

# Asthma in Adults

## Highlights

### FDA Panel Votes to Ban Two Asthma Drugs

In December 2008, an FDA advisory panel voted to ban two long-acting beta2-agonists drugs, salmeterol (Serevent) and formoterol (Foradil), for treatment of asthma in children and adults. These drugs can increase the risk of asthma death unless used in combination with an inhaled steroid. The FDA panel decided that salmeterol-fluticasone (Advair) and formoterol-budesonide (Symbicort), which combine two drugs in a single inhaler, can remain on the market. At the time of this report, the FDA had not yet made a final decision.

### FDA Advisory: Montelukast (Singulair)

In 2008, the FDA recommended that patients who take montelukast (Singulair), or other leukotriene antagonist drugs, be monitored for signs of behavioral and mood changes, and signs of suicidal thoughts.

### Asthma Guidelines

The U.S. National Asthma Education and Prevention Program (NAEPP) guidelines for the diagnosis and management of asthma recommend:

- *Assessment and Monitoring.* Doctors should use multiple measures to determine a patient's current condition and future risk for worsening of condition. Even patients who show few daily effects of asthma may be in danger of sudden worsening of symptoms.
- *Patient Education.* Patients should be taught skills to self-monitor and manage asthma. Doctors should give patients a written asthma action plan, which includes information on daily treatment and ways to recognize worsening asthma.
- *Control of Environmental Factors and Other Asthma Triggers.* The guidelines outline new approaches for reducing exposure to allergens. They also address how treating co-existing chronic conditions (such as rhinitis, sinusitis, gastroesophageal reflux, and obesity) can help improve asthma control.
- *Medications.* A stepwise approach is recommended where medication types and doses are increased or decreased based on the level of asthma control.

## Introduction

The word *asthma* originates from an ancient Greek word meaning panting. Essentially, asthma is an inflammatory lung condition that makes it difficult to breathe properly. When any person inhales, the air travels through the following structures:

- Air passes into the lungs and flows through progressively smaller airways called *bronchi* and then *bronchioles*. The lungs contain millions of these airways.
- All bronchioles lead to *alveoli*, which are microscopic sacs where oxygen and carbon dioxide are exchanged.

The major features of the lungs include the bronchi, the bronchioles, and the alveoli. The alveoli are the microscopic blood vessel-lined sacks in which oxygen and carbon dioxide gas are exchanged.

Asthma is a chronic condition in which these airways undergo changes when stimulated by allergens or other environmental triggers. Such changes appear to be two specific responses:

- The *hyperreactive* response (also called hyperresponsiveness)
- The *inflammatory* response

These actions in the airway cause coughing, wheezing, and shortness of breath (dyspnea), the classic symptoms of asthma.

### **Hyperreactive Response**

In the hyperreactive response, smooth muscles in the airways of the lungs constrict and narrow excessively in response to inhaled allergens or other irritants. Everyone's airways respond by constricting when exposed to allergens or irritants, but a special hyperreactive response occurs in people with asthma:

- When people *without* asthma breathe in and out deeply, the airways relax and open to rid the lungs of the irritant.
- When people *with* asthma try to take those same deep breaths, their airways do not relax and narrow, causing patients to pant for breath. Smooth muscles in the airways of people with asthma may have a defect, perhaps a deficiency in a critical chemical that prevents the muscles from relaxing. And, during an asthma attack the airways narrow, making breathing difficult.

### **Inflammatory Response**

The hyperreactive stage is followed by the *inflammatory* response, which generally contributes to asthma in the following way:

- In response to allergens or other environmental triggers, the immune system delivers white blood cells and other immune factors to the airways.
- These so-called inflammatory factors cause the airways to swell, to fill with fluid, and to produce a thick sticky mucus.
- This combination results in wheezing, breathlessness, an inability to exhale properly, and a phlegm-producing cough.

Inflammation appears to be present in the lungs of all patients with asthma, even those with mild cases, and plays a key role in all forms of the disease.

### **Causes**

The exact cause of asthma is unknown. Asthma is most likely caused by a combination of genetic (inherited) factors and environmental triggers (such as allergens and infections). Asthma tends to run in families, so children whose parents have asthma are more likely to develop it themselves.

## **The Allergic Response (Allergens)**

Nearly half of adults with asthma have an allergy-related condition, which, in most cases developed first in childhood. (In patients who first develop asthma during adulthood, the allergic response usually does not play a strong causal role.)

In people with allergies, the immune system overreacts to exposure to allergens. Allergic asthma is triggered by inhaling certain substances (allergens) such as:

- Dust mites, specifically mite feces, which are coated with enzymes that contain a powerful allergen. These are the primary allergens in the home.
- Animal dander. Cats harbor significant allergens, which can even be carried on clothing; dogs usually cause fewer problems. People with asthma who already have pets and are not allergic to them probably have a low risk for developing such allergies later on.
- Molds.
- Cockroaches. Cockroach dust is a major asthma trigger and may reduce lung function even in people without a history of asthma.
- Pollen, from plants.

