

Medications for Chronic Asthma

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ABSTRACT

Chronic asthma is a major health concern for children and adults worldwide. The goal of treatment is to prevent symptoms by reducing airway inflammation and hyperreactivity. Step-up therapy for symptom control involves initiation with low-dose treatment and increasing intensity at subsequent visits if control is not achieved. Step-down therapy starts with a high-dose regimen, reducing intensity as control is achieved. Multiple randomized controlled trials have shown that inhaled corticosteroids are the most effective monotherapy. Other agents may be added to inhaled corticosteroids if optimal symptom control is not initially attained. Long-acting beta₂ agonists are the most effective addition, but they are not recommended as monotherapy because of questions regarding their safety. Leukotriene receptor antagonists can be used in addition to inhaled corticosteroids, but they are not as effective as adding a long-acting beta₂ agonist. Patients with mild persistent asthma who prefer not to use inhaled corticosteroids may use leukotriene receptor antagonists as monotherapy, but they are less effective. Because of their high cost and a risk of anaphylaxis, monoclonal antibodies should be reserved for patients with severe symptoms not controlled by other agents. Immunotherapy should be considered in persons with asthma triggered by confirmed allergies if they are experiencing adverse effects with medication or have other comorbid allergic conditions. Many patients with asthma use complementary and alternative agents, most of which lack data regarding their safety or effectiveness.

Keywords: Chronic asthma, airway inflammation and hyperreactivity

Approximately 25.7 million persons in the United States, including 7 million children, had the diagnosis of asthma as of 2010.¹ It is reported that 4.1 million children experienced at least one asthma exacerbation in 2011.² Between 1995 and 2010, exacerbations accounted for one-third of all hospital admissions for children younger than 15 years.³ Asthma caused 3,345 U.S. deaths in 2011,⁴ and it accounts for \$50.1 billion annually in direct health care costs.⁵ The management of asthma involves care plans, chronic medications, and monitoring and self-care for acute exacerbations. Therapeutic agents used in the chronic management of asthma aim to prevent symptoms by controlling airway inflammation and hyperreactivity. This article reviews the currently available medications and complementary agents for chronic asthma management. A previous article in

American Family Physician discussed the management of acute exacerbations.⁶

ASSESSMENT

To provide appropriate long-term medication, physicians should assess asthma severity and symptom control at diagnosis and at each subsequent visit using one of several validated tools, such as the Asthma Control Test (<https://www.asthma.com/additional-resources/asthma-control-test.html>).⁷⁻⁹ The 2007 National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) recommends classifying disease severity based on level of impairment and risk of adverse events (Figure 1, eFigure A, and eFigure B).¹⁰ Once disease severity is determined, the physician must then decide on medication and self-care management options.

STEP-UP AND STEP-DOWN THERAPY

Two general approaches when choosing asthma medication regimens are step-up and step-down therapy (Figure 2, eFigure C, and eFigure D).¹⁰ Step-up therapy involves initiating treatment at a low dose and assessing symptom control at subsequent visits (every two to four weeks), increasing the intensity of therapy as needed if control is not initially achieved. Step-down

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therapy starts with patients receiving a high-dose regimen, the intensity of which is reduced as control is achieved. The latter approach could be preferred, for example, to obtain rapid control in a patient who has significant symptoms at the time of diagnosis. Steps 4 and 5 within the EPR-3 Stepwise Approaches, which recommend the use of a medium- or high-dose inhaled corticosteroid plus a long-acting beta₂ agonist (LABA), are common starting points in step-down therapy.

A small randomized trial found that patients with moderate persistent asthma who were started on a high-dose corticosteroid followed by the step-down approach experienced a more prompt improvement in respiratory function and asthma symptoms, as well as a lower maintenance dose of inhaled corticosteroids, compared with patients treated with a step-up approach.¹¹ The EPR-3 guidelines advise that treatment generally be maintained at a high-dose level with patients experiencing good symptom control for three months before stepping down in intensity; reliable patients with well-controlled asthma may be able to step down earlier. Physicians should monitor symptom control in the period after a step down in therapy because patients may have increased symptoms, particularly when an LABA is discontinued.¹²⁻¹⁴ Medications commonly used in these two approaches are listed in Table 1, with additional information on dosing and adverse effects for these drugs available in eTable A.

