P=0.039), but similar for MF and placebo (P=0.130). AQLQ(S) outcomes did not differ significantly for F vs placebo at any time point during treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 wakenings due to asthma requiring the use of SABA vs 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 vs 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%).
Bateman et al.[140] (2003) Budesonide-formoterol 160-4.5 µg, 1 inhalation BID vs fluticasone propionate 250 µg, 1 inhalation BID	DB, DD, PG, RCT 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 medication, symptom-free days, asthma control days, night-time awakenings, and risk of having an exacerbation	Primary: Patients in the budesonide-formoterol group had significantly greater increases in morning PEF than those in the fluticasone propionate group (27.4 vs 7.7 L/minute, respectively; P<0.001). Secondary: Those in the budesonide-formoterol group had a significant improvement in their evening PEF and FEV_1 compared to the fluticasone propionate group (P values not reported). 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 propionate 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 vs those in the fluticasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				propionate group (60.4 vs 55.5%, 57.8 vs 52.4% and 7.9 vs 9.6%, respectively; P values not reported).
Ericsson et al.[141] (2006) Budesonide-formoterol 160-4.5 µg BID vs fluticasone propionate 250 µg BID	DB, DD, MC, PG, RT Patients ≥18 years of age with moderate-persistent asthma, diagnosis ≥6 months, on ICS (200 to 1,000 µg) ≥30 days, FEV_1 60 to 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 vs –0.13 inhalations/day, respectively; P=0.04).
Akamatsu et al.[142] (2013) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID vs fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID	AC, RCT Patients >18 years of age with asthma for ≥6 months who were able to perform expiratory maneuvers and were receiving fluticasone propionate -salmeterol for ≥8 weeks	N=66 12 weeks	Primary: ACQ5, pulmonary function tests and exhaled NO parameters Secondary: Not reported	Primary: There was no change in ACQ5 between patients treated with budesonide-formoterol and fluticasone propionate -salmeterol; however, the proportion of patients with an improvement in ACQ5 was significantly higher in the budesonide-formoterol group compared to the fluticasone propionate -salmeterol group (51.6 vs 16.7%; P=0.003). The minimum PEF and maximum PEF significantly improved (P=0.021 and P=0.0054, respectively) in patients treated with budesonide-formoterol but not for patients in the fluticasone propionate -salmeterol group; however, there was no significance between the two treatment groups overall (P=0.573 and P=0.092, respectively). The changes in exhaled NO parameters after 12 weeks of treatment demonstrated significant improvements in CANO (P=0.007) and CANOcorr (P=0.008) in the budesonide-formoterol group but not in the fluticasone propionate -salmeterol group. The differences between the treatment groups were statistically significant, favoring budesonide-formoterol (P=0.047 and P=0.037, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Larsson et al.[143] (2013) Budesonide-formoterol vs fluticasone propionate -salmeterol	OS, RETRO Patients with COPD	N=9,893 Duration not reported	Primary: COPD exacerbations, emergency visits, utilization of steroids or antibiotics and utilization of other medications used in managing COPD Secondary: Not reported	Primary: The COPD exacerbation rates were 0.80 and 1.09 per patient-year in the budesonide-formoterol and fluticasone propionate -salmeterol treatment groups, respectively, representing a 26.6% reduction in exacerbation rate in the budesonide-formoterol group (rate ratio, 0.74; 95% CI, 0.69 to 0.79; P<0.0001). This corresponded to a NNT of 3.4 with budesonide-formoterol compared to fluticasone propionate -salmeterol to prevent one exacerbation per patient-year. In budesonide-formoterol-treated patients, the yearly rate of COPD-related hospitalizations was 0.15 compared to 0.21 in patients treated with fluticasone propionate -salmeterol (P<0.0001), a difference of 29.1% (rate ratio, 0.71; 95% CI, 0.65 to 0.78; P<0.0001). The NNT to prevent one COPD-related hospitalization per patient-year was 16 with budesonide-formoterol compared to fluticasone propionate -salmeterol. There were 27% fewer days in the hospital due to exacerbations of COPD with budesonide-formoterol compared to fluticasone propionate -salmeterol (0.63 vs 0.95 days/year; rate ratio, 0.66; 95% CI, 0.62 to 0.71; P<0.0001). There were 21% fewer emergency visits in the budesonide-formoterol treatment group compared to the fluticasone propionate -salmeterol group (0.027 vs 0.034 events/patient-year; rate ratio, 0.79; 95% CI, 0.71 to 0.89; P=0.0003). Patients treated with budesonide-formoterol experienced 26% fewer courses of oral steroids (0.63 vs. 0.85 events per year; rate ratio, 0.74; 95% CI, 0.68 to 0.81; P<0.0001) and 29% fewer antibiotic courses (0.38 vs 0.54 events per year; rate ratio, 0.70; 95% CI, 0.66 to 0.75; P<0.0001) than patients treated with fluticasone propionate -salmeterol. The number of patients who required tiotropium in addition to the ICS/LABA combination was 16% lower for the budesonide-formoterol group compared to fluticasone propionate -salmeterol group (rate ratio, 0.84; 95% CI, 0.79 to 0.89; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Price et al.[144] (2007) Budesonide-formoterol 200-6 µg, 2 inhalations BID (adjustable maintenance dose) vs fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID (stable dose) During weeks 1 to 4, patients received either 1 inhalation of fluticasone propionate -salmeterol 250-50 µg BID or 2 inhalations of budesonide-formoterol 200-6 µg and during weeks 5 to 52, those who met the criteria, received budesonide/formoterol-AMD or	DB, DD, MC, PG, RCT Outpatients 18 to 70 years of age, with a clinical asthma history, an FEV_1 60 to 90% predicted normal, had received an ICS dose equal to 200 to 500 µg/day of beclomethasone and LABA, or an ICS alone at dose equal to >500 to 1,000 µg beclomethasone (≥12 weeks prior to enrollment)	N=688 1 year	Primary: Symptom-free days (defined as symptom score of zero in a 24-hour period) Secondary: Rate of exacerbations	Primary: Patients in the fluticasone propionate -salmeterol group had a significantly greater percentage of symptom/free days (58.8%) over the entire year, compared to patients in the budesonide/formoterol group (52.1%; P=0.034). Secondary: The adjusted annual mean exacerbation rate was also significantly lower in the fluticasone propionate -salmeterol group compared to the budesonide/formoterol group (47%; P=0.008)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate -salmeterol-FD.				
Vogelmeier et al.[145] (2012) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via Turbuhaler SMART™ [plus additional inhalations as needed] vs fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID via Diskus [plus salbutamol as needed] Maintenance doses could be titrated by clinicians after the first four weeks.	PH, SA Asian outpatients ≥12 years of age with asthma for ≥6 months that used ≥500 µg/day of budesonide or fluticasone propionate (or ≥1,000 µg of another ICS) for ≥1 month prior to study entry, had pre-terbutaline FEV_1 40 to 90% of predicted and at least one severe exacerbation >2 weeks and ≤12 months before study start; patients also had used as-needed medications on ≥4 of the past 7 days of run-in	N=404 12 months	Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit, the need for oral steroids ≥3 days or unscheduled visit leading to treatment change) Secondary: Asthma control (assessed using ACQ-5), quality of life (using AQLQ(S))	Primary: The time to the first severe exacerbation was significantly longer in patients treated with maintenance plus as-needed budesonide-formoterol compared to patients treated with fluticasone propionate -salmeterol plus as-needed salbutamol (230 vs 45 days; P=0.024). Patients treated with the adjusted budesonide-formoterol regimen had a 44% reduction in risk of a first exacerbation compared to patients treated with fluticasone propionate -salmeterol plus salbutamol (95% CI, 0.32 to 0.95; P=0.033). The rate of severe exacerbations was lower in the maintenance plus as-needed budesonide-formoterol treatment group (0.16/patient/year) compared to the fluticasone propionate -salmeterol plus salbutamol treatment group (0.26/patient/year) (RR, 0.62/patient/year; 95% CI, 0.41 to 0.94; P=0.024). Secondary: The mean changes in overall ACQ-5 scores for the maintenance plus as-needed budesonide-formoterol treatment group and the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group were -0.702 and -0.655, respectively, although this difference was not statistically significant. The mean change in overall AQLQ(S) scores for the maintenance plus as-needed budesonide-formoterol treatment group and the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group were 0.843 and 0.727, respectively, although this difference was not statistically significant. A total of 33 serious adverse events occurred, 14 in the maintenance plus as-needed budesonide-formoterol treatment group and 19 in the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group. Headache occurred more frequently in the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				budesonide-formoterol treatment group (5 vs 2%; P=0.033). The most commonly reported adverse events included upper respiratory tract infections, nasopharyngitis, pharyngolaryngeal pain, headache and hoarseness. With the exception of headache, the rates of adverse events were similar in both groups.
Fitzgerald et al.[146] (2005) Budesonide-formoterol 200-6 µg BID via DPI vs salmeterol-fluticasone propionate 50-250 µg BID via DPI	DB, DD, RCT Individuals 18 to 70 years of age, with an documented clinical history of asthma and an FEV_1 between 60 to 90% of projected normal	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, and nighttime awakenings due to asthma	Primary: The percentage of symptom-free days was higher with fluticasone propionate -salmeterol compared to budesonide-formoterol (58.8 vs 52.1%; P=0.034). The percentage of symptom-free days was significantly higher with fluticasone propionate -salmeterol compared to budesonide-formoterol during weeks five through 52 (73.8 vs 64.9%; P=0.030). Secondary: In the fluticasone propionate -salmeterol group there was a significant difference in the adjusted annual mean exacerbation rate compared to the budesonide-formoterol group (0.18 vs 0.33; P=0.008). The median value for the percentage of days free of rescue medication over weeks five through 52 was 94.5% in the fluticasone propionate -salmeterol group compared to 90.7% in the budesonide-formoterol group (P=0.008). Over the 52-week treatment period the mean morning PEF was significantly higher in the fluticasone propionate -salmeterol group compared to the budesonide-formoterol group (400.1 vs 390.6 L/minute; P=0.006).
Ringdal et al.[147] (2002) EDICT Fluticasone propionate -salmeterol 250-50 µg, 1 inhalation	DB, DD, PG, RCT Patients 16 to 75 years of age with a clinical history of reversible airway obstruction, symptomatic on	N=428 12 weeks	Primary: Mean morning PEF (during week 12 of treatment) Secondary: Morning and evening PEF, day	Primary: Patients in the per-protocol population had an increase in mean morning PEF of 343 to 386 L/minute with fluticasone propionate -salmeterol compared to an increase of 348 to 389 L/minute observed with budesonide-formoterol (-3.2 L/minute 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs budesonide 800 µg and formoterol 12 µg, 1 inhalation BID	1,000 to 1,600 µg/day of budesonide, beclomethasone or flunisolide, or 500 to 800 µg/day of fluticasone propionate, FEV_1 50 to 85%, increased symptom scores or reliever use		and nighttime symptom scores, nighttime awakenings, FEV_1, rate and severity of exacerbations, and use of rescue medication, withdrawals from study	population for both treatment groups. Secondary: The mean rate of exacerbation/patient/84 days of treatment was significantly lower in the fluticasone propionate -salmeterol group in comparison to the budesonide-formoterol 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 propionate -salmeterol group had a statistically significant greater percentage of nights with no awakenings, without symptoms and a symptom score of <2 in comparison to those in the budesonide-formoterol 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.
Bousquet et al.[148] (2007) Fluticasone propionate -salmeterol 500-50 µg, 1 inhalation BID via Diskus and terbutaline as needed vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID and as needed via DPI	DB, MC, PG, RCT Patients ≥12 years of age with symptomatic asthma, FEV_1 ≥50%, and had experienced an asthma exacerbation in the previous year	N=2,309 6 months	Primary: Time to first severe exacerbation (defined as asthma deterioration leading to hospitalization or emergency room visit or use of oral corticosteroids for ≥3 days) Secondary: Rate of severe exacerbations, risk of first hospitalization, rate of hospitalization, FEV_1, morning and	Primary: The time to first severe exacerbation was not statistically different between the treatment groups (HR, 0.82; P=0.12). Secondary: There was a 21% reduction in the overall exacerbation rate in the budesonide-formoterol group compared to the fluticasone propionate -salmeterol group (25 vs 31 events/100 patients/year). The difference between groups was significant (P=0.039). The risk of hospitalization or emergency room visit was decreased in the budesonide-formoterol group when compared to the fluticasone propionate -salmeterol group (HR, 0.64; P=0.031). There was a 31% reduction in the rate of hospitalization with budesonide-formoterol compared to fluticasone propionate -salmeterol (9 vs 13 events/100 patients/year; P=0.046). FEV_1 increased in both groups from 2.29 to 2.52 L in the budesonide-formoterol group and from 2.70 to 2.49 L in the fluticasone propionate -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			evening PEF, as needed medication utilization, asthma control days, symptom free days, and safety	salmeterol group. There was no difference between the treatments (P value not reported). Morning and evening PEF scores improved in both treatment groups (for budesonide-formoterol there was an increase from 330.1 to 359.5 L/minute in the morning PEF and an increase from 336.7 to 362.3 in evening PEF; for fluticasone propionate -salmeterol there was an increase from 329.0 to 359.4 in the morning PEF and an increase from 337.7 to 361.7 in the evening PEF; a difference that was not statistically significant (morning; P=0.67, evening; P=0.42 evening). Use of high number as needed medication inhalations of >4, >6 and >8 inhalations/day was reported in 29, 13 and 4% of patients using the fluticasone propionate -salmeterol treatment and in 27, 9 and 3% using the budesonide-formoterol treatment. The differences were not significant (P=0.36). Asthma control days increased in both treatment groups from 6.3 and 5.8% at baseline to 44.0 and 44.9% in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. The difference was not statistically significant (P=0.37). Symptom free days improved from 10.7 and 11.2 at baseline to 47.2 and 48.1 in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. The difference was not statistically significant (P=0.73). Adverse events were reported in 39 and 40% of patients in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. Serious adverse events were three percent in both groups. There were 11 and 20 patients who discontinued the study due to adverse events in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. One death occurred in the study due to typhoid fever; however, it was not linked to the study medications.
Dahl et al.[149] (2006)	DB, MC, PG, RCT Patients with	N=1,391 24 weeks	Primary: Rate of exacerbations	Primary: There were no statistically significant differences in mean rate of exacerbations over 24 weeks, or severity of exacerbations observed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone propionate - salmeterol 250-50 µg, 1 inhalation BID vs budesonide-formoterol 200-6 µg, 2 inhalations BID	persistent asthma, currently receiving 1,000 to 2,000 µg/day of ICS, FEV_1 reversibility of ≥12% (and ≥200 mL), 15 min after salbutamol† 200 to 400 µg, and an asthma symptom score of at least 2 on at least 4 of the last 7 evaluable days of the run-in period		Secondary: Lung function, asthma symptoms, use of rescue medications, adverse events	between treatment groups. The adjusted mean rates of moderate/severe exacerbations per year calculated at weeks one to 24, one to eight, and nine to 16 were similar between treatment groups (P=NS). The adjusted mean rate of moderate/severe exacerbations per year calculated at weeks 17 to 24 of fluticasone propionate -salmeterol was lower than budesonide-formoterol (P=0.006). 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.
Lötvall et al.[150] (2006) Study A Fluticasone propionate - salmeterol 100-50 µg as a single dose vs budesonide-formoterol 160-4.5 µg as a single dose vs placebo Study B Fluticasone propionate -	Study A: DB, PC, RT, SC, 3-way XO Study B: DB, MC, RT, XO Patients ≥18 years of age with asthma for ≥6 months, pre bronchodilator FEV_1 of >50% predicted of normal, FEV_1 ≥15% of predicted value 15 min after receiving 400 µg salbutamol; in Study A, patients were receiving budesonide 400 to 1,200 µg (or equivalent) at least	Study A N=33 3 weeks Study B N=75 12 weeks	Study A Primary: Mean change from predose FEV_1 to 16 hours postdose Secondary: Mean change in FEV_1 from predose over 24 hours postdose Study B Primary: Slope of decline in FEV_1 from two hours postdose, area under FEV_1 curve, mean change from predose FEV_1 at 12 hours postdose	Study A: Primary: Patients in both the fluticasone propionate -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). Secondary: Patients in both the fluticasone propionate -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 propionate -salmeterol and budesonide-formoterol groups in regards to all primary endpoints.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 100-50 µg, 1 inhalation BID vs budesonide-formoterol 160-4.5 µg, 1 inhalation BID	4 weeks prior to study; in Study B, patients were receiving budesonide or beclomethasone 800 to 1,200 µg/day or fluticasone propionate 400 to 600 µg/day for at least 4 weeks prior to study		Secondary: Serial FEV_1 measurements following single dose after 4 weeks treatment	Secondary: There was no statistically significant difference in mean FEV_1 from baseline or FEV_1 from predose over 24 hours after four weeks treatment between the active treatment groups.
O'Connor et al.[151] (2010) Month 1: Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via PMDI vs fluticasone propionate - salmeterol 250-50 µg, 1 inhalation BID via DPI Months 2 to 7: Patients receiving fluticasone propionate - salmeterol continued therapy (FD), whereas those who received	OL, Phase III, RCT Patients ≥12 years of age with moderate to severe asthma	N=1,225 7 months	Primary: AQLQ, ACQ, ATSM and OEQ Secondary: Not reported	Primary: For AQLQ, no differences were observed between treatment groups in the percentages of patients with clinical meaningful improvements (≥0.5) in overall score. Although improvements were statistically significantly greater (P≤0.04) in the majority of domains for AMD vs either FD regimens, no clinically meaningful between group differences were noted. There were no statistically significant differences between FD regimens in mean improvement from baseline for overall or individual domain scores at the end of treatment. At the end of treatment, the mean change from baseline for all treatment groups exceeded the minimum important difference (0.5) for the ACQ, with no statistically significant or clinically meaningful between group changes noted (P values not reported). As indicated by the ATSM overall score at the end of treatment, patients reported significantly greater treatment satisfactions with AMD vs FD fluticasone propionate -salmeterol (P=0.020); there was no significant between group differences between the budesonide-formoterol FD and fluticasone propionate -salmeterol FD groups. Patients in both budesonide-formoterol groups reported significantly greater treatment satisfaction than those in the fluticasone propionate -salmeterol group for the attributes of timely relief of symptoms (P≤0.037) and feel medication working (P≤0.020). Patients in the budesonide-formoterol AMD group reported significantly greater treatment satisfaction for the attribute of dosing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide-formoterol were randomized to continue budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI (FD) OR to budesonide-formoterol 160-4.5, 2 inhalations QD or 4 inhalations BID (AMD). All patients received their usual asthma therapy for 10 to 14 days prior to randomization.				management than patients in the fluticasone propionate -salmeterol FD group (P<0.001), and reported significantly greater treatment satisfaction of the attributes of daily activity, leisure activity and dosing management than patients in the budesonide-formoterol group FD (P≤0.048). For the predefined item "During the past week, you could feel your study medication begin to work right away", 71, 71 and 59% of patients in the budesonide-formoterol AMD, budesonide/formoterol FD and fluticasone propionate -salmeterol FD groups responded positively at the end of treatment. The differences observed between the budesonide-formoterol groups and the fluticasone propionate -salmeterol groups were statistically significant (P≤0.002). For the predefined item "During the past week, you were satisfied with how quickly you felt your study medication begin to work", 78, 80 and 73% of patients in the budesonide-formoterol AMD, budesonide-formoterol FD and fluticasone propionate -salmeterol FD groups responded positively at the end of treatment. The difference between the FD budesonide-formoterol and fluticasone propionate -salmeterol groups was small but statistically significant (P=0.025). Secondary: Not reported
Busse et al.[152] (2008) <u>Treatment period I:</u> Fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID via Diskus vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI (FD)	MC, OL, RCT, Patients ≥12 years of age with an asthma diagnosis for ≥6 months and who are in stable condition, required to have a pre bronchodilator FEV_1 ≥50% of predicted normal and to have been maintained on a daily medium dose ICS or ICS/LABA	N=1,225 Treatment Period I: 1 month Treatment Period II: 6 months	Primary: Number of exacerbations/patient-treatment year, percentage of patients with ≥1 exacerbations, and time from first dose to first exacerbation Secondary: Predose FEV_1, morning PEF, morning and evening asthma	Primary: There was no significant difference seen in the treatment groups and the time to first exacerbation (P value not reported). There was no significant difference seen in the treatment groups and the percentage of patients with at least one exacerbation, for the AMD budesonide-formoterol group the percentage was 8.0, 8.8% in the FD budesonide-formoterol group and 9.2% in the fluticasone propionate -salmeterol group (P value not reported). There was no significant difference seen in the treatment groups and the total number of exacerbations/patient treatment year, for the AMD budesonide-formoterol group the value was 0.196, 0.240 in the FD budesonide-formoterol group and 0.189 in the fluticasone propionate -salmeterol group (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment period II: Fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID via Diskus vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI (FD) vs budesonide-formoterol 160-4.5 µg AMD (adjustable from 2 inhalations BID to 2 inhalations QD or 4 inhalations BID all via Diskus)	for ≥12 weeks before screening		symptom scores, nighttime awakenings, daily rescue medication use, average daily symptom scores, symptom-free days, rescue medication-free days, and safety	Secondary: No statistically significant differences were seen in predose FEV_1, for the AMD budesonide-formoterol group the change was 0.13 L, 0.15 L in the FD budesonide-formoterol group and 0.16 L in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in morning PEF, for the AMD budesonide-formoterol group the change was 34.73 L/minute, 30.86 L/minute in the FD budesonide-formoterol group and 33.59 L/minute in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in morning and evening asthma symptom scores, for the AMD budesonide-formoterol group the change was -0.39, for the FD budesonide-formoterol group the score was -0.37 and -0.35 L in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in nighttime awakenings. For the adjustable dose budesonide-formoterol group the percent change was 10.03%, 10.02% in the FD budesonide-formoterol group and 7.73% in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in the percentage of symptom-free days, for the AMD budesonide-formoterol group the percent change was 26.59%, 25.80% in the FD budesonide-formoterol group and 25.39% in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in the percentage of rescue medication-free days, for the AMD budesonide-formoterol group the percent change was 41.84%, 41.24% in the FD budesonide-formoterol group and 38.85% in the fluticasone propionate -salmeterol group (P value not reported). All treatment groups were well tolerated. Adverse events were in general mild (56.1%) or moderate (38.4%), and no study medication adverse events were considered serious.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kuna et al.[153] (2007) Budesonide-formoterol 160-/4.5 µg, 1 inhalation BID, and additional inhalations as needed vs budesonide-formoterol 320-9 µg, 1 inhalation BID and terbutaline as needed vs fluticasone propionate -salmeterol 125-25 µg, 2 inhalations BID and terbutaline as needed Both FD treatment groups also had terbutaline as an as needed reliever medication.	DB, DD, PG, RCT Patients ≥12 years of age with an asthma diagnosis ≥6 months, using an ICS ≥3 months, FEV_1 ≥50% predicted normal, and ≥12% reversibility following terbutaline and ≥1 asthma exacerbation in previous 1 to 12 months	N=3,335 6 months	Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit or the need for oral steroids ≥3 days) Secondary: Exacerbation rates, total number of severe exacerbations, number of patients having ≥1 hospitalization, number of mild exacerbation days, asthma symptom total score, morning and evening PEF, FEV_1, asthma symptom score, asthma induced night-awakenings, symptom-free days, as-needed medication free days, asthma-control days, number of mild exacerbations	Primary: The budesonide-formoterol 160-4.5 µg group prolonged the time to first severe exacerbation when compared to the fluticasone propionate -salmeterol (P=0.0034) and budesonide-formoterol 320-9 µg groups (P=0.023). There was a 33% reduction in the HR for a first severe exacerbation with the budesonide-formoterol 160-4.5 µg group compared to the fluticasone propionate -salmeterol group (P=0.003), and a 26% reduction when compared to the budesonide-formoterol 320-9 µg group (P=0.026). Secondary: Exacerbation rates were 19, 16 and 12 events/100 patients/six months for the fluticasone propionate -salmeterol group, the budesonide-formoterol 320-9 µg group and the budesonide-formoterol 160-4.5 µg group. The difference between the budesonide-formoterol 160-4.5 µg group, the fluticasone propionate -salmeterol group (P<0.001) and the budesonide-formoterol 320-9 µg group (P=0.0048) were statistically significant. However the difference between the fluticasone propionate -salmeterol group and the budesonide-formoterol 320-9 µg group was not statistically significant (P=0.1). The total number of severe exacerbations were 208, 173, and 125 in the fluticasone propionate -salmeterol, budesonide-formoterol 320-9 µg and budesonide-formoterol 160-4.5 µg groups, respectively (P value not reported). The percentage of patients having at least one hospitalizations/emergency room visit was 6, 5 and 4% in the fluticasone propionate -salmeterol, budesonide-formoterol 320-9 µg and budesonide-formoterol 160-4.5 µg groups, respectively. The difference was significant between the budesonide-formoterol 160-4.5 µg group and the fluticasone propionate -salmeterol group (P=0.047), but not between the two budesonide-formoterol groups or between the budesonide-formoterol 320-9 µg and fluticasone propionate -salmeterol groups (P=0.066). There were no significant differences seen between the three treatment groups in the number of mild exacerbation days. Overall 59, 63 and 61%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(defined as a day with any of one the following: morning PEF ≥20% below baseline, daily as-needed medication use ≥2 inhalations or a night with asthma-related awakenings), and safety	in the fluticasone propionate -salmeterol group, the budesonide-formoterol 320-9 µg group and the budesonide-formoterol 160-4.5 µg group experienced a mild exacerbation (P value not reported). There were no significant differences between all three treatment groups in asthma symptom total score (1.03,1.07 and1.06), percentage of symptom-free days (46.0, 44.6 and 44.2%), percentage of asthma-control days (43.7, 42.2 and 41.3%), percentage of night-time awakenings (14.0,14.6 and 14.1%), total number of inhalations/day (0.96,1.05 and 1.02) for the fluticasone propionate -salmeterol, the budesonide-formoterol 320-9 µg and the budesonide-formoterol 160-4.5 µg groups, respectively (P values not reported). There were no significant differences found between all three treatment groups in FEV_1 (2.67, 2.66 and 2.69 L), morning PEF (367, 362 and 363 L/minute), evening PEF (370, 366 and 368 L/minute) for the fluticasone propionate -salmeterol, the budesonide-formoterol 320-9 µg and the budesonide-formoterol 160-4.5 µg groups, respectively (P values not reported). All three treatment groups reported no significant differences in the number or severity of adverse events. The most frequently reported adverse events were upper respiratory tract infection, pharyngitis and nasopharyngitis.
Palmqvist et al.[154] (2001) Budesonide-formoterol 160-4.5 µg, 1 inhalation as a single dose vs budesonide-formoterol 160-4.5 µg, 2 inhalations as	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 three minutes, and	Primary: Both budesonide-formoterol doses demonstrated improvements in FEV_1 compared to fluticasone propionate -salmeterol and placebo at 15 minutes postdose (P<0.001). Secondary: At one hour, bronchodilation was achieved in 47% of patients in the fluticasone propionate -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 three minutes (P<0.001) and at 60 minutes (P

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
a single dose vs fluticasone propionate -salmeterol 250-/50 µg, 1 inhalation as a single dose vs placebo			FEV_1 at time points ≤60 minutes	values not reported) compared to fluticasone propionate -salmeterol and placebo.
Aalbers et al.[155] (2004) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (AMD) vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID (FD) vs fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID (FD) During a 4 week	DB (4 weeks), ES (6 months), OL Patients with moderate-severe asthma, mean symptom score 1.5, mean FEV_1 84% predicted, mean ICS dose 735 µg/day	N=658 4 week DB period plus a 6 month OL extension	Primary: Odds of achieving a WCAW Secondary: Exacerbation rate and use of reliever medication	Primary: There was no difference in the OR pertaining to WCAW observed in the FD treatment groups (P value not reported). There was a significant increase in the odds of achieving WCAW observed in the budesonide-formoterol AMD group in comparison to the budesonide-formoterol FD group during the open 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 propionate -salmeterol group, and a 32% lower exacerbation rate compared to those in the budesonide-formoterol FD group (P=0.018 and P value not significant, respectively). Patients in the budesonide-formoterol AMD group used significantly less reliever medication during the open study period vs those in the budesonide-formoterol and the fluticasone propionate -salmeterol FD groups (P=0.001 and P=0.011, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DB period, the budesonide-formoterol AMD and FD groups received 2 inhalations BID, and those in the fluticasone propionate - salmeterol group received 1 inhalation BID. During a 6 month extension period, all FD groups remained the same and the budesonide-formoterol AMD group could decrease dose to 1 inhalation BID, or increase dose up to 4 inhalations BID for 7 to 14 days based on asthma symptoms.				
Edwards et al.[156] (2007) Budesonide vs budesonide-formoterol (FD)	MA Patients with moderate to severe asthma	15 trials 12 to 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 vs the budesonide-formoterol FD group, there was no significant difference detected (RR, 0.88; 95% CI, 0.77 to 1.02; P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide-formoterol (AMD) vs fluticasone propionate -salmeterol (FD)				There was no significant difference observed between those in the budesonide-formoterol group and those in the fluticasone propionate -salmeterol group in regards to treatment failure (P=0.86). Secondary: Patients in the fluticasone propionate -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). Patients in the budesonide-formoterol-AMD treatment group had a 28% risk reduction in hospitalizations/accident and emergency visits vs 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 vs those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; P=0.01).
Cates et al.[157] (2013) Budesonide-formoterol vs ICS plus reliever therapy vs	MA (13 RCTs) Adults and children with chronic asthma	N=13,152 At least 12 weeks	Primary: Exacerbations requiring hospitalization, exacerbations requiring oral corticosteroids, serious adverse events (including mortality and life-threatening events) and growth (in	Primary: Exacerbations of asthma causing hospital admissions Twenty one adults and adolescents treated with budesonide-formoterol 160-4.5 µg experienced an exacerbation leading to hospitalization compared to 26 patients treated with current best practice (Peto OR, 0.81; 95% CI, 0.45 to 1.44). Compared to ICS with a separate reliever medication, there was no statistically significant difference in exacerbations of asthma causing hospital admissions with budesonide-formoterol (Peto OR, 0.56; 95% CI, 0.28 to 1.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
current best practice			children) Secondary: Severe exacerbations (composite outcome of hospitalization/ emergency room visit/oral steroid course), morning and evening PEF, FEV_1, rescue medication use per day, symptoms/sympto m-free days, nocturnal awakenings and quality of life	Significantly fewer children treated with budesonide-formoterol were hospitalized for asthma exacerbations compared to those treated with higher doses of ICS (OR, 0.33; 95% CI, 0.15 to 0.77). *Exacerbations of asthma treated with oral corticosteroids* There was a statistically significant reduction between treatment with budesonide-formoterol 160-4.5 µg and current best practice with regard to the risk of asthma exacerbation requiring treatment with oral corticosteroids (Peto OR, 0.83; 95% CI, 0.70 to 0.98). The NNT was 90. There was a significant reduction in the number of patients requiring a course of steroids with budesonide-formoterol compared to ICS plus a separate reliever medication (OR, 0.54; 95% CI, 0.45 to 0.64). The NNT was 14. *Serious adverse events* No significant differences were reported between budesonide-formoterol 160-4.5 µg and current best practice in the risk of fatal or non-fatal serious adverse events (fatal events: Peto OR, 1.95; 95% CI, 0.53 to 7.21; non-fatal events: OR, 1.20; 95% CI 0.90 to 1.60). The overall number of events was too small to rule out the possibility of a clinically important increase or decrease in serious adverse events. No significant difference was observed in either fatal (Peto OR, 0.37; 95% CI, 0.05 to 2.62) or non-fatal adverse events (OR, 0.97; 95% CI, 0.73 to 1.29) between budesonide-formoterol and ICS plus a separate reliever medication. Secondary: Severe exacerbations requiring medical intervention In seven studies, there was no significant reduction in the time to a severe exacerbation between patients treated with budesonide-formoterol 160-4.5 µg or current best practice (HR, 0.94; 95% CI, 0.85 to 1.04). There was a significant reduction in the time to a serious exacerbation with budesonide-formoterol compared to high dose ICS plus a separate reliever therapy (HR 0.59; 95% CI 0.49 to 0.70).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Change in morning PEF and FEV_1 Data were not available for this outcome for budesonide-formoterol 160-4.5 µg treatment compared to current best practice. There was a significant increase in PEF in the budesonide-formoterol group compared to treatment with a higher dose of budesonide (mean difference, 22.29 L/min; 95% CI, 17.62 to 26.95). There was an increase in FEV_1 with budesonide-formoterol compared to higher doses of budesonide (mean difference, 0.10 L; 95% CI, 0.07 to 0.13). There was no significant difference in PEF for FEV_1 between patients treated with budesonide-formoterol compared to higher doses of ICS. *Rescue medication use* One study evaluated rescue medication use and reported a difference of -0.16 puffs/day (95% CI, -0.27 to -0.05) with budesonide-formoterol 160-4.5 µg compared to current best practice. There was a reduction in rescue medication use in favor of budesonide-formoterol compared to higher doses of budesonide (mean difference, -0.37 puffs per day; 95% CI, -0.49 to -0.25). *Quality of life* On average, children treated with budesonide-formoterol experienced two fewer nocturnal awakenings per night compared to children treated with higher doses of ICS (95% CI, -3.33 to -0.67). *Annual height gain* The mean increase in height over one year in the budesonide-formoterol group was 5.3 cm (range 1 to 14 cm), significantly higher compared to 4.3 cm (range -2 to 15 cm) in the ICS treatment group.
Sears et al.[158] (2008)	MC, OL, PG, RCT Patients ≥12 with	N=1,538 6 months	Primary: Time to first severe asthma	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide-formoterol 160-4.5 µg, 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)	asthma for a minimum of 3 months, use of ≥400 µg 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		exacerbation Secondary: Number of severe asthma exacerbations, mean use of as needed medication, PEF, ACQ-5	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).
Louis et al.[159] (2009) Budesonide-formoterol 160-4.5 µg, 1 inhalation BID with additional inhalations as needed via MDI vs	MC, OL, PG, RCT Patients ≥12 years of age with an asthma diagnosis for >3 months and prescribed ICS at a dose of ≥500 µg/day beclomethasone dipropionate equivalent with or without other controller therapies,	N=908 26 weeks	Primary: Time to first severe asthma exacerbation (defined as deterioration in asthma leading to hospitalization, emergency room visit, or equivalent) or oral steroid treatment for ≥3 days	Primary: There was no difference in the time to first severe asthma exacerbation for patients treated with budesonide-formoterol compared to CBP (P=0.75). Secondary: Only 2.7% of patients who received budesonide/formoterol and 4.1% of patients treated according to CBP experienced a severe asthma exacerbation during treatment. Twelve patients in the budesonide-formoterol group experienced a total of 14 exacerbations, and 19 patients in the CBP group experienced a total of 25 exacerbations (annual rate including all patients, 0.074 vs 0.13 per patient-year; P=0.09). A similar percentage of patients in both groups had ≥1 day during which at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
conventional best practice (CBP) treatment (multiple controller therapies allowed, ICS and ICS/LABAs at any dose and add-on oral leukotriene antagonist or xanthenes if warranted) The CBP group was treated in a stepwise approach in accordance with the Global Initiative for Asthma guidelines.	if a patient was using ICS monotherapy, they needed to use ≥3 inhalations of as-needed medication for symptom relief during the last 7 days before enrolment		Secondary: Number of severe asthma exacerbations, the mean use of as-needed medication (reliever medication) and prescribed asthma medications and scores on ACQ5, SATQ	least one dose of an as-needed medication was required (58.5 and 63.5% for budesonide-formoterol and CBP groups, respectively; P value not reported). The mean daily dose of inhaled steroid was significantly lower in the budesonide-formoterol group compared to the CBP group (482 vs 589 µg daily; P<0.0001). In the budesonide/formoterol group, the mean ACQ5 score assessing symptom control and activity limitation during the treatment period, decreased by -0.30 compared to -0.17 in the CBP group (P<0.01). Both groups showed similar overall treatment satisfaction (improvement in SATQ overall score) from enrolment to the end of the study (P value not reported).
Marceau et al.[160] (2006) Fluticasone propionate - salmeterol or budesonide-formoterol (fixed-dose inhaler) vs combination of ICS (fluticasone propionate, budesonide, or beclomethasone) and a LABA	RETRO Patients 16 to 44 years of age who had not been on combination or concurrent ICS and LABA therapy within the past year	N=5,118 1 year	Primary: Number of prescription renewals during the first year of treatment Secondary: The rate of moderate to severe asthma exacerbations (defined as a filled prescription of an ICS, an emergency department visits or hospitalization for asthma) during	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). 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) emergency department 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(salmeterol or formoterol)			the first year of treatment, and weekly number of doses of short-acting inhaled β_2-agonists	
Scicchitano et al.[161] (2004) Budesonide-formoterol 160-4.5 µg, 2 inhalations QD with additional inhalations as needed vs budesonide 160 µg, 2 inhalations BID plus terbutaline 0.4 mg inhalations as needed	DB, PG, RCT Patients 11 to 80 years of age with symptomatic asthma, mean FEV_1 70% of predicted, mean ICS dose 746 µg/day	N=1,890 12 months	Primary: Time to first severe exacerbation (defined as hospital/emergency room visit, oral steroids or fall in morning PEF to <70% of baseline for two consecutive days) Secondary: Number of severe exacerbations, use of as needed medication, mean daily ICS dose, and number of asthma control 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 the budesonide group (P<0.001). Secondary: Patients in the budesonide-formoterol group had 45% fewer severe exacerbations resulting in medical interventions/patient compared to those in the budesonide group (P<0.001). Patients in the budesonide-formoterol group also had less utilization of as-needed medication (P<0.001), and a lower mean daily ICS dose (466 vs 640 µg/day, respectively) compared to those in the budesonide group. Overall, those in the budesonide-formoterol group experienced 31 more asthma control days and 12 more undisturbed nights/patient-year vs those in the budesonide group (P value not reported).
Rabe et al.[162] (2006) Budesonide-formoterol 80-4.5 µg, 2 inhalations QD in the evening with additional inhalations as needed	AC, DB, MC, PG, RCT Patients 11 to 79 years of age with an asthma diagnosis for ≥6 months, FEV_1 60 to 100% predicted normal, >12% reversibility of baseline FEV_1 15	N=697 6 months	Primary: Morning PEF Secondary: FEV_1, evening PEF, as needed inhalations, as needed medication-free days, asthma symptom score,	Primary: Patients in the budesonide-formoterol group had greater improvements in morning PEF from baseline than those in the budesonide group and was maintained throughout the six month treatment period (34.5 vs 9.5 L/minute, 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 160 µg, 2 inhalations QD in the evening plus terbutaline 0.4 mg as needed	minutes after terbutaline 1 mg inhalation, all patients had received an ICS 200 to 500 µg/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		nighttime awakenings, symptom free days, asthma control days, and risk of exacerbation	Patients in the budesonide-formoterol group also had greater improvements in evening PEF from baseline than those in the budesonide group. Patients in the budesonide-formoterol 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 group vs those in the budesonide group (P<0.01). Those in the budesonide-formoterol group had less utilization of as-needed medication, along with eight percent more as-needed medication-free days vs those in the budesonide group (P<0.001). Patients in the budesonide-formoterol had a 54% lower risk in having an exacerbation in comparison to those in the budesonide group (P=0.0011), as well as 90% fewer hospitalizations/emergency department treatments vs those in the budesonide group (P=0.026).
Maspero et al.[163] (2008) Fluticasone propionate - salmeterol 100-50 µg, 1 inhalation BID vs montelukast 5 mg QD	AC, DB, 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 propionate 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 propionate group; 153/267 [57%] in the montelukast group). The mean exacerbation rates over 12 weeks were 0.12 in the salmeterol-fluticasone propionate group and 0.30 in the montelukast group (P<0.001).
Sorkness et al.[164] (2007) Fluticasone	DB, PG, RCT Patients 6 to 14 years of age with	N=285 48 weeks	Primary: Percent of asthma control days; use of oral	Primary Percent of asthma control days averaged 64.2% for fluticasone propionate monotherapy, 59.6% for PACT combination, and 52.5% for montelukast monotherapy. The fluticasone propionate monotherapy group gained an

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propionate - salmeterol 100-50 µg QAM and salmeterol 50 µg QPM (PACT combination) vs fluticasone propionate 100 µg BID (fluticasone propionate monotherapy) vs montelukast 5 mg QPM (montelukast monotherapy)	mild to moderate asthma, >4 hour post-bronchodilator FEV_1 ≥80% of predicted normal and ≥70% at randomization plus methacholine FEV_1 ≤12.5 mg/ml		corticosteroids; use of non-study asthma medications; daytime symptoms; nighttime awakenings; unscheduled health care visits; emergency department 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; pulmonary function and growth	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 propionate monotherapy vs montelukast, and PACT combination vs montelukast, but not for fluticasone propionate monotherapy vs PACT combination. During the 48 weeks, the percentages of patients who achieved 20% more asthma control days during the treatment period compared with the run-in period were 65% for fluticasone propionate monotherapy, 66% for PACT combination, and 50% for montelukast. The NNT for both fluticasone propionate monotherapy and PACT combination compared with montelukast was approximately 6.5, meaning that seven patients would need to be treated with fluticasone propionate 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 propionate monotherapy and PACT combination led to a greater percentage of episode-free days. Significant superiority of fluticasone propionate vs montelukast monotherapy (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, five with fluticasone propionate, eight with PACT combination, and 15 with montelukast, with the comparison for fluticasone propionate vs montelukast monotherapy significant (P=0.04). No significant difference between fluticasone propionate monotherapy vs PACT combination, or PACT combination vs montelukast in regard to ACQ score improvement, there was a significant difference with fluticasone propionate compared with montelukast (P=0.018). Pre bronchodilator FEV_1 (percent predicted) and FEV_1/FVC (percent) increased more with fluticasone propionate monotherapy than montelukast

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(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 percent predicted from baseline was 6.32% with fluticasone propionate 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 propionate 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 propionate monotherapy, compared with a 0.3% increase with PACT combination and a 1.69% increase with montelukast (P<0.001, fluticasone propionate vs montelukast). For the participant-measured outcome of percent predicted pre bronchodilator AM and PM PEFs, fluticasone propionate 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 propionate 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 propionate 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 propionate monotherapy and PACT combination compared with montelukast monotherapy respectively, but of no statistical significance.
Peters et al.[165] (2007) LOCSS Fluticasone propionate -	DB, MC, RCT Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-bronchodilator,	N=500 16 weeks	Primary: Time to treatment failure Secondary: Measures of pulmonary	Primary: The rates of treatment failure were 20.2% in the fluticasone propionate group, 20.4% in the fluticasone propionate -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
salmeterol 100-50 µg QHS vs fluticasone propionate 100 µg BID vs montelukast 5 to 10 mg QD	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 µg BID and step-down therapy was being attempted		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 pre bronchodilator FEV_1 values were higher in the fluticasone propionate group (91.1% of the predicted value) and the fluticasone propionate -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 propionate group and in the fluticasone propionate -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 propionate -salmeterol group (22.9 vs 17.1%; P=0.06) and in the fluticasone propionate group (22.9 vs 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone propionate group than in the montelukast group (16.7 vs 25.4%; P=0.04), with a similar trend in the fluticasone propionate -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.[166] (2008) Fluticasone propionate -salmeterol 100-50 µg QAM and salmeterol 50 µg QPM vs fluticasone propionate 100 µg BID	DB, PC, PG, RCT Children 6 to 14 years of age with documented mild-moderate persistent asthma	N=285 48 weeks	Primary: Regression modeling was used to look for factors predictive of exacerbation Secondary: Not reported	Primary: Treatment with montelukast vs fluticasone propionate monotherapy (OR, 2.00; P=0.005) was a positive predictor for exacerbations. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs montelukast 5mg QD				
Ringdal et al.[167] (2003) Fluticasone propionate - salmeterol 100-50 µg BID plus oral placebo vs fluticasone propionate 100 µg BID and montelukast 10 mg QD	DB, DD, MC, PG RCT Patients 14 to 79 years of age with a diagnosis of asthma, history of receiving ICSs for ≥4 weeks prior to randomization, reversible airway obstruction, ≥15% increase in FEV_1 after β_2-agonist use, mean morning PEF 50 to 85% predicted, cumulative symptom score ≥8 during last 7 days of run-in period and symptoms on ≥4 of last 7 days of run-in	N=806 14 weeks	Primary: Mean morning PEF value Secondary: Evening PEF values, β_2-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 physician assessment of effectiveness of treatment	Primary: Statistically significant improvement in morning PEF values in the fluticasone propionate -salmeterol group compared to the fluticasone propionate plus montelukast group (361 vs 191 L/minute; P<0.05). Secondary: Statistically significant improvement in FEV_1 values in the fluticasone propionate - salmeterol group compared to the fluticasone propionate plus montelukast group (mean treatment difference, 0.11 L; P<0.05). The fluticasone propionate -salmeterol group was significantly more likely to have a symptom-free day compared to the fluticasone propionate plus montelukast group (OR, 1.32; 95% CI, 1.05 to 1.65; P<0.05). The fluticasone propionate -salmeterol group was significantly more likely to have a rescue free day compared to the fluticasone propionate plus montelukast group (OR, 1.29; 95% CI, 1.02 to 1.63; P=0.03), but rescue-free nights did not reach statistical significance. A significantly lower number of patients in the fluticasone propionate - salmeterol group had an asthma exacerbation compared to patients in the fluticasone propionate plus montelukast group (9.6 vs 14.6%; P<0.05), but no significant difference between the groups in percentage of patients having moderate or severe asthma exacerbation (P=0.07) was noted. The time to first exacerbation was longer in the fluticasone propionate - salmeterol group compared to the fluticasone propionate plus montelukast group (P<0.05). Patient and physician satisfaction and assessment of treatment was higher in the fluticasone propionate -salmeterol group compared to the fluticasone propionate plus montelukast group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lemanske et al.[168] (2010) Fluticasone propionate 250 µg, BID (ICS step up therapy) vs fluticasone propionate - salmeterol 100-50 µg, BID (LABA step up therapy) vs fluticasone propionate 100 µg BID plus montelukast 5 or 10 mg/day (LTRA step up therapy) All patients received fluticasone propionate 100 µg BID during a 2 to 8 week run-in period. A treatment period was ranked as better than another if the total amount	DB, RCT, XO Patients 6 to 17 years of age with mild to moderate asthma diagnosed by a physician, the ability to perform reproducible spirometry, an FEV_1 ≥60% before bronchodilation, an increase in the FEV_1 ≥12% (bronchodilator reversibility) or a methacholine provocation concentration causing a 20% fall in the FEV_1 of ≤12.5 mg/mL	N=182 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: the need for treatment with oral prednisone for acute exacerbations, the number of asthma control days and FEV_1 Secondary: Not reported	Primary: Differential response to the three step up therapies A differential response occurred in 161/165 (98%) patients. The percentage of asthma control days differed according to season in all study groups, ranging from 71 to 79% in the winter and summer months. Asthma exacerbations were most frequent during winter months. The average FEV_1 varied by less than one percent across seasons. In pairwise comparisons, the proportion of patients who had a better response to LABA step up therapy was higher than the proportion with a better response to LTRA step up therapy (52 vs 34%; P=0.02), and the proportion with a better response to LABA step up therapy was higher than the proportion of with a better response to ICS step up therapy (54 vs 32%; P=0.004), whereas the response to LTRA and ICS step up therapies were similar. The primary outcome of the trial, a three-way comparison of step-up therapy with the use of rank-ordered logistic regression, predicted that the response to LABA step up was significantly more likely to be the best response, as compared to 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 therapy (relative probability, 1.7; 95% CI, 1.2 to 2.4; P=0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of prednisone received during treatment was ≤180 mg, if the number of annualized asthma control days during the final 12 weeks of the period was increased by ≥31 days or if the FEV_1 at the end of the period was ≥5% higher. If the prednisone threshold was met, the number of asthma control days and FEV_1 were ignored. If the threshold for asthma control days was met, the FEV_1 was ignored. Otherwise the order of response was determined by the FEV_1.				
Nguyen et al.[169] (2005) Fluticasone propionate -	DB, RCT Pediatric patients 4 to 17 years of age with asthma, parent	N=39 12 months	Primary: Reducing the number of emergency department visits	Primary: Statistically significant decrease in the number of emergency department visit/year in the study group compared to the control group (1.2 to 0.8; P=0.017).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 100-50 to 250-50 µg BID vs usual care (all patients received ICS at some point during the study)	reported emergency room visits ≥5 in the past 2 years or 2 to 3 in the past 2 months, enrolled in Medicaid in Tennessee, Mississippi or Arkansas		and hospitalizations in minority inner-city children Secondary: Not reported	The risk of experiencing at least one hospitalization was reduced by 43% in the treatment group compared to the placebo group (risk ratio, 0.57; 95% CI, 0.19 to 1.71; P=0.31). The risk of experiencing an asthma exacerbation was reduced by 23% in the treatment group compared to the placebo group (P=0.09). Secondary: Not reported
Chronic Obstructive Pulmonary Disease				
Weir et al.[170] (1999) Beclomethasone 750 to 1,000 µg BID vs placebo	DB, PC, PG, RCT 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 reported).
Bourbeau et al.[171] (1998) Budesonide 400 µg BID vs placebo	DB, PC, PG, RCT Patients with COPD 40 years of age 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, PEFR, respiratory	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			symptom scores	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.[172] (1999) Budesonide 400 µg BID vs placebo	DB, MC, PC, PG, RCT Current smokers 30 to 65 years of age 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.[173] (1999) Budesonide 800 µg QAM and 400 µg QPM for six months, followed by 400 µg BID for 30 months vs	DB, PC, PG, RCT Patients with COPD	N=290 36 months	Primary: Rate of FEV_1 decline Secondary: Decrease in symptoms	Primary: No significant effect of budesonide was found on the rate of FEV_1 decline. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Burge et al.[174] (2000) Fluticasone propionate 500 µg BID vs placebo	DB, PC, RCT 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 disease, morning serum cortisol levels, adverse events	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 propionate group (P=0.16). The predicted mean FEV_1 at three and 36 months in the fluticasone group was 76 and 100 mL higher, respectively, than in the placebo group (P<0.001). Secondary: The median yearly exacerbation rate was lower in the fluticasone propionate group (0.99 per year) compared with the placebo group (1.32 per year), a reduction of 25% in those receiving fluticasone propionate (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 propionate group (2.0 units per year) (P=0.004). More patients in the placebo group than in the fluticasone propionate group withdrew because of respiratory disease (25 vs 19%, respectively, P=0.034). There was a small decrease in mean cortisol concentrations with fluticasone propionate 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 propionate group than with placebo.
Paggiaro et al.[175] (1998)	DB, PC, RCT	N=281	Primary: Number of patients	Primary: More patients in the placebo group (37%) experienced at least one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone propionate 500 µg BID vs placebo	Patients 50 to 75 years of age with COPD	6 months	who had at least one exacerbation at the end of the study period Secondary: Mean change from baseline in PEFR, daily symptom scores, frequency of adverse events	exacerbation than in the fluticasone propionate 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 propionate group ([9-26], P<0.001). Symptom scores showed a distribution of significantly lower median daily cough scores in the fluticasone propionate 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 and 64% of patients receiving fluticasone propionate.
Martinez et al.[176] (2013) Fluticasone furoate-vilanterol 100-25 µg QD vs fluticasone furoate-vilanterol 200-25 µg QD vs fluticasone furoate 200 µg QD vs fluticasone furoate 100 µg QD	DB, MC, PC, PG, RCT Patients aged ≥40 years of age with stable, moderate to severe COPD, a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70% predicted and a score of ≥2 on the mMRC Dyspnea Scale	N=1,224 24 weeks	Primary: Zero to four hour weighted mean postdose-FEV_1 and trough-FEV_1 Secondary: CRQ-SAS, peak FEV_1, time to ≥100 mL improvement from baseline in FEV_1 on day one, time to ≥12% improvement in FEV_1 over the first four hours post-dose on day one, use of rescue medications, nighttime awakenings and safety parameters	Primary: The 100-25 µg and 200-25 µg combination regimens were associated with improvement in weighted mean postdose-FEV_1 compared to placebo (214 mL; 95% CI, 161 mL to 266 mL for the 100 µg dose comparison; and 209 mL; 95% CI, 157 mL to 261 mL for the 200 µg dose comparison, respectively) and fluticasone furoate monotherapy (168 mL; 95% CI, 116 mL to 220 mL for the 100 µg dose comparison; 168 mL; 95% CI, 117mL to 219 mL for the 200 µg dose comparison, respectively). In addition, the combination regimens were associated with an increase in trough FEV_1 compared to placebo (144 mL; 95% CI, 91 mL to 197 mL for the 100 µg dose comparison; and 131 mL; 95% CI, 80 mL to 183 mL for the 200 µg dose comparison, respectively). However, there was no significant difference between the combination regimen and vilanterol alone (45 mL; 95% CI, -8 mL to 97 mL for the 100 µg dose comparison; and 32 mL; 95% CI, -6 mL to 102 mL for the 200 µg dose comparison, respectively) Secondary: From day one of the study postdose-FEV_1 and trough-FEV_1 were greater with fluticasone furoate-vilanterol and vilanterol compared to fluticasone furoate and placebo. Both parameters increased rapidly from day 1 to day 14 and were generally maintained thereafter. Over six months, scores on the dyspnea domain of the CRQ-SAS declined

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vilanterol 25 µg QD vs placebo Albuterol was allowed for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward.				relative to placebo with both strengths of fluticasone furoate, but improved with both strengths of fluticasone furoate-vilanterol and with vilanterol alone. In the fluticasone furoate 100 µg and 200 µg arms adjusted mean peak FEV_1 was 24 mL (95% CI, -6 to 55) and 7 mL (95% CI, -23, to 37) respectively, greater than placebo while for vilanterol the adjusted mean increase from placebo was 147 mL (95% CI, 117 to 177). The equivalent values for fluticasone furoate-vilanterol 100-25 µg and 200-25 µg were 152 mL (95% CI, 122 to 182) and 141 ml (95% CI, 111 to 171), respectively. Other efficacy comparisons generally favored the use of fluticasone furoate-vilanterol compared to placebo. No increase was seen in on-treatment adverse events or serious adverse events, with active therapy vs. placebo. Exacerbations were infrequent but occurred more often in the placebo arm (21 events) than in any active treatment arm and more frequently in the vilanterol arm (18 events) than in the fluticasone furoate-containing arms (14 events).
Kerwin et al.[177] (2013) Fluticasone furoate-vilanterol 50-25 µg QD vs fluticasone furoate vilanterol 100-25 µg QD vs	DB, MC, PC, PG, RCT Patients aged ≥40 years of age with stable, moderate to severe COPD, a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70%	N=1,030 24 weeks	Primary: Zero to four hour weighted mean postdose-FEV_1 and trough-FEV_1 Secondary: CRQ-SAS, peak FEV_1, time to ≥100 ml improvement from baseline in FEV_1 on day one, time to ≥12% improvement in FEV1 over the first	Primary: The 100-25 µg combination regimen was associated with improvement in weighted mean postdose-FEV_1 compared to placebo (173 mL; 95% CI, 123 to 224 mL) and fluticasone furoate monotherapy (120 mL; 95% CI, 70 to 170 mL). In addition, the combination regimen was associated with an increase in trough FEV_1 compared to placebo (115 mL; 95% CI, 60 mL to 169 mL). However, there was no significant difference between the combination regimen and vilanterol alone (48 mL; 95% CI, -6 to 102 mL). Similar results were observed with the 50 µg-25 µg compared to placebo. Secondary: For FEV_1 at other time points over 24 weeks, both strengths of fluticasone furoate-vilanterol showed rapid and sustained improvements over placebo, and were greater than the vilanterol monotherapy arm at all time points from day 14. Similarly, both combination strengths and vilanterol showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone furoate 200 µg QD vs vilanterol 25 µg QD vs placebo Albuterol was allowed for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward.	predicted and a score of ≥2 on the mMRC Dyspnea Scale		four hours post-dose on day one, use of rescue medications, nighttime awakenings and safety parameters	rapid and sustained effects on trough FEV_1 compared to placebo, and both combination strengths provided greater lung function effects than vilanterol at days 7, 28, 56, 84, 140 and 168, but only the 50 µg-25 µg strength provided greater lung function effects at day 2, day 112 and day 169, and only the 100 µg-25 µg strength provided greater lung function effects at day 14. Both fluticasone furoate-vilanterol arms showed greater improvements compared to placebo in diary card symptoms, rescue use or rescue-free 24-h periods, nighttime awakenings and morning peak flow. The incidence of on-treatment adverse events was higher with active therapy compared to placebo, but the reports of serious adverse events were similar across arms. Reported adverse events included nasopharyngitis, local steroidal effects (candidiasis, oropharyngeal pain) and upper respiratory tract infection.
Agusti et al.[178] (2013) Fluticasone furoate- vilanterol 100-25 µg QD vs fluticasone propionate-salmeterol 500-50 µg BID	DB, DD, MC, PG, RCT Patients aged ≥40 years of age with a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70% predicted and at	N=528 12 weeks	Primary: 24-hour effect on lung function after 12 weeks assessed by change from baseline in weighted mean FEV_1 Secondary: Time to 100 mL increase from baseline from zero to four hours on	Primary: On day 84, there was no significant difference in improvement from baseline between the fluticasone propionate-salmeterol (108±221 mL) and fluticasone furoate-vilanterol (130±222 mL) groups (P=0.282). Secondary: Because statistical significance was not achieved for the primary endpoint, statistical significance in the secondary endpoints could not be inferred. The mean change from baseline in trough FEV_1 on day 85 was 88 mL in the fluticasone propionate-salmeterol group compared to 111 mL in the fluticasone furoate-vilanterol (mean treatment different, 23 mL; 95% CI, -21 to 66).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	least one moderate COPD exacerbation within the last 2 years.		day one, change from baseline in trough FEV_1 on day 85 and change in health status	The median time to reach an increase of ≥100 mL in FEV_1 was 28 minutes in the fluticasone propionate-salmeterol group compared to 16 minutes in the fluticasone furoate-vilanterol. There was no significant difference in the proportion of rescue free 24-hour periods between the groups. The rate of adverse events was similar between the groups.
Mansori et al.[179] (2010) Salmeterol 50 µg, BID vs fluticasone propionate - salmeterol 250-50 µg, BID All patients received theophylline sustained release 200 mg BID and ipratropium 40 µg QID before starting the trial.	RCT Male COPD patients with FEV_1 <65%, an FEV_1/FVC <70%, >2 COPD exacerbations within the previous 2 years, with a smoking history >20 packs/year but were ex-smokers in the last 2 years	N=40 3 months	Primary: Pulmonary function tests, SABA use, and six minute walk distance Secondary: Not reported	Primary: Changes in six minute walk distance, FVC, FEV_1, PEF and the frequency of using a SABA with fluticasone propionate -salmeterol were significantly greater compared to those receiving salmeterol (P<0.01 to P<0.001). The number of exacerbations during 90 days in the last year before the trial was not statistically different between the two groups; however, the number of exacerbations during the 90 day treatment period in patients treated with fluticasone propionate was significantly lower compared to the other patients (P<0.001). Secondary: Not reported
Ohar et al.[180] (2014) Fluticasone propionate-salmeterol 250-50 µg BID (FP/SAL)	AC, DB, PG, RCT Patients with COPD aged ≥40 years with recent (≤14 days) history of exacerbation	N=639 26 weeks	Primary: Estimated annualized rate of exacerbations requiring hospitalization	Primary: There was no statistically significant treatment difference in rates of recurrent severe exacerbations (treatment ratio 0.92 [95% CI, 0.58 to 1.45]) and moderate/severe exacerbations (0.82 [0.64 to 1.06]) between FP/SAL and SAL in the intent-to-treat population. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs salmeterol 50µg BID (SAL)	requiring: hospitalization for ≤10 days, emergency room observation of duration ≥24 hours during which oral steroids ±antibiotics treatment was administered, or physician's office or emergency room visit of <24 hours duration with steroids ±antibiotics treatment plus 6-month history of exacerbation-related hospitalization		Secondary: Rate of exacerbations requiring treatment with oral steroids, antibiotics, and/or hospitalization	Pre-dose morning FEV_1 change from baseline was greater (0.10 L [0.04 to 0.16]) with FP/SAL than SAL. No treatment difference was seen for other endpoints including patient-reported health outcomes and biomarker levels for the full cohort.
Dal Negro et al.[181] (2003) Fluticasone propionate -salmeterol 250-50 µg BID vs salmeterol 50 µg BID vs placebo	DB, PC, PG, RCT Patients 53 to 78 years of age with moderate COPD who were naïve to ICS, FEV_1 ≤80% predicted value but >800 mL, FEV_1/FVC ratio ≤70% predicted value, FEV_1 change of ≤12% following β-agonist administration, receiving regular treatment with oral theophylline 200	N=18 52 weeks	Primary: FEV_1, morning PEF values, COPD symptom scores, number of exacerbations, and β-agonist use Secondary: Not reported	Primary: Increase in FEV_1 percent predicted noted in fluticasone propionate -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 propionate -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 propionate -salmeterol group compared to placebo (180.0 to 255.4 L/min compared to 18,606.0 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 propionate -salmeterol group (P=0.008), but not in salmeterol group. Statistically significant reduction in β-agonist use in fluticasone propionate -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
	mg BID, SABA as needed current or ex-smokers with history of at least 10 pack years			Statistically significant decrease in exacerbations in fluticasone propionate -salmeterol group (P<0.001), but not in salmeterol group.
Hanania et al.[182] (2003) Fluticasone propionate -salmeterol 250-50 µg BID vs fluticasone propionate 250 µg BID vs salmeterol 50 µg BID vs placebo	DB, MC, PC, MC, RCT Patients 40 to 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 two hour post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, chronic respiratory disease questionnaire, chronic bronchitis symptom questionnaire, exacerbations, and supplemental albuterol use	Primary: Statistically significant increase in pre-dose FEV_1 in fluticasone propionate -salmeterol group compared to the salmeterol group (91 mL; P=0.012) and placebo (1 mL; P<0.001). No significant difference between fluticasone propionate -salmeterol group and fluticasone propionate group. Statistically significant increase in two hour post-dose FEV_1 in fluticasone propionate -salmeterol group compared to the salmeterol group (281 vs 200 mL; P<0.001), placebo (281 vs 58 mL; P<0.001), and fluticasone propionate group (281 vs 147 mL; P<0.001). Secondary: Statistically significant increase in morning PEF values in fluticasone propionate -salmeterol group compared to the salmeterol group, placebo group, and fluticasone propionate group (P≤0.034), though improvements were also seen from baseline in salmeterol and fluticasone propionate monotherapy groups (P<0.001). Statistically significant improvements in dyspnea index observed in fluticasone propionate -salmeterol group (P=0.023) compared to placebo, in addition to improvements in fluticasone propionate (P=0.057) and salmeterol (P=0.043) monotherapy groups compared to placebo (NOTE: difference in fluticasone propionate monotherapy group not significant). Statistically significant reduction in supplemental albuterol use in fluticasone propionate -salmeterol group compared to fluticasone propionate 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 propionate -salmeterol group compared to salmeterol monotherapy group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Statistically significant increase in chronic bronchitis symptom questionnaire scores in fluticasone propionate -salmeterol group and fluticasone propionate monotherapy group compared to placebo ($P \leq 0.017$). There was significant difference between treatment groups in terms of exacerbations or time to first exacerbation.
Calverley et al.[183] (2003) Fluticasone propionate - salmeterol 500-50 µg BID vs fluticasone propionate 500 µg BID vs salmeterol 50 µg BID vs placebo	DB, PC, PG, RCT Patients with COPD, pre-dose FEV_1 25 to 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 six 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 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 propionate, and P<0.001 for fluticasone propionate - salmeterol) and statistically significant improvement in fluticasone propionate -salmeterol group compared to fluticasone propionate 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 propionate, and P<0.001 for fluticasone propionate -salmeterol) and there was a statistically significant improvement in pre-dose FVC in fluticasone propionate -salmeterol group when compared to fluticasone propionate and salmeterol monotherapy groups (P=0.006 for salmeterol and P<0.001 for fluticasone propionate). Postbronchodilator FEV_1 improved significantly in fluticasone propionate and fluticasone propionate -salmeterol group compared to placebo (P=0.013 for fluticasone propionate and P<0.001 for fluticasone propionate -salmeterol) and there was a statistically significant difference between fluticasone propionate -salmeterol group compared to salmeterol and fluticasone propionate 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 propionate -salmeterol group compared to fluticasone propionate and salmeterol monotherapy (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 propionate -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 propionate). Statistically significant reduction in nighttime awakenings in fluticasone propionate -salmeterol group compared to placebo and salmeterol groups (P=0.006 and P=0.011 respectively) but there was no significant difference between fluticasone propionate -salmeterol and fluticasone propionate monotherapy groups (P=0.591). Fluticasone propionate -salmeterol combination therapy showed significant improvement in St. George's Respiratory Questionnaire scores compared to placebo and fluticasone propionate groups (P=0.0003 and P=0.021 respectively), but no difference between fluticasone propionate -salmeterol and salmeterol monotherapy groups (P=0.071).
Vestbo et al.[184] (2005) Fluticasone propionate -salmeterol 500-50 µg BID vs fluticasone propionate 500µg BID vs salmeterol 50 µg	DB, PC, PG, RCT Patients with COPD, pre-dose FEV_1 25 to 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	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 Secondary: Not reported	Primary: Significant increase in PEF in fluticasone propionate -salmeterol and salmeterol monotherapy groups over placebo after one day (P<0.001). This was also observed in the fluticasone propionate group on day two (P<0.001). Increase in PEF values in the fluticasone propionate -salmeterol group was significantly better than the other treatment arms after day one (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 propionate -salmeterol groups and P=0.016 for fluticasone propionate monotherapy group). No mention of comparison between groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs placebo	exacerbation per year for previous 3 years, and one of them requiring oral corticosteroids, antibiotics, or both			
Calverley et al.[185] (2007) Fluticasone propionate - salmeterol 500-50 µg BID vs salmeterol 50 µg BID vs fluticasone propionate 500 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 40 to 80 years of age with COPD, current or former smokers, ≥10 pack-year history, pre bronchodilator FEV_1 <60% of predicted value, an increase of FEV_1 <10% of predicted value with use of 400 µg of albuterol, and FEV1/FVC ratio of ≤0.70	N=6112 3 years	Primary: Death from any cause Secondary: 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	Primary: The proportions of deaths from any cause at three 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 propionate group. The absolute risk reduction for death in the combination-therapy group as compared with 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 propionate 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 propionate (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 NNT of four to prevent one exacerbation in one year. Annual rates of exacerbations in the salmeterol group and the fluticasone propionate group were significantly lower than in the placebo group. Overall, 26% of the patients were hospitalized at least once during the three-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 NNT of 32 to prevent one hospitalization in one year. Total scores on the St. George's Respiratory Questionnaire initially

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 three 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 FEV_1 in the combination-therapy group was 1.236 liters with an average increase of 0.029 liter; in the placebo group, the mean baseline FEV_1 was 1.257 liters and a decrease of 0.062 liter. Averaged over three 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 FEV_1 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 three-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 propionate group ($P<0.001$ for the comparison between both the combination-therapy and fluticasone propionate 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.
Rennard et al.[186] (2009) Budesonide-formoterol 160-4.5 µg, 2 inhalations	MC, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a mean	N=1,964 12 months	Primary: Mean improvement in baseline pre-dose FEV_1 and one-hour post-dose FEV_1	Primary: The budesonide-formoterol 160-4.5 µg treatment group, demonstrated significantly greater improvements in pre-dose and one hour post-dose FEV_1 when compared to the formoterol monotherapy group ($P\leq0.023$). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID via MDI vs budesonide-formoterol 80-4.5 µg, 2 inhalations BID via MDI vs formoterol 4.5 µg, 2 inhalations BID via DPI vs placebo	percent predicted FEV_1 at baseline ranging from 33.7 to 35.5%		Secondary: Improvement in morning and evening PEF, exacerbation rates, BCS scores, sleep scores, awakening free nights, use of rescue medications, and safety	Both budesonide-formoterol dose treatment groups had significantly greater improvements in morning and evening PEF when compared to both the formoterol and placebo treatment groups (P≤0.017). Exacerbation rates were significantly reduced by 25 to 30% in both the budesonide-formoterol dose treatment groups when compared to the formoterol treatment group, and by 40% when compared to placebo (P≤0.004). Both budesonide-formoterol treatment groups had significantly greater improvements in the sleep score and rescue medication when compared to the formoterol treatment group (P<0.038). Only the budesonide-formoterol 160-4.5 µg treatment group had a significantly greater improvement in the BCS scores compared to the formoterol treatment group (P value not reported), and only the budesonide-formoterol 80/4.5 µg treatment group had a significant improvement in the awakening-free nights compared to formoterol (P<0.038). Both budesonide-formoterol were well tolerated compared to both formoterol and placebo. The incidence of pneumonia related adverse events were similar for all active treatment arms, when compared to placebo. The most common adverse events seen in the budesonide-formoterol treatment groups were oral candidiasis, dysphonia and muscle spasms.
Tashkin et al.[187] (2008) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI vs budesonide-	MC, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a mean percent predicted FEV_1 at baseline ranging from 33.5 to 34.7%	N=1,704 6 months	Primary: Mean improvement in baseline pre-dose FEV_1 and one-hour post-dose FEV_1 Secondary: Improvement in morning and evening PEF, BCS	Primary: The budesonide-formoterol 160-4.5 µg treatment group demonstrated a significantly greater improvement from baseline in pre-dose FEV_1 (0.08 L, 10.7%) when compared to the formoterol monotherapy group (0.04 L, 6.9%; P=0.026) and placebo group (0.01, 2.2%; P value not reported). Patients receiving the budesonide-formoterol 80-4.5 µg combination therapy did not report a significantly greater improvement in pre-dose FEV_1 when compared to the formoterol monotherapy group. Both combination budesonide/formoterol treatment arms demonstrated a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
formoterol 80-4.5 µg 2 inhalations BID via MDI vs budesonide 160 µg, 2 inhalations BID via MDI and formoterol 4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg 2 inhalations BID via MDI vs formoterol 4.5 µg 2 inhalations BID via DPI vs placebo			scores, sleep scores, awakening free nights, use of rescue medications when compared to placebo, and safety	significantly greater improvement in pre-dose FEV_1 and one hour post-dose FEV_1 when compared to the budesonide monotherapy treatment arm (P<0.001). The budesonide-formoterol 160-4.5 µg treatment group demonstrated a significantly greater improvement from baseline in one hour post-dose FEV_1 (0.20 L, 22.6%; P value not reported) when compared to the budesonide monotherapy group (0.03 L, 4.9%; P<0.001) and placebo (0.03 L, 4.1%; P value not reported). Secondary: Improvements in both morning and evening PEF values were significantly greater in both budesonide-formoterol combination treatment arms, when compared to the budesonide monotherapy, formoterol monotherapy and placebo groups (P≤0.016). Both budesonide-formoterol treatment groups significantly improved BCS scores, sleep scores, awakening free nights and use of rescue medications when compared to placebo (P<0.028). Both budesonide-formoterol treatment doses were well tolerated for the six months of treatment. The most common adverse events reported were oral candidiasis, dysphonia and headache. The incidences of pneumonia-related adverse events were similar across for all active treatment groups compared to placebo.
Lindberg et al.[188] (2007) Budesonide-formoterol 160-4.5 µg vs	DB, DD, MC, RCT, XO Patients ≥40 years of age with COPD and FEV_1 30 to 70% predicted	N=90 17 days	Primary: Change in FEV_1 five minutes after drug inhalation Secondary: Change in FEV_1 at three minutes and 180 minutes;	Primary: Budesonide-formoterol improved FEV_1 at five minutes to a greater extent than either fluticasone propionate -salmeterol (ratio, 105%; 95% CI, 103 to 108; P=0.0001) or placebo (ratio, 116%; 95% CI, 113 to 119; P<0.0001) and to a similar extent as salbutamol (ratio, 99%; 95% CI, 97 to 101; P=0.35). Secondary: Findings similar to above were observed for FEV_1 at three minutes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate -salmeterol 250-25 µg vs salbutamol 100 µg vs placebo			maximal change in FEV_1; change in inspiratory capacity at 15 minutes; maximal change in inspiratory capacity and average effect on inspiratory capacity during observation interval; yes or no answer by patient to perception of onset of effect question; adverse events	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 propionate -salmeterol than with salbutamol, as demonstrated by FEV_1 at 180 minutes, ratio 107% (95% CI, 104 to 109) for budesonide-formoterol and 106% (95% CI, 103 to 108) for fluticasone propionate -salmeterol vs salbutamol; both P<0.0001). Maximal increases in FEV_1 were 0.35, 0.32, 0.34 and 0.14 L for budesonide-formoterol, fluticasone propionate -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, 0.53, 0.54 and 0.28 L for budesonide-formoterol, fluticasone propionate -salmeterol, salbutamol and placebo respectively, representing a 4% greater increase for budesonide-formoterol vs fluticasone propionate -salmeterol (ratio, 104; 95% CI, 101 to 107; P=0.0184) and a 13% greater increase vs placebo (ratio, 113%; 95% CI, 110 to 117; P<0.0001). There were no differences between the active treatments in average inspiratory capacity over 185 minutes. The effect of budesonide-formoterol and fluticasone propionate -salmeterol on inspiratory capacity was of longer duration than that of salbutamol. Perception of onset of effect: 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 propionate -salmeterol, salbutamol and placebo, respectively. Time to perception of onset of effect was 10 minutes faster (95% CI, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 perception of onset of effect was slightly slower with fluticasone propionate -salmeterol, being observed five minutes faster (95% CI, -75.0 to 0.0) than placebo All active treatments resulted in a significantly faster time to perception of onset of effect than placebo (all P<0.001). Median time to perception of onset of effect was five 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.
Larsson et al.[189] (2013) Budesonide-formoterol vs fluticasone propionate-salmeterol -94.	OS, RETRO Patients with COPD	N=9,893 Duration not reported	Primary: COPD exacerbations, emergency visits, utilization of steroids or antibiotics and utilization of other medications used in managing COPD Secondary: Not reported	Primary: The COPD exacerbation rates were 0.80 and 1.09 per patient-year in the budesonide-formoterol and fluticasone propionate-salmeterol treatment groups, respectively, representing a 26.6% reduction in exacerbation rate in the budesonide-formoterol group (rate ratio, 0.74; 95% CI, 0.69 to 0.79; P<0.0001). This corresponded to a NNT of 3.4 with budesonide-formoterol compared to fluticasone propionate-salmeterol to prevent one exacerbation per patient-year. In budesonide-formoterol-treated patients, the yearly rate of COPD-related hospitalizations was 0.15 compared to 0.21 in patients treated with fluticasone propionate-salmeterol (P<0.0001), a difference of 29.1% (rate ratio, 0.71; 95% CI, 0.65 to 0.78; P<0.0001). The NNT to prevent one COPD-related hospitalization per patient-year was 16 with budesonide-formoterol compared to fluticasone propionate-salmeterol. There were 27% fewer days in the hospital due to exacerbations of COPD with budesonide-formoterol compared to fluticasone propionate-salmeterol (0.63 vs 0.95 days/year; rate ratio, 0.66; 95% CI, 0.62 to 0.71;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.0001). There were 21% fewer emergency visits in the budesonide-formoterol treatment group compared to the fluticasone propionate-salmeterol group (0.027 vs 0.034 events/patient-year; rate ratio, 0.79; 95% CI, 0.71 to 0.89; P=0.0003). Patients treated with budesonide-formoterol experienced 26% fewer courses of oral steroids (0.63 vs. 0.85 events per year; rate ratio, 0.74; 95% CI, 0.68 to 0.81; P<0.0001) and 29% fewer antibiotic courses (0.38 vs. 0.54 events per year; rate ratio, 0.70; 95% CI, 0.66 to 0.75; P<0.0001) than patients treated with fluticasone propionate-salmeterol. The number of patients who required tiotropium in addition to the ICS/LABA combination was 16% lower for the budesonide-formoterol group compared to fluticasone propionate-salmeterol group (rate ratio, 0.84; 95% CI, 0.79 to 0.89; P<0.0001). Secondary: Not reported
Welte et al.[190] (2009) Budesonide-formoterol 320-9 µg BID and tiotropium 18 µg QD vs tiotropium 18 µg QD	DB, MC, PG, RCT 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: PEF, 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). Secondary: 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 one, 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 emergency department visits were decreased by 65% in the budesonide-formoterol group compared to the tiotropium group (RR, 0.35; 95% CI, 0.16 to 0.78; P=0.011). There were no differences in tolerability between the regimens.
Wedzicha et al.[191] (2008) Fluticasone propionate -salmeterol 500-50 µg BID vs tiotropium 18 µg 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 propionate -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 propionate -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 propionate -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 propionate -salmeterol treated patients and 19 (3%) tiotropium treated patients.
Make et al.[192] (2005) Fluticasone propionate -salmeterol 250-50 µg BID vs ipratropium-albuterol 36-206 µg QID	DB, MC, PG, RCT Patients 40 to 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	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 propionate -salmeterol group compared to ipratropium-albuterol group (P<0.001). Secondary: Statistically significant improvement in mean FEV_1 AUC in fluticasone propionate -salmeterol group at week eight compared to ipratropium-albuterol group (P=0.002). Statistically significant improvement in morning PEF values in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group at week one and throughout study (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	short acting bronchodilator for COPD for ≥30 days			Mean post-administration FEV_1 values significantly higher in the ipratropium-albuterol group at 0.5, one, and two hours compared to fluticasone propionate -salmeterol group (P<0.001), but higher in the fluticasone propionate -salmeterol group at six hours (P=0.003). Dyspnea scores significantly higher in fluticasone propionate -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 propionate -salmeterol group compared to ipratropium-albuterol group (change from baseline, -46.7 vs -28.1; P=0.024). Statistically significant increase in albuterol-free nights in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group (change from baseline is 19 vs 7.3%; P<0.001), and a similar increase in albuterol-free days (change from baseline is 34.7 vs 26.7%; P=0.021).
Rabe et al.[193] (2008) Fluticasone propionate 500 µg and salmeterol 50 µg BID vs tiotropium 18 µg QD and formoterol 12µg 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 Secondary: Not reported	Primary: Lung function profiles in the group receiving tiotropium plus formoterol were superior to those in the group receiving salmeterol plus fluticasone propionate (mean difference in FEV_1 $AUC_{0–12}$, 78 mL; P=0.0006; mean difference in FVC $AUC_{0–12}$, 173 mL; P<0.0001). Peak responses were in favor of tiotropium plus formoterol (difference in peak FEV_1, 103 mL; P<0.0001; difference in peak FVC, 214 mL; P<0.0001), as were FEV_1 and FVC at each individual time point after dose (P<0.05). Both treatments were well tolerated. Secondary: Not reported
Aaron et al.[194] (2007) Fluticasone propionate -	DB, MC, PC, RCT Patients ≥ 35 years of age with ≥ 1 COPD exacerbation	N=449 1 year	Primary: Proportion of patients who experienced an exacerbation of	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). The proportion of patients in the tiotropium group who

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 250-25 µg, 2 inhalations BID and tiotropium 18 µg QD vs tiotropium 18 µg QD and salmeterol 25 µg, 2 inhalations BID vs tiotropium 18 µg QD	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 ≤65% of the predicted value		COPD requiring treatment with systemic steroids or antibiotics Secondary: Not reported	experienced an exacerbation (62.8%) did not differ from that in the tiotropium+fluticasone propionate -salmeterol group (60.0%; difference, 2.8 percentage points; CI, -8.2 to 13.8). Tiotropium+fluticasone propionate -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 OL inhaled steroids or LABA. Secondary: Not reported
Lee et al.[195] (2008) Exposure to ICSs, ipratropium, LABAs, theophylline and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICSs and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICSs and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICSs (OR, 0.88; 95% CI, 0.79 to 1.00), however, this also did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICSs, 1.08 for ipratropium and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICSs with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.

Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QID=four times daily, QPM=every evening
Study abbreviations: AC=active control, ANOVA=analysis of variance, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, XO=cross over
Miscellaneous abbreviations: ACT=asthma control test, AMP PC_{20}=provocation dose of AMP to decrease forced vital capacity by 20%, AQLQ=asthma quality of life questionnaire, CFC=chlorofluorocarbon, DPI=dry-powder inhaler, eNO=exhaled nitric oxide, $FEF_{25\ to\ 75\%}$=forced expiratory flow at 25 to 75% of FVC, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL=health-related quality of life, ICS=inhaled corticosteroid, LABA=long-acting β_2-agonist, MDI=metered-dose inhaler, NO=nitrous oxide, NRQLQ=Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQS=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PPB=parts per billion, SABA=short acting β_2-agonist, SF-36=Short-Form-36, WMD=weighted mean difference, wmFEV= weighted mean FEV_1

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.[196] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[196] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[196] 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.[197] Adherence to inhaled therapy is often poor, with rates of 40 to 72% being reported.[198] Patient preference should be considered when selecting an inhalation delivery device.[197] 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.[197]

Dorais et al. analyzed pharmacy claims to assess adherence with leukotriene modifiers and inhaled corticosteroids.[199] 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 (relative risk, 0.46; 95% confidence interval, 0.85 to 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 propionate -salmeterol, fluticasone propionate plus salmeterol in separate inhalers, fluticasone propionate plus montelukast, fluticasone propionate monotherapy, and montelukast monotherapy.[200] Patients in the fluticasone propionate -salmeterol group had significantly more refills compared to patients receiving other fluticasone propionate 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.[201] In addition, the mean number of short-acting bronchodilator prescriptions was significantly lower in patients receiving fluticasone propionate -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.[202] 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.[203] 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.[204] 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 propionate.[35] There was a significant improvement in emergency room visits with fluticasone propionate compared to flunisolide (P=0.004). Mean hospital admissions for asthma were also lower in the fluticasone propionate 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.[205]

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 14. Relative Cost of the Respiratory Agents-Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Beclomethasone	aerosol inhaler	QVAR®	$$$$$	N/A
Budesonide	dry powder inhaler, inhalation suspension	Pulmicort ®*	$$$$$	$$$$$
Ciclesonide	aerosol inhaler	Alvesco®	$$$$$	N/A
Flunisolide	aerosol inhaler	Aerospan®	$$$$	N/A
Fluticasone furoate	dry powder inhaler	Arnuity Ellipta®	$$$$	N/A
Fluticasone	aerosol inhaler, dry powder inhaler	Flovent Diskus®, Flovent HFA®	$$$$$	N/A
Mometasone	dry powder inhaler	Asmanex®	$$$$$	N/A
Combination Products				
Budesonide and formoterol	aerosol inhaler	Symbicort®	$$$$$	N/A
Fluticasone and salmeterol	aerosol inhaler, dry powder inhaler	Advair Diskus®, Advair HFA®	$$$$$	N/A
Fluticasone and vilanterol	dry powder inhaler	Breo Ellipta®	$$$$$	N/A
Mometasone and formoterol	aerosol inhaler	Dulera®	$$$$$	N/A

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

X. Conclusions

The respiratory agents-corticosteroids (inhaled corticosteroids) are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-17] They are available as single entity products, as well as in combination with a long-acting β_2- agonist (formoterol, salmeterol, or vilanterol). 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.[18, 25-27] 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.[18] However, due to variability in individual responses and poor adherence, some patients may need higher doses to achieve adequate control of their asthma symptoms.[25] 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 five to 12 years of age and adults.[18,25-27] However, an increased risk of asthma-related death has been reported with the use of a LABA.[6,12-14,17] 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 propionate -salmeterol, fluticasone furoate-vilanterol, 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.[6,12-14,17] 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.[6,12-14,17]The available data also suggest that the LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.[206] 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.[206]

Numerous trials have been conducted with the inhaled corticosteroids. 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. Several studies have demonstrated similar outcomes with the fixed-dose combination inhalers compared to the coadministration of their individual components as separate inhalers. Studies directly comparing the fixed-dose combination products (budesonide-formoterol vs fluticasone propionate -salmeterol) have shown conflicting results with regards to asthma outcomes.

Most studies have indicated that the existing medications to treat COPD do not modify the long-term decline in lung function.[20] 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.[20-24] 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 a forced expiratory volume in one second (FEV_1) <50% predicted.[20-14] 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. 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 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.[196] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[171] 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.[196]

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 generic 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 generic 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 LABA to control their respiratory symptoms.

XI. Recommendations

Alabama Medicaid should work with manufacturers on cost proposals so that at least one single entity brand respiratory agents-corticosteroids is selected as a preferred agent.

No brand fixed-dose combination respiratory agents-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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Respiratory Smooth Muscle Relaxants
AHFS Class 861600
November 4, 2015

I. Overview

The respiratory smooth muscle relaxants (xanthines) are approved for the treatment of asthma, chronic bronchitis, and emphysema. 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.[1-9]

Theophylline is the reference xanthine derivative from which aminophylline and dyphylline were developed. Aminophylline is a 2:1 complex of theophylline and ethylenediamine.[1,2] 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 to 20 µg/mL. Of the xanthines, dyphylline has the shortest serum half-life. The xanthines generally share similar side effect profiles, precautions, and contraindications.[1,2]

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 except for dyphylline. This class was last reviewed in August 2013.

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	N/A	aminophylline
Dyphylline	tablet	Lufyllin®	none
Theophylline	elixir*, extended-release capsule, extended-release tablet*, injection*, solution*	Elixophyllin®*, Theo-24®	theophylline

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

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.

Table 2. Treatment Guidelines Using the Respiratory Smooth Muscle Relaxants

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2015)**[10]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking and occupational exposure to dusts/chemicals. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator FEV_1/FVC <0.70 and FEV_1 <80% predicted confirms the presence of airflow limitation that is not fully reversible. • A detailed medical history should be obtained for all patients suspected of developing COPD.

Clinical Guidelines	Recommendations

	• Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
	• Bronchodilator reversibility testing should be performed to rule out the possibility of asthma.
	• Chest radiograph may be useful to rule out other diagnoses.
	• Arterial blood gas measurements should be performed in advanced COPD.
	• Screening for α_1-antitrypsin deficiency should be performed in patients who are from areas with a particularly high prevalence of the deficiency. Typical patients develop COPD at 45 years of age or younger and have lower lobe emphysema.
	• Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis.
	
	<u>Therapeutic options</u>
	• In patients who smoke, smoking cessation is the intervention with the greatest capacity to influence COPD. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
	• The management of COPD should be individualized to address symptoms and improve the patient's quality of life.
	• None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications.
	• COPD patients should receive an annual influenza vaccine.
	• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value.
	• Patients who get short of breath while walking at their own pace on level ground should be offered rehabilitation.
	
	<u>Pharmacologic therapy for stable COPD</u>
	• Bronchodilators
	  o Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations.
	  o Principle bronchodilators include β_2-agonists, anticholinergics, and theophylline used as monotherapy or in combination.
	  o The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.
	  o For single-dose, as needed use, there is no advantage in using levalbuterol over conventional bronchodilators.
	  o Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable.
	• Corticosteroids
	  o Inhaled corticosteroids (ICSs) should be used in patients with an FEV_1 <60% of the predicted value.
	  o Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio.
	• Combination inhaled corticosteroid/ bronchodilator
	  o An inhaled corticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD.
	• Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended.

Clinical Guidelines	Recommendations
	Management of stable COPD • Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quite. • The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients and individualized assessment of symptoms and risk of exacerbation should also be considered. • Pharmacologic therapy is used to reduce symptoms, reduce frequency of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function. • For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators. • Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations. • Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD. • The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 <50% predicted, chronic bronchitis, and frequent exacerbations. • Influenza vaccines can reduce the risk of serious illness and death in COPD patients. • Currently, the use of antibiotics is not indicated in COPD, other than for treating infectious exacerbations of COPD and other bacterial infections. Management of exacerbations • The most common causes of an exacerbation are viral upper respiratory tract infections and infection of the tracheobronchial tree. • Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation. • Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function, and reduce the risk of early relapse, treatment failure, and length of hospital stay.

National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[11]
 	
Reviewed July 2014
	Diagnosis
	• Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze.
	• The primary risk factor is smoking.
	• Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%.
	
	Treatment
	• Smoking cessation should be encouraged for all patients with COPD.
	• Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.
	• Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.
	• Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist.
	  o FEV_1 ≥50% predicted: LABA or long-acting anticholinergic antagonist.
	  o FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a

Clinical Guidelines	Recommendations
	combination inhaler or a long-acting anticholinergic antagonist. • In patients with stable COPD and $FEV_1 \geq 50\%$ who remain breathless or have exacerbations despite maintenance therapy with a long acting bet agonist (LABA), consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined. • Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs. • In most cases, inhaled bronchodilator therapy is preferred. • Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of exacerbations • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic**	Diagnosis • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and $FEV_1 < 60\%$ predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an $FEV_1 < 60\%$ predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief.

Clinical Guidelines	Recommendations
Society, and European Respiratory Society (2011)[12]	• Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
International Primary Care Respiratory Group: **Management of Chronic Obstructive Pulmonary Disease (2006)**[13]	• 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/European Respiratory Society: **Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease (2004)**[14]	<u>Diagnosis</u>
	• 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:
	  o Mild COPD: FEV_1/FVC ≤0.70 and FEV_1 ≥80% predicted.
	  o Moderate COPD: FEV_1/FVC ≤0.70; FEV_1 ≥50% and <80% predicted.
	  o Severe COPD: FEV_1/FVC ≤0.70; FEV_1 ≥30% and <50% predicted.
	  o Very Severe COPD: FEV_1/FVC ≤0.70 and FEV_1 <30% predicted.
	
	<u>Treatment</u>
	• 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:
	  o Intermittent symptoms: Short-acting bronchodilator as needed for symptom control.
	  o 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.

Clinical Guidelines	Recommendations
	▪ 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 three months than either agent alone. • Anticholinergics given four times a day can improve health status over a three-month period compared with placebo. • LABA 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 LABA and ipratropium leads to fewer exacerbations than either drug alone. • No good comparative data between different LABA are presently available although it is likely that their effects will be similar. • Combining LABA 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 LABA in its effect and in one clinical trial appeared to be superior to salmeterol in some measures over six 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 three-year 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 chromones (mast-cell stabilizers) in COPD.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2015)**[15]	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. • Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. • Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. • Control-based management means that treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects. • For population-level decisions about asthma management, the 'preferred option' at each step represents the best treatment for most patients, based on group mean data for efficacy, effectiveness, and safety from randomized controlled trials, meta-analyses, and observational studies, and net cost.

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	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	Treatment overview
	• At present, step 1 treatment is with as-needed short-acting beta$_2$ agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a lack of studies of inhaled corticosteroids (ICS) in such populations.
	• Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	• For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities.
	  o For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta$_2$ agonist (LABA).
	  o For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller plus as-needed SABA.
	  o For children six to 11 years, increasing the ICS dose is preferred over combination ICS/LABA.
	• Consider step down once good asthma control has been achieved and maintained for about three months to find the patient's lowest treatment that controls both symptoms and exacerbations.
	  o Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit.
	  o Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
	• For all patients with asthma:
	  o Provide inhaler skills training.
	  o Encourage adherence with controller medication, even when symptoms are infrequent.
	  o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations and need for healthcare utilization.
	• For patients with one or more risk factors for exacerbations:
	  o Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients.
	  o Identify and address modifiable risk factors (e.g., smoking, low lung function).
	  o Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction.
	
	Categories of asthma medications
	• *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
	• *Reliever (rescue medications)*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
	• *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized

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treatment with high dose controller medications and treatment of modifiable risk factors.

Stepwise approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years old

- Initial controller treatment: For best outcomes, regular daily controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.
- Once treatment has been commenced (see table below), ongoing treatment decisions are based on a cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - Incorrect inhaler technique.
  - Poor adherence.
  - Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as beta-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - Incorrect diagnosis.

Stepwise approach to control symptoms and minimize future risk					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller choice		Low dose ICS	Low dose ICS/LABA*	Med/high ICS/LABA	Refer for add-on treatment (e.g., anti-IgE)
Other controller options	Consider low dose ICS	Leukotriene receptor antagonist (LTRA) or low dose theophylline*	Med/high dose ICS or low dose ICS+LTRA (or + theoph*)	High dose ICS + LTRA (or + theoph*)	Add low dose oral corticoste-roids
Reliever	As-needed SABA		As-needed SABA or low dose ICS/formoterol**		

*For children six to 11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium-dose ICS.
**Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclomethasone/formoterol maintenance and reliever therapy.

Management of worsening asthma and exacerbations

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

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

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><th colspan="5">Stepwise approach to long-term management of asthma in children 5 years and younger</th></tr>
<tr><th></th><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th></tr>
<tr><td>Preferred controller choice</td><td></td><td>Daily low dose ICS</td><td>Double ‘low dose’ ICS</td><td>Continue controller & refer for to specialist</td></tr>
<tr><td>Other controller options</td><td></td><td>Leukotriene receptor antagonist (LTRA)
Intermittent ICS</td><td>Low dose ICS + LTRA</td><td>Add LTRA
↑ ICS frequency
Add intermitt ICS</td></tr>
<tr><td>Reliever</td><td colspan="4">As-needed SABA (all children)</td></tr>
</table>
<table>
<tr><td rowspan="2">Consider this step for children with:</td><td rowspan="2">Infrequent viral wheezing and no or few interval symptoms</td><td>Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year</td><td>Asthma diagnosis, and not controlled on low dose ICS</td><td>Not controlled on double ICS</td></tr>
<tr><td>Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6 to 8 weeks. Give diagnostic trial for 3 months</td><td colspan="2">First check diagnosis, inhaler skills, adherence, exposures</td></tr>
</table>
<u>Management of worsening asthma and exacerbations in children five and younger</u>

Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.

Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
Parents/carers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
There is only weak evidence to support patient-initiated oral corticosteroids.

In children presenting to primary care or an acute care facility with an asthma exacerbation:

Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94-98%).
Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink or has subcostal retractions or cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
Give oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years.

Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one week of an exacerbation to plan ongoing asthma management.

</td></tr>
<tr><td>The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: Guidelines for the Diagnosis and</td><td><u>Diagnosis</u>

To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded.
The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses.
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Clinical Guidelines	Recommendations
Management of Asthma (2007)[16]	• A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids. <u>Long-term control medications</u> • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma. <u>Quick-relief medications</u> • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.

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	• There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol. • Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations. • Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations. • The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma. Assessment, treatment and monitoring • A stepwise approach to managing asthma is recommended to gain and maintain control of asthma. • Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control. • The stepwise approach for managing asthma is outlined below:

Inter-mittent Asthma	Persistent Asthma: Daily Medication				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Preferred SABA as needed	Preferred Low-dose ICS Alternative Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline	Preferred Low-dose ICS+LABA or medium-dose ICS Alternative Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred Medium-dose ICS+LABA Alternative Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton	Preferred High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies	Preferred High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies

Management of exacerbations
• Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

Special populations
• For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs.
• The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm.
• Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
• Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.
• ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.

British Thoracic Society/ Scottish Intercollegiate	Diagnosis in children • The diagnosis is based on recognizing a characteristic pattern of episodic respiratory symptoms and signs in the absence of an alternative explanation for

Clinical Guidelines	Recommendations

Guidelines Network: **British Guideline on the Management of Asthma (2014)**[17]	them.
	• Presence of the following factors increases the probability that a child with respiratory symptoms will have asthma: age at presentation, sex, severity and frequency of previous wheezing episodes, coexistence of atopic disease, family history of atopy, and abnormal lung function.
	• Focus the initial assessment in children suspected of having asthma on presence of key features in the history and examination and careful consideration of alternative diagnoses.
	
	<u>Diagnosis in adults</u>
	• The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them.
	• Confirmation of airflow obstruction is vital for diagnosis of asthma. Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction.
	
	<u>Pharmacological management</u>
	• The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication.
	• Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.
	• Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors.
	• Step 1: Mild intermittent asthma:
	  o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma.
	• Step 2: Introduction of regular preventer therapy:
	  o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma.
	  o ICS should be considered for patients with any of the following asthma-related features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 who have had an asthma attack requiring oral corticosteroids in the last two years.
	  o ICS should initially be administered twice daily, except ciclesonide which is administered once daily.
	  o Once a day ICS at the same total daily dose can be considered if good control is established.
	  o In patients >12 years of age, health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers.
	• Step 3: Initial add-on therapy:
	  o In adults and children five to 12 years of age, the first choice for add-on therapy to ICS is an inhaled LABA, which should be considered before going above a dose of 400 µg beclomethasone or equivalent per day and certainly before going >800 µg beclomethasone or equivalent.
	  o In adults and children five to 12 years of age, if asthma control remains suboptimal after the addition of an inhaled LABA then the dose of ICS should be increased to 800 µg/day in adults or 400 µg/day in children five to 12 years of age if not already receiving these doses.
	  o In children <5 years of age, the first choice for add-on therapy to ICS is leukotriene receptor antagonists.
	  o LABAs should only be started in patients who are already on ICS, and

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the ICS should be continued.
  - Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence.
- Step 4: Poor control on moderate dose of ICS plus add-on therapy (addition of fourth drug):
  - If control remains inadequate on ICS 800 µg beclomethasone daily in adults and 400 µg beclomethasone daily in children plus LABA, consider the following interventions:
    - Increasing ICS to 2,000 (adults) or 800 (children five to 12 years of age) µg BDP daily.
    - Leukotriene receptor antagonists.
    - Theophyllines.
    - Slow-release β_2-agonist tablets, though caution needs to be used in patients already on LABAs.
- Step 5: Continuous or frequent use of oral steroids:
  - In adults, the recommended method of eliminating or reducing the dose of steroid tablets is ICS, at doses of up to 2,000 µg/day, if required.
  - In children 5 to 12 years of age, consider very carefully before going above 800 µg/day of ICS.
  - For all patients, there is a role for a trial of treatment with LABAs, leukotriene receptor antagonists, and theophylline for about six weeks. They should be stopped if no improvement in steroid dose, symptoms, or lung function is detected.
  - The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children.
- A summary of the stepwise management of asthma is outlined below:

Children <5 Years Old	Children 5 to 12 Years Old	Adults and Children >12 Years Old
Step 1: Mild Intermittent Asthma		
• Inhaled SABA as required	• Inhaled SABA as required	• Inhaled SABA as required
Step 2: Regular Preventer Therapy		
• Add ICS 200 to 400 µg/day*† or leukotriene antagonist if ICS cannot be used • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 400 µg/day* (other preventer drug if ICS cannot be used) • Start at dose of ICS appropriate to severity of disease	• Add ICS 200 to 800 µg/day* • Start at dose of ICS appropriate to severity of disease
Step 3: Initial Add-on Therapy		
• In those taking ICS 200 to 400 µg/day, consider addition of leukotriene receptor antagonist • In those taking a leukotriene receptor antagonist alone, reconsider addition of an ICS 200 to 400 µg/day • In children under 2 years, consider proceeding to step 4	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 400 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 400 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline	• Add inhaled LABA • If good response to LABA: continue LABA • If benefit from LABA, but control still inadequate: continue LABA and increase ICS dose to 800 µg/day* (if not already on this dose) • If no response to LABA: stop LABA and increase ICS to 800 µg/ day.* If control still inadequate, consider leukotriene receptor antagonist or sustained-release theophylline
Step 4: Persistent Poor Control		
• Refer to a respiratory pediatrician	• Increase ICS up to 800 µg/day*	Consider trials of: • Increase ICS up to 2,000 µg/day* • Add a fourth drug (leukotriene receptor

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	antagonist, sustained-release 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 ICS at 800 µg/day* • Refer to respiratory pediatrician • Use daily corticosteroid tablet in lowest dose providing adequate control • Maintain high-dose ICS at 2,000 µg/day* • Consider other treatments to minimize use of corticosteroid tablets • Refer patient for specialist care
	*Beclomethasone or equivalent. †Higher nominal doses may be required if drug delivery is difficult. Specific management issues • For adults and children 5 to 12 years of age, if exercise is a specific problem in patients taking ICS who are otherwise well controlled, consider adding one of the following: leukotriene receptor antagonists, LABAs, chromones, oral β_2-agonists, or theophyllines. • For adults and children 5 to 12 years of age, immediately prior to exercise inhaled SABAs are the drug of choice.
International Primary Care Respiratory Group: **Management of Asthma (2006)**[18]	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: o Short-acting β_2-agonists as needed for symptoms and for exercise-induced bronchospasm. o In patients >60 years of age, consider an anticholinergics agent. • Step 2: mild persistent asthma: o Low-dose ICS. • Step 3: moderate persistent asthma: o Combination therapy with an ISC and a LABA. o An alternative treatment option includes using the combination of an ICS and a leukotriene modifier or sustained-release theophylline. • Step 4: severe persistent asthma: o Combination therapy with a high-dose ICS and LABA. o An alternative treatment option includes high-dose ICS and sustained-release theophylline. o An alternative treatment option includes high-dose ICS and a leukotriene modifier. o Oral corticosteroids can be used over the short-term. General treatment consideration • 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 ICS. • For moderate or severe persistent asthma, the preferred treatment is regular treatment with a combination of ICS and a LABA. Alternatives are combinations of ICS with sustained-release theophylline or with leukotriene receptor antagonists.

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[1-9]

Indication(s)	Aminophylline	Dyphylline	Theophylline
Asthma			
Relief of acute bronchial asthma		✔	
Treatment of acute exacerbations of the symptoms and reversible airflow obstruction associated with asthma	✔ * (injection)		✔ * (injection)
Treatment of the symptoms and reversible airflow obstruction associated with asthma			✔
Chronic Bronchitis and Emphysema			
Relief of reversible bronchospasm associated with chronic bronchitis and emphysema		✔	
Treatment of acute exacerbations of the symptoms and reversible airflow obstruction associated with chronic bronchitis and emphysema	✔ * (injection)		✔ * (injection)
Treatment of the symptoms and reversible airflow obstruction associated with chronic bronchitis and emphysema			✔

*Indicated as an adjunct to inhaled beta-2 selective agonists and systemically administered corticosteroids.

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[2]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-life (hours)
Aminophylline	IV: within minutes PO: 0.25 to 0.5	Variable	100	40	Liver (90)	Renal (10 to 13)	3.7 to 12.0*
Dyphylline	0.75	Variable	Rapid (% not reported)	Not reported	Not reported	Renal (82 to 88)	2
Theophylline	ER: 8 IR: 0.25 to 0.5	Variable	Complete (% not reported)	40	Liver (90)	Renal (10)	3.7 to 12.0*

*Elimination half-life highly variable and dependent upon age, liver function, cardiac function, presence of lung disease, and smoking history.
ER=extended-release, IR=immediate-release, IV=intravenous, PO=oral

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
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	1	Halothane	Halothane may cause catecholamine-induced arrhythmias in a patient who has taken theophylline.
Respiratory smooth muscle relaxants (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.
Respiratory smooth muscle relaxants (dyphylline)	1	Acitretin	Dyphylline may increase plasma concentrations and toxic effects of acitretin.
Respiratory smooth muscle relaxants (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.
Respiratory smooth muscle relaxants (dyphylline)	1	Insulin	Dyphylline may increase the hypoglycemic effect of insulin.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Adenosine	The pharmacologic effects of adenosine may be decreased by xanthines. Adenosine may lose its pharmacologic effect in patients treated with xanthines.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Barbiturates	Barbiturates may increase the metabolism and clearance of xanthines by inducing cytochrome P450 enzymes resulting in decreased asthma control.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	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. 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.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Dipyridamole	Xanthines may attenuate the pharmacologic action of intravenous dipyridamole, leading to false negative dipyridamole-thallium-201 cardiac imaging studies.

Generic Name(s)	Significance Level	Interaction	Mechanism
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Hydantoins	Pharmacologic effects of xanthines and hydantoins may be decreased since reduced plasma concentrations of xanthines and phenytoin may occur.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Lithium	The pharmacologic effects of lithium may be decreased by xanthines. The renal excretion of lithium may be increased by xanthines.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Mexiletine	Mexiletine may impair hepatic elimination and increase plasma concentrations of xanthines. Additive arrhythmogenic effects may also occur.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Nondepolarizing muscle relaxants	Xanthines may cause a dose-dependent reversal of neuromuscular blockade induced by a nondepolarizing relaxant.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Tacrine	Xanthines given concomitantly with tacrine increases the half-life of xanthines and plasma concentrations by approximately two-fold.
Respiratory smooth muscle relaxants (aminophylline, dyphylline, theophylline)	2	Zileuton	Zileuton increases serum levels of xanthines resulting in increased pharmacologic and toxic effects, possibly through the inhibition of theophylline metabolism.
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 (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 (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

Generic Name(s)	Significance Level	Interaction	Mechanism
			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 (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.
Respiratory smooth muscle relaxants (dyphylline)	2	Acetaminophen	The risk of acetaminophen-induced hepatotoxicity may be increased by chronic intake of dyphylline.
Respiratory smooth muscle relaxants (dyphylline)	2	Benzodiazepines	The central nervous system depressant effects of benzodiazepines and dyphylline may be increased. Excessive sedation and impaired psychomotor function may occur.
Respiratory smooth muscle relaxants (dyphylline)	2	Furazolidone	The combination of dyphylline and furazolidone may produce acute alcohol intolerance in some patients.
Respiratory smooth muscle relaxants (dyphylline)	2	Metronidazole	Combination of metronidazole and dyphylline may produce alcohol intolerance since metronidazole may inhibit aldehyde dehydrogenase-mediated metabolism of ethanol.
Respiratory smooth muscle relaxants (dyphylline)	2	Metformin	The hypoglycemic effects of metformin may be increased by dyphylline.
Respiratory smooth muscle relaxants (dyphylline)	2	Probenecid	The renal excretion of dyphylline is decreased by probenecid.
Respiratory smooth muscle relaxants (dyphylline)	2	Sodium Oxybate	Concurrent use of sodium oxybate and dyphylline may result in an increase in sleep duration and central nervous system depression.

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 µg/mL, whereas they are more common and severe when the serum concentration exceeds 20 µg/mL.[1,2]

Table 6. Adverse Drug Events (%) Reported with the Respiratory Smooth Muscle Relaxants[1-10]

Adverse Events	Aminophylline	Dyphylline	Theophylline
Cardiovascular			
Arrhythmia	✔	✔	✔
Bradycardia	✔	-	-
Cardiac arrest	✔	-	-
Circulatory failure	✔	✔	✔
Extrasystoles	✔	✔	✔
Hypotension	✔	✔	✔
Palpitations	✔	✔	✔
Premature ventricular contraction	✔	-	✔
Tachycardia	1 to 10	1 to 10	1 to 10
Central Nervous System			
Dizziness	✔	✔	✔
Headache	✔	✔	✔
Insomnia	<1	✔	<1
Irritability	<1	✔	<1
Nervousness	1 to 10	1 to 10	1 to 10
Reflex hyperexcitability	✔	✔	✔
Restlessness	1 to 10	1 to 10	1 to 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 serum glutamic oxaloacetic transaminase	✔	✔	✔
Hyperglycemia	✔	✔	✔
Syndrome of inappropriate antidiuretic hormone	✔	✔	✔
Gastrointestinal			
Abdominal cramping	✔	✔	✔
Anorexia	✔	✔	✔
Diarrhea	✔	✔	✔
Epigastric pain	✔	✔	✔
Hematemesis	✔	✔	✔
Nausea	1 to 10	1 to 10	1 to 10
Vomiting	1 to 10	1 to 10	1 to 10
Genitourinary			
Albuminuria	✔	✔	✔
Diuretic effect	✔	✔	✔
Excretion of renal tubular cells	✔	✔	✔
Hematologic			
Bone marrow suppression	✔	✔	✔
Hemorrhagic diathesis	✔	✔	✔
Leukopenia	✔	✔	✔
Thrombocytopenia	✔	✔	✔
Laboratory Test Abnormalities			

Adverse Events	Aminophylline	Dyphylline	Theophylline
Elevated plasma glucose	-	-	✔
Elevated uric acid	✔	✔	✔
Elevated free fatty acid	-	-	✔
Elevated total cholesterol	-	-	✔
Elevated high density lipoprotein	-	-	✔
Elevated high density lipoprotein/low density lipoprotein 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.

VII. Dosing and Administration

The usual dosing regimens for the respiratory smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Respiratory Smooth Muscle Relaxants[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aminophylline	Asthma, chronic bronchitis, and emphysema: Injection: initial, 6 mg/kg intravenous over 20 to 30 mins; maintenance, 0.5 mg/kg/hr continuous infusion ; maximum, 900 mg/day theophylline or 13 mg/kg/day theophylline, whichever is less	Asthma, chronic bronchitis, and emphysema: Injection: initial, 6 mg/kg IV over 20 to 30 mins; maintenance, 0.5 to 1 mg/kg/hr; maximum, 900 mg/day theophylline or 13 to 24 mg/kg/day theophylline, whichever is less	Injection: 250mg/10 mL 500 mg/20 mL
Dyphylline	Asthma, chronic bronchitis and emphysema: Tablet: up to 15 mg/kg every six hours	Safety and efficacy in children have not been established	Tablet: 200 mg 400 mg
Theophylline	Asthma, chronic bronchitis and emphysema: Elixir and 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 Extended-release capsule: initial, 300 to 400 mg once daily; maintenance, may increase dose to	Asthma, chronic bronchitis and emphysema: Elixir and 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	Elixir: 80 mg/15 mL Extended-release capsule: 100 mg 200 mg 300 mg 400 mg Extended-release tablet: 100 mg 200 mg 300 mg 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	400 to 600 mg once daily after 3 days, if dose greater then 600mg/day, titrate according to blood levels Extended-release tablet: 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 Injection: initial, 4.6 mg/kg over 20 to 30 mins; maintenance, 0.3 to 0.4 mg/kg/hr continuous infusion; maximum, 900 mg/day unless serum levels indicate need for larger doses	mg/day Extended-release capsule: initial, 12 to 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 than 600 mg/day, titrate according to blood levels Extended-release tablet: initial, 12 to 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 Injection: initial, 4.6 mg/kg over 20 to 30 mins; maintenance, 0.5 to 0.8 mg/kg/hr; maximum, 900 mg/day unless serum levels indicate need for larger doses	450 mg 600 mg 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

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory smooth muscle relaxants are summarized in Table 8.

Table 8. 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				
Yung et al.[19] (1998) Aminophylline IV 10 mg/kg loading dose, followed by continuous infusion of 1.1 mg/kg/hr (<10 years old) or 0.7 mg/kg/hr (≥10 years old) vs placebo	DB, PC, RCT 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 8 to 10 L/min), inhaled ipratropium (250 µg every 4 to 6 hours), and IV steroids (1mg/kg every 6 hours, followed by oral prednisone 1 mg/kg BID during convalescence)	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, intubation duration	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 to 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 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.[20] (1998) Aminophylline IV 6 mg/kg loading dose, followed by 1.2 mg/kg/hr	DB, PC, PRO, RCT Patients 1 to 7 years of age with moderate bronchoconstriction despite 3 sequential fenoterol*	N=43 12 to 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	nebulizations, history of 2 similar episodes, and Wood-Downes score between 3 and 6, persisting symptoms lasting ≥2 days			
Roberts et al.[21] (2003) Aminophylline infusion (5 mg/kg over 20 minutes), followed by 0.9 mg/kg/hr infusion vs albuterol IV bolus (15 µg/kg over 20 minutes), followed by saline infusion	DB, RCT 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 µg, 250 µg 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.[22] (2001) Aminophylline 7 mg/kg IV bolus, followed by theophylline infusion (to achieve serum levels between 12 to 17 µg/mL; age-related dosing protocol: 6 to 12 months 0.5	DB, PRO, RCT Patients between 13 months and 17 years with severe status asthmaticus admitted to the pediatric intensive care unit for ≤2 hours with intractable wheezing and a modified Wood-	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/hr, 1 to 9 years 0.8 mg/kg/hr, ≥10 years 0.65 mg/kg/hr) in addition to continuous albuterol nebulization, intermittent, inhaled ipratropium, and IV methyl-prednisolone vs continuous albuterol nebulization, intermittent, inhaled ipratropium, and IV methyl-prednisolone	Downes clinical asthma score of ≥5 and treated with an aggressive regimen consisting of continuous albuterol nebulization 0.3 mg/kg/hr at 7 to 8 L/min, intermittent inhaled ipratropium during first 48 hours of hospitalization at 250 to 500 µg 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		events	no statistically significant effect relative to the total incidence of side effects.
Yamauchi et al.[23] (2005) Theophylline 200 mg IV vs placebo	PG, RCT, SB Patients with mild acute exacerbation of bronchial asthma who were currently treated with oral SR theophylline and theophylline levels <13 µg/mL	N=22 2 hours	Primary: Spirometry and asthma symptoms (Borg Scale, wheezing index, coughing, and sputum production) Secondary: Not reported	Primary: There was a significant improvement in PEFR (from 313±82 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 IV 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 IV theophylline. Secondary: Not reported
Wheeler at al.[24] (2005) Theophylline IV	DB, PRO, RCT Patients between 3 and 15 years old	N=40 4 to 5 days	Primary: Change in clinical asthma score over time	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bolus (6.4 mg/kg), followed by a continuous infusion and terbutaline IV bolus (20 µg/kg), followed by continuous infusion (0.4 µg/kg/hr) vs terbutaline IV bolus (20 µg/kg), followed by continuous infusion (0.4 µg/kg/hr) vs theophylline IV bolus (6.4 mg/kg), followed by a continuous infusion	who are critically ill with status asthmaticus and potential respiratory failure, admitted ≤2 hours; receiving continuous nebulized albuterol (10 mg/hr) and IV methylprednisolone (2 mg/kg every 6 hours for 24 hours followed by 1 mg/kg every 6 hours until discharge)		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	Secondary: With the exception of more reported nausea in patients receiving both theophylline and 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 four 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 vs 51.6±33.3 vs 47.1±38.3 hours, respectively; P<0.05).
Helms et al.[25] (1983) Theophylline 10 mg/kg TID, followed by aminophylline SR 14 mg/kg BID vs aminophylline SR 14 mg/kg BID, followed by	DB, PG, XO Children between 7 and 13 years old with chronic asthma and mean daily PEFR <75% of that predicted on stature over a 4 week assessment period	N=25 8 weeks	Primary: Pharmacokinetics and therapeutic effects (morning and evening PEFRs, weighted drug score, daily symptoms scores) Secondary: Not reported	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 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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
theophylline 10 mg/kg TID vs theophylline 10 mg/kg TID vs aminophylline CR 14 mg/kg BID				
Dombrowski et al.[26] (2004) Theophylline 400 to 800 mg/day (to achieve serum level between 8 to 12 µg/mL) vs beclomethasone inhaler 4 puffs TID	DB, PC, PRO, RCT 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 one 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 and 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 and 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 to 0.9; P=0.016).
Reed et al.[27] (1998) Theophylline SR 100 to 300 mg (to achieve a serum level between 8 to	DB, DD, MC, RCT Patients between 6 and 65 years old with asthma associated with symptoms of	N=747 12 months	Primary: Daily diary symptoms; PEFR; supplemental bronchodilator use; doctor's office or hospital	Primary: Compared to theophylline, treatment with beclomethasone resulted in a greater reduction in symptom scores (P=0.002 at six months), symptoms days (P=0.002 at six months), supplemental bronchodilator use (P=0.038 at six months), systemic glucocorticoid doses (P=0.009 at six months), bronchial hyperresponsiveness (P<0.05 at six months; P<0.001 at one year), and eosinophilia (P=0.001 at one year).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
15 µg/mL) vs beclomethasone inhaler 2 inhalations (42 mg/inhalation) QID	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		visits and absence from work or school; spirometry; methacholine testing; adverse experiences; cortical blood measurements Secondary: Not reported	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 and 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. Secondary: Not reported
Tinkleman et al.[28] (1994) Theophylline SR administered BID (to achieve serum levels between 8 to 15 µg/mL) vs beclomethasone inhaler 2 inhalations (42 µg/inhalation) QID	DB, DD, MC, 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 Secondary: Not reported	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 five, P=0.025 at month six, 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 and 5.5 cm/yr, respectively; P=0.005) and in prepubescent males only (4.3 and 6.2 cm/yr, respectively; P=0.005). Secondary: Not reported
Ukena et al.[29]	DB, PG, RCT	N=133	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Theophylline 250 to 375 mg BID and beclomethasone inhaler 200 µg BID vs beclomethasone inhaler 400 µg BID	Patients with mild to moderate asthma with FEV_1 of 50 to 85% predicted normal and FEV_1 increase of 15% after bronchodilator who remained symptomatic on beclomethasone 400 µg/day or equivalent ICS dose	6 weeks	Improvement of PEFR at six weeks over baseline Secondary: Asthma symptoms, albuterol use	Both theophylline/beclomethasone and beclomethasone regimens demonstrated equal efficacy in increasing FEV_1 and PEFR at week six (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 and 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 and beclomethasone and beclomethasone regimens.
Lim et al.[30] (2000) Theophylline SR 200 mg BID and beclomethasone inhaler 200 µg BID vs beclomethasone inhaler 200 µg BID vs beclomethasone inhaler 500 µg BID	DB, PG, RCT 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 ICS 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-agonist, symptom scores, asthma exacerbations, 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 and theophylline (P=0.006). Significant improvement was observed in mean evening PEF in patients receiving low-dose beclomethasone and 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.
Wang et al.[31] (2005) Theophylline SR 200 µg BID and beclomethasone inhaler	OL, PG, RCT Patients between 18 and 70 years old with asthma showing FEV_1 increase of greater	N=41 6 weeks	Primary: Lung function testing, sputum induction (cell differential counts and interleukin-5), PEFR, symptom	Primary: Both the beclomethasone and beclomethasone and 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
250 µg BID vs beclomethasone inhaler 500 µg BID	than 15% and 20 mL over baseline after bronchodilator use and use of an ICS with a dose ≤1,000 µg		score, β_2-agonist use Secondary: Not reported	There was no significant difference in all primary study parameters between the two treatment groups. Both treatment regimens were well tolerated. Secondary: Not reported
Spears et al.[32] (2009) Theophylline 400 mg QD and beclomethasone inhaler 200 µg QD vs theophylline 400 mg QD vs beclomethasone inhaler 200 µg QD	DB, DD, PG, RCT Patients 18 to 60 years of age with mild to moderate asthma who were current smokers and who were receiving ≤1,000 µg/day of beclomethasone (or equivalent)	N=68 4 weeks	Primary: Change in lung function and ACQ scores Secondary: Inflammatory biomarkers in sputum	Primary: The addition of theophylline to inhaled beclomethasone resulted in statistically significant improvements in morning PEF (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 FVC (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 beclomethasone 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 interleukin-8 (P=0.009) and myeloperoxidase (P=0.026).
Morali et al.[33] (2001) Theophylline 200 mg BID vs budesonide inhaler 2 inhalations (800 µg) BID	DB, PG, RCT Patient between 18 and 45 years old with mild to moderate asthma with baseline FEV_1 greater than 60% of predicted value and FEV_1 increased by 20% after bronchodilator use	N=38 4 weeks	Primary: Clinical, functional, anti-inflammatory effects Secondary: Not reported	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 (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Evans et al.[34] (1997) Theophylline 250 to 375 mg BID and budesonide inhaler 400 µg BID vs budesonide inhaler 800 µg BID	DB, PC, RCT Patients 18 to 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 µg budesonide or equivalent ICS dose	N=62 3 months	Primary: PEFR, albuterol usage, 4-point scale for symptom severity Secondary: Not reported	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. Secondary: Not reported
Yurdakul et al.[35] (2003) Theophylline SR 400 mg QD vs budesonide inhaler 400 µg QD vs montelukast tablet 10 mg QD	PG, RCT 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 µg of albuterol	N=74 3 months	Primary: Lung function (PEFR, FEV_1), asthma symptom scores, supplemental β_2-agonist use, adverse events, asthma exacerbations Secondary: Not reported	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 12.0, 16.0, and 16.7%, respectively. Asthma exacerbation percentage for montelukast, theophylline, and budesonide were 16.0, 12.5, and 0%. Secondary: Not reported
Furukawa et al.[36] (1984) Theophylline SR	DB, PC, RCT Patients between 5 and 15 years old	N=46 3 months	Primary: Home assessment (symptom, PEFR), office	Primary: Both theophylline and cromolyn demonstrated similar effects relative to symptom scores, increased pulmonary function, and decreased use of the bronchodilator.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 to 300 mg BID (to achieve serum levels between 10 to 15 µg/mL) vs cromolyn sodium inhaler QID	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		assessment (FVC, FEV_1, PEFR, and forced mid-expiratory flow rate, asthma score) Secondary: Not reported	Compared to cromolyn, theophylline use was associated with more side effects (nausea, nervousness; P<0.02) and doctor visits (P<0.01). Secondary: Not reported
Hendeles et al.[37] (1995) Theophylline SR every morning (to achieve serum levels between 10 to 20 µg/mL) vs cromolyn inhaler 2 inhalations QID vs placebo	DB, DD, RCT, 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 Secondary: Not reported	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). Secondary: Not reported
Burki et al.[38] (1997) Theophylline 300 to 700 mg (to achieve serum levels between 10 to 20 µg/mL) and ipratropium inhaler (40 µg)	DB, PC, RCT, XO Patients with mild to moderate stable asthma with FEV_1 of 70% of the predicted normal and a FEV_1 increase of 15% within 30 minutes of 2	N=19 7 days	Primary: Efficacy Secondary: Not reported	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 three hours, treatment with theophylline/ipratropium led to a significantly greater increase in FEV_1 than theophylline or ipratropium monotherapy (3.00, 2.48, 2.61 L, respectively; P<0.05). There were no significant differences in side effects when comparing all study regimens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs theophylline 300 to 700 mg (to achieve serum levels between 12 to 18 µg/mL) vs ipratropium inhaler (40 µg) vs placebo	inhalations of isoproterenol			Secondary: Not reported
Yurdakul et al.[39] (2002) Theophylline SR 400 mg QD and budesonide inhaler 400 µg BID vs formoterol inhaler 9 µg BID and budesonide inhaler 400 µg BID vs zafirlukast 20 mg BID and budesonide inhaler 400 µg BID	OL, PG, RCT 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 Secondary: Not reported	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, 20.0, and 20.0%, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vatrella et al.[40] (2005) Theophylline SR 600 mg x 1 dose vs salmeterol 50 µg x 1 dose vs theophylline SR 600 mg and salmeterol 50 µg x 1 dose vs placebo	PC, RCT, SB, XO Patients with moderate to severe asthma	N=10 4 days	Primary: Changes in FEV_1 Secondary: Not reported	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). Secondary: Not reported
Nutini et al.[41] (1998) Theophylline SR 150 mg BID (to achieve plasma levels between 10 to 20 µg/mL) vs salmeterol 50 µg BID	MC, OL, PG, RCT Patients ≥18 years of age with asthma, FEV_1 between 50 to 80% predicted value, FEV_1 increase of 15% after 200 µg 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 evaluated by examining a synthetic score ranging from a minimum of 0 to	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
			maximum of 20	
Dawson et al.[42] (1986) Theophylline SR 10 mg/kg BID vs theophylline syrup 5 mg/kg QID	OL, PRO 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 Secondary: Not reported	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. Secondary: Not reported
Schwartz et al.[43] (1998) Theophylline SR 200 to 400 mg BID (to achieve serum levels of 8 to 15 µg/mL) vs zileuton 400 mg QID	AC, DB, MC, PG, RCT Patients 18 and 60 years old with moderate asthma, FEV_1 40 to 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 two week comparison (95% CI, -33.5 to 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 zileuton 400 mg, zileuton 600 mg, and theophylline groups (121, 117, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				110, respectively). The clinical significance is unknown.
Faillers et al.[44] (1978) Theophylline elixir (150 mg) 5.5 mg/kg, ephedrine hydrochloride (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 hydrochloride (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 to 75% and improved FEV_1 by ≥20% after inhaled isoproterenol	N=20 18 days	Primary: Pulmonary function tests (FEV_1, FVC, $FEV_{25\ to\ 75\%}$, FEF_{max}, FRC, Raw, TGV, Gaw/V_L) Secondary: Not reported	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, and 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 and 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 and 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 $FEV_{25\ to\ 75\%}$ (P<0.05). Compared to patients receiving ephedrine-butabarbital, patients receiving theophylline, ephedrine, guaifenesin and butabarbital experienced statistically significant improvements in FEV_1 (P<0.05), FVC (P<0.05), $FEV_{25\ to\ 75\%}$ (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 and butabarbital, patients receiving ephedrine experienced statistically significant improvements in only FEV_1 (P<0.05). Compared to patients receiving ephedrine, patients receiving theophylline

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 hydrochloride (25 mg/15 mL) 0.93 mg/kg; complete dosing regimen not specified vs placebo elixir				and 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. Secondary: Not reported
Chronic Obstructive Pulmonary Disorder				
Duffy et al.[45] (2005) Aminophylline IV 5 mg/kg loading dose, followed by 0.5 mg/kg/hr infusion (to achieve goal theophylline serum levels) vs	DB, PC, RCT Patients between 40 and 80 years old admitted due to a non-acidotic exacerbations of COPD 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 ($P=0.19$).

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			Aminophylline was associated with more nausea compared to placebo (44 vs 22%, respectively; P<0.05).
Rice et al.[46] (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/hr infusion (to achieve adequate theophylline serum levels) vs placebo Patients were also treated with metaproterenol, methyl-prednisolone, ampicillin, and supplemental oxygen (as needed).	DB, PC, RCT Patients admitted due to an exacerbation of COPD 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, adverse events Secondary: Not reported	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). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jenkins et al.[47] (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 to 15% reversibility of airway obstruction after 200 µg of inhaled albuterol	N=20 6 weeks	Primary: PEFR, daily symptom score (cough, wheeze, chest tightness), β-agonist inhaler usage Secondary: Not reported	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. Secondary: Not reported
Rossi et al.[48] (2002) Theophylline SR 200 to 300 mg BID (to achieve serum levels between 8 to 20 µg/mL) vs formoterol inhaler 12 µg BID vs formoterol inhaler 24 µg BID vs placebo	MC, PC, PG, RCT 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 three 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 µg, P=0.016 for 24 µg, 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 µg dose, P=0.019, respectively). Compared to theophylline, formoterol use was associated with a significantly greater reduction in AUC for FVC at three 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. Patients receiving theophylline experienced a significant increased risk for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				discontinuing treatment compared to placebo (P=0.002), formoterol 12 µg (P=0.001), and formoterol 24 µg (P=0.001). Compared to theophylline, both doses of formoterol was overall more effective (P≤0.026).
Crimi et al.[49] (1995) Theophylline SR 250 mg BID for 4 days, then 350 mg BID thereafter (to achieve serum levels of 10 to 20 µg/mL) vs nedocromil sodium 2 inhalations QID	DB, DD, PG, RCT 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 Secondary: Not reported	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. Secondary: Not reported
Broseghini et al.[50] (2005) Theophylline SR (to achieve serum levels between 10 to 20 µg/mL) vs salmeterol 50 µg BID vs salmeterol 100 µg	DB, DD, RCT, 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 Secondary: Not reported	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 µg) 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
BID vs placebo				Secondary: Not reported
ZuWallack et al.[51] (2001) Theophylline SR 100 mg BID (to achieve serum levels between 10 to 20 µg/mL) and salmeterol 42 µg BID vs theophylline SR 100 mg BID (to achieve serum levels between 10 to 20 µg/mL) vs salmeterol 42 µg BID	DB, DD, PG, RCT Patients >45 years of age with COPD, FEV_1 ≥0.7 L, FEV_1 ≤65% of predicted, and FEV_1/FVC ratio ≤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 and 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≤0.021 except for FVC at week 12, respectively). Treatment with salmeterol and 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≤0.048), albuterol use reduction (P≤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≤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≤0.028).
Cazzola et al.[52] (2004) Theophylline SR BID (to achieve serum levels between 10 to 20 µg/mL) and fluticasone 500 µg	OL, RCT 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 FEV_1/FVC ratio	N=66 4 months	Primary: Pulmonary function, dyspnea, supplemental albuterol use Secondary: Not reported	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 and fluticasone group (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs salmeterol-fluticasone 50-500 µg BID (fixed-dose combination product)	<70% after albuterol 400 µg			Secondary: Not reported
Cazzola et al.[53] (2000) Theophylline BID (to achieve goal serum levels) and salmeterol 50 µg BID vs salmeterol 50 µg BID vs salmeterol 50 µg and fluticasone 250 µg BID vs salmeterol 50 µg and fluticasone 500 µg BID	OL, RCT 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 µg, FEV_1 post-bronchodilator <85%, and good metered-dose inhaler technique	N=80 3 months	Primary: FEV_1, FVC Secondary: Not reported	Primary: All treatment groups demonstrated statistically significant gradual improvements in FEV_1 ($P<0.05$). Salmeterol 50 µg/fluticasone 500 µg group demonstrated a statistically significant difference in its greater effect on FEV_1 compared to salmeterol and theophylline and salmeterol only treatment groups ($P<0.05$). Secondary: Not reported
Lee et al.[554]	RETRO	N=183,573	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Theophylline-containing drug regimens vs drug regimens not containing theophylline	Male patients aged 45 years or older with a diagnosis of COPD who received respiratory medications who were identified through the National Veterans Affairs inpatient, outpatient, pharmacy, and mortality databases	4 years	All-cause mortality, COPD Exacerbations, and COPD-related hospitalizations Secondary: Not reported	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 to 1.18) for the combination of ipratropium plus theophylline to 1.31 (95% CI, 1.11 to 1.55) for ICS plus long acting β_2-agonist and theophylline. Theophylline regimens containing solely ipratropium or an ICS, 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 ICS). Secondary: Not reported
Lee et al.[55] (2008) Exposure to ICS, ipratropium, LABA, theophylline, and short-acting β_2-agonist	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABA were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABA was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABA (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00), however this did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABA (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABA. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Exercise-Induced Bronchospasm				
Furukawa et al.[56] (1983) Dyphylline 10 mg/kg administered 1 hour prior to exercise vs dyphylline 15 mg/kg administered 1 hour prior to exercise vs	DB, PC, RCT, XO Patients between 12 and 17 years old with exercise-induced bronchospasm (≥20% decrease in FEV_1 during treadmill exercise test)	N=20 1 day	Primary: Spirometry, PEFR, physical examination, subjective symptoms Secondary: Not reported	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, and 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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dyphylline 20 mg/kg administered 1 hour prior to exercise vs theophylline 6 mg/kg administered 2 hours prior to exercise vs placebo				

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, IV=intravenous, QID=four times daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, XO=crossover
Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, AUC=area under the curve, CI=confidence interval, COPD=chronic obstructive pulmonary disease, FEF=forced expiratory flow, FEV_1=forced expiratory volume in 1 second, FRC=functional residual capacity, FVC=forced vital capacity, ICS=inhaled corticosteroid, LABA=long-acting beta-2 agonist, OR=odds ratio, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, RR=relative risk, TGV=thoracic gas volume

Additional Evidence

Dose Simplification
Kelloway et al. analyzed pharmacy claims to assess adherence with theophylline and inhaled anti-inflammatory medications. Adherence was found to be better with theophylline than inhaled treatments (P=0.001).[57] Sherman et al. evaluated adherence rates with asthma medications in children with persistent asthma who were Medicaid recipients. 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.[58]

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. 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.[59] Tinkelman et al. also demonstrated comparable efficacy for theophylline and beclomethasone in decreasing physician visits and hospitalizations.[28] The available data demonstrates that aminophylline does not reduce the length of hospital stay during the acute management of asthma or COPD.[35-37,48,50]

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	N/A	N/A	$
Dyphylline	tablet	Lufyllin®	$$$$	N/A
Theophylline	elixir*, extended-release capsule, extended-release tablet*, injection*, solution*	Elixophyllin®*, Theo-24®	$$$$	$

*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.[1-9] All of the products are available in a generic formulation except for dyphylline.

For the treatment of asthma, guidelines recommend the use of an inhaled corticosteroid (ICS) as initial therapy. When additional therapy is needed, it is recommended that a long-acting β_2-agonist (LABA) be added to the regimen. Theophylline is considered an alternative treatment option for the management of asthma.[15-18] For the treatment of mild airflow obstruction associated with chronic obstructive pulmonary disease (COPD), guidelines recommend the use of a short-acting bronchodilator as needed to relieve breathlessness and exercise limitation. For patients who require daily maintenance therapy to control symptoms, an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic). 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.[10-14]

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. The use of theophylline and aminophylline is often associated with a greater discontinuation rate due to adverse events than comparator drugs.[19-56] Trials comparing the various dosage forms of xanthines are limited; most dosage form comparison studies have evaluated pharmacokinetic data.[60-63]

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 to 20 µg/mL are generally needed to produce bronchodilation. Serum levels >20 µg/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 generic 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.

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Pharmacotherapy Review of Intranasal Corticosteroids
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I. Overview

Intranasal corticosteroids are primarily used to treat perennial and seasonal allergic rhinitis and may be useful in the treatment of some forms of nonallergic rhinitis.[1] Symptoms associated with allergic rhinitis include nasal congestion, rhinorrhea, sneezing, and/or nasal itching. These symptoms result from a complex allergen driven mucosal inflammation caused by resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators.[2] Intranasal corticosteroids downregulate the inflammatory response by binding to the intracellular glucocorticoid receptors of inflammatory cells and causing a conformational change, thereby controlling the rate of protein synthesis and suppressing the transcription of cytokine and chemokine genes.[1]

All intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of perennial and seasonal allergic rhinitis.[3-15] Mometasone (Nasonex®) carries an additional indication for the prophylaxis of seasonal allergic rhinitis.[11] Two currently available intranasal corticosteroids, beclomethasone (Beconase AQ®) and mometasone, are also FDA-approved for the management of nasal polyps.[3,11] Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction.[2] Beclomethasone is principally used to prevent recurrence of nasal polyps following surgical removal.[1]

Beclomethasone and fluticasone propionate (Flonase®) are approved for the management of nonallergic rhinitis (e.g., infectious rhinitis, hormonal rhinitis, and vasomotor nonallergic rhinitis with eosinophilia syndrome).[1,10] Unlike allergic rhinitis, nonallergic rhinitis is characterized by periodic or perennial symptoms that are not a result of immunoglobulin E-dependent events.[16]

Flunisolide, fluticasone propionate, and triamcinolone are currently available generically.[14] Beclomethasone (QNASL®) and ciclesonide (Zetonna®) were approved in 2012 and are the only two intranasal corticosteroid products formulated as a "dry" nasal aerosol; all other products in within the class are formulated as aqueous suspensions.[3-13] Fluticasone furoate (Veramyst®), mometasone, and triamcinolone are approved for use in children two years of age and older.[9,11,12] Dymista® (azelastine hydrochloride-fluticasone propionate) is a combination product that utilizes both an intranasal antihistamine and an intranasal corticosteroid to manage the symptoms of allergic rhinitis.[13]

The intranasal corticosteroids that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Budesonide, flunisolide, fluticasone propionate, and triamcinolone are available in a generic formulation. This class was last reviewed in August 2013.

Table 1. Intranasal Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Beclomethasone	aerosol nasal spray, nasal spray	Beconase AQ®, QNASL®	Beconase AQ®
Budesonide	nasal spray	Rhinocort Aqua®*	budesonide
Ciclesonide	aerosol nasal spray, nasal spray	Omnaris®, Zetonna®	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	N/A	triamcinolone

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Combination Products			
Azelastine and fluticasone	nasal spray	Dymista®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the intranasal corticosteroids are summarized in Table 2.

Table 2. Treatment Guidelines Using the Intranasal Corticosteroids

Clinical Guideline	Recommendation(s)
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)**[2]	Pharmacologic treatment of allergic rhinitis • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.

Clinical Guideline	Recommendation(s)
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[17]	Pharmacologic therapy • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. Oral antihistamines • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. Intranasal antihistamines • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. Oral decongestants • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations.

Clinical Guideline	Recommendation(s)
	• The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • 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 in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <u>Oral corticosteroids</u> • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <u>Intranasal cromolyn</u> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has

Clinical Guideline	Recommendation(s)
	not been adequately studied in comparison with leukotriene antagonists or antihistamines. Intranasal anticholinergics • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. Oral antileukotriene agents • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. Omalizumab • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)**[18]	Strep pharyngitis • Penicillin is the drug of choice for treatment of culture positive cases of group A beta streptococcal pharyngitis. In children and patients unable to swallow pills, amoxicillin is an acceptable alternative due to the poor palatability of the penicillin suspension. • In penicillin-allergic patients, options include cephalosporins (for some types of allergies), macrolides, and clindamycin. Consider reevaluating patient for carrier status. Although macrolides may be an acceptable alternative, clinicians should check their local resistance patterns. • Alternative medication recommendations include macrolides, cephalexin, clindamycin, amoxicillin-clavulanate, and rocephin. Non-infectious rhinitis • With the exception of systemic steroids, intranasal corticosteroids are the most effective single agents for controlling allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. Systemic corticosteroid use should be reserved for refractory or severe cases only and given as a short burst. Injectable corticosteroids are generally not recommended as they are invasive and tend to have a longer course of action than typical courses of corticosteroids. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They are less than intranasal corticosteroids, but can be used either on a daily basis or on an as-needed basis. • Second-generation antihistamines are less sedating than first-generation antihistamines, and cause less central nervous system impairment. Adverse events commonly associated with first-generation antihistamines include somnolence,

Clinical Guideline	Recommendation(s)
	decreased alertness, and anticholinergic effects. These agents may cause central nervous system impairment and impair driving performance. • Oral decongestants can reduce nasal congestion but can result in side effects such as irritability, insomnia, and palpitations. Topical decongestants are used for short-term or intermittent/episodic therapy. Routine daily use is not recommended because of the risk for the development of rhinitis medicamentosa. Both oral and topical decongestants should be used with caution in older adults, children under the age of six, and patients of any age who have a history of the following: arrhythmia, angina, cerebrovascular disease, high blood pressure, bladder neck obstruction, glaucoma, or hyperthyroidism. • Cromolyn is less effective than intranasal corticosteroids, and is most effective when used regularly prior to the onset of allergic symptoms. Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in patients with allergic and non-allergic rhinitis. They have no effect on congestion, sneezing, or itching. • Montelukast is a leukotriene receptor antagonist that is as effective as loratadine and less effective than nasal steroids. It is generally well tolerated and may be considered as a third-line option to add after the failure of a nasal corticosteroid and an oral antihistamine. • Ophthalmic preparations contain antihistamines, decongestants, corticosteroids, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers. Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. <u>Non-allergic rhinitis</u> • Treatment of symptomatic nasal obstruction due to non-allergic rhinitis includes the use of azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants, nasal strips, and topical antihistamines. • Intranasal corticosteroids can be used to treat chronic nasal congestion secondary to non-allergic rhinitis. Intranasal corticosteroids have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic symptoms. • Intranasal cromolyn may improve sneezing and congestion scores, and it can be safely used in children two years of age and older. • Some patients find oral decongestants helpful at relieving symptomatic nasal obstruction secondary to non-allergic rhinitis. Oral decongestants have a relatively rapid onset of action and therefore are particularly useful for sporadic symptoms. Patients using oral decongestants should be monitored for hypertension. • Nasal strips may be effective for patients with nocturnal symptoms. They are more effective for patients with narrow noses or with anterior septal deviations. Daytime use of nasal strips is not usually practical. • Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis. • Conservative treatment of symptomatic non-purulent chronic posterior nasal drainage includes increased water intake, decreased caffeine and alcohol intake, nasal saline irrigation, use of petroleum jelly or antibiotic ointment for nasal crusting, and the addition of humidity in bedroom, if significantly less than 50%. In addition, it should be determined if the patient is using any medications that may cause oral or nasal dryness. • Medical treatment of symptomatic non-purulent chronic posterior nasal drainage includes intranasal corticosteroids. • Treatment of symptomatic bilateral chronic anterior rhinorrhea due to non-allergic rhinitis includes avoidance of triggers, intranasal corticosteroids, intranasal ipratropium bromide, and nasal saline.

Clinical Guideline	Recommendation(s)
	Bacterial sinusitis • Intranasal corticosteroids may be rational but is an unproved adjunctive therapy for acute sinusitis. This therapy may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology. • Antibiotics should be reserved for those patients who failed decongestant therapy, those we present with symptoms and signs of a more severe illness, and those who have complications of acute sinusitis.
International Primary Care Respiratory Group Guidelines: **Management of Allergic Rhinitis (2006)**[19]	Mild intermittent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. o Decongestant. AND/OR o Intranasal saline. • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe intermittent allergic rhinitis treatment options). Moderate/severe intermittent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal saline. o Intranasal glucocorticosteroid. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis and compliance, query infections and other causes, then consider trial of different treatment option or specialist referral. Mild persistent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal glucocorticosteroid. o Intranasal saline. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe persistent allergic rhinitis treatment options). Moderate/severe persistent allergic rhinitis • Recommended therapy: o Intranasal glucocorticosteroid.

Clinical Guideline	Recommendation(s)
	o Decongestant. o Oral H_1-blocker. o Intranasal saline. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then choose one or more of the following options: o Increase nasal steroid dose, consider trial of different treatment option, or consider referral to specialist. o If sneeze/itch: add H_1-blocker. o If rhinorrhea: add ipratropium. o If blockage: add decongestant or short course of oral steroids. <u>General treatment considerations</u> • First generation H_1-antihistamines cause sedation and central nervous system impairment. These side effects may adversely affect cognition, learning and driving. These side effects may be potentiated by alcohol and other sedatives. Adverse events may not always be perceived by patients. • Second generation H_1-antihistamines are associated with less sedation and impairment than first generation antihistamines. • Intranasal and intraocular H_1-antihistamines are as effective as oral antihistamines at the site of their administration. • Intranasal glucocorticosteroids are the most effective class of medications available for the treatment of allergic and nonallergic rhinitis. Oral glucocorticosteroids are rarely needed to control severe symptoms of allergic rhinitis. • Mast cell stabilizers reduce symptoms of allergic rhinitis, but are generally less effective than other treatments and require frequent administration. Ocular mast cell stabilizers are effective and have a role in the treatment of allergic conjunctivitis. • Anticholinergic agents can reduce rhinorrhea, but have little effect on other symptoms of allergic rhinitis. • Antileukotriene agents are effective for the treatment of allergic rhinitis and asthma. They have been shown to be as effective as oral antihistamines, but have a greater effect on nasal obstruction. They may have an additive effect with antihistamines.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the intranasal corticosteroids are noted in Tables 3 and 4. 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 Single Entity Intranasal Corticosteroids[3-12,14-15]

Indication	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone	Triamcinolone
Allergic Rhinitis								
Prophylaxis of seasonal allergic rhinitis in patients ≥12 years of age							✔	
Treatment of nasal congestion associated with seasonal allergic rhinitis in patients ≥2 years of age							✔	
Relief of the symptoms of seasonal or perennial allergic rhinitis	✔ (Beconase AQ®)			✔				
Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in patients four years of age and older	✔ (QNASL®)							
Treatment of seasonal or perennial allergic rhinitis in adults and children ≥6 years of age		✔						
Treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children six years of age and older			✔ (Omnaris®)					
Treatment of perennial allergic rhinitis in adults and adolescents 12 years of age and older			✔					
Treatment of seasonal allergic rhinitis in adults and adolescents 12 years of age and older			✔ (Zetonna®)					

Indication	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone	Triamcinolone
Treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children ≥2 years					✔		✔	✔
Management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older						✔		
Nasal Polyps								
Prevention of recurrence of nasal polyps following surgical removal	✔ (Beconase AQ®)							
Treatment of nasal polyps in patients ≥18 years of age							✔	
Nonallergic Rhinitis								
Relief of the symptoms of nonallergic rhinitis	✔ (Beconase AQ®)							
Management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients four years of age and older						✔		

Table 4. FDA-Approved Indications for the Combination Intranasal Corticosteroids[13-15]

Indication	Azelastine and Fluticasone
Relief of symptoms of seasonal allergic rhinitis in patients six years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the intranasal corticosteroids are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Intranasal Corticosteroids[3-15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Beclomethasone	Not available	Not reported	Hepatic and respiratory	Renal (<10) Feces (main, percent not specified)	2.8
Budesonide	21	85 to 90	Hepatic extensive	Renal (60) Feces (15.1 to 29.6)	2.0 to 3.6
Ciclesonide	<1	≥99	Hepatic predominantly, respiratory	Renal (<20) Feces (66)	6 to 7
Flunisolide	50	Not reported	Hepatic	Renal (65 to 70) Feces (percent not reported)	1 to 2
Fluticasone furoate	0.5	>99	Hepatic	Renal (2) Feces (90)	15.1
Fluticasone propionate	<2	91	Hepatic	Renal (<5) Feces (95)	3.2 to 11.2
Mometasone	Undetectable	98 to 99	Hepatic, extensive	Renal (8) Feces (74)	5.0 to 5.8
Triamcinolone	Not reported	68	Hepatic	Renal (40) Feces (60)	3.1
Combination Products					
Azelastine and fluticasone	A: 40 F: 0.5	A: not reported F: >99	A: Hepatic, extensive (percent not reported) F: Hepatic	A: Renal (25) Feces (50 to 75) F: Renal (2) Feces (90)	A: 22 to 25 F: 15.1

V. Drug Interactions

Significant drug interactions with the intranasal corticosteroids are listed in Table 6.

Table 6. Significant Drug Interactions with the Intranasal Corticosteroids[14]

Generic Name(s)	Significance Level	Interaction	Mechanism
Budesonide, fluticasone	1	Human immunodeficiency virus (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 protease inhibitors may decrease the metabolic elimination of specific inhaled steroids. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur.
Budesonide, fluticasone	2	Azole antifungals	Azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids (budesonide and fluticasone only) resulting in

Generic Name(s)	Significance Level	Interaction	Mechanism
			enhanced corticosteroid effects and toxicity.
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	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	Mifepristone	The pharmacologic effects of budesonide may be reduced. Mifepristone antagonizes the pharmacologic effects of budesonide. Coadministration of budesonide with mifepristone is contraindicated.
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 budesonide. Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of budesonide.

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 Tables 7 and 8.