## **Environmental Factors (Irritants)**

An asthma attack can also be induced or aggravated by direct irritants to the lungs. Important irritants involved in asthma include cigarette smoke, indoor chemicals, and air pollution.

## **Infections**

Respiratory viral and bacterial infections play a role in some cases of adult-onset asthma. In both children and adults with existing allergic asthma an upper respiratory tract infection often worsens an attack.

## **Risk Factors**

About 22 million Americans have asthma.

## **Gender**

Before puberty, asthma occurs more often in males, but after adolescence, it is common in females. In adults with similar cases of actual airway obstruction, women are likely to report more severe symptoms than men.

Hormonal fluctuations or changes in hormone levels may play a role in the severity of asthma in women. Between 30 - 40% of women with asthma experience fluctuations in severity that are associated with their menstrual cycle. Some women first develop asthma during or shortly after pregnancy, while others first develop it around the time of menopause (perimenopause).

## **Race and Ethnicity**

African-Americans have higher rates of asthma than Caucasians or other ethnic groups. They are also more likely to die of the disease. Ethnicity and genetics, however, are less likely to play a role in these differences than socioeconomic differences, such as having less access to optimal health care, and greater likelihood of living in an urban area (another asthma risk factor).

## **Obesity**

Studies report a strong association between obesity and asthma. Evidence also suggests that people who are overweight (body mass index greater than 25) have more difficulty getting their asthma under control. Weight loss in anyone who is obese and has asthma or shortness of breath helps reduce airway obstruction and improve lung function. [For more information, see *In-Depth Report #53: Weight control and diet.*]

## **Other Risk Factors**

*GERD.* At least half of patients with asthma have gastroesophageal reflux disease (GERD), the cause of heartburn. It is not entirely clear which condition causes the other or whether they are both due to common factors. Treating GERD does not appear to improve asthma control. [For more information, see *In-Depth Report #85: Heartburn and gastroesophageal reflux disease.*]

*Aspirin-Induced Asthma.* About 10% of adults and fewer children have aspirin-induced asthma (AIA). With this condition, asthma gets worse when patients take aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). AIA often develops after a viral infection. It is a particularly severe asthmatic condition, associated with many asthma-related hospitalizations. In about 5% of cases, aspirin is responsible for a syndrome that involves multiple attacks of asthma, sinusitis, and nasal congestion. Such patients also often have polyps (small benign growths) in the nasal passages. Patients with aspirin-induced asthma (AIA) should avoid aspirin and other NSAIDs, including ibuprofen (Advil) and naproxen (Aleve).

## **Prognosis**

Asthma is usually chronic, although it occasionally goes into long periods of remission. Long-term outlook generally depends on severity:

- In mild-to-moderate cases, asthma can improve over time, and many adults even become symptom free.
- Even in some severe cases, adults may experience improvement depending on the degree of obstruction in the lungs and the timeliness and effectiveness of treatment.
- In about 10% of severe persistent cases, changes in the structure of the walls of the airways lead to progressive and irreversible problems in lung function, even in aggressively treated patients.

Lung function declines faster than average in people with asthma, particularly in those who smoke and in those with excessive mucus production (an indicator of poor treatment control). Overall, one study reported that 72% of men and 86% of women with asthma had symptoms 15 years after an initial diagnosis. Only 19% of these people, however, were still seeing a doctor, and only 32% used any maintenance medication.

Death from asthma is a relatively uncommon event, and most asthma deaths are preventable. It is very rare for a person who is receiving proper treatment to die of asthma.

However, even when it is not life threatening, asthma can be debilitating and frightening. Asthma that is not properly controlled can interfere with school and work, as well as daily activities.

## **Symptoms**

Asthma symptoms vary in severity from occasional mild bouts of breathlessness to daily wheezing that lasts even when a patient takes large doses of medication. After exposure to asthma triggers, symptoms rarely develop abruptly but progress over a period of hours or days. Occasionally, the airways have become seriously obstructed by the time the patient calls the doctor.

The classic symptoms of an asthma attack include:

- Wheezing when breathing out is nearly always present during an attack. Usually the attack begins with wheezing and rapid breathing, and, as it becomes more severe, all breathing muscles become visibly active.
- Shortness of breath (*dyspnea*). Shortness of breath is a major source of distress in patients with asthma. However, the severity of this symptom does not always reflect the degree to which lung function is impaired. Some patients are not even aware that they are experiencing shortness of breath. These patients are at particular risk for very serious and even life-threatening asthma attacks, since they are less conscious of symptoms.
- Coughing. In some people, the first symptom of asthma is a nonproductive cough. Some patients find this cough even more distressing than wheezing or sleep