INHALED CORTICOSTEROIDS

Inhaled corticosteroids are the most effective long-term medication for asthma.^{10,15-18} They have been shown to reduce symptom severity, systemic steroid use, emergency department visits, hospitalizations, and deaths caused by asthma, and improve asthma control, quality of life, and objective measures of lung function.^{10,15-18} Adverse effects of inhaled corticosteroids are limited, with only a slight effect on linear growth of approximately 0.5 cm per year noted in children. The effect on linear growth lessens after the first year of medication use and seems to be independent of patient age or the type of corticosteroid, dose, or delivery mechanism. It is unclear if inhaled corticosteroid use has an impact on final adult height.¹⁹ Other adverse effects, such as dysphonia, are generally self-limited or may be improved by changing the delivery mechanism of the inhaled corticosteroid.²⁰ There are clinically significant differences in patient response to corticosteroids that are associated with age, race, and risk factors such as smoking. Black children and smokers have an increased risk of corticosteroid insensitivity.^{21,22} In general,

Table 1. Common Asthma Medications

Short-acting bronchodilators

Albuterol DPI
Albuterol HFA
Albuterol nebulized
Ipratropium/albuterol inhaled
Ipratropium/albuterol nebulized
Levalbuterol HFA
Levalbuterol nebulized

Inhaled corticosteroids

Beclomethasone HFA
Budesonide DPI
Budesonide nebulized
Ciclesonide HFA
Flunisolide HFA
Fluticasone furoate DPI
Fluticasone propionate DPI
Fluticasone propionate HFA
Mometasone DPI
Mometasone HFA

Long-acting beta₂ agonists

Budesonide/formoterol
Fluticasone/salmeterol DPI
Fluticasone/salmeterol HFA
Fluticasone/vilanterol

Leukotriene receptor antagonists

Montelukast
Zafirlukast

Leukotriene inhibitor

Zileuton

Methylxanthines

Theophylline

Cromolyn

Monoclonals

Omalizumab

DPI = Dry powder inhaler; HFA = Hydrofluoroalkane.

delivery mechanism and type of steroid have little impact on the clinical effectiveness of corticosteroids, with the notable exception of a spacer device, which can result in a 20% to 30% increase in the amount of medication that is deposited in the lungs.²³ Dosing of inhaled corticosteroids should be managed in a step-up or step-down fashion based on an assessment of symptom control and severity (Figure 2, eFigure C,

and eFigure D).¹⁰ Whereas abrupt cessation of inhaled corticosteroids predisposes patients to acute asthma exacerbations, changing the dosage of an inhaled corticosteroid does not increase exacerbation risk.^{24,25}

LONG-ACTING BETA₂ AGONISTS

LABAs are effective for the control of persistent asthma symptoms. They initially have an action of more than 12 to 24 hours. Available non-combination LABAs include salmeterol and formoterol. Duration of action decreases to less than five hours with chronic regular use of LABAs,¹⁰ excluding those that contain vilanterol which currently lack data regarding duration of action decrease. The addition of an LABA to inhaled corticosteroid therapy is superior to the addition of leukotriene receptor antagonists (LTRAs) to inhaled corticosteroids in reducing asthma exacerbations requiring oral corticosteroid use, as well as improving quality-of-life measures and the effects and frequency of rescue inhaler use.²⁶ Current evidence shows no clear difference in the risk of fatal adverse events between LABA monotherapy and combination therapy with inhaled corticosteroids. The risk of nonfatal adverse events is increased with salmeterol monotherapy, but it is not significantly increased with either formoterol monotherapy or combination therapy with inhaled corticosteroids and either LABA option.²⁷ Current recommendations discourage the use of LABA monotherapy for long-term control of asthma.¹⁰

COMBINATION THERAPY

The combination of an inhaled corticosteroid and an LABA is considered a preferred therapy by the EPR-3 for the control of moderate persistent asthma in children five to 11 years of age and those 12 years and older.¹⁰ Combination therapy offers the best prevention of severe asthma exacerbations.²⁸ A 2013 study confirmed the overall safety of combination inhaled corticosteroid and LABA therapy, especially compared with LABA monotherapy.²⁹ Combination therapy dosing should be managed in a step-up or step-down approach similar to the management of inhaled corticosteroid therapy. Slight differences in when to start combination therapy are noted between the EPR-3 and Global Initiative for Asthma (GINA) guidelines.^{10,30} For example, according to step 3 of the EPR-3 stepwise approach for patients 12 years and older, either a low-dose inhaled corticosteroid plus an LABA, or a medium-dose inhaled corticosteroid alone is appropriate (Figure 2).¹⁰ The GINA guidelines recommend a low-dose inhaled corticosteroid plus an LABA as the preferred selection in this age group, with a medium-dose inhaled corticosteroid considered the secondary option.