Table 7. Adverse Drug Events (%) Reported with the Single Entity Intranasal Corticosteroids[3-12,14-15]

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone	Triamcin-olone
Cardiovascular								
Chest pain	-	-	-	-	-	-	2 to <5	-
Palpitations	-	✔	-	-	-	-	-	-
Central Nervous System								
Dizziness	-	-	✔	-	-	1 to 3	-	✔
Headache	<5	-	6.0 to 6.6	≤5	8 to 9	6.6 to 16.1	26	5.5
Insomnia	-	-	-	-	-	-	-	✔
Lightheadedness	<5	-	-	-	-	-	-	-
Gastrointestinal								
Abdominal pain	-	-	-	-	-	1 to 3	-	4.7
Diarrhea	-	-	-	-	-	1 to 3	2 to <5	3
Dyspepsia	-	-	-	-	-	-	2 to <5	3.4
Nausea	<5	-	>2[†]	≤5	-	2.6 to 4.8	2 to <5	✔
Vomiting	-	-	-	≤5	-	2.6 to 4.8	5	-
Hypersensitivity reactions								
Anaphylaxis	✔	✔	-	-	✔	✔	✔	-
Angioedema	✔	✔	-	-	✔	✔	✔	-
Bronchospasm	✔	2	-	-	-	✔	-	-
Dermatitis	-	✔	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	✔	-	✔
Edema of face/ tongue	-	-	-	-	-	✔	-	-
Pruritus	-	✔	-	-	-	✔	-	✔
Rash	✔	✔	-	-	✔	✔	-	2.5
Wheezing	✔	✔	-	-	-	✔	2 to <5	-
Urticaria	✔	✔	-	-	✔	✔	-	-
Ophthalmic								
Blurred vision	-	-	-	-	-	✔	-	-
Cataracts	✔	✔	✔	-	✔	✔	✔	✔
Conjunctivitis	-	-	-	-	-	✔	2 to <5	-
Dry/irritated eyes	-	-	-	-	-	✔	-	-
Glaucoma	✔	✔	✔	-	✔	✔	✔	✔

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone	Triamcin-olone
Increased intraocular pressure	✔	✔	-	-	-	✔	-	✔
Watery eyes	<3	-	-	≤5	-	-	-	-
Respiratory								
Asthma symptoms	-	-	-	-	-	3.3 to 7.2	2 to <5	2.5
Bronchitis	-	-	≥2	-	-	1 to 3	2 to <5	3.4
Cough	-	2	≥2	>1	3 to 4	3.6 to 3.8	7	2.1 to 8.4
Epistaxis	<3	8	4.9 to 11.4†	3 to 9	4 to 6	6.0 to 6.9	1 to 13	2.7 to 5.1
Hoarseness	-	-	-	≤1	-	✔	-	-
Mild nasopharyngeal irritation	24*	-	-	-	-	-	-	-
Nasal burning/ stinging	-	-	-	13 to 45	-	2.4 to 3.2	✔	-
Nasal congestion	-	-	✔	-	-	-	-	-
Nasal discomfort	5.2†	-	3.2 to 5.7†	-	-	-	-	-
Nasal dryness	✔	-	-	>1	-	-	-	-
Nasal irritation	✔	2	≥3	≤5	-	-	2 to <5	✔
Nasal mucosal ulceration	✔	-	✔	≤1	1	✔	✔	-
Nasal septal perforation	✔	✔	✔	✔	-	✔	✔	✔
Nasal stuffiness/ congestion	<3	-	✔	≤5	-	-	-	✔
Nasopharyngitis	-	-	3.7 to 6.6	-	-	-	-	5.1
Pharyngitis	-	4	<3.4	>1	2 to 4	6 to 7.8	12	5.1 to 7.8
Rhinitis	-	-	-	-	-	-	2 to <5	-
Rhinorrhea	<3	-	-	-	-	1 to 3	-	2.1
Sinusitis	-	-	≥3	≤1	-	-	5	-
Sneezing	4*	-	-	≤5	-	-	-	-
Streptococcal pharyngitis	-	-	>2†	-	-	-	-	-
Throat discomfort (burning, itching, swelling, pain)	-	✔	-	≤5	-	✔	-	-
Throat dryness/ irritation	✔	✔	-	-	-	✔	-	-
Upper respiratory	-	-	>2†	-	-	-	5 to 7	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone	Triamcin-olone
tract infection								
Voice changes	-	-	-	-	-	✔	-	-
Miscellaneous								
Aches and pains	-	-	-	-	-	1 to 3	-	-
Aftertaste	-	-	-	8 to 17	-	-	-	-
Arthralgia	-	-	-	-	-	-	2 to <5	-
Back pain	-	-	≥3	-	1	-	-	-
Dysmenorrhea	-	-	-	-	-	-	5	-
Earache	-	-	2.2	-	-	-	2 to <5	-
Excoriation	-	-	-	-	-	-	-	2.5
Fatigue	-	-	-	-	-	-	-	✔
Fever	-	-	-	-	4 to 5	1 to 3	-	-
Flu-like symptoms	-	-	-	-	-	1 to 3	2 to <5	-
Growth suppression	✔	✔	✔	✔	✔	✔	✔	✔
Immunosuppression	-	✔	✔	-	✔	-	✔	✔
Impaired wound healing	-	✔	✔	-	✔	-	✔	✔
Infection	✔	✔	✔	✔	✔	✔	✔	✔
Influenza	-	-	≥3	-	-	-	-	8.9
Loss of taste/smell	✔	✔	-	✔	-	✔	-	-
Muscle strain	-	-	>2†	-	-	-	-	-
Myalgia	-	-	-	-	-	-	2 to <5	-
Otitis media	-	-	-	-	-	-	2 to <5	-
Skin trauma	-	-	-	-	-	-	2 to <5	-
Tooth disorder	-	-	-	-	-	-	-	3.4
Unpleasant taste/ smell	✔	-	-	-	-	-	✔	✔
Urinary tract infection	-	-	≥3	-	-	-	-	-
Viral infection	-	-	-	-	-	-	14	-

✔ Percent not specified.
- Event not reported.
*Beconase AQ® only.
†Aerosol formulation only.

Table 8. Adverse Drug Events (%) Reported with the Combination Intranasal Corticosteroids[13-15]

Adverse Event(s)	Azelastine and Fluticasone
Central Nervous System	
Dizziness	-
Dysesthesia	-
Headache	≥2
Somnolence	-
Gastrointestinal	
Diarrhea	≥2
Nausea	-
Respiratory	
Asthma	-
Cold symptoms	-
Epistaxis	≥2
Nasal burning	-
Nasal congestion	≥2
Nasal discomfort	-
Nasal ulcers	-
Paroxysmal sneezing	-
Pharyngitis	≥2
Pharyngolaryngeal pain	-
Rhinitis	≥2
Sinusitis	-
Sneezing	-
Upper respiratory tract infection	≥2
Other	
Bitter taste	-
Conjunctivitis	-
Cough	≥2
Dry mouth	-
Dysgeusia	4
Fatigue	-
Pain	≥2
Pyrexia	≥2
Viral infection	≥2
Weight increase	-

- Event not reported or below the 2% reported frequency threshold.

VII. Dosing and Administration

The usual dosing regimens for the intranasal corticosteroids are listed in Table 9.

Table 9. Usual Dosing Regimens for the Intranasal Corticosteroids[3-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Beclomethasone	Nasal polyps, nonallergic (vasomotor) rhinitis: Suspension: one to two inhalations in each nostril BID Perennial allergic rhinitis, seasonal allergic rhinitis: Aerosol: two 80 µg inhalations in	Nasal polyps, nonallergic (vasomotor) rhinitis, perennial allergic rhinitis, seasonal allergic rhinitis in children six to 12 years old: Suspension: initial, one inhalation in each nostril BID; maximum, two inhalations in	Aerosol for nasal inhalation: 40 µg/actuation 80 µg/actuation (120 actuations) Suspension for nasal inhalation:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	each nostril QD Suspension: one to two inhalations in each nostril BID	each nostril BID Perennial allergic rhinitis, seasonal allergic rhinitis in children 4 to 11 years old: Aerosol: one 40 µg inhalations in each nostril QD Perennial allergic rhinitis, seasonal allergic rhinitis in children ≥12 years old: Aerosol: two 80 µg inhalations in each nostril QD Suspension: one to two inhalations in each nostril BID	42 µg/inhalation (180 metered doses)
Budesonide	Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: one inhalation in each nostril QD; maximum, four inhalations in each nostril QD	Perennial allergic rhinitis, seasonal allergic rhinitis in children six to 12 years old: Suspension: one inhalation in each nostril QD; maximum, two inhalations in each nostril QD	Suspension for nasal inhalation: 32 µg/inhalation (120 metered doses)
Ciclesonide	Perennial allergic rhinitis, seasonal allergic rhinitis: Aerosol: one inhalation in each nostril QD Suspension: two inhalations in each nostril QD	Perennial allergic rhinitis, seasonal allergic rhinitis in children ≥12 years old: Aerosol: one inhalation in each nostril QD Suspension: two inhalations in each nostril QD Seasonal allergic rhinitis in children six years of age and older: Suspension: two inhalations in each nostril QD	Aerosol for nasal inhalation: 37 µg/actuation (60 actuations) Suspension for nasal inhalation: 50 µg/inhalation (120 metered doses)
Flunisolide	Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: two inhalations in each nostril BID; maximum, right inhalations in each nostril daily	Perennial allergic rhinitis, seasonal allergic rhinitis in children six to 14 years old: Suspension: one inhalation in each nostril TID or two inhalations in each nostril BID; maximum, four inhalations in each nostril daily	Suspension for nasal inhalation: 25 µg/inhalation (200 metered doses)
Fluticasone furoate	Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: two inhalations in each nostril QD; maintenance, one inhalation in each nostril QD	Perennial allergic rhinitis, seasonal allergic rhinitis in children two to 11 years old: Suspension: one inhalation in each nostril QD; maximum, two inhalations in each nostril QD	Suspension for nasal inhalation: 27.5 µg/inhalation (120 metered doses)
Fluticasone propionate	Nonallergic (vasomotor) rhinitis, perennial allergic rhinitis, seasonal rhinitis:	Nonallergic (vasomotor) rhinitis, perennial allergic rhinitis, seasonal rhinitis in	Suspension for nasal inhalation: 50 µg/inhalation

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension: two inhalations in each nostril QD or one inhalation in each nostril BID; maintenance, one inhalation in each nostril QD	children four years of age and older: Suspension: one inhalation in each nostril QD; maximum, two inhalations in each nostril QD	(120 metered sprays)
Mometasone	Nasal congestion associated with seasonal allergic rhinitis: Suspension: two inhalation in each nostril QD Nasal polyps in adults ≥18 years old: Suspension: two inhalations in each nostril QD to BID Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: two inhalations in each nostril QD Prophylaxis of seasonal allergic rhinitis in individuals >12 years old: Suspension: two inhalations in each nostril QD	Nasal congestion associated with seasonal allergic rhinitis in children two to 11 years old: Suspension: one inhalation in each nostril QD Perennial allergic rhinitis, seasonal allergic rhinitis in children two to 11 years old: Suspension: one inhalation in each nostril QD	Suspension for nasal inhalation: 50 µg/inhalation (120 metered doses)
Triamcinolone	Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: two inhalations in each nostril QD; maintenance, one inhalation in each nostril QD	Perennial allergic rhinitis, seasonal allergic rhinitis in children two to five years old: Suspension: one inhalation in each nostril QD Perennial allergic rhinitis, seasonal allergic rhinitis in children six to 12 years old: Suspension: one or two inhalations in each nostril QD; maintenance, one inhalation in each nostril QD	Suspension for nasal inhalation: 55 µg/inhalation (120 metered doses)
Combination Products			
Azelastine and fluticasone	Seasonal allergic rhinitis: Suspension: one inhalations in each nostril BID	Seasonal allergic rhinitis in children ≥6 years old: Suspension: one inhalations in each nostril BID	Suspension for nasal inhalation: 137-50 µg/inhalation

BID=twice daily, QD=once daily, BID=twice daily, TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the intranasal corticosteroids are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Intranasal Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Allergic Rhinitis (Perennial and Seasonal)				
Meltzer et al.[20] (2012) Beclomethasone 320 µg QD (QNASL®) vs placebo	DB, MC, PC, RCT Patients ≥12 years of age with a ≥2 year history of PAR, a positive skin test to ≥1 perennial allergen	N=474 6 weeks	Primary: Change from baseline in rTNSS Secondary: Change from baseline in iTNSS, individual symptom scores, PNSS, RQLQ and safety	Primary: After six weeks of treatment, subjects treated with beclomethasone reported significantly greater improvement from baseline in rTNSS compared to subjects treated with placebo. (LS mean change of -2.46 vs -1.63; P<0.001). Secondary: A significantly greater improvement in iTNSS was achieved over six weeks in the beclomethasone treatment group compared to the placebo group (LS mean change of -2.14 vs -1.36; P<0.001). As demonstrated with overall nasal symptom improvement, beclomethasone significantly improved reflective and instantaneous individual nasal symptom scores for all four of the components of the TNSS compared to placebo (P<0.05 for all). The change from baseline in PNSS was significantly greater with beclomethasone compared to placebo over six weeks (P<0.001). Furthermore, patients treated with beclomethasone achieved significant improvements in all individual symptoms of the PNSS compared to subjects treated with placebo (P≤0.001 for all). Beclomethasone treatment significantly improved RQLQ scores compared to placebo (P=0.001). There were no differences between beclomethasone and placebo with regard to the incidence, type and severity of adverse events. Nasal discomfort was frequently reported with both beclomethasone and placebo treatment (5.9 and 5.0%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Van Bavel et al.[21] (abstract) (2012) Beclomethasone 320 µg QD (QNASL®) vs placebo	DB, PC, RCT Patients ≥12 years of age with SAR	N=340 2 weeks	Primary: Changes in rTNSS, iTNSS, RQLQ score, rTOSS, iTOSS, PNSS scores and safety Secondary: Not reported	Primary: Patients treated with beclomethasone experienced a significantly greater improvement from baseline in average morning and evening rTNSS compared to treatment with placebo (treatment difference, -0.91; 95% CI, -1.3 to -0.5; P<0.001) over two weeks of treatment. Greater improvements in rTNSS with beclomethasone compared to placebo were evident by day two of treatment and were maintained throughout the treatment period. Similarly, beclomethasone treatment significantly improved iTNSS (P<0.001) and RQLQ score (P=0.005) compared to placebo. Treatment with beclomethasone was associated with greater improvements in rTOSS (P=0.002), iTOSS (P=0.003) and PNSS (P<0.001) compared to treatment with placebo. The overall safety profile was similar between patients treated with beclomethasone or placebo. Secondary: Not reported
Chervinsky et al.[22] (2007) Ciclesonide 200 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2 year history of PAR, who require continuous treatment and demonstrated skin prick test sensitivity to at least one allergen known to induce PAR	N=663 52 weeks	Primary: Treatment-emergent adverse events, 24 hour urinary free cortisol and morning cortisol levels at weeks 24 and 48 Secondary: Change from baseline in patient evaluated morning 24 hour rTNSS, PANS score at the end of treatment, combined RQLQ	Primary: There were no clinically significant differences in the incidence of treatment-emergent adverse events with ciclesonide compared to placebo (75.1 vs 74.3%; P value not reported). No clinically significant differences were seen between the ciclesonide and placebo groups with regards to 24 hour urinary free cortisol and morning cortisol levels and ocular examinations. Secondary: There was a significantly greater reduction from baseline in 24 hour rTNSS in the ciclesonide group (-2.3) compared to placebo (-1.8) (P<0.001). No appreciable differences were found between ciclesonide and placebo groups in PANS score at the end of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			scores at end point	At the end point, ciclesonide produced a greater improvement in combined RQLQ scores compared to placebo (-1.07 vs -0.88; P=0.04).
Meltzer et al.[23] (2007) Ciclesonide 200 µg QD vs placebo	DB, MC, PC, RCT Patients ≥12 years of age with a ≥2 year history of PAR, who required continuous or intermittent treatment and demonstrated skin prick test sensitivity to ≥1 allergen known to induce PAR	N=676 6 weeks	Primary: Change from baseline in the average of morning and evening rTNSS Secondary: Average morning and evening patient evaluated iTNSS, PANS score at end of treatment, combined RQLQ score at the end of treatment	Primary: Ciclesonide significantly reduced average morning and evening rTNSS compared to placebo (-2.51 vs -1.89; P<0.001). Secondary: Ciclesonide significantly reduced average morning and evening iTNSS through six weeks of therapy (P=0.001). A greater decrease from baseline was observed at the end of treatment in PANS scores for the ciclesonide group compared to the placebo group (P=0.051). There was a significant improvement seen in the ciclesonide group compared to placebo in combined RQLQ scores at the end of treatment (-1.30 vs -1.01; P=0.01).
Ratner et al.[24] (2006) Ciclesonide 200 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of SAR who require treatment and demonstrated skin prick test sensitivity to mountain cedar pollen	N=327 4 weeks	Primary: Change from baseline in average morning and evening rTNSS Secondary: Patient assessed iTNSS, PANS score at days 15 and 29, combined RQLQ scores at days 15 and 29, individual nasal symptoms, time to onset of effect and adverse events	Primary: Over two weeks, ciclesonide significantly improved the average morning and evening rTNSS compared to placebo (-2.40 vs -1.50; P<0.001). The change from baseline over the entire study period was significant for the ciclesonide group compared to placebo (P<0.001). Secondary: By two weeks, ciclesonide improved iTNSS compared to placebo (P<0.001). At day 15, treatment with ciclesonide provided significantly greater improvements in overall PANS and combined RQLQ scores compared to placebo (P≤0.002). By the end of the study, statistically significant differences were not seen between the ciclesonide and placebo groups (P value not reported). The ciclesonide group had a greater response in nonnasal symptom scores compared to placebo; however, this was not statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant (-1.73 vs -1.30; P=0.071). By day 15, treatment differences for nasal symptoms favoring ciclesonide were evident (P<0.001). Significant improvements in average morning and evening rTNSS with ciclesonide over placebo were seen by the second day of treatment (P<0.05). The frequency of adverse events was similar between the ciclesonide and placebo treatment groups (40.2 vs 39.3%, respectively; P value not reported). The most common adverse events for the ciclesonide group included nasal passage irritation (6.1%) and headache (5.5%).
Ratner et al.[25] (2010) Ciclesonide 80 µg QD (Zetonna®) vs ciclesonide 160 µg QD (Zetonna®) vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with SAR to for ≥2 years and a sensitivity to mountain cedar pollen through a standard skin prick test	N=777 2 weeks	Primary: Change from baseline in rTNSS Secondary: Change from baseline in iTNSS, rTOSS, iTOSS, individual symptom scores, RQLQ and safety	Primary: The 80 and 160 µg treatment groups experienced a 15.1 and 16.0% reduction in rTNSS, respectively, compared to a 3.7% reduction for the placebo group (P<0.001 for both). Secondary: Patients randomized to receive 80 or 160 µg of ciclesonide experienced a 14.3 and 15.4% reduction, respectively, in iTNSS score compared to placebo (3.9%; P<0.001 for both). Both the 80 and 160 µg doses of ciclesonide were associated with statistically significant improvements in rTOSS compared to placebo (15.7 and 15.0 vs 6.8%, respectively; P<0.01). An improvement from baseline in iTOSS was also achieved with both 80 µg (P=0.008) and 160 µg (P=0.002) of ciclesonide compared to placebo. Furthermore, individual morning and evening reflective and instantaneous nasal symptom scores of nasal congestion, runny nose, sneezing, and nasal itching were significantly improved with 80 and 160 µg doses of ciclesonide compared to placebo (P<0.001 for both). Overall, both doses of ciclesonide were associated with statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant improvements in RQLQ scores from baseline compared to patients receiving placebo (P<0.001 for both). The incidence of adverse events was comparable between the ciclesonide treatment groups and placebo. The incidence of nasal erosions was 1.3% in the 80 µg treatment group and 0.9% in the 160 µg treatment groups. These erosions were assessed as mild in intensity and did not lead to discontinuation from the study.
Berger et al.[26] (abstract) (2012) Ciclesonide 74 µg QD (Zetonna®) vs ciclesonide 148 µg QD (Zetonna®) vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of PAR	N=1,111 26 weeks	Primary: Change from baseline in rTNSS, iTNSS, RQLQ and treatment-related adverse events Secondary: Not reported	Primary: Patients receiving the 74 or 148 µg ciclesonide dose experienced a statistically significant improvement from baseline in rTNSS compared to placebo (LS mean change of 0.65 and 0.52, respectively; P≤0.01 for both compared to placebo). The total scores for iTNSS were significantly improved with both the 74 and 148 µg ciclesonide doses compared to placebo (LS mean change of 0.51 and 0.42, respectively; P<0.05). Both ciclesonide doses were associated with statistically significant improvements in RQLQ scores compared to placebo over 26 weeks (P<0.01). The overall incidence of adverse events was comparable between the treatment groups. Secondary: Not reported
Ratner et al.[27] (abstract) (2012) Ciclesonide 74 µg QD (Zetonna®) vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of SAR from mountain cedar pollen	N=671 2 weeks	Primary: Change from baseline rTNSS, iTNSS, rTOSS and safety Secondary: Not reported	Primary: Patients randomized to either the 74 or 148 µg ciclesonide doses experienced a statistically significant improvement from baseline in rTNSS compared to placebo (LS mean change of 1.04 and 1.02, respectively; P≤0.01 for both compared to placebo). Patients who received either the 74 or 148 µg ciclesonide dose experienced significant improvements in iTNSS from baseline compared to the placebo group (LS mean change of 0.90 and 0.83

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ciclesonide 148 µg QD (Zetonna®) vs placebo				respectively; P<0.001 for both compared to placebo). Only the 74 µg ciclesonide treatment group experienced a statistically significant improvement in rTOSS compared to placebo (LS mean change of 0.52; P=0.0124). The overall incidence of adverse events was low and comparable between the treatment groups. Secondary: Not reported
Mohar et al.[28] (abstract) (2012) Ciclesonide 74 µg QD (Zetonna®) vs ciclesonide 148 µg QD (Zetonna®) vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of PAR	N=1,111 26 weeks	Primary: Change from baseline to six weeks in rTNSS, iTNSS, RQLQ scores and adverse events Secondary: Not reported	Primary: Patients randomized to either the 74 or 148 µg ciclesonide doses experienced a statistically significant improvement from baseline in rTNSS compared to placebo (LS mean change of 0.70 and 0.54, respectively; P≤0.01 for both). After six weeks of treatment, total iTNSS scores were significantly improved in both the 74 or 148 µg ciclesonide treatment groups compared to placebo (LS mean change of 0.58 and 0.42, respectively; P<0.05 for both). Six weeks of treatment with either dose of ciclesonide was associated with statistically significant improvements in RQLQ scores compared to placebo (P<0.01 for both). The overall incidence of adverse events was similar between the ciclesonide treatment groups and placebo over 26 weeks. Secondary: Not reported
LaForce et al.[29] (2009) Ciclesonide 300 µg QD (Zetonna®)	DB, MC, PC, PG, RCT Patients ≥12 years of age with SAR for ≥2 years and a	N=513 2 weeks	Primary: Change from baseline in rTNSS Secondary: Change from baseline	Primary: The change from baseline in rTNSS was 0.81 (95% CI, 0.32 to 1.29; P=0.001), 0.90 (95% CI, 0.40 to 1.39; P<0.001) and 0.66 (95% CI, 0.16 to 1.16; P=0.01) for the ciclesonide 300, 150 and 75 µg groups, respectively, compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ciclesonide 150 µg QD (Zetonna®) vs ciclesonide 75 µg QD (Zetonna®) vs placebo	sensitivity to grass or tree pollen via skin prick		in iTNSS, morning iTNSS, RQLQ, rNNSS, PNSS and safety	Secondary: All ciclesonide doses significantly improved the average morning and evening iTNSS during the study period compared to placebo. Treatment differences were 0.75 (95% CI, 0.26 to 1.23; P=0.002), 0.86 (95% CI, 0.36 to 1.35; P=0.001) and 0.75 (95% CI, 0.25 to 1.25; P=0.003) for the ciclesonide 300, 150 and 75 µg groups, respectively, compared to placebo. Treatment differences for the reduction in the morning iTNSS were 0.86 (95% CI, 0.36 to 1.35; P<0.001), 1.03 (95% CI, 0.52 to 1.53; P<0.001) and 0.88 (95% CI, 0.37 to 1.39; P<0.001) for the ciclesonide 300, 150 and 75 µg groups, respectively, compared to placebo. Statistically significant improvements in RQLQ scores occurred with ciclesonide 300 µg (0.54; 95% CI, 0.10 to 0.98; P=0.02) and 75 µg (0.61; 95% CI, 0.16 to 1.06; P=0.008) compared to placebo, but not for the 150 µg treatment group (0.38; 95% CI, -0.06 to 0.81; P=0.09). Significant improvements in PNSS scores occurred with ciclesonide 300 µg (0.91; 95% CI, 0.25 to 1.58; P=0.007), 150 µg (0.73; 95% CI, 0.05 to 1.40; P=0.04) and 75 µg (0.94; 95% CI, 0.25 to 1.62; P=0.007) compared to placebo. No differences in the type or severity of adverse events were reported between treatment groups. The most frequently reported adverse events were headache and nasal discomfort.
Ratner et al.[30] (2006) Ciclesonide 25 µg QD vs ciclesonide 50 µg QD	DB, MC, PC, PG, Phase II, RCT Adult patients 18 to 65 years of age with a ≥2-year history of SAR, experiencing nasal allergy symptoms,	N=726 2 weeks	Primary: Change from baseline in sum of morning and evening rTNSS Secondary: Change from baseline in the sum of morning and evening iTNSS and use of rescue medications	Primary: Ciclesonide 100 and 200 µg, significantly improved the sum of morning and evening rTNSS compared to placebo (P=0.04 and P=0.003). The average change from baseline in rTNSS was -4.2 for placebo and -4.8, -4.8, -5.3 and -5.8 for ciclesonide 25, 50, 100 and 200 µg, respectively. Secondary: Both ciclesonide 100 and 200 µg demonstrated greater improvements in iTNSS compared to placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ciclesonide 100 µg QD vs ciclesonide 200 µg QD vs placebo				There were no appreciable differences in the use of rescue medication, chlorpheniramine, across all treatment groups.
Fokkens et al.[31] (2007) Fluticasone furoate 110 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with SAR, and either a positive skin prick test to grass pollen or a positive in vitro test for specific IgE, within 12 months prior to the study	N=285 2 weeks	Primary: Mean change from baseline over the entire treatment period in daily rTNSS Secondary: Mean change from baseline over the entire treatment period in daily rTOSS, morning predose iTNSS, overall evaluation of response to therapy, mean change from baseline in RQLQ, iTOSS, daily reflective and instantaneous individual symptom scores, time to onset of action	Primary: The mean change from baseline in daily rTNSS over the treatment period was greater for fluticasone furoate as compared to placebo (-4.94 vs -3.18; P<0.001). Secondary: Fluticasone furoate was significantly more effective than placebo in improving daily rTOSS (-3.00 vs -2.26; P<0.001) as well as in improving morning predose iTNSS (-4.50 vs -2.60; P<0.001). In terms of overall response to therapy, 67% of patients receiving fluticasone furoate reported significant or moderate improvement, compared to 39% of patients given placebo (P<0.001). Overall RQLQ core decreased by 2.23 points in the fluticasone furoate group and by 1.53 points in the placebo group (P<0.001).
Gradman et al.[32] (2007)	DB, NI, PC, RCT, XO	N=58 2 weeks	Primary: Mean growth rate in lower-leg length	Primary: A prespecified cutoff of no more than -0.20 mm/week was determined to be NI. The treatment difference in adjusted mean lower-leg growth

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone furoate 110 µg QD vs placebo	Prepubertal children (6 to 11 years of age) with a diagnosis of PAR or SAR for ≥1 year, and either a positive skin prick test or a positive test for the specific IgE to an appropriate seasonal or perennial allergen		Secondary: Adverse events	rate between fluticasone furoate and placebo was -0.016 mm/week (95% CI, -0.13 to 0.10) demonstrating NI. Secondary: Reported adverse events were similar between the two groups.
Kaiser et al.[33] (2007) Fluticasone furoate 110 µg QD vs placebo	DB, PC, PG, RCT Patients ≥12 years of age with SAR caused by ragweed pollen, with seasonal allergy symptoms during each of the past two fall allergy seasons; positive skin prick test response to ragweed allergen within 12 months prior to start of study	N=299 2 weeks	Primary: Mean change from baseline over the entire treatment period in daily rTNSS Secondary: Mean change from baseline over the entire treatment period in daily rTOSS, morning predose iTNSS, overall evaluation of response to therapy, HRQL based on RQLQ	Primary: Fluticasone furoate significantly reduced nasal symptoms compared to placebo, with a treatment difference of -1.473 (P<0.001). Secondary: An observed difference of -0.600 (P=0.004) favoring fluticasone furoate over placebo was recorded for the mean change from baseline in daily rTOSS over the entire treatment period. Fluticasone furoate demonstrated a significant reduction in morning predose iTNSS of -1.375 compared to placebo (P<0.001). A total of 73% of patients receiving fluticasone furoate compared to 52% of placebo-treated patients reported improvement in their overall evaluation of response to therapy (P<0.01). Fluticasone furoate-treated patients reported significant improvements in the overall RQLQ score compared to patients in the placebo group (-0.606; P<0.001). Adverse events occurred in 21% of patients receiving fluticasone furoate and 12% of patients that received placebo. The most common adverse event was headache (>3%), which was seen more often with fluticasone furoate than placebo; epistaxis was also commonly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported.
Nathan et al.[34] (2008) Fluticasone furoate 110 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with PAR and a positive result to a skin prick test within 12 months of study entry or at study entry	N=455 4 weeks	Primary: Change from baseline in daily rTNSS Secondary: Change from baseline in AM predose iTNSS, AM and PM rTNSS, individual nasal symptoms, ocular symptoms, itching, QoL and response to therapy	Primary: The LS mean change from baseline during the treatment period in daily rTNSS was significantly greater in fluticasone furoate-treated patients compared to patients receiving placebo (treatment difference, -0.706; P=0.005). Secondary: The LS mean change from baseline in AM predose iTNSS during the entire treatment period was significantly greater in the fluticasone furoate treatment group compared to placebo (treatment difference, -0.705; P=0.006). Patients treated with fluticasone furoate experienced a significantly greater mean reduction in morning rTNSS (P=0.004) and evening rTNSS (P=0.011) compared to patients randomized to placebo. The changes from baseline in AM and PM rTNSS scores for rhinorrhea, sneezing and nasal itching were significantly greater with fluticasone furoate treatment compared to placebo (P≤0.05 for all). There was no difference between treatments with regard to ocular symptoms. A significantly higher percentage of patients treated with fluticasone furoate reported treatment to be effective compared to patients receiving placebo (P=0.005).
Okubo et al.[35] (2014) Fluticasone furoate 55 µg QD vs placebo	DB, MC, PC, RCT Japanese patients aged 6 to <15 years with a history of PAR for one year or more, and positive for both a specific IgE antibody test	N=261 2 weeks	Primary: Mean change from baseline in 3TNSS Secondary: 3 TNSS, 4 TNSS, TOSS, overall evaluation of response to therapy	Primary: The 3TNSS was greater for fluticasone furoate (-1.98) than for placebo (-0.89), and the difference (-1.089) was significant (P<0.001). Secondary: A significant treatment difference in mean change from baseline for 3TNSS was first observed on day 2 (P<0.001) for treatment compared with placebo. Treatment significantly improved all four individual nasal symptoms assessed and the 4TNSS compared with placebo in terms of the LS mean change from baseline in Weeks 1, 2, and over the entire treatment period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	to a PAR allergen (house dust mite or house dust) and nasal eosinophil counts, and with the three TNSS of 4 to <8 at baseline			TOSS was reduced significantly in the treatment group compared with placebo in the second week and reduced numerically but not significantly in the first week. A significantly greater decrease in the mean change from baseline over the entire treatment period with respect to the score for troubles with daily life was observed in the treatment group compared with placebo (LS mean difference: -0.302; 95% CI, -0.42 to -0.19; P<0.001). A greater percentage of patients receiving fluticasone furoate (parent/guardian/patient: 21%, investigator: 24%) rated the overall response to therapy as "significantly improved" compared with patients receiving placebo (parent/guardian/patient: 2%, investigator: 9%). Adverse events reported during the study were of mild or moderate intensity and of similar type and frequency across the two treatment groups.
Meltzer et al.[36] (2009) Fluticasone furoate 110 µg QD vs fluticasone furoate 55 µg QD vs placebo	DB, MD, PC, PG, RCT Patients 2 to 11 years of age with symptoms of SAR in the previous allergy season with a positive skin prick test for a specific IgE within previous 12 months	N=554 2 weeks	Primary: Change from baseline in daily rTNSS Secondary: Change from baseline in AM predose iTNSS, response to therapy, adverse events, laboratory tests, nasal examinations, vital signs and ECG	Primary: The change from baseline during the treatment period in daily rTNSS was significantly greater in the fluticasone furoate 110 µg treatment group compared to placebo (-3.16 vs -2.54; P=0.025). Patients receiving the 55 µg dose of fluticasone furoate experienced a numerically greater reduction in daily rTNSS compare to placebo (-2.71 vs -2.54), although this was not statistically significant (P=0.553). Secondary: The mean change in AM predose iTNSS was significantly greater for fluticasone furoate 110 µg compared to placebo (-2.80 vs -2.13; P=0.015), but not for the 55 µg fluticasone furoate dose (P value not reported). The overall response to therapy was significantly higher for the fluticasone furoate 110 µg treatment group compared to placebo (P<0.001), but not for the fluticasone furoate 55 µg treatment group compared to placebo (P=0.083). Adverse events were similar among treatment groups; however, the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				incidence was higher with the fluticasone 110 and 55 µg doses compared to placebo (30 vs 20%; P value not reported). There were no differences in laboratory tests or vital signs between the three treatment groups. The findings from nasal examinations and ECGs were similar between the treatment groups.
Maspero et al.[37] (2008) Fluticasone furoate 110 µg QD vs fluticasone furoate 55 µg QD vs placebo	DB, MC, PC, PG, RCT Pediatric patients 2 to 11 years of age with a ≥6 month history PAR documented by a positive skin prick test against an appropriate perennial allergen	N=558 12 weeks	Primary: Mean change from baseline in daily rTNSS over four weeks Secondary: Mean change from baseline in daily iTNSS, overall response to therapy and safety	Primary: Improvements in daily rTNSS over four weeks were not statistically significant compared to placebo for the fluticasone furoate 110 µg group (-0.452; P=0.073). Patients treated with fluticasone furoate 55 µg had statistically significant improvements in daily rTNSS compared to placebo (-0.754; P=0.003). Secondary: Both fluticasone furoate 55 (-0.751) and 110 µg (-0.651) demonstrated significant improvements from baseline in daily iTNSS compared to placebo (P=0.002 and P=0.009). Treatment differences, determined by overall response to therapy, were not significant for patients in the fluticasone furoate 110 µg group compared to placebo (P=0.414) but were significant for the fluticasone furoate 55 µg group (P=0.024). Treatment with both doses of fluticasone furoate was well-tolerated over the 12-week period. Nasal examinations were similar across all three treatment groups and ophthalmic examinations revealed no differences between groups in terms of mean change from baseline intraocular pressure in each eye. Treatment differences for mean change from baseline in 24 hour urinary cortisol excretion from placebo at either dose of fluticasone furoate were not statistically significant (P value not reported).
Martin et al.[38] (2007) Fluticasone furoate 55 µg QD	DB, PC, PG, RCT Patients ≥12 years of age with SAR during the past 2 mountain cedar	N=642 14 days	Primary: Mean change from baseline in daily rTNSS Secondary: Mean change from	Primary: Fluticasone furoate 55, 110, 220 and 440 µg demonstrated statistically significant improvements with respect to the mean change from baseline in daily rTNSS compared to placebo (P<0.001 for all). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone furoate 110 µg QD vs fluticasone furoate 220 µg QD vs fluticasone furoate 440 µg QD vs placebo	allergy seasons and a positive skin test to mountain cedar allergy		baseline in morning predose iTNSS, mean change from baseline in daily rTOSS and iTOSS, mean change from baseline in morning and evening rTNSS and iTNSS and overall response to therapy	Fluticasone furoate was significantly more effective than placebo for mean changes from baseline in morning predose iTNSS (P<0.001 each dose vs placebo), daily rTOSS (P≤0.013 each dose vs placebo), and iTOSS (P≤0.019 for all). Over the entire treatment period, all doses of fluticasone furoate demonstrated significantly greater efficacy compared to placebo with regards to morning and evening rTNSS and iTNSS scores (P<0.001 for all). At the end of the treatment period, patients treated with fluticasone furoate rated their overall response to therapy significantly better than those treated with placebo (P<0.001).
Rosenblut et al.[39] (2007) Fluticasone furoate 110 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-history of PAR and a positive skin-prick test to an appropriate allergen either within the last 12 months prior to or at screening	N=806 12 months	Primary: Safety and tolerability based on adverse event data graded by severity (mild, moderate, or severe) as well as through the use of 24-hour urine samples, ECG, other laboratory measures and eye examinations Secondary: Not reported	Primary: Adverse events occurred in 77% of fluticasone furoate-treated patients and 71% of patients receiving placebo, where most were mild to moderate in intensity. The most frequently reported adverse events were headache and nasopharyngitis. Epistaxis was more frequently reported with patients treated with fluticasone furoate. There was no evidence of clinically relevant systemic corticosteroid exposure or impairment of HPA-axis function. Fluticasone furoate-treated patients had similar 24-hour urine cortisol results to those receiving placebo. There were no clinically meaningful differences between the groups in terms of other safety assessments, including mean changes in ophthalmic parameters.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Vasar et al.[40] (2008) Fluticasone furoate 110 µg QD vs placebo	DB, PC, PG, RCT Patients ≥12 years of age with a history of PAR for ≥2 years and a positive skin-prick test to an appropriate perennial allergen	N=302 6 weeks	Primary: Mean change from baseline in rTNSS Secondary: Mean change from baseline in morning predose iTNSS, daily rTNSS, daily PNIF, and RQLQ scores, overall response to therapy and safety	Primary: The mean change from baseline in rTNSS was significantly greater in the fluticasone furoate group compared to placebo (-3.95 vs -2.69; P<0.001). Secondary: The mean change from baseline in morning predose iTNSS was significantly greater in fluticasone furoate patients compared to placebo (-3.82 vs -2.36; P<0.001). Treatment with fluticasone furoate demonstrated significantly greater efficacy compared to placebo in terms of improvements in daily iTNSS (P=0.004), PNIF (P=0.004) and overall RQLQ scores (P<0.001). Thirty seven percent of patients treated with fluticasone furoate rated their overall response to therapy as "significantly improved" compared to 14% of patients treated with placebo (P<0.001). Treatment was well tolerated over the six week period.
Prenner et al.[41] (2010) Mometasone 100 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with SAR for ≥2 years, a positive skin prick test response and clinically symptomatic at screening	N=429 15 days	Primary: Change from baseline in iTOSS and iTNSS Secondary: Change from baseline in daily rTOSS and rTNSS, instantaneous nasal congestions scores, RQLQ, change from baseline in instantaneous and reflective individual symptom scores, subject and investigator	Primary: A significant reduction in iTOSS was observed in the mometasone group compared to placebo (P=0.026). A reduction in iTNSS was observed in the mometasone group compared to placebo (P<0.001). Secondary: A significant reduction in the LS mean change from baseline in rTOSS was observed in the mometasone group compared to placebo (P=0.005). A significant reduction in the LS mean change from baseline in rTNSS was observed in the mometasone group compared to placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			evaluations of overall condition and therapeutic response	A significant improvement in instantaneous ocular symptoms of itching/burning and watering/tearing was observed in the mometasone group compared to placebo (P<0.05). No significant difference was observed in the instantaneous eye redness score. A significant improvement in individual reflective ocular symptom scores was observed in the mometasone group compared to placebo (P<0.05). A significant improvement in all individual instantaneous and reflective nasal symptoms scores was observed in the mometasone group compared to placebo (P<0.05). Greater improvements in overall SAR condition from baseline were observed in the mometasone group compared to placebo as rated by investigators and subjects (P<0.001 for both). Greater improvements in the RQLQ were observed in the mometasone group compared to placebo (P<0.001). The mometasone group showed a significantly greater response to therapy compared to the placebo group as rated by both investigators and subjects (P<0.001).
Makihara et al.[42] (2012) Mometasone 200 µg QD vs placebo	DB, PC, PG, RCT Patients 16 to 65 years of age with a ≥2 year history of Japanese cedar/cypress pollinosis sensitivity assessed by skin price	N=50 12 weeks	Primary: Change from baseline in TNSS Secondary: Change from baseline in TOSS, T5SS, QoL, daytime sleepiness, smell disturbances, frequency of rescue medication use, ECP	Primary: Compared to the placebo group, TNSS scores were significantly lower in the mometasone treatment group following 12 weeks of treatment (P<0.05). Secondary: After 12 weeks of treatment, there was no statistically significant difference between the mometasone and placebo treatment groups with regard to TOSS (P=NS). Compared to placebo, mometasone was associated with a statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			levels in nasal secretions and safety	significant reduction in T5SS at 12 weeks (P<0.05). A statistically significant improvement in QoL occurred with mometasone compared to placebo at weeks two through 10 (P<0.05); however, the difference was not significant at week 12. There was no statistically significant difference between mometasone and placebo with regard to daytime sleepiness and smell disturbances at 12 weeks (P>0.05). No difference in rescue medication use with loratadine was reported between the treatment groups (P>0.05). At 12 weeks, there was no statistically significant difference between treatment groups with regard to nasal secretion levels of ECP (P=0.063). There was no difference in the rate of adverse events between the treatments. There were no patients that discontinued the study medication due to adverse events.
Baena-Cagnani et al.[43] (2010) Mometasone 100 µg QD vs placebo	DB, MC, PC, PG, RCT Patients 3 to 11 years of age with ≥1 year history of PAR requiring over-the-counter or prescription treatment and a positive skin prick test to one clinically significant perennial allergen	N=381 4 week efficacy phase followed by 6 month OL safety period	Primary: Change from baseline to day 15 in physician assessed TNSS Secondary: Change from baseline to day 15 in subject assessed TNSS, TSS, TNNSS, individual symptom scores and condition of PAR between baseline and endpoint	Primary: Patients randomized to mometasone experienced a significantly greater reduction in physician-assessed change in TNSS at day 15 compared to patients receiving placebo (-2.8 [-39%] vs -2.2 [-32%]; P=0.02). The changes in TNSS were also significant in favor of mometasone at days eight and 29 (P≤0.02 for both). Secondary: A significantly greater improvement in subject-assessed TNSS scores at day 15 occurred with mometasone compared to placebo (-1.7 [-28%] vs -1.1 [-18%]; P≤0.01). Mometasone treatment was associated with lower subject-assessed TSS scores at day 15 compared to placebo (-2.1 [-27%] vs -1.4 [-16%]; P<0.001). At day 15, subject assessed TNNSS scores were not significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				different between the treatment groups. Subject evaluations of all individual nasal symptom scores showed significantly greater improvement with mometasone compared to placebo over the first 15 days (P≤0.03 for all). Physician evaluation of the patients' condition favored mometasone treatment over placebo at both day 15 (P<0.01) and 29 (P=0.02).
Weinstein et al.[44] (2009) Triamcinolone 110 µg, 1 spray per nostril QD vs placebo	DB, MC, PG, RCT Patients 2 to 5 years of age with at least 1 year history of PAR	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).
Svendsen et al.[45] (1989) Beclomethasone vs flunisolide	DB, RCT, XO Patients with PAR	N=23 8 weeks	Primary: Rhinitis symptoms and patient preference Secondary: Not reported	Primary: There were no statistically significant differences in rhinitis symptoms or patient preference between treatments (P value not reported). Secondary: Not reported
Al-Mohaimeid et al.[46] (1993) Budesonide 200 µg BID vs	RCT, SB Patients 18 to 70 years of age with PAR	N=120 3 weeks	Primary: Nasal symptoms Secondary: Not reported	Primary: There were significantly fewer reports of sneezing with budesonide compared to beclomethasone (P=0.04). No statistically significant differences in symptoms of blocked nose, runny nose, itchy nose, runny eyes and sore eyes were reported (P>0.05). After three weeks of treatment, more patients reported being free of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
beclomethasone 200 µg BID				symptoms with budesonide compared to beclomethasone (38 vs 27%; P value not reported). More patients reported the treatment as noticeably, very, or totally effective with budesonide than with beclomethasone (72 vs 58%; P value not reported). Secondary: Not reported
McArthur et al.[47] (1994) Budesonide 200 µg BID vs beclomethasone 200 µg BID	DB, RCT Adults with SAR	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 to beclomethasone at all time points (P<0.05), but the greatest difference occurred at 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 (P value not reported). Secondary: Adverse events for both treatments were mild and transient.
Vanzieleghem et al.[48] (1987) Budesonide as needed, up to 2 sprays of 50 µg/spray in each nostril QID vs beclomethasone as needed, up to 2 sprays of 50 µg/spray in each	DB, DD, RCT Patients with SAR 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nostril QID				
Andersson et al.[49] (1995) Budesonide 200 or 400 µg QD vs fluticasone propionate 200 µg QD vs placebo	MC, PC, PG, RCT Patients with PAR	N=98 6 weeks	Primary: Rhinitis symptoms, use of terfenadine as rescue medication Secondary: Safety as assessed by rhinoscopy, urine cortisol and adverse events	Primary: There were no significant differences in nasal symptoms or eye symptoms between active treatment groups (P value not reported). All active treatments reduced terfenadine use compared to baseline, but this was 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 (P value not reported).
Day et al.[50] (1998) Budesonide 256 µg QD vs fluticasone propionate 200 µg QD	DB, MC, PC, PG, RCT Patients ≥18 years of age with ≥1 year history of PAR 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 to placebo (P≤0.0012). Budesonide showed greater improvement in combined nasal symptom scores (P=0.031) and nasal blockage (P value not reported) than fluticasone propionate, but no statistically significant differences in runny nose or sneezing symptoms were detected (P value not reported). Significant improvements in nasal symptoms were seen at 36 hours with budesonide and 60 hours with fluticasone propionate (P value not reported). At six 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 (no P values reported) between treatment groups. Secondary: The rates of reported adverse events were 46% with budesonide, 37% with fluticasone propionate and 36% with placebo (P values not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). No signs of fungal infection were detected in the study population.
Shah et al.[51] (2003) Study 1: Budesonide 32 µg in each nostril for one dose vs fluticasone propionate 100 µg in each nostril for one dose Study 2: Budesonide 32 µg in each nostril for one dose vs fluticasone propionate 50 µg in each nostril for one dose	MC, RCT, SB, XO Patients ≥18 years of age with ≥1year history of allergic rhinitis and experiencing mild to moderate symptoms	N=181 (Study 1) N=190 (Study 2) 1 day	Primary: Sensory Perceptions Questionnaire and patients' product preference Secondary: Adverse events	Primary: In study one, 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 propionate. In study two, significantly fewer patients detected an altered scent or taste with budesonide compared to fluticasone propionate (P<0.001). There were no significant differences between budesonide and fluticasone propionate in aftertaste, throat rundown, and nose run out. More patients perceived the spray in the throat as less wet (P<0.004 for study one and P<0.002 for study two) and therefore preferred the feel of the spray in the throat (P<0.001 for both studies) of budesonide to that of fluticasone propionate. 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 propionate. Significantly more patients perceived a less forceful spray with budesonide and therefore preferred budesonide to fluticasone propionate (P<0.001). Overall, significantly more patients preferred budesonide compared to fluticasone propionate (P=0.02). Secondary: Budesonide and fluticasone propionate were both well tolerated.
Stern et al.[52] (1997) Budesonide 128 µg or 256 µg QD	MC, PC, PG, RCT Patients 18 to 72 years of age, with ≥2-year history of	N=635 4 to 6 weeks	Primary: Nasal and eye symptoms Secondary: Adverse events	Primary: Budesonide and fluticasone propionate treatment resulted in significant improvements in individual nasal symptoms such as blocked nose, runny nose, sneezing (P<0.001), combined nasal symptoms (P<0.001), eye symptoms (P value not reported) and overall substantial or total control of symptoms (P<0.001) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone propionate 200 µg QD vs placebo	allergic rhinitis			Budesonide produced a significant reduction in sneezing compared to fluticasone propionate (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 (P values not reported). Secondary: Budesonide and fluticasone propionate were well tolerated, with reported adverse events mild to moderate in severity.
Naclerio et al.[53] (2003) Budesonide 32 µg in each nostril QD vs mometasone 100 µg in each nostril QD	PG, RCT Patients >18 years of age with PAR, who were symptomatic on the majority of days of each year and had a positive skin test to dust mites	N=20 2 weeks	Primary: Symptomatic relief and QoL as assessed by the RQLQ and nasal clearance Secondary: Not reported	Primary: The RQLQ scores demonstrated that both budesonide and mometasone resulted in a significant improvement in QoL compared to baseline (P value not reported). There were no significant differences between treatment groups for any of the individual domains in the RQLQ (P value not reported). Data on nasal clearance could not be interpreted by the authors. Secondary: Not reported
Varshney et al.[54] (2012) Ciclesonide 200 µg once vs fluticasone propionate 200 µg once	DB, RCT, XO Patients ≥12 years of age with allergic rhinitis for ≥1 year	N=74 1 day	Primary: Sensory attributes, TNSS, patient preference and adverse events Secondary: Not reported	Primary: Significantly more patients preferred fluticasone propionate compared to ciclesonide with regard to satisfying scent (50.00 vs 8.11%; P<0.001) and "providing a more soothing feel" (56.76 vs 20.27%; P<0.001). Moreover, significantly fewer patients treated with fluticasone propionate compared to ciclesonide reported nasal irritation (1.35 vs 28.38%; P=0.002). The number of patients reporting immediate taste, aftertaste, run down to throat and run off from nose were less with ciclesonide compared to fluticasone propionate; however, the difference was not statistically significant. Treatment with either ciclesonide or fluticasone propionate decreased TNSS compared to baseline, as well as individual symptom scores in majority of the subjects, within 10 minutes of administration. The median (interquartile range) TNSS declined from eight (seven to nine) at baseline to three (two to four) following administration in patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treated with ciclesonide first. In the fluticasone first group, the corresponding decline was from eight (six to 10) to two (two to four). This difference was not statistically significant. Differences were also not significant when the proportions reporting decrease in individual symptom scores, rather than total score, were compared. Significantly more patients preferred treatment with fluticasone propionate compared to treatment with ciclesonide (55.41 vs 25.68%; P=0.007). Not all patients reported a preference for treatment. Overall, 9.46% of patients reported adverse events. Two patients reported minor headache following ciclesonide first, while three felt minor headache, one dizziness, and one nasal congestion following initial treatment with fluticasone propionate. No delayed adverse events were reported at the 24 hour follow-up interview. Secondary: Not reported
Aasand et al.[55] (1982) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	MC, PG, SB Patients with ≥2-year history of SAR	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; P value not reported). Secondary: The only reported adverse event with both medications was mild stinging of transient duration.
Langrick et al.[56] (1984) Flunisolide 200 µg daily, administered as 2 sprays in each	PG, RCT, SB Patients 18 to 60 years 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	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 (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nostril BID vs beclomethasone 400 µg daily, administered as 2 sprays in each nostril BID			treatment Secondary: Adverse events	One patient in the flunisolide group reported a dry throat of moderate severity. One patient in the beclomethasone group reported a mild tickling sensation inside the nose.
McAllen et al.[57] (1980) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	SB, XO Patients 19 to 58 years with PAR with or without seasonal exacerbations and had moderate to severe symptoms	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 to baseline (P value not reported). There were no statistical differences between the flunisolide and beclomethasone treatment groups in nasal symptoms, physicians' and patients' preference, and interference with routine life (P value not reported). Secondary: Neither treatment resulted in Candida growth. Adverse events were minor and were mostly nasal irritation or dryness.
Sahay et al.[58] (1980) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	OL, PG Patients with PAR, with or without SAR	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 compared to baseline (P<0.01 for all). There were no statistically significant differences in control of symptoms between the two treatment groups (P value not reported). Secondary: There were no signs of adrenal suppression or Candida growth in either group. There were four adverse events in the flunisolide group and five in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				beclomethasone group that were considered to be probably drug related (P value not reported).
Sipila et al.[59] (1983) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	OL, PG Patients with allergic rhinitis and seasonal symptoms for ≥2 years	N=45 4 weeks	Primary: Daily symptoms and severity of nasal symptoms Secondary: Adverse events	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 (P value not reported). Improvement in the severity of nasal symptoms compared with baseline was similar in both treatment groups (P value not reported). Secondary: The reported adverse events were mild and primarily consisted of local irritation.
Kubavat et al.[60] (2011) Fluticasone furoate 110 µg QD vs fluticasone propionate 200 µg QD	AC, MC, OL Patients ≥18 years of age with complaints of allergic rhinitis with nasal/ocular symptoms	N=220 2 weeks	Primary: Change from baseline in TSS Secondary: Change from baseline in TNSS and TOSS, individual nasal and ocular symptoms	Primary: The mean change in TSS score was significantly greater for patients receiving fluticasone furoate compared to fluticasone propionate over two weeks (-10.4 vs -8.9; P<0.005). A significantly greater proportion of patients experienced complete relief from all nasal and ocular symptoms (i.e. a TSS of zero during the course of the study) with fluticasone furoate treatment compared to fluticasone propionate (45.3 vs 31.4%; P<0.05). Secondary; A statistically significant reduction in TNSS occurred with fluticasone furoate treatment compared to fluticasone propionate (-7.3 vs -6.2; P<0.05). There was no statistically significant difference in TOSS between fluticasone furoate treatment and fluticasone propionate following two weeks of treatment (-3.1 vs -2.7; P=NS). There were statistically significant improvements in symptom scores with fluticasone furoate compared to fluticasone propionate for nasal congestion (P<0.05), nasal itching (P<0.001) and tearing/watery eyes (P<0.05). There were no other statistically significant differences in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				individual symptom scores between the treatments (P=NS).
Meltzer et al.[61] (2010) Fluticasone furoate 100 µg QD for 1 week vs fluticasone propionate 200 µg QD for 1 week vs placebo	DB, PC, RCT, XO Patients ≥18 years of age with SAR and nasal symptoms during previous fall allergy seasons and a positive skin test result and exposure to fall allergens	N=360 21 days	Primary: Patient preference at the end of the second XO period based on scent or odor Secondary: Patient preference at the end of the second XO period based on leaking out of the nose and down the throat, ease of use, and gentleness of mist, delivery of consistent dose/use, comfort of nose tip, spray delivery method, aftertaste and TNSS	Primary: Twice as many patients preferred fluticasone furoate compared to fluticasone propionate based on scent or odor (P<0.001). Fifteen percent of patients had no preference for either product based on scent or odor. Secondary: Significantly more patients preferred fluticasone furoate compared to fluticasone propionate based on medication leaking out of the nose and down the throat, gentleness of the mist, and less aftertaste (P<0.001). No statistically significant differences were observed between products in ease of use, consistency of medication dose delivered, delivery method or device comfort. The TNSS were similar between treatment groups. Fluticasone furoate and fluticasone propionate significantly reduced TNSS compared to their respective placebo (P≤0.01). The proportion of patients with any adverse event was similar between treatments.
Meltzer et al.[62] (2008) Fluticasone furoate 110 µg as a single dose (FF) vs fluticasone propionate 200 µg as a single dose (FP)	DB, MC, RCT, XO Patients ≥18 years of age with allergic rhinitis	N=127 1 day	Primary: Overall patient preference Secondary: Patient preference for individual sensory attributes and their ratings	Primary: Significantly more patients favored fluticasone furoate compared to fluticasone propionate (P=0.003). Secondary: Significantly more patients favored fluticasone furoate compared to fluticasone propionate based on odor, taste, aftertaste drip down the throat and nose runoff (P≤0.037 for all). No significant differences were observed between groups with respect to whether the medication felt soothing, caused nasal irritation or caused sneezing.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A ten minute washout period occurred between XO treatments.				
Haye et al.[63] (1993) Fluticasone propionate 200 µg BID vs beclomethasone 200 µg BID	DB, MC, PG, RCT Patients ≥16 years of age with PAR	N=251 1 year	Primary: Rhinitis symptoms Secondary: Safety	Primary: Fluticasone propionate treatment resulted in significantly less nasal blockage (P=0.002), nasal discharge (P=0.002) and eye watering/irritation (P=0.048) compared to 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 (P value not reported), nasal examination by rhinoscopy, hematologic, biochemical, and urinary parameters, plasma cortisol level or adverse events (P values not reported) between treatment groups.
LaForce et al.[64] (1994) Fluticasone propionate 100 µg BID or 200 µg QD vs beclomethasone 168 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with ≥2-year history of SAR, who have positive skin test to ≥1 spring allergen and moderate to severe symptoms	N=238 4 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: Fluticasone propionate reduced patient-rated nasal symptom scores significantly more 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 (P value not reported).
Ratner et al.[65] (1992)	DB, MC, PC, PG, RCT	N=313 2 weeks	Primary: Nasal symptoms, overall response to	Primary: Significant improvements in nasal symptoms and overall response to treatment were seen with fluticasone propionate and beclomethasone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone propionate 200 µg QD vs beclomethasone 168 µg BID vs placebo	Adult patients with ≥2-year history of SAR and moderate to severe symptoms and positive skin test to mountain cedar		treatment, and use of rescue medication (chlorpheniramine) Secondary: Adverse events	compared to placebo as evaluated by the clinicians and patients (P<0.05 for all). There were no statistically significant differences between treatment groups in nasal symptoms as rated by the clinicians or the patients or overall response to treatment (P value not reported). Compared to placebo, there was a significant reduction in the use of rescue medication with fluticasone propionate and beclomethasone (P<0.05). There was no statistically significant difference between treatment groups in the amount of rescue medication used (P value not reported). Secondary: No clinically significant differences in any of the safety variables between treatment groups were reported.
Van As et al.[66] (1993) Fluticasone propionate 100 µg BID or 200 µg QD vs beclomethasone 168 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 to 71 years of age, with PAR 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 propionate and beclomethasone reduced nasal obstruction, rhinorrhea, sneezing, nasal itching and nasal eosinophilia compared to placebo (P value not reported). 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 (P value not reported). Secondary: No evidence of systemic effects with drug treatment was reported.
Okubo et al.[67] (2009) Fluticasone furoate 110 µg	DB, MC, PC, PG, RCT Patients ≥16 years of age with cedar	N=446 2 weeks	Primary: Mean change in 3TNSS (the sum of three individual symptom scores for sneezing,	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD (FFNS) vs fluticasone propionate 100 µg BID (FPNS) vs placebo	pollinosis		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 Secondary: Not reported	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 two 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. Secondary: Not reported
Bachert et al.[68] (2004) Fluticasone propionate 200 µg QD vs triamcinolone 220 µg QD vs	DB, PC, RCT, XO Healthy volunteers 18 to 65 years of age	N=23 12 days	Primary: Suppression of the HPA axis as measured by 12-hour overnight urinary cortisol excretion and serum cortisol concentrations Secondary: Adverse events	Primary: Overnight urinary cortisol concentrations showed that there was no significant difference in HPA axis suppression with fluticasone propionate (P=0.609) or triamcinolone (P=0.194) compared to placebo. Neither fluticasone propionate (P=0.999) nor triamcinolone (P=0.521) showed a significant effect on the HPA axis activity when compared to placebo, as assessed by the mean peak serum cortisol concentrations before and after ACTH stimulation. Secondary: Both medications were well-tolerated. There were no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				differences in the number of subjects who experienced adverse events between treatment groups (one with fluticasone propionate, two with triamcinolone, three with placebo; P value not reported).
Ratner et al.[69] (2009) Mometasone 100 µg QD vs beclomethasone 168 µg QD	MC, SB, SC Children 6 to 11 years of age with ≥1 year history of PAR	N=255 12 months	Primary: Changes in overall PAR symptoms and response to treatment, as well as safety Secondary: Not reported	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. 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 HPA axis suppression in children. Secondary: Not reported
Drouin et al.[70] (1996) Mometasone 100 µg in each nostril QD vs beclomethasone 100 µg in each nostril BID vs placebo	DB, DD, MC, PC, PG, RCT Patients ≥12 years of age who were allergic to ≥1 perennial allergen, with adequate symptomatology	N=427 12 weeks	Primary: Change from baseline in TNSS over the first 15 days of treatment Secondary: TNSS 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 TNSS 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 (P value not reported). The rates of adverse events were similar for all groups (43% for mometasone, 42% for beclomethasone and 36% for placebo; P value

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not reported).
Graft et al.[71] (1996) Mometasone 100 µg in each nostril QD vs beclomethasone 84 µg in each nostril BID vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of moderate to severe SAR 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 TNSS compared with placebo (P≤0.01 for all). There was no statistically significant difference in the percentage of days with minimal symptoms between treatment groups (P value not reported). Nasal symptom scores for the treatment period prior to the allergy season onset were significantly lower with mometasone than beclomethasone (P=0.05). Secondary: The percentage of patients experiencing at least one adverse event that was considered possibly related to treatment was: 16% of the mometasone group, 14% of the beclomethasone group and 19% of the placebo group (P value not reported). The adverse events were generally mild to moderate and of short duration.
Hebert et al.[72] (1996) Mometasone 100 to 200 µg QD, administered as 2 sprays of 25 or 50 µg/spray in each nostril QD vs beclomethasone 100 µg in each nostril BID	DB, DD, MC, PC, PG, RCT Patients ≥18 years of age with moderate to severe SAR who have a positive skin test to ≥1 tree and/or grass aeroallergen	N=501 4 weeks	Primary: Nasal symptom score, physicians' and patients' evaluation of response to therapy, and use of loratadine as rescue medication Secondary: Adverse events	Primary: Nasal symptoms (P≤0.01) and use of rescue medication (P≤0.05) were significantly improved in all three treatment groups compared to placebo. There were no significant differences between treatment groups in nasal symptom score, physicians' evaluation of nasal symptoms, overall condition, and response to treatment, or use of rescue medication (P value not reported). Secondary: The rate of adverse events were similar in all groups (25% with mometasone 100 µg, 26% with mometasone 200 µg, 30% with beclomethasone, 28% with placebo; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				
Mandl et al.[73] (1997) Mometasone 100 µg in each nostril QD vs fluticasone propionate 100 µg in each nostril QD vs placebo	DB, DD, PC, PG, RCT Patients 12 to 77 years of age, who are allergic to ≥1 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 propionate produced significantly greater improvements in nasal symptoms compared to placebo (P<0.01). The difference in reduction of nasal symptom score between mometasone and fluticasone propionate was not significant at any time point (-37 vs -39%, respectively; P≥0.43). Secondary: Physicians' evaluation of nasal symptoms and response to therapy were similar for mometasone and fluticasone propionate (P value not reported). The rates of adverse events were similar for all groups (33% for mometasone, 38% for fluticasone propionate and 37% for placebo; P value not reported).
Meltzer et al.[74] (2005) Mometasone vs fluticasone propionate 200 µg	DB, RCT, XO Patients with allergic rhinitis	N=100 Duration not specified	Primary: Individual product sensory attributes and overall sensory preference Secondary: Not reported	Primary: Significantly more patients preferred mometasone to fluticasone propionate 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 propionate 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 propionate (47 vs 25%; P=0.03). Secondary: Not reported
Mak et al.[75]	AC, PRO, RCT	N=94	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2013) Mometasone 100 µg QD vs fluticasone propionate 100 µg QD	Children 6 to 12 years of age with PAR for ≥2 years, a positive reaction to mite-specific IgE and allergy to dust mites confirmed by skin response to test	4 weeks	Change in TSS, PRQLQ, nPEFR and eosinophil percentage Secondary: Not reported	Patients treated with mometasone experienced statistically significant improvements in TSS for rhinorrhea (P=0.035), nasal stuffiness (P=0.029), nasal itching (P=0.031) and sneezing (P=0.009) compared to baseline. No significant improvements in nonnasal symptoms were reported (throat itching, eye itching, tearing and eye congestion; P>0.05 for all). Fluticasone propionate treatment significantly improved symptoms of nasal itching compared to baseline (P=0.007); however, no significant improvements in rhinorrhea, nasal stuffiness or nasal itching were reported (P>0.05 for all). Significant improvements in eye itching were also reported (P=0.014). Patients in both treatment groups experienced significant reductions from baseline in PRQLQ scores (P<0.01); however, the difference between the treatment groups was not statistically significant (P=0.224). The mometasone group exhibited a significant improvement on the PRQLQ for all symptoms with the exception of swollen eyes (P=0.148) and sore eyes (P=0.086), thirst (P=0.056) and tiredness (P=0.09). The fluticasone propionate group also showed improvement in all categories excluding watery eyes (P=0.054) and sore eyes (P=0.291). Only the mometasone treatment group experienced a significant improvement in nPEFR at four weeks compared to baseline (P<0.05). There were statistically significant improvements from baseline in eosinophil percentage in nasal smears for both the mometasone (from 54.68±16.10 at baseline to 39.30±15.09; P<0.01) and fluticasone propionate (from 59.08±16.38 at baseline to 40.92±14.84; P<0.01). No significant differences were observed between the two groups (P=0.26). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lumry et al.[76] (2003) Triamcinolone 220 µg QD vs beclomethasone 168 µg BID	MC, PG, RCT, SB Patients ≥18 years of age with SAR to ragweed pollen for ≥2 years	N=152 3 weeks	Primary: Nasal symptoms, eye symptoms, HRQL, and patient preference for sensory attributes Secondary: Adverse events	Primary: Significant improvements from baseline in rhinitis related-nasal and eye symptoms were seen with triamcinolone and beclomethasone (P value not reported). There were no significant differences in nasal stuffiness, nasal discharge, nasal index, nasal itching, total eye symptoms, patients' or physicians' overall assessment of efficacy or HRQL between the treatment groups (P value not reported). 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 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; P value not reported).
Winder et al.[77] (1993) Triamcinolone 220 µg QD vs beclomethasone 84 µg BID	MC, PG, RCT, SB Patients 18 to 64 years of age with PAR for ≥2 years 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 reported in rhinorrhea, congestion, sneezing, sum of primary symptom scores or physicians' global evaluations between treatment groups (P value not reported). Patients' global evaluation of treatment with triamcinolone was 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 was significantly more medication-induced sneezing with triamcinolone compared to beclomethasone (P=0.024).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was significantly more medication runoff from the nose and throat with beclomethasone than triamcinolone (P<0.05).
Gross et al.[78] (2002) Triamcinolone 110 µg in each nostril QD vs fluticasone 100 µg in each nostril QD	AC, PG, RCT, SB Patients 12 to 70 years of age, with fall SAR and positive skin test to ragweed	N=352 3 weeks	Primary: Nasal symptoms, effects on HRQL as measured by RQLQ and adverse events Secondary: Not reported	Primary: No statistically significant differences were reported between the treatment groups in daily TNSS (P=0.332), individual symptom scores (P value not reported), treatment-related adverse events (P value not reported), overall HRQL scores (P=0.4) or overall RQLQ scores (P value not reported). Secondary: Not reported
Small et al.[79] (1997) Triamcinolone 110 µg in each nostril QD vs fluticasone 100 µg in each nostril QD	MC, PG, RCT, SB Patients 12 to 70 years of age with spring pollen SAR for ≥2 years	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 change 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 (P value not reported). Fluticasone propionate 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). Triamcinolone was rated as significantly more intolerable than fluticasone propionate 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 propionate (P value not reported).
Berger et al.[80] (2003)	AC, MC, PG, SB	N=295	Primary: Mean TNSS	Primary: Both triamcinolone and fluticasone propionate were effective at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Triamcinolone 110 µg in each nostril QD vs fluticasone propionate 100 µg in each nostril QD	Patients 12 to 70 years of age with SAR for ≥2 years and a positive epicutaneous or intradermal test to 1 or more tests of grass pollen, tree pollen, and/or outdoor molds present in their environment	21 days	Secondary: Mean individual symptom scores, dropout rate due to insufficient therapeutic effect, RQLQ scores and SAQ scores	significantly reducing TNSS scores from baseline (P<0.05). After 21 days, there was no difference between treatments in regard to change in TNSS scores (95% CI, 0.7391 to 0.3693). Secondary: Both treatments were equally effective at reducing symptom scores from baseline including nasal discharge (P=0.9539), nasal stuffiness (P=0.7666), sneezing (P=0.5559) and nasal itching (P=0.7858). Zero patients discontinued study the study medications due to lack of therapeutic effect. There were no significant differences in mean overall RQLQ scores (P=0.54) or in individual domain scores between treatments. All changes were statistically significant compared to baseline scores (P<0.001). On the SAQ, patients reported significantly less odor with triamcinolone compared to fluticasone propionate (12.3 vs 40.7%; P<0.0001).
Welsh et al.[81] (1987) Beclomethasone 336 µg/day, administered as 2 sprays in each nostril BID vs flunisolide 200 µg/day, administered as 2 sprays in each nostril BID	PC, RCT Patients 12 to 50 years of age with ≥2 year history of SAR and positive skin test to crude short ragweed extract	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 to placebo (P<0.001). 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 (P value not reported). Secondary: There was significantly more nasal burning with flunisolide compared to other treatments (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cromolyn 41.6 mg/day, administered as 1 spray in each nostril QID vs placebo				
Stokes et al.[82] (2004) Triamcinolone 220 µg one time vs fluticasone 200 µg one time vs mometasone 200 µg one time	DB, MC, RCT, XO Patients 18 to 70 years of age with ≥2-year history of allergic rhinitis, who were symptomatic at baseline	N=215 1 day	Primary: Patients' sensory perception measured by the NSEQ, patients' preference measured by the ONSEQ, patients' self-reported expected compliance score using the four-point Likert scale Secondary: Not reported	Primary: The NSEQ scores for triamcinolone were significantly higher than fluticasone propionate and mometasone (78.6 vs 72.3 and 69.3, respectively; P<0.001 for all). Based on the ONSEQ scores, significantly more patients preferred triamcinolone (50% for triamcinolone, 25% for fluticasone propionate and 25% mometasone; P<0.001 for all). A larger percentage of the patients reported a Likert score of one or "definitely complying" with triamcinolone (62.5% for triamcinolone, 49.0% for fluticasone and 51.0% for mometasone; P<0.01 for all). Secondary: Not reported
Bachert et al.[83] (2002) Triamcinolone 110 µg in each nostril QD vs fluticasone 100 µg in each nostril	DB, MC, RCT, XO Patients ≥18 years of age with s ≥2-year history of allergic rhinitis	N=95 1 day	Primary: Sensory perceptions, patient preferences, and likelihood of compliance Secondary: Not reported	Primary: Overall, more patients preferred triamcinolone to fluticasone propionate (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 propionate and mometasone (P<0.05 for all). Triamcinolone was preferred more than mometasone for the taste, comfort and less irritation (P<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD vs mometasone 100 µg in each nostril QD				Fluticasone propionate was also preferred more than mometasone in terms of taste, comfort and amount of irritation (P≤0.05). There were no significant differences between fluticasone propionate and mometasone in aftertaste and amount of irritation (P value not reported). Patients reported a higher likelihood of compliance with triamcinolone (67.4%) compared to fluticasone propionate and mometasone (54.7 and 49.5%, respectively; P value not reported). Secondary: Not reported
Khanna et al.[84] (2005) Beclomethasone vs budesonide vs fluticasone vs mometasone	SB, XO Patients with allergic rhinitis	N=114 Duration not specified	Primary: Sensory perceptions and patient reference Secondary: Not reported	Primary: Significantly more patients preferred mometasone and reported less irritation, odor and aftertaste (P values not reported). Fluticasone propionate was reported by patients as having a significantly higher odor strength and amount of irritation (P values not reported). Eighty percent of the patients predicted better compliance with their preferred drug. Secondary: Not reported
Garris et al.[85] (2009) Fluticasone furoate, dose not specified vs	RETRO Patients ≥4 years of age with ≥1 one pharmacy claim for a branded intranasal corticosteroid	N=793,349 10 months	Primary: Time to concomitant use of a prescription non-sedating antihistamine, montelukast, or ocular medications	Primary: A higher proportion of patients in the fluticasone furoate cohort did not have concomitant prescription medication use during follow-up compared to the other cohorts. Patients in the fluticasone furoate cohort had, on average, a 21% lower risk of having a concomitant prescription for allergic rhinitis compared to the other cohorts (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
budesonide, dose not specified vs mometasone, dose not specified vs triamcinolone, dose not specified	between April 2007 and July 2007		Secondary: Not reported	The risk reduction was the greatest for concomitant use of a non-sedating antihistamine followed by ocular medications (25 and 16% respectively; P<0.05). No significant difference was observed between the fluticasone furoate cohort, the combination cohort of any other branded corticosteroid, mometasone or triamcinolone in the time to use of montelukast. Secondary: Not reported
Ratner et al.[86] (2008) Azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) and placebo nasal spray once in the morning vs fluticasone nasal spray, 2 sprays in each nostril QD in the morning and placebo nasal spray BID vs azelastine nasal spray, 2 sprays in	DB, DD, MC, PG, R Patients 12 years and older with a minimum 2-year history of allergy to Texas mountain cedar confirmed in the past year by positive skin test	N=151 2 weeks	Primary: Change from baseline in TNSS Secondary: Change from baseline for each individual treatment day, change from baseline for each individual symptom score, change from baseline in the RQLQ, safety	Primary: Compared to baseline all three treatment groups significantly improved TNSS (P<0.001). In the azelastine, fluticasone and combination groups the mean improvement from baseline TNSS was 4.8±4.3, 5.2±4.6, and 7.4±5.6, respectively. The improvement from baseline TNSS was 27.1% with fluticasone, 24.8% with azelastine, and 37.9% with the combination (P<0.05 for the combination vs either agent alone). Compared to the azelastine and fluticasone there were absolute improvements of 11.0 (P=0.007) and 13.0% (P=0.02) with the combination, respectively. Secondary: Compared to either single treatment the combination was significantly more efficacious in treating the symptoms of congestion and itchy nose (P<0.05). Compared to fluticasone the combination was significantly more efficacious in treating the symptom of runny nose (P<0.05). Compared to azelastine the combination was significantly more efficacious in treating the symptom of sneezing (P<0.05). On study days three to 14 the combination was significantly more efficacious than azelastine alone (P<0.05). On study days four and six

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
each nostril BID (Astelin®) and fluticasone nasal spray, 2 sprays in each nostril QD in the morning				to 11 the combination was significantly more efficacious than fluticasone alone (P<0.05). Compared to baseline all three treatments significantly improved overall RQLQ as well as the individual domains of RQLQ (P<0.01). In the overall RQLQ score the mean change from baseline was greater for the combination (1.92) compared to azelastine (1.21) and fluticasone (1.40). The difference was significant compared with azelastine but not fluticasone. Bitter taste was the most common adverse event with azelastine (8.2 vs 2.0% in the fluticasone group and 13.5% in the combination group). In 4.1% of the azelastine group, 4.0% of the fluticasone group and 5.8% of the combination group headache was reported.
Meltzer et al.[87] (2012) Azelastine-fluticasone propionate 137/50 µg 1 spray in each nostril BID vs azelastine 137 µg 1 spray in each nostril BID vs fluticasone propionate 50 µg 1 spray in each nostril BID vs	AC, MC, PC, PG, RCT Patients 12 years of age and older with moderate-to-severe SAR and a positive skin prick test to a local, prevalent, seasonal allergen and a 12-hour rTNSS of ≥8 at a minimum of three assessments during the lead-in period,	N=770 14 days	Primary: 12-hour rTNSS Secondary: Change in individual symptom scores, onset of action, 12-hour rTOSS and the RQLQ overall score	Primary: Patients receiving the combination of azelastine and fluticasone propionate experienced significant reductions in the mean rTNSS (-5.54) compared to fluticasone propionate (-4.55; P=0.038), azelastine (-4.54; P=0.032) and placebo (-3.03; P<0.001). Combination therapy improved the rTNSS score by 39% compared to fluticasone propionate alone. Secondary: Patients receiving combination therapy achieved significant improvement in all individual symptoms (nasal congestion, runny nose, itchy nose and sneezing) compared to placebo (P<0.001 for all), In particular, combination therapy significantly improved nasal congestion compared to azelastine and fluticasone propionate (P≤0.046). The azelastine-fluticasone propionate combination demonstrated a rapid onset of action, with a statistically significant improvement in the TNSS compared with placebo at 30 minutes following the first dose. The significant improvements in the TNSS over placebo were sustained at each subsequent evaluation point during the four-hour observation period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				The mean improvement from baseline in the 12-hour rTOSS was significantly greater with combination therapy (-3.56) compared to fluticasone propionate (-2.68; P=0.009); however, there was no statistically significant difference compared to azelastine (-2.96; P=0.069). There was a significant increase in RQLQ score with combination therapy compared to both azelastine and placebo (P<0.05 for both), but not compared to fluticasone propionate.
Hampel et al.[88] (2010) Azelastine-fluticasone propionate 137/50 µg 1 spray in each nostril BID vs azelastine 137 µg 1 spray in each nostril BID vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of allergy to Texas mountain cedar pollen, as confirmed by a positive prick-puncture skin test result and a 12-hour reflective TNSS of ≥8/12 and a congestion score of 2 or 3	N=610 14 days	Primary: Change from baseline in 12-hour rTNSS Secondary: Change from baseline in individual symptom scores, TNSS on each study day, TOSS, individual ocular symptom scores, RQLQ and safety	Primary: The mean improvement from baseline TNSS was -5.31 with combination therapy compared to -3.25 with azelastine (P<0.01), -3.84 with fluticasone propionate (P<0.01) and -2.2 with placebo. Both azelastine and fluticasone monotherapy were also significantly more effective compared to placebo (P≤0.02 for both). Secondary: Combination therapy significantly improved the individual TNSS symptoms of nasal congestion, itchy nose, and sneezing compared to azelastine, fluticasone, or placebo (P<0.05 for all). Combination therapy significantly improved runny nose compared to azelastine and placebo (P<0.01), but not compared to fluticasone. The combination of azelastine and fluticasone was associated with statistically significant improvements in TNSS on all study days compared to azelastine and placebo (P≤0.01 for both). Combination therapy improved TNSS compared to fluticasone propionate on all days except days 10 and 11 (P≤0.01). Patients treated with combination therapy significantly improved overall TOSS scores compared to patients randomized to either fluticasone or placebo (P<0.01); however, the difference between combination therapy and azelastine was not statistically significant. Combination therapy significantly improved individual ocular symptoms compared to azelastine, fluticasone, or placebo, with the exception of azelastine for watery eyes (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The combination of azelastine and fluticasone significantly improved the overall RQLQ score compared to azelastine (P<0.05) and placebo (P<0.001) but not fluticasone (P=0.29). The most commonly reported adverse events were bitter taste (2.0% with azelastine, 0.0% with fluticasone, and 7.2% with combination therapy). No significant changes in vital signs were reported.
Carr et al.[89] (2012) Azelastine-fluticasone propionate 137/50 µg 1 spray in each nostril BID vs azelastine 137 µg 1 spray in each nostril BID vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	MA (3 RCT) Subjects ≥12 years of age with a ≥2 year history of moderate-to-severe SAR and current clinical rhinitis symptoms, a positive skin prick test response to relevant pollen and a rTNSS of at least 8/12, with a congestion score of 2 or 3 during screening	N=3,398 14 days	Primary: Change from baseline in the AM and PM sum rTNSS score Secondary: Change from baseline in iTNSS, rTOSS and RQLQ	Primary: Over the entire 14-day treatment period, combination treatment with azelastine-fluticasone propionate significantly reduced the mean rTNSS sum from baseline compared to azelastine, fluticasone and placebo (-5.7 vs -4.1, -5.1 and -3.0, respectively; P<0.001 for all). Secondary: Patients randomized to receive combination therapy achieved significant reductions in iTNSS scores (-5.2) compared to azelastine (-4.1; P<0.001), fluticasone (-4.8; P=0.022) and placebo (-2.6; P<0.001). More patients receiving combination therapy (12.4%) also exhibited complete or near-complete elimination of their symptoms (e.g., reduction in all nasal symptoms scores to <1) compared to those treated with fluticasone (9.3%; P=0.033), azelastine (7.1%; P<0.001), or placebo (4.2%; P<0.001). Over the entire 14-day treatment period, combination treatment reduced the mean rTOSS score from baseline was significantly greater with combination therapy (-3.2) compared to fluticasone (-2.8; P=0.003) and placebo (-1.8; P<0.001), but not compared to monotherapy with azelastine (-2.9; P=0.196). By day 14 of treatment, all three active treatment groups significantly improved RQLQ scores compared to placebo (P<0.001 for all).
Treatment of Nonallergic Rhinitis				
Scadding et al.[90] (1995)	DB, MC, PC, PG, RCT	N=not specified	Primary: Nasal symptoms	Primary: There were no significant differences between active treatment groups in regard to nasal symptoms (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone propionate 200 µg QD or BID vs beclomethasone 200 µg BID vs placebo	Patients with allergic and nonallergic perennial rhinitis	12 weeks	Secondary: Adverse events	Secondary: Few adverse events and no treatment-related abnormalities in laboratory measurements were reported.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MC=multi-center, NI=non inferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blinded, XO=cross-over
Miscellaneous abbreviations: ACTH=adrenocorticotropic hormone, ECG=electrocardiogram, ECP=eosinophil cationic protein, HRQL=health related quality of life, HPA=hypothalamic-pituitary-adrenal, IgE=immunoglobulin E, iTNSS=instantaneous total nasal symptom score, iTOSS=instantaneous total ocular symptom score, LS=least square, NSEQ=nasal spray evaluation questionnaire, nPEFR=nasal peak expiratory flow rate, ONSEQ=overall nasal spray evaluation questionnaire, PANS=physician assessed overall nasal signs and symptoms, PAR=perennial allergic rhinitis, PNIF=peak nasal inspiratory flow, PNSS=physician-assessed nasal symptom score, PRQLQ=pediatric rhinoconjunctivitis quality of life questionnaire, QoL=quality of life, rNNSS= reflective non-nasal symptom score, RQLQ=rhinoconjunctivitis quality of life questionnaire, rTNSS=reflective total nasal symptom score, rTOSS=reflective total ocular nasal symptom score, SAQ=sensory attributes questionnaire, SAR=seasonal allergic rhinitis, T5SS=total five symptom score, TNNSS=total nonnasal symptom score, TNSS=total nasal symptom score, TOSS=total ocular symptom score, TSS=total symptom score

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 (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.62 to 0.91) and hospitalizations (OR, 0.56; 95% CI, 0.42 to 0.76).[91] 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.[92]

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 11. Relative Cost of the Intranasal Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Beclomethasone	aerosol nasal spray, nasal spray	Beconase AQ®, QNASL®	$$$$$	N/A
Budesonide	nasal spray	Rhinocort Aqua®*	$$$$	$$$$
Ciclesonide	aerosol nasal spray, nasal spray	Omnaris®, Zetonna®	$$$$$	N/A
Flunisolide	nasal spray	N/A	N/A	$$$
Fluticasone furoate	nasal spray	Veramyst®	$$$$$	N/A
Fluticasone propionate	nasal spray	Flonase®*	$$$	$
Mometasone	nasal spray	Nasonex®	$$$$$	N/A
Triamcinolone	nasal spray	N/A	N/A	$$$
Combination Products				
Azelastine and fluticasone	nasal spray	Dymista®	$$$$	N/A

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

X. Conclusions

Intranasal corticosteroids are used for the management of allergic rhinitis, some forms of nonallergic rhinitis, and nasal polyps. They are generally well tolerated and are associated with limited drug interactions due to their localized administration and limited systemic absorption. Like other corticosteroids, intranasal corticosteroids carry warnings regarding the use in patients with active infection and the development of signs of adrenal insufficiency with the administration of higher than recommended doses.

Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of one intranasal corticosteroid product over another. [2,17-19] All the available intranasal corticosteroids have demonstrated safety and efficacy for their respective indications. These agents have been shown to be effective in reducing rhinitis-related nasal symptoms such as congestion, rhinorrhea, sneezing, nasal itch, and postnasal drip. The differences in tolerability and sensory perceptions noted in clinical trials were minor and did not translate into improved outcomes. The results of multiple head-to-head trials have generally failed to demonstrate clinically significant differences between products.[20-96]

Fluticasone furoate (Veramyst®), mometasone (Nasonex®), and triamcinolone are Food and Drug Administration (FDA)-approved for use in children two years of age and older and fluticasone propionate (Flonase®) and beclomethasone (QNASL®) are FDA-approved for use in children four years of age and older. Beclomethasone (Beconase AQ®), budesonide (Rhinocort Aqua®), ciclesonide (Omnaris®), and flunisolide are approved for use in children six years of age and older.[3-12,14] The combination product of azelastine and fluticasone propionate (Dymista®) is approved for use in children six years of age and older who require treatment with both components for symptomatic relief.[13] Two nasal aerosol formulations of existing drugs, beclomethasone (QNASL®) and ciclesonide (Zetonna®), have recently been approved by the FDA for the relief of symptoms associated with perennial and season allergic rhinitis. The other intranasal corticosteroid products are formulated as aqueous suspensions which may be bothersome to patients due to the potential of the suspension to drip down or out of the nose following administration. Budesonide, flunisolide, fluticasone propionate, and triamcinolone are available in a generic formulation.[14]

Comparative clinical trials have demonstrated similar efficacy with the intranasal steroids for the majority of the endpoints assessed in patients with allergic rhinitis. 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.[2,17-19]

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 generic 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Antiallergic Agents
AHFS Class 520200
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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.[1-15] 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. Seasonal allergic conjunctivitis is precipitated by environmental allergens and the symptoms are usually mild and recurrent.[16] 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.[16] 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. 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.[17]

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.[1,2]

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 August 2013.

Table 1. EENT Antiallergic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alcaftadine	solution*	Lastacaft®	none
Azelastine	solution*†	Astepro®*†‡, Optivar®*‡	azelastine
Bepotastine	solution*	Bepreve®	none
Cromolyn	solution*†‡§	N/A	cromolyn*†§
Emedastine	solution*	Emadine®	none
Epinastine	solution*	Elestat®‡	epinastine
Lodoxamide	solution*	Alomide®	none
Nedocromil	solution*	Alocril®	none
Olopatadine	solution*†	Pataday®*, Patanase®*†‡, Patanol®*, Pazeo®*	olopatadine, Pataday®*

*Ophthalmic formulation.
†Nasal formulation.
‡Generic is available in at least one dosage form and/or strength.
^Generic product requires prior authorization.
§Product is available over-the-counter (cromolyn nasal formulation only).
N/A=not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the eye, ear, nose, and throat (EENT) antiallergic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the EENT Antiallergic Agents

Clinical Guideline	Recommendation(s)
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)**[18]	Pharmacologic treatment of allergic rhinitis • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma, and Immunology/ American	Pharmacologic therapy • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most

Clinical Guideline	Recommendation(s)
College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[17]	prominent symptoms, severity, and patient age. <u>Oral antihistamines</u> • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. <u>Intranasal antihistamines</u> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone.

Clinical Guideline	Recommendation(s)
	• Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • 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 in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <u>Oral corticosteroids</u> • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <u>Intranasal cromolyn</u> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines.

Clinical Guideline	Recommendation(s)
	Intranasal anticholinergics • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. Oral antileukotriene agents • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. Omalizumab • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)**[19]	Strep pharyngitis • Penicillin is the drug of choice for treatment of culture positive cases of group A beta streptococcal pharyngitis. In children and patients unable to swallow pills, amoxicillin is an acceptable alternative due to the poor palatability of the penicillin suspension. • In penicillin-allergic patients, options include cephalosporins (for some types of allergies), macrolides, and clindamycin. Consider reevaluating patient for carrier status. Although macrolides may be an acceptable alternative, clinicians should check their local resistance patterns. • Alternative medication recommendations include macrolides, cephalexin, clindamycin, amoxicillin-clavulanate, and rocephin. Non-infectious rhinitis • With the exception of systemic steroids, intranasal corticosteroids are the most effective single agents for controlling allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. Systemic corticosteroid use should be reserved for refractory or severe cases only and given as a short burst. Injectable corticosteroids are generally not recommended as they are invasive and tend to have a longer course of action than typical courses of corticosteroids. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They are less than intranasal corticosteroids, but can be used either on a daily basis or on an as-needed basis. • Second-generation antihistamines are less sedating than first-generation antihistamines, and cause less central nervous system impairment. Adverse events commonly associated with first-generation antihistamines include somnolence, decreased alertness, and anticholinergic effects. These agents may cause central nervous system impairment and impair driving performance. • Oral decongestants can reduce nasal congestion but can result in side effects

Clinical Guideline	Recommendation(s)
	such as irritability, insomnia, and palpitations. Topical decongestants are used for short-term or intermittent/episodic therapy. Routine daily use is not recommended because of the risk for the development of rhinitis medicamentosa. Both oral and topical decongestants should be used with caution in older adults, children under the age of six, and patients of any age who have a history of the following: arrhythmia, angina, cerebrovascular disease, high blood pressure, bladder neck obstruction, glaucoma, or hyperthyroidism. • Cromolyn is less effective than intranasal corticosteroids, and is most effective when used regularly prior to the onset of allergic symptoms. Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in patients with allergic and non-allergic rhinitis. They have no effect on congestion, sneezing, or itching. • Montelukast is a leukotriene receptor antagonist that is as effective as loratadine and less effective than nasal steroids. It is generally well tolerated and may be considered as a third-line option to add after the failure of a nasal corticosteroid and an oral antihistamine. • Ophthalmic preparations contain antihistamines, decongestants, corticosteroids, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers. Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. <u>Non-allergic rhinitis</u> • Treatment of symptomatic nasal obstruction due to non-allergic rhinitis includes the use of azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants, nasal strips, and topical antihistamines. • Intranasal corticosteroids can be used to treat chronic nasal congestion secondary to non-allergic rhinitis. Intranasal corticosteroids have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic symptoms. • Intranasal cromolyn may improve sneezing and congestion scores, and it can be safely used in children two years of age and older. • Some patients find oral decongestants helpful at relieving symptomatic nasal obstruction secondary to non-allergic rhinitis. Oral decongestants have a relatively rapid onset of action and therefore are particularly useful for sporadic symptoms. Patients using oral decongestants should be monitored for hypertension. • Nasal strips may be effective for patients with nocturnal symptoms. They are more effective for patients with narrow noses or with anterior septal deviations. Daytime use of nasal strips is not usually practical. • Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis. • Conservative treatment of symptomatic non-purulent chronic posterior nasal drainage includes increased water intake, decreased caffeine and alcohol intake, nasal saline irrigation, use of petroleum jelly or antibiotic ointment for nasal crusting, and the addition of humidity in bedroom, if significantly less than 50%. In addition, it should be determined if the patient is using any medications that may cause oral or nasal dryness. • Medical treatment of symptomatic non-purulent chronic posterior nasal drainage includes intranasal corticosteroids. • Treatment of symptomatic bilateral chronic anterior rhinorrhea due to non-allergic rhinitis includes avoidance of triggers, intranasal corticosteroids, intranasal ipratropium bromide, and nasal saline.

Clinical Guideline	Recommendation(s)
	Bacterial sinusitis • Intranasal corticosteroids may be rational but is an unproved adjunctive therapy for acute sinusitis. This therapy may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology. • Antibiotics should be reserved for those patients who failed decongestant therapy, those we present with symptoms and signs of a more severe illness, and those who have complications of acute sinusitis.
International Primary Care Respiratory Group Guidelines: **Management of Allergic Rhinitis (2006)**[20]	Mild intermittent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. o Decongestant. AND/OR o Intranasal saline. • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe intermittent allergic rhinitis treatment options). Moderate/severe intermittent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal saline. o Intranasal glucocorticosteroid. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis and compliance, query infections and other causes, then consider trial of different treatment option or specialist referral. Mild persistent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal glucocorticosteroid. o Intranasal saline. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe persistent allergic rhinitis treatment options). Moderate/severe persistent allergic rhinitis • Recommended therapy: o Intranasal glucocorticosteroid.

Clinical Guideline	Recommendation(s)
	o Decongestant. o Oral H_1-blocker. o Intranasal saline. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then choose one or more of the following options: o Increase nasal steroid dose, consider trial of different treatment option, or consider referral to specialist. o If sneeze/itch: add H_1-blocker. o If rhinorrhea: add ipratropium. o If blockage: add decongestant or short course of oral steroids. General treatment considerations • First generation H_1-antihistamines cause sedation and central nervous system impairment. These side effects may adversely affect cognition, learning and driving. These side effects may be potentiated by alcohol and other sedatives. Adverse events may not always be perceived by patients. • Second generation H_1-antihistamines are associated with less sedation and impairment than first generation antihistamines. • Intranasal and intraocular H_1-antihistamines are as effective as oral antihistamines at the site of their administration. • Intranasal glucocorticosteroids are the most effective class of medications available for the treatment of allergic and nonallergic rhinitis. Oral glucocorticosteroids are rarely needed to control severe symptoms of allergic rhinitis. • Mast cell stabilizers reduce symptoms of allergic rhinitis, but are generally less effective than other treatments and require frequent administration. Ocular mast cell stabilizers are effective and have a role in the treatment of allergic conjunctivitis. • Anticholinergic agents can reduce rhinorrhea, but have little effect on other symptoms of allergic rhinitis. • Antileukotriene agents are effective for the treatment of allergic rhinitis and asthma. They have been shown to be as effective as oral antihistamines, but have a greater effect on nasal obstruction. They may have an additive effect with antihistamines.
American Academy of Ophthalmology Preferred Practice Pattern Guidelines: **Conjunctivitis (2013)**[16]	Seasonal allergic conjunctivitis • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a low-potency topical corticosteroid can be added to the regimen. • A nonsteroidal anti-inflammatory agent (ketorolac) has been Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. • Additional measures include the use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful. • Use of topical mast-cell stabilizers can also be helpful in alleviating symptoms of allergic rhinitis, and intranasal corticosteroids are not effective for the treatment of seasonal allergic conjunctivitis.

Clinical Guideline	Recommendation(s)
	Vernal/atopic conjunctivitis • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) 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 warranted rarely. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma.
American Optometric Association: **Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2007)**[21]	Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) • The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. • The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. • Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). • Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1 receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. • Topical diclofenac and ketorolac, which are both NSAIDS, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. • Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%[†]) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2[†] or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. • Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is

Clinical Guideline	Recommendation(s)
	more effective in relieving the itching and redness associated with acute allergic conjunctivitis. • Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. • Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness. <u>Viral conjunctivitis</u> • Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. • Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates, or alleviating symptoms. • Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. • The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. • Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. • Topical steroids are specifically contraindicated for treating herpes simplex conjunctivitis.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the eye, ear, nose, and throat (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[3-15]

Indication(s)	Alcaftadine	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Conjunctivitis									
Prevention of itching due to allergic conjunctivitis	✔					✔			
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander									
Temporary relief of signs and symptoms of allergic conjunctivitis					✔				
Treatment of itching associated with allergic conjunctivitis		✔ *	✔					✔	✔ †
Treatment of signs and symptoms of allergic conjunctivitis									✔ ‡
Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis				✔ *			✔		
Rhinitis									
Prevent and relieve nasal symptoms of hay fever and other nasal allergies				✔ §					
Relief of the symptoms of seasonal and perennial allergic rhinitis		✔ ‖							
Treatment of the symptoms of seasonal allergic rhinitis		✔ ¶							✔ §
Treatment of the symptoms of vasomotor rhinitis		✔ ¶							

*Ophthalmic formulation.
†Patanase® and Pazeo® ophthalmic solution.
‡Patanol® ophthalmic solution.
§Nasal formulation.
‖Astepro® nasal formulation.
¶ Astelin® nasal formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the eye, ear, nose, and throat (EENT) antiallergic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the EENT Antiallergic Agents[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Alcaftadine	Not reported	39.2	Liver (% not reported)	Renal (% not reported)	2*
Azelastine	N: 40 O: not reported	N: not reported O: 78 to 97	Liver, extensive (% not reported)	Renal (25) Feces (50 to 75)	22 to 25†
Bepotastine	Not reported	55	Liver, minimal (% not reported)	Renal (75 to 90)	Not reported
Cromolyn	N: <7 O: <1	Not reported	Not metabolized	Renal (30 to 50) Feces (80 to 87)	<1†
Emedastine	Negligible (% not reported)	Negligible (% not reported)	Liver, extensive (% not reported)	Renal (44)	2 to 7†
Epinastine	Minimal (% not reported)	64	Liver (% not reported)	Renal (55)*	12
Lodoxamide	Not detectible (% not reported)	Not reported	Not reported	Not reported	8.5
Nedocromil	<4	Not reported	Not metabolized	Renal (70)	1.5 to 3.3†
Olopatadine	N: 57 O: minimal (% not reported)	N: 55 O: not reported	Not reported	N: Renal (70) Feces (17) O: Renal (60 to 70)	N: 8 to 12 O: 3

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

V. Drug Interactions

There are no significant drug interactions with the eye, ear, nose, and throat (EENT) antiallergic agent.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the eye, ear, nose, and throat (EENT) antiallergic agents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the EENT Antiallergic Agents[3-15]

Adverse Events	Alcaftadine	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Lodoxamide	Nedocromil	Olopatadine
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 to 10†	-	-	-	-	-	-	-
Fever	-	<2*	-	-	-	-	-	-	-
Headache	<4	8 to 15‡; 1 to 3§;15†	2 to 5	1 to 10*	11	1 to 3	<2	40	<7†
Heat sensation	-	-	-	-	-	-	<1	-	-
Hypoesthesia	-	<2*	-	-	-	-	-	-	-
Malaise	-	<2*	-	-	-	-	-	-	-
Nervousness	-	<2*	-	-	-	-	-	-	-
Paresthesia	-	<1*	-	-	-	-	-	-	-
Sleep disorder	-	<2*	-	-	-	-	-	-	-
Somnolence	-	<1 to 12*	-	-	-	-	<1	-	1*
Vertigo	-	<2*	-	-	-	-	-	-	-
Dermatological									
Contact dermatitis	-	<2*	-	-	-	-	-	-	-
Dermatitis	-	-	-	-	<5	-	-	-	-
Eczema	-	<2*	-	-	-	-	-	-	-
Facial edema	-	<1*	-	-	-	-	-	-	-
Furunculosis	-	<2*	-	-	-	-	-	-	-
Hair and follicle infection	-	<2*	-	-	-	-	-	-	-

Adverse Events	Alcaftadine	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Pruritus	-	<1*	-	-	<5	-	-	-	-
Skin irritation	-	<1*	-	-	-	-	-	-	-
Skin laceration	-	<2*	-	-	-	-	-	-	-
Endocrine and Metabolic									
Amenorrhea	-	<2*	-	-	-	-	-	-	-
Breast pain	-	<2*	-	-	-	-	-	-	-
Dysmenorrhea	-	-	-	-	-	-	-	-	-
Gastrointestinal									
Abdominal pain	-	<2*	-	-	-	-	-	-	-
Aphthous stomatitis	-	<2*	-	-	-	-	-	-	-
Appetite increased	-	<2*	-	-	-	-	-	-	-
Bitter taste	-	8 to 20*; 6 to 7†	-	-	-	-	-	-	13*
Constipation	-	<2*	-	-	-	-	-	-	-
Diarrhea	-	<2*	-	-	-	-	-	-	-
Gastroenteritis	-	<2*	-	-	-	-	-	-	-
Glossitis	-	<2*	-	-	-	-	-	-	-
Loss of taste	-	<2*	-	-	-	-	-	-	-
Nausea	-	3*	-	-	-	-	<1	-	≤5†
Stomach discomfort	-	-	-	-	-	-	<1	-	-
Taste abnormality	-	-	25	1 to 10*	<5	-	-	10 to 30	≤5†
Toothache	-	<2*	-	-	-	-	-	-	-
Vomiting	-	<2*	-	-	-	-	-	-	-
Ulcerative stomatitis	-	<2*	-	-	-	-	-	-	-
Xerostomia	-	3*	-	-	-	-	-	-	1*
Genitourinary									
Albuminuria	-	<2*	-	-	-	-	-	-	-
Hematuria	-	<2*	-	-	-	-	-	-	-
Polyuria	-	<2*	-	-	-	-	-	-	-
Urinary retention	-	<1*	-	-	-	-	-	-	-
Urinary tract infection	-	-	-	-	-	-	-	-	1*
Hepatic									
Alanine aminotransferase increased	-	<2*	-	-	-	-	-	-	-
Transaminases increased	-	<1*	-	-	-	-	-	-	-
Musculoskeletal									
Back pain	-	<2*	-	-	-	-	-	-	≤5†
Extremity pain	-	<2*	-	-	-	-	-	-	-
Hyperkinesia	-	<2*	-	-	-	-	-	-	-
Involuntary muscle contractions	-	<1*	-	-	-	-	-	-	-
Myalgia	-	≤2*	-	-	-	-	-	-	-
Rheumatoid arthritis	-	<2*	-	-	-	-	-	-	-
Temporomandibular dislocation	-	<2*	-	-	-	-	-	-	-

Adverse Events	Alcaftadine	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Weakness	-	-	-	-	<5	-	-	-	≤5†
Ocular									
Anterior chamber cells	-	-	-	-	-	-	<1	-	-
Blepharitis	-	-	-	-	-	-	<1	-	-
Blurred vision	-	<1*; 1 to 10†	-	-	<5	-	1 to 5	-	≤5†
Burning/stinging	<4	30†	-	-	<5	1 to 10	15	10 to 30	≤5†
Chemosis	-	-	-	-	-	-	<1	-	-
Conjunctival injection	-	-	-	✔ †	-	-	-	-	-
Conjunctivitis	-	≤2 to 5* 1 to 10†	-	-	-	-	-	1 to 10	≤5†
Corneal abrasion	-	-	-	-	-	-	<1	-	-
Corneal erosion/ulcer	-	-	-	-	-	-	<1	-	-
Corneal infiltrates	-	-	-	-	<5	-	-	-	-
Corneal staining	-	-	-	-	<5	-	-	-	-
Crystalline deposits	-	-	-	-	-	-	1 to 5	-	-
Discharge	-	-	-	-	-	-	-	-	-
Discomfort	-	-	-	-	-	-	15	-	-
Dry eyes	-	<1*	-	✔ †	<5	-	1 to 5	-	≤5†
Epitheliopathy	-	-	-	-	-	-	<1	-	-
Eye pain	-	<2*; 1 to 10†	-	-	-	-	<1	-	≤5†
Eye redness	<4	-	-	-	-	-	-	1 to 10	-
Eyelid disorder	-	-	-	-	-	-	-	-	-
Eyelid edema	-	-	-	✔ †	-	-	<1	-	≤5†
Folliculosis	-	-	-	-	-	1 to 10	-	-	-
Foreign body sensation	-	-	-	-	<5	-	1 to 5	-	≤5†
Hyperemia	-	-	-	-	<5	1 to 10	1 to 5	-	≤5†
Hypersensitivity reactions	-	-	-	✔ †	-	-	-	-	-
Irritation	<4	-	2 to 5	✔ †	-	-	-	10 to 30	-
Keratitis	-	-	-	-	<5	-	<1	-	≤5†
Mydriasis	-	-	-	-	-	-	-	-	-
Ocular fatigue	-	-	-	-	-	-	<1	-	-
Photophobia	-	-	-	-	-	-	-	1 to 10	-
Pruritus	<4	1 to 10†	-	✔ †	-	1 to 10	1 to 5	-	≤5†
Puffy eyes	-	-	-	✔ †	-	-	-	-	-
Rash	-	<1*	-	-	-	-	-	-	-
Scales on lid/lash	-	-	-	-	-	-	<1	-	-
Styes	-	-	-	✔ †	-	-	-	-	-
Tearing	-	<2*	-	✔ †	<5	-	1 to 5	-	-
Visual disturbances	-	<1*	-	-	-	-	-	-	-

Adverse Events	Alcaftadine	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Warming sensation	-	-	-	-	-	-	<1	-	-
Respiratory									
Asthma	-	5*; 1 to 10†	-	-	-	-	-	1 to 10	-
Bronchitis	-	<2*	-	-	-	-	-	-	-
Bronchospasm	-	<2*	-	-	-	-	-	-	-
Cold/flu syndrome	-	2 to 17*; 1 to 10†	-	-	-	-	-	-	<10†
Cough	-	11*	-	1 to 10*	-	1 to 3	-	-	1*; ≤5†
Dyspnea	-	<1*; 1 to 10†	-	✔ †	-	-	-	-	-
Epistaxis	-	2 to 3*	-	<1*	-	-	-	-	3*
Hoarseness	-	-	-	1 to 10*	-	-	-	-	-
Laryngitis	-	<2*	-	-	-	-	-	-	-
Loss of smell	-	<1*	-	-	-	-	-	-	-
Nasal burning	-	4*	-	>10*	-	-	-	-	-
Nasal congestion	-	<2*	-	-	-	-	-	10 to 30	-
Nasal dryness	-	-	-	-	-	-	<1	-	-
Nasal ulceration	-	-	-	-	-	-	-	-	9*
Nasopharyngitis	<4	-	2 to 5	-	-	-	-	-	-
Nocturnal dyspnea	-	<2*	-	-	-	-	-	-	-
Paroxysmal sneezing	-	3*	-	-	-	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	-	-	-	-	2*
Pharyngitis	-	4*; 1 to 10†	-	-	-	1 to 3	-	-	<10†
Postnasal drip	-	<2*	-	1 to 10*	-	-	-	-	2*
Rhinitis	-	2 to 17*; 1 to 10†	-	-	<5	1 to 3	-	1 to 10	≤5†
Sinus hypersecretion	-	<2*	-	-	-	-	-	-	-
Sinusitis	-	3*	-	-	<5	1 to 3	-	-	≤5†
Sneezing	-	-	-	>10*	-	-	<1	-	-
Throat burning/irritation	-	<2*	-	-	-	-	-	-	1*
Other									
Allergic reaction	-	<2*	-	-	-	-	<1	-	-
Anaphylaxis	-	<1*	-	-	-	-	-	-	-
Application site irritation	-	<1*	-	-	-	-	-	-	-
Creatine phosphokinase increased	-	-	-	-	-	-	-	-	1*
Hypersensitivity	-	-	-	-	-	-	-	-	≤5†
Infection	-	-	-	-	-	10	-	-	≤5†
Influenza	<4	-	-	-	-	-	-	-	1*
Parosmia	-	<1*	-	-	-	-	-	-	-
Tolerance	-	<1*	-	-	-	-	-	-	-

Adverse Events	Alcaftadine	Azelastine	Bepotastine	Cromolyn	Emedastine	Epinastine	Lodoxamide	Nedocromil	Olopatadine
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 eye, ear, nose, and throat (EENT) antiallergic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the EENT Antiallergic Agents[3-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alcaftadine	Allergic conjunctivitis: Solution: instill 1 drop in each eye once daily	Allergic conjunctivitis in patients ≥2 years of age: Solution: instill 1 drop in each eye once daily	Solution: 0.25%
Azelastine	Allergic conjunctivitis: Solution (ophthalmic): instill 1 drop twice daily Allergic rhinitis (perennial): Solution (nasal spray; Astepro® 0.15%): 2 sprays per nostril once daily Allergic rhinitis (seasonal): Solution (nasal spray): 1 to 2 sprays per nostril twice daily Solution (nasal spray; Astepro®): 1 to 2 sprays per nostril once daily Vasomotor rhinitis: Solution (nasal spray): 2 sprays per nostril twice daily	Allergic conjunctivitis in patients >3 years of age: Solution (ophthalmic): instill 1 drop twice daily Allergic rhinitis (perennial) in patients >12 years of age: Solution (nasal spray; Astepro® 0.15%): 2 sprays per nostril twice daily Allergic rhinitis (seasonal) in patients 5 to 11 years of age: Solution (nasal spray): 1 spray per nostril once daily Allergic rhinitis (seasonal) in patients ≥12 years of age: Solution (nasal spray): 1 to 2 sprays per nostril twice daily Solution (nasal spray; Astepro®): 2 sprays per nostril once daily Vasomotor rhinitis in patients >12 years of age: Solution (nasal spray): 2 sprays per nostril twice daily	Solution (nasal spray): 137 µg (0.1%) 205.5 µg (0.15%) Solution (ophthalmic): 0.05%
Bepotastine	Allergic conjunctivitis: Solution: 1 drop twice daily	Allergic conjunctivitis in patients ≥2 years of age: Solution: 1 drop twice daily	Solution: 1.5%
Cromolyn	Nasal symptoms of hay fever and other nasal allergies: Solution (nasal spray): 1 spray in each nostril 3 to 6 times per day; maximum, 6 times per day Vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis: Solution (ophthalmic): 1 to 2 drops in each eye 4 to 6 times per day	Nasal symptoms of hay fever and other nasal allergies in patients ≥2 years of age: Solution (nasal spray): 1 spray in each nostril 3 to 6 times per day; maximum, 6 times per day Vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis in patients ≥4years of age: Solution (ophthalmic): 1 to 2 drops in each eye 4 to 6 times per day	Solution (ophthalmic): 4%
Emedastine	Allergic conjunctivitis:	Allergic conjunctivitis in	Solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Solution: instill 1 drop in each eye up to 4 times daily	patients ≥3 years of age: Solution: instill 1 drop in each eye up to 4 times daily	0.05%
Epinastine	Allergic conjunctivitis: Solution: instill 1 drop in each eye twice daily	Allergic conjunctivitis in patients ≥3 years of age: Solution: instill 1 drop in each eye twice daily	Solution: 0.05%
Lodoxamide	Vernal conjunctivitis, vernal keratoconjunctivitis, vernal keratitis: Solution: instill 1 to 2 drops in each eye 4 times daily for up to 3 months	Vernal conjunctivitis, vernal keratoconjunctivitis, vernal keratitis in patients ≥2 years of age: Solution: instill 1 to 2 drops in each eye 4 times daily for up to 3 months	Solution: 0.1%
Nedocromil	Allergic conjunctivitis: Solution: instill 1 to 2 drops in each eye twice daily	Allergic conjunctivitis in patients ≥3 years of age: Solution: instill 1 to 2 drops in each eye twice daily	Solution: 2%
Olopatadine	Allergic conjunctivitis: Solution (ophthalmic; 0.1%): 1 drop in each eye twice daily every 6 to 8 hours Solution (ophthalmic; 0.2%): 1 drop in each eye once daily Solution (ophthalmic; 0.7%): 1 drop in each eye once daily Allergic rhinitis (seasonal): Solution (nasal spray): 2 sprays per nostril twice daily	Allergic conjunctivitis in patients ≥3 years of age: Solution (ophthalmic; 0.1%): 1 drop in each eye twice daily every 6 to 8 hours Allergic conjunctivitis in patients ≥2 years of age: Solution (ophthalmic; 0.2%): 1 drop in each eye once daily Solution (ophthalmic; 0.7%): 1 drop in each eye once daily Allergic rhinitis (seasonal) in patients 6 to 11 years of age: Solution (nasal spray): 1 spray per nostril twice daily Allergic rhinitis (seasonal) in patients ≥12 years of age: Solution (nasal spray): 2 sprays per nostril twice daily	Solution (nasal spray): 0.6% Solution (ophthalmic): 0.1% 0.2% 0.7%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the eye, ear, nose, and throat (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				
Torkildsen et al.[22] (2011) Alcaftadine 0.25% 1 drop in each eye QD vs placebo	DB, MC, PC, RCT Patients >10 years of age with a history of allergic conjunctivitis and a reproducible, positive reaction to a CAC	N=58 4 visits (study duration not reported)	Primary: Ocular itching (assessed by subject at three, five and seven minutes following CAC) and conjunctival redness (assessed by investigator at seven, 15 and 20 minutes following CAC) Secondary: Other signs and symptoms of allergic conjunctivitis (assessed by investigator at seven, 15 and 20 minutes following CAC)	Primary: Alcaftadine was associated with a statistically significant reduction in conjunctival redness following the 16-hour (duration of action) and 15-minute (onset of action) CAC tests compared to placebo. The differences in mean ocular itching scores at the 16-hour CAC test were -1.731, -1.687, and -1.576 at three, five, and seven minutes following CAC, respectively, compared to placebo (P<0.001 for all time points). The differences in mean ocular itching scores at the 15 minute CAC test were -1.500, -1.491, and -1.474 at three, five, and seven minutes following CAC, respectively, compared to placebo (P<0.001 for all time points). Mean conjunctival redness scores were significantly improved for patients receiving alcaftadine compared to the placebo group at seven, 15 and 20 minutes following the 15 minute and 16 hour CAC tests (P<0.05 for all time points). The differences between groups were not clinically significant (>1 point difference in absolute mean scores groups). Secondary: Alcaftadine was associated with a statistically significant reduction in most secondary endpoints following the 16-hour and 15-minute CAC tests compared to placebo. Adverse events occurred more frequently in the placebo group compared with alcaftadine group (13.3 vs 6.7%; P value not reported).
Greiner et al.[23] (2011) Alcaftadine 0.05%, dose and frequency	AC, DB, PC, PRO, RCT Patients ≥18 years of age with a history	N=170 5 weeks	Primary: Ocular itching (at visit four, five minutes after an allergen	Primary: All active treatment groups exhibited greater clinically (≥1 unit difference) and statistically significant (P<0.001) reductions in itching scores at all time points following the 15 minute CAC test compared to placebo. At seven minutes following a CAC test, alcaftadine 0.25% was significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
not reported vs alcaftadine 0.01%, dose and frequency not reported vs alcaftadine 0.25%, dose and frequency not reported vs olopatadine 0.1%, dose and frequency not reported vs placebo	of ocular allergies and/or a positive skin test reaction to specified allergens within the last 24 months and best-corrected visual acuity of 0.6 log MAR or better in each eye		challenge), conjunctival redness (at visit four, 15 minutes after an allergen challenge) Secondary: Ciliary and episcleral redness, chemosis, lid swelling, tearing, ocular mucus discharge, nasal symptoms and adverse events	more effective at preventing ocular itching compared to olopatadine (P=0.017). At the 15-minute CAC test, mean conjunctival redness scores for all active treatments were significantly lower at every time point compared to placebo (P<0.05 for all). Mean reductions in scores for olopatadine (-1.27 units) and alcaftadine 0.25% (-1.35 units) achieved clinical significance compared to placebo at seven minutes following CAC test (P value not reported). At the 16-hour CAC test (duration of action), alcaftadine was associated with lower mean ocular itching scores compared to both placebo and olopatadine (P values not reported). At seven minutes following CAC test, ocular itching scores were significantly lower with alcaftadine 0.25% compared to olopatadine (P=0.017). At the 16-hour CAC test, alcaftadine 0.25% and olopatadine exhibited statistically significant reductions in mean conjunctival redness scores compared with placebo (P<0.05). Secondary: At both the 15-minute and 16-hour CAC tests, all treatment groups exhibited significantly greater improvements in all secondary endpoints compared to placebo (P<0.05). All ocular adverse events were self-limited and mild in severity. The most common non-ocular adverse event was nasopharyngitis. No ocular adverse events were reported in the olopatadine treatment group.
James et al.[24] (2003) Azelastine in both eyes BID vs	DB (azelastine vs placebo), MC, PG, OL (azelastine vs cromolyn) Patients with SAC or rhino-conjunctivitis and	N=144 2 weeks	Primary: Ocular signs and symptoms, global assessment of efficacy and safety Secondary: Not reported	Primary: Both azelastine and cromolyn demonstrated an effect on itching, tearing and conjunctival redness on day three with a sustained improvement on days seven and 14 compared to placebo. A clear response to treatment occurred in 85.4% of azelastine patients and 83.0% of cromolyn patients compared to 56.3% of patients receiving placebo (P=0.005 and P=0.007, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cromolyn in both eyes QID vs placebo	symptomatic at time of inclusion			Global assessment of efficacy was at least satisfactory for 90.0% of azelastine patients, 81.3% of cromolyn patients and 66.3% of placebo-treated patients (P values not reported). The most frequent adverse events were transient application site reactions, which tended to disappear with increasing duration of treatment, and, less frequently, taste perversion. Secondary: Not reported
Abelson et al.[25] (2009) Bepotastine 1.0% 1 drop in each eye vs bepotastine 1.5% 1 drop in each eye vs placebo	DB, PC, RCT 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 CAC Secondary: Not reported	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 eight-hour duration-of-action CAC tests (P<0.001 for all). The clinical significance associated with bepotastine 1.5% was similar between the 15-minute and eight-hour CAC tests, whereas the 1.0% solution appeared to be less effective at eight hours compared to 15 minutes after administration. At visit five, 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 to placebo (1.5, 0, and 1.5%; P≤0.003 for all). Mean conjunctival hyperemia scores were improved with bepotastine 1.0% vs placebo at all three time points in the 15-minute onset-of-action CAC test (P≤ 0.001 for all). 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 seven minutes on the eight-hour CAC (P=0.01). Secondary: Not reported
Williams et al.[26]	DB, PC, RCT	N=107	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Bepotastine 1% one drop in each eye once vs bepotastine 1.5% one drop in each eye once vs placebo	Patients ≥10 years of age with a history of ocular allergies, positive skin test to cat hair, cat dander, grasses, ragweed, and/or trees within the past 24 months and positive bilateral CAC reaction within 10 minutes of allergen instillation	3 weeks (4 visits)	Patient-assessed ocular itching, physician-assessed conjunctival redness and safety Secondary: Patient-assessed tearing, ciliary and episcleral redness, eyelid swelling, chemosis and mucous discharge	The mean ocular itching scores in the per protocol population were significantly lower with bepotastine 1 and 1.5% compared to placebo (P<0.001 for both). There was a statistically significant reduction in CAC-induced ocular itching 16 hours following administration of bepotastine 1 and 1.5% compared to placebo in the intention-to-treat populations (P≤0.001 for both). In the per protocol population, 40.0% of patients receiving bepotastine 1.5% experienced a two-unit reduction in ocular itching at one or more CAC time points compared to 34.3% of those in the bepotastine 1% group and 5.9% in the placebo group (P<0.05 for both compared to placebo). Of patients with severe itching, a two-unit reduction in ocular itching score at one or more time points occurred in 8.7% of the placebo group compared to 37.5 and 43.5% of patients receiving bepotastine 1% (P=0.001) and 1.5% (P=0.008), respectively. Bepotastine 1% was significantly more effective compared to placebo for reducing mean conjunctival redness seven minutes following the 16-hour CAC test (P≤0.012). There were no clinically significant differences (one unit or more change) in conjunctival redness between bepotastine (1 or 1.5%) and placebo at any time point 16 hours after dosing. Secondary: Compared to placebo, bepotastine 1 and 1.5% were associated with statistically significant reductions in eyes with tearing (51.2 and 85.6 vs 27.5%, respectively; P<0.05 for both compared to placebo). Improvements in tearing were significantly greater in patients receiving bepotastine 1.5% compared to those treated with bepotastine 1% (P=0.0046).
Macejko et al.[27] (2010) Bepotastine 1.0% 1 drop in each eye vs	DB, MC, PC, RCT Patients ≥10 years of age with a positive allergen skin test	N=130 Single dose	Primary: Ocular itching and conjunctival hyperemia following CAC Secondary: Not reported	Primary: Bepotastine (1.0 and 1.5%) demonstrated a reduction in ocular itching (P<0.0001) compared to placebo (within three minutes after a CAC and at every other time point after a CAC performed 15 minutes or eight hours after test agent instillation). Bepotastine 1.5% demonstrated a slightly higher degree of reduced ocular itching than seen for the 1.0% formulation.

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				An improvement in conjunctival redness was observed at most time points at the onset of action CAC test for both bepotastine formulations (P<0.0125). There was less conjunctival redness improvement seen at the eight- and 16-hour duration-of-action CAC tests. Secondary: Not reported
Torkildsen et al.[28] (2010) Bepotastine 1.5% 1 drop in each eye vs placebo	DB, PC, RCT Patients ≥10 years of age with a history of allergic conjunctivitis	N=70 Single dose	Primary: Non-ocular effectiveness following CAC Secondary: Not reported	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 NOCS score was improved with bepotastine compared to placebo at most time points for at least 16 hours after dosing (P≤0.01). Secondary: Not reported
McCabe et al.[29] (2012) Bepotastine 1.5% 1 drop in affected eye(s) BID vs olopatadine 0.2% 1 drop in affected eye(s) QD	AC, RCT, SB, XO Patients ≥18 years of age with allergic conjunctivitis and no concurrent unrelated ocular diseases and no plans to undergo ocular surgery during the study period	N=30 2 weeks	Primary: Relief of ocular itch, itchy/runny nose, ocular allergy symptoms, eye drop comfort and patient preference Secondary: Not reported	Primary: There was a similar improvement in the relief of morning ocular itch between patients receiving bepotastine and olopatadine (P value not reported). Patients treated with bepotastine reported a significantly greater relief in evening ocular itch compared to patients receiving olopatadine (P=0.011). Olopatadine was significantly more effective at relieving ocular itching in the morning compared to the evening (P<0.0001), whereas bepotastine was equally effective at both time points. For the all-day relief of ocular itching, significantly more patients favored treatment with bepotastine compared to treatment with olopatadine (63.3 vs 36.7%; P=0.04). Bepotastine was significantly more effective at relieving morning and evening itchy/runny nose compared to olopatadine (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Bepotastine provided significantly more itchy/runny nose relief in the evening compared to the morning (P<0.035), whereas olopatadine provided a similar relief between morning and evening. A significantly greater proportion of patients preferred bepotastine compared to olopatadine for all-day relief of itchy/runny nose (66.7 vs 33.3%; P=0.01). A greater proportion of patients preferred bepotastine with regard to eye drop comfort compared to olopatadine (56.7 vs 43.3%; P value not reported). Treatment with bepotastine was significantly more effective for relief of morning and evening ocular allergy symptoms (P=0.032 and P<0.0001, respectively) compared to treatment with olopatadine. Bepotastine was equally efficacious for improving ocular allergy symptoms in the morning and evening, whereas olopatadine was significantly more effective in the morning (P<0.001). Significantly more patients preferred bepotastine for the overall treatment of allergic conjunctivitis compared to olopatadine (66.7 vs 33.3%; P=0.01). Secondary: Not reported
Greiner et al.[30] (abstract) (2002) Cromolyn 4% in 1 eye QID for 2 weeks, followed by 1 drop once at the final visit	AC, SB Patients who responded to the conjunctival provocation test, study used CAC model	N=56 2 weeks	Primary: Ocular itching, tearing and redness following CAC, comfort and safety Secondary: Not reported	Primary: At the 15-minute and four-hour CAC tests, ketotifen was significantly more effective than cromolyn in preventing itching (P<0.001) and redness (P≤0.001) at most assessments. Tearing scores were higher in patients receiving cromolyn compared to patients receiving ketotifen. Patients reported greater comfort in the eyes treated with ketotifen compared to cromolyn; however, the difference was not statistically significant (P=0.066). The most common adverse event associated with cromolyn was burning/stinging.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo other eye QID for 2 weeks, followed by ketotifen 0.025% 1 drop once at the final visit				A single dose of ketotifen was more effective than a two-week regimen of cromolyn in alleviating symptoms of allergic conjunctivitis in the CAC model. Secondary: Not reported
Figus et al.[31] (2010) Cromolyn sodium 4% and chlorpheniramine 0.2% BID vs diclofenac 0.1% BID vs epinastine 0.05% BID vs fluorometholone 0.2% BID vs ketotifen 0.05% BID vs	MC, RCT, SB 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 Secondary: Not reported	Primary: Naphazoline and 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 and 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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levocabastine 0.05% BID vs naphazoline and antazoline 0.25-5 mg/mL BID vs olopatadine 0.1% BID				
D'Arienzo et al.[32] (2002) Emedastine 0.05% in 1 eye and placebo in the contralateral eye vs ketotifen 0.025% in 1 eye and placebo in the contralateral eye vs emedastine 0.05% in 1 eye and ketotifen 0.025% in the contralateral eye	DB, PC, RCT Patients with allergic conjunctivitis	N=45 Single dose	Primary: Signs and symptoms following CAC Secondary: Not reported	Primary: Treatment with emedastine and ketotifen resulted in significant reductions in raw mean itching scores at all time points compared to placebo ($P<0.05$). This was seen at both the five- and 15-minute challenges. There were no significant differences in itching scores between emedastine and ketotifen at either the five- or 15-minute challenge. Secondary: Not reported
Orfeo et al.[33]	AC, DB, PC, RCT,	N=30	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(abstract) (2002) Emedastine 0.05% in 1 eye once and placebo other eye once vs nedocromil 2% in 1 eye once and placebo other eye once Each patient received both study drugs on two different visits.	XO Patients with a history of allergic conjunctivitis, study used CAC model	Duration not reported (3 visits)	Ocular itching and redness at three, 10 and 20 minutes following CAC Secondary: Not reported	Emedastine and nedocromil were significantly more effective compared to placebo in controlling ocular itching and redness following CAC test (P<0.01). Emedastine was significantly more effective in alleviating redness and itching at three and 10 minutes after the allergen CAC test compared to nedocromil (P<0.01). Secondary: Not reported
Fujishima et al.[34] (2014) Epinastine 0.05% vs olopatadine 0.1% *and* Epinastine 0.05% vs placebo	AC, DB, PC, RCT Adults with a history of seasonal allergic conjunctivitis and cedar pollen-specific IgE who were asymptomatic before the allergen challenge, study used CAC model (cedar pollen)	N=87 Duration not reported (7 visits)	Primary: Ocular itching score and conjunctival hyperemia score at 3 specified time points after CAC (ocular itching at 3, 5, and 10 minutes; conjunctival hyperemia at 5, 10, and 20 minutes) Secondary: Safety	*Epinastine vs placebo (superiority study)* Primary: The mean ocular itching scores (mean ± SE) for the 3 time points after allergen challenge at 4 hours were 0.4 ± 0.1 and 1.7 ± 0.1 for epinastine and placebo, respectively (P<0.001). The mean conjunctival hyperemia scores (mean ± SE) for the 3 time points after the allergen challenge at 4 hours were 2.7 ± 0.1 and 4.1 ± 0.2 for epinastine and placebo, respectively (P<0.001). *Epinastine vs olopatadine (noninferiority study)* Primary: Noninferiority of epinastine to olopatadine with respect to the mean ocular itching score and conjunctival hyperemia score was verified. *Data from all patients contributed to safety outcomes* Secondary: Adverse events were reported in 5 of the 87 subjects included in the safety analysis set (nasopharyngitis, urticaria, wound formation, oropharyngeal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				discomfort, and conjunctivitis). All events were considered unrelated to the study drug.
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).	DB, RCT, XO Patients ≥18 years of age with allergic conjunctivitis	N=40 Single dose	Primary: Ocular comfort Secondary: Not reported	Primary: The mean comfort score was significantly lower (indicating more comfort) with epinastine than azelastine at 0.5, one, two, and five minutes after instillation (P<0.001, P<0.001, P=0.001, and P=0.019, respectively) and compared to ketotifen immediately after instillation (P=0.014). The mean comfort score was significantly lower with ketotifen compared to azelastine at 0.5, one, and two 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. Secondary: Not reported
Greiner et al.[36] (2002) Ketotifen 0.025% as a single dose vs cromolyn sodium 4% QID for 2 weeks (as a loading dose)	AC, RCT, SB Patients ≥18 years of age with a history of allergy to environmental allergens not currently in season	N=56 Single dose	Primary: Signs and symptoms following CAC Secondary: Not reported	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 seven and 15 minutes (P<0.001). Following the 15 minute challenge, cromolyn-treated eyes exhibited more tearing than ketotifen-treated eyes at seven minutes (28 vs 9%) and 15 minutes (13 vs 4%). Following the four-hour challenge, more tearing occurred in cromolyn-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
One eye was treated with the study drug and the other eye was treated with placebo.				treated than in ketotifen-treated eyes at seven minutes (13 vs 6%) and 15 minutes (15 vs 9%). Secondary: Not reported
Greiner et al.[37] (2003) Ketotifen 0.025% in 1 eye and nedocromil 2% in the contralateral eye vs ketotifen 0.025% in 1 eye and artificial tears in the contralateral eye vs nedocromil 2% in 1 eye and artificial tears in the contralateral eye	AC, DB, PC, RCT Patients ≥10 years of age with a history of allergic hypersensitivity	N=59 Single dose	Primary: Ocular itching following CAC Secondary: Not reported	Primary: Peak itching occurred in the range of four to ten minutes after the allergen challenge. The itching response diminished after ten minutes. At both five 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 five-minute data and every time point after 90 seconds post-challenge in the 12-hour data. These treatment differences were significant from two to 18 minutes in the 5-minute data (P<0.05 for all) and from three to 12 minutes in the 12-hour data (P<0.05 for all). Onset of action: The comparison of ketotifen-treated eyes with those that received placebo showed a significant difference from two 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 two 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 three 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. 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 one, two, five, and ten minutes after eye drop instillation (P<0.05). Ketotifen showed no difference from placebo in terms of comfort.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 to 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 to 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. Secondary: Not reported
Avunduk et al.[38] (2005) Ketotifen 0.025% 2 drops in each eye BID vs olopatadine 0.1% 2 drops in each eye BID vs artificial tears 2 drops in each eye BID	DB, RCT 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 bilateral signs of at least moderate severity: conjunctival redness,	N=39 30 days	Primary: Clinical scores (itching, tearing, redness, eyelid, swelling, and chemosis) Secondary: Not reported	Primary: In the ketotifen group, the mean itching scores were significantly lower on days 15 and 30 compared to 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 to 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 to those in the artificial tears 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 to the baseline score (P=0.008 and P=0.014, respectively). The mean tearing scores were significantly lower in the ketotifen-treated patients compared to those in the artificial tears 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 to that on day 0 (P=0.018 and P=0.016, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	conjunctival chemosis, and eyelid swelling			Olopatadine-treated patients had a significantly lower mean tearing score compared to that in the artificial tears 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. Secondary: Not reported
Abelson et al.[39] (2007) Olopatadine 0.1% 1 drop in 1 eye every eight hours for two doses vs olopatadine 0.2% 1 drop in 1 eye once vs placebo Study medications were administered contralaterally.	DB, PC, RCT Patients who responded to the ocular allergen challenge, study used CAC model	N=23 3 weeks (3 visits)	Primary: Ocular itching at three, five and seven minutes following CAC (allergen administered 24 hours after study drug instilled) and safety Secondary: Not reported	Primary: At the 24-hour CAC test, olopatadine 0.1 and 0.2% significantly reduced itching scores compared to placebo (P=0.002 and P=0.0007, respectively). There were no statistically significant differences between patients receiving olopatadine 0.1 and 0.2% (P=0.081). Olopatadine 0.1 and 0.2% were both found to be safe and well tolerated as used in this study. No adverse events were reported. Secondary: Not reported
Spangler et al.[40] (2001) Olopatadine 0.1% in 1 eye and artificial tears in	DB, MC, RCT Patients with allergic conjunctivitis	N=111 Single dose	Primary: Ocular itching following CAC Secondary: Not reported	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
the contralateral eye vs azelastine 0.05% in 1 eye and artificial tears in the contralateral eye vs olopatadine 0.1% in 1 eye and azelastine 0.05% in the contralateral eye				Secondary: Not reported
Katelaris et al.[41] (2002) Olopatadine 0.1% BID vs cromolyn sodium 2% QID	MC, RCT Patients with seasonal allergic conjunctivitis	N=185 6 weeks	Primary: Ocular itching and conjunctival redness Secondary: Not reported	Primary: By day 42, olopatadine was significantly more effective in reducing itching and redness compared to cromolyn sodium (P<0.05). Secondary: Not reported
Lanier et al.[42] (2004) Olopatadine 0.1% in 1 eye and epinastine 0.05% in the contralateral eye	DB, RCT Patients with allergic conjunctivitis	N=66 Single dose	Primary: Itching and conjunctival redness following CAC Secondary: Not reported	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs olopatadine 0.1% in 1 eye and placebo in the contralateral eye vs epinastine 0.05% in 1 eye and placebo in the contralateral eye				Secondary: Not reported
Mah et al.[43] (2007) Olopatadine 0.2% in 1 eye and epinastine 0.05% in the contralateral eye vs olopatadine 0.2% in 1 eye and placebo in the contralateral eye vs epinastine 0.05% in 1 eye and placebo in the contralateral eye vs	DB, PC, RCT Patients with allergic conjunctivitis	N=92 Single dose	Primary: Efficacy and comfort following CAC Secondary: Not reported	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 itching scores in comparison to epinastine 0.05% at five minutes (P=0.024) and seven minutes (P=0.003). There was no significant difference in mean itching scores at three minute post-challenge. Compared to placebo, epinastine 0.05% demonstrated lower mean ciliary redness scores at seven 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 two and five 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 one minute time point (P=0.030). There were no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				differences in eye drop comfort scores at two and five minutes post-instillation. Secondary: Not reported
Aguilar et al.[44] (2000) Olopatadine 0.1% 1 drop every 12 hours vs ketotifen 0.05% 1 drop every 12 hours	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 Secondary: Not reported	Primary: In the olopatadine group, 42.5 to 62.5% of patients showed improvement in signs and symptoms assessed between 0 and 30 minutes 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 seven days of treatment, complete control of all evaluated signs and symptoms was achieved in 80 to 87.5% of patients. In the ketotifen group, 20.0 to 47.5% of patients showed improvement in the signs and symptoms assessed between 0 and 30 minutes 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 seven days of treatment, 60 to 75% of patients showed improvements. With continued treatment through day 14, control of all signs and symptoms evaluated was observed in 67.5 to 75% of patients. Secondary: Not reported
Berdy et al.[45] (2000) Olopatadine 0.1% vs ketotifen 0.025%	DB, RCT Patients with allergic conjunctivitis	N=32 Single dose	Primary: Ocular itching and patient satisfaction following CAC Secondary: Not reported	Primary: Olopatadine was significantly more effective than ketotifen at all time points (three, five, 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 three and five 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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were more satisfied with ketotifen and identified ketotifen as the more tolerable formulation. Secondary: Not reported
Ganz et al.[46] (2003) Olopatadine 0.1% BID vs ketotifen 0.025% BID	AC, DB, PG, RCT 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 two (P<0.0001) and for the patient (P=0.0001) and investigator (P<0.0001) evaluations at visit three. Secondary: The patient-assessed mean global efficacy scores were significantly lower with ketotifen than olopatadine at day five (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 five (P=0.001) and day 21 (P<0.0001). The ketotifen group had significantly lower scores for conjunctival hyperemia at day five (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 five (right; P=0.007, left; P=0.008), and day 21 (right; P<0.0001, left; P<0.0001) compared to olopatadine. There was no significant difference in tearing among the treatment groups at day five or day 21. Between baseline and visit two (days five to eight), 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 one (mild, slightly perceptible sensation). No significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences were found between treatments.
Borazan et al.[47] (2009) Olopatadine 0.1% BID vs ketotifen 0.025% BID vs epinastine 0.05% BID vs emedastine 0.05% BID vs fluorometholone 0.1% BID One eye was treated with study drug and the other eye was treated with placebo.	DB, PC, RCT Patients with seasonal allergic conjunctivitis	N=100 2 weeks	Primary: Patient-assessed signs and symptoms Secondary: Not reported	Primary: Scores for ocular itching, conjunctival redness, tearing, chemosis and eyelid swelling were significantly improved in drug-treated eyes compared to 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 to 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 seven and 14 in the placebo-treated eyes. Secondary: Not reported
Leonardi et al.[48] (2004)	DB, MC Patients with	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	seasonal or perennial allergic conjunctivitis		Secondary: Not reported	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). Secondary: Not reported
Butrus et al.[49] (2000) Olopatadine 0.1% as a single dose vs nedocromil 2% administered for 2 weeks (loading dose)	DB, RCT Patients with allergic conjunctivitis	N=52 Single dose	Primary: Ocular itching and comfort following CAC Secondary: Not reported	Primary: Olopatadine was more efficacious than nedocromil at reducing itching at all time points (three, five, 10 minutes; P<0.0001). Olopatadine was more comfortable than nedocromil (P=0.034). Secondary: Not reported
Alexander et al.[50] (2000)	OL, RCT, XO	N=28	Primary: Patient satisfaction,	Primary: Mean symptom scores for seven ocular symptoms were comparable with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Olopatadine 0.1% 1 drop into each eye BID for 1 week vs nedocromil 2% 1 drop into each eye BID for 1 week	Patients ≥7 years of age with perennial allergic conjunctivitis and use of olopatadine within the previous 12 months	2 weeks	severity of ocular symptoms, clinical signs, quality of life, and global assessments of effectiveness Secondary: Not reported	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.
Owen et al.[51] (2004) Ophthalmic antihistamines (antazoline* one trial, azelastine one trial, emedastine one trial, levocabastine* six trials) vs ophthalmic mast cell stabilizers (cromolyn 17 trials, lodoxamide one trial and nedocromil five trials)	MA (40 DB, RCTs) Patients with seasonal allergic conjunctivitis	N=not reported Duration varied	Primary: Subjective symptoms (e.g., ocular itching, burning, soreness and lacrimation) and patient's perception of improvement in subjective symptoms Secondary: Not reported	Primary: Most trials showed improvement in symptoms, especially for itching, in those treated with antihistamines compared to placebo. No antihistamine was more effective than another. Limited evidence suggests that antihistamines have a faster therapeutic effect compared to mast cell stabilizers; however, there was little difference in treatment efficacy after two weeks. Two short-term allergen provocation trials reported significantly less ocular itching and redness in patients treated with antihistamines compared to patients treated with mast cell stabilizers (P<0.05); however, no significant differences in subjective symptoms were noted in six long-term studies. Patients using antihistamines were 1.3 times (95% CI, 0.8 to 2.2) more likely to perceive a "good" treatment effect compared to patients using mast cell stabilizers; however, this was not statistically significant. Eight studies recorded subjective symptoms comparing cromolyn to placebo. An improvement in subjective symptoms was reported in five studies with no difference between treatments reported in three trials. A

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ophthalmic mast cell stabilizers (cromolyn five trials, lodoxamide one trial and nedocromil two trials) vs placebo				MA of six trials demonstrated that patients using cromolyn were 17 times (95% CI, 4 to 78) more likely to perceive benefit than those using placebo (of note, trials reporting marked and statistically significant benefits of cromolyn over placebo had small sample sizes.) No clinically relevant adverse events were reported with cromolyn treatment. In a small trial lasting four weeks, patients using lodoxamide reported significantly fewer symptoms of burning and itching, eyelid swelling, lacrimation and photophobia compared to those using placebo (P values not reported). Subjective symptoms were less pronounced in patients using nedocromil compared to patients using placebo with the differences reported as statistically significant in three studies. Patients using nedocromil were 1.8 times (95% CI, 1.3 to 2.6) more likely to report that their symptoms were "moderately" or "totally" controlled than those receiving placebo. Unpleasant taste following administration was the most reported adverse event. Patients using mast cell stabilizers were 4.9 times (95% CI, 2.5 to 9.6) more likely to perceive benefit from treatment compared to patients receiving placebo. No trials directly compared mast cell stabilizers with one another. Secondary: Not reported
Allergic Rhinitis				
Stern et al.[52] (1998) Azelastine nasal spray vs budesonide nasal spray	DB, MC, PC, PG, RCT 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	Primary: The reduction in all individual nasal symptoms from baseline was greater with the budesonide group compared to those treated with azelastine ($P \leq 0.05$). 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 six weeks of therapy showed that budesonide was significantly more effective compared to both azelastine and placebo (P=0.013 and P=0.0003 respectively). There was no significant difference between azelastine and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			terfenadine tablets as rescue medication Secondary: Not reported	placebo with respect to the degree of symptom control achieved (P=0.20). The reduction in the use of terfenadine from baseline was significantly greater for budesonide (P=0.0033) and azelastine (P=0.0015) compared to placebo, but there was no difference between the two active treatments (P=0.80). Secondary: Not reported
Corren et al.[53] (2005) Azelastine nasal spray vs cetirizine 10 mg tablets	DB, MC, PG, RCT Patients with moderate to severe seasonal allergic rhinitis	N=229 2 weeks	Primary: Change from baseline to day 12 in the 12-hour reflective TNSS, including rhinorrhea, sneezing, itchy nose, nasal congestion Secondary: Not reported	Primary: Both groups had significant improvements in the TNSS compared to baseline (P<0.001). The overall TNSS was significantly greater with azelastine nasal spray compared to cetirizine (P=0.015). Azelastine nasal spray significantly improved the instantaneous TNSS compared to cetirizine at 60 and 240 minutes after the initial dose (P=0.040). Secondary: Not reported
Shah et al.[54] (2009) Olopatadine 0.6% 2 sprays in each nostril BID vs azelastine 0.1% 2 sprays in each nostril BID vs	AC, DB, MC, PC, PG, RCT Patients ≥12 years of age with a history of seasonal allergic rhinitis	N=544 16 days	Primary: TNSS, quality of life (RQLQ), tolerability Secondary: Not reported	Primary: The mean change from baseline in overall TNSS was significantly greater with olopatadine (26.8%) compared to placebo (18.4%; P=0.003). The mean change from baseline in overall TNSS was 29.9% with azelastine. 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 olopatadine compared to placebo (P=0.005). There was no significant difference between active treatments. The most commonly reported adverse event in the olopatadine and azelastine 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				significantly lower in the olopatadine treatment group compared to the azelastine group (P=0.05). Among patients who reported bitter taste, the proportion who rated the event as severe was significantly lower in the olopatadine group compared to the azelastine group (0 vs 8.1%; P=0.005). The majority of bitter taste events reported in the olopatadine group were mild (72.7%), whereas the majority of these events in the azelastine group were reported as moderate (56.8%). Secondary: Not reported
Meltzer et al.[55] (2008) Olopatadine 0.6% 2 sprays in each nostril vs azelastine 0.1% 2 sprays in each nostril	DB, MC, RCT, 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 Secondary: Not reported	Primary: Overall, 60.6% of the patients favored olopatadine, 30.3% favored azelastine, and 9.2% indicated no preference. Olopatadine was more effective than azelastine in patient perceptions of aftertaste (P<0.0005). For overall patient preference, olopatadine was more effective than azelastine at visit 4 was (P=0.0001). The mean response for likelihood of use (0.8 U) indicated a preference for olopatadine over azelastine (P=0.0004). Overall, 62.4 and 60.9% of patients favored olopatadine in regards to patient preference and likelihood of use, respectively. Olopatadine was shown to be statistically superior to azelastine in patient perceptions of taste immediately after study drug administration (P<0.0001). Immediately after dosing, patients reported a significant difference in favor of olopatadine relative to azelastine 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 olopatadine relative to azelastine was observed for nasal irritation (P=0.0048), urge to sneeze (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 olopatadine in all of the assessed variables

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P≤0.0036 for each variable). Secondary: Not reported
Multiple Ocular Infections				
Kjellman et al.[56] Nedocromil 2% BID or QID vs placebo Additional information was not provided.	MA (26 trials) Patients 3 to 76 years of age with seasonal allergic conjunctivitis, perennial allergic conjunctivitis, and vernal kerato-conjunctivitis	N=2,905 Duration varied	Primary: Efficacy, safety Secondary: Not reported	Primary: In the treatment of vernal keratoconjunctivitis, nedocromil QID was significantly more effective than placebo (P value not reported). Clinicians reported good control in 76 and 46% of patients receiving nedocromil and placebo, respectively (P<0.001). Nedocromil when dosed either BID or QID was statistically better than placebo for the treatment of seasonal allergic conjunctivitis (P value not reported). The speed of action was assessed in seven trials with 50 and 74% of patients experiencing relief of symptoms within 15 and 60 minutes after dosing, respectively. Patients with chronic symptoms of perennial allergic conjunctivitis responded better to nedocromil QID compared to BID, and significantly more patients were effectively controlled by nedocromil QID (72%) compared to placebo (47%; P value not reported). Nedocromil was well accepted in both adults and children with no major adverse events reported. Minor irritations, burning, or stinging of the eyes and a distinctive taste were reported more frequently with nedocromil than placebo (P values not reported). Secondary: Not reported
Vernal Keratoconjunctivitis				
Foster.[57] (1998) Cromolyn 4% both eyes vs	DB, MC, PC, RCT Patients with bilateral vernal kerato-conjunctivitis (age not reported)	N=65 6 weeks	Primary: Signs and symptoms, symptoms summary score Secondary:	Primary: Cromolyn was found to be significantly more effective than placebo in treating the signs and symptoms of vernal keratoconjunctivitis, such as conjunctival injection, limbal injection, limbal edema, tearing, and symptoms summary score (P values not reported). There were few side effects (primarily mild stinging and burning, which

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Additional information was not reported.			Not reported	did not require drug discontinuation). Secondary: Not reported
Leonardi et al.[58] (1997) Cromolyn 4% both eyes QID vs lodoxamide 0.1% both eyes QID	DB, RCT Patients with mild to moderate vernal kerato-conjunctivitis, mean age 12 years	N=30 10 days	Primary: Clinical score for major signs and symptoms of vernal kerato-conjunctivitis Secondary: Not reported	Primary: The mean clinical score for signs and symptoms of vernal keratoconjunctivitis did not improve significantly from baseline in patients treated with cromolyn but improved significantly in patients treated with lodoxamide (P<0.001). The mean clinical score was unchanged in 42 and 15% of the cromolyn and lodoxamide treated eyes, respectively. Lodoxamide was significantly more effective than cromolyn (P<0.005) in reducing chemosis, discharge, foreign body sensation, hyperemia, itching, photophobia, tearing, and corneal epitheliopathy; but not limbal infiltrates and papillae. Secondary: Not reported
Caldwell et al.[59] (1992) Cromolyn 4% QID vs lodoxamide 0.1% QID Additional information was not reported.	DB, MC, PG Patients with vernal kerato-conjunctivitis	N=120 28 days	Primary: Signs and symptoms Secondary: Not reported	Primary: On various follow-up visits, the clinical efficacy of lodoxamide was statistically "superior" to cromolyn in alleviating five of the major signs (Trantas' dots, palpebral conjunctival changes, bulbar conjunctival hyperemia, erythema/swelling of eyelids and periorbital tissues, and epithelial disease) and four of the primary symptoms (discomfort, foreign body sensation, itching, and tearing) of vernal keratoconjunctivitis (P values not reported). At no time during the study was cromolyn statistically "superior" to lodoxamide in demonstrating improvements in clinical signs and symptoms of vernal keratoconjunctivitis. The physician's clinical judgment of patients' response to treatment showed lodoxamide produced a greater and earlier improvement than cromolyn. Both drugs were safe for topical ophthalmic use when used QID for up to 28 days.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Avunduk et al.[60] (2000) Cromolyn 4% 2 drops both eyes QID vs lodoxamide 0.1% 2 drops both eyes QID	DB, RCT Patients with vernal kerato-conjunctivitis, mean age 13 years	N=30 Duration not reported	Primary: Eye symptom severity scores Secondary: Not reported	Primary: Patient symptom scores and clinical signs were significantly lower after treatment with either cromolyn or lodoxamide compared to pretreatment values (P<0.025). Patients treated with lodoxamide had significantly lower symptom scores and clinical signs than patients treated with cromolyn (P<0.025). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily
Study Design abbreviations: AC=active controlled, DB=double blind, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=cross over
Miscellaneous abbreviations: CAC=conjunctival allergen challenge, CI=confidence interval, MAR=minimum angle of resolution, NOCS=non-ocular composite symptom, OPI=Ocular Protection Index, RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire, TNSS=total nasal symptom score

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 Eye, Ear, Nose, and Throat (EENT) Antiallergic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alcaftadine	solution*	Lastacaft®	$$$$	N/A
Azelastine	solution*†	Astepro®*†‡, Optivar®*‡	$$$$	$$$$
Bepotastine	solution*	Bepreve®	$$$$	N/A
Cromolyn	solution*†§	N/A	N/A	$$$$
Emedastine	solution*	Emadine®	$$$$	N/A
Epinastine	solution*	Elestat®‡	$$$$	$$$$
Lodoxamide	solution*	Alomide®	$$$$	N/A
Nedocromil	solution*	Alocril®	$$$$	N/A
Olopatadine	solution*†	Pataday®*, Patanase®*†‡, Patanol®*, Pazeo®*	$$$$	$$$$

*Ophthalmic formulation.
†Nasal formulation.
‡Generic is available in at least one dosage form and/or strength.
§Product is available over-the-counter (cromolyn nasal formulation only).
N/A=not available.

X. Conclusions

The eye, ear, nose, and throat (EENT) antiallergic agents are approved for the treatment of allergic conjunctivitis and rhinitis. They are available in both nasal and ophthalmic formulations.[1-15] Emedastine is a relatively selective,

histamine H_1-receptor antagonist. Cromolyn, lodoxamide, nedocromil, and pemirolast are mast cell stabilizers. Azelastine, bepotastine, epinastine, and olopatadine have dual actions that offer a combination of these two mechanisms (i.e., they are antihistamines with mast cell stabilizing properties).[1,2] 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. 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. 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 five to fourteen days; therefore, they are not useful for treating acute symptoms.[16-21]

There are relatively few comparative studies that have been conducted with the EENT antiallergic agents in a 'real-life' setting. 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.[23,24,29,35,38,41,44,46-48,50,54,55,58-60] Many comparative studies have been performed using environmental challenge chambers. However, the antiallergic agents are typically administered as a single dose and the clinical outcomes are assessed after several minutes or hours.[32-34,36,37,40,42,43,45,49]

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 generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand eye, ear, nose, and throat (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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Antibacterials
AHFS Class 520404
November 4, 2015

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.[1-40] 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.[8]

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.[41,42] Bacterial conjunctivitis is highly contagious and symptoms include redness of the eye and thick, purulent discharge.[43,44] Common pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis,* and *Haemophilus influenzae*.[44] Bacterial conjunctivitis is a self-limiting condition; however, the use of topical antibacterials may shorten the clinical course and reduce transmission to others.[43,44] 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. Antibacterials containing corticosteroids are generally not appropriate for the acute treatment of bacterial conjunctivitis.[44] Corneal abrasions may occur spontaneously or may be due to trauma, the presence of a foreign body, or contact lenses. The prophylactic use of topical antibacterials is often employed to prevent superinfections.[45] Keratitis is an inflammatory condition affecting the cornea and is associated with moderate to intense pain.[46] Common pathogens include *Staphylococcus* species, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae,* and polymicrobial isolates. 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.[46,47] Antibacterials containing corticosteroids should not be used in the initial treatment of bacterial keratitis.[46] 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.[46,48] Staphylococci are the major pathogens in endophthalmitis. 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.[48]

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.[49,50] Topical antibacterials (alone or in combination with a corticosteroid) are very effective and systemic therapy is generally not required.[49,51] Acute otitis media is an inflammatory condition of the middle ear with middle ear effusion and symptoms include otalgia, hearing loss, and vertigo. Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis*.[52,53] 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.[53,54]

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 human immunodeficiency virus infection. 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.[55,56]

Periodontitis is an inflammatory condition of the periodontium, which is due to the presence of bacterial plaque on adjacent teeth.[57] 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.[8,58] 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.[8]

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. This class was last reviewed in August 2013.

Table 1. EENT Antibacterials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Azithromycin	solution*	AzaSite®	none
Bacitracin	ointment*	N/A	bacitracin
Besifloxacin	suspension*	Besivance®	none
Ciprofloxacin	ointment*, solution*§‡	Ciloxan®§	ciprofloxacin
Doxycycline	tablet	N/A	doxycycline
Erythromycin base	ointment*	Ilotycin®§	erythromycin base
Gatifloxacin	solution*	Zymaxid®§	gatifloxacin
Gentamicin	ointment*, solution*	Garamycin®§	gentamicin
Levofloxacin	solution*	N/A	levofloxacin
Moxifloxacin	solution*	Moxeza®, Vigamox®	none
Mupirocin	nasal ointment	Bactroban Nasal®	Bactroban Nasal®
Ofloxacin	solution*†	Ocuflox®§	ofloxacin
Sulfacetamide	ointment*, solution*	Bleph-10®§	sulfacetamide
Tobramycin	ointment*, solution*	Tobrex®§	tobramycin, Tobrex®§
Combination Products			
Bacitracin and polymyxin B	ointment*	N/A	bacitracin and polymyxin B
Ciprofloxacin and dexamethasone	suspension†	Ciprodex®	Ciprodex®
Ciprofloxacin and hydrocortisone	suspension†	Cipro HC®	Cipro HC®
Gentamicin and prednisolone	ointment*, suspension*	Pred-G®	none
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
Neomycin, polymyxin B and hydrocortisone	solution†, suspension*†	N/A	neomycin, polymyxin B and hydrocortisone
Polymyxin B and trimethoprim	solution*	Polytrim®§	polymyxin B and trimethoprim
Sulfacetamide and prednisolone	ointment*, solution*§, suspension*	Blephamide®	sulfacetamide and prednisolone, Blephamide®,

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
			Blephamide S.O.P.®
Tobramycin and dexamethasone	ointment*, suspension*	TobraDex®, TobraDex ST®	tobramycin and dexamethasone
Tobramycin and loteprednol	suspension*	Zylet®	none

*Ophthalmic formulation.
†Otic formulation.
‡Otic formulation available generically in at least one dosage form and/or strength.
§Generic is available in at least one dosage form and/or strength.
N/A=Not available, PDL=Preferred Drug List

The EENT antibacterials have been shown to be active against the strains of microorganisms indicated in Tables 2 and 3. 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 5 and 6.

Table 2. Microorganisms Susceptible to the EENT Antibacterials-Single Entity Agents[1-40]

Organism	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Gram-Positive Aerobes														
CDC coryneform group g	✔		✔											
Corynebacterium propinquum							✔							
Corynebacterium pseudodiphtheriticum			✔											
Corynebacterium striatum			✔											
Corynebacterium species		✔				✔			✔	✔				
Micrococcus luteus										✔				
Staphylococcus aureus	✔	✔	✔	✔		✔	✔	✔	✔	✔		✔	✔	✔
Staphylococcus aureus (methicillin-resistant)											✔			
Staphylococcus epidermidis			✔	✔			✔	✔	✔	✔		✔		✔
Staphylococcus haemolyticus										✔				
Staphylococcus hominis			✔							✔				
Staphylococcus lugdunensis			✔											
Staphylococcus species		✔												
Staphylococcus warneri										✔				
Streptococcus mitis group	✔		✔				✔							
Streptococcus oralis			✔				✔							
Streptococcus pneumoniae	✔	✔	✔	✔		✔	✔	✔	✔	✔		✔	✔	✔
Streptococcus pyogenes		✔				✔		✔						
Streptococcus salivarius			✔											
Streptococcus species		✔												✔
Streptococcus (Groups C/F)									✔					
Streptococcus (Group G)									✔					
Streptococcus (Viridans Group)				✔		✔			✔	✔			✔	
Gram-Negative Aerobes														
Acinetobacter calcoaceticus														✔
Acinetobacter lwoffi									✔	✔				
Chlamydia trachomatis						✔				✔				
Enterobacter aerogenes								✔						✔
Enterobacter cloacae												✔		
Enterobacter species													✔	
Escherichia coli								✔				✔	✔	✔
Haemophilus aegyptius														✔
Haemophilus influenzae	✔		✔	✔		✔	✔	✔	✔	✔		✔	✔	✔
Haemophilus parainfluenzae										✔				
Klebsiella pneumoniae								✔					✔	✔
Moraxella catarrhalis												✔		
Moraxella lacunata			✔											✔
Morganella morganii														✔
Neisseria gonorrhea		✔				✔		✔						
Neisseria species		✔												✔

Organism	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Proteus mirabilis												✔		✔
Proteus vulgaris														✔
Pseudomonas aeruginosa				✔				✔	✔			✔		
Serratia marcescens				✔				✔	✔			✔		
Anaerobic Species														
Propionibacterium acnes												✔		

Table 3. Microorganisms Susceptible to the EENT Antibacterials-Combination Products[1-40]

Organism	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth-oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Gram-Positive Aerobes														
Corynebacterium species	✔													
Micrococcus luteus														
Staphylococcus aureus	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Staphylococcus aureus (methicillin-resistant)														
Staphylococcus epidermidis													✔	✔
Staphylococcus haemolyticus														
Staphylococcus hominis														
Staphylococcus species	✔													
Staphylococcus warneri														
Streptococcus pneumoniae	✔	✔		✔	✔	✔			✔		✔	✔	✔	✔
Streptococcus pyogenes	✔			✔										
Streptococcus species	✔												✔	✔
Streptococcus (Groups C/F)														
Streptococcus (Group G)														

Organism	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth-oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Streptococcus (Viridans Group)												✔		
Gram-Negative Aerobes														
Acinetobacter calcoaceticus													✔	✔
Acinetobacter lwoffi														
Chlamydia trachomatis														
Enterobacter aerogenes	✔			✔							✔		✔	✔
Enterobacter species					✔	✔	✔	✔	✔	✔		✔		
Escherichia coli	✔			✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Haemophilus aegyptius													✔	✔
Haemophilus influenzae	✔	✔		✔	✔	✔		✔	✔	✔	✔	✔	✔	✔
Haemophilus parainfluenzae														
Klebsiella pneumoniae	✔			✔	✔	✔	✔				✔	✔	✔	✔
Klebsiella species								✔	✔	✔				
Moraxella catarrhalis		✔												
Moraxella lacunata													✔	✔
Morganella morganii													✔	✔
Neisseria gonorrhoeae	✔			✔										
Neisseria species	✔				✔	✔		✔	✔	✔			✔	✔
Proteus mirabilis			✔										✔	✔
Proteus species											✔			
Proteus vulgaris													✔	✔
Pseudomonas aeruginosa	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔
Serratia marcescens				✔										

BAC=bacitracin, CIPRO=ciprofloxacin, COL=colistin, DEX=dexamethasone, GRAM=gramicidin, HYDRO=hydrocortisone, NEO=neomycin, POLY=polymyxin B, PRED=prednisolone, THON=thonzonium, TOBY=tobramycin

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the eye, ear, nose, and throat (EENT) antibacterials are summarized in Table 4.

Table 4. Treatment Guidelines Using the EENT Antibacterials

Clinical Guideline	Recommendations

American Academy of Ophthalmology: **Preferred Practice Pattern: Blepharitis (2013)**[41]	• Topical antibiotics have been shown to provide some symptomatic relief, and they have been effective in decreasing bacteria from the eyelid margin in cases of anterior blepharitis.
	• Eyelid hygiene may provide symptomatic relief for both anterior and posterior blepharitis.
	• Evidence on the effectiveness of other treatments for blepharitis, such as topical corticosteroids or oral antibiotics, has been shown to be inconclusive, and cure is not possible in most cases.
	• Treatments that are helpful include the following:
	  o Warm compresses.
	  o Eyelid cleansing, including eyelid massage in cases of meibomian gland dysfunction (MGD) to express the meibomian glands.
	  o Antibiotics (topical and/or systemic).
	  o Ophthalmic anti-inflammatory agents (e.g., corticosteroids, cyclosporine).
	• These treatment options are often used in combination.
	• Eyelid cleansing is especially useful for anterior blepharitis, and warm compresses are especially helpful for posterior blepharitis.
	• Optimal treatment regimens often require a trial and error approach.
	• An ophthalmic antibiotic ointment such as ophthalmic bacitracin or ophthalmic erythromycin can be prescribed and applied on the eyelid margins one or more times daily or at bedtime for one or more weeks. The frequency and duration of treatment should be guided by the severity of the blepharitis and response to treatment. In severe cases or for patients who do not tolerate ointment, metronidazole gel applied to the eyelid skin is an alternative treatment, although it has not been approved by the Food and Drug Administration (FDA) for this indication.
	• The combination of tobramycin/dexamethasone ophthalmic suspension and azithromycin in a sustained-release system has been evaluated and appears to reduce some of the symptoms of blepharitis, but its use for this indication has not been approved by the FDA.
	• For patients with MGD, whose chronic signs and symptoms 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 recolonization of normal flora.
	• Ophthalmic corticosteroid eye drops or ointments are typically applied several times daily to the eyelids or ocular surface.
	• Once the inflammation is controlled, the ophthalmic corticosteroid can be tapered and discontinued and then used intermittently to maintain patient comfort.
	• The minimal effective dose of ophthalmic corticosteroid should be utilized, and long-term ophthalmic corticosteroid therapy should be avoided if possible.
	• Potential adverse effects of ophthalmic corticosteroid use, including the risk for developing increased intraocular pressure and cataracts may be minimized by using a site-specific ophthalmic corticosteroid such as ophthalmic loteprednol etabonate and ophthalmic corticosteroids with limited ocular penetration, such as ophthalmic fluorometholone.
	• Topical cyclosporine may be helpful in some patients with posterior blepharitis.

Clinical Guideline	Recommendations
	• 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 (2013)**[43]	Seasonal allergic conjunctivitis • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a low-potency topical corticosteroid can be added to the regimen. • A nonsteroidal anti-inflammatory agent (ketorolac) has been Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. • Additional measures include the use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful. • Use of topical mast-cell stabilizers can also be helpful in alleviating symptoms of allergic rhinitis, and intranasal corticosteroids are not effective for the treatment of seasonal allergic conjunctivitis. Vernal/atopic conjunctivitis • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) 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 warranted rarely. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma.
American Optometric Association: **Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2007)**[59]	Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) • The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. • The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. • Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). • Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1

Clinical Guideline	Recommendations
	receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. • Topical diclofenac and ketorolac, which are both NSAIDS, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. • Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%†) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2† or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. • Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. • Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. • Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness. <u>Viral conjunctivitis</u> • Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. • Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates, or alleviating symptoms. • Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. • The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. • Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. • Topical steroids are specifically contraindicated for treating herpes simplex conjunctivitis.
American Academy of Ophthalmology: **Preferred Practice Pattern: Bacterial Keratitis (2013)**[47]	<u>Initial treatment</u> • Ophthalmic antibiotic eye drops are the preferred method of treatment in most cases of bacterial keratitis. • Ophthalmic ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy. • Ophthalmic broad-spectrum antibiotics are used initially in the empiric treatment of bacterial keratitis.

Clinical Guideline	Recommendations

	• The recommended ophthalmic empiric treatments include:
	  o No organism identified or multiple types of organisms: ophthalmic cefazolin sodium (with gentamicin sulfate/tobramycin) or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones).
	  o Gram-positive cocci: ophthalmic cefazolin sodium, vancomycin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), ophthalmic bacitracin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones).
	  o Gram-negative rods: ophthalmic formulations of tobramycin or gentamicin sulfate, ceftazidime, or fluoroquinolones.
	  o Gram-negative cocci: ophthalmic ceftazidime, ceftriaxone sodium, or fluoroquinolones (systemic therapy is necessary for suspected gonococcal infection).
	  o Nontuberculous mycobacteria: ophthalmic amikacin sulfate, azithromycin, clarithromycin, or fluoroquinolones.
	  o Nocardia: ophthalmic amikacin sulfate, sulfacetamide sodium, or trimethoprim/sulfamethoxazole.
	• Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics. Ciprofloxacin 0.3%, ofloxacin 0.3% and levofloxacin 1.5% are FDA-approved for this indication. The fourth generation fluoroquinolones (gatifloxacin and moxifloxacin) have not been approved for the treatment of bacteria keratitis; however, both agents have performed at least as well as standard therapy, fortified cefazolin/tobramycin combination therapy and potentially better than ciprofloxacin.
	• Some pathogens (e.g., *Streptococci*, anaerobes) reportedly have variable susceptibility to ophthalmic fluoroquinolones, and the prevalence of resistance to fluoroquinolones appears to be increasing.
	• Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to initial treatment.
	• Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with laser in situ keratomileusis.
	• MRSA has been isolated with increasing frequency from patients with bacterial keratitis and has been reported following kerato-refractive surgery. Ophthalmic fluoroquinolones are generally poorly effective against MRSA ocular isolates. MRSA isolates are generally sensitive to ophthalmic 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>Corticosteroid therapy</u>
	• Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis due to the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss.
	• Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting and increased intraocular pressure.
	• There is no conclusive evidence that ophthalmic corticosteroids alter clinical

Clinical Guideline	Recommendations
	outcome. • Despite risks involved, it is believed that sensible use of ophthalmic corticosteroids can reduce morbidity. • Patients being treated with ophthalmic corticosteroids at the time of presentation of suspected bacterial keratitis should have their ophthalmic corticosteroid regimen reduced or eliminated until the infection has been controlled. • Inflammation may temporarily increase as ophthalmic corticosteroids are reduced. • The minimum amount of ophthalmic corticosteroid required should be used to achieve control of inflammation. • Ophthalmic 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 ophthalmic corticosteroids in the initial treatment of corneal ulcers has been determined to be a risk factor for requiring a penetrating keratoplasty. • Ophthalmic antibiotics, which are generally administered more frequently than ophthalmic corticosteroids during treatment of active infection, are continued at high levels and tapered gradually. • Patient compliance is essential; intraocular pressure must be monitored frequently, and the patient should be examined within one to two days after initiation of ophthalmic corticosteroid therapy. Modification of therapy • Efficacy of the regimen is judged primarily by 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. • The initial therapeutic regimen should be modified (change in type, concentration or frequency of antibiotic) when the eye shows a lack of improvement or stabilization within 48 hours. • Most antibiotic eye drops should not be tapered below three to four times a day, because low doses are sub-therapeutic and may increase the risk of developing antibiotic resistance.
American Optometric Association: **Care of the Patient with Ocular Surface Disorders (2010)**[60]	Blepharitis • Lid hygiene is essential but alone will not resolve blepharitis. • Appropriate anti-infective drugs can be administered topically, systemically, or in combination. • Aggressive therapy should initially include a minimum of six weeks of lid hygiene and appropriate anti-infective medications to gain control of the condition, followed by maintenance therapy. • For patients without lid margin disease, the initial treatment consists of topical tear supplements and immunomodulators. Failure to respond should prompt pursuit of signs of posterior blepharitis. Staphylococcal blepharitis • Treatment includes an antibiotic ointment to control the infection, as well as lid hygiene. • Erythromycin, bacitracin, polymyxin B and bacitracin combination, 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

Clinical Guideline	Recommendations
	steroids may be used for a limited time.
American Academy of Otolaryngology-Head and Neck Surgery Foundation: **Clinical Practice Guideline: Acute Otitis Externa (2014)**[49]	• Other causes of otalgia, otorrhea, and inflammation of the external ear canal should be distinguished when diagnosing patients with diffuse acute otitis externa (AOE). • Patients with diffuse AOE should be assessed for factors that modify management strategies such as nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, and prior radiotherapy. • A diagnosis of diffuse AOE requires rapid onset of symptoms with signs of ear canal inflammation. Other symptoms include otalgia, itching, or fullness, with or without hearing loss or ear canal pain on chewing. In addition, tenderness of the tragus (when pushed), pinna (when pulled up and back), or both is a hallmark sign of diffuse AOE. • The management of diffuse AOE should include an assessment of pain with the clinician recommending analgesic treatment based on severity. • Clinicians should use topical preparations for initial therapy of diffuse, uncomplicated AOE. If the infection extends outside of the ear canal or there is presence of specific host factors that would indicate for systemic therapy, systemic antimicrobial therapy should be administered. • Topical preparations are recommended as initial therapy because of safety and efficacy over placebo in randomized controlled trials, and excellent clinical and bacteriologic outcomes in comparative studies. • The choice of topical antimicrobial agent should be based upon efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost. • Most of the currently available agents provide antimicrobial activity through an antibiotic, which may be an aminoglycoside, polymyxin B, a quinolone, or a combination of these agents; a steroid, such as dexamethasone or hydrocortisone; or a low pH antiseptic, such as acetic acid or aluminum acetate. • No significant differences in clinical outcomes of AOE were found for use of antimicrobial vs an antiseptic, a quinolone antibiotic vs a nonquinolone antibiotic(s), or a steroid-antimicrobial agent vs an antimicrobial agent alone. • Due to the lack of differences in efficacy among most topical antimicrobial and steroid preparations, patient preference and clinician experience are important aspects when selecting therapy. In addition, cost, adherence to therapy, and adverse events must also be taken into consideration. • Clinicians should inform patients of the proper way to administer topical drops. When the ear canal is obstructed, delivery of topical preparations should be enhanced by aural toilet, placement of a wick, or both. • When the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube, the clinician should prescribe a non-ototoxic topical preparation. • Patients who fail to respond to initial therapy within 48 to 72 hours should be reassessed to confirm the diagnosis of AOE and to exclude other causes of illness.
American Academy of Otolaryngology–Head and Neck Surgery: **Consensus Panel on Role of Potentially Ototoxic Antibiotics for Topical Middle Ear Use (2004)**[61]	• When possible, topical antibiotic preparations free of potential ototoxicity should be used in preference to ototopical preparations that have the 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.

Clinical Guideline	Recommendations
	• 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: **Diagnosis and Treatment of Otitis Media in Children (2008)**[62]	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 to 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: **Diagnosis and Management of Acute Otitis Media (2013)**[52]	• Clinicians should diagnose acute otitis media (AOM) in children who present with moderate to severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa. • Clinicians should diagnose AOM in children who present with mild bulging of the TM and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM. • The management of AOM should include an assessment of pain. The management of pain, especially during the first 24 hours of an episode of AOM, should be addressed regardless of the use of antibiotics. • The clinician should prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 months and older with severe signs or symptoms (i.e., moderate or severe otalgia or otalgia for at least 48 hours, or temperature 102.2°F or higher). • The clinician should prescribe antibiotic therapy for bilateral AOM in children younger than 24 months without severe signs or symptoms (i.e., mild otalgia for less than 48 hours, temperature less than 102.2°F). • The clinician should either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for unilateral AOM in children 6 months of age and older without severe signs or symptoms. • High-dose amoxicillin is recommended as the first-line treatment in most

Clinical Guideline	Recommendations
	patients, although there are a number of medications that are clinically effective. • Clinicians should prescribe amoxicillin for AOM when a decision to treat with antibiotics has been made and the child has not received amoxicillin in the past 30 days or the child does not have concurrent purulent conjunctivitis or the child is not allergic to penicillin. • Clinicians should prescribe an antibiotic with additional β-lactamase coverage for AOM when a decision to treat with antibiotics has been made and the child has received amoxicillin in the past 30 days or has concurrent purulent conjunctivitis or has a history of recurrent AOM unresponsive to amoxicillin. • Clinicians should reassess the patient if the caregiver reports that the child's symptoms have worsened or failed to respond to the initial antibiotic treatment within 48 to 72 hours and determine whether a change in therapy is needed. • In children with persistent, severe symptoms of AOM and unimproved otologic findings after initial treatment, the clinician may consider changing the antibiotic. If the child was initially treated with amoxicillin and failed to improve, amoxicillin-clavulanate should be used. Patients who were given amoxicillin-clavulanate or oral third-generation cephalosporins may receive intramuscular ceftriaxone (50 mg/kg). • In the treatment of AOM unresponsive to initial antibiotics, a 3-day course of ceftriaxone has been shown to be better than a 1-day regimen. • Clinicians should NOT prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM.
Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **Strategies to Prevent Transmission of Methicillin-Resistant *Staphylococcus aureus* in Acute Care Hospitals (2014)**[63]	• 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 eye, ear, nose, and throat (EENT) antibacterials are noted in Tables 5 and 6. 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 5. FDA-Approved Indications for the EENT Antibacterials-Single Entity Agents[1-40]

Indication(s)	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Ocular Disorders														
Acute bacterial meibomianitis								✔						
Bacterial blepharitis								✔						
Bacterial blepharoconjunctivitis								✔						
Bacterial conjunctivitis	✔		✔	✔		✔	✔	✔	✔	✔		✔	✔	
Bacterial corneal ulcers				✔ *		✔		✔				✔		
Bacterial dacryocystitis								✔						
Bacterial keratitis								✔						
Bacterial keratoconjunctivitis								✔						
Ocular infections due to susceptible microorganisms		✔											✔	✔
Prophylaxis of ophthalmia neonatorum due to *N gonorrhoeae* or *C trachomatis*						✔								
Otic Disorders														
Acute otitis media				✔								✔		
Chronic suppurative otitis media												✔		
Otitis externa												✔		
Miscellaneous Disorders														
Adjunct in systemic sulfonamide therapy of trachoma													✔ *	
Adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis					✔									
Eradication of nasal colonization with methicillin-resistant *S aureus* in adult patients											✔			

Indication(s)	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant *S aureus* infection during institutional outbreaks of infections with this pathogen														

*Solution.

Table 6. FDA-Approved Indications for the EENT Antibacterials-Combination Products[1-40]

Indication(s)	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth-oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Ocular Disorders														
Bacterial blepharitis					✓				✓					
Bacterial blepharo-conjunctivitis					✓				✓		✓			
Bacterial conjunctivitis	✓				✓				✓		✓			
Bacterial corneal ulcers	✓													
Bacterial keratitis					✓				✓					
Bacterial kerato-conjunctivitis					✓				✓					
Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists				✓		✓		✓		✓*		✓	✓	✓
Otic Disorders														
Acute otitis externa		✓	✓											

Indication(s)	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth-oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Acute otitis media		✔												
Bacterial infections of the external auditory canal							✔			✔				
Infections of mastoidectomy and fenestration cavities							✔			✔*				

*Suspension.
BAC=bacitracin, CIPRO=ciprofloxacin, COL=colistin, DEX=dexamethasone, GRAM=gramicidin, HYDRO=hydrocortisone, NEO=neomycin, POLY=polymyxin B, PRED=prednisolone, THON=thonzonium, TOBY=tobramycin

IV. Pharmacokinetics

There is limited or no data available regarding the pharmacokinetic properties of the eye, ear, nose, and throat (EENT) antibacterial agents.[1-40] The pharmacokinetic parameters of oral doxycycline are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Eye, Ear, Nose, and Throat (EENT) Antibacterials[2]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Doxycycline	Well absorbed (% not reported)	80 to 93	Liver (50)	Renal (35 to 45)	15 to 24

V. Drug Interactions

In general, drug interaction studies have not been completed with the eye, ear, nose, and throat (EENT) antibacterial agents. Significant drug interactions with oral doxycycline are listed in Table 8.

Table 8. Significant Drug Interactions with the Eye, Ear, Nose, and Throat (EENT) Antibacterials[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
EENT antibacterials (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.
EENT antibacterials (doxycycline)	1	Anticoagulants	Hypoprothrombinemic effects of anticoagulants may be increased by doxycycline. Bleeding may occur.
EENT antibacterials (doxycycline)	1	Isotretinoin	Concurrent administration of isotretinoin and doxycycline may increase the risk of pseudotumor cerebri. The mechanism of this interaction is unknown.
EENT antibacterials (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.
EENT antibacterials (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.
EENT antibacterials (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.
EENT antibacterials (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
EENT antibacterials (doxycycline)	2	Digoxin	Tetracyclines may reverse the gastrointestinal metabolism of digoxin to inactive metabolites by altering gastrointestinal flora, allowing for more digoxin to be absorbed and increasing digoxin serum levels.
EENT antibacterials (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.
EENT antibacterials (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.
EENT antibacterials (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 gastrointestinal disturbances (vomiting and diarrhea). Lower plasma concentrations of certain contraceptive steroids (because of reduced enterohepatic circulation/reabsorption) may result.
EENT antibacterials (doxycycline)	2	Penicillins	The antimicrobial effectiveness of penicillins may be decreased. Doxycycline may interfere with the bactericidal activity of penicillins.
EENT antibacterials (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 eye, ear, nose, and throat (EENT) antibacterials are listed in Tables 9 and 10.

Table 9. Adverse Drug Events (%) Reported with the EENT Antibacterials-Single Entity Agents[1-40]

Adverse Event(s)	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Central Nervous System														
Dizziness	-	-	-	-	-	-	-	-	-	-	-	≤1	-	-
Hallucinations	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Headache	-	-	1 to 2	2 to 3	26	-	1 to 4	-	1 to 10	-	9	≤1	-	-
Migraine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Vertigo	-	-	-	-	-	-	-	-	-	-	-	≤1	-	-
Dermatological														
Alopecia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Contact dermatitis	<1	-	-	-	-	-	-	-	-	-	-	-	-	-
Edema	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fungal dermatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	-	-	-	1	1 to 4	-	-
Rash	-	-	-	-	4	-	-	-	-	1 to 4	<1	1	-	-
Urticaria	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal														
Acid indigestion	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	6	-	-	-	1 to 2	-	<1	-	-	-
Dysgeusia	-	-	-	-	-	-	≥1	-	-	-	-	-	-	-
Dyspepsia	-	-	-	-	6	-	-	-	1 to 2	-	-	-	-	-
Nausea	-	-	-	<1	8	-	-	-	1 to 2	-	<1	-	-	-
Taste disturbance	<1	-	-	<10	-	-	1 to 4	-	-	-	-	-	-	-
Ophthalmic/Otic														
Application site reaction	-	-	-	-	-	-	-	-	-	-	-	1 to 17	-	-
Blepharitis	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Blurred vision	-	-	1 to 2	-	-	-	-	-	1 to 2	-	-	-	-	-
Burning	<1	-	-	✔	-	-	-	✔	1 to 2	1 to 6	-	✔	✔	-
Chemosis	-	-	-	-	-	-	1 to 4	-	<1	-	-	-	-	-
Conjunctival epithelial defects	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Conjunctival hemorrhage	-	-	-	-	-	-	1 to 4	-	-	1 to 6	-	-	-	-
Conjunctival redness	-	-	2	<10	-	✔	5 to 10	-	-	1 to 6	-	✔	✔	✔
Conjunctivitis	-	-	-	-	-	-	-	✔	-	-	-	-	-	-
Corneal erosion	<1	-	-	-	-	-	-	-	<1	-	-	-	✔	-
Corneal infiltrates	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Corneal staining	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Crystals/scales	-	-	-	<10	-	-	-	-	-	-	-	-	-	-
Decreased vision	-	-	-	<1	-	-	1 to 4	-	-	-	-	-	-	-

Adverse Event(s)	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Decreased visual acuity	-	-	-	-	-	-	-	-	-	1 to 6	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-	<1		-	-	-	-
Discomfort	-	-	-	✔	-	-	-	-	1 to 2	1 to 6	-	-	-	-
Dry eyes	<1	-	-	-	-	-	1 to 4	-		1 to 6	-	✔	-	-
Earache	-	-	-	-	-	-	-	-	-	-	-	≤1	-	-
Ear congestion	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear debris	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear discomfort	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear erythema	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear infection	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear pain	-	-	-	-	-	-	≥1	-	-	-	<1	-	-	-
Ear precipitate	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear pruritus	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eye discharge	<1	-	-	-	-	-	1 to 4	-	-	-	-	-	-	-
Eye irritation	1 to 2	-	1 to 2	-	-	-	≥1	-	-	-	-	-	-	-
Eye pain	-	-	1 to 2	-	-	-	1 to 4	-	-	-	-	-	-	-
Eye pruritus	-	-	1 to 2	<10	-	-	-	-	-	-	-	-	-	-
Floaters	-	-	-	-	-	-	-	-	<1	-	-	-	-	-
Foreign body sensation	-	-	-	<10	-	-	-	-	1 to 3	-	-	✔	-	-
Hyperemia	-	-	-	-	-	-	-	✔	<1	1 to 6	-	-	-	-
Irritation	<1	-	-	-	-	✔	-	✔	1 to 2	1 to 6	-	✔	✔	-
Keratopathy/keratitis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Lid edema	-	-	-	<1	-	-	1 to 4	-	<1	-	-	✔	-	✔
Lid erythema	-	-	-	-	-	-	-	-	<1	-	-	-	-	✔
Lid margin crusting	-	-	-	<10	-	-	-	-	-	-	-	-	-	-
Lid pruritus	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Ocular infection	-	-	-	-	-	-	-	-	1 to 2	-	-	-	✔	-
Ocular pain	-	-	-	-	-	-	-	-	1 to 2	1 to 6	-	✔	-	-
Otitis media	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-	-
Papillary conjunctivitis	-	-	-	-	-	-	5 to 10	-	-	-	-	✔	-	-
Photophobia	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Punctate keratitis	<1	-	-	-	-	-	-	-	-	1 to 6	-	✔	-	-
Stinging	<1	-	-	-	-	-	-	-	1 to 2	1 to 6	-	✔	✔	-
Tearing	-	-	-	<1	-	-	5 to 10	-	-	1 to 6	-	✔	-	-
White crystalline precipitates	-	-	-	17	-	-	-	-	-	-	-	-	-	-
Worsening of conjunctivitis	-	-	-	-	-	-	≥1	-	-	-	-	-	-	-
Other														
Allergic reactions	-	-	-	<1	-	-	-	✔	-	-	-	-	-	-
Application site pain	-	-	-	2 to 3	-	-	-	-	-	-	-	-	-	-
Back ache	-	-	-	-	2	-	-	-	-	-	-	-	-	-
Back pain	-	-	-	-	3	-	-	-	-	-	-	-	-	-
Bronchitis	-	-	-	-	3	-	-	-	-	-	-	-	-	-
Burning/stinging, nasal	-	-	-	-	-	-	-	-	-	-	2	-	-	-
Common cold	-	-	-	-	22	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Single Entity Agents													
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Mup-irocin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Cough	-	-	-	-	4	-	-	-	-	1 to 4	2	-	-	-
Epistaxis	-	-	-	-	-	-	-	-	-	-	<1	-	-	-
Fever	-	-	-	-	-	-	-	-	1 to 3	1 to 4	-	-	-	-
Flu symptoms	-	-	-	-	11	-	-	-	-	-	-	-		
Fungal ear superinfection	-	-	-	2 to 3	-	-	-	-	-	-	-	-		
Gum pain	-	-	-	-	<1	-	-	-	-	-	-	-		
Hypersensitivity	-	-	-	-	-	✔	-	-	<1	-	-	✔	✔	✔
Infection	-	-	-	-	2	-	-	-	-	1 to 4	-	-	-	-
Injury	-	-	-	-	5	-	-	-	-	-	-	-	-	-
Joint pain	-	-	-	-	6	-	-	-	-	-	-	-	-	-
Menstrual cramp	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Muscle pain	-	-	-	-	1	-	-	-	-	-	-	-	-	-
Nasal congestion	<1	-	-	-	-	-	-	-	-	-	-	-	-	-
Pain	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Periodontal abscess	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	-	-	-	-	1 to 3	1 to 4	4	-	-	-
Respiratory disorder	-	-	-	-	-	-	-	-	-	-	5	-	-	-
Rhinitis	-	-	-	-	-	-	-	-	-	1 to 4	6	-	-	-
Sinus congestion	-	-	-	-	5	-	-	-	-	-	-	-	-	-
Sinus headache	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Sinusitis	<1	-	-	-	3	-	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	5	-	-	-	-	-	-	-	-	-
Taste disturbance	-	-	-	-	-	-	-	-	8 to 10	-	3	-	-	-
Taste perversion	-	-	-	-	-	-	-	-	-	-	-	7	-	-
Throat irritation	-	-	-	-	-	-	-	-	1 to 2	-	-	-	-	-
Tinnitus	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-	-
Tooth ache	-	-	-	-	7	-	-	-	-	-	-	-	-	-
Tooth disorder	-	-	-	-	6	-	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported.

Table 10. Adverse Drug Events (%) Reported with the EENT Antibacterials-Combination Products[1-40]

Adverse Events	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth -oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Central Nervous System														
Headache	-	-	✔	-	-	-	-	-	-	-	-	-	<1	14
Migraines	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Dermatological														
Alopecia	-	-	✔	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth -oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Edema	✔	-	-	-	✔	✔	-	-	✔	-	-	-	-	-
Fungal dermatitis	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Pruritus	✔	-	✔	-	✔	✔	-	-	✔	-	-	-	-	-
Rash	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Skin sensitization	-	-	-	-	-	-	✔	-	-	✔	-	-	-	-
Urticaria	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal														
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taste disturbance	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Ophthalmic/Otic														
Blepharitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blurred vision	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Burning	-	-	-	✔	-	✔	-	-	-	-	✔	✔	-	9
Cataract formation	-	-	-	-	-	-	-	-	-	-	-	✔	✔	✔
Chemosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctival epithelial defects	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctival hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctival redness	✔	-	-	-	✔	✔	-	-	✔	-	-	✔	✔	✔
Conjunctivitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Corneal erosion/ ulceration	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Corneal deposits	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Decreased visual acuity	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Discharge	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Discomfort	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dry eyes	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear congestion	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Ear debris	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Ear discomfort	-	3	-	-	-	-	-	-	-	-	-	-	-	-
Ear erythema	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Ear infection	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Ear pain	-	<2	-	-	-	-	-	-	-	-	-	-	-	-
Ear precipitate	-	<1	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth -oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Ear pruritus	-	1	-	-	-	-	-	-	-	-	-	-	-	-
Elevated intraocular pressure	-	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	10
Eye irritation	✔	-	-	-	-	-	-	-	-	-	-	-	-	-
Floaters	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Foreign body sensation	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Infection	-	-	-	-	-	-	-	-	-	-	-	-	-	20
Irritation	-	-	-	✔	✔	✔	-	-	-	-	✔	✔	-	-
Keratopathy/ keratitis	✔	-	-	-	-	-	-	-	-	-	-	-	-	-
Lacrimation disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Lid disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Lid edema	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Lid erythema	-	-	-	-	-	✔	-	-	-	-	-	✔	✔	✔
Lid pruritus	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Ocular infection	-	-	-	✔	-	-	-	✔	-	-	-	✔	✔	✔
Ocular pain	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Optic nerve damage	-	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	✔
Otitis media	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ototoxicity	-	-	-	-	-	✔	✔	✔	✔	✔	-	-	-	-
Photophobia	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Posterior subcapsular cataract formation	-	-	-	✔	-	✔	-	✔	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Punctate keratitis	-	-	-	✔	-	-	-	-	-	-	-	✔	-	15
Stinging	-	-	-	✔	-	✔	-	-	-	-	✔	✔	✔	9
Tearing	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vision disorders	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Other														
Allergic reactions	✔	-	-	✔	✔	✔	✔	✔	✔	✔	-	-	-	-
Anaphylaxis	-	-	-	-	✔	✔	-	-	-	-	-	-	-	-
Burning/stinging (nasal)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cough	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Delayed wound healing	-	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	✔

Adverse Events	Combination Products													
	BAC and POLY	CIPRO and DEX	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimeth -oprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lote-prednol
Epistaxis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	✔	-	✔	-	-	-	-	✔	-	✔	✔
Hypertension	-	-	-	-	-		--	-		-	-	-	<1	-
Infection (systemic)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nephrotoxicity	-	-	-	-	✔	✔	✔	✔	✔	✔	-	-	-	-
Pharyngitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Photosensitivity	-	-	-	-	-	-	-	-	-	-	✔	-	-	-
Respiratory disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taste disturbance	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Throat irritation	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thrombocytopenic purpura	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	-	-	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported.
BAC=bacitracin, CIPRO=ciprofloxacin, COL=colistin, DEX=dexamethasone, GRAM=gramicidin, HYDRO=hydrocortisone, NEO=neomycin, POLY=polymyxin B, PRED=prednisolone, THON=thonzonium, TOBY=tobramycin

VII. Dosing and Administration

The usual dosing regimens for the eye, ear, nose, and throat (EENT) antibacterials are listed in Table 11.

Table 11. Usual Dosing Regimens for the EENT Antibacterials[1-40]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Azithromycin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first 2 days and then instill 1 drop in the affected eye(s) once daily for the next 5 days	Bacterial conjunctivitis in children ≥1 year of age: Ophthalmic solution: instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first 2 days and then instill 1 drop in the affected eye(s) once daily for the next 5 days	Ophthalmic solution: 1%
Bacitracin	Ocular infections due to susceptible microorganisms: Ophthalmic ointment: instill ¼ inch to ½ inch ribbon every 3 to 4 hours into conjunctival sac for acute infections, or 2 to 3 times per day for mild-to-moderate infections for 7 to 10 days	Ocular infections due to susceptible microorganisms: Ophthalmic ointment: instill ¼ inch to ½ inch ribbon every 3 to 4 hours into conjunctival sac for acute infections, or 2 to 3 times per day for mild-to-moderate infections for 7 to 10 days	Ophthalmic ointment: 500 units/G
Besifloxacin	Bacterial conjunctivitis: Ophthalmic suspension: instill 1 drop into the affected eye(s) 3 times per day, four to twelve hours apart for 7 days	Bacterial conjunctivitis in children ≥1 year of age: Ophthalmic suspension: 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 media: 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 to 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. Bacterial corneal ulcers: Ophthalmic solution: instill 2 drops into the affected eye every 15 minutes for the first 6 hours and then every 30	Acute otitis media in patients ≥1 year of age: 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 (patients ≥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 (patients ≥1 year of age): instill 1 to 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	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3% Otic solution: 0.2%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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).	Bacterial corneal ulcers: Ophthalmic solution (children ≥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).	
Doxycycline	Periodontitis: Tablet: 20 mg twice daily for up to 9 months	Safety and effectiveness have not been established in pediatric patients.	Tablet: 20 mg
Erythromycin base	Bacterial conjunctivitis, bacterial corneal ulcers: Ophthalmic ointment: apply approximately 1 cm to the affected eye(s) up to 6 times daily, depending on the severity of the infection	Bacterial conjunctivitis, bacterial corneal ulcers: Ophthalmic ointment: apply approximately 1 cm to the affected eye(s) up to 6 times daily, depending on the severity of the infection Prophylaxis of ophthalmia neonatorum due to *N gonorrhoeae* or *C trachomatis*: Ophthalmic ointment: apply approximately 1 cm into each lower conjunctival sac	Ophthalmic ointment: 5 mg/G
Gatifloxacin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 drop into affected eye(s) every 2 hours while awake (up to 8 times daily) for the first day, then two to four times daily for 6 days	Bacterial conjunctivitis (patients ≥1 year of age): Ophthalmic solution (0.5%): instill 1 drop 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	Ophthalmic solution: 0.5%
Gentamicin	Acute bacterial meibomianitis, bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial corneal ulcers, bacterial dacryocystitis, bacterial keratitis, bacterial keratoconjunctivitis: Ophthalmic ointment: apply approximately ½ inch to the affected eye(s) 2 to 3 times a day Ophthalmic solution: instill 1 or	Acute bacterial meibomianitis, bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial corneal ulcers, bacterial dacryocystitis, bacterial keratitis, bacterial keratoconjunctivitis: Ophthalmic ointment: apply approximately ½ inch to the affected eye(s) 2 to 3 times a day	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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 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.	
Levofloxacin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 to 2 drops into affected eye(s) every 2 hours while awake (up to 8 times per day) for 2 days, then 1 to 2 drops every 4 hours while awake (up to 4 times per day) for 5 days	Bacterial conjunctivitis (patients ≥1 year of age): Ophthalmic solution: instill 1 to 2 drops into affected eye(s) every 2 hours while awake (up to 8 times per day) for 2 days, then 1 to 2 drops every 4 hours while awake (up to 4 times per day) for 5 days	Ophthalmic solution: 0.5%
Moxifloxacin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 drop into affected eye(s) three times daily for 7 days	Bacterial conjunctivitis (patients ≥1 year of age): Ophthalmic solution: instill 1 drop into affected eye(s) three times daily for 7 days	Ophthalmic solution: 0.5%
Mupirocin	Eradication of nasal colonization with methicillin-resistant *S aureus*: Nasal ointment: divide approximately ½ of ointment from single-use tube between nostrils and apply twice daily for 5 days	Eradication of nasal colonization with MRSA (patients ≥12 years of age): Nasal ointment: divide approximately ½ of ointment from single-use tube between nostrils and apply twice daily for 5 days	Nasal ointment: 2%
Ofloxacin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 to 2 drops every 2 to 4 hours into the affected eye(s) for 2 days, then 1 to 2 drops 4 times daily for 5 days Bacterial corneal ulcer: Ophthalmic solution: Days 1-2, instill 1 to 2 drops into the affected eye(s) every 30 minutes while awake. Awaken at ~4 and 6 hours after retiring and instill 1 to 2 drops; Days 3 through 7 to 9, instill 1 to 2 drops hourly while awake; Days 7 to 9 through treatment completion, instill 1 to 2 drops 4 times daily Chronic suppurative otitis media (perforated tympanic membranes): Otic solution: instill 10 drops into affected ear(s) twice daily	Acute otitis media (tympanostomy tubes) (patients ≥1 year of age): Otic solution: instill 5 drops into affected ear(s) twice daily for 10 days Bacterial conjunctivitis (patients ≥1 year of age): Ophthalmic solution: instill 1 to 2 drops every 2 to 4 hours into the affected eye(s) for 2 days, then 1 to 2 drops 4 times daily for 5 days Bacterial corneal ulcer (patients ≥1 year of age): Ophthalmic solution: Days 1-2, instill 1 to 2 drops into the affected eye(s) every 30 minutes while awake. Awaken at ~4 and 6 hours after retiring and instill 1 to 2 drops; Days 3 through 7 to	Ophthalmic solution: 0.3% Otic solution: 0.3%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	for 14 days Otitis externa: Otic solution: instill 10 drops into affected ear(s) once daily for 7 days	9, instill 1 to 2 drops hourly while awake; Days 7 to 9 through treatment completion, instill 1 to 2 drops 4 times daily Chronic suppurative otitis media (perforated tympanic membranes) (patients ≥12 years of age): Otic solution: instill 10 drops into affected ear(s) twice daily for 14 days Otitis externa: Otic solution (patients ≥6 months to 13 years of age): instill 5 drops into affected ear(s) once daily for 7 days Otic solution (patients ≥13 years of age): instill 10 drops into affected ear(s) once daily for 7 days	
Sulfacetamide	Bacterial conjunctivitis and other superficial ocular infections: Ophthalmic ointment: apply ½ inch ribbon into the conjunctival sac(s) of the affected eye(s) every 3 to 4 hours and at bedtime for 7 to 10 days Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 to 3 hours for 7 to 10 days Trachoma: Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 hours	Bacterial conjunctivitis and other superficial ocular infections (patients ≥2 months of age): Ophthalmic ointment: apply ½ inch ribbon into the conjunctival sac(s) of the affected eye(s) every 3 to 4 hours and at bedtime for 7 to 10 days Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 to 3 hours for 7 to 10 days Trachoma: Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 hours	Ophthalmic ointment: 10% Ophthalmic solution: 10%
Tobramycin	Ocular infections due to susceptible microorganisms: Ophthalmic solution (mild to moderate infections): instill 1 to 2 drops into the affected eye(s) every 4 hours Ophthalmic solution (severe infections): instill 2 drops into the affected eye(s) hourly until improvement, following which treatment should be reduced	Ocular infections due to susceptible microorganisms (patients ≥2 months of age): Ophthalmic solution (mild to moderate infections): instill 1 to 2 drops into the affected eye(s) every 4 hours Ophthalmic solution (severe infections): instill 2 drops into the affected eye(s)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	prior to discontinuation Ophthalmic ointment (mild to moderate infections): apply ½ inch into the affected eye(s) 2 to 3 times per day Ophthalmic ointment (severe infections): apply ½ inch into the affected eye(s) every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation	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 to 3 times per day Ophthalmic ointment (severe infections): apply ½ inch into the affected eye(s) every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation	
Combination Products			
Bacitracin and polymyxin B	Bacterial conjunctivitis and bacterial corneal infections: Ophthalmic ointment: apply every 3 to 4 hours for 7 to 10 days, depending on severity of infection	Bacterial conjunctivitis or bacterial corneal infections: Ophthalmic ointment: apply every 3 to 4 hours for 7 to 10 days, depending on severity of infection	Ophthalmic ointment: 500-10KU/G
Ciprofloxacin and dexamethasone	Acute otitis externa: Otic suspension: instill 4 drops into affected ear(s) twice daily for 7 days	Acute otitis externa (patients ≥6 months of age): Otic suspension: instill 4 drops into affected ear(s) twice daily for 7 days Acute otitis media (tympanostomy tubes) (patients ≥6 months of age): Otic suspension: instill 4 drops into affected ear(s) twice daily for 7 days	Otic suspension: 0.3-0.1%
Ciprofloxacin and hydrocortisone	Acute otitis externa: Otic suspension: instill 3 drops into affected ear 2 times a day for 7 days	Acute otitis externa (patients ≥1 year of age): Otic suspension: instill 3 drops into affected ear 2 times a day for 7 days	Otic suspension: 0.2-1%
Gentamicin and prednisolone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: apply ½ inch in the conjunctival sac 1 to 3 times per day Ophthalmic suspension: instill 1 drop into affected eye(s) 2 to 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 to 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%
Neomycin,	Bacterial blepharitis, bacterial	Safety and effectiveness	Ophthalmic ointment:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
bacitracin and polymyxin B	blepharoconjunctivitis, bacterial conjunctivitis, bacterial keratitis, and bacterial keratoconjunctivitis: Ophthalmic ointment: apply ointment to affected eye(s) every 3 to 4 hours for 7 to 10 days, depending on the severity of the infection	have not been established in pediatric patients.	3.5 mg-400 units-10,000 units
Neomycin, bacitracin, polymyxin B and hydrocortisone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: 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: Otic suspension: instill 5 drops into affected ear(s) 3 to 4 times daily	Bacterial infections of the external auditory canal (patients ≥1 year of age): Otic suspension: instill 4 drops into affected ear(s) 3 to 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: Ophthalmic ointment, ophthalmic suspension: instill 1 to 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 (patients ≥2 years of age): Ophthalmic ointment, ophthalmic suspension: instill 1 to 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: 3.5 mg-10,000 units-0.1%
Neomycin, polymyxin B and gramicidin	Bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial keratitis, and bacterial keratoconjunctivitis: Ophthalmic solution: instill 1 to 2 drops into affected eye(s) every 4 hours for 7 to 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-0.025 mg
Neomycin, polymyxin B and hydrocortisone	Bacterial infections of the external auditory canal: Ophthalmic suspension: instill 4 drops into affected ear(s) 3 to 4 times daily Steroid-responsive inflammatory conditions and	Bacterial infections of the external auditory canal (patients ≥2 years of age): Ophthalmic suspension: instill 3 drops into affected ear(s) 3 to 4 times daily	Ophthalmic suspension: 3.5 mg-10,000 units-1% Otic solution: 3.5 mg-10,000 units-1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	superficial ocular infections: Otic solution, otic suspension: instill 1 to 2 drops into affected eye(s) 2 to 4 times per day, or more frequently as required for severe infections		Otic suspension: 3.5 mg-10,000 units-1%
Polymyxin B and trimethoprim	Bacterial blepharoconjunctivitis and bacterial conjunctivitis: Ophthalmic solution: instill 1 drop in the affected eye(s) every 3 hours for 7 to 10 days	Bacterial blepharoconjunctivitis and bacterial conjunctivitis (patients ≥2 months of age): Ophthalmic solution: instill 1 drop in the affected eye(s) every 3 hours for 7 to 10 days	Ophthalmic solution: 10,000 units-0.1%
Sulfacetamide and prednisolone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: apply ½ inch to affected eye(s) 3 to 4 times per day and 1 to 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 (patients ≥6 years of age): Ophthalmic ointment: apply ½ inch to affected eye(s) 3 to 4 times per day and 1 to 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	Ophthalmic ointment: 10-0.2% Ophthalmic solution: 10-0.25% Ophthalmic suspension: 10-0.2%
Tobramycin and dexamethasone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: apply ½ inch to affected eye(s) up to 3 to 4 times per day Ophthalmic suspension (0.3-0.05%): instill 1 drops into affected eye(s) every 4 to 6 hours Ophthalmic suspension (0.3-0.1%): instill 1 to 2 drops into affected eye(s) every 4 to 6 hours	Steroid-responsive inflammatory conditions and superficial ocular infections (patients ≥2 years of age): Ophthalmic ointment: apply ½ inch to affected eye(s) up to 3 to 4 times per day Ophthalmic suspension (0.3-0.05%): instill 1 drops into affected eye(s) every 4 to 6 hours Ophthalmic suspension (0.3-0.1%): instill 1 to 2 drops into affected eye(s) every 4 to 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: Ophthalmic suspension: instill 1 to 2 drops into the affected eye(s) every 4 to 6	In a trial to evaluate the safety and efficacy in pediatric patients aged zero to six years with lid inflammation, tobramycin/loteprednol with	Ophthalmic suspension: 0.3-0.5%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	hours	warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. There were no differences in safety assessments between the treatment groups.	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the eye, ear, nose, and throat (EENT) antibacterials are summarized in Table 12.

Table 12. 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.[64] (2008) Azithromycin 1% ophthalmic solution, frequency not reported vs erythromycin ophthalmic ointment, frequency not reported	PRO Patients with chronic mixed anterior blepharitis	N=75 (150 eyes) 8 weeks	Primary: Clinical response Secondary: Not reported	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 eight patients treated with topical erythromycin ophthalmic ointment, five patients (10 eyes) had unresolved blepharitis with inadequate clinical improvement after one month of treatment. Fifty percent (eight of 16 eyes) of patients treated with erythromycin required eight weeks of treatment as compared to 1.5% (two of 134 eyes) of patients treated with azithromycin. The average initial blepharitis grade of patients and the average blepharitis grade taken at four and eight 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 four weeks of treatment was statistically significant in favor of azithromycin (P=0.0237). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Blepharokeratoconjunctivitis				
Rhee et al.[65] (2007) TOBY and DEX 0.3-0.1% ophthalmic solution BID vs TOBY and loteprednol 0.3-0.5% ophthalmic solution BID	DB, RCT Patients with moderate blepharokerato-conjunctivitis in at least 1 eye	N=40 (40 eyes) 3 to 5 days	Primary: Ocular signs and symptoms Secondary: Not reported	Primary: TOBY and DEX significantly decreased clinical signs of ocular inflammation, including blepharitis (P=0.017), conjunctivitis (P=0.013), ocular discharge (P=0.025) and total posttreatment symptom scores (P<0.05) compared to TOBY and loteprednol. Mean keratitis scores did not differ between the treatment groups (P=0.065). Mean total ocular scores for TOBY and DEX were greater than those for TOBY and loteprednol at the post-visit 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. Secondary: Not reported
White et al.[66] (2008) TOBY and DEX 0.3-0.1% ophthalmic solution QID for 3 to 5 days vs TOBY and loteprednol 0.3-0.5% ophthalmic solution QID for 3 to 5 days	MC, RCT Patients with blepharokerato-conjunctivitis	N=276 15 days	Primary: Change from baseline to day 15 for ocular signs and 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 seven and day three in the signs/ symptoms composite	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 TOBY and loteprednol and -15.6 for TOBY and DEX-treated patients, representing a 78% reduction from baseline for both treatments. There was no significant difference between the treatment groups. At day three and day seven, the mean change from baseline in the signs and symptoms composite score for the ITT population was -7.1 and -12.3 for TOBY and loteprednol-treated patients and -7.6 and -13.2 for TOBY and DEX-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 TOBY and loteprednol-treated patients and TOBY and DEX-treated patients, respectively. There was no significant difference between the treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			score; change from baseline to each visit in the signs composite score and symptoms composite score; adverse events	Based on the investigator global assessment, the percentage of TOBY and loteprednol and TOBY and DEX study eyes considered 'cured' was 2.2 and 0.7% at day three, 20.1 and 16.5% at day seven, 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 TOBY and loteprednol and TOBY and DEX was -3.3and -3.4 at day three, -6.1 and -6.4 at day seven, 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 TOBY and loteprednol and TOBY and DEX was -3.8 and -4.2 at day three, -6.2 and -6.8 at day seven, 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, with one subject in the TOBY and DEX group reporting a serious adverse event. Most non-ocular adverse events were considered mild to moderate in severity, with the exception of hypertension in the TOBY and DEX group and one instance of headache in the TOBY and loteprednol group, which were considered severe. A total of four patients (2.9%) in the TOBY and loteprednol group and nine patients (6.5%) in the TOBY and DEX group reported treatment-emergent ocular adverse events in the study eye. All treatment-emergent ocular adverse events 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				'none', 'minimal/trace', 'mild', or 'moderate' cataract over the course of the study. Patients treated with TOBY and DEX experienced a statistically significant increase in IOP compared to patients treated with TOBY and loteprednol at day seven (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).
Chen et al.[67] (2012) TOBY and loteprednol 0.3-0.5% ophthalmic suspension QID for 2 weeks vs TOBY and DEX 0.3-0.1% ophthalmic suspension QID for 2 weeks	MC, PG, SB, RCT Chinese patients ≥18 years of age with ocular inflammation associated with blepharokerato-conjunctivitis	N=308 15 days	Primary: Change in baseline in the signs and symptoms composite score to visit four (day 15) Secondary: Safety, biomicroscopy findings, changes in visual acuity and IOP	Primary: A significant change from baseline in composite signs and symptoms was seen with both treatments at each follow-up visit (P< 0.0001). The mean±SD change from baseline at visit four was -11.63±4.56 and -12.41±4.71 with TOBY and loteprednol and TOBY and DEX, respectively. The upper bound of the 90% CI for the difference was less than the prespecified NI margin. Secondary: Comparable results were found for secondary efficacy outcomes. Patients treated with TOBY and DEX experienced a significantly greater increase in mean change from baseline in IOP compared to patients treated with TOBY and loteprednol at all follow-up visits (P≤0.0186) and nearly twice as many IOP evaluations ≥5 mm Hg (P=0.0020).
Conjunctivitis				
Abelson et al.[68] (2008) Azithromycin 1% ophthalmic solution 1 drop BID on days 1 and 2, followed by QD on days 3 through 5 vs placebo	Phase 3 DB, MC, PC, PG, RCT Patients ≥1 year of age with a positive clinical diagnosis of bacterial conjunctivitis with signs and symptoms present for less than three days and a best-corrected visual acuity score of	N=685 5 days	Primary: Clinical resolution at the TOC visit (visit three on day six or seven) Secondary: Bacterial eradication at visit three, as indicated by the absence of bacterial growth and incidence of adverse events	Primary: Clinical resolution rates at visit three were significantly higher with azithromycin compared to placebo (63.1 vs 49.7%, respectively; P=0.03). Secondary: Bacterial eradication rates measured at visit three were significantly higher with azithromycin compared to placebo (88.5 vs 66.4%; P<0.001). The rate of overall adverse events see with azithromycin was 12.3% compared to 12.0% with placebo, with the most common adverse effects seen including conjunctival chemosis, lid swelling, and other lid events (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≥20/100 in each eye			
Abelson et al.[69] (2007) Azithromycin 1% ophthalmic solution BID on days 1 and 2, followed by QD for 3 days vs TOBY 0.3% ophthalmic solution QID for 5 days	AC, DB, RCT 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 TOBY achieved clinical resolution in 78.3% of participants (P=0.783). At day three, 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 TOBY achieved bacterial eradication in 94.3% (P=0.073).
Protzko et al.[70] (2007) Azithromycin 1% ophthalmic solution BID on days 1 and 2, followed by QD for 3 days vs TOBY 0.3% ophthalmic solution QID for 5 days	AC, DB, RCT 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 Secondary: Not reported	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 TOBY 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 three 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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Cochereau et al.[71] (2007) Azithromycin 1.5% ophthalmic solution 1 drop BID for 3 days vs TOBY 0.3% ophthalmic solution 1 drop every 2 hours up to 8 times a day for 2 days, followed by QID for 5 days	MC, NI, PG, RCT Patients ≥1 day old with a diagnosis of purulent bacterial conjunctivitis defined as bulbar injection and purulent discharge	N=1,043 9 days	Primary: Clinical efficacy, microbiological assessment and safety Secondary: Not reported	Primary: Clinical efficacy, measured as the number of patients cured on day nine, showed that azithromycin was non inferior to TOBY (87.8 vs 89.4%, respectively; 95% CI, -7.5 to 4.4). NI was also found for all efficacy criteria at assessment days three and nine (95% CI, -5.3 to 8.3 and -6.6 to 3.0, respectively). Additionally, azithromycin showed a statistically higher cure rate than TOBY (29.8 vs 18.6%, respectively; P value not reported). The rate of bacteriological resolution for azithromycin was found to be non-inferior to TOBY at both day three (85.2 vs 83.8%; 95% CI, not reported) and day nine (92.8 vs 94.6%; 95% CI, not reported). Adverse events reported were mile to moderate. Four patients presented with treatment-related adverse events, three from the azithromycin group (two with burning and one with burning/foreign body sensation) and one from the TOBY group for discharge. Secondary: Not reported
Bremond-Gignac et al.[72] (2014) Azithromycin 1.5% ophthalmic solution one drop BID for 3 days vs TOBY 0.3% ophthalmic solution one to two drops every 2 hours up to	MC, RCT, SB Children (from 1 day to 18 years old, average age of 3 years) with purulent bacterial conjunctivitis, defined by mild to severe bulbar conjunctival injection and purulent discharge in at least one eye	N=203 7 days	Primary: Clinical cure (as defined by the absence of bulbar conjunctival injection and purulent discharge in the worse eye on day 3) Secondary: Clinical cure on day 7, other ocular signs, symptoms of bacterial	Primary: On day 3, the clinical sure rate was higher in the azithromycin group compared with the TOBY group (47.1 vs 28.7%, respectively; P=0.013). Secondary: On day 7 there was no significant difference in clinical cure rates between treatment groups (89.2 vs 78.2%, respectively; P=0.077), and non-inferiority of azithromycin to tobramycin was demonstrated. Improvements of other ocular signs (folliculo-papillary reaction, eyelid erythema, eyelid swelling) were noted on days 3 and 7, but were not significantly different between groups (Day 3: P=0.067, Day 7: P=0.172).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
8 times a day for 2 days, followed by one drop QID for 5 days			conjunctivitis scored on a four-point ordinal scale	
Gigliotti et al.[73] (abstract) (1984) BAC and POLY ophthalmic ointment QID for seven days vs placebo	DB, RCT Patients 1 month to 18 years of age with acute conjunctivitis	N=102 10 days	Primary: Clinical cure rate and bacterial pathogen eradication Secondary: Not reported	Primary: During days three through five, significantly more patients treated with BAC and POLY were clinically cured compared to patients treated with placebo (62 vs 28%, respectively; P<0.02). However, on days eight through ten, the difference between the treatments was not significant (91 vs 72%; P value not reported). It was found that the bacterial pathogen was eradicated in significantly more patients in the treatment group compared to the placebo group on days three to five, as well as on days eight to 10 (72 vs 19% and 79 vs 31%, respectively; P<0.001 for both). Secondary: Not reported
Sheikh et al.[74] (2006) BAC and POLY ophthalmic ointment 500-10,000 units/g vs CIPRO 0.3% vs chloramphenicol 0.5%* vs	MA Patients ≥1 month of age with acute bacterial conjunctivitis and symptoms of less than four weeks duration	N=1,034 Duration not specified	Primary: Early clinical remission, early microbiological remission, late clinical remission and late microbiological remission Secondary: Not reported	Primary: When BAC and POLY was compared to vehicle with regard to early clinical remission at days three through five, BAC and POLY was favored (RR, 2.20; 95% CI, 1.19 to 4.06). When BAC and POLY was compared to vehicle with regard to microbiological remission during days three through five, BAC and POLY was favored (RR, 3.76; 95% CI, 1.77 to 8.00). CIPRO was also favored when compared to vehicle with regard to early microbiological remission at day three (RR, 1.59; 95% CI, 1.21 to 2.08). BAC and POLY was favored over vehicle with regard to late clinical remission at days eight to 10 (RR, 1.27; 95% CI, 1.00 to 1.61) as well as for late microbiological remission in days eight through ten (RR, 2.54; 95% CI, 1.48 to 4.37). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fusidic acid gel 1%* vs norfloxacin 0.3%* vs vehicle				
DeLeon et al.[75] (2012) Besifloxacin 0.6% ophthalmic suspension BID for 3 days vs placebo	DB, MC, PC, PG, RCT Patients ≥1 years of age with bacterial conjunctivitis	N=474 7 days	Primary: Bacterial eradication and clinical resolution at day 4/5 Secondary: Bacterial eradication and clinical resolution at day seven, safety	Primary: Bacterial eradication and clinical resolution rates were significantly higher with besifloxacin compared to placebo (115/135 [85.2%] vs 77/141 [54.6%]; P<0.001, and 89/135 [65.9%] vs 62/141 [44.0%]; P<0.001, respectively) at day 4/5. Secondary: Rates of bacterial eradication continued to be significantly greater with besifloxacin (115/135 [85.2%] vs 91/141 [64.5%], respectively; P<0.001) at day 7±1; however, the rates of clinical resolution did not differ between the two treatments (103/135 [76.3%] and 94/141 [66.7%]; P=0.209) at this visit. Clinical resolution and bacterial eradication with Gram-positive or Gram-negative organisms were consistent with the overall findings. All adverse events with both treatments were of mild or moderate severity and were considered unrelated to the treatment.
Karpecki et al.[76] (2009) Besifloxacin 0.6% ophthalmic suspension TID for 5 days vs placebo	DB, MC, PC, RCT 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 two; eradication of baseline bacterial	Primary: Clinical resolution of baseline conjunctivitis at visit three was significantly better in patients who received besifloxacin compared to placebo (73.3 vs 43.1%, respectively; P<0.001). Eradication of bacterial infection at visit three also was significantly greater in the besifloxacin group compared to placebo (88.3 vs 60.3%; P<0.001). Secondary: There was no difference in clinical resolution of conjunctivitis at visit two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			infection at visit two; and improvements in investigators' ratings of individual signs and symptoms, global change in clinical signs and symptoms, microbiologic outcomes, and clinical outcomes	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 to placebo (90.0 vs 46.6%; P<0.001). Investigators' ratings of individual signs and symptoms were significantly better with besifloxacin compared to placebo at visit two (ocular discharge; P=0.008, bulbar conjunctival injection; P=0.014) and visit three (P=0.003 and P=0.013, respectively), as were investigators' ratings of global changes in signs and symptoms at visit two (P=0.004) and visit three (P<0.001). There was no difference between the besifloxacin and placebo groups in the cumulative frequency of patients with at least one 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%).
Tepedino et al.[77] (2009) Besifloxacin 0.6% ophthalmic suspension QID for 5 days vs placebo	DB, MC, PC, RCT Patients ≥1 year of age with bacterial conjunctivitis	N=390 9 days	Primary: Clinical resolution and microbiological eradication of baseline infection at visit two (day five) Secondary: Clinical resolution and microbial eradication at visit three (day eight or nine), 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 (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 (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 three (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 three (88.4 and 71.7%, respectively; P<0.0001). The percentage of patients treated with besifloxacin ophthalmic

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				suspension who had resolution of ocular discharge was significantly greater at visit two (73.9 vs 57.6%; P=0.0012) and at visit three (93.0 vs 79.1%; P=0.0002) compared to 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 two (52.3 vs 36.1%; P=0.0007) and visit three (84.9 vs 70.7%; P=0.0011). At visit two, 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 three, 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. A significantly greater percentage of eyes treated with vehicle experienced at least one ocular adverse event compared to those treated with besifloxacin ophthalmic suspension (13.9 vs 9.2%; P=0.0047).
Silverstein et al.[78] (2011) Besifloxacin 0.6% ophthalmic suspension 1 drop BID for 3 days vs placebo	DB, MC, PG, PRO, RCT Patients ≥1 year of age with a clinical diagnosis of acute bacterial conjunctivitis with purulent discharge, crusty or sticky eyelids ocular surface redness and a minimum of grade one severity for both discharge and bulbar conjunctival	N=202 7 days	Primary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit two Secondary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit three and individual clinical outcomes at the follow- up visits	Primary: At visit two, clinical resolution of conjunctivitis in the study eye was significantly higher with besifloxacin compared to placebo (69.8 vs 37.5%, respectively; P<0.001). The eradication of bacterial infection at visit two occurred in significantly more patients with besifloxacin compared to placebo (86.8 vs 57.1%; P<0.001). Secondary: Rates of eradication of bacterial infection in the study eye at visit three were significantly greater with besifloxacin compared to placebo (86.8 vs 69.6%, respectively; P=0.038). Rates of clinical resolution of bacterial conjunctivitis at visit three did not differ significantly between besifloxacin and placebo (73.6 vs 66.1%; P=0.717).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	injection in ≥1 eye			At visit two, the percentage of patients treated with besifloxacin who had resolution of ocular discharge was significantly greater compared to those who received placebo (83.0 vs 55.4%, respectively; P=0.002), but not at visit three (86.8 vs 76.8%; P value not reported). The proportion of patients treated with besifloxacin who had resolution of bulbar conjunctival injection was significantly greater compared to patients receiving placebo at visit two (77.4 vs 44.6%; P<0.001), but not at visit three (83.0 vs 73.2%; P value not reported).
Silverstein et al.[79] (2012) Besifloxacin 0.6% ophthalmic suspension 1 drop BID or TID vs placebo or moxifloxacin 0.5% ophthalmic solution 1 drop TID	Post-hoc analysis of 4 trials Patients ≥1 year of age with a clinical diagnosis of bacterial conjunctivitis as evidenced by a grade one or greater severity of both purulent ocular discharge and bulbar conjunctival injection in at least one eye, had culture-confirmed *P aeruginosa* infections and had pinhole visual acuity of ≥20/200	N=9 3 to 5 days	Primary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit two or three Secondary: Ocular and non-ocular adverse events, changes in visual acuity and biomicroscopy and ophthalmoscopy findings at follow-up visits	Primary: Of a total of 2,859 patients across of the four trials, nine patients had culture-confirmed *P aeruginosa* infections. Five of these patients received besifloxacin, all of whom had bacterial eradication of the baseline infections at visits two and three. Clinical resolution was reported in two of these patients by visit two and in four of these patients by visit three. Data on patients who received vehicle or moxifloxacin was not reported. Secondary: No adverse events were reported in the five patients who received besifloxacin. There were no clinically meaningful changes in visual acuity or any biomicroscopy or ophthalmoscopy findings.
Comstock et al.[80] (2010) Besifloxacin 0.6% ophthalmic suspension 1 drop	Post-hoc analysis of 3 trials Patients 1 to 17 years of age with bacterial	N=815 8 to 9 days	Primary: Clinical resolution and microbial eradication Secondary:	Primary: *PC trials* The percentage of eyes with clinical resolution was significantly higher (P<0.05) in the besifloxacin group than in the placebo group at visit two (53.7 vs 41.3%) and visit three (88.1 vs 73.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TID daily for 5 days vs moxifloxacin 0.5% ophthalmic solution (1 trial) vs placebo (2 trials)	conjunctivitis		Not reported	Microbial eradication was significantly better (P<0.05) with besifloxacin than with placebo at visit two (85.8 vs 56.3%) and visit three (82.8 vs 68.3%). *Moxifloxacin controlled trial* 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. *Adverse events* 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. Secondary: Not reported
McDonald et al.[81] (2009) Besifloxacin 0.6% ophthalmic suspension TID for 5 days vs moxifloxacin 0.5% ophthalmic solution TID for 5 days	DB, MC, PG, RCT 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 five in patients with culture-confirmed bacterial conjunctivitis Secondary: Clinical resolution and microbial eradication on day	Primary: On day five 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 eight, 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 five, microbial eradication occurred in 93.3% of patients receiving besifloxacin and 91.1% of patients receiving moxifloxacin (P=0.1238). On day eight,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			eight, individual clinical outcomes, microbial and clinical outcomes by bacterial species, and safety	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 five (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 one ocular adverse events (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 besifloxacin and in 1.4% treated with moxifloxacin (P=0.0201).
Leibowitz et al.[82] (abstract) (1991) CIPRO 0.3% ophthalmic solution vs TOBY 0.3% ophthalmic solution vs placebo	2 MC, PRO, RCT Patients with bacterial conjunctivitis	N=288 Duration not specified	Primary: Antibacterial efficacy and eradication of bacterial pathogens Secondary: Not reported	Primary: In one trial, CIPRO was shown to be significantly more effective than placebo (P<0.001) and eradicated or reduced the various bacterial pathogens in more patients when compared to placebo (93.6 vs 59.5%; P value not reported). In a second trial CIPRO and TOBY were found to be equally effective in antibacterial efficacy (94.5 vs 91.9%; P value not reported). Secondary: Not reported
Gross et al.[83] (1997)	DB, MC, RCT	N=257	Primary: Microbiological	Primary: Microbiological eradication on follow-up was observed in 90.1% of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 0.3% ophthalmic solution administered every 2 hours for 2 days, followed by every 4 hours for 3 to 7 days vs TOBY 0.3% ophthalmic solution administered every 2 hours for 2 days, followed by every 4 hours for 3 to 7 days	Children 0 to 12 years of age with a diagnosis of acute (<7 days) bacterial conjunctivitis	7 days	efficacy, physician's impression of condition, and severity of signs/symptoms Secondary: Not reported	ciprofloxacin group and 84.3% of the TOBY group (P=0.29). Microbiological reduction was observed in 2.8% of the ciprofloxacin group and 2.9% of the TOBY group (P=0.29). No significant treatment difference was found for physician's judgment on day three (P=0.63) or day seven (P=0.60). Physicians judged 87.0% of the ciprofloxacin patients and 89.9% of the TOBY patients clinically cured on day seven. 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 one and days three and seven 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 TOBY 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. Secondary: Not reported
Yee et al.[84] (2005) Gatifloxacin 0.3% ophthalmic solution BID for 5 days vs gatifloxacin 0.3% ophthalmic solution QID for 5 days	MC, TCT 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	N=104 5 days	Primary: Clinical cure on day five in the ITT population Secondary: Clinical cure on day five in the per protocol population, safety	Primary: The clinical cure rates in the BID group were 86.5 and 71.2% in the QID group on day five (95% CI, -0.03 to 30.80; P=0.096). Secondary: Clinical cure rates at day five in the per protocol 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	scale)			QID groups (P>0.999).
Hwang et al.[85] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 to 2, followed by every 4 hours on days 3 to 5 vs placebo	DB, MC, PC, RCT Patients ≥2 years of age with bacterial conjunctivitis, characterized by purulent ocular discharge and redness in at least one eye	N=117 5 days	Primary: Antimicrobial efficacy, clinical efficacy, resolution of ocular signs and symptoms, safety Secondary: Not reported	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 (two to 11 years of age) achieved microbial eradication, compared to 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. 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%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Lichtenstein et al.[86] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 and 2, followed by every 4 hours on days 3 through 5 vs ofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 and 2, followed by every 4 hours on days 3 through 5 vs placebo	Subset analysis of 2 trials Pediatric patients aged 1 to 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 Secondary: Not reported	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 (two to 11 years of age), this finding was statistically significant in favor of 0.5% levofloxacin compared to 0.3% ofloxacin (87 vs 62%; P≤0.032) and for 0.5% levofloxacin compared to 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 pediatric patients (89%) that was greater than that attained with placebo treatment (50%). This finding was statistically significant in children (two to 11 years) with clinical cure rates of 88% with 0.5% levofloxacin vs 53% with placebo (P≤0.034). Physicians judged 99% of pediatric patients treated with 0.5% levofloxacin to be resolved or improved compared to 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 to 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%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Szaflik et al.[87] (2009) Levofloxacin 0.5% ophthalmic solution TID for 5 days vs levofloxacin 0.5% ophthalmic solution administered every 2 hours for the first 2 days, followed by every 4 hours for the next 3 days	OL, RCT 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 to 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 to 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.
Schwab et al.[88] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours for the first 2 days, followed by every 4 hours on days 3 through 5 vs ofloxacin 0.3% ophthalmic solution administered every 2 hours for the first 2 days, followed by every 4 hours on	AC, DB, RCT 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 to 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 to 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 (two to 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 to 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% of patients in each treatment group were considered to be clinically cured. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days 3 through 5				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 to 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 to 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 to 58% of patients in the 0.3% ofloxacin treatment group (P=0.025). Burning/stinging worsened in more patients treated with 0.3% ofloxacin (5%) compared to 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Tuber et al.[89] (2010) Moxifloxacin ophthalmic solution (Moxeza®) BID for 3 days vs placebo	DB, MC, PG, RCT, VC Patients ≥28 days of age with a diagnosis of bacterial conjunctivitis in one or both eyes based on bulbar conjunctival injection and discharge (score ≥1 on a four-point scale for each sign) and matting	N=1,180 6 days	Primary: Clinical cure rate and eradication rates by species Secondary: Not reported	Primary: Patients treated with moxifloxacin BID for three days had a microbiological success rate of 74.5% compared to 56.0% of patients treated with vehicle (P<0.0001). Moxifloxacin administered BID was significantly more effective than vehicle in eradicating the three principle conjunctivitis pathogens, *H influenzae* (98.5 vs 59.6%; P<0.001), *S pneumoniae* (86.4 vs 50.0%; *P*<0.001) and *S aureus* (94.1 vs 80.0%; P<0.001). Secondary: Not reported
Silver et al.[90] (2005) Moxifloxacin 0.5% ophthalmic solution 1 drop TID for 4 days vs ofloxacin 0.3% ophthalmic solution	MA Patients of any race with a diagnosis of bacterial conjunctivitis	N=1,978 7 to 9 days	Primary: Safety Secondary: Not reported	Primary: The most frequent adverse events experienced by all patients were ocular discomfort and transient burning and stinging, which were reported in more patients in the moxifloxacin group compared to the placebo group (2.8 vs 2.1%; P value not reported). In pediatric patients, similar results were found with ocular discomfort, transient burning and stinging reported as the most frequent adverse events experienced; these adverse events were reported in fewer patients in the moxifloxacin group when compared to the placebo group (1.9 vs 2.2%; P value not reported). The most common systemic adverse event reported in pediatric patients was increased cough that occurred in more patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 drop QID for 4 days vs CIPRO 0.3% ophthalmic solution 1 drop TID for 4 days vs placebo				the moxifloxacin group than the placebo group (3.2 vs 2.8%; P value not reported). Similar rates of adverse events were reported in a study comparing moxifloxacin to ofloxacin with regard to keratitis, corneal infiltrate and ocular hyperemia (P value not reported). In a study comparing moxifloxacin to CIPRO, adverse events were also similar between the two groups with regard to tearing, ocular hyperemia, rash and rhinitis (P value not reported). Secondary: Not reported
Granet et al.[91] (2008) Moxifloxacin 0.5% ophthalmic solution TID for 7 days vs POLY and trimethoprim ophthalmic solution QID for 7 days	DB, MC, RCT 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 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	Primary: *Culture-positive eyes* A significantly greater percentage of culture-positive eyes in the moxifloxacin group achieved clinical cure compared to eyes in the POLY and 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). At the 24-hour visit, more eyes treated with moxifloxacin showed a combined clinical cure and improvement (77.8%) than eyes treated with POLY and trimethoprim (59.4%; P=0.1011). *Culture-positive and culture-negative eyes* An analysis of all eyes showed moxifloxacin to be more effective at 48 hours than POLY and 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 to 19.5% in the POLY and trimethoprim group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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) Secondary: Not reported	A telephone interview on day seven 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. Secondary: Not reported
Kodjikian et al.[92] (abstract) (2010) Moxifloxacin vs ofloxacin vs levofloxacin	MA (5 RCTs) Patients with a clinical diagnosis of acute bacterial conjunctivitis in one or more eyes	N=not reported Duration not reported	Primary: Clinical efficacy and drop-out rates for all reasons including lack of efficacy Secondary: Not reported	Primary: Treatment with moxifloxacin was more likely to achieve a clinical cure (OR, 1.59; 95% CI, 1.21 to 2.04; P<0.001) and were less likely to experience a treatment failure compared to treatment with placebo (OR, 3.61; 95% CI, 2.30 to 5.65; P<0.001). Moxifloxacin treatment was associated with a lower risk of therapy discontinuation compared to treatment with placebo (OR, 2.22; 95% CI, 1.62 to 3.03; P<0.001). In comparison to ofloxacin, patients treated with moxifloxacin had fewer dropouts for reasons other than treatment failure (OR, 1.92; 95% CI, 1.28 to 2.89; P=0.02) and fewer dropouts for treatment failure (OR, 2.53; 95% CI, 1.41 to 4.56; P=0.002). Secondary: Not reported
Williams et al.[93] (2013) POLY and trimethoprim ophthalmic solution 1 drop QID for 7 days	RCT, SB Patients 1 to 18 years of age with acute conjunctivitis	N=114 7 days	Primary: Clinical cure rate Secondary: Not reported	Primary: At the four-to-six day follow-up visit, 72 and 77% of patients in the POLY and trimethoprim and moxifloxacin groups were considered clinically cured, defined as a complete resolution of all signs and symptoms of conjunctivitis (P=0.59). Treatment with POLY and trimethoprim was shown to be non-inferior to moxifloxacin with a non-inferiority margin of 20% (difference, -0.05; 90% CI, -0.20 to 0.11). At the seven-to-ten day follow-up visit, 96 and 95% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs moxifloxacin 0.5% ophthalmic solution 1 drop TID for 7 days				POLY and trimethoprim and moxifloxacin groups were considered clinically cured (P value not reported). Bacteriologist cure rate was 61% in the POLY and trimethoprim group and 79% in the moxifloxacin group (P=0.52). Secondary: Not reported
Genée et al.[94] (1982) POLY and trimethoprim administered 6 times daily for 10 days vs POLY, NEO, and gramicidin administered 6 times daily for 10 days	DB, RCT Patients between the age of 8 and 80 years with a presumptive diagnosis of bacterial conjunctivitis	N=48 12 to 15 days	Primary: Microbiological eradication and sign/symptoms of bacterial conjunctivitis Secondary: Not reported	Primary: Bacteria were eradicated in all except two of the patients receiving POLY, NEO, and gramicidin and in all patients receiving POLY and trimethoprim (in whom bacteria were cultured at baseline). There was no significant difference between POLY and trimethoprim and POLY, NEO, and gramicidin 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 POLY, NEO, and gramicidin and before and after treatment with POLY and trimethoprim. No patient reported adverse reactions from either antibacterial preparation. Secondary: Not reported
Lohr et al.[95] (1988) POLY and trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours while awake for 10 days	DB, RCT Patients between the ages of 2 months and 22 years of age with bacterial conjunctivitis	N=158 10 days	Primary: Clinical and bacteriological responses Secondary: Not reported	Primary: At the first follow-up visit, clinical cure or improvement was seen in 92, 95, and 89% of the patients treated with POLY and trimethoprim, gentamicin, and sulfacetamide, 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 POLY and trimethoprim,