LEUKOTRIENE MODIFIERS

Leukotriene modifiers include LTRAs and leukotriene inhibitors, which both act as anti-inflammatory medications. LTRAs block leukotriene receptors, whereas leukotriene inhibitors block the production of 5-lipoxygenase. The two LTRAs licensed in the United States are montelukast and zafirlukast. LTRAs may be used as monotherapy for mild persistent asthma, but are considered second-line agents based on the EPR-3¹⁰ and GINA guidelines.³⁰ For mild to moderate asthma, the risk of exacerbation is approximately 50% less in patients prescribed an inhaled corticosteroid compared with those prescribed an LTRA.¹⁵ A 2014 Cochrane review found an LABA plus inhaled corticosteroid to be modestly superior to an LTRA plus inhaled corticosteroid in adults with inadequately controlled asthma.²⁶ LTRAs are best used to improve pulmonary function in patients with aspirin-sensitive asthma³¹ and to decrease symptoms in exercise-induced bronchospasm.^{32,33} They should also be considered in patients with mild persistent asthma who prefer not to use inhaled corticosteroids. Although LTRAs generally have few adverse effects, physicians should be aware of rare case reports of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), psychiatric symptoms, hypertriglyceridemia, angioedema, urticaria, and glomerulonephritis.³⁴

Leukotriene inhibitors, such as zileuton, are a more recent addition to the treatment of asthma. Limited data show some improvement in peak flows with zileuton compared with montelukast.³⁵ However, zileuton is extremely expensive and has not been shown to improve symptom scores.

METHYLYXANTHINES

Theophylline, the most commonly used methylxanthine in asthma patients, acts as a bronchodilator at high serum concentrations (10 to 20 mcg per L [56 to 111 µmol per L]), but has an anti-inflammatory effect at lower serum concentrations (5 to 10 mcg per L [28 to 56 µmol per L]).^{36,37} Theophylline administered with inhaled corticosteroids decreases exacerbations,³⁸ but it has similar effects to increasing the dosage of the inhaled corticosteroid.^{39,40} The EPR-3 specifies that theophylline is a nonpreferred alternative to inhaled corticosteroid.¹⁰ The GINA guidelines recommend a trial of increased dosage of inhaled corticosteroid before considering theophylline, unless steroid sparing is necessary, such as in patients with severe glaucoma or active tuberculosis infection.³⁰ Patients in developing

countries are more likely to use low-dose theophylline than inhaled corticosteroids because it is a cheaper option.^{39,40} Although theophylline is considered safer at lower serum concentrations, care of patients who use theophylline should be comanaged with an asthma subspecialist because of the narrow therapeutic range of this drug and the risk of death from an overdose.^{36,40} Theophylline is metabolized in the liver and is susceptible to drug-drug interactions through cytochrome P450 1A2 (Table 2).^{37,41}

CROMOLYN

Cromolyn decreases bronchospasm through an anti-inflammatory effect.⁴² A 2008 Cochrane review found insufficient evidence of benefit of cromolyn over

Table 2. Common Drug-Drug Interactions with Theophylline

Medication or substance	Approximate effect on serum levels of theophylline
Alcohol	30% increase
Ciprofloxacin	40% increase
Diltiazem	Increase or no effect
Erythromycin	35% increase
Oral contraceptives	30% increase
Phenytoin	40% decrease
Propranolol	100% increase
Verapamil	20% increase

Information from references 37 and 41.