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 vs sulfacetamide 10% ophthalmic solution administered every 3 hours while awake for 10 days				gentamicin, and sulfacetamide, respectively; P>0.1). Secondary: Not reported
Gibson et al.[96] (1983) POLY and trimethoprim 10,000 units-0.1% QID daily for 7 days vs POLY, NEO, and gramicidin 5000 units-1700 units-25 units/mL QID for 7 days vs chloramphenicol 5 mg/mL* QID daily for 7 days	DB, MC, RCT Patients between 1 and 70 years of age with presumptive bacterial conjunctivitis	N=272 10 to 14 days	Primary: Signs and symptoms of bacterial conjunctivitis Secondary: Not reported	Primary: There was no significant difference between POLY and trimethoprim and POLY, NEO, and gramicidin (P>0.05) in reducing overall initial scores by 100% (cure) and 90% (very good improvement). POLY and trimethoprim was significantly more effective than chloramphenicol (P=0.03) in reducing overall initial scores by 100% (cure) and 90% (very good improvement. Secondary: Not reported
Kernt et al.[97]	MC, PG, RCT, SB	N=276	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) TOBY 0.3% ophthalmic solution (enhanced viscosity) 1 drop BID for 7 days vs TOBY 0.3% ophthalmic solution 1 drop QID for 7 days	Male and female patients with a negative pregnancy test prior to study entry who agreed to use birth control throughout the study, ≥1 year of age with bacterial conjunctivitis based on clinical observation	12 days	Percentage of patients with sustained cure/ presumed bacterial eradication based on final clinical judgment at TOC visit Secondary: Lid erythema/ swelling, palpebral conjunctiva, bulbar conjunctiva, conjunctival discharge/ exudates, tearing and epithelial disease; microbiology; safety	At the TOC visit, no statistically significant differences were seen between TOBY BID and TOBY QID with regard to sustained cure/presumed eradication (98 vs 99%, respectively; P=0.604). Secondary: No statistically significant differences were seen between the two groups with regard to lid erythema/swelling, palpebral conjunctiva, bulbar conjunctiva, conjunctival discharge/exudates and tearing (P value not reported). Persistence of the original infecting organism was confirmed in two patients treated with TOBY BID and in six patients treated with TOBY QID (P value not reported). Adverse events reported were mild to moderate in severity and were reported in 5.8% of the total number of patients in both groups. The most frequent ocular adverse events in the TOBY BID group were ocular pruritus (1.5%), ocular hyperemia (1.5%) and tearing (1.5%). Only ocular pruritus (0.7%) was reported in the TOBY QID (P value not reported).
Eradication of Nasal Colonization with *S aureus*				
Mody et al.[98] (2003) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for up to 2 weeks vs placebo	DB, PC, RCT Residents of Veterans Affairs and community long-term facilities with *S aureus* colonization	N=127 6 months	Primary: Nosocomial *S aureus* infection, nasal carriage of *S aureus* Secondary: Not reported	Primary: By the end of the treatment period, 93% of patients randomized to receive mupirocin ointment were no longer colonized with *S aureus*, compared to 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 six months after study onset (P<0.4). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wertheim et al.[9] (2004) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs placebo	DB, MC, PC, RCT 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 eight 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.[100] (1999) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs placebo	DB, PC, RCT Patients ≥16 years old with 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 to 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 to 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 to 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.[101] (2002)	DB, PC, RCT 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 one month of study onset, no nasal or facial bone disruption		nasal carriage of *S aureus* Secondary: Not reported	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 to 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 six or more doses of mupirocin exhibited a greater rate of *S aureus* elimination (93.3%) compared to patients getting three to five doses of mupirocin ointment (81.3). Secondary: Not reported
van Rijen et al.[102] (2008) Mupirocin calcium nasal ointment vs placebo, no treatment or alternative topical treatment	MA (9 RCTs) Studies of nasal carriers of *S aureus* that were using hospital services (either as inpatient or outpatient)	N=3,396 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The infection rate caused by microorganisms other than *S aureus* was significantly higher in patients treated with mupirocin compared to control patients (RR, 1.38; 95% CI, 1.118 to 1.72).
Soto et al.[103] (1999) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs BAC 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 Secondary: Not reported	Primary: Nasal carriage was eradicated in 44% of patients randomized to BAC ointment as compared to 94% of patients receiving mupirocin therapy, as assessed 72 to 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 BAC 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. Secondary: Not reported
Sit et al.[104] (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 for at least six months	N=49 1 year	Primary: Eradication of *S aureus* nasal carriage, incidence of peritonitis, exit site infection rates Secondary: Not reported	Primary: At the beginning of the study, the frequency of *S aureus* nasal carriage was similar in the two 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Loeb et al.[105] (2003) Topical regimens (antibiotic or antiseptic ointments, antiseptic detergents) vs systemic antimicrobial agents vs placebo Results in this table are specific to mupirocin therapy.	MA (6 RCTs) Patients with nasal or extra-nasal MRSA colonization	N=384 Up to 6 months	Primary: MRSA eradication from all sites and incidence of MRSA infections Secondary: Not reported	Primary: *Mupirocin vs placebo* 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 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). *Mupirocin vs topical fusidic acid and oral trimethoprim-sulfamethoxazole* 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). Secondary: Not reported
van Rijen et al.[106] (2008) Mupirocin nasal ointment administered before surgery vs placebo or no treatment	MA (4 RCTs) Mupirocin-treated surgical patients with *S aureus* nasal carriage	N=1,372 5 days	Primary: Post-operative *S aureus* infection rate Secondary: Not reported	Primary: *Eradication of carriage* Perl et al. showed that nasal carriage of *S aureus* was eliminated in 83% of patients who received mupirocin, as compared to 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). *Post-operative S aureus infection rate* Perl et al. showed a significant effect of mupirocin on the rate of *S. aureus*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). Secondary: Not reported
Ammerlaan et al.[107] (2009) Topically applied antibiotics (mupirocin nasal ointment, BAC nasal ointment, tea tree oil) vs oral antibiotics (tetracyclines, fusidic acid, macrolides, ciprofloxacin, rifampin, and trimethoprim-sulfamethoxazole) vs topical and oral antibiotic combination therapy	MA (23 RCTs) MRSA carriage in healthy individuals, health care workers, hospitalized patients and patients visiting outpatient clinics, and nursing home patients	N=2,114 Variable duration	Primary: Eradication of *S aureus* carriage Secondary: Not reported	Primary: *Topical treatments* The efficacy of mupirocin was comparable among studies that included only 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 RR 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 to 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 to 0.50). Eradication had been successful in 65% (range, 25 to 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 to 0.64) and 0.40 (range, 0.34 to 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 to 0.74) compared to studies that only tested for nasal carriage (pooled RRs, 0.38; range, 0.32 to 0.45). BAC nasal ointment only eradicated carriage in 29% of MRSA and MSSA carriers at one week after treatment (range, 13 to 44%), and tea tree oil eliminated MRSA carriage in 44% of carriers at two weeks after treatment. Compared to mupirocin, estimated pooled RRs of treatment failure of BAC and tea tree oil at the end of treatment was 1.88 (range, 0.57 to 6.15).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Systemic treatments The overall pooled RRs of treatment failure of oral antibiotics, compared to placebo or no treatment, was 0.47 (range, 0.39 to 0.57) one week after treatment and 0.54 (range, 0.33 to 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 to that of placebo or no treatment, was not higher in studies that determined eradication by means of nasal cultures only (pooled RRs, 0.74; range, 0.65 to 0.85), compared to 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 eight 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 DOXY, rifampin, mupirocin, and chlorhexidine was associated with MRSA eradication in 74% of patients after three months. Rifampin as part of combination therapy with other oral and/or topical antibiotics was associated with eradication of MRSA in 62% of carriers. Secondary: Not reported
Keratitis				
Leibowitz et al.[108] (1991) Ciprofloxacin 0.3% ophthalmic solution administered every 15 minutes for the first 6 hours, followed by every	MC, OL, PRO 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 Secondary:	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.

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30 minutes for the remainder of day 0, followed by every hour on day 1, followed by every 4 hours on days 2 to 14			Not reported	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. Secondary: Not reported
Parmar et al.[109] (2006) Gatifloxacin 0.3% ophthalmic solution, frequency not reported vs ciprofloxacin 0.3% ophthalmic solution, frequency not reported	DB, RCT Patients with a diagnosis of bacterial keratitis	N=104 (104 eyes) Duration not specified	Primary: Healing of ulcers and microbiological outcomes Secondary: Not reported	Primary: Of the 41 eyes in the gatifloxacin 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 ciprofloxacin group (P=0.042). There was one severe ulcer with complete follow-up in each group. The 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 gatifloxacin or ciprofloxacin (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 gatifloxacin group compared to the ciprofloxacin group (93.3 vs 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 gatifloxacin group compared to the ciprofloxacin group (100 vs 93.3%, respectively; P=0.40). Considering culture-positive eyes alone, there was no significant difference between gatifloxacin and ciprofloxacin 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 gatifloxacin group was 13.9 days which did not differ significantly from that in the ciprofloxacin group (16. 8 days; P=0.43). The number of ulcers caused by gram-positive cocci that healed in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				gatifloxacin group were significantly higher than in the ciprofloxacin 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 gatifloxacin and ciprofloxacin groups did not differ significantly. Secondary: Not reported
Prajna et al.[110] (2001) Ofloxacin 0.3% ophthalmic solution administered every 30 minutes on day 1, followed by every hour on days 2 to 4, followed by every 2 hours on days 5 to 21 vs ciprofloxacin 0.3% ophthalmic solution administered every 30 minutes on day 1, followed by every hour on days 2 to 4, followed by every 2 hours on days 5 to 21	DB, PG, RCT Patients with a microbiologic diagnosis of bacterial keratitis	N=217 3 weeks	Primary: Time to healing and reepithelialization accompanied by no progression of infiltration Secondary: Biomicroscopic findings, microbiologic findings on organism susceptibility and resistance, and patient reported symptoms	Primary: No significant differences were observed between the ofloxacin and ciprofloxacin treatment groups with regard to ulcer healing (85 vs 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. The average time to corneal healing was comparable in patients treated with either ofloxacin or ciprofloxacin, 13.7±0.7 and 14.4±0.8 days, respectively (P=0.80). Within seven 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 to those that healed (P=0.003). The stromal infiltration was also significantly larger in those patients who experienced perforation compared to those who did

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[111] (1994) Ciprofloxacin 0.3% ophthalmic solution administered every 2 hours on days 0 to 1, followed by every 4 hours on days 2 to 6 vs TOBY 0.3% ophthalmic solution administered every 2 hours on days 0 to 1, followed by every 4 hours on days 2 to 6	DB, MC, RCT Patients with blepharitis or blepharo-conjunctivitis	N=464 7 days	Primary: Efficacy, signs and symptoms, physicians' impression of efficacy Secondary: Not reported	Primary: There were no significant differences in the treatment groups with regards to bacterial eradication, reduction, persistence, or proliferation after seven days of treatment. The majority of cases of blepharoconjunctivitis organisms were eradicated by treatment and blepharitis was either reduced or eradicated. Over the seven day period, significant reductions in scores for clinically apparent symptoms and signs were observed in both ciprofloxacin and TOBY treated groups. There were no significant differences between the two treatments (P<0.05). The physicians' overall impression of efficacy after seven days of treatment were as follows: improved or cured was noted in 82% of ciprofloxacin-treated patients and 84% of TOBY-treated patients; unchanged was noted in 18% (ciprofloxacin) and 15% (TOBY) of patients; worse was noted in one TOBY 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 TOBY-treated patients. Adverse events led to the discontinuation of TOBY in a significantly higher proportion of cases than of ciprofloxacin (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kanda et al.[112] (2012) Levofloxacin 0.5% ophthalmic solution	MC, RETRO Patients who received ophthalmic levofloxacin for blepharitis, dacryocystitis, hordeolum, conjunctivitis, tarsadenitis, keratitis and/or corneal ulcer	N=6,686 (safety) N=5,929 (efficacy) Median 29 days for dacryo-cystitis; 8 to 9 days for all other infections	Primary: Adverse events, clinical response Secondary: Not reported	Primary: Forty-six adverse events were reported in 42 patients, with an overall incidence of 0.63%. The most commonly reported adverse events were ocular disorders such as blepharitis (0.1%), eye irritation (0.09%) and punctuate keratitis (0.07%). None of the reported adverse events were considered serious. A clinical response was observed in 95.5% of the 5,929 patients. Patients who were treated for dacryocystitis had a significantly lower response rate (88.3%) compared to patients treated for other diagnoses (overall, 95.8%; P<0.001). Secondary: Not reported
Gwon[113] (1992) Ofloxacin 0.3% ophthalmic solution administered 6 times daily on days 1 to 2, followed by QID on days 3 to 10 vs gentamicin 0.3% ophthalmic solution administered 6 times daily on days 1 to 2, followed by QID on days 3 to 10	DB, RCT 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 Secondary: Not reported	Primary: Among patients treated with ofloxacin, 98% were either clinically cured or improved by day 11, compared to 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 to 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 to 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 to 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 to 58% after gentamicin treatment. Proliferation occurred in 16% of the ofloxacin group vs 27% of gentamicin-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Among the ofloxacin patients, 78% improved overall (both clinically and microbiologically) compared to 63% of gentamicin patients. The observed differences in clinical, microbiological, or overall improvement rates between the ofloxacin and gentamicin groups were not statistically significant. Adverse reactions were reported by in 3.2% of ofloxacin patients and 7.1% of gentamicin patients. Secondary: Not reported
Gwon[114] (1992) Ofloxacin 0.3% ophthalmic solution 1 drop every 2 to 4 hours on days 1 and 2, followed by QID on days 3 through 10 vs TOBY 0.3% ophthalmic solution 1 drop every 2 to 4 hours on days 1 and 2, followed by QID on days 3 through 10	DB, MC, RCT Patients with the presence of conjunctival hyperemia, either eyelid crusting or discharge and positive bacterial culture	N=345 11 days	Primary: Clinical, microbiological and overall improvement rates Secondary: Change in cumulative summary score of 10 key biomicroscopic and symptomatologic variables and safety	Primary: Ofloxacin was found to have higher rates of microbiological (85.2 vs 77.6%) and overall (84.0 vs 77.6%) improvement rates when compared to TOBY at day 11, while TOBY was shown to have a higher clinical improvement rate (98.9 vs 100%); however, none of these differences were statistically significant (P=0.089 for all outcomes). Secondary: The decrease in cumulative summary score was found to be significantly greater in the ofloxacin group when compared to the TOBY group at visits on days three to five (P<0.050). Adverse reactions occurred more frequently in the TOBY group; however, this difference was not significant (0.6 vs 2.9%, respectively; P value not reported).
Foulks et al.[115] (1988) POLY and trimethoprim 10,000 units-0.1%	DB, RCT Patients ≥2 months of age with bacterial ocular surface infections	N=39 3 to 6 days	Primary: Clinical improvement, cure rates, microbiological cure rates	Primary: Clinical improvement was similar in both treatment arms (POLY and trimethoprim, 20%; POLY, trimethoprim, and sulfacetamide, 29%) as were the cure rates (POLY and trimethoprim, 80%; POLY, trimethoprim, and sulfacetamide, 71%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ophthalmic solution administered every 3 hours for 10 days vs POLY, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days	(conjunctivitis, blepharitis or blepharo-conjunctivitis)		Secondary: Not reported	Microbiologic cure rates were similar among the treatment groups with POLY and trimethoprim showing a pathogen eradication rate of 87% and POLY, trimethoprim, and sulfacetamide an eradication rate of 93%. Differences in clinical and microbiologic responses were not statistically significant. Adverse events were similar between the treatment groups. Secondary: Not reported
Lamberts et al.[116] (1984) <u>Study 1</u> POLY, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (Solution 1) vs NEO, POLY, and gramicidin 2.5 mg-5,000 units-0.025 mg/mL ophthalmic solution administered every 3 hours for 10 days	DB, RCT Patients ≥2 months of age with conjunctivitis, blepharitis, or blepharo-conjunctivitis	N=68 17 days	Primary: Cure or clinical improvement, microbiological cure, adverse events Secondary: Not reported	Primary: *Study 1* Clinical cure or improvement was observed in 95% of patients receiving 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Solution 2) Study 2 POLY, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (Solution 1) vs POLY and trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours for 10 days (Solution 3)				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. Secondary: Not reported
Laibson et al.[117] (1981) TOBY 0.3% ophthalmic solution administered every 2 hours for 2 days, followed by every 4 hours for 8 days vs gentamicin 0.3% ophthalmic solution administered every 2	DB, RCT Patients with acute superficial ocular inflammations of presumed bacterial origin	N=66 10 days	Primary: Cure or clinical improvement Secondary: Not reported	Primary: The cure and improvement frequencies of the two drugs were similar, 93% for TOBY 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 TOBY had adverse reactions. The difference was not statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours for 2 days, followed by every 4 hours for 8 days				
Leibowitz et al.[118] (1981) TOBY 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3, followed by TID on days 4 to 10 vs gentamicin 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3, followed by TID on days 4 to 10	DB, RCT Patients with superficial bacterial infections	N=93 10 days	Primary: Clinical response, physicians' judgment of clinical response to therapy, antibacterial efficacy, adverse reactions Secondary: Not reported	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 TOBY-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 TOBY-treated patients, 9.3% experienced adverse reactions compared to 17.6% of patients in the gentamicin treatment group. Secondary: Not reported
Cagle et al.[119] (1981) TOBY 0.3% ophthalmic solution administered every 2 hours on days 1 to 2, followed by QID on days 3 to 10 vs TOBY 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3,	DB, MC, RCT Patients with acute bacterial infections with ocular inflammation, including conjunctivitis, blepharitis, blepharo-conjunctivitis and blepharokerato-conjunctivitis	N=511 11 days	Primary: Cure or clinical improvement, microbiological improvement, adverse events Secondary: Not reported	Primary: There were no significant differences in efficacy between the gentamicin solution and ointment formulations or between the TOBY solution and ointment formulations. TOBY (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 TOBY and gentamicin when the two solutions or ointments were compared separately. TOBY 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 TOBY and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by TID on days 4 to 10 vs gentamicin 0.3% ophthalmic solution administered every 2 hours on days 1 to 2, followed by QID on days 3 to 10 vs gentamicin 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3, followed by TID on days 4 to 10				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 TOBY ointment (P=0.017). Secondary: Not reported
Otitis Externa				
Drehobl et al.[120] (2008) Ciprofloxacin 0.2% otic solution BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic solution TID for 7 days	MC, PG, RCT Patients ≥2 years of age with acute diffuse otitis externa of less than 3 weeks' duration	N=630 15 to 17 days	Primary: Clinical cure of otitis symptoms at the TOC visit Secondary: Clinical cure at the EOT visit, percentage of patients with clinical improvement, resolution and/or improvement of otalgia at EOT and TOC visits,	Primary: The percentage of patients with clinical cure at the TOC visit in the clinical intent-to-treat population was 81.4% in the ciprofloxacin group and 76.7% in the NEO, POLY, and HYDRO group. In the clinical per-protocol population, clinical cure at the TOC visit was 86.6% in the ciprofloxacin group and 81.1% in the NEO, POLY, and HYDRO 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 NEO, POLY, and HYDRO 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 to 88.5% in the NEO, POLY, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events	HYDRO group. At the TOC visit, clinical improvement was similar in the ciprofloxacin group (89.5%) and the NEO, POLY, and HYDRO group (83.1%). Patients treated with ciprofloxacin and NEO, POLY, and HYDRO 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 to 59.8% in the NEO, POLY, and HYDRO 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 NEO, POLY, and HYDRO group. In both treatment groups, most treatment-emergent adverse events 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.[121] (2004) CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	MC, PG, RCT Patients ≥1 year of age with a clinical diagnosis of mild, moderate, or severe AOE and intact tympanic membranes	N=468 18 days	Primary: Clinical cure rates at the day 18 (TOC) visit, microbiologic 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	Primary: The clinical cure rate at the day 18 (TOC) visit was significantly higher with CIPRO and DEX than with NEO, POLY, and HYDRO (90.9 vs 83.9%; P=0.0375). The microbiologic eradication rate in the culture positive patient population was significantly higher with CIPRO and DEX treatment than with NEO, POLY, and HYDRO 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 CIPRO and DEX to be significantly more effective than NEO, POLY, and HYDRO in achieving a clinical cure at the day three and day 18 visits (P=0.0279 and P=0.0321, respectively). The two treatments were equally effective at day eight. Analyses of the individual signs and symptoms of AOE showed that CIPRO and DEX treatment was significantly more effective in reducing inflammation than NEO, POLY, and HYDRO treatment at day 18

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(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 three patients (1.3%) receiving CIPRO and DEX and nine patients (3.8%) receiving NEO, POLY, and HYDRO.
Roland et al.[122] (2007) CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	MC, PG, RCT Patients ≥1 year of age with a clinical diagnosis of moderate (constant but tolerable pain) or severe (intense and unrelenting pain) 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 three, eight, and 18 Secondary: Not reported	Primary: Patient-reported results revealed a greater percentage of CIPRO and 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 to NEO, POLY, and HYDRO-treated patients. CIPRO and DEX-treated patients had significantly less pain than NEO, POLY, and HYDRO-treated patients on day two (P=0.0204) and day three (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 CIPRO and DEX at the investigator assessment on day three. 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. No patients in either treatment group discontinued the study because of treatment-related adverse events. Secondary: Not reported
Rahman et al.[123] (2007) CIPRO and DEX 0.3-0.1% otic	Pooled analysis of 2 RCTs Patients ≥1 year of age diagnosed	N=1,072 18 days	Primary: Clinical cure rates and time to cure Secondary:	Primary: Following seven days of therapy, 98.1% of CIPRO and DEX-treated patients and 95.7% of NEO, POLY, HYDRO-treated patients were clinically cured.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
suspension BID for 7 days vs NEO, POLY, HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	with AOE		Not reported	The mean time to cure was 9.7 days in the CIPRO and DEX group compared to 10.3 days in the NEO, POLY, HYDRO group. The proportion of patients cured at the day-three, -eight, and -18 assessments between the CIPRO and DEX and NEO, POLY, HYDRO 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 two 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%). Secondary: Not reported
Dohar et al.[124] (2009) CIPRO and DEX 0.3-0.1% otic suspension 3 to 4 drops BID for 7 days vs NEO, POLY, HYDRO 3.5 mg-10,000 units-1% otic suspension BID to TID for 7 days	Pooled analysis of 2 RCTs Patients >1 year of age with AOE and intact tympanic membranes who were positive for *P aeruginosa* and *S aureus* at baseline	N=789 18 days	Primary: Treatment failure rates, MIC_{50}, and MIC_{90} values for *P aeruginosa* and *S aureus* Secondary: Not reported	Primary: Treatment with CIPRO and DEX was associated with a significantly lower treatment failure rate against *P aeruginosa* (5.1%) than NEO, POLY, HYDRO (13.0%; P=0.0044). For *P aeruginosa*, the MIC_{50} values were lowest for CIPRO (0.13 mg/mL), followed by POLY (0.5 mg/mL), NEO (8 mg/mL), and POLY and NEO combined (1.0 and 3.2 mg/mL). MIC_{90} values of each antibiotic preparation were 2- to 4-fold higher than MIC_{50} except for POLY, which had identical MIC_{50} and MIC_{90} values. The overall treatment failure rates for *S aureus* were similar between CIPRO and DEX and NEO, POLY, HYDRO (7.3 vs 6.9%; P=0.9463). For *S aureus*, the CIPRO MIC_{50} was 0.25 mg/mL; the POLY MIC_{50} was 65 mg/mL, the NEO MIC_{50} was 0.5 mg/mL, and the POLY and NEO MIC_{50} was 0.25 and 0.80 mg/mL. MIC_{90} were 2- to 4-fold higher than MIC_{50} values. Secondary: Not reported
Pistorius et al.[125] (1999)	RCT	N=842	Primary: Clinical success	Primary: For the per-protocol population, clinical success at the end of therapy was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CIPRO 0.2% otic solution or CIPRO and HYDRO 0.2-1.0% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	Patients ≥2 years of age with acute diffuse bacterial otitis externa of less than 3 weeks' duration	14 to 28 days posttreatment	(resolution or improvement), bacteriological eradication, and adverse events Secondary: Not reported	reported in 93% of CIPRO-treated patients, 90% of CIPRO and HYDRO-treated patients, and 87% of NEO, POLY, and HYDRO-treated patients. CIPRO and CIPRO and HYDRO were found to be statistically equivalent to NEO, POLY, and HYDRO therapy (95% CI, -0.0 to 10.5 for CIPRO vs NEO, POLY, and HYDRO; 95% CI, -3.3 to 8.0 for CIPRO and HYDRO vs NEO, POLY, and HYDRO). For the intent-to-treat population, the clinical response was also statistically equivalent between CIPRO or CIPRO and HYDRO and NEO, POLY, and HYDRO. At the end of therapy, clinical success was reported in 91%, 91%, and 89% of the intent-to-treat patients in the CIPRO, CIPRO and HYDRO, and NEO, POLY, and HYDRO treatment groups, respectively. At the follow-up evaluation, continued resolution was observed in 97% of CIPRO-, 98% of CIPRO and HYDRO-, and 95% of NEO, POLY, and HYDRO-treated patients. Estimated median time-to-end of ear pain in the population valid for efficacy was 4.7 days for the CIPRO group, 3.8 days for the CIPRO and DEX group, and 4.1 days for the NEO, POLY, and HYDRO group. Treatment with CIPRO and HYDRO resulted in a statistically significantly shorter time-to-end of ear pain when compared to CIPRO (P=0.039). The percentage of patients who took pain medications was similar across the treatment groups. Fifty percent of the CIPRO patients, 51% of the CIPRO and HYRDO patients, and 53% of the NEO, POLY, and HYDRO patients used analgesics for ear pain. The median time to a 50% reduction in ear pain was 2.47 days for CIPRO, 2.08 days for CIPRO and HYDRO, and 2.03 days for NEO, POLY, and HYDRO. Bacteriologic eradication at the end of therapy was 92% in the CIPRO-, 95% in the CIPRO and HYDRO-, and 87% in the NEO, POLY, and HYDRO-treatment groups (95% CI, -2.0 to 12.4 for CIPRO vs NEO, POLY, and HYDRO; 95% CI, 0.3 to 13.7 for CIPRO and HYDRO vs NEO, POLY, and HYDRO).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At least one treatment- emergent event was reported in 23% of CIPRO-, 25% of CIPRO and HYDRO-, and 20% of NEO, POLY, and HYDRO-treated patients. Drug-related events were similar among the three treatment groups (6% CIPRO, 5% CIPRO and HYDRO, 5% NEO, POLY, and HYDRO). 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% CIPRO, 94% CIPRO and HYDRO, 95% NEO, POLY, and HYDRO) and improved or resolved with sufficient follow- up. Secondary: Not reported
Jones et al.[126] (1997) Ofloxacin 0.3% otic solution BID for 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic solution QID for 10 days	2 RCTs Adults (≥12 years of age) and children (≥1 and ≤11 years of age) with clinically diagnosed, unilateral or bilateral, stable or exacerbating otitis externa of 2 weeks' duration or less with purulent or mucopurulent otorrhea	N=314 17 to 20 days	Primary: Overall clinical efficacy in the clinically evaluable population Secondary: Not reported	Primary: The overall clinical response was cure in 97% of ofloxacin-treated children and 95% of NEO, POLY, and HYDRO-treated children (P=0.48). The overall clinical response was cure in 82% of ofloxacin-treated adults and 84% of NEO, POLY, and HYDRO-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 NEO, POLY, and HYDRO demonstrated comparable efficacy (≥98%) in eradicating all pathogens. Compliance in adults was comparable in both treatment groups (91% for ofloxacin-treated and 86% for NEO, POLY, and HYDRO-treated patients). Compliance in children was also comparable in both treatment groups (94% for ofloxacin-treated and 84% for NEO, POLY, and HYDRO-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 common treatment-related adverse events reported in adults were pruritus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(6.3 and 3.8% of ofloxacin- and NEO, POLY, and HYDRO-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 NEO, POLY, and HYDRO-treated children and no ofloxacin-treated children. Secondary: Not reported
Schwartz et al.[127] (2006) Ofloxacin 0.3% otic suspension QD for 7 to 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension QID for 7 to 10 days	MC, PG, RCT Pediatric patients aged ≥6 months and ≤12 years with stable or exacerbating symptoms of otitis externa of less than 2 weeks' duration	N=278 17 to 20 days	Primary: Overall clinical response (defined as cure in the clinically evaluable patients demonstrated by resolution of otitis externa 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 (seven to 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 NEO, POLY, and HYDRO 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 NEO, POLY, and HYDRO-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 NEO, POLY, and HYDRO 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 NEO, POLY, and HYDRO group. The mean overall percent compliance for ofloxacin patients was 93.2 vs 84.1% for patients taking NEO, POLY, and HYDRO 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 NEO, POLY, and HYDRO-treated patients with a microbiological assessment of eradication were clinically cured. At the test of cure visit, 100.0% (54/54) of the ofloxacin-treated patients and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				97.0% (33/34) of the NEO, POLY, and HYDRO-treated patients with a microbiological assessment of eradication were clinically cured (combined sustained clinical cure and subsequent clinical cure). Treatment-related adverse events were similar in both treatment groups and were mild to moderate in severity. The adverse events reported with highest frequency were application-site reaction (22.3 and 20.3% of the ofloxacin-treated and NEO, POLY, and HYDRO-treated patients, respectively) and earache (7.2 and 4.3% of the ofloxacin treated and NEO, POLY, and HYDRO-treated patients, respectively).
Rosenfeld et al.[128] (2006) Various topical antimicrobials with or without corticosteroids	MA (20 RCTs) Patients with diffuse AOE	N=3,289 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 Secondary: Not reported	Primary: *Antimicrobial vs placebo* Topical antimicrobial increased absolute clinical cure rates of AOE by 46% and bacteriologic cure rates by 61% compared to placebo. The 95% CI for the clinical cure rate is consistent with a NNT of 1.5 to 3.5 patients. Treatment with topical NEO, colistin, and HYDRO was associated with less severe edema and itching at day three compared to placebo (P<0.05), and less severe edema, itching, redness, scaling, and weeping at day seven (P<0.05). *Antiseptic vs antibiotic* Topical antiseptic and topical antibiotic achieved comparable clinical cure rates at seven to 14 days. *Quinolone antibiotic vs non-quinolone antibiotic* Topical quinolone antibiotic and topical non-quinolone antibiotic achieved comparable clinical cure rates at three to four days, seven to 10 days, and 14 to 28 days and comparable clinical improvement rates at seven to 10 days. Quinolones used in the meta-analyses were ofloxacin, CIPRO alone, or CIPRO combined with DEX or HYDRO. The antibiotic comparators used were gentamicin, TOBY, or POLY and HYDRO combined with NEO or oxytetracycline. None of the comparisons were statistically significant. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				excluded from the MA, 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 NEO, POLY, and HYDRO. 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. *Antimicrobial/steroid vs antimicrobial alone* Topical antimicrobial/steroid and topic antimicrobial alone achieved comparable clinical and bacteriologic cure rates at seven days. Antimicrobial and steroid combinations used in the MAs were CIPRO and HYDRO, CIPRO and DEX, and acetic acid and triamcinolone. The antibiotic comparator in all studies was the same antimicrobial without the steroid. *Steroid/antibiotic vs steroid alone* Topical steroid alone increased absolute clinical cure rates by 20% at seven to 11 days compared to topical steroid and antibiotic combination therapy. Steroids used in the MAs were betamethasone and HYDRO butyrate. The antibiotic and steroid comparator was oxytetracycline, POLY, and HYDRO in both trials. 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 (five to 33 patients) cannot exclude a trivial effect. Secondary: Not reported
Otitis Media				
Miro et al.[129] (2000) CIPRO 0.2% otic solution BID for 10 days	MC, OL, RCT Patients 14 to 71 years of age with chronic suppurative otitis	N=232 1 month following the end of therapy	Primary: Clinical response at visit two Secondary: Clinical response	Primary: In the per protocol population, 91% of patients in the CIPRO and 87% of patients in the NEO, POLY, and HYDRO group were cured at visit two (90% CI, -8.86 to 4.8; P value not significant). In the evaluable patients and the randomized patients, the percentages of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension QID 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 two and three	patients classified as cured at visit two were 90% and 87%, respectively in the CIPRO group and 81% and 76%, respectively in the NEO, POLY, and HYDRO group (P value not significant). Secondary: At visit three (one month after the end of treatment), 78% of patients in both the CIPRO and NEO, POLY, and HYDRO groups had sustained cure and 5% of patients (4% in the CIPRO group and 6% in the NEO, POLY, and HYDRO group) showed a relapse of otorrhea. The rate of bacterial eradication was 79% in the CIPRO group and 76% in the NEO, POLY, and HYDRO group. The most frequently reported adverse events were pruritus, stinging, earache, passage of the medication into the mouth, vertigo, and cephalea.
Dohar et al.[130] (2006) CIPRO and DEX0.3-0.1% otic suspension 4 drops BID for 7 days vs amoxicillin and clavulanic acid 600-42.9 mg every 12 hours for 10 days	MC, PG, RCT Children 6 months to 12 years of age with AOM 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 TOC Secondary: Microbiologic response	Primary: The median time to cessation of otorrhea for CIPRO and DEX was 4.0 days (ITT and modified ITT) compared to 7.0 days (ITT) and 9.5 days (modified ITT) for amoxicillin and clavulanic acid (ITT; P=0.006, modified ITT; P=0.0011). Clinical cure at TOC occurred in 84.6 and 80.7% of patients receiving CIPRO and DEX (ITT and modified ITT, respectively) compared to 58.5 and 55.2% of patients receiving amoxicillin and clavulanic acid (ITT and modified ITT, respectively; P=0.0100 and P=0.0340, respectively). Secondary: The difference in the microbiologic response between the two treatment groups in the modified per-protocol data set was not statistically significant (83 vs 63%).
Roland et al.[131] (2003) CIPRO and DEX 0.3-0.1% otic	MC, PG, RCT Children 6 months to 12 years of age with AOM with	N=201 17 days	Primary: Time to cessation of otorrhea	Primary: The mean time to cessation of otorrhea in the culture-positive population was 4.22 days in patients receiving CIPRO and DEX compared to 5.31 days in those receiving CIPRO alone (P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
suspension 3 drops BID for 7 days vs CIPRO 0.3% otic solution 3 drops BID for 7 days	tympanostomy tubes and otorrhea for ≤3 weeks' duration		Secondary: Physicians' assessment of the clinical response, reduction of granulation tissue, antimicrobial response	Secondary: Patients receiving CIPRO and DEX showed significantly improved clinical responses at the day three (P<0.0001) and day eight (P<0.0499) visits in comparison with those receiving CIPRO 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 CIPRO and DEX-treated group, 68 patients were microbiological successes, with all pretherapy pathogens eradicated. There were seven microbiological failures in this treatment group, giving an overall CIPRO and DEX success rate of 90.7%. Of the 64 evaluable patients in the CIPRO-treated group, 51 patients were microbiological successes, with all pretherapy pathogens eradicated. There were 14 microbiological failures in this treatment group, giving an overall CIPRO success rate of 79.7%. There was no significant difference between the treatment groups (P=0.0660).
Roland et al.[132] (2004) CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs ofloxacin 0.3% otic solution BID for 10 days	PG, RCT Children who were aged 6 months to 12 years and had patent tympanostomy tubes and a clinical diagnosis of uncomplicated AOM with otorrhea of less than 3 weeks' duration in one or both ears	N=599 21 days	Primary: Clinical response to therapy at the TOC visit (21 days), microbiological response, and treatment failure rate Secondary: Time to cessation of otorrhea, and physicians' assessment of clinical response at each visit	Primary: CIPRO and DEX 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 CIPRO and DEX 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 CIPRO and DEX (4%) compared to ofloxacin (14%; P=0.0017). Secondary: There was a significant difference in the median time to cessation of otorrhea with CIPRO and DEX (four days) compared to ofloxacin (six days; P=0.0209).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The physicians' assessment of clinical response at each visit showed significantly greater cure rates with CIPRO and DEX at day three (P=0.0001), day 11 (P=0.0001), and day 18 (P=0.0023). The adverse-event profiles of CIPRO and DEX 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.[133] (1998) Ofloxacin 0.3% otic solution BID for 10 days vs amoxicillin-clavulanic acid oral suspension 40 mg/kg/day	MC, PG, RCT Patients 1 to 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 Secondary: Not reported	Primary: There was no significant difference in the overall clinical cure rates among patients receiving ofloxacin (76%) compared to patients receiving amoxicillin-clavulanic acid (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 amoxicillin-clavulanic acid-treated patients (67%; P<0.001). Pathogen persistence occurred in one ofloxacin-treated patient (1%) and 26 amoxicillin-clavulanic acid -treated patients (28%). There was recurrence in two ofloxacin-treated patients (2%) and four amoxicillin-clavulanic acid treated patients (4%). Reinfection was noted in only one subject, in the amoxicillin-clavulanic acid treatment arm (1%). There were significantly higher eradication rates in the ofloxacin-treated group than in the amoxicillin-clavulanic acid-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 patients and 67% (62:93) for the amoxicillin-clavulanic acid-treated group. There was no significant difference among the treatment groups. A significantly lower percentage of adverse events occurred in ofloxacin-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated patients (42%) than in amoxicillin-clavulanic acid-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 amoxicillin-clavulanic acid-treated patients (31%; P<0.001). A significantly higher percentage of amoxicillin-clavulanic acid-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). Secondary: Not reported
Periodontitis				
Caton et al.[134] (2000) DOXY 20 mg BID for 9 months vs placebo At the baseline visit, scaling and root planing was performed on the qualifying quadrants until the tooth and root surfaces were free from deposits as determined by visual or tactile examination.	DB, PC, RCT 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 and probing depth, microbial outcomes Secondary: Not reported	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 DOXY at months three, six, and nine than with adjunctive placebo (P<0.05). After nine months of treatment, the mean attachment gains were 1.03 mm and 0.86 mm for the DOXY and the placebo groups, respectively (P<0.05). In tooth sites with severe disease (baseline probing depth ≥7 mm), improvements in attachment were demonstrated for both treatment groups at all time points. The per-patient attachment gains were significantly greater with DOXY than placebo (P<0.05). In tooth sites with mild-to-moderate disease, reductions in probing depth from baseline were demonstrated for both treatment groups. The per-patient reductions in probing depth were significantly greater for the DOXY group at every post-baseline time point than for placebo (P<0.005). In tooth sites with severe disease (baseline probing depth ≥7 mm), treatment with DOXY significantly reduced probing depth compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment with placebo at all time points (P<0.01). Treatment with DOXY also significantly reduced probing depth 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 three, six, and nine of the treatment period were demonstrated between the DOXY and placebo groups (P<0.05), with lower proportions of small, intermediate, and large spirochetes present in the DOXY 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. Secondary: Not reported
Caton et al.[135] (2001) DOXY 20 mg BID for 9 months vs placebo At the baseline visit, scaling and root planing was performed on the qualifying quadrants until the tooth and root surfaces were free from deposits as determined by visual or tactile examination.	DB, PC, RCT 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, clinical attachment level, adverse events, microbial outcomes Secondary: Not reported	Primary: During active treatment (months three, six, and nine), per-patient reductions in probing depth from baseline were significantly greater for the DOXY group than for the placebo group (P<0.05). The incremental reductions in probing depth demonstrated in the DOXY group over nine months of active treatment were maintained through three additional months of no treatment (month 12). For tooth sites with mild to-moderate disease, reductions in probing depth from baseline were significantly greater for the DOXY group than for the placebo group at months three and nine of active treatment, and at the end of the no-treatment follow-up (month 12; P<0.05). Statistically significant treatment differences favoring DOXY over placebo were demonstrated between the treatment groups at months three and six of active treatment (P<0.05). Improvements in clinical attachment level demonstrated in the DOXY group during active treatment were maintained three months posttreatment (month 12); however, this difference was not statistically significant. During the three-month follow-up, the most frequent adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 differences in the proportions of selected bacterial morphotypes between the treatment groups in samples taken from the scaling and root planing quadrants at month 9 (end of active treatment) and month 12 (end of no-treatment followup). No significant differences were demonstrated between the DOXY 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). Secondary: Not reported
Deo et al.[136] (2010) DOXY 20 mg BID vs placebo All patients underwent scaling and root planing prior to receiving study treatment.	PC, PG, RCT Patients with periodontitis and type 2 diabetes mellitus	N=20 6 months	Primary: Probing pocket depth, clinical attachment level, and gingival recession Secondary: Not reported	Primary: The mean probing pocket depth reduction was 3.06 mm with DOXY and 2.54 mm with placebo (P<0.05). The mean clinical attachment level gain was 2.25 mm with DOXY and 1.58 mm with placebo (P<0.05). The mean increase in gingival recession was 0.80 mm in the DOXY group and 0.93 mm in the placebo group (P<0.05). Secondary: Not reported
Gapski et al.[137] (2010) DOXY 20 mg BID	DB, MC, PC, RCT Patients with chronic severe periodontitis with	N=70 12 months	Primary: Clinical attachment levels, probing depth, bleeding on probing, gingival	Primary: *Pooled surgical sites* Both placebo and DOXY groups demonstrated a significant reduction in probing depth compared to baseline; however, there were no significant differences between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients received full mouth scaling and root planing within 90 days before randomization. They also received access flap surgery in a minimum of one sextant.	at least three teeth in the same sextant demonstrating both probing depth and clinical attachment level ≥5 to ≤12 mm and bleeding on probing with at least 10 teeth in the functional dentition		crevicular fluid bone marker assessment Secondary: Not reported	Surgical therapy resulted in mean clinical attachment level gains in both groups (P<0.05). DOXY-treated patients demonstrated a significant reduction in GCF ICTP levels compared to placebo immediately after the surgery (two months; P=0.03). *Moderate sites (baseline probing depth 5 to 6 mm)* There were significant reductions in probing depth and gains in clinical attachment level compared to baseline for the DOXY and placebo groups. The DOXY group demonstrated a significant decrease in the expression of GCF ICTP levels compared to placebo immediately after the surgery (two months; P=0.001). There was a significant reduction in percentage of bleeding on probing sites at three months between DOXY and placebo (P=0.02). Both DOXY and placebo showed comparable levels in percentage of sites bleeding on probing after the patients discontinued drug therapy (P>0.05). *Deep sites (baseline probing depth ≥7 mm)* Greater reductions in probing depth were noted for both DOXY and placebo. DOXY resulted in greater reductions in probing depth compared to controls at three months (P=0.004). DOXY-treated patients demonstrated a significant increase in clinical attachment level compared to placebo during the drug administration (three months; P=0.02; six months; P=0.005). Secondary: Not reported
Preshaw et al.[138] (2004) DOXY 20 mg BID with scaling and root planing vs	DB, MC, RCT Patients with moderate to severe chronic periodontitis	N=209 9 months	Primary: Changes in clinical attachment level and probing depth from baseline, and the total number of sites with attachment gains and probing depth	Primary: Improvements in clinical attachment level and probing depth were greater following SRP with adjunctive DOXY than scaling and root planing with placebo, achieving statistical significance in all baseline disease categories at month nine (P<0.05). At month nine, 42.3% of sites in the DOXY group demonstrated clinical attachment level 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo with scaling and root planing			reductions ≥2 mm and ≥3 mm from baseline Secondary: Not reported	DOXY group compared to 10.6% of sites in the placebo group (P<0.05). When considering the same thresholds of change in probing depth, 42.9% of sites in the DOXY group compared to 31.1% of sites in the placebo group demonstrated probing depth reduction ±2 mm (P<0.01), and 15.4% of sites in the DOXY group compared to 9.1% of sites in the placebo group demonstrated probing depth reduction ±3 mm (P<0.01). Secondary: Not reported
Haffajee et al.[139] (2007) DOXY 20 mg BID for 12 weeks vs azithromycin 500 mg QD for 3 days vs metronidazole 250 mg TID for 14 days (MET) vs scaling and root planing	RCT, SB Patients with chronic periodontitis	N=92 1 year	Primary: Clinical parameters Secondary: Not reported	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 pocket depth reduction and attachment-level gain over time. Patients receiving either systemically administered azithromycin or metronidazole showed greater mean pocket depth reduction post-therapy compared to patients in the DOXY- and SRP-only groups. The differences among treatment groups were statistically significant at 6 and 12 months. After adjusting for multiple comparisons, metronidazole was significantly different from DOXY at 12 months (P<0.05) and the metronidazole 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 attachment level post-therapy at initially deeper sites was observed for the metronidazole group, and the antibiotic groups showed greater improvement than the DOXY and scaling and root planing groups. Differences among treatment groups were significant at 12 months and approached significance at six months. Metronidazole was significantly different from scaling and root planing (P<0.05) at 12 months after adjusting for multiple comparisons. Patients showed attachment loss at 12 months ranging from 15 to 39% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients in the DOXY and scaling and root planing only groups respectively. Secondary: Not reported
Prophylaxis of Ophthalmia Neonatorum				
Ali et al.[140] (2007) Erythromycin 0.5% ointment applied to eyes during the first few hours of birth vs betadine 2.5% applied to eyes during the first few hours of birth vs no prophylaxis	RCT Healthy newborns without congenital eye abnormalities from mothers who had not used any form of antibiotics within the last 48 hours prior to delivery, without rupture of membranes for more than 18 hours and absence of meconium aspiration	N=330 14 days	Primary: Rate of conjunctival symptoms Secondary: Not reported	Primary: The betadine group and erythromycin group had significantly fewer reports of conjunctival redness and tearing or serious or purulent discharge during the first 24 hours through two weeks of birth when compared to the group that did not receive prophylaxis (9.0 and 18.4 vs 22.4%, respectively; P=0.030). Secondary: Not reported
Bell et al.[141] (1993) Erythromycin 0.5% ointment applied to eyes of child at birth vs silver nitration applied to eyes of child at birth	DB, RCT Women from the University of Washington Medical Center-associated obstetric clinics	N=669 60 days	Primary: Frequency of conjunctivitis and duration of prophylaxis Secondary: Not reported	Primary: After two months of observation it was found that infants who received prophylaxis had lower rates of conjunctivitis, with only silver nitrate showing a statistically significant decrease. Rates of conjunctivitis were 22% in the no prophylaxis group, 16% in the erythromycin group and 14% in the silver nitrate group (P value not reported). Patients who received silver nitrate at birth had a 39% lower rate of conjunctivitis (HR, 0.61; 95% CI, 0.39 to 0.97), while those who received erythromycin had a 31% lower rate of conjunctivitis (HR, 0.69; 95% CI, 0.44 to 1.07). When cases of conjunctivitis were compared before and after two weeks

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs no prophylaxis				of birth, the protective effect of prophylaxis was found to be most effective prior to two weeks of birth. The efficacy of erythromycin from days zero to 14 was 9.0% as compared to 15.0% with no prophylaxis (P=0.050). This was not found to be statistically significant from days 15 to 60 (7.0 vs 8.0%, respectively; P=0.920). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study design abbreviations: AC=active comparator, DB=double blind, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind
Miscellaneous abbreviations: AOE=acute otitis externa, AOM=acute otitis media, BAC=bacitracin, CI=confidence interval, CIPRO=ciprofloxacin, DEX=dexamethasone, DOXY=doxycycline, EOT=end-of-treatment, HYDRO=hydrocortisone, HR=hazard ratio, IOP=intraocular pressure, GCF ICTP=gingival crevicular fluid type 1 collagen carboxyterminal peptide, ITT=intention-to-treat, MIC=minimum inhibitory concentration, MITT=modified intention-to-treat, MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-sensitive *Staphylococcus aureus*, NNT=number needed to treat, OR=odds ratio, POLY=polymyxin B, RR=relative risk, SD=standard deviation, TOBY=tobramycin, TOC=test-of-cure

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 13. Relative Cost of the EENT Antibacterials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Azithromycin	solution*	AzaSite®	$$$	N/A
Bacitracin	ointment*	N/A	N/A	$$$
Besifloxacin	suspension*	Besivance®	$$$$	N/A
Ciprofloxacin	ointment*, solution*†‡	Ciloxan®§	$$	$$$$
Doxycycline	tablet	N/A	N/A	$
Erythromycin base	ointment*	Ilotycin®§	$	$
Gatifloxacin	solution*	Zymaxid®*	$$$	$$$$
Gentamicin	ointment*, solution*	Garamycin®§	$	$$$
Levofloxacin	solution*	N/A	N/A	$$$
Moxifloxacin	solution*	Moxeza®, Vigamox®	$$$$	N/A
Mupirocin	nasal ointment	Bactroban Nasal®	$$$$	N/A
Ofloxacin	solution*†	Ocuflox®§	$$$$$	$
Sulfacetamide	ointment*, solution*	Bleph-10®§	$$$$$	$
Tobramycin	ointment*, solution*	Tobrex®§	$$$$	$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Combination Products				
Bacitracin and polymyxin B	ointment*	N/A	N/A	$
Ciprofloxacin and dexamethasone	suspension†	Ciprodex®	$$$$	N/A
Ciprofloxacin and hydrocortisone	suspension†	Cipro HC®	$$$$$	N/A
Gentamicin and prednisolone	ointment*, suspension*	Pred-G®	$$$	N/A
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®	$$$	N/A
Neomycin, polymyxin B and dexamethasone	ointment*, suspension*	Maxitrol®§	$	$
Neomycin, polymyxin B and gramicidin	solution*	Neosporin®§	$	$
Neomycin, polymyxin B and hydrocortisone	solution†, suspension*†	N/A	N/A	$$$$$
Polymyxin B and trimethoprim	solution*	Polytrim®§	$	$
Sulfacetamide and prednisolone	ointment*, solution*§, suspension*	Blephamide®	$$$$$	$$$$
Tobramycin and dexamethasone	ointment*, suspension*	TobraDex ST®	$$$$	$$$$$
Tobramycin and loteprednol	suspension*	Zylet®	$$$$$	N/A

*Ophthalmic formulation.
†Otic formulation.
‡Otic formulation available generically in at least one dosage form and/or strength.
§Generic is available in at least one dosage form and/or strength.
N/A=not available.

X. Conclusions

The eye, ear, nose, and throat (EENT) antibacterials effectively treat a variety of infections.[1-40] 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. Corticosteroids may also be used to control inflammation and maintain patient comfort; however, adverse effects (increased intraocular pressure and cataracts) should be considered.[41,42] Bacterial conjunctivitis is often a self-limiting condition and resolves spontaneously without specific treatment.[43,44] 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.[43,59] 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.[44] For the empiric treatment of bacterial keratitis, topical broad-spectrum antibacterials are used initially. Guidelines recommend the use of a quinolone if the organism is

unknown or if multiple types of organisms are identified.[47] Numerous clinical trials have demonstrated similar clinical cure rates with the ophthalmic antibacterial agents.[64-97,108-119,140,141]

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.[49] 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.[49,142] Guidelines recommend the use of an oral antibacterial agent for the treatment of acute otitis media.[49,52,61,62] Topical antibacterials may be used as an alternative treatment option in patients with perforated tympanic membranes, tympanostomy tubes, or chronic suppurative otitis media.[53,54] Several clinical trials have demonstrated similar cure rates with the otic antibacterials. Relatively few studies have demonstrated greater efficacy with one agent over another.[120-133]

Mupirocin 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] The majority of the published trials evaluating mupirocin utilized placebo or no treatment as a comparator. Several clinical trials have demonstrated that mupirocin eradicates *Staphylococcus aureus* and MRSA nasal colonization in a variety of patient populations immediately following therapy. 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.[97-107] There is insufficient evidence that mupirocin prevents autoinfection of patients from their own nasal colonization with *S. aureus*.[16] Mupirocin nasal ointment is not available in a generic formulation.

Doxycycline is approved for use as an adjunct to scaling and root planing to promote attachment level gain and reduce pocket depth in adult patients with periodontitis.[8] Studies have shown that the adjunctive use of doxycycline with scaling and root planing was more effective than scaling and root planing alone.[134-139] 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 generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand eye, ear, nose, and throat (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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Vasoconstrictors
AHFS Class 523200
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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. 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.[1-5]

Rhinitis medicamentosa (rebound congestion) can occur following the use of a nasal vasoconstrictor for several days. 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.[1-5]

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 August 2013.

Table 1. EENT Vasoconstrictors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Naphazoline	solution†‡	N/A	naphazoline
Phenylephrine	solution†	Mydfrin®‡	phenylephrine
Tetrahydrozoline	solution*	Tyzine Pediatric®	none

*Nasal formulation.
†Ophthalmic formulation.
‡Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the eye, ear, nose, and throat (EENT) vasoconstrictors are summarized in Table 2.

Table 2. Treatment Guidelines Using the EENT Vasoconstrictors

Clinical Guideline	Recommendation(s)
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)[6]**	<u>Pharmacologic treatment of allergic rhinitis</u> • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with

Clinical Guideline	Recommendation(s)
	persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[7]	<u>Pharmacologic therapy</u> • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. <u>Oral antihistamines</u> • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied.

Clinical Guideline	Recommendation(s)
	• Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. <u>Intranasal antihistamines</u> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age.

Clinical Guideline	Recommendation(s)
	However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. Topical decongestants • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. Intranasal corticosteroids • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • 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 in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. Oral corticosteroids • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. Intranasal cromolyn • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines. Intranasal anticholinergics • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. Oral antileukotriene agents • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. Omalizumab • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline

Clinical Guideline	Recommendation(s)
	• Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2013)**[8]	Strep pharyngitis • Penicillin is the drug of choice for treatment of culture positive cases of group A beta streptococcal pharyngitis. In children and patients unable to swallow pills, amoxicillin is an acceptable alternative due to the poor palatability of the penicillin suspension. • In penicillin-allergic patients, options include cephalosporins (for some types of allergies), macrolides, and clindamycin. Consider reevaluating patient for carrier status. Although macrolides may be an acceptable alternative, clinicians should check their local resistance patterns. • Alternative medication recommendations include macrolides, cephalexin, clindamycin, amoxicillin-clavulanate, and rocephin. Non-infectious rhinitis • With the exception of systemic steroids, intranasal corticosteroids are the most effective single agents for controlling allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. Systemic corticosteroid use should be reserved for refractory or severe cases only and given as a short burst. Injectable corticosteroids are generally not recommended as they are invasive and tend to have a longer course of action than typical courses of corticosteroids. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They are less than intranasal corticosteroids, but can be used either on a daily basis or on an as-needed basis. • Second-generation antihistamines are less sedating than first-generation antihistamines, and cause less central nervous system impairment. Adverse events commonly associated with first-generation antihistamines include somnolence, decreased alertness, and anticholinergic effects. These agents may cause central nervous system impairment and impair driving performance. • Oral decongestants can reduce nasal congestion but can result in side effects such as irritability, insomnia, and palpitations. Topical decongestants are used for short-term or intermittent/episodic therapy. Routine daily use is not recommended because of the risk for the development of rhinitis medicamentosa. Both oral and topical decongestants should be used with caution in older adults, children under the age of six, and patients of any age who have a history of the following: arrhythmia, angina, cerebrovascular disease, high blood pressure, bladder neck obstruction, glaucoma, or hyperthyroidism. • Cromolyn is less effective than intranasal corticosteroids, and is most effective when used regularly prior to the onset of allergic symptoms. Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in patients with allergic and non-allergic rhinitis. They have no effect on congestion, sneezing, or itching. • Montelukast is a leukotriene receptor antagonist that is as effective as loratadine and less effective than nasal steroids. It is generally well tolerated

Clinical Guideline	Recommendation(s)
	and may be considered as a third-line option to add after the failure of a nasal corticosteroid and an oral antihistamine. • Ophthalmic preparations contain antihistamines, decongestants, corticosteroids, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers. Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. Non-allergic rhinitis • Treatment of symptomatic nasal obstruction due to non-allergic rhinitis includes the use of azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants, nasal strips, and topical antihistamines. • Intranasal corticosteroids can be used to treat chronic nasal congestion secondary to non-allergic rhinitis. Intranasal corticosteroids have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic symptoms. • Intranasal cromolyn may improve sneezing and congestion scores, and it can be safely used in children two years of age and older. • Some patients find oral decongestants helpful at relieving symptomatic nasal obstruction secondary to non-allergic rhinitis. Oral decongestants have a relatively rapid onset of action and therefore are particularly useful for sporadic symptoms. Patients using oral decongestants should be monitored for hypertension. • Nasal strips may be effective for patients with nocturnal symptoms. They are more effective for patients with narrow noses or with anterior septal deviations. Daytime use of nasal strips is not usually practical. • Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis. • Conservative treatment of symptomatic non-purulent chronic posterior nasal drainage includes increased water intake, decreased caffeine and alcohol intake, nasal saline irrigation, use of petroleum jelly or antibiotic ointment for nasal crusting, and the addition of humidity in bedroom, if significantly less than 50%. In addition, it should be determined if the patient is using any medications that may cause oral or nasal dryness. • Medical treatment of symptomatic non-purulent chronic posterior nasal drainage includes intranasal corticosteroids. • Treatment of symptomatic bilateral chronic anterior rhinorrhea due to non-allergic rhinitis includes avoidance of triggers, intranasal corticosteroids, intranasal ipratropium bromide, and nasal saline. Bacterial sinusitis • Intranasal corticosteroids may be rational but is an unproved adjunctive therapy for acute sinusitis. This therapy may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology. • Antibiotics should be reserved for those patients who failed decongestant therapy, those we present with symptoms and signs of a more severe illness, and those who have complications of acute sinusitis.
International Primary Care Respiratory Group Guidelines: **Management of Allergic Rhinitis (2006)**[9]	Mild intermittent allergic rhinitis • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. o Decongestant. AND/OR o Intranasal saline.

Clinical Guideline	Recommendation(s)
	• Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe intermittent allergic rhinitis treatment options). <u>Moderate/severe intermittent allergic rhinitis</u> • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal saline. o Intranasal glucocorticosteroid. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, consider stepping down therapy. • If failure, review diagnosis and compliance, query infections and other causes, then consider trial of different treatment option or specialist referral. <u>Mild persistent allergic rhinitis</u> • Recommended therapy: o Oral H_1-blocker. o Intranasal H_1-blocker. AND/OR o Decongestant. o Intranasal glucocorticosteroid. o Intranasal saline. o Mast cell stabilizer. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe persistent allergic rhinitis treatment options). <u>Moderate/severe persistent allergic rhinitis</u> • Recommended therapy: o Intranasal glucocorticosteroid. o Decongestant. o Oral H_1-blocker. o Intranasal saline. o Antileukotriene (preferred in patients with coexisting asthma). • Review patient after two to four weeks. If improved, continue treatment for at least one month after symptoms resolve. Consider stepping down dose. • If failure, review diagnosis, review compliance, query infections and other causes, then choose one or more of the following options: o Increase nasal steroid dose, consider trial of different treatment option, or consider referral to specialist. o If sneeze/itch: add H_1-blocker. o If rhinorrhea: add ipratropium. o If blockage: add decongestant or short course of oral steroids. <u>General treatment considerations</u>

Clinical Guideline	Recommendation(s)
	• First generation H_1-antihistamines cause sedation and central nervous system impairment. These side effects may adversely affect cognition, learning and driving. These side effects may be potentiated by alcohol and other sedatives. Adverse events may not always be perceived by patients. • Second generation H_1-antihistamines are associated with less sedation and impairment than first generation antihistamines. • Intranasal and intraocular H_1-antihistamines are as effective as oral antihistamines at the site of their administration. • Intranasal glucocorticosteroids are the most effective class of medications available for the treatment of allergic and nonallergic rhinitis. Oral glucocorticosteroids are rarely needed to control severe symptoms of allergic rhinitis. • Mast cell stabilizers reduce symptoms of allergic rhinitis, but are generally less effective than other treatments and require frequent administration. Ocular mast cell stabilizers are effective and have a role in the treatment of allergic conjunctivitis. • Anticholinergic agents can reduce rhinorrhea, but have little effect on other symptoms of allergic rhinitis. • Antileukotriene agents are effective for the treatment of allergic rhinitis and asthma. They have been shown to be as effective as oral antihistamines, but have a greater effect on nasal obstruction. They may have an additive effect with antihistamines.
American Academy of Ophthalmology Preferred Practice Pattern Guidelines: **Conjunctivitis (2013)**[10]	Seasonal allergic conjunctivitis • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a low-potency topical corticosteroid can be added to the regimen. • A nonsteroidal anti-inflammatory agent (ketorolac) has been Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. • Additional measures include the use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful. • Use of topical mast-cell stabilizers can also be helpful in alleviating symptoms of allergic rhinitis, and intranasal corticosteroids are not effective for the treatment of seasonal allergic conjunctivitis. Vernal/atopic conjunctivitis • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) 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 warranted rarely. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer

Clinical Guideline	Recommendation(s)
	or lymphoma.
American Optometric Association: **Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2007)**[11]	Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) • The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. • The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. • Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). • Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1 receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. • Topical diclofenac and ketorolac, which are both NSAIDS, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is Food and Drug Administration (FDA) approved for this indication. • Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%[†]) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2[†] or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. • Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. • Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. • Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness.

Clinical Guideline	Recommendation(s)
	Viral conjunctivitis • Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. • Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates, or alleviating symptoms. • Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. • The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. • Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. • Topical steroids are specifically contraindicated for treating herpes simplex conjunctivitis.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the eye, ear, nose, and throat (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[1-5]

Indication	Naphazoline	Phenylephrine	Tetrahydrozoline
Nasal Decongestant			
For decongestion of nasal and nasopharyngeal mucosa			✔
Ocular Vasoconstrictor			
For use as a topical ocular vasoconstrictor	✔		
To dilate the pupil		✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the EENT Vasoconstrictors[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Naphazoline	Not reported	Not reported	Not reported	Not reported	Not reported
Phenylephrine	Variable (% not reported)	Not reported	Intestinal wall, Liver (% not reported)	Renal (80 to 86)	2 to 3
Tetrahydrozoline	Good (% not reported)	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Significant drug interactions with the eye, ear, nose, and throat (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 (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	Monoamine oxidase inhibitors	Monoamine oxidase 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 eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the EENT Vasoconstrictors[1-5]

Adverse Events	Naphazoline	Phenylephrine	Tetrahydrozoline
Cardiovascular			
Arrhythmia	✔	✔	-
Hypertension	✔	✔	-
Myocardial infarction	-	✔	-
Palpitation	-	-	✔
Subarachnoid hemorrhage	-	✔	-
Syncope	-	✔	-
Central Nervous System			
Dizziness	✔	-	-
Drowsiness	-	-	✔
Headache	✔	-	✔
Insomnia	-	-	✔
Lightheadedness	-	-	✔
Nervousness	✔	-	-
Gastrointestinal			
Nausea	✔	-	-
Musculoskeletal			
Tremor	-	-	✔
Weakness	✔	-	✔
Ocular			
Blurred vision	✔	-	-
Burning/stinging	-	✔	-
Discomfort	✔	-	-
Floaters	-	✔	-
Intraocular pressure increased	✔	-	-
Irritation	✔	✔	-
Keratitis	✔	-	-
Mydriasis	✔	-	-
Rebound miosis	-	✔	-
Redness increased	✔	-	-
Tearing	✔	-	-

Adverse Events	Naphazoline	Phenylephrine	Tetrahydrozoline
Visual disturbances	-	✔	-
Respiratory			
Nasal burning/stinging	-	-	✔
Nasal congestion (rebound)	-	-	✔
Nasal dryness	-	-	✔
Sneezing	-	-	✔
Other			
Hyperglycemia	✔	-	-
Sweating	✔	-	-

✔ Percent not specified.
-Incidence not reported.

VII. Dosing and Administration

The usual dosing regimens for the eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 7.