Table 3. Select Complementary and Alternative Asthma Treatments

Name	Comments	Effectiveness for treatment
Black seed (<i>Nigella sativa</i>)	One small RCT showed improved pulmonary function testing and decreased symptoms compared with placebo. ⁵⁹ Effect on pulmonary function testing was less than with theophylline. ⁶⁰	Possibly effective
Butterbur	Traditionally used in Taiwan to treat asthma. Has anti-inflammatory properties. ⁶¹ A small non-randomized open trial showed 48% decrease in exacerbations, and 40% of patients were able to reduce their dosage of inhaled corticosteroids, but results potentially biased due to study design. Blinded RCT is needed to determine true benefit and adverse effects. ⁶²	Possibly effective
Caffeine	Improves airway function for up to four hours and may impact pulmonary function testing. No evidence that results have clinical or quality-of-life significance. ⁶³	Not effective
Fish oil (omega-3)	Theoretically acts to decrease inflammation. Studies of its effectiveness have inconsistent results and are poorly designed. A large, well-designed RCT is needed to determine if there is any benefit. ⁶⁴	Effectiveness unknown
Ginkgo	No clinical evidence available. Effect on asthma is theoretical via anti-inflammatory effect in an animal model. ⁶⁵ Increases metabolism of theophylline by four times via cytochrome P450 1A2. ⁶⁶	Effectiveness unknown
Homeopathy	A 2004 Cochrane review found no evidence of benefit, citing a lack of quality studies. ⁶⁷	Not effective
Magnesium	Associated with bronchodilatory and anti-inflammatory effects. Small, blinded RCT showed improved peak expiratory flow and quality of life and decreased bronchial activity with 340 mg of supplementation per day. Larger RCT is needed. ⁶⁸	Possibly effective
Pycnogenol	Small, blinded RCT showed improved peak expiratory flow and decreased use of rescue medication compared with placebo group. ⁶⁹ A 2012 Cochrane review concluded insufficient evidence is available. ⁷⁰ Larger RCT is needed.	Possibly effective
Soy	Small RCT showed no significant difference compared with placebo. ⁷¹	Not effective
Vitamins C and E	Associated with anti-inflammatory effects. A 2014 Cochrane review found insufficient evidence due to limited small studies and lack of clinically important end points. ⁷²	Effectiveness unknown
Vitamin D	Used to treat deficiency associated with severe asthma, ⁷³ however, an RCT showed vitamin D ₃ supplementation had no effect on exacerbation rate in vitamin D-deficient patients with asthma. ⁷⁴	Not effective

RCT = Randomized controlled trial.

Information from references 59 through 74.

placebo.⁴³ Because cromolyn is less effective and less cost-effective than an inhaled corticosteroid, its use should be limited to patients who cannot tolerate inhaled corticosteroids.⁴⁴ Cromolyn is beneficial for exercise-induced bronchospasm but is considered second-line therapy.^{44,45}

MONOCLONAL ANTIBODIES

Omalizumab is currently the only monoclonal anti-immunoglobulin E (IgE) antibody with a U.S. Food and Drug Administration indication for asthma.⁴⁶ It binds the free IgE antibodies, decreasing the release of inflammatory mediators from mast cells. In a randomized trial, omalizumab reduced the rate of exacerbations in inner-city children from 48.8% to 30.3%, resulting in decreased reliance on an inhaled corticosteroid.⁴⁷ A 2014 Cochrane review found omalizumab effective in reducing exacerbations, decreasing the dosage of inhaled corticosteroid used, and improving health-related quality of life.⁴⁸ Because of its high cost and the risk of anaphylaxis, omalizumab should be considered only for adults and children 12 years and older with confirmed IgE-dependent allergic asthma that is uncontrolled with conventional medications.^{49,50}

IMMUNOTHERAPY

Subcutaneous and sublingual immunotherapies involve repeated patient exposure to antigens to desensitize the patient to the antigen. Immunotherapy

is effective in reducing exacerbations, need for medication use, and overall cost of care in patients with allergic asthma.⁵¹⁻⁵³

A 2010 Cochrane review found a number needed to treat of 4 to avoid one deterioration in asthma symptoms, but it could not determine the size of effect compared with other therapies.⁵⁴ Immunotherapy should be considered in patients with asthma triggered by confirmed allergies who are experiencing adverse effects from medication or have other comorbid allergic conditions.

ALTERNATIVE TREATMENTS

The rate of complementary and alternative medicine (CAM) use in children and adolescents with asthma is as high as 71% to 84%, but 54% of parents do not disclose the use of these methods.^{55,56} CAM use is more common among children with poorly controlled asthma and those with barriers to treatment.^{57,58} However, data indicate that CAM treatment is typically not used as a substitute for conventional medicine.⁵⁷ Patients who are receiving CAM substances should be cautioned that there is little regulation to ensure the consistency and purity of the contents and that CAM is never a substitute for rescue medication. Common CAM treatments and their effects on asthma symptoms are listed in Table 3.⁵⁹⁻⁷⁴

Note: For complete article visit: www.aafp.org/afp.

eTable A. Common Asthma Medications		
Drug	Dosage	Adverse effects
Short-acting bronchodilators		
Albuterol DPI	Age > 11 years: 180 mcg every 4 to 6 hours as needed	Same as albuterol nebulized
Albuterol HFA	Age 4 to 11 years: 180 mcg every 4 to 6 hours as needed Age > 11 years: 180 mcg every 4 to 6 hours as needed	Same as albuterol nebulized
Albuterol nebulized	Age < 2 years: 0.05 to 0.15 mg per kg every 1 to 6 hours as needed, max 1.25 mg per dose Age 2 to 5 years: 0.1 to 0.15 mg per kg every 4 to 6 hours as needed, max 2.5 mg per dose Age 5 to 11 years: 2.5 mg every 4 to 6 hours as needed, max 10 mg per day Age > 11 years: 2.5 to 10 mg every 1 to 4 hours as needed	Angina, arrhythmia, bad taste, cough, dizziness, headache, hyperglycemia, hypertension, hypokalemia, nausea, nervousness, palpitations, tachycardia, throat irritation, tremor
Ipratropium/albuterol inhaled	Age < 13 years: 80 mcg/400 mcg to 160 mcg/800 mcg every 20 minutes as needed for up to 3 hours Age ≥ 13 years: 160 mcg/800 mcg every 20 minutes as needed for up to 3 hours	Same as ipratropium/albuterol nebulized

continues

eTable A. Common Asthma Medications (*continued*)

Drug	Dosage	Adverse effects
Ipratropium/albuterol nebulized	Age < 13 years: 0.25 mg/1.25 mg to 0.5 mg/2.5 mg every 20 minutes for three doses, then as needed for up to 3 hours Age ≥ 13 years: 0.5 mg/2.5 mg every 20 minutes for 3 doses, then as needed for up to 3 hours	Angina, arrhythmia, cardiac arrest, glaucoma, hyperglycemia, hyperlactatemia, hypertension, hypokalemia, hypotension, pharyngitis
Levalbuterol HFA	Age 4 to 11 years: 90 mcg every 4 to 6 hours as needed, max 540 mcg per day Age > 11 years: 90 mcg every 4 to 6 hours as needed, max 540 mcg per day	Same as albuterol nebulized
Levalbuterol nebulized	Age 6 to 11 years: 0.31 to 0.63 mg three times a day as needed, max dose 0.63 mg Age > 11 years: 0.63 to 1.25 mg three times a day as needed	Same as albuterol nebulized
Inhaled corticosteroids		
Beclomethasone HFA	Age 5 to 11 years: 40 to 160 mcg per day Age > 11 years: 40 to 640 mcg per day	Adrenal suppression, cataracts, cough, dysmenorrhea, dysphonia, eosinophilia, glaucoma, hypercorticism, growth suppression, Churg-Strauss syndrome, oral candidiasis, osteoporosis
Budesonide DPI	Age 6 to 11 years: 180 to 720 mcg per day Age > 11 years: 180 to 1,440 mcg per day	Same as beclomethasone HFA
Budesonide nebulized	Age 1 to 8 years: 0.25 to 1.0 mg daily	Same as beclomethasone HFA
Ciclesonide HFA	Age > 11 years: 80 to 640 mcg per day	Same as beclomethasone HFA
Flunisolide HFA	Age 6 to 11 years: 160 to 320 mcg per day Age > 11 years: 160 to 640 mcg per day	Same as beclomethasone HFA
Fluticasone furoate DPI	Age > 11 years: 100 to 200 mcg per day	Same as beclomethasone HFA
Fluticasone propionate DPI	Age 4 to 11 years: 100 to 200 mcg per day Age > 11 years: 100 to 1,000 mcg per day	Same as beclomethasone HFA
Fluticasone propionate HFA	Age 4 to 11 years: 88 to 176 mcg per day Age > 11 years: 88 to 880 mcg per day	Same as beclomethasone HFA
Mometasone DPI	Age 4 to 11 years: 110 mcg per day Age > 11 years: 220 to 440 mcg per day	Same as beclomethasone HFA
Mometasone HFA	Age > 11 years: 400 to 800 mcg per day	Same as beclomethasone HFA
Long-acting beta₂ agonists		
Budesonide/formoterol	Age > 11 years: 320 mcg/18 mcg to 640 mcg/18 mcg per day	Adrenal suppression, angina, arrhythmia, cardiac arrest, cataracts, cough, dysmenorrhea, dysphonia, eosinophilia, glaucoma, growth suppression, hypercorticism, hyperglycemia, hypertension, hypokalemia, hypotension, oral candidiasis, osteoporosis, palpitations, Churg-Strauss syndrome, tremor