Table 7. Usual Dosing Regimens for the EENT Vasoconstrictors[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Naphazoline	Topical ocular vasoconstrictor: Ophthalmic solution: 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 solution: 0.1%
Phenylephrine	Mydriasis: Ophthalmic solution: 1 drop every 3 to 5 minutes as needed, up to 3 drops per eye; if necessary dose may be repeated	Mydriasis (in patients <1 year of age): Ophthalmic solution (2.5% solution only): 1 drop every 3 to 5 minutes, up to 3 drops per eye Mydriasis (in patients ≥1 year of age): Ophthalmic solution (2.5% or 10%): 1 drop every 3 to 5 minutes, up to 3 drops per eye	Ophthalmic solution: 2.5% 10%
Tetrahydrozoline	Decongestion of nasal and nasopharyngeal mucosa: 2 to 4 drops or 3 to 4 sprays instilled in each nostril as needed, never more often than every 3 hours	Decongestion of nasal and nasopharyngeal mucosa (in patients ≥6 years of age): Nasal solution (0.1%): 2 to 4 drops or 3 to 4 sprays instilled in each nostril as needed, never more often than every 3 hours Decongestion of nasal and nasopharyngeal mucosa (in patients 2 to 5 years of age): Nasal solution (0.05%): 2 to 3 drops instilled in each nostril as needed, and never more often than every 3 hours	Nasal solution (drops): 0.05%

VIII. Effectiveness

There were no clinical trials identified in the medical literature that directly compared the safety and efficacy of the ophthalmic or nasal eye, ear, nose, and throat (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
Naphazoline	solution†‡	N/A	N/A	$
Phenylephrine	solution†	Mydfrin®‡	$$	$
Tetrahydrozoline	solution*	Tyzine Pediatric®	$$$	N/A

*Nasal formulation.
†Ophthalmic formulation.
‡Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The eye, ear, nose, and throat (EENT) vasoconstrictors are approved for use in a variety of ophthalmic conditions/procedures and to treat nasal congestion.[1-5] 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.[6,7,9] 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. 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.[6,7]

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 generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand eye, ear, nose, and throat (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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Androgens
AHFS Class 680800
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I. Overview

The androgens are approved for a variety of indications, including hypogonadism and delayed puberty in males, endometriosis and fibrocystic breast disease in females, promotion of weight gain, relief of bone pain, and treatment of anemias.[1-20] Danazol is an oral synthetic derivative of ethisterone with a weak androgenic activity. It suppresses the pituitary-ovarian axis possibly by inhibiting the release of pituitary gonadotropins, altering sex steroid metabolism and interacting with sex hormone receptors. It reduces ovarian estrogen production by depressing the release of follicle-stimulating hormone and luteinizing hormone. Danazol may also have inhibitory effects at gonadal sites. It decreases concentrations of immunoglobulins (Ig) IgA, IgG, and IgM as well as phospholipids and IgG isotope autoantibodies in patients with endometriosis and hereditary angioedema. Danazol increases serum concentrations of C1 esterase inhibitor in patients with hereditary angioedema.[1,2] Fluoxymesterone and methyltestosterone are oral, synthetic, alkylated testosterone derivatives with significant androgen activity.[1,3-6] Oxandrolone and oxymetholone are anabolic steroids. Oxandrolone suppresses gonadotropic functions of the pituitary gland and exhibits direct action on the testes. It also increases low-density lipoprotein and decreases high-density lipoprotein. Oxymetholone enhances the production and urinary excretion of erythropoietin in patients with anemias due to bone marrow failure and often stimulates erythropoiesis in anemias due to deficient red cell production.[1,7-8] Testosterone is an endogenous androgen that plays a role in the normal growth and development of the male sex organs as well as the maintenance of secondary sex characteristics.[1]

With the exception of danazol, oxandrolone, and oxymetholone, all agents in this review are Food and Drug Administration (FDA)-approved for the management of male hypogonadism. The oral synthetic testosterones (fluoxymesterone and methyltestosterone) and the injectable testosterone, testosterone enanthate, are also FDA-approved for the treatment of delayed puberty in males and metastatic mammary cancer in females. Danazol is FDA-approved for the treatment of endometriosis, fibrocystic breast cancer, and hereditary angioedema, though it is not indicated for the management of male hypogonadism. Oxandrolone is approved for adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. This agent is also approved to offset the protein catabolism associated with prolonged administration of corticosteroids and for the relief of the bone pain frequently accompanying osteoporosis. Oxymetholone is approved for the treatment of anemias caused by deficient red cell production.[1-20] Testosterone undecanoate (Aveed®) was FDA approved in March 2014 and is a longer-acting injectable formulation of testosterone. Maintenance treatment occurs every 10 weeks; however, patients need to be observed for at least 30 minutes after injection due to the risk of serious pulmonary oil microembolism reactions and anaphylaxis. Aveed® includes a boxed warning regarding this risk and is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.[19]

Hypogonadism is a defect of the reproductive system which results in a lack of function of the gonads (testes). It can be categorized by the level of the reproductive system that is defective.[21] Primary hypogonadism is hypogonadism resulting from a defect of the gonads while secondary hypogonadism, also known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary.[22] Male hypogonadism may manifest with testosterone deficiency and/or infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor ability to concentrate, and an increased risk of osteoporosis and fractures.[21] Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients. The oral alkylated androgens are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects.[21,23-25]

The androgens that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Danazol, fluoxymesterone, methyltestosterone, oxandrolone, testosterone cypionate, and testosterone enanthate are available in a generic formulation. This class was last reviewed in August 2013.

Table 1. Androgens Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Danazol	capsule	N/A	danazol
Fluoxymesterone	tablet	N/A	fluoxymesterone
Methyltestosterone	capsule, tablet	Android®*, Testred®*	methyltestosterone
Oxandrolone	tablet	N/A	oxandrolone
Oxymetholone	tablet	Anadrol®	none
Testosterone	buccal, implant, nasal gel, transdermal gel, transdermal patch, transdermal solution	Androderm®, AndroGel®*, Axiron®, Fortesta®*, Natesto®, Striant®, Testim®* ,Testopel®, Vogelxo®*	testosterone
Testosterone cypionate	solution for injection	Depo®-Testosterone*	testosterone cypionate
Testosterone enanthate	solution for injection	N/A	testosterone enanthate
Testosterone undecanoate	oil for injection	Aveed®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the androgens are summarized in Table 2.

Table 2. Treatment Guidelines Using the Androgens

Clinical Guideline	Recommendation(s)
The American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients (2002)**[21]	• Testosterone replacement therapy should maintain testosterone levels within the physiologic range (280 and 800 ng/dL). • Testosterone replacement therapy can be used in men with hypogonadism who are not interested in fertility or who are not able to achieve fertility. • Treatment of men with hypogonadism with testosterone replacement therapy results in increased sexual interest and increased number of spontaneous erections. • Secondary sex characteristics (i.e., increased muscle mass, beard growth, growth of pubic and axillary hair and phallus growth) improve with testosterone replacement therapy. • In adolescent male patients with hypogonadotropic hypogonadism, testosterone replacement therapy increases bone mineral density in comparison with that in male patients with hypogonadism not receiving testosterone replacement therapy. In prepubertal-onset hypogonadotropic hypogonadism, diminished bone mass may be only marginally improved by testosterone replacement therapy. • No specific recommendations can be made on the possible normalization of growth hormone levels in elderly men with testosterone replacement therapy. Further research is needed to clarify the potential risks and benefits associated with therapy. • Whether testosterone replacement therapy in men with hypogonadism increases, decreases, or has a neutral effect on cardiovascular risk remains uncertain. • Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful. The orally administered alkylated androgen preparations currently available in the Unites States are generally not recommended because of poor androgen effects, adverse lipid changes and hepatic side effects, such as hemorrhagic liver cysts, cholestasis and hepatocellular adenoma.
International Society of Andrology, International Society for the Study of the	• Late-onset hypogonadism is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range). This condition may result in significant detriment in the quality of life and adversely

Clinical Guideline	Recommendation(s)
Aging Male, European Association of Urology, European Academy of Andrology, American Society of Andrology: International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, American Society of Andrology: **Recommendations: Investigation, Treatment and Monitoring of Late-Onset Hypogonadism in Males (2009)**[24]	affect the function of multiple organ systems. • Response to testosterone replacement therapy should be assessed. If there is no improvement of signs symptoms within a reasonable time interval (three to six months is adequate for libido and sexual function, muscle function and improved body fat; a longer interval is required to see improvement in bone mineral density), testosterone replacement therapy should be withdrawn. Further investigation for other causes of symptoms is then mandatory. • Testosterone replacement therapy improves body composition (i.e., decrease of fat mass, increase of lean body mass) in men with hypogonadal values of testosterone. Secondary benefits of these changes of body composition on strength, muscle function, metabolic and cardiovascular dysfunction are suggested by available data but require confirmation by large-scale studies. • Osteopenia, osteoporosis and fracture prevalence rates are greater in hypogonadal younger and older men. Bone density in hypogonadal men of all ages increases under testosterone replacement therapy. Fracture data are not yet available and thus the long-term benefit of testosterone replacement therapy requires further investigation. • Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone replacement therapy. In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short (i.e., three months) therapeutic trial may be justified. An absence of response calls for discontinuation of testosterone replacement therapy. There is evidence suggesting therapeutic synergism with combined use of testosterone replacement therapy and phosphodiesterase-5 inhibitors in hypogonadal or borderline eugonadal men; however, these observations require additional study. The combination treatment should be considered in hypogonadal patients with erectile dysfunction failing to respond to either treatment alone. It is unclear whether men with hypogonadism and erectile dysfunction should be treated initially with testosterone, phosphodiesterase-5 inhibitors, or the combination. • Currently available intramuscular (IM), subdermal, transdermal, oral and buccal preparations of testosterone are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation should be a joint decision of an informed patient and physician. • Short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with late-onset hypogonadism because of the possible development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. • Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety. For the present time, mid-to-lower young adult male serum testosterone levels seem appropriate as the therapeutic goal. Sustained supraphysiological levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels. • The 17-α-alkylated androgen preparations such as methyltestosterone are obsolete because of their potential liver toxicity and should no longer be prescribed. • Due to insufficient data regarding the therapeutic and adverse effects of human chorionic gonadotropin treatment in older men and its higher cost, the treatment cannot be recommended in late-onset hypogonadism except when fertility is an issue. Antiestrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels. Adequate evidence does not exist to recommend their use. • Testosterone replacement therapy is contraindicated in men with prostate or breast cancer. Testosterone replacement therapy is relatively contraindicated in

Clinical Guideline	Recommendation(s)
	men at high risk of developing prostate cancer. It is unclear whether localized low-grade prostate cancer represents a relative or absolute contraindication for treatment. • Men with significant erythrocytosis, untreated obstructive sleep apnea and untreated severe congestive heart failure should not be started on testosterone replacement therapy without prior resolution of the comorbid condition. • Age is not a contraindication to initiate testosterone replacement therapy. Individual assessment of comorbidities (as possible causes of symptoms) and potential risks vs benefits of testosterone replacement therapy is particularly important in elderly men.

The Endocrine Society: Clinical Practice Guidelines: **Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes (2010)**[23]	• Testosterone replacement therapy is recommended for symptomatic men with classical androgen deficiency syndromes to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength and bone mineral density.
	• Testosterone replacement therapy is not recommended for use in patients with breast or prostate cancer.
	• Testosterone replacement therapy is not recommended without further urological evaluation in patients with palpable prostate nodule or induration or a prostate specific antigen 4 or 3 ng/mL in men at high risk of prostate cancer (i.e., African Americans or men with first degree relatives with prostate cancer).
	• Testosterone replacement therapy is not recommended in patients with a hematocrit >50%, untreated severe sleep apnea, severe lower urinary tract symptoms, uncontrolled or poorly controlled heart failure or in those desiring fertility).
	• Initiating testosterone replacement therapy is recommended with any of the following regimens after evaluating patient preference, consideration of pharmacokinetics, treatment burden, cost:
	  o Testosterone enanthate or cypionate: 75 to 100 mg intramuscular weekly; or 150 to 200 mg intramuscular every two weeks.
	  o Testosterone patches: one or two 5-mg non-genital patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas.
	  o Testosterone 1% gel: 5 to 10 g applied daily over a covered area of non-genital skin (patients should wash hands after application).
	  o Testosterone buccal: apply one 30 mg tablet to buccal mucosa every 12 hours.
	  o Testosterone pellets implanted subcutaneously at intervals of three to six months; the dose and regimen vary with the formulation used.
	  o Oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch and testosterone pellets where available. (Note: testosterone undecanoate is not available in the United States.)
	  o Monitoring is advised three to six months after treatment initiation and then annually to assess symptom response, the presence of any adverse effects and to check compliance.
	  o Recommendations aim at achieving serum testosterone levels during treatment in the mid-normal range. In men receiving testosterone enanthate or cypionate, aiming for testosterone levels between 400 and 700 ng/dL one week after the injection is recommended.
	  o Hematocrit monitoring is advised at baseline, at three to six months, then annually; if exceeds 54% therapy should be discontinued until reduced to a safe level.
	  o Bone mineral density testing of the lumbar spine, femoral neck and hip after one to two years of testosterone therapy is advised in hypogonadal men with osteoporosis or low trauma fracture.
	  o Digital rectal exam is advised in men ≥40 years with a baseline prostate

Clinical Guideline	Recommendation(s)
	specific antigen >0.6 ng/mL, prior to initiating therapy, at three to six months, and then based upon evidence-based guideline recommendations. o Urological consultation is advised if there is an increase in serum or plasma prostate specific antigen >1.4 ng/mL within any 12-month period of testosterone treatment; a prostate specific antigen velocity of more than 0.4 ng/mL*yr using the prostate specific antigen level after six months of testosterone administration as the reference (prostate specific antigen velocity should be used only if there are longitudinal prostate specific antigen data for more than two years); detection of a prostatic abnormality on digital rectal examination; or a American Urological Association/International Prostate Symptom Score >19.0. o Testosterone replacement therapy should be offered to men with low testosterone levels and low libido to improve libido and to men with erectile dysfunction who have low testosterone levels after evaluation of underlying causes of erectile dysfunction and consideration of established therapies for erectile dysfunction. o Testosterone replacement therapy should not be offered to all older men with a low testosterone level. o Clinicians should consider offering testosterone replacement therapy on an individualized basis to older men with low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency. • Short-term testosterone replacement therapy may be considered as adjunctive therapy in human immunodeficiency virus-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in lean body mass and muscle strength. • Short-term testosterone replacement therapy may be offered to men receiving high dose glucocorticoids who have low testosterone levels to promote preservation of lean body mass and bone mineral density.
American Society for Reproductive Medicine: **Treatment of Pelvic Pain Associated with Endometriosis: A Committee Opinion (2014)**[25]	• Both medical and surgical treatments for endometriosis are effective. • Oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone agonists and anti-progestogens all have been employed for the treatment of endometriosis. • No clinical trials have compared directly medical vs surgical treatment of endometriosis; therefore, there is no substantial evidence to establish the superiority of one approach over the other. • Costs and side effects often dictate the choice of medical treatment. • In women with symptoms of pelvic pain, visible endometriosis observed during surgery should be treated. • Surgical treatment for endometriosis, followed by medical therapy, offers longer symptom relief compared to surgery alone. • Definitive treatment of endometriosis should be reserved for women with debilitating symptoms that can reasonably be attributed to the disease who have completed childbearing and have failed to respond to alternative treatments. • Further clinical trials designed to compare medical and surgical treatment are clearly warranted.
American Congress of Obstetricians and Gynecologists: **American Congress of Obstetricians and Gynecologists Practice Bulletin: Management of Endometriosis (2010)**[26]	• Transvaginal ultrasonography is the imaging modality of choice when assessing the presence of endometriosis. • Medical suppressive therapy improves pain symptoms; however, recurrence rates are high after the medication is discontinued. • After an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives (OCs)and non-steroidal anti-inflammatory drugs (NSAIDs), empiric therapy with a 3-month course of a gonadotropin-releasing hormone (GnRH) agonist is

Clinical Guideline	Recommendation(s)
Reaffirmed 2014	appropriate. • In patients with known endometriosis and dysmenorrhea, OCs and oral norethindrone or depot medroxyprogesterone acetate (DMPA) are effective compared with placebo and are equivalent to other more costly regimens. • GnRH agonists may have significant side effects, including hot flushes, vaginal dryness, and osteopenia. • Danazol has a side effect profile, which includes acne, hirsutism, and myalgias, that is more severe than other drugs available. • Long-term (at least 24 months) OC use is effective in reducing endometrioma recurrence as well as a reduction in the frequency and severity of dysmenorrhea. • Hormone therapy with estrogen is not contraindicated after hysterectomy and bilateral salpingo-oophorectomy for endometriosis. • There is significant short-term improvement in pain after conservative surgical treatment; however, as with medical management, there is also a significant rate of pain recurrence. • Medical suppressive therapies such as OCs or GnRH agonists for endometriosis-associated infertility are ineffective. • Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude of improvement is unclear. • When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH agonist-induced bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief.
Hereditary Angioedema International Working Group: **Evidence-Based Recommendations for the Therapeutic Management of Angioedema Owing to Hereditary C1 Inhibitor Deficiency (2012)**[27]	Treatment of acute attacks • All patients should have access to at least one of the specific medications, plasma-derived and recombinant C1 inhibitors, icatibant and ecallantide, even if still asymptomatic. • Whenever possible, patients should have the acute medication at home and be trained to self-administer these medications. • All attacks, regardless of location, should be treated as soon as they are recognized by the patients, ideally before the development of visible or disabling symptoms. • Report to the hospital immediately if laryngeal symptoms persist after an initial acute treatment. Prophylactic treatment • On-demand treatment for acute attacks should be the initial goal for all patients. Long-term prophylactic treatment is appropriate for patients in whom on-demand acute treatment was inadequate. • 17-α-alkylated androgens (e.g., danazol) can be considered in patients ≥16 years of age and women who are not pregnant or breastfeeding. Doses exceeding 200 mg/day are not recommended. • Plasma-derived C1inhibitors can be considered with individualized dosing to optimize clinical response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for androgens 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 Androgens[1-20]

Indication	Danazol	Fluoxy-mesterone	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Buccal, Intranasal, Transdermal Patch and Gel)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Delayed puberty (males)		✔	✔					✔	
Hypogonadotropic hypogonadism (congenital or acquired in males)		✔	✔			✔	✔	✔	✔
Metastatic mammary cancer (female)		✔	✔					✔	
Primary hypogonadism (congenital or acquired in males)		✔	✔			✔	✔	✔	✔
Treatment of endometriosis amenable to hormonal management (female)	✔								
Treatment of fibrocystic breast disease (female)	✔								
Prevention of attacks of angioedema of all types (males and females)	✔								
Adjunctive therapy to promote weight gain after weight loss following: extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight				✔					
To offset the protein catabolism associated with prolonged administration of corticosteroids				✔					
For the relief of the bone pain frequently accompanying osteoporosis				✔					
The treatment of anemias caused by deficient red cell production					✔				

IV. Pharmacokinetics

The pharmacokinetic parameters of the androgens are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Androgens[1]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Danazol	Well absorbed (% not reported)	Not reported	Liver	Renal (% not reported) and fecal (% not reported)	9 to 23.7 hours
Fluoxymesterone	Not reported	98	Liver	Renal (90), fecal (6)	9.2 hours
Methyltestosterone	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 minutes
Oxandrolone	High (% not reported)	94 to 97	Not reported	Renal (60), feces (3)	5 to 13 hours
Oxymetholone	Not reported	Not reported	Not reported	Not reported	Not reported
Testosterone	10 (gel)	98	Liver	Renal (90), fecal (6)	5.7 hours (buccal); 10 to 100 minutes (gel, patch); 70.8 days (implant)
Testosterone cypionate	Not reported	98	Liver	Renal (90), fecal (6)	8 days
Testosterone enanthate	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 minutes
Testosterone undecanoate	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 minutes

V. Drug Interactions

Significant drug interactions with the androgens are listed in Table 5.

Table 5. Significant Drug Interactions with the Androgens[20]

Generic Name(s)	Significance Level	Interaction	Mechanism
Danazol, fluoxymesterone, methyltestosterone, oxandrolone, oxymetholone	1	Warfarin	Androgens may decrease anticoagulant requirements. Monitor anticoagulant effects.
Danazol	1	Lovastatin, simvastatin	Severe myopathy or rhabdomyolysis may occur with coadministration of these drugs. When possible, consider avoiding this drug combination and administering alternative therapy.
Danazol	2	Carbamazepine	Danazol may increase serum carbamazepine levels. Monitor serum carbamazepine levels and modify therapy as needed.
Danazol, methyltestosterone	2	Cyclosporine	Increased cyclosporine blood concentrations with possible toxicity. Consider monitoring serum bilirubin, serum creatinine, and cyclosporine concentrations in patients receiving cyclosporine and an androgen concurrently. Adjust the dose of

Generic Name(s)	Significance Level	Interaction	Mechanism
			cyclosporine or androgen as needed.

Significance level 1=major severity, significance level 2=moderate severity.

VI. Adverse Drug Events

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

Table 6. Adverse Drug Events (%) Reported with the Androgens[1-20]

Adverse Event	Danazol	Fluoxy-mesterone	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Buccal)	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Central Nervous System											
Abnormal dreams	-	-	-	-	-	-	1.3 (gel)	-	-	-	-
Anxiety	-	✔	✔	✔	✔	-	✔ (solution)	✔ (implant)	✔	✔	-
Asthenia	-	-	-	-	-	-	0 to 3 (gel)	-	-	-	-
Depression	-	✔	✔	✔	✔	-	0 to 1 (gel); 3 (patch)	✔ (implant)	✔	✔	-
Dizziness	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Emotional lability	✔	-	-	-	-	-	0 to 3 (gel); ✔ (solution)	-	-	-	✔
Headache	-	✔	✔	-	-	3.1	0 to 4 (gel); 4 (patch); 5 to 6 (solution)	✔ (implant) ≥3 (nasal)	✔	✔	✔
Insomnia	-	-	-	✔	✔	-	-	-	-	-	✔
Libido, increased or decreased	-	✔	✔	✔	✔	-	0 to 3 (gel)	✔ (implant)	✔	✔	-
Migraine	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Nervousness	✔	-	-	-	-	-	0 to 3 (gel)	-	-	-	-
Paresthesia, generalized	-	✔	✔	-	-	-	-	✔ (implant)	✔	✔	-
Taste bitter	-	-	-	-	-	4.1	-	-	-	-	-
Taste perversion	-	-	-	-	-	2	-	-	-	-	-
Dermatologic											
Acne	✔	✔	✔	✔	✔	-	1 to 8 (gel); ✔ (solution)	✔ (implant)	✔	✔	5.2
Allergic contact dermatitis	-	-	-	-	-	-	✔ (gel); 4 (patch)	-	-	-	-
Alopecia	-	-	-	-	-	-	0 to 1 (gel)	-	-	-	-
Application site edema	-	-	-	-	-	-	✔ (solution)	-	-	-	-
Application site erythema	-	-	-	-	-	-	✔ (gel); 7 (patch); 5 to 7 (solution)	-	-	-	-
Application site irritation	-	-	-	-	-	-	✔ (gel); 7 to 8 (solution)	-	-	-	-
Application site reaction	-	-	-	-	-	-	2 to 6 (gel)	✔ (implant)	-	-	-

Adverse Event	Danazol	Fluoxy-mesterone	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Buccal)	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Application site warmth	-	-	-	-	-	-	✔ (solution)	-	-	-	-
Burning at application site	-	-	-	-	-	-	3 (patch)	-	-	-	-
Burn-like blister reaction under system	-	-	-	-	-	-	12 (patch)	-	-	-	-
Dry skin	-	-	-	-	-	-	2 (gel)	-	-	-	-
Folliculitis	-	-	-	-	-	-	✔ (solution)	-	-	-	-
Hair loss	✔	-	-	-	-	-	-	-	-	-	-
Hirsutism	✔	✔	✔	✔	✔	-	-	✔ (implant)	✔	✔	-
Hyperhidrosis	-	-	-	-	-	-	-	-	-	-	✔
Inflammation and pain at injection site	-	-	-	-	-	-	-	-	✔	✔	4.6
Induration at application site	-	-	-	-	-	-	3 (patch)	-	-	-	-
Male pattern baldness	-	✔	✔	✔	✔	-	-	-	✔	✔	-
Pruritus	-	-	-	-	-	-	2 (gel); 37 (patch)	-	-	-	-
Rash	-	-	-	-	-	-	2 (patch)	-	-	-	-
Seborrhea	✔	-	-	-	-	-	-	-	✔	-	-
Skin reactions	-	-	-	✔	✔	-	16 (gel)	-	-	-	-
Vesicles at application site	-	-	-	-	-	-	6 (patch)	-	-	-	-
Endocrine and Urogenital											
Amenorrhea	-	✔	✔	-	-	-	-	-	-	✔	-
Benign prostatic hyperplasia	-	-	-	-	-	-	0 to 1 (gel)	-	-	-	-
Breast pain	-	-	-	-	-	-	1 to 3 (gel) ✔ (solution)	-	-	-	-
Erectile dysfunction	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Estradiol increased	-	-	-	-	-	-	-	-	-	-	2.6
Flushing	✔	-	-	-	-	-	-	-	-	-	-
Gynecomastia	-	✔	✔	✔	✔	-	0 to 3 (gel)	✔ (implant)	✔	✔	-
Hot flushes	-	-	-	-	-	-	0 to 1 (gel)	-	-	-	-
Hypogonadism	-	-	-	-	-	-	-	-	-	-	2.6
Inhibition of gonadotropin secretion	-	✔	✔	✔	✔	-	-	-	-	✔	-
Menstrual disturbances	✔	✔	✔	✔	✔	-	-	-	-	✔	-
Oligospermia	-	✔	✔	✔	✔	-	-	-	✔	✔	-
Penile erections, excessive frequency and	-	✔	✔	✔	✔	-	✔ (gel)	✔ (implant)	✔	✔	-

Adverse Event	Danazol	Fluoxy-mesterone	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Buccal)	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
duration											
Prostate carcinoma	-	-	-	-	-	-	1 (gel)	-	-	-	✔
Prostate disorder	-	-	-	-	-	-	3 to 5 (gel); 5 (patch)	-	-	-	-
Prostate enlarged	-	-	-	-	-	-	12 (gel)	-	-	-	-
Prostate specific antigen increased	-	-	-	-	-	-	0 to 11 (gel); 1 to 4 (solution)	≥3 (nasal)	-	-	4.6
Semen and sperm abnormalities	✔	-	-	✔	✔	-	✔	-	-	-	-
Spontaneous penile erection	-	-	-	✔	✔	-	0 to 1 (gel)	-	-	-	-
Sweating	✔	-	-	-	-	-	-	-	-	-	-
Testis disorder	-	-	-	-	-	-	0 to 3 (gel)	-	-	-	-
Urinary symptoms	-	-	-	-	-	-	4 (gel)	-	-	-	-
Vaginal dryness	✔	-	-	-	-	-	-	-	-	-	-
Virilization	-	✔	✔	-	-	-	-	-	-	✔	-
Fluid and Electrolyte Disturbances											
Edema	✔	-	-	✔	✔	-	-	-	-	-	-
Retention of calcium, chloride, inorganic phosphates, potassium, sodium and water	-	✔	✔	✔	✔	-	-	-	✔	✔	-
Gastrointestinal											
Abdominal symptoms	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Alterations in liver function tests	-	✔	✔	✔	✔	-	-	✔ (implant)	✔	✔	-
Cholestatic jaundice	-	✔	✔	✔	✔	-	-	-	✔	✔	-
Diarrhea	-	-	-	-	-	-	3 to 4 (solution)	-	-	-	✔
Gastrointestinal bleeding	-	-	-	-	-	-	2 (patch)	-	-	-	-
Nausea	-	✔	✔	✔	✔	-	-	✔ (implant)	✔	✔	-
Vomiting	-	-	-	✔	✔	-	3 to 4 (solution)	-	-	-	-
Hematologic											
Anemia	-	-	-	-	-	-	3 (gel)	-	-	-	-
Hematocrit/ hemoglobin increased	-	-	-	✔	✔	-	0 to 3 (gel); 4 to 7 (solution)	-	-	-	✔
Suppression of clotting factors II, V, VII and X	-	✔	✔	-	-	-	-	✔ (implant)	✔	✔	-
Polycythemia	-	✔	✔	-	-	-	✔ (gel)	✔ (implant)	✔	✔	-
Metabolic											

Adverse Event	Danazol	Fluoxy-mesterone	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Buccal)	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Blood glucose increased	-	-	-	✔	✔	-	✔ (solution)	-	-	-	-
Cholesterol, increased	-	✔	✔	-	-	-	-	✔ (implant)	✔	✔	-
Weight gain	✔	-	-	-	-	-	-	-	-	-	✔
Other											
Blood pressure increased	-	-	-	-	-	-	✔ (solution)	✔ (nasal)	-	-	✔
Epistaxis	-	-	-	-	-	-	-	≥3 (nasal)	-	-	-
Fatigue	-	-	-	-	-	-	✔ (gel)	-	-	-	✔
Gum edema	-	-	-	-	-	2	-	-	-	-	-
Gum or mouth irritation	-	-	-	-	-	9.2	-	-	-	-	-
Gum pain	-	-	-	-	-	3.1	-	-	-	-	-
Gum tenderness	-	-	-	-	-	3.1	-	-	-	-	-
Hypersensitivity	-	✔	-	-	-	-	-	-	✔	-	-
Hypertension	-	-	-	-	-	-	0 to 3 (gel)	-	-	-	-
Influenza-like illness/malaise	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Laboratory test abnormality	-	-	-	-	-	-	3 to 9 (gel)	✔ (implant)	-	-	-
Lacrimation increased	-	-	-	-	-	-	✔ (solution)	-	-	-	-
Nasopharyngitis	-	-	-	-	-	-	✔ (solution)	≥3 (nasal)	-	-	✔
Pain in extremities	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Rhinorrhea	-	-	-	-	-	-	-	≥3 (nasal)	-	-	-
Vitreous detachment	-	-	-	-	-	-	✔ (gel)	-	-	-	-
Voice change	✔	-	-	✔	✔	-	-	-	-	-	-

✔ Incidence not specified.
-Event not reported or incidence <1%.

Table 7. Boxed Warning for Danazol[20]

WARNING
Use of danazol in pregnancy is contraindicated. A sensitive test (e.g., beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy. Additionally, a nonhormonal method of contraception should be used during therapy. If a patient becomes pregnant while taking danazol, discontinue administration of the drug and apprise the patient of the potential risk to the fetus. Thromboembolism, thrombotic and thrombophlebitic events, including sagittal sinus thrombosis and life-threatening or fatal strokes have been reported. Experience with long-term therapy with danazol is limited. Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intra-abdominal hemorrhage. Therefore, alert the physician to this possibility. Attempts should be made to determine the lowest dose that will provide adequate protection (see Warnings). Danazol has been associated with several cases of benign intracranial hypertension also known as pseudotumor cerebri. Early signs and symptoms of benign intracranial hypertension include papilledema, headache, nausea and vomiting, and visual disturbances. Screen patients with these symptoms for papilledema and, if present, advise the patients to discontinue danazol immediately and refer them to a neurologist for further diagnosis and care.

Table 8. Boxed Warning for Oxandralone[20]

WARNING
Peliosis hepatis: Peliosis hepatis, a condition in which liver and, sometimes, splenic tissue is replaced with blood-filled cysts, has occurred in patients receiving androgenic anabolic steroids. These cysts are sometimes present with minimal hepatic dysfunction and have been associated with liver failure. Often, they are not recognized until life-threatening liver failure or intra-abdominal hemorrhage develops. Withdrawal of drug usually results in complete disappearance of lesions. Liver cell tumors: Most often these tumors are benign and androgen-dependent, but fatal malignant tumors have occurred. Withdrawal of drug often results in regression or cessation of tumor progression. However, hepatic tumors associated with androgens or anabolic steroids are much more vascular than other hepatic tumors and may be silent until life-threatening, intra-abdominal hemorrhage develops. Blood lipid changes: Blood lipid changes associated with increased risk of atherosclerosis are seen in patients treated with androgens and anabolic steroids. These changes include decreased high-density lipoprotein (HDL) and, sometimes, increased low-density lipoprotein (LDL). The changes may be very marked and could have a serious impact on the risk of atherosclerosis and coronary artery disease.

Table 9. Boxed Warning for Oxymetholone[20]

WARNING
Peliosis hepatis: Peliosis hepatis, a condition in which liver and, sometimes, splenic tissue is replaced with blood-filled cysts, has occurred in patients receiving androgenic anabolic steroids. These cysts are sometimes present with minimal hepatic dysfunction and have been associated with liver failure. Often, they are not recognized until life-threatening liver failure or intra-abdominal hemorrhage develops. Withdrawal of drug usually results in complete disappearance of lesions. Liver cell tumors: Most often these tumors are benign and androgen-dependent, but fatal malignant tumors have occurred. Withdrawal of drug often results in regression or cessation of tumor progression. However, hepatic tumors associated with androgens or anabolic steroids are much more vascular than other hepatic tumors and may be silent until life-threatening, intra-abdominal hemorrhage develops. Blood lipid changes: Blood lipid changes associated with increased risk of atherosclerosis are seen in patients treated with androgens and anabolic steroids. These changes include decreased high-density lipoprotein (HDL) and, sometimes, increased low-density lipoprotein (LDL). The changes may be very marked and could have a serious impact on the risk of atherosclerosis and coronary artery disease.

Table 10. Boxed Warning for Transdermal Testosterone[20]

WARNING
Virilization has been reported in children who were secondarily exposed to transdermal testosterone. Ensure that children avoid contact with unwashed or unclothed application sites in men using transdermal testosterone. Advise patients to strictly adhere to recommended instructions for use.

Table 11. Boxed Warning for Testosterone Undecanoate[20]

WARNING
WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS • Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. • Following each injection of testosterone undecanoate, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis. • Because of the risks of serious POME reactions and anaphylaxis, testosterone undecanoate is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Aveed REMS Program.

VII. Dosing and Administration

The usual dosing regimens for the androgens are listed in Table 12.

Table 12. Usual Dosing Regimens for the Androgens[1-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Danazol	Treatment of endometriosis amenable to hormonal management (female): Capsule: initial, 200 to 800 mg in two divided doses; continue therapy uninterrupted for three to six months (up to nine months) Treatment of fibrocystic breast disease (females): Capsule: initial, 100 to 400 mg in two divided doses Prevention of attacks of angioedema of all types (males and females): Capsule: initial, 200 mg given two to three times a day; after a favorable response, decrease dose by 50% or less at intervals of one to three months or longer depending on the frequency of attacks; if an attack occurs, increase dose by up to 200 mg/day	Safety and effectiveness in pediatric patients have not been established.	Capsule: 50 mg 100 mg 200 mg
Fluoxymesterone	Hypogonadotropic hypogonadism	Delayed puberty (males):	Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
(CIII)	(congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Tablet: 5 to 20 mg/day Metastatic mammary cancer (females): Tablet: 10 to 40 mg/day in divided doses for three months or more	Tablet: 2.5 to 20 mg/day for a limited duration (e.g., four to six months) Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation.	10 mg
Methyltestosterone (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Capsule, tablet: 10 to 50 mg/day Metastatic mammary cancer (females): Capsule, tablet: 50 to 200 mg/day	Delayed puberty (males): Capsule, tablet: 10 to 50 mg/day for a limited duration (e.g., four to six months) Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation.	Capsule (Android®, Testred®): 10 mg Tablet: 10 mg
Oxandrolone (CIII)	Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis: Tablet: 2.5 to 20 mg given in two to four divided doses for two to four weeks; this may be repeated intermittently as indicated	Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis: Tablet: ≤0.1 mg/kg body weight or ≤0.045 mg/lb of body weight; repeated intermittently as indicated	Tablet: 2.5 mg 10 mg
Oxymetholone (CIII)	The treatment of anemias caused by deficient red cell production: Tablet: 1 to 5 mg/kg body weight per day; usual effective dose is 1 to 2 mg/kg/day but higher doses may be required, and the dose should be individualized; response is not often immediate, and a minimum trial of three to six months should be given; following remission, some patients may be maintained without the drug; others may be	The treatment of anemias caused by deficient red cell production: Tablet: 1 to 5 mg/kg body weight per day; usual effective dose is 1 to 2 mg/kg/day but higher doses may be required, and the dose should be individualized; response is not often immediate, and a minimum trial of three to six months should be given;	Tablet: 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintained on an established lower daily dosage; continued maintenance dose is usually necessary in patients with congenital aplastic anemia	following remission, some patients may be maintained without the drug; others may be maintained on an established lower daily dosage; continued maintenance dose is usually necessary in patients with congenital aplastic anemia	
Testosterone (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Buccal system: 30 mg applied twice daily Testopel®: Pellets: 150 to 450 mg subcutaneous implantation every 3 to 6 months Natesto®: Nasal gel: 11 mg of testosterone (2 pump actuations; 1 actuation per nostril) administered intranasally three times daily for a total daily dose of 33 mg Testim® 1% and AndroGel® 1%: Topical gel: initial, 5 g applied once daily (preferably in the morning); maintenance, 5 to 10 g/day; maximum, 10 g/day AndroGel® 1.62%: Topical gel: initial, 40.5 mg applied once daily (preferably in the morning); maintenance, 20.25 to 81 mg/day; maximum, 10 g/day Fortesta®: Topical gel: initial, 40 mg applied once daily (preferably in the morning); maintenance, 10 to 70 mg/day; maximum, 70 mg/day Topical solution: initial, 60 mg applied once daily in the morning; maintenance, 30 to 120 mg once daily; maximum, 120 mg daily Transdermal system: initial, 4 mg/day patch applied once nightly; maintenance, 2 to 6 mg/day applied at night	Safety and effectiveness in pediatric male patients below the age of 18 have not yet been established.	Buccal system (Striant®): 30 mg Implant (Testopel® pellets) 75 mg Nasal gel (Natesto®): 5.5 mg/actuation Topical gel: AndroGel® 1%: Metered-dose pumps: 1.25 g per pump (12.5 mg of testosterone) Unit-dose packets: 1.25 g (20.25 mg of testosterone) 2.5 g (25 mg of testosterone) 2.5 g (40.5 mg of testosterone) 5 g (50 mg of testosterone) AndroGel® 1.62%: Metered-dose pumps: 1.25 g per pump (20.25 mg of testosterone) Fortesta®: Metered-dose pumps: 0.5 g per pump (10 mg of testosterone) Testim® 1%: Unit-dose tubes: 5 g per tube (50 mg of testosterone) Topical solution

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			(metered-dose pumps (Axiron®): 90 mL per pump (30 mg of testosterone) Transdermal system (Androderm®): 2 mg/day 4 mg/day
Testosterone cypionate (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Injection: 50 to 400 mg intramuscularly every two to four weeks	Safety and effectiveness in pediatric patients below the age of 12 years have not been established.	Injectable solution: 100 mg/mL 200 mg/mL
Testosterone enanthate (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Injection: 50 to 400 mg intramuscularly every two to four weeks Metastatic mammary cancer (females): Injection: 200 to 400 mg intramuscularly every two to four weeks	Delayed puberty: Injection: 50 to 200 mg intramuscularly every two to four weeks for a limited duration (e.g., four to six months) Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation.	Injectable solution: 200 mg/mL
Testosterone undecanoate (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Injection: 750 mg intramuscularly at initiation, at four weeks, and every 10 weeks thereafter	Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	Injectable oil: 750 mg/ 3 mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the androgens are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Androgens

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Male Hypogonadism				
Morales et al.[28] (1994) Methyltestosterone (dose not reported)	OL Hypogonadal men with impotence associated with low total serum androgen levels (age not reported)	N=22 1 month	Primary: Recovery of sexual function; changes in levels of energy, mood or feeling of well being Secondary: Not reported	Primary: Only 9% of the patients reported a complete recovery of sexual function. The positive responses were recorded in men with the most profound testosterone deficiency. Visual analogue scales did not reveal noticeable changes for any individual in the levels of energy, mood or feeling of wellbeing between pretreatment and post-treatment assessments. The authors concluded that exogenous administration of androgens to impotent men should be limited to those with profound hypogonadism as documented by at least two abnormal serum free testosterone determinations. Secondary: Not reported
Kaufman et al.[29] (2011) Testosterone 1.62% (AndroGel) 2.5 g once daily vs placebo Doses were titrated up or down in 1.25 g increments to between 1.25 g	DB, MC, PC, RCT Hypogonadal men 18 to 80 years of age who were otherwise healthy, naïve to androgen replacement therapy or undergone appropriate washout period, had a serum testosterone <300, and BMI ≥18	N=274 182 days	Primary: Percentage of patients achieving serum total testosterone average concentrations within normal range of 300 to 1,000 ng/dL Secondary: Percentage of patients with maximum testosterone serum	Primary: The testosterone treatment group met the success criterion of ≥75% of patients achieving testosterone levels within the normal range on all time points with the exception of day 14. There were significantly more patients in the testosterone group compared to placebo achieving total testosterone average concentrations within normal range at 14, 56, 112, and 182 days (P<0.0001 for all comparisons). Secondary: For patients in the testosterone group, 88.8 to 97.3% had maximum testosterone concentrations ≤1,500 ng/dL, 0.5 to 4.5% between 1,800 and 2,500 ng/dL and 0.5 to 5.6% >2,500 dL compared to ≥96% had maximum testosterone concentrations ≤1,500 ng/dL. Estradiol concentrations were within the normal range of 10 to 40 ng/mL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily and 5.0 g daily until day 42 at which time the doses were not changed.	kg/m^2 to ≤40 kg/m^2		concentrations in the ranges ≤1,500 ng/dL, between 1,800 and 2,500 ng/dL and >2,500 dL; and measurements of SHBG, LH, FSH, serum inflammatory and cardiovascular risk factors, waist-to-hip ratio, and serum markers of bone metabolism	for the testosterone-treated patients, except for day 56 with patients treated with 1.25 g which was above the upper limit of normal. At day 84, there was a significant decrease in sex hormone binding globulin from baseline (P=0.0012), but was not significant on day 182. When compared to placebo, this difference was statistically significant on day 84 (P=0.0193). There were significant decreases in LH and FSH on days 84 and 182 (P<0.0001) in the testosterone group; however, there was no significant difference in the placebo group. There were significant decreases of IL-10 on days 84 (P<0.0001) and 182 (P=0.0132) in the testosterone groups. When compared to the placebo group, the difference was statistically significant (P=0.0254) on day 84. There were no significant changes in other inflammatory cytokines. There was a significant increase in serum marker of bone formation (serum bone-specific alkaline phosphatase) at day 182 (P<0.0001); however this was not significantly different from placebo. There was a significant decrease in serum marker of bone resorption (serum type-I cross-linked C telopeptide) at days 84 and 182 (P<0.001); however, only day 84 was significantly different from placebo (P<0.05). Serious treatment-emergent adverse effects were 2.1% in testosterone treated patients and 2.5% in placebo. In the testosterone groups, 55.6% of patients experienced at least on treatment-emergent adverse effect compared to 37.5% in the placebo group.
Kaufman et al.[30] (2012) Testosterone 1.62% (AndroGel) 1.25 to 5.00 g once daily Doses were titrated up or down in 1.25	OL, ES (Kaufman [2011]) Hypogonadal men 18 to 80 years of age who were otherwise healthy, naïve to androgen replacement	N=191 1 year	Primary: Percentage of patients achieving serum total testosterone average concentrations within normal range of 300 to 1,000 ng/dL	Primary: On day 364, 77.9% (95% CI, 70.0% to 84.6%) of patients continuing on testosterone treatment achieved testosterone levels within the normal range which met the success criterion of ≥75% of patients achieving testosterone levels within the normal range. The patient continuing on testosterone also achieved the success criterion on day 266; however, the group previously treated with placebo only reached the criterion on day 264.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
g increments on days 182, 96, 210 and 266 to between 1.25 g daily and 5.0 g.	therapy or undergone appropriate washout period, had a serum testosterone <300, and BMI ≥18 kg/m2 to ≤40 kg/m2		Secondary: Percentage of patients with maximum testosterone serum concentrations in the ranges ≤1,500 ng/dL, between 1,800 and 2,500 ng/dL and >2,500 dL; and measurements of SHBG, LH, FSH, serum inflammatory and cardiovascular risk factors, waist-to-hip ratio, and serum markers of bone metabolism	Secondary: For all patients, 93.5% had maximum testosterone serum concentrations ≤1,500 ng/dL, 3.4% were between 1,800 and 2,500 ng/dL and no patients were >2,500 dL. Mean dihydrotestosterone levels were in the eugonadal reference range (11.2 to 95.5 ng/dL) except for the formerly placebo treated 3.75g treated patients. Mean estradiol levels were in the normal range (10 to 40 pg/dL). There was a significant increase in SHBG from baseline on days 266 (P<0.0001) and 364 (P<0.0166) in the continuing treatment group. There were significant decreases in luteinizing hormone from baseline on days 266 and 364 for the continuing active treatment group (P<0.0001 for both days) and the formerly placebo treated group (P<0.0054 and P=0.0309, respectively). There were significant decreases in FSH from baseline on days 266 and 364 for the continuing active treatment group (P<0.0001 for both days) and the formerly placebo treated group (P<0.0001 and P<0.0087, respectively). There were significant decreases of interleukin-10 on day 364 in the continuing active treatment group (P<0.001) and day 266 in the formerly placebo treated group (P<0.0089). The matrix metalloprotease-9 levels decreases significantly from baseline on days 266 (P<0.0080) and 364 (P<0.0055) in the continuing active treatment group, but not he formerly placebo group. There was a significant increase in serum bone-specific alkaline phosphatase on day 264 (P<0.0001), but on day 364. There was a significant decrease in serum type-I cross-linked C telopeptide on days 266 and 364 (P<0.001) for the continuing active treatment group, but not the formerly placebo group. The most common treatment-emergent adverse effect leading to discontinuation was an increase in prostate specific antigen levels (5.2%). There were 79 (41.4%) patients that experienced at least one treatment-emergent adverse effect. The most common treatment-emergent adverse effects were increased prostate specific antigen, upper respiratory tract infection, nasopharyngitis, hypertension, influenza, sinusitis and acne.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pexman-Fieth et al.[31] (2014) ESPRIT Testosterone 1% (AndroGel) 50 to 100 mg once daily	OL, OS Hypogonadal men ≥ 18 years of age who were otherwise healthy, naïve to testosterone therapy	N=712 6 months	Primary: Effect of treatment on hypogonadal symptoms and quality of life as assessed by Aging Males' Symptoms (AMS) scale Secondary: Erectile dysfunction (International Index of Erectile Function [IIEF]), fatigue (Multidimensional Fatigue Inventory [MFI]), and surrogates for body composition (waist circumference, body mass index [BMI])	Primary: In both the responder (patients with one or more documented total testosterone level within the normal range while receiving treatment) and nonresponder (patients with no documented total testosterone level within the normal range while receiving treatment) groups, the AMS score decreased significantly. Secondary: In both responders and nonresponders, mean total IIEF scores increased significantly (P<0.0001 in both) over six months. The mean MFI total score decreased significantly in both responders and nonresponders (P<0.0001 for both). Mean BMI decreased significantly (P<0.0001) in responders but remained stable in nonresponders. In both responders and nonresponders, the mean waist circumference decreased significantly from baseline and the decrease became significant at three months (P<0.0001).
Dobs et al.[32] (2004) Testosterone buccal (Striant®) 30 mg two times a day vs testosterone 1% gel (AndroGel®) 50 mg daily	OL, PG, RCT Men 18 to 80 years of age with testosterone deficiency with serum testosterone <8.7 mmol/L (2.5 ng/mL) and BMI <35 kg/m^2	N=25 14 days	Primary: Percentage of patients who achieved average serum testosterone within normal range 3.0 to 10.5 ng/mL Secondary: Average, maximum and minimum serum testosterone, time to maximum and minimum serum testosterone and percentage of time	Primary: Twelve of 13 (92.3%) patients using testosterone buccal and 10 of 12 (83.3%) patients using testosterone gel achieved average 24-hour serum testosterone within normal range (P value not reported). Secondary: All pharmacokinetic parameters were similar between the two groups. In the testosterone buccal and testosterone gel groups, the average serum testosterone was 4.8±1.4 and 4.4±1.4 ng/mL, maximum concentration was 8.5±3.3 and 7.5±3.5 ng/mL, minimum concentration was 2.5±0.8 and 2.5±0.9 ng/mL, time to maximum concentration was 13.4±9.9 and 13.6±7.9 ng/mL and time to minimum concentration was 7.9±7.4 and 9.3±6.6 ng/mL, respectively (P>0.05 for all). During a 24-hour period, 83.4 and 75.3% of patients in the buccal and gel groups, respectively, had a serum testosterone within the normal range

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			that serum testosterone was within the normal range	(P>0.05).
Korbonits et al.[33] (2004) Testosterone buccal (Striant®) 30 mg two times a day vs testosterone patch (Andropatch®‡ or Androderm® TD) 5 mg once daily	MC, RCT Men with testosterone deficiency with a morning serum testosterone <6.94 nmol/L, normal age-related PSA levels and Hct <50	N=66 7 days	Primary: Non-inferiority analysis (endpoints not defined) Secondary: Efficacy analysis of superiority (endpoints not defined)	Primary: Investigators concluded that non-inferiority was established (results not reported). Secondary: In the buccal testosterone group, the mean testosterone concentrations at all measured time points (days three, four, six, seven and eight) were within the physiological range; whereas mean concentrations at five time points were outside of the physiological range among patients in the testosterone patch group. For both mean (0 to24 hour) and minimum testosterone levels, the proportion of patients with levels outside the physiological range was lower in the buccal group than in the patch group (the differences; P<0.001 for each). The serum testosterone concentrations over the 24-hour period were higher for patients receiving buccal testosterone compared to those receiving the patch (mean AUC±SD; 451.31±140.71 h*nmol/L vs 304.63±134.46 h*nmol/L; 95% CI, 1.25 to 1.91; P<0.00001). The mean maximum and mean minimum 24-hour testosterone levels were within the physiological range for the testosterone buccal group. Comparatively, the mean maximum 24-hour testosterone level was within the physiological range for the testosterone patch group; however, the mean minimum 24-hour testosterone level was below the physiological range. A total of 84.8% of patients in the buccal group were within the physiological range over 24 hours compared to 55.1% of patients in the patch group. Testosterone concentrations were within the physiological range in the buccal group for a significantly greater portion of the 24-hour treatment period compared to the patch group (84.9 vs 54.9%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean DHT levels were within the normal range (1.03 to 2.92 nmol/L) for both the buccal group (2.36±0.99 nmol/L) and the patch group (1.2±0.57 nmol/L). The median E2 concentrations increased from baseline to day seven, but returned to baseline levels at the follow-up visit. The median increase from baseline to day seven was greater in the buccal group (55.07 pmol/liter) compared to the patch group (34.87 pmol/L; P<0.001). A total of 51.5% of patients in the buccal group reported an adverse event compared to 47.1% in the patch group. The most commonly reported adverse events among both groups were application site disorders.
Swerdloff et al.[34] (2000) Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs testosterone patch (Androderm®) 2.5 mg 2 patches daily At 60 days, men with serum testosterone levels <10.4 nmol/L who were applying	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years of age, morning serum testosterone level ≤10.4 nmol/L at screening	N=227 180 days	Primary: Serum testosterone and free testosterone levels at 0, one, 30, 90 and 180 days; safety; serum DHT, E_2, FSH, LH, SHBG levels on 0, 30, 60, 90, 120, 150 and 180 days Secondary: Not reported	Primary: At 30 and 90 days, testosterone gel 100 mg produced significantly higher average concentration testosterone levels over testosterone 50 mg and testosterone patch (27.46±1.12 vs 19.17±1.06 and 14.46±0.68 nmol/L, respectively; P=0.0001). At 180 days, serum testosterone levels and pharmacokinetics parameters were similar to those on days 30 and 90 in those patients who continued their initial randomized treatment. Patients switched to testosterone gel 75 mg had an average concentration testosterone level of 20.84±1.76 nmol/L at 180 days. This value was between the 180 day average concentration testosterone levels achieved with testosterone gel 50 mg (19.24±1.18) and testosterone gel 100 mg (24.72±1.05). Pharmacokinetics parameters of serum free testosterone levels on days one, 30, 90 and 180 mirrored those of serum testosterone levels. The free testosterone levels in the testosterone gel 100 mg group was 1.4- and 1.7-fold higher than the testosterone gel 50 mg and testosterone patch groups (P=0.001). The discontinuation rate at 90 days for the testosterone patch (27.6%) was significantly higher than testosterone gel 50 and 100 mg (8.2 and 6.4%, respectively; P=0.0002). Most patients discontinued treatment due to adverse skin reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AndroGel® 50 mg and men with serum testosterone levels >34.7 nmol/L who were applying AndroGel® 100 mg were instructed to apply AndroGel® 75 mg once daily for days 91 through 180.				Throughout the 180 days, increases in serum DHT levels were significant with testosterone gel 50 and 100 mg over the testosterone patch (P=0.0001). Mean serum increases to stable levels of E_2 occurred in 9.2, 30.9 and 45.5% of patients in the testosterone patch, testosterone gel 50 and testosterone gel 100 mg groups, respectively (P=0.001). All three treatment groups showed a small decrease in serum SHBG levels (P=0.0046). The mean percent suppression of serum LH levels was the smallest with testosterone patch (30 to 40%), intermediate with testosterone gel 50 mg (55 to 60%) and greatest with testosterone gel 100 mg (80 to 85%; P<0.01). The suppression of serum FSH paralleled that of serum LH levels. Secondary: Not reported
Wang et al.[35] (2000) Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs testosterone patch (Androderm®) 2.5 mg two patches daily	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years of age, morning serum testosterone level ≤10.4 nmol/L at screening	N=227 180 days	Primary: Mean change from baseline in serum testosterone concentrations, body composition and muscle strength at 90 and 180 days; mean change from baseline in sexual function and mood at 30, 60, 90, 120, 150 and 180 days; degree of skin irritation; mean change from baseline in serum PSA levels at 30 and 90 days; mean change from	Primary: On day 90 the average serum testosterone concentration with testosterone gel 100 mg (27.46±1.12 nmol/L) was 1.4-fold higher than testosterone gel 50 mg (19.17±1.06 nmol/L) and 1.9-fold higher than the testosterone patch (14.46±0.68 nmol/L; P value not reported). On day 180 average serum testosterone concentrations for the treatment groups were 24.72±1.05, 19.24±1.18 and 14.14±0.88 nmol/L, respectively. The percent body fat and fat mass decreased in all treatment groups but was only significant with testosterone gel. At 90 days the total fat mass was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (P=0.0065 and P=0.0001, respectively). At 180 days the total fat mass decreased further with testosterone gel 100 mg (P=0.008). At 90 days, the percent body fat was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (P=0.0018 and P=0.001) and remained significant at 180 days. Significant increases in arm and leg muscle strength were seen in all three treatment groups without intergroup differences on days 90 and 180 (P values compared to baseline ranged between 0.0001 and 0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
At 90 days, dose adjustments were made in the AndroGel® groups based on the pre-application serum testosterone levels on day 60. Twenty subjects in the AndroGel® 50 mg group had their dose increased to 75 mg and 20 subjects in the AndroGel® 100 mg group had their dose reduced to 75 mg.			baseline in Hgb, Hct, lipid profiles and blood chemistries Secondary: Not reported	All subjects, regardless of treatment group, showed significant improvement in sexual motivation (P=0.0001), sexual desire (P=0.0001), sexual performance (P=0.0001), self-assessment of satisfaction of erection (P=0.0001) and percentage of full erection (P=0.0001). All three treatment groups showed significant improvement in positive mood scores (P=0.0001) and a decrease in negative mood scores (P=0.0001) without significant between-group differences. Minimal skin irritation at the application site was seen in 5.7 and 5.3% of patients in the testosterone gel 50 and 100 mg group. Minimal to severe skin irritation occurred in 65.8% of patients in the testosterone patch group. Mean serum PSA levels significantly increased with testosterone gel 100 mg (P=0.008) and testosterone gel 50 mg (P=0.05) with no significant increase with testosterone patch. As a group, both Hgb and Hct increased (P=0.0001) with statistical significance across treatment groups (P=0.0001). There were no overall treatment effects or intergroup differences in serum concentrations of TC, HDL-C, LDL-C or TG (data not provided). Secondary: Not reported
Wang et al.[36] (2004) Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 75 mg daily	ES, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years of age, single morning serum testosterone level at screening ≤10.4 nmol/L	N=163 36 months	Primary: Mean changes from baseline in serum testosterone, free testosterone, DHT, E2, SHBG, LH and FSH; mean changes from baseline in sexual function and mood, body composition, bone turnover markers,	Primary: Mean serum testosterone levels were significantly different (P=0.012) between dosing groups at baseline (six months of testosterone replacement therapy). At 12 months, differences among the dosing groups became smaller but remained significant (P=0.042). Serum free testosterone levels followed the same pattern as testosterone. Mean serum DHT levels were different in the three dosing groups at 12 (P=0.0031) and 24 (P=0.018) months with the highest levels seen with testosterone gel 100 mg. Mean serum E_2 levels progressively increased from six to 24 months (P=0.0001) with significant differences between groups. The highest levels of serum E_2 were seen with testosterone gel

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs testosterone gel (AndroGel®) 100 mg daily			muscle strength and BMD; mean changes from baseline in Hgb, Hct, lipid profiles and blood chemistries; mean changes from baseline in serum PSA and prostate disease; safety Secondary: Not reported	100 mg. No significant change in SHBG was seen. Suppression of LH and FSH was maintained throughout with no significant changes after six months. The suppression was more pronounced with testosterone gel 100 mg. Significant improvements in sexual desire, enjoyment with or without a partner, percent full erection and self-assessment of satisfaction with erections were maintained as a group throughout the study period. Positive mood scores were improved with treatment and were sustained (P=0.0022). Negative mood parameters were decreased and remained significantly lower (P=0.0013) than baseline without further changes after six months. Average total body mass increased by 1.2+0.3 kg at six months (P=0.0157) and did not significantly change with continued therapy. LBM increased significantly (P=0.0001) from baseline and remained increased throughout the study. A significant decrease in fat mass was seen at 30 months (P=0.088) without significant differences between doses. Serum PTH levels significantly increased from baseline (P=0.0001) and continued to increase from six (P=0.0002) until 12 months when it remained stable throughout the rest of the treatment period. Serum SALP levels followed the same pattern (P=0.001). At 12 months serum osteocalcin was significantly elevated and remained elevated throughout treatment (P=0.0001). Serum procollagen levels transiently increased then steadily increased from six months to reach significant levels by 36 months (P=0.0001). Muscle strength increased but did not reach significance over time due to the large variation in patients. BMD of the hip (P=0.0004) and spine (P=0.0001) showed a gradual and progressive increase with treatment. No significant differences among treatment doses or older and younger patients were observed. Serum Hgb and Hct concentrations increased, compared to month zero

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.0001) and month six (P=0.001) and plateaued at 12 months. Small statistically significant increases in serum HDL-C levels (P<0.001), creatinine (P<0.001) and total bilirubin (P=0.001) were seen but were not clinically significant. No significant changes in TC, LDL-C, serum liver enzymes, or other clinical chemistry parameters were observed. The mean serum PSA was 1.11+0.08 at six months and showed no further significant increases with continued treatment. Application-site reactions occurred in 12 of the 163 (7.4%) patients. Acne occurred in 12 (7.4%) of patients and gynecomastia was observed in eight more patients. Secondary: Not reported
Grober et al.[37] (2008) Testosterone gel (AndroGel®) 5 to 10 g vs testosterone gel (Testim®) 5 to 10 g	OL Hypogonadal men on testosterone gel who underwent a brand substitution due to initial suboptimal biochemical or symptomatic response, mean age of men switched to Testim® was 60, mean age of men switched to AndroGel® was 52	N=370 Treatment duration after switch, 4 weeks	Primary: Reasons for brand substitution, total and free testosterone, presence of hypo-gonadal symptoms Secondary: Not reported	Primary: Of the 370 hypogonadal men using testosterone gel, 20% underwent a brand substitution. The reasons for switching from AndroGel® to Testim® (N=62) were poor efficacy (92%), hypertension (2%), skin reaction (2%), worsening symptoms (2%) and insurance coverage (2%). The reasons for switching from Testim® to AndroGel® (N=13) were scent (46%), poor efficacy (30%), fear of transfer to partner (8%), flushing (8%) and skin reaction (8%). Prior to substitution, patients initially treated with AndroGel®, had mean total and free testosterone levels of 311.0 ng/dL and 10.4 pg/mL, respectively. Total testosterone levels were <300 ng/dL in 58% of these patients. Following a change to Testim®, mean total and free testosterone levels increased to 484.0 ng/dL (P<0.001) and 14.6 pg/mL (P=0.01), respectively. Total testosterone levels remained <300 ng/dL in 17% of these patients. Among patients initially treated with Testim®, the mean total and free testosterone levels were 544.0 ng/dL and 18.0 pg/dL, respectively. Total testosterone levels were <300 ng/dL in 15% of men. Following a change to AndroGel®, mean total and free testosterone levels were 522.0 ng/dL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.7) and 16.1 pg/mL (P=0.6), respectively. Total testosterone levels remained <300 ng/dL in 27% of these patients. Secondary: Not reported
Dobs et al.[38] (2012) Testosterone gel (Fortesta®) 40 mg applied to the thighs once daily Dose adjustments allowed for a downward titration to a minimum of 10 mg daily and an upward titration to 70 mg daily.	MC, OL Men 18 to 75 years of age, with primary or secondary hypo-gonadism (defined as a single serum testosterone concentration <250 ng/dL or two consecutive serum testosterone levels <300 ng/dL at least one week apart) and a BMI ≥22 and <35 kg/m^2	N=149 90 days	Primary: The average serum total testosterone concentration over 24 hours (average concentration 0 to 24 hours) on day 90 Secondary: The maximum serum testosterone concentration (C_{max}) on day 90	Primary: Of the 129 patients with available data for analysis, the mean average concentration over 24 hours was 438.56±162.51 ng/dL with 77.5% of patients achieving a mean serum testosterone level within the pre-defined normal physiological range (≥300 and ≤1,140 ng/dL) (95% CI, 70.3 to 84.7). By day 35, 76.2% (95% CI, 68.8 to 83.6) of patients had reached the primary endpoint. On day 90, 22.5% of patients had a total testosterone level <300 ng/dL. Secondary: The maximum concentration±SD was 827.6±356.5 ng/dL on day 90. At endpoint, a total of 94.6% of patients achieved a maximum concentration ≤1,500 ng/dL, 1.6% of patients had levels between 1,880 and 2,500 ng/dL, and no patients had levels >2,500 ng/dL. This maximum concentration was evident by treatment day 35. Adverse events were reported in 46.3% of patients; however on 22.8% were considered related to the study medication. The most commonly reported adverse events were skin reactions, upper respiratory infections and sinusitis. Skin reactions were considered 'possibly' or 'probably' related to study medication in 16.1% of patients, of which 79.2% were mild in severity.
McNicholas et al.[39] (2003) Testosterone gel (Testim®) 50 mg daily in the morning vs testosterone gel	AC, DB, MC, OL, RCT Hypogonadal men, 31 to 80 years of age, morning serum testosterone level ≤10.4 nmol/L at screening with one or more	N=208 90 days	Primary: 24-hour pharma-cokinetics profiles at 30, 60 and 90 days; treatment effectiveness as measured by body composition, mood and sexual function data at 30, 60 and	Primary: At 90 days, mean increases in serum testosterone levels were significant for testosterone gel 100 mg (12.41 nmol/L) over testosterone gel 50 mg (6.54 nmol/L; P<0.05) and testosterone patch (3.82 nmol/L; P<0.001). Results at 30 and 60 days were consistent with those at 90 days. The same results were also seen with the mean increase from baseline in free testosterone levels. At 90 days, the mean change in DHT levels with testosterone gel 100 mg were significant over testosterone gel 50 mg (P<0.05) and testosterone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Testim®) 100 mg daily in the morning vs testosterone patch (Andropatch®‡) 2.5 mg two patches daily in the morning	symptoms of low testosterone		90 days; safety Secondary: Not reported	patch (P<0.001). In addition, the mean change in DHT levels with testosterone gel 50 mg was also significant over testosterone patch at 90 days (P<0.001). Results at 30 and 60 days were consistent with those at 90 days. Significant within-treatment group changes in LBM were seen for all three treatment groups; 0.9 (P<0.05), 1.5 kg (P<0.001) and 1.0 kg (P<0.05) for testosterone gel 50 mg, testosterone gel 100 mg and testosterone patch, respectively. Significant within-treatment group mean changes in percentage fat were only seen with testosterone gel 100 mg (–0.7; P<0.05). There were no statistically significant changes in BMD within any of the three treatment groups. No significant differences in improvement in positive mood were seen among the three treatment groups. There were significant differences between treatment groups at 90 days in the alleviation of negative mood favoring testosterone gel over the testosterone patch (P<0.05). At 90 days there were significant within-treatment group improvements from baseline in all three groups in sexual motivation, sexual desire and sexual performance (P<0.05). Both testosterone gel groups had a statistically significant within-treatment improvement in spontaneous erections at all times from baseline (P<0.05). Testosterone patch produced no significant improvement in spontaneous erections at any time. The incidence of treatment-emergent adverse events was 35% for testosterone gel 50 mg, 29% for testosterone gel 100 mg and 63% for testosterone patch groups. The most commonly reported adverse events were erythema, irritation and reactions at the application site. Secondary: Not reported
Steidle et al.[40] (2003) Testosterone gel (Testim®) 50 mg	AC, DB, MC, OL, PC, RCT Hypogonadal men, 20 to 80 years of	N=406 90 days	Primary: Periodic 24-hour pharmacokinetics profiles; effect of normalizing serum	Primary: At 30 days, all treatment groups had increased mean serum testosterone and DHT concentrations. Testosterone gel 100 mg had a significant increase in mean changes in testosterone concentrations over the testosterone patch (P<0.001). Testosterone gel 50 and 100 mg resulted in

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daily in the morning vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Androderm®) 2.5 mg 2 patches daily in the morning vs placebo	age, morning serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone		testosterone on body composition, sexual function, mood and BMD; safety Secondary: Not reported	significant increases in mean changes in DHT concentrations compared to the testosterone patch (P<0.001 for each comparison). By 90 days, similar results were seen across treatment groups. At 90 days, mean change in LBM was 1.5±4.5, 1.7±2.6, 0.9±1.8 and 0.6±1.8 kg for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch and placebo, respectively. Increases in LBM were significantly higher for testosterone gel 100 mg than the testosterone patch and placebo (P<0.05 for each comparison). With the exception of placebo treatment, all treatments resulted in a significant decrease in fat mass compared to placebo (P<0.01). At 90 days, when compared to placebo, testosterone gel 100 mg had significant improvements in spontaneous erections (P<0.001), sexual motivation (P<0.05), sexual desire (P<0.01) and sexual performance (P<0.05). No other treatment groups had significant improvements compared to the placebo group. All treatments resulted in mean improvements from baseline in both positive and negative mood scores with no significant differences among the treatment groups. The incidence of treatment-related adverse events was 29.1, 36.9, 62.7 and 40.4% for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch and placebo, respectively. At 90 days, clinically notable decreases in TC, LDL-C and HDL-C were seen with testosterone gel 100 mg (P value not reported). Increases in Hgb and Hct were the highest with testosterone gel compared to The testosterone patch and placebo. Increases in PSA values were highest in the testosterone patch group (6.6%). Secondary: Not reported
Wang et al.[41] (2011)	OL with ES Men ≥18 years of	N=155 OL study	Primary: Total testosterone and DHT (OL	Primary: At day 120, the proportion of patients completing the study with an average testosterone concentration (average concentration) in the normal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Testosterone topical solution (Axiron®) 60 mg applied to each axilla once daily	age with androgen deficiency (diagnosis of hypogonadism) and a BMI <35.0 kg/m^2 with testosterone levels on two consecutive samples <10.4 nmol/L and a baseline Hgb level ≥1,10.5 g/L	120 days N=71 ES 60 days	phase) Secondary: PDQ domain assessing sexual desire, enjoyment and performance, sexual activity and mood, SF-36 health survey (ES phase)	range was 84.1%. Also, 76.1 and 84.8% of patients completed the study with an average concentration in the responder range on days 15/16 and 60/61, respectively. The mean serum testosterone level before and after dosing was within the adult male range over the 24-hour period on days 15, 60 and 120. The geometric mean of serum testosterone over 24 hours was 15.62 nmol/L (coefficient of variation; 38%). Among subjects who were responders at day 120, the geometric mean of serum testosterone values for subjects on any dose was 16.86 nmol/L. Serum DHT levels and serum free testosterone remained relatively stable over the 24-hours following dosing. The mean day 15 baseline pre-dose DHT/testosterone ratio was 0.23, and the mean DHT/testosterone ratio remained between 0.17 and 0.26 throughout the 24-hour period. The ratio values among patients completing the study and among responders remained relatively constant from baseline. Secondary: Improvements in sexual desire and activity were apparent 15 days after application of testosterone and were sustained throughout the study. Statistically significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood as assessed by the PDQ domain for the seven days prior to visits one, 15, 60 and 120. Significant mean changes from day one to 120 for SF-36 Physical Component and SF-36 Mental Component scores were 1.55 (SD, 7.72; P=0.0254) and 4.54 (SD, 9.20; P<0.0001), respectively. Treatment-emergent adverse events occurring in >2% of patients receiving at least one dose of testosterone in the OL study included: application site irritation, application site erythema, headache, increased Hct, nasopharyngitis, diarrhea and vomiting. Three patients withdrew from the OL phase of the study due to adverse events, including superficial thrombophlebitis, effects on lability/anger and malignant melanoma; while two patients withdrew from the extension phase of the study due to application site irritation and application site erythema.
Sih et al.[42]	DB, PC, RCT	N=32	Primary:	Primary:

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(1997) Testosterone cypionate 200 mg intramuscularly biweekly vs placebo	Hypogonadal men with testosterone <60 ng/dL, mean ages 65 to 68 in the treatment arms	12 months	Changes in grip strength, Hgb, Hct, PSA, leptin and memory Secondary: Not reported	Testosterone cypionate improved bilateral grip strength (P<0.05) and increased Hgb compared to placebo (P<0.001). The men assigned to testosterone cypionate had greater decreases in leptin than those assigned to placebo (P<0.02). There were no significant changes in PSA or memory (P values not reported). Three men receiving placebo withdrew from the study. Seven men receiving testosterone cypionate withdrew from the study of which three were due to abnormal elevations in Hct. Secondary: Not reported
Snyder et al.[43] (1980) Testosterone enanthate 100 mg intramuscularly once a week (n=12) vs testosterone enanthate 200 mg every two weeks (n=10) vs testosterone enanthate 300 mg every three weeks (n=9)	OL Men 24 to 67 years of age with primary hypogonadism defined by testosterone <300 ng/dL, FSH >14 mIU/mL and LH >18 mIU/mL	N=23 12 to 16 weeks	Primary: Changes in serum testosterone, FSH and LH levels Secondary: Not reported	Primary: All four regimens produced serum testosterone concentrations that fluctuated largely within the normal range; the average concentration between doses was highest with 100 mg and lowest with 400 mg (P values not reported). The regimens of testosterone enanthate 200 mg every two weeks and 300 mg every three weeks appeared to be the most effective of those tested in terms of suppression of serum LH concentration to normal and in frequency of administration. Testosterone enanthate 100, 200 and 300 mg regimens all suppressed the initially elevated serum LH concentrations to normal, but not the 400 mg regimen. Testosterone enanthate 100 and 200 mg regimens suppressed the initially elevated serum FSH concentrations to normal, but not the 300 and 400 mg regimens (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs testosterone enanthate 400 mg every four weeks (n=6)				
Zitzmann et al.[44] (2013) IPASS Testosterone undecanoate treatment (initial intramuscular injections with a 6-week interval, the following intervals between two injections are almost always 12 weeks)	OS, PRO, Post-Authorisation Surveillance Study Men diagnosed with hypogonadism (aged 49.2 ± 13.9 years)	N=1,438 Patients received up to five testosterone undecanoate injections during 9 to 12 months.	Primary: Parameters of erectile function, libido, vigor/ vitality, mood, and ability to concentrate assessed by physician interview. Physical and circulatory parameters as well as hematocrit, PSA levels, glucose control, and lipid profiles Secondary: Not reported	Primary: There was a significant improvement of the overall levels of sexual desire/libido: a very low/low level at baseline decreased from 64% of patients to 13% after two injections and to 10% at the time of injection 5. A high/very high level of libido increased from 10% of patients at baseline to 42% after two injections to 61% at the time of injection 5 (overall chi-square test: P<0.0001). Improvements in vigor/vitality, mood, and ability to concentrate showed significant improvements. Blood pressure and serum lipid profiles changed during treatment in a favorable and significant manner. PSA exceeded 4 ng/mL in 11 men. There were clinical reasons to perform a prostate biopsy in four cases, but in no case prostate cancer was observed. Hematocrit rose gradually from 42.8 ± 6.6% at baseline to 44.5 ± 6.1% at the time of injection 5 (P<0.0001). Secondary: Not reported
Tan et al.[45] (2013) Testosterone undecanoate intramuscular injection every 10 to 14 weeks vs placebo	DB, PC, RCT Men in Malaysia aged 40 to 70 years, with testosterone deficiency (serum total testosterone ≤12 nmol/L) and a PSA <4 ng/mL within the past year	N=114 48 weeks	Primary: Hemoglobin, hematocrit, serum total testosterone, lipid profile, fasting blood glucose, sex hormone-binding globulin, liver function test, PSA, and adverse events Secondary: Not reported	Primary: Significant increase in serum total testosterone (P<0.001), PSA (P=0.010), hematocrit (P<0.001), hemoglobin (P<0.001) and total bilirubin (P=0.001) were seen in the treatment arm over the 48-week period compared with the placebo group. A total of 26 (44.8%) men in the control group and 19 (33.9%) men in the treatment group reported adverse events. The most common adverse event in both groups were itching, swelling or pain at the site of injection (control group: n=16 [39.0%] vs treatment group: n=7 [25.9]). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hackett et al.[46] (2013) Testosterone undecanoate (TU) 1,000 mg intramuscularly at week 0, 6, and 18 vs placebo	DB, PC, RCT followed by OL Men aged 18 and over from the type 2 diabetes registers of the eight general practices based on the initial finding of either total testosterone (TT) between 8.1 and 12 nmol/L or free testosterone (FT) from 0.181 to 0.25 nmol/L (mild group) or TT of 8.0 nmol/L or less or FT of 0.18 nmol/L or less (severe group).	N=190 DB, PC for 30 weeks, followed by 52-week OL	Primary: International Index of Erectile Function (IIEF) Secondary: Aging Male Symptom (AMS), Hospital Anxiety and Depression Scale (HADS), and Global Efficacy Question	Primary: Testosterone replacement therapy with long-acting TU improved all domains of sexual function at 30 weeks (erectile function [EF], P=0.005; intercourse satisfaction, P=0.015; sexual desire, P=0.001; overall satisfaction, P=0.05; and orgasm, P=0.04), with benefit as early as 6 weeks. Secondary: Improvements in AMS score were significant in men without depression (P=0.02) and the presence of depression at baseline was associated with marked reduction in response to both sexual function and psychological scores. All responses in sexual function continued to improve significantly up to 18 months with an improvement in EF score of 4.31 from baseline. In a small cohort of 35 men taking phosphodiesterase type 5 inhibitors, there was no change during the double-blind phase but a nine-point improvement in EF domain during 52-week open-label treatment. After 30 weeks, 46 vs 17% of patients on active therapy vs placebo felt that the treatment had improved their health, reaching 70% after open-label therapy. Less obese and older patients responded better to testosterone therapy. There were no significant adverse events.
Endometriosis				
Selak et al.[47] (2007) Danazol 200 mg three times a day alone or as adjunctive therapy vs placebo	MA of 5 RCT (literature search included Medline 1966 to April 2007) Women of reproductive age with the diagnosis of endometriosis made by direct visualization (mean ages 28 to 33)	N=370 Treatment: 3 to 6 months; Follow-up: 6 to 36 months	Primary: Improvement in pain Secondary: Changes in AFS scores and safety	Primary: One study found a significant decrease in the levels of pelvic pain, lower back pain, defecation pain and total pain in patients treated with danazol without surgery compared to those treated with placebo, at three and six months of therapy and six months after medication (P values not reported). In patients receiving danazol and surgery, a significant decrease in the levels of total pain and pelvic pain was reported compared to placebo at six months of therapy (P values not reported). This improvement in pain scores was still present six months after the end of therapy with danazol. Secondary: Two studies examined the change in AFS scores at repeat laparoscopy six months after the end of medication. While there was no significant

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				difference in total AFS score, danazol without surgery caused a decrease in peritoneal AFS scores (P values not reported). In patients treated with danazol and surgery, a significant decrease in total and peritoneal AFS scores compared to placebo was noted (P values not reported). Only one study evaluated adverse effects. This study found a significant increase in acne, muscle cramps and edema in women receiving danazol without surgery at six months (P value not reported). When danazol was used with surgery, a significant increase in acne, weight gain and spotting was reported at 6 months (P value not reported).
Beaumont et al.[48] (2007) Danazol vs other medical therapy (norethisterone, mefenamic acid, progesterone intrauterine device, medroxy-progesterone, low-dose oral contraceptives) vs placebo	MA (9 RCTs) Women of reproductive years with regular heavy menstrual blood loss and recruited from primary care, family planning or specialist clinic setting	N=353 ≤3 months	Primary: Reduction in objectively measured menstrual blood loss during and after intervention, reduction in subjectively measured blood loss by the woman, QOL, side effects, withdrawals, reduction in symptoms of dysmenorrhea Secondary: Weight gain, subjective efficacy of intervention, subjective time to relapse, duration of menses, resources use (women, general practitioner, hospital, health	Primary: One trial compared danazol to placebo; however, menstrual blood loss, duration of menses could not be assessed for differences. There were no significant differences between the danazol and placebo groups in withdrawals due to side effects (P=0.56). Five trials compared danazol with a progestin (norethisterone or medroxyprogesterone). For one trial measuring mean menstrual blood loss, there was no significant difference between the groups. For two trials measuring weight gain as a QOL outcome, there were no significant differences between the groups. In one trial that evaluated the interventions at a three month follow up, the progestin group has significantly lower menstrual blood loss (P=0.025). Two trails compared different doses of danazol; however, there were no significant differences in outcomes. Three trials compared danazol with mefenamic acid. There was no significant difference in the improvement of dysmenorrhea between the groups. There were significantly more side effects reported in the danazol group compared to mefenamic acid group (P=0.0062). However, in a trial evaluating acceptability of treatment, there was no significant difference between the groups. Mean menstrual blood loss was significantly lower in the danazol treatment groups compared to mefenamic acid (P<0.00001). One trial compared danazol with an oral contraceptive. Menstrual blood loss was significantly lower in the danazol group after two months

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			service	(P=0.02). Secondary: In the trial comparing danazol to placebo, weight gain was significantly greater than in the danazol group compared to placebo (P=0.022). For the trials comparing danazol to a progestin, there were significantly more patients in the danazol group rating as high or moderate efficacy (P=0.037);whereas, another trial found no significant difference with rating menstrual blood loss as none or moderate (P=0.10). There were significantly more patients in the danazol group compared to the progestin group that reported side effects (P=0.0030). There was no significant difference in duration of menses and withdrawals due to side effects between the groups. Mean weight gain was significantly higher with danazol compared to progestins (P<0.00001) in the one trial measuring this outcome. In one trial objectively measuring menstrual blood loss, danazol had lower menstrual blood loss compared to progestins (P=0.025). In the trials comparing danazol to mefenamic acid, the duration of menses was significantly shorter in the danazol group compared to mefenamic acid group (P=0.0074). One trial compared danazol to a progesterone intrauterine device. The duration of menses was significantly shorter in the danazol group (P<0.0001).
Hereditary Angioedema				
Gelfand et al.[49] (1976) Danazol (dose not reported) vs placebo	DB Patients with hereditary angioedema (age not reported)	N=9 Duration not reported	Primary: Number of attacks of hereditary angio-edema, safety and changes in biochemical markers Secondary: Not reported	Primary: Prophylaxis with danazol resulted in only one attack per 46 danazol courses compared to 44 attacks per 47 placebo courses (P value not reported). Side effects were minimal, and virilization was not observed in the women studied. Danazol increased C1 esterase inhibitor levels by three to four folds and levels of the fourth component of complement by 15 folds. These changes

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				began during the first day of therapy and were maximal by the first one to two weeks. After therapy was stopped, C1 esterase inhibitor and fourth component of complement levels rapidly decreased. Secondary: Not reported
Bork et al.[50] (2008) Danazol (dosage range from 100 mg to >600 mg per day)	RETRO Male and female patients with a mean age of 33 with hereditary angioedema	N=118 2 months to 30 years	Primary: Frequency and severity of acute attacks before and during danazol therapy and safety Secondary: Not reported	Primary: In all, 94.1% of patients responded to danazol. During treatment, 45.8% of patients became symptom free or had one attack or less per year. In the other patients, hereditary angioedema ran a mild course. The frequency of acute attacks during danazol treatment was reduced to 16.2%, and the attacks were considerably milder than before treatment. Laryngeal edema was reduced to 4.8%. Adverse effects (depression, headache, menstrual irregularities, liver adenomas and virilization) occurred in 78.8% of patients and led to discontinuation of danazol therapy in 25.4% of patients. Secondary: Not reported
Anemia				
Davies et al.[51] (1972) Oxymetholone 100 mg daily for three months then placebo for three months vs placebo for three months then oxymetholone 100 mg daily for three months	DB, RCT, XO Men and women treated with hemodialysis for up to five years	N=55 6 months	Primary: Change from baseline in Hgb and Hct Secondary: Not reported	Primary: There were no significant difference between the groups in mean changes in Hgb and Hct. Secondary: Not reported

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Aramwit et al.[52] (Abstract; 2010) Oxymetholone 50 mg twice daily plus erythropoietin vs placebo plus erythropoietin	DB, PC Patients on continuous ambulatory peritoneal dialysis	N=24 6 months	Primary: Changes from baseline in Hct, Hgb and muscle mass Secondary: Not reported	Primary: At six months, the Hct and Hgb were significantly higher in the oxymetholone group compared to placebo (38.1±1.0 vs 32.8±0.9%; P= 0.001 and 12.9±0.3 vs 11.0±0.3 g/dL; P = 0.001, respectively). After six months, albumin, protein and LBM were significantly increased in the oxymetholone group compare to baseline (P<0.05), but none of the measures were significantly different in the placebo group. Secondary: Not reported
Bacigalupo et al.[53] (1992) Oxymetholone 2 mg/kg once daily starting on day 6 plus antilymphocyte globulin 15 mg/kg for five days daily and methylprednisolone 5 mg/kg daily for 5 days followed by dose reduction vs placebo starting on day 6 plus antilymphocyte globulin and methylprednisolone 5 mg/kg daily for 5 days followed by dose reduction	MC, PC, RCT Men and women 1 to 70 years of age diagnosed within 30 days with acquired aplastic anemia without concomitant or proceeding neoplasia, anemia requiring red blood cell support and/or thrombocytopenia requiring platelet transfusions, and at least one of the following: hypoplastic marrow without blasts, a neutrophil count of <0.5x10^9/L, or a platelet counts of <20x0.5x10^9/L	N=140 120 days	Primary: Rate of complete responders (transfusion independent with neutrophil count >2x10^9/L and platelet count >100x10^9/L), partial responders (transfusion independent with neutrophil count >0.5x10^9/L and platelet count >30x10^9/L) and non-responders (requirement of transfusions) Secondary: Not reported	Primary: At days 120, the number of responders was significantly higher in the oxandrolone group compared to placebo (68 vs 48%; P=0.02). When including early deaths of patients in the analysis, there was still a significant difference between the oxandrolone and placebo groups (56 vs 40%; P=0.04). The number of complete responders was not significantly different between the groups (P=0.5). After stratifying patients by neutrophil counts, patients with counts ≤0.5x10^9/L had a greater proportion of responders/non-responders in the oxandrolone group compared to the placebo group (P=0.007). There was also a significantly higher proportion of complete responders with oxandrolone compared to placebo (44 vs 20%; P=0.02). There was no significant difference in rate of responders in patients with higher neutrophil count. In patients with neutrophil counts of ≤0.5x10^9/L, women had a significantly greater response rate with oxandrolone compared to placebo (P=0.01); however this is not seen with men (P=0.2). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weight Gain				
Porro et al.[54] (2012) Oxandrolone 0.1 mg/kg twice daily for 12 months vs placebo	RCT Children 0 to 18 years of age at the time of burn with >30% total body surface area affected and the need for at least one surgical intervention	N=222 5 years	Primary: Changes from baseline in growth, body composition, muscle strength, resting energy expenditure, liver and cardiac function, serum markers, hormones, bone mass and sexual maturation Secondary: Changes in bone-age and psychosocial function	Primary: There was a significant decrease in percent predicted resting energy expenditure in patients treated with oxandrolone (P<0.01). There was a significant difference between the oxandrolone and placebo groups until six months post-burn (P<0.004). The percentage of patients >2 SDs below mean high velocity was significantly different between the oxandrolone and placebo groups at year one (8 vs 48%; P<0.05) and year two (7 vs 32%; P<0.05), but not at years three, four, and five. Patients in the placebo group had negative percent change in height velocity compared to a positive percent change with patients treated with oxandrolone (P<0.05). The percentage of patients >2 SDs below mean weight velocity was significantly lower in the oxandrolone group compared to the placebo group at year one (28 vs 46%; P<0.05) but not at any other year. There was a significant higher change in bone mineral content in the oxandrolone group compared to the placebo group in patients seven to 18 years of age from years two through five (P<0.001). There were no significant differences in patients <7 years of age. BMD was not significantly different between the groups. LBM was not significantly different between the groups (P=0.06). Serum constitutive proteins, prealbumin, retinol-binding protein, and transferrin were significantly higher in the oxandrolone treated patients compared to placebo (P<0.05). Serum albumin and total protein were not significantly different between the groups. IGF-1 was significantly higher in the oxandrolone group compared to placebo from discharge to two years (P<0.05). There were no differences in IGFBP-3 between the groups. There were no significant differences in PTH, free thyroid index, and T3 uptake. The cardiac output, percent predicted cardiac output, percent predicted heart rate were significantly lower in the oxandrolone group compared to placebo at year one (P<0.05). Percent predicted cardiac output and heart rate were also significantly lower at year two in in the oxandrolone group

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				compared to placebo (P<0.05). Liver length and weight were not significantly different between the groups. Secondary: There was no significant difference in bone age between the groups. There was no effect of oxandrolone on psychosocial outcomes.
Grunfeld et al.[55] (2006) Oxandrolone 20 mg once daily vs oxandrolone 40 mg once daily vs oxandrolone 80 mg once daily vs placebo During the OL extension phase, all patients were switched to 20 mg once daily.	DB, MC, PC, PG, RCT (OL extension) HIV-infected men ≥18 years of age with 10 to 20% unintentional weight loss from premorbid weight documented in medical records or BMI ≤20 kg/m^2, a Karnofsky Performance Scale score >60%, a life expectancy of >6 months, and the ability to consume a normal well-balanced diet	N=262 12 weeks (DB) 12 weeks (OL)	Primary: Change from baseline in body weight at two, four, eight and 12 weeks in DB phase and at 14, 18 and 24 weeks in OL phase Secondary: Change from baseline of fat and BCM at all time points, health-related QOL, physical capability at weeks two and 12, and safety measures of HIV RNA levels, CD4 counts, complete blood counts and blood chemistry	Primary: There were significant increases in body weight for all groups (including placebo) as soon as two weeks and continuing through 12 weeks (P<0.014 vs baseline at 12 weeks). When compared to placebo, weight gain was significantly greater in patients treated with oxandrolone 40 mg at weeks two, four, eight and 12 (P<0.0040 for all comparisons). Weight gain in the patients treated with 80 mg was significantly greater than placebo at weeks four and eight (P<0.017 for both), but not significantly different at weeks two and 12 (P=0.045 for 12 weeks). During the OL extension phase, all patients continued to gain weight; however, the weight gain was not significantly different between the groups. Secondary: There were significant increases in BCM compared to baseline in all groups (P value not reported). There were significantly greater increases in BCM compared to placebo in patients treated with 40 mg (P<0.0049) and 80 mg (P<0.0002) at 12 weeks. There were no significant differences in fat in any group. There were no significant differences in health-related QOL and physical capacity for any treatment group. There was a dose-dependent increase in platelet count in patients treated with oxandrolone compared to placebo (P<0.017 for all doses of oxandrolone vs placebo). There were significant increase in creatinine and creatine kinase in patients treated with oxandrolone compared to placebo (P<0.017 for all doses of oxandrolone vs placebo). Compared to placebo, there were dose dependant significant increases in ALT for patients treated with 40 and 80 mg (P<0.017 for both doses) and AST for patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated with 80 mg (P<0.017). There were a significant decreases in uric acid and HDL in patients treated with all doses of oxandrolone (P<0.017 for all comparisons). For patients treated with 40 and 80 mg, there were significant increase in LDL compared to placebo (P<0.017 for both). There were no significant differences in other measures.
Mwamburi et al.[56] (2004) Oxandrolone 10 mg twice daily vs megestrol 800 mg once daily	RCT HIV positive men and women (average age 40 years) receiving stable highly active antiretroviral therapy that unintentionally lost ≥5% of their body weight during the preceding six months	N=40 2 months	Primary: Change from baseline in body weight and composition Secondary: Patient tolerance and adverse event profile	Primary: Compared to baseline, there were statistically significant increases in total body weight, BMI, and LBM for the oxandrolone group (P=0.001; P=0.001; P=0.04) and the megestrol group (P=0.01; P=0.005; P=0.02). There were no significant differences between the treatment groups in any measure. Secondary: The most common adverse effects in patients treated with megestrol were nausea and vomiting and feeling bloated and swollen. The most common adverse event reported with oxandrolone was elevated transaminases.

‡Agent not available in the United States.
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SD=standard deviation
Miscellaneous abbreviations: AFS=American Fertility Society, ALT= alanine aminotransferase, AST= aspartate aminotransferase, AUC=area under the curve, BCM=body cell mass, BMD=bone mineral density, BMI=body mass index, DHT=dihydrotestosterone, E2=Estradiol, FSH=follicle-stimulating hormone, Hct=hematocrit, HDL=high density lipoprotein, Hgb=hemoglobin, HIV=human immunodeficiency virus, IGF=insulin growth factor, IGFBP=insulin growth factor binding proteins, LBM=lean body mass, LDL=low density lipoprotein, LH=luteinizing hormone, PSA=prostate specific antigen, PTH=parathyroid hormone, QOL=quality of life, RNA=ribonucleic acid, SALP=bone-specific alkaline phosphatase, SF-36=short form-36, SHBG=sex hormone-binding globulin, 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 14. Relative Cost of the Androgens

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Danazol	capsule	N/A	N/A	$$$$$
Fluoxymesterone	tablet	N/A	N/A	$$$
Methyltestosterone	capsule, tablet*	Android®, Testred®	$$$$$	$$$
Oxandrolone	tablet	N/A	N/A	$$$$
Oxymetholone	tablet	Anadrol-50®	$$$$$	N/A
Testosterone	buccal, implant, nasal gel, transdermal gel, transdermal patch, transdermal solution	Androderm®, AndroGel®*, Axiron®, Fortesta®*, Natesto®, Striant®, Testim®*, Testopel®, Vogelxo®*	$$$$$	$$$$$
Testosterone cypionate	solution for injection	Depo®-Testosterone*	$$$$$	$$
Testosterone enanthate	solution for injection	N/A	N/A	$$$
testosterone undecanoate	oil for injection	Aveed®	$$$$$	N/A

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

X. Conclusions

The androgens are approved for a variety of conditions and, with the exception of danazol, oxandrolone, and oxymetholone, all agents in this review are Food and Drug Administration (FDA)-approved for the management of male hypogonadism. The oral synthetic testosterones (fluoxymesterone and methyltestosterone) and the injectable testosterone enanthate are also FDA-approved for the treatment of delayed puberty in males and metastatic mammary cancer in females. Danazol is FDA-approved for the treatment of endometriosis, fibrocystic breast cancer and hereditary angioedema, though it is not indicated for the management of male hypogonadism. Oxandrolone is approved for adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. This agent is also approved to offset the protein catabolism associated with prolonged administration of corticosteroids and for the relief of the bone pain frequently accompanying osteoporosis. Oxymetholone is approved for the treatment of anemias caused by deficient red cell production.[1-20]

In clinical studies, testosterone buccal and topical products have been shown to increase serum testosterone levels and/or improve lean body mass, decrease body fat, and improve sexual function in men with hypogonadism.[24,29-38] Head-to-head studies comparing testosterone topical gel to testosterone transdermal system have shown greater improvement in serum testosterone levels, lean body mass, and sexual function as well as fewer adverse events with testosterone gel compared to testosterone patches in men with hypogonadism.[32-33,37-38] Severe hepatotoxicities have been associated more commonly with oral androgen than topical androgen therapy and liver function tests should be monitored periodically.[1-20]According to current consensus guidelines, intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral androgen therapies are generally not recommended for this condition due to poor androgen effects, adverse lipid changes, and hepatic side effects. The selection of a specific testosterone replacement therapy should be a joint decision between an informed patient and physician after considering patient preferences, the pharmacokinetic profiles of the respective agents, and treatment burden. Furthermore, currently available guidelines do not give preference to one topical preparation vs another.[21,24]

Currently, danazol, fluoxymesterone, methyltestosterone, oxandrolone, testosterone cypionate, and testosterone enanthate are available generically.

There is insufficient evidence to support that one brand androgen 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 androgens within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand androgen 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review of Afrezza®
Insulins: AHFS Class 682008
November 4, 2015

I. Overview

Insulins stimulate peripheral glucose uptake by skeletal muscle and fat, decrease hepatic glucose production, inhibit lipolysis and proteolysis, and enhance protein synthesis.[1-3] There are two types of insulin preparations currently available: human insulin and insulin analogs. Human insulin is derived from a biosynthetic process and is structurally identical to endogenous insulin. Insulin analogs are structurally different than human insulin. Each insulin analog differs in the addition, deletion, or substitution of amino acids on the B chain. These modifications lead to a faster onset and shorter duration of action (for rapid-acting insulin analogs) or slower absorption and a longer duration of action (for long-acting insulin analogs) than human insulins.[1,2]

The insulin preparations are further categorized based on their duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions. Regular insulin as used in Afrezza® is rapid-acting.[3] They may also be administered continuously via an infusion pump. Intermediate- and long-acting insulins are administered once or twice daily. They act as basal insulin to decrease hepatic glucose production and lower fasting plasma glucose concentrations.[1,2]

Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection. [1-4] Regular insulin is also formulated as an inhalation.[3] Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere®, which provide a more efficient inhalation device than what has been used in the past.[3] Another inhaled formulation of regular insulin, Exubera®, was previously FDA-approved; however, this agent was removed from the market in 2007 due to low patient and provider acceptance.[5]

The insulins that are included in this review are listed in Table 1. There are no generic formulations of insulin; however, there are several products available over-the-counter.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Insulin regular, human	Inhalation powder	Afrezza®	none

PDL=Preferred Drug List

II. Evidence- Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines for Diabetes Mellitus

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Medical Care in Diabetes (2015)**[6]	<u>Current criteria for the diagnosis of diabetes</u> • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <u>Prevention/delay of type 2 diabetes</u> • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should be encouraged in patients with impaired glucose tolerance, impaired fasting

Clinical Guideline	Recommendation(s)

	glucose, or an HbA_{1c} 5.7 to 6.4%.
	• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.7%, especially for those with a body mass index >35 kg/m^2, age <60 years, and women with prior gestational diabetes mellitus.
	
	<u>Glycemic goals in adults</u>
	• Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%.
	• It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.
	• Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.
	
	<u>Pharmacologic and overall approaches to treatment-type 1 diabetes</u>
	• Recommended therapy consists of the following components:
	  o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy.
	  o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity.
	  o Most patients should use of insulin analogs to reduce hypoglycemia risk.
	
	<u>Pharmacologic and overall approaches to treatment-type 2 diabetes</u>
	• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.
	• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset.
	• A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences.
	• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin.
	• Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered**	<u>Key points</u> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions.

Clinical Guideline	Recommendation(s)
Approach (2012)[4]	Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <u>Initial drug therapy</u> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <u>Advancing to dual combination therapy</u> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability. <u>Advancing to triple combination therapy</u> • Some trials have shown advantages of adding a third non-insulin agent to a two

Clinical Guideline	Recommendation(s)
	drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. **Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**

Initial Drug Monotherapy	Metformin				
Efficacy (↓HbA_{1c})	High				
Hypoglycemia	Low risk				
Weight	Neutral/loss				
Side Effects	Gastrointestinal/lactic acidosis				
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)					
Two Drug Combin-ations	Metformin + sulfonyl-urea	Metformin + thia-zolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
Efficacy (↓HbA_{1c})	High	High	Inter-mediate	High	Highest
Hypo-glycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major Side Effects	Hypo-glycemia	Edema, heart failure, bone fracture	Rare	Gastro-intestinal	Hypo-glycemia
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)					
Three Drug Combin-ations	Metformin + sulfonyl-urea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +
	TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, TZD, or insulin	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, or GLP-1 receptor agonist
If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents					
More Complex Insulin Strategies	Insulin (multiple daily doses)				

American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered**	This article should be read as an addendum to the previous full account, summarized above. <u>Sodium–Glucose Cotransporter 2 Inhibitors</u> • These agents reduce HbA_{1c} by 0.5 to 1.0% (5.5 to 11 mmol/mol) versus placebo • Advantages include: action independent of insulin allowing use even after insulin secretion has waned, modest weight loss (about 2 kg, stabilizing over 6 to 12 months), lowering of blood pressure by about 2 to 4/ 1 to 2 mmHg.

Clinical Guideline	Recommendation(s)
Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes (2015)[7]	• Side effects include genital mycotic infections, at rates of about 11% higher in women and about 4% higher in men compared with placebo, diuretic effect, increased urine calcium excretion, increase in LDL cholesterol (about 5%), and renal function restrictions. Thiazolidinediones • Earlier concerns with risk of bladder cancer have been allayed by subsequent evidence. Dipeptidyl Peptidase 4 Inhibitors • There is mixed evidence for DPP-4 inhibitors and cardiovascular risk or benefit. Until further trials are completed these agents should be used cautiously, if at all, in patients with preexisting heart failure. Initial drug therapy • Metformin remains the optimal drug for monotherapy. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)**[8]	Management of prediabetes • Lifestyle modifications, including initial attempts to lose 5 to 10% of body weight if overweight or obese and participate in moderate physical activity (e.g., walking) at least 150 minutes per week should be initiated. • Medications including metformin, acarbose, or thiazolidinediones (TZDs) should be considered for patients who are at moderate-to-high risk for developing diabetes mellitus, such as those with a first-degree relative with diabetes. Antihyperglycemic pharmacotherapy for type 2 diabetes • Pharmacotherapy should be prescribed based on sustainability for the individual patient. • Initiate with metformin, a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose cotransporter 2 (SGLT2) inhibitor, or an α-glucosidase inhibitor for patients with an entry A1C <7.5%. • A TZD, sulfonylurea, or glinide may be considered as alternative therapies but should be used with caution due to side-effect profiles. • For patients with entry A1C levels >7.5%, initiate treatment with metformin (unless contraindicated) plus a second agent, with preference given to agents with a low potential for hypoglycemia that are weight neutral or associated with weight loss. This includes GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors as the preferred second agents. • Colesevelam, bromocriptine, or an α-glucosidase inhibitor have limited glucose-lowering potential but also carry a low risk of adverse effects and may be useful for glycemic control in some situations. • Sulfonylureas and glinides are considered the least desirable alternatives due to the risk of hypoglycemia. • For patients with an entry A1C >9.0% who have symptoms of hyperglycemia, insulin therapy alone or in combination with metformin or other oral agents is recommended. • Insulin should be considered for T2D when noninsulin antihyperglycemic

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	therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
	• Therapy with long-acting basal insulin should be the initial choice in most cases. The insulin analogs glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because analog insulins are associated with less hypoglycemia.
	• When control of postprandial hyperglycemia is needed, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or inhaled insulin) over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia.
	
	Management of type 1 diabetes
	• Insulin must be used to treat type 1 diabetes. Physiologic insulin regimens, which provide both basal and prandial insulin, should be used. Approaches include:
	  • Multiple daily injections (MDI), which usually involve 1 to 2 subcutaneous injections daily of basal insulin to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or inhaled insulin before each meal to control meal-related glycemia.
	  • Continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia.

American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[9]	Principles underlying the algorithm • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. Monotherapy • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable

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	therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. • TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <u>Combination therapy</u> • Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides. <u>Three-drug combination therapy</u> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors. o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides

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	Insulin therapy algorithm • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
National Institute for Health and Care Excellence: **The Management of Type 2 Diabetes (Issued 2009, last modified July 2014)**[10]	Metformin • Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone. • Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight. • Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added. • Step up metformin therapy gradually over weeks to minimize risk of gastrointestinal (GI) side effects. Consider a trial of extended release metformin

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	if GI tolerability prevents continuation of therapy.
	
	Insulin secretagogues
	• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or it is contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.
	• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.
	• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.
	• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.
	
	Rapid-acting insulin secretagogues
	• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.
	
	Acarbose
	• Consider acarbose for a patient unable to use other oral glucose-lowering medications.
	
	DPP-4 inhibitors
	• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA_{1c} ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA_{1c} ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.
	• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%) and insulin is unacceptable or inappropriate.
	• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA_{1c} in 6 months).
	• A DPP-4 inhibitor may be preferable to a thiazolidinedione (TZD) if:
	  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.
	  o A thiazolidinedione is contraindicated.
	  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.
	There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.
	
	TZDs
	• Consider adding a TZD to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA_{1c} ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a TZD to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA_{1c} ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.
	• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%) and insulin is unacceptable or inappropriate.

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	• Do not use a TZD is people who have heart failure, or who are at higher risk of fracture.
	• Only continue TZD therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA_{1c} in 6 months).
	• Consider combining TZD with insulin therapy for a person who previously had a marked glucose-lowering response to TZD therapy or who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.
	• A TZD may be preferable to a DPP-4 inhibitor if:
	  o The person has marked insulin insensitivity.
	  o A DPP-4 inhibitor is contraindicated.
	  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.
	There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.
	
	<u>Gliptins: GLP-1 enhancers</u>
	• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.
	
	<u>GLP-1 mimetics</u>
	• 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 (HbA_{1c} ≥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).
	  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 HbA_{1c} and weight loss ≥3% of initial body weight at six months).
	
	<u>Insulin therapy</u>
	• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.
	• When starting basal insulin therapy:
	  o Continue with metformin and the sulfonylurea (and acarbose, if used).
	  o Review the use of the sulfonylurea if hypoglycemia occurs.
	• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):
	  o Continue with metformin.
	  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs.
	• Begin with human NPH insulin injected at bedtime or twice daily according to need.
	• Consider using a long-acting insulin analogue if:
	  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.
	  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.
	  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.
	  o The person cannot use the device to inject NPH insulin.
	• Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA_{1c}

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	≥9.0%). A once-daily regimen may be an option.
	• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:
	  o A person prefers injecting insulin immediately before a meal.
	  o Hypoglycemia is a problem.
	  o Blood glucose levels rise markedly after meals.
	• Consider switching to a long-acting insulin analogue from NPH insulin in people:
	  o Who do not reach their target HbA_{1c} because of significant hypoglycemia.
	  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached.
	  o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.
	  o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.
	• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).

Institute for Clinical Systems Improvement: **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)**[11]	• Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when:
	  o Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria).
	  o Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance.
	  o Inability to comply with standard goals, such as polypharmacy issues.
	  o Limited life expectancy or estimated survival of less than 10 years.
	  o Cognitive impairment.
	  o Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications.
	• A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains.
	• Recommend education and self-management, as appropriate.
	• Initiate metformin as first-line pharmacotherapy for patients with type 2 diabetes, unless medically inappropriate.
	  o Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain.
	  o Metformin can also be used in combination with all other glucose-lowering agents.
	• Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.

International Diabetes Federation Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes**	<u>Lifestyle management</u> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals.

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(2012)[12]	• Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol.
	• Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals.
	• Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week.
	• Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity.
	
	<u>Glucose control levels</u>
	• Maintaining HbA_{1c} below 7% minimizes the risk of developing complications.
	• A lower HbA_{1c} target may be considered if it is easily and safely achieved.
	• A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia.
	
	<u>Oral therapy</u>
	• Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications.
	• Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months.
	• First-line therapy
	  o Begin with metformin unless there is evidence of renal impairment or other contraindication.
	  o Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 mL/min/1.73m^2.
	  o Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot.
	  o In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets.
	• Second-line therapy
	  o When glucose control targets are not achieved, add a sulfonylurea.
	  o Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas.
	• Third-line therapy
	  o When glucose control targets are no longer being achieved, start insulin or add a third oral agent.
	  o If starting insulin, add basal insulin or use premix insulin.
	  o If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD.
	  o Another option is to add a glucagon-like peptide-1 (GLP-1) agonist.
	• Fourth-line therapy
	  o Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are

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	unable to maintain target glucose control. Insulin therapy • Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response. • Provide education and appropriate self-monitoring. • Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day. • Continue metformin. Other oral agents may also be continued. • Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin). • Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional. • Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL). • Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.
American Diabetes Association: **Care of Children and Adolescents with Type 1 Diabetes (2005)**[13]	• Insulin type, mixture of insulins, site of injection, and individual patient response differences can all affect the onset, peak, and duration of insulin activity. • Children with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal blood glucose control. • The basal/bolus insulin regimen uses a long-acting insulin analog combined with a rapid-acting insulin analog given before meals and snacks. This regimen has been shown to result in stable glycemic control and less hypoglycemia compared with regimens using intermediate and short insulin regimens. • Many young children and teenagers consume multiple snacks throughout the day. An ideal basal/bolus regimen may consist of as many as six to seven insulin injections per day. A combination of rapid-acting insulin with small amounts of intermediate-acting insulin to allow coverage for snacks may be an appropriate alternative to the basal/bolus plan. However, two or three doses of mixed rapid-acting or short-acting insulin with intermediate-acting insulin generally cannot maintain HbA_{1c} levels within the target range. Recommendations now support moving toward a basal/bolus insulin regimen for most patients. • The combination of rapid-acting insulin analogs and a long-acting insulin offers an excellent option for basal and bolus insulin administration. • Basal/bolus regimens have been shown to result in lower fasting blood glucose levels with less nocturnal hypoglycemia than regimens that use NPH insulin in children/adolescents, as well as in adults.

American Academy of Pediatrics:
Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents (2013)[14]
	• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between types 1 and 2 diabetes mellitus is unclear and, in usual cases, should initiate insulin therapy for patients
	  o Who have random venous or plasma blood glucose (BG) concentrations ≥250 mg/dL.
	  o Whose HbA_{1c} is >9%.
	• In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.
	• Monitoring of HbA_{1c} concentrations is recommended every three months and intensifying treatment is recommended if treatment goals for finger-stick BG

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	and HbA_{1c} concentrations are not being met.
	• Advise patients to monitor finger-stick BG concentrations in patients who:
	  o Are taking insulin or other medications with a risk of hypoglycemia; or
	  o Are initiating or changing their diabetes treatment regimen; or
	  o Have not met treatment goals; or
	  o Have intercurrent illnesses.
	• Incorporate the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.
	• Encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic "screen time" to less than two hours a day.

National Institute for Health and Care Excellence:
Type 1 diabetes in adults: diagnosis and management (2015)[15]
	<u>Blood glucose management</u>
	• Measure HbA_{1c} levels every three to six months in adults with type 1 diabetes.
	• Consider measuring HbA_{1c} levels more often in adults with type 1 diabetes if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA_{1c} level has risen unexpectedly above a previously sustained target.
	• Use methods to measure HbA1c that have been calibrated according to International Federation of Clinical Chemistry (IFCC) standardization.
	• Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimize the risk of long-term vascular complications.
	• Agree an individualized HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia.
	• Ensure that aiming for an HbA1c target is not accompanied by problematic hypoglycemia in adults with type 1 diabetes.
	• Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least 4 times a day, including before each meal and before bed.
	
	<u>Insulin therapy</u>
	• Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens.
	• Do not offer adults newly diagnosed with type 1 diabetes non-basal–bolus insulin regimens (that is, twice-daily mixed, basal only or bolus only).
	• Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes.
	• Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:
	  o An existing insulin regimen being used by the person that is achieving their agreed targets.
	  o Once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated.
	• Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes.
	• Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes.

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	• If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. • Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. • Consider a trial of a twice-daily analogue mixed insulin regimen if an adult using a twice-daily human mixed insulin regimen has hypoglycemia that affects their quality of life. • Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimizing their effective insulin dose. <u>Insulin delivery</u> • Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. • Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. • Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. • Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. • Check injection site condition at least annually and if new problems with blood glucose control occur.

National Institute for Health and Care Excellence:
Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015)[16]
	<u>Insulin therapy for children and young people with type 1 diabetes</u>
	• While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen:
	  o Multiple daily injection basal–bolus insulin regimens: injections of short-acting insulin or rapid-acting insulin analogue before meals, together with 1 or more separate daily injections of intermediate-acting insulin or long-acting insulin analogue.
	  o Continuous subcutaneous insulin infusion (insulin pump therapy): a programmable pump and insulin storage device that gives a regular or continuous amount of insulin (usually a rapid-acting insulin analogue or short-acting insulin) by a subcutaneous needle or cannula.
	  o One, two or three insulin injections per day: these are usually injections of short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin.
	• Take into account the personal and family circumstances of the child or young person with type 1 diabetes and discuss their personal preferences with them and their family members or carers (as appropriate) when choosing an insulin regimen.
	• Offer children and young people with type 1 diabetes multiple daily injection basal–bolus insulin regimens from diagnosis. If a multiple daily injection regimen is not appropriate for a child or young person with type 1 diabetes, consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.
	
	<u>Oral medicines for children and young people with type 1 diabetes</u>
	• Metformin in combination with insulin is suitable for use only within research studies because the effectiveness of this combined treatment in improving blood glucose control is uncertain.

Clinical Guideline	Recommendation(s)
	• Do not offer children and young people with type 1 diabetes acarbose or sulphonylureas (glibenclamide, gliclazide, glipizide, tolazamide or glyburide) in combination with insulin because they may increase the risk of hypoglycemia without improving blood glucose control. Management for children and young people with type 2 diabetes • At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this. • Offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.
American Diabetes Association: **Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association (2014)**[17]	Nutritional therapy • Individualized medical nutrition therapy is recommended for all people with type 1 diabetes as an effective component of the overall treatment plan. • Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. • If adults with type 1 diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). Discussion with a health care provider is advised to explore potential interactions with medications. Adults should be advised that alcohol can lower blood glucose levels and that driving after drinking alcohol is contraindicated. Physical activity and exercise • Exercise should be a standard recommendation as it is for individuals without diabetes; however, recommendations may need modifications due to the presence of macro- and microvascular diabetes complications. • Patients of all ages (or caregivers of children) should be educated about the prevention and management of hypoglycemia that may occur during or after exercise. • Patients should be advised about safe preexercise blood glucose levels (typically 100 mg/dL or higher depending on the individual and type of physical activity). • Reducing the prandial insulin dose for the meal/snack preceding exercise and/or increasing food intake can be used to help raise the preexercise blood glucose level and reduce hypoglycemia. • A reduction in overnight basal insulin the night following exercise may reduce the risk for delayed exercise-induced hypoglycemia. • Self-monitoring of blood glucose should be performed as frequently as needed, and sources of simple carbohydrate should be readily available to prevent and treat hypoglycemia. Glycemic control goals • The American Diabetes Association strongly believes that blood glucose and HbA_{1c} targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia and maintaining normal growth and development. • An HbA_{1c} goal of <7.5% is recommended across all pediatric age-groups. • A reasonable HbA_{1c} goal for many nonpregnant adults with type 1 diabetes is <7%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for select individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. • Less stringent HbA_{1c} goals (such as <8.5%) may be appropriate for patients with

Clinical Guideline	Recommendation(s)
	a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced microvascular/ macrovascular complications, or extensive comorbid conditions. Insulin therapy • Most individuals with type 1 diabetes should be treated with multiple daily insulin injections (three or more injections per day of prandial insulin and one to two injections of basal insulin) or continuous subcutaneous insulin infusion. • Most individuals should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. • Most individuals should use insulin analogs to reduce hypoglycemia risk. • All individuals with type 1 diabetes should be taught how to manage blood glucose levels under varying circumstances, such as when ill or receiving glucocorticoids or for those on pumps, when pump problems arise. • Child caregivers and school personnel should be taught how to administer insulin based on provider orders when a child cannot self-manage and is out of the care and control of his or her parent/guardian. Adjunctive therapies • Pramlintide may be considered for use as adjunctive therapy to prandial insulin in adults with type 1 diabetes failing to achieve glycemic goals. • Evidence suggests that adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/ obese patients and poorly controlled adolescents with type 1 diabetes, but evidence from larger longitudinal studies is required. • Current type 2 diabetes medications (GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) may be potential therapies for type 1 diabetic patients, but require large clinical trials before use in type 1 diabetic patients.

III. Indications

The Food and Drug Administration (FDA)-approved indications for inhaled human insulin 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 Inhaled Human Insulin[3]

Indication	Inhaled Human Insulin
Improve glycemic control in adult patients with diabetes mellitus	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of inhaled human insulin are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Inhaled Human Insulin [1]

Generic Name(s)	Onset (minutes)	Peak (minutes)	Duration (minutes)	Half-Life (minutes)	Mixing of Insulins
Inhaled human insulin	Not reported	12 to 15	160	28 to 39	Not applicable

V. Drug Interactions

Significant drug interactions with the insulins are listed in Table 5.[2] Inhaled human insulin (Afrezza®) has an additional drug interaction with bronchodilators and inhaled steroids. Albuterol increased the area under the curve of insulin by 25% in patients with asthma. Effect of fluticasone on insulin exposures following Afrezza® administration has not been evaluated in patients with asthma; however, no significant change in insulin exposure was observed in a study in healthy volunteers. Frequent glucose monitoring and dose reduction may be necessary for Afrezza® if it is co-administered with albuterol.[3]

Table 5. Significant Drug Interactions with the Insulins[2]

Generic Name(s)	Significance Level	Interaction	Mechanism
Insulin	2	β-Adrenergic blocking agents (β-blockers), nonselective	β-blockers may blunt the sympathetic mediated response to hypoglycemia and may mask hypoglycemic symptoms. Discontinue nonselective β-blocker therapy or switch to a β-blocker with selective activity if possible.
Insulin	2	Fenfluramine	Fenfluramine may potentiate the hypoglycemic effects of insulin. Monitor blood glucose concentrations and adjust dose of insulin as needed to avoid hypoglycemia.
Insulin	2	Monoamine oxidase inhibitors (MAOIs)	MAOIs may potentiate the hypoglycemic effects of insulin by stimulating insulin secretion and inhibiting gluconeogenesis. Monitor blood glucose concentrations and adjust the dose of insulin as needed.
Insulin	2	Salicylates	Salicylates increase basal insulin secretion and acute insulin response to a glucose load. The hypoglycemic effects of insulin may be potentiated. Monitor blood glucose concentrations and adjust the dose of insulin as needed.

Significance level 1 = major severity, significance level 2 = moderate severity

VI. Adverse Drug Events

Adverse events with the insulin products are rare and are similar among the various products, with the exception of inhaled human insulin (Afrezza®) having several additional adverse reactions due to its route of administration.[1-3] Hypoglycemia is the most common adverse event reported with insulin therapy. Inhaled human insulin (Afrezza®) has a rate of hypoglycemia similar to other insulin preparations. Unlike the injectable products, inhaled human insulin has several respiratory adverse events which include cough (27%), throat pain/irritation (5%) and bronchitis (2.5%). Additionally, patients treated with inhaled regular insulin had a greater decrease in forced expiratory volume in one second (FEV_1) by 40 mL (95% CI, -80 to -1) compared to patients treated with other antidiabetic treatments in a clinical trial. The decline occurred during the first three months of therapy and persisted over two years. A ≥15% decline in FEV_1 occurred in 6% of patients treated with inhaled regular insulin compared to 3% of comparator-treated subjects.[3] The boxed warning for Afrezza® is summarized in Table 7. Due to these risks, a Risk Evaluation and Mitigation Strategy is required by the FDA for the use of Afrezza®.[3]

Table 6. Boxed Warning for Afrezza®

WARNING
WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE • Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza®. • Afrezza® is contraindicated in patients with chronic lung disease such as asthma or COPD. • Before initiating Afrezza®, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients.

VII. Dosing and Administration

The usual dosing regimens for inhaled human insulin are listed in Table 7.

Table 7. Usual Dosing Regimens for Inhaled Human Insulin[3]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Inhaled human insulin	To improve glycemic control in diabetes mellitus: Inhalation: Initial (insulin-naïve), 4 units with each meal; dose must be individualized based on response or conversion from other formulations; for doses greater than 8 units, multiple cartridges will be needed	Inhalation: Safety and efficacy have not been established in pediatric patients.	Inhalation powder (Afrezza®): 4 units/cartridge 8 units/cartridge 12 units/cartridge

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of inhaled human insulin are summarized in Table 8.

Table 8. Comparative Clinical Trials with Inhaled Human Insulin (Afrezza®)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tack et al.[18] (2008) Technosphere® Inhaled Insulin (TI) at four different doses (equivalent to 3.6, 7.3, 10.9, and 14.6 U subcutaneous regular human insulin) vs Technosphere® Powder Placebo All patients received basal insulin glargine	DB, MC, PC, PRO Adult patients aged 18 to 80 years with type 2 diabetes mellitus poor glycemic control (HbA_{1c} between 7 and 12%) with a minimum of 2 months of treatment with a stable dose of ≥1 antihyperglycemic agent and/or basal insulin glargine therapy	N=227 11 weeks	Primary: Change in HbA_{1c} of each randomized dose from baseline Secondary: PPG, safety	Primary: Mean reductions in HbA_{1c} from baseline were statistically significant for all treatment groups and increased with increasing TI doses. The greatest reduction from Technosphere powder alone was seen in the TI 14.6 U-equivalent group (0.78%). Secondary: TI treatment significantly reduced PPG excursions after a mixed meal. Over the 11-week treatment period, dose-dependent and statistically significant mean reductions from baseline were seen in postprandial $AUC_{glucose}$ at 0 to 300 minutes for the 7.3, 10.9, and 14.6 U-equivalent groups ($P \leq 0.001$ for these groups). Patients randomized to the highest TI doses experienced more hypoglycemic events than those randomized to Technosphere powder alone or to the lowest two TI doses. Cough was reported by 10 subjects in the Technosphere powder alone group and by 4 to 12 subjects in the TI groups. Changes in pulmonary function parameters (FVC, FEV_1, and DL_{CO}) were minimal during the study period.
Rosenstock et al.[19] (2008) Technosphere® Inhaled Insulin vs Technosphere® Powder Placebo	DB, MC, PC, PG, RCT Insulin-naive patients (aged 18 to 80 years with diabetes duration of 2 to 12 years), treated with at least one OAD, were on a stable regimen for at	N=126 12 weeks	Primary: Change in HbA_{1c} from baseline to study end Secondary: PPG concentrations after the meal at baseline and after 4, 8, and 12 weeks	Primary: After 12 weeks of treatment, mean HbA_{1c} decreased by −0.7% with Technosphere insulin and by −0.3% with Technosphere powder (P=0.003) from baselines of 8.0 and 7.8%, respectively. Secondary: Postprandial glucose excursions were reduced by 56% with Technosphere insulin compared with baseline, and maximal postprandial glucose levels were reduced by 43% compared with Technosphere powder. Incidences of hypoglycemia and hyperglycemia were similar for both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Each group in addition to oral antidiabetic (OAD) agents	least three months before enrollment		of treatment, safety	groups, with no significant between-group differences (P=0.321 and P=0.871, respectively). Coughing episodes were similar in both groups. Pulmonary function outcomes were not considered clinically relevant.
Rosenstock et al.[20] (2010) Prandial Technosphere inhaled insulin powder plus bedtime insulin glargine vs twice daily premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin).	OL, PG, RCT Adult patients aged 18 to 80 years with type 2 diabetes mellitus poor glycemic control (HbA_{1c} between 7 and 11%) despite insulin therapy, with or without oral antidiabetes drugs	N=677 52 weeks	Primary: Change in HbA_{1c} from baseline to study end Secondary: Change from baseline in plasma glucose concentrations, proportion of patients achieving HbA_{1c} ≤7%, change in FPG, weight, safety	Primary: Mean changes in HbA_{1c} from baseline to week 52 were similar across all analysis populations with all upper 95% CIs <0.4, showing that inhaled insulin is non-inferior to biaspart insulin. Secondary: Mean fasting plasma glucose values at week 52 were 7.8 mmol/L for inhaled insulin plus insulin glargine and 8.7 mmol/L for biaspart insulin. The between-group difference was −1.0 mmol/L (SD 0.3, 95% CI −1.6 to −0.3, P=0.0029. The proportion of patients with HbA_{1c} of 7.0% or less at week 52 was similar between patients on inhaled insulin and insulin glargine (22%) and those on biaspart insulin (27%, P=0.2793). Mean weight gain was significantly lower with inhaled insulin plus insulin glargine 0.9 kg (SD 0.3, 95% CI 0.3 to 1.5) than with biaspart insulin 2.5 kg (0.3, 1.9 to 3.0), with a treatment difference of −1.6 kg (SD 0.4, 95% CI −2.4 to −0.7, P=0.0002). In the safety population, adverse events occurred in 272 patients (84%) on inhaled insulin plus insulin glargine and 296 (89%) of those on biaspart insulin, with hypoglycemia being the most frequent adverse event, occurring in 31% of inhaled insulin patients and 49% of biaspart insulin patients. 103 patients (32%) treated with inhaled insulin plus insulin glargine reported cough compared with 14 (4%) receiving biaspart insulin.
Raskin et al.[21] (2012) Prandial inhaled Technosphere Insulin (TI) vs	MC, OL, RCT Patients aged 18 to 80 years, with type 1 or type 2 diabetes for at least 2 years and HbA_{1c} ≥6.6% and ≤12.0%	N=1699 2 years	Primary: Change from baseline in pre-bronchodilator FEV_1 at month 24 between the diabetes treatment groups	Primary: Over 2 years, small declines from baseline in FEV_1 were observed in all groups, with the smallest change in those without diabetes. The adjusted mean treatment group difference in change in FEV_1 from baseline to month 24 was 0.037 (0.0119) l (95% CI, 0.014 to 0.060). The upper limit of the 95% CI for the treatment group difference in FEV_1 change at month 24 was less than the pre-specified non-inferiority margin of 100 mL (50 mL/year), demonstrating non-inferiority with TI over usual care.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
standard antidiabetes treatment (usual care) Control group of non-diabetic patients also included with no intervention			Secondary: Treatment group difference in the incidence of FEV_1 findings (≥15% decline) and change from baseline in FVC, TLC, DL_{CO} and HbA_{1c}	Secondary: At month 24, the adjusted treatment group difference in mean FVC was small [0.034 l (standard error of the mean 0.0135)]. TLC and DL_{CO} treatment group differences were not statistically significant. In all, 42 of 730 (5.75%) patients receiving TI and 27 of 824 (3.28%) receiving usual care had protocol-predefined FEV_1 findings (≥15% decrease from baseline) at last measurement. Treatment group difference (usual care—TI) in the percentage of patients with FEV_1 decline of ≥15% from baseline was −2.48% (95% CI, −4.5578 to 0.3956). Lower bound of 95% CI did not exceed −5%, thereby demonstrating that TI was non-inferior to usual care. Mean (standard deviation) change in HbA_{1c} from baseline to month 24 was comparable between treatment groups. More treatment-emergent adverse events (TEAE) were reported in patients receiving TI (n=729 [79.0%]) than in patients receiving usual care (n=674 [71.0%]; The most common TEAE in both treatment groups was hypoglycemia. Cough, the second most common TEAE, was more frequent with TI than with usual care.

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, OL=open label, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous: BMI=body mass index, DL_{CO}= capacity for carbon monoxide, eGFR= estimated glomerular filtration rate, FEV_1= forced expiratory volume in one second, FPG=fasting plasma glucose, FVC=forced vital capacity, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, PPG=postprandial glucose, SBP=systolic blood pressure, T2DM=type 2 diabetes mellitus, TLC=total lung capacity

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 Empagliflozin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Insulin regular, human	Inhalation powder	Afrezza®	$$$$$	N/A

N/A=Not available

X. Conclusions

Inhaled human insulin (Afrezza®) is approved to improve glycemic control in adult patients with diabetes mellitus.[3] There are currently no generic products available.

According to current clinical guidelines regarding the management of type 1 diabetes, initiation of individualized, intensive insulin therapy at the time of diagnosis is recommended. Furthermore, overall approaches for management include the use of multiple dose injections or a subcutaneous insulin infusion, and matching of pre-prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. According to the American Diabetes Association, insulin analogs should be utilized in most patients. In addition, use of a continuous subcutaneous insulin infusion is indicated in certain clinical settings, particularly when glycemic control is difficult to achieve, during pregnancy, or when the patient does not demonstrate a willingness to comply with a multiple injection regimen. As mentioned previously, insulin regimens should be tailored to the specific clinical circumstances in individual patients, and patients should have access to the types (preparation and species) of insulin therapy they find allow them optimal well-being. In general, pre-prandial rapid-acting insulin analogs

should be administered 20 to 30 minutes prior to a meal. Some patients treated with basal, or long-acting, insulin may require twice-daily dosing to achieve greater control. In general, no one specific insulin product among the various classifications is recommended or preferred over another. Again, insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control in patients with type 1 diabetes. Insulin therapy may also be appropriate in the management of type 2 diabetes; however, traditionally oral antidiabetic agents are utilized. Of note, many patients with type 2 diabetes will ultimately require insulin therapy, alone or in combination with other agents, to maintain glucose control. Insulin is recognized as a potential option to be added to current oral antidiabetic agent regimens in patients not achieving glycemic goals. It may also be appropriate to initiate insulin therapy at the time of diagnosis in certain clinical settings, particularly in patients with a high baseline glycosylated hemoglobin (HbA_{1c}) (≥9.0%), or in patients presenting with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c}. Furthermore, such therapy is mandatory when catabolic features are exhibited or if ketonuria is demonstrated. The role of inhaled human insulin (Afrezza®) is not presently addressed in the guidelines.[4-17]

At this time, there is insufficient data to conclude that inhaled human insulin (Afrezza®) is safer or more efficacious than other brand or generic products within this class, and that it offers a significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand inhaled human insulin 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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review of Jardiance®
Sodium-Glucose Cotransporter 2 Inhibitor: AHFS Class 682018
November 4, 2015

I. Overview

Sodium-glucose cotransport 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents recently approved by the Food and Drug Association (FDA). The kidneys play a pivotal role in controlling plasma glucose concentration, reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is reabsorbed in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2]

SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, including weight loss and small decreases in systolic and diastolic blood pressure as observed during clinical trials.[1-4] Empagliflozin (Jardiance®) is a once daily tablet indicated an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[5]

The empagliflozin products included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available.

Table 1. Empagliflozin Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Empagliflozin	tablet	Jardiance®	none

PDL=Preferred Drug List

II. Evidence- Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 2. Treatment Guidelines Using the Sodium-glucose Cotransport 2 Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association: **Standards of Medical Care in Diabetes (2015)**[6]	<u>Current criteria for the diagnosis of diabetes</u> • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <u>Prevention/delay of type 2 diabetes</u> • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity should

Clinical Guideline	Recommendation(s)

	be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%.
	• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.7%, especially for those with a body mass index >35 kg/m^2, age <60 years, and women with prior gestational diabetes mellitus.
	
	<u>Glycemic goals in adults</u>
	• Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%.
	• It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.
	• Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.
	
	<u>Pharmacologic and overall approaches to treatment-type 1 diabetes</u>
	• Recommended therapy consists of the following components:
	  o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy.
	  o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity.
	  o Most patients should use of insulin analogs to reduce hypoglycemia risk.
	
	<u>Pharmacologic and overall approaches to treatment-type 2 diabetes</u>
	• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.
	• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset.
	• A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences.
	• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin.
	• Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-**	<u>Key points</u> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug.

Clinical Guideline	Recommendation(s)
Centered Approach (2012)[7]	• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <u>Initial drug therapy</u> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a glucagon-like peptide (GLP)-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <u>Advancing to dual combination therapy</u> • If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. • On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. • If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. • Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. • It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. • For all medications, consideration should also be given to overall tolerability.

Clinical Guideline	Recommendation(s)
	Advancing to triple combination therapy • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. • Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. • In using triple combinations the essential consideration is to use agents with complementary mechanisms of action. • Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations

Initial Drug Monotherapy	Metformin				
Efficacy (↓HbA_{1c})	High				
Hypoglycemia	Low risk				
Weight	Neutral/loss				
Side Effects	Gastrointestinal/lactic acidosis				
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)					
Two Drug Combin-ations	Metformin + sulfonyl-urea	Metformin + thia-zolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
Efficacy (↓HbA_{1c})	High	High	Inter-mediate	High	Highest
Hypo-glycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major Side Effects	Hypo-glycemia	Edema, heart failure, bone fracture	Rare	Gastro-intestinal	Hypo-glycemia
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)					
Three Drug Combin-ations	Metformin + sulfonyl-urea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +
	TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, TZD, or insulin	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, or GLP-1 receptor agonist
If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents					
More Complex Insulin Strategies	Insulin (multiple daily doses)				

American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-**	This article should be read as an addendum to the previous full account, summarized above. Sodium–Glucose Cotransporter 2 Inhibitors • These agents reduce HbA_{1c} by 0.5 to 1.0% (5.5 to 11 mmol/mol) versus placebo • Advantages include: action independent of insulin allowing use even after

Clinical Guideline	Recommendation(s)
Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes (2015)[8]	insulin secretion has waned, modest weight loss (about 2 kg, stabilizing over 6 to 12 months), lowering of blood pressure by about 2 to 4/ 1 to 2 mmHg. • Side effects include genital mycotic infections, at rates of about 11% higher in women and about 4% higher in men compared with placebo, diuretic effect, increased urine calcium excretion, increase in LDL cholesterol (about 5%), and renal function restrictions. <u>Thiazolidinediones</u> • Earlier concerns with risk of bladder cancer have been allayed by subsequent evidence. Dipeptidyl Peptidase 4 Inhibitors • There is mixed evidence for DPP-4 inhibitors and cardiovascular risk or benefit. Until further trials are completed these agents should be used cautiously, if at all, in patients with preexisting heart failure. <u>Initial drug therapy</u> • Metformin remains the optimal drug for monotherapy. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.
American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[9]**	• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. • Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)[10]**	<u>Management of prediabetes</u> • Lifestyle modifications, including initial attempts to lose 5 to 10% of body weight if overweight or obese and participate in moderate physical activity (e.g., walking) at least 150 minutes per week should be initiated. • Medications including metformin, acarbose, or thiazolidinediones (TZDs) should be considered for patients who are at moderate-to-high risk for developing diabetes mellitus, such as those with a first-degree relative with diabetes. <u>Antihyperglycemic pharmacotherapy for type 2 diabetes</u> • Pharmacotherapy should be prescribed based on sustainability for the individual patient. • Initiate with metformin, a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose cotransporter 2 (SGLT2) inhibitor, or an α-glucosidase inhibitor for patients with an entry A1C <7.5%. • A TZD, sulfonylurea, or glinide may be considered as alternative therapies but should be used with caution due to side-effect profiles. • For patients with entry A1C levels >7.5%, initiate treatment with metformin (unless contraindicated) plus a second agent, with preference given to agents with a low potential for hypoglycemia that are weight neutral or associated with weight loss. This includes GLP-1 receptor agonists, SGLT2 inhibitors, or

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	DPP-4 inhibitors as the preferred second agents.
	• Colesevelam, bromocriptine, or an α-glucosidase inhibitor have limited glucose-lowering potential but also carry a low risk of adverse effects and may be useful for glycemic control in some situations.
	• Sulfonylureas and glinides are considered the least desirable alternatives due to the risk of hypoglycemia.
	• For patients with an entry A1C >9.0% who have symptoms of hyperglycemia, insulin therapy alone or in combination with metformin or other oral agents is recommended.
	• Insulin should be considered for T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
	• Therapy with long-acting basal insulin should be the initial choice in most cases. The insulin analogs glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because analog insulins are associated with less hypoglycemia.
	• When control of postprandial hyperglycemia is needed, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or inhaled insulin) over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia.
	
	<u>Management of type 1 diabetes</u>
	• Insulin must be used to treat type 1 diabetes. Physiologic insulin regimens, which provide both basal and prandial insulin, should be used. Approaches include:
	  • Multiple daily injections (MDI), which usually involve 1 to 2 subcutaneous injections daily of basal insulin to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or inhaled insulin before each meal to control meal-related glycemia.
	  • Continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia.

American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[11]	<u>Principles underlying the algorithm</u> • Lifestyle optimization is essential for all patients with diabetes; however, it should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn insulin

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	because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk.
	
	<u>Monotherapy</u>
	• Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} <7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients.
	• In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include:
	  o GLP-1 receptor agonists.
	  o DPP-4 inhibitors.
	  o Alpha-glucosidase inhibitors.
	  o Sodium glucose cotransporter 2 (SGLT-2) inhibitors.
	• TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia.
	
	<u>Combination therapy</u>
	• Patients who present with an initial HbA_{1c} >7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin.
	• Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy.
	• In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used.
	• Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus:
	  o GLP-1 receptor agonists.
	  o DPP-4 inhibitors.
	  o TZD.
	  o SGLT-2 inhibitors.
	  o Basal insulin.
	  o Colesevelam.
	  o Bromocriptine quick release.
	  o Alpha-glucosidase inhibitors.
	  o Sulfonylureas and glinides.
	
	<u>Three-drug combination therapy</u>
	• Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent.
	• Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy.
	• Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent.
	• Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered.
	• Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin.

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	• Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus:
	  o GLP-1 receptor agonists.
	  o TZD.
	  o SGLT-2 inhibitors.
	  o Basal insulin.
	  o DPP-4 inhibitors.
	  o Colesevelam.
	  o Bromocriptine quick release.
	  o Alpha-glucosidase inhibitors.
	  o Sulfonylureas and glinides
	
	<u>Insulin therapy algorithm</u>
	• Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents.
	• Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss.
	• Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy.
	• Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs.
	
	<u>Basal insulin</u>
	• Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen.
	• Titrate insulin dose every two to three days to reach glycemic goals.
	• Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection.
	• Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia.
	
	<u>Basal-bolus insulin regimens</u>
	• Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin.
	• A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content.
	• Doses of insulin may be titrated every two to three days to reach glycemic goals.
	
	<u>Basal insulin and incretin therapy regimens</u>
	• Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes.
	• The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and

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	postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.

National Institute for Health and Care Excellence: **The Management of Type 2 Diabetes (Issued 2009, last modified July 2014)**[12]	Metformin
	• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.
	• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.
	• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.
	• Step up metformin therapy gradually over weeks to minimize risk of gastrointestinal (GI) side effects. Consider a trial of extended release metformin if GI tolerability prevents continuation of therapy.
	
	Insulin secretagogues
	• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or it is contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.
	• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.
	• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.
	• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.
	
	Rapid-acting insulin secretagogues
	• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.
	
	Acarbose
	• Consider acarbose for a patient unable to use other oral glucose-lowering medications.
	
	DPP-4 inhibitors
	• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA_{1c} ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA_{1c} ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.
	• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%) and insulin is unacceptable or inappropriate.
	• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA_{1c} in 6 months).
	• A DPP-4 inhibitor may be preferable to a thiazolidinedione (TZD) if:
	  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.
	  o A thiazolidinedione is contraindicated.
	  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.
	There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.

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	TZDs
	• Consider adding a TZD to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (HbA_{1c} ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a TZD to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (HbA_{1c} ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.
	• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥7.5%) and insulin is unacceptable or inappropriate.
	• Do not use a TZD is people who have heart failure, or who are at higher risk of fracture.
	• Only continue TZD therapy if the person has had a beneficial metabolic response (≥0.5% reduction in HbA_{1c} in 6 months).
	• Consider combining TZD with insulin therapy for a person who previously had a marked glucose-lowering response to TZD therapy or who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.
	• A TZD may be preferable to a DPP-4 inhibitor if:
	  o The person has marked insulin insensitivity.
	  o A DPP-4 inhibitor is contraindicated.
	  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.
	There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.
	
	Gliptins: GLP-1 enhancers
	• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.
	
	GLP-1 mimetics
	• 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 (HbA_{1c} ≥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).
	  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 HbA_{1c} and weight loss ≥3% of initial body weight at six months).
	
	Insulin therapy
	• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.
	• When starting basal insulin therapy:
	  o Continue with metformin and the sulfonylurea (and acarbose, if used).
	  o Review the use of the sulfonylurea if hypoglycemia occurs.
	• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):
	  o Continue with metformin.
	  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs.

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	• Begin with human NPH insulin injected at bedtime or twice daily according to need. • Consider using a long-acting insulin analogue if: o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily. o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes. o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs. o The person cannot use the device to inject NPH insulin. • Consider twice-daily pre-mixed (biphasic) human insulin (particularly if HbA_{1c} ≥9.0%). A once-daily regimen may be an option. • Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if: o A person prefers injecting insulin immediately before a meal. o Hypoglycemia is a problem. o Blood glucose levels rise markedly after meals. • Consider switching to a long-acting insulin analogue from NPH insulin in people: o Who do not reach their target HbA_{1c} because of significant hypoglycemia. o Who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA_{1c} reached. o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made. o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. • Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).
Institute for Clinical Systems Improvement: **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults (2014)**[13]	• Personalize goals to achieve glycemic control with a hemoglobin HbA_{1c} in the range of <7 or 8% based on the risks and benefits of each patient. A goal of <8% may be more appropriate when: o Known cardiovascular disease or high cardiovascular risk, may be determined by the Framingham or ACC/AHA Cardiovascular Risk Calculator, or alternatively as having two or more cardiovascular risks (BMI >30, hypertension, dyslipidemia, smoking, and microalbuminuria). o Inability to recognize and treat hypoglycemia, including a history of severe hypoglycemia requiring assistance. o Inability to comply with standard goals, such as polypharmacy issues. o Limited life expectancy or estimated survival of less than 10 years. o Cognitive impairment. o Extensive comorbid conditions such as renal failure, liver failure, and end-stage disease complications. • A multifactorial approach to diabetes care that includes emphasis on blood pressure, lipids, glucose, aspirin use, and non-use of tobacco will maximize health outcomes far more than a strategy that is limited to just one or two of these clinical domains. • Recommend education and self-management, as appropriate. • Initiate metformin as first-line pharmacotherapy for patients with type 2

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	diabetes, unless medically inappropriate. o Metformin may reduce HbA_{1c} by 1 to 1.5%, rarely causes hypoglycemia when used as monotherapy and does not cause weight gain. o Metformin can also be used in combination with all other glucose-lowering agents. • Improved microvascular and macrovascular outcomes have been demonstrated in large clinical trials.
International Diabetes Federation Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes (2012)**[14]	<u>Lifestyle management</u> • Changing patterns of eating and physical activity can be effective in controlling many of the adverse risk factors found in type 2 diabetes. • Match the timing of medication (including insulin) and meals. • Reduce energy intake and control of foods with high amounts of added sugars, fats, or alcohol. • Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals. • Encourage increased duration and frequency of physical activity (where needed), up to 30 to 45 minutes on three to five days per week, or an accumulation of 150 minutes per week of moderate-intensity aerobic activity (50 to 70% of maximum heart rate). In the absence of contraindications, encourage resistance training three times per week. • Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity. <u>Glucose control levels</u> • Maintaining HbA_{1c} below 7% minimizes the risk of developing complications. • A lower HbA_{1c} target may be considered if it is easily and safely achieved. • A higher HbA_{1c} target may be considered for people with comorbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia. <u>Oral therapy</u> • Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Maintain support for lifestyle measures throughout the use of these medications. • Consider each initiation or dose increase of an oral glucose lowering medication as a trial, monitoring response in three months. • First-line therapy o Begin with metformin unless there is evidence of renal impairment or other contraindication. o Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance. Monitor renal function and use metformin with caution if estimated glomerular filtration rate <45 $mL/min/1.73m^2$. o Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or α-glucosidase inhibitors in some populations; these agents can also be used initially where metformin cannot. o In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets. • Second-line therapy o When glucose control targets are not achieved, add a sulfonylurea. o Other options include adding metformin if not used first-line, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a

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	thiazolidinedione (TZD). A rapid-acting insulin secretagogue is an alternative option to sulfonylureas.
	• Third-line therapy
	  o When glucose control targets are no longer being achieved, start insulin or add a third oral agent.
	  o If starting insulin, add basal insulin or use premix insulin.
	  o If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD.
	  o Another option is to add a glucagon-like peptide-1 (GLP-1) agonist.
	• Fourth-line therapy
	  o Begin insulin therapy when optimized oral blood glucose lowering mediations (and/or GLP-1 agonist) and lifestyle interventions are unable to maintain target glucose control.
	
	<u>Insulin therapy</u>
	• Do not unduly delay the commencement of insulin. Maintain lifestyle measures. Consider every initiation or dose increase of insulin as a trial, monitoring the response.
	• Provide education and appropriate self-monitoring.
	• Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30 to 100 units/day.
	• Continue metformin. Other oral agents may also be continued.
	• Begin with a basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir, or once or twice daily premix insulin (biphasic insulin).
	• Initiate insulin using a self-titration regimen (dose increases of two units every three days) or with biweekly or more frequent contact with a health-care professional.
	• Aim for pre-meal glucose levels of <6.5 mmol/L (<115 mg/dL).
	• Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.

III. Indications

The Food and Drug Administration (FDA)-approved indications for empagliflozin 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 Empagliflozin[5]

Indication	Empagliflozin
Type 2 diabetes mellitus, an adjunct to diet and exercise to improve glycemic control	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of empagliflozin are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Sodium-glucose Cotransport 2 Inhibitors[3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Empagliflozin	Not reported	86	Glucuronidation	Urine (54) Feces (41)	12.4

V. Drug Interactions

There are no significant drug interactions reported with empagliflozin.[4] Coadministration of empagliflozin with diuretics may result in increased urine volume and frequency of voids, which can increase the risk of volume depletion.[5]

VI. Adverse Drug Events

The most common adverse drug events reported with empagliflozin are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Empagliflozin[4]

Adverse Event	Empagliflozin
Gastrointestinal	
Nausea	2
Genitourinary	
Genitourinary fungal infection	5 to 6 (female)† 2 to 3 (male)‡
Increased urination§	3
Urinary tract infection	18 (females) 4 (males)
Endocrine and metabolic	
Dyslipidemia	4
Hypovolemia	✔
Increased LDL cholesterol	5 to 7
Renal	
Decreased estimated GFR	✔
Increased serum creatinine	✔
Other	
Hypotension	✔
Increased hematocrit	3 to 4
Thirst	✔

†Including bacterial vaginosis, cervicitis, vulvitis, vulvovaginal candidiasis, vulvovaginal infection, vulvovaginitis.
‡Including balanitis, balanoposthitis, genitourinary fungal infection, penile infection, scrotal abscess.
§Including polyuria, pollakiuria, nocturia.
-Incidence not reported or <1%.
✔ Incidence not specified.

VII. Dosing and Administration

The usual dosing regimens for empagliflozin are listed in Table 6.

Table 6. Usual Dosing Regimens for Empagliflozin[5]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Empagliflozin	Type 2 diabetes mellitus, as an adjunct to diet and exercise to improve glycemic control: Tablet: initial, 10 mg once daily in the morning; in patients tolerating empagliflozin who require additional glycemic control, the dose can be increased to 25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 10 mg 25 mg

VIII. Effectiveness

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

Table 7. Comparative Clinical Trials with Empagliflozin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
Roden et al.[15] (2013) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%	N=986 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons) . In the active comparator analysis, adjusted mean differences in change from baseline HbA_{1c} at week 24 was -0.73% (-0.88 to -0.59; P<0.0001) for sitagliptin compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo. SBP was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. There were 140 (61%) patients in the placebo group that reported adverse events (four [2%] severe and six [3%] serious), as did 123 (55%) patients in the empagliflozin 10 mg group (eight [4%] severe and eight [4%] serious), 135 (60%) patients in the empagliflozin 25 mg group (seven [3%] severe and five [2%] serious), and 119 (53%) patients in the sitagliptin group (five [2%] severe and six [3%] serious).
Barnett et al.[16] (2014) Empagliflozin 10 mg QD	DB, MC, PC, PG, RCT Patients with type 2 DM, HbA_{1c} of ≥7%	N=738; 290 with mild renal impairment [eGFR ≥60 to	Primary: HbA_{1c} Secondary: FPG, body weight,	Primary: At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA_{1c} relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs. empagliflozin 25 mg QD vs placebo Patients with Stage III chronic kidney disease (eGFR ≥ <60 mL/min/1.73 m2] were only assigned to the empagliflozin 25 mg QD arm.	to <10%, BMI ≤45 kg/m^2 and a baseline eGFR <90 mL/min/1.73 m^2	<90 mL/min/1.73 m^2], 374 with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2], and 74 with severe renal impairment [eGFR <30 mL/min/1.73 m^2]). 52 weeks	SBP and safety evaluations	function in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA_{1c} and FPG showed no discernible treatment effect compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG in the mild renal impairment group (-13.86 mg/dL and –18 mg/dL vs. 5.58 mg/dL, respectively; P<0.0001) and moderate renal impairment group (-9 mg/dL vs. 10.8 mg/dL, respectively; P<0.0001). Significant body weight and SBP decreases were noted in most treatment comparisons. Adverse events included UTI and genital mycotic infections.
Type 2 Diabetes – Combination Therapy				
Häring et al.[17] (2014) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with	DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%,inade-quately controlled on ≥ 1,500 mg of metformin per day	N=637 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Confirmed hypoglycemic adverse events were reported in 0.5%, 1.8%, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin.				1.4% of patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1%, and 5.6% of patients, and events consistent with genital infections were reported in 0%, 3.7%, and 4.7% of patients, respectively.
Ridderstråle et al.[18] (2014) empagliflozin 25 mg QD vs glimepiride 1 to 4 mg QD Patients continued treatment with metformin.	AC, DB, MC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on metformin monotherapy	N=1,545 104 weeks	Primary: HbA_{1c} (tested for non-inferiority at week 52, tested for superiority at week 104) Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 52, empagliflozin 25 mg meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs -0.7%). Non-inferiority continued to be demonstrated at week 104. In addition, at week 104, adjusted mean difference in change from baseline in HbA1c with empagliflozin versus glimepiride was -0.11% (95% CI, -0.19 to -0.02; P=0.0153 for superiority). Secondary: At week 52, There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs 2 kg; P values not reported). SBP was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs. 2.2 mmHg; P<0.0001).[1,5] Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride.
Häring et al.[19] (2013) Empagliflozin 10 mg QD	DB, MC, PC, RCT Patients aged ≥18 years with type 2	N=666 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight,	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.8% and -0.8% vs. -0.2%, respectively; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs empagliflozin 25 mg QD vs placebo Patients continued treatment with metformin and sulfonylurea.	DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on ≥ 1,500 mg of metformin per day and a sulfonylurea		SBP and safety evaluations	Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. Decreases in SBP were also significantly greater with both empagliflozin doses than placebo. Adverse events were reported in 62.7, 67.9, and 64.1% of patients on placebo and empagliflozin 10 and 25 mg, respectively. Events consistent with urinary tract infection were reported in 8.0, 10.3, and 8.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 13.3, 18.0, and 17.5%, respectively; males: 2.7, 2.7, and 0%, respectively). Events consistent with genital infection were reported in 0.9, 2.7, and 2.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 0.9, 4.5, and 3.9%, respectively; males: 0.9% in each group).
Kovacs et al.[20] (2014) Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with pioglitazone with or without	DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day	N=498 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs. -0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-17 mg/dL and -22 mg/dL vs. 7 mg/dL, respectively; P<0.001) and body weight (-2.0 kg and -1.8 kg vs. -0.6 kg, respectively; P<0.001) compared with placebo. Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin.				treated with glimepiride. Similar proportions of patients reported adverse events with empagliflozin (67.3-71.4%) and placebo (72.7%). Confirmed hypoglycemia was reported by 1.2-2.4% of patients on empagliflozin and 1.8% on placebo.

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, OL=open label, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous: BMI=body mass index, eGFR= estimated glomerular filtration rate, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, PPG=postprandial glucose, SBP=systolic blood pressure, T2DM=type 2 diabetes mellitus

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 Empagliflozin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Empagliflozin	tablet	Jardiance®	$$$$$	N/A

N/A=Not available

X. Conclusions

Empagliflozin is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[5] There are currently no generic products available.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin (HbA_{1c}) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.[6-14] The role of SGLT2 inhibitors as a class are addressed in treatment guidelines and are recommended as a potential first, second, or third-line treatment option to be added as an alternative to or in combination with metformin in patients not achieving glycemic goals.[8,10,11] SGLT2 inhibitors are acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia.[11]

Empagliflozin is available as an oral once-daily tablet and has demonstrated to be significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}).[15-17,19,20] Limited trials have compared empagliflozin to other classes of oral antidiabetic agents: Studies thus far have demonstrated noninferiority to glimepiride.[18]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with empagliflozin or any other antidiabetic drug.[5]

There is insufficient evidence to support that one brand empagliflozin product 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 products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand empagliflozin 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

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