continues

eTable A. Common Asthma Medications (continued)

Drug	Dosage	Adverse effects
Fluticasone/salmeterol DPI	Age 4 to 11 years: 200 mcg/100 mcg per day Age > 11 years: 200 mcg/100 mcg to 1,000 mcg/100 mcg per day	Same as budesonide/formoterol
Fluticasone/salmeterol HFA	Age > 11 years: 180 mcg/84 mcg to 920 mcg/84 mcg per day	Same as budesonide/formoterol
Fluticasone/vilanterol	Age ≥ 18 years: 100 mcg/25 mcg to 200 mcg/25 mcg per day	Same as budesonide/formoterol
Leukotriene receptor antagonists		
Montelukast	Age 1 to 5 years: 4 mg every evening Age 6 to 14 years: 5 mg every evening Age ≥ 15 years: 10 mg every evening	Cough, dyspepsia, fatigue, gastroenteritis, headache, nasal congestion, Churg-Strauss syndrome, rare elevations of LFTs, rash ^{A1}
Zafirlukast	Age 5 to 11 years: 10 mg twice a day Age ≥ 12 years: 20 mg twice a day	Diarrhea, headache, nausea, Churg-Strauss syndrome, rare elevations of LFTs ^{A2}
Leukotriene inhibitor		
Zileuton	Age > 12 years: 600 mg four times a day	Abdominal pain, dyspepsia, headache, myalgia, nausea; rare sleep disorders and behavior changes ^{A3}
Methylxanthines		
Theophylline	300 to 600 mg by mouth, divided, twice a day	Serum level < 20 mg per L (111 μmol per L): Headache, insomnia, nausea, vomiting Serum level > 20 mg per L: Arrhythmias, seizures ^{A4}
Cromolyn	20-mg inhalation nebulizer four times a day	Cough, nasal congestion, nausea, sneezing, wheezing ^{A5}
Monoclonals		
Omaliuzumab	Age > 12 years: 150 to 375 mg subcutaneously every 2 to 4 weeks	Headache, injection site reaction, pharyngitis, sinusitis, upper respiratory tract infection, viral infections ^{A6}

DPI = Dry powder inhaler; HFA = Hydrofluoroalkane; LFT = Liver function tests.

Information from:

^{A1}Montelukast [package insert]. Whitehouse Station, N.J.: Merck; 2016. https://www.merck.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf. Accessed July 28, 2016.

^{A2}Zafirlukast [package insert]. <http://druginserts.com/lib/rx/meds/accolate-2/>. Accessed August 20, 2015.

^{A3}Zileuton [package insert]. <http://druginserts.com/lib/rx/meds/zyflo-1/>. Accessed August 20, 2015.

^{A4}Theophylline [package insert]. <http://druginserts.com/lib/rx/meds/theophylline-8/>. Accessed August 20, 2015.

^{A5}Cromolyn sodium [package insert]. <http://druginserts.com/lib/rx/meds/cromolyn-sodium-8/>. Accessed August 20, 2015.

^{A6}Omaliuzumab [package insert]. East Hanover, N.J.: Novartis; 2016. http://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed July 25, 2016.

REFERENCES

- Centers for Disease Control and Prevention. National Center for Health Statistics. National surveillance of asthma: United States, 2001-2010. http://www.cdc.gov/nchs/data/series/sr_03/sr03_035.pdf. Accessed March 15, 2015.
- Centers for Disease Control and Prevention. National Center for Health Statistics, National Health Interview Survey raw data, 2011. Analysis by the American Lung Association Research and Health Education Division using SPSS and SUDAAN software.
- Centers for Disease Control and Prevention. National Center for Health Statistics, National Hospital Discharge Survey, 1995-2010. Analysis by the American Lung Association Research and Health Education Division using SPSS software.

4. Centers for Disease Control and Prevention. National Center for Health Statistics. CDC Wonder On-line Database, compiled from Compressed Mortality File 1999-2011 Series 20 No. 2Q, 2014.
5. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol.* 2011;127(1):145-152.
6. Pollart SM, Compton RM, Elward KS. Management of acute asthma exacerbations. *Am Fam Physician.* 2011;84(1):40-47.
7. Halbert RJ, Tinkelman DG, Globe DR, Lin SL. Measuring asthma control is the first step to patient management: a literature review. *J Asthma.* 2009;46(7):659-664.
8. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol.* 2006;117(3):549-556.
9. Wood PR, Smith B, O'Donnell L, et al. Quantifying asthma symptoms in adults: the Lara Asthma Symptom Scale. *J Allergy Clin Immunol.* 2007;120(6):1368-1372.
10. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007. NIH publication no. 07-4051. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>. Accessed March 11, 2016.
11. Adachi M, Kohno Y, Minoguchi K. Step-down and step-up therapy in moderate persistent asthma. *Int Arch Allergy Immunol.* 2001;124(1-3):414-416.
12. Koenig SM, Ostrom N, Pearlman D, et al. Deterioration in asthma control when subjects receiving fluticasone propionate/salmeterol 100/50 mcg Diskus are "stepped-down". *J Asthma.* 2008;45(8):681-687.
13. Godard P, Greillier P, Pigearias B, Nachbaur G, Desfougères JL, Attali V. Maintaining asthma control in persistent asthma: comparison of three strategies in a 6-month double-blind randomised study. *Respir Med.* 2008;102(8):1124-1131.
14. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol.* 2006;117(3):563-570.
15. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2012;(5):CD002314.
16. Guevara JP, Ducharme FM, Keren R, Nihtianova S, Zorc J. Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. *Cochrane Database Syst Rev.* 2006;(2):CD003558.
17. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev.* 2005;(1):CD002738.
18. Adams NP, Bestall JC, Lasserson TJ, Jones P, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2008;(4):CD003135.
19. Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. *Cochrane Database Syst Rev.* 2014;(7):CD009471.
20. DelGaudio JM. Steroid inhaler laryngitis: dysphonia caused by inhaled fluticasone therapy. *Arch Otolaryngol Head Neck Surg.* 2002;128(6):677-681.
21. Chan MT, Leung DY, Szeffler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immunol.* 1998;101(5):594-601.
22. Federico MJ, Covar RA, Brown EE, Leung DY, Spahn JD. Racial differences in T-lymphocyte response to glucocorticoids. *Chest.* 2005;127(2):571-578.
23. Dolovich MB, Ahrens RC, Hess DR, et al.; American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest.* 2005;127(1):335-371.
24. Hagan JB, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after reducing inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *Allergy.* 2014;69(4):510-516.
25. Rank MA, Hagan JB, Park MA, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol.* 2013;131(3):724-729.
26. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev.* 2014;(1):CD003137.
27. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2014;(2):CD010314.
28. Loymans RJ, Gemperli A, Cohen J, et al. Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. *BMJ.* 2014;348:g3009.
29. Mansur AH, Kaiser K. Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. *J Aerosol Med Pulm Drug Deliv.* 2013;26(4):190-199.
30. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Revised 2016. <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed June 9, 2016.
31. Dahlén SE, Malmström K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002;165(1):9-14.

32. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med.* 1998;339(3):147-152.
33. Duong M, Amin R, Baatjes AJ, et al. The effect of montelukast, budesonide alone, and in combination on exercise-induced bronchoconstriction. *J Allergy Clin Immunol.* 2012;130(2):535-539.e3.
34. Calapai G, Casciaro M, Miroddi M, Calapai F, Navarra M, Gangemi S. Montelukast-induced adverse drug reactions: a review of case reports in the literature. *Pharmacology.* 2014;94(1-2):60-70.
35. Kubavat AH, Khippal N, Tak S, et al. A randomized, comparative, multicentric clinical trial to assess the efficacy and safety of zileuton extended-release tablets with montelukast sodium tablets in patients suffering from chronic persistent asthma. *Am J Ther.* 2013;20(2):154-162.
36. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma [published correction appears in *Lancet.* 1994;343(8904):1006-1008]. *Lancet.* 1994;343(8904):1006-1008.
37. Markham A, Faulds D. Theophylline. A review of its potential steroid sparing effects in asthma. *Drugs.* 1998;56(6):1081-1091.
38. Nie H, Zhang G, Liu M, Ding X, Huang Y, Hu S. Efficacy of theophylline plus salmeterol/fluticasone propionate combination therapy in patients with asthma. *Respir Med.* 2013;107(3):347-354.
39. Wang Y, Lin K, Wang C, Liao X. Addition of theophylline or increasing the dose of inhaled corticosteroid in symptomatic asthma: a meta-analysis of randomized controlled trials. *Yonsei Med J.* 2011;52(2):268-275.
40. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med.* 1997; 337(20):1412-1418.
41. Theophylline: package insert and label information. <http://druginserts.com/lib/rx/meds/theophylline-8/>. Accessed August 20, 2015.
42. Hoshino M, Nakamura Y. The effect of inhaled sodium cromoglycate on cellular infiltration into the bronchial mucosa and the expression of adhesion molecules in asthmatics. *Eur Respir J.* 1997;10(4):858-865.
43. van der Wouden JC, Uijen JH, Bernsen RM, Tasche MJ, de Jongste JC, Ducharme F. Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev.* 2008;(4):CD002173.
44. Andersson F, Kjellman M, Forsberg G, Möller C, Arheden L. Comparison of the cost-effectiveness of budesonide and sodium cromoglycate in the management of childhood asthma in everyday clinical practice. *Ann Allergy Asthma Immunol.* 2001;86(5):537-544.
45. Kelly K, Spooner CH, Rowe BH. Nedocromil sodium vs. sodium cromoglycate for preventing exercise induced bronchoconstriction in asthmatics. *Cochrane Database Syst Rev.* 2000;(4):CD002731.
46. Bonini M, Di Maria G, Paggiaro P, et al. Potential benefit of omalizumab in respiratory diseases. *Ann Allergy Asthma Immunol.* 2014;113(5):513-519.
47. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med.* 2011;364(11):1005-1015.
48. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev.* 2014;(1):CD003559.
49. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol.* 2004;114(2):265-269.
50. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol.* 2007;120(5):1146-1152.
51. Ariano R, Berto P, Incorvaia C, et al. Economic evaluation of sublingual immunotherapy vs. symptomatic treatment in allergic asthma. *Ann Allergy Asthma Immunol.* 2009;103(3):254-259.
52. Reinhold T, Ostermann J, Thum-Oltmer S, Brüggjenjürgen B. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma. *Clin Transl Allergy.* 2013;3(1):30.
53. Penagos M, Passalacqua G, Compalati E, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest.* 2008;133(3):599-609.
54. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev.* 2010;(8):CD001186.
55. Reznik M, Ozuah PO, Franco K, Cohen R, Motlow F. Use of complementary therapy by adolescents with asthma. *Arch Pediatr Adolesc Med.* 2002;156(10):1042-1044.
56. Sidora-Arcoleo K, Yoos HL, Kitzman H, McMullen A, Anson E. Don't ask, don't tell: parental nondisclosure of complementary and alternative medicine and over-the-counter medication use in children's asthma management. *J Pediatr Health Care.* 2008;22(4):221-229.
57. McQuaid EL, Fedele DA, Adams SK, et al. Complementary and alternative medicine use and adherence to asthma medications among Latino and non-Latino white families. *Acad Pediatr.* 2014;14(2):192-199.
58. Shen J, Oraka E. Complementary and alternative medicine (CAM) use among children with current asthma. *Prev Med.* 2012;54(1):27-31.
59. Boskabady MH, Javan H, Sajady M, Rakhshandeh H. The possible prophylactic effect of *Nigella sativa* seed extract in asthmatic patients [published correction appears in *Fundam Clin Pharmacol.* 2008;22(1):105]. *Fundam Clin Pharmacol.* 2007;21(5):559-566.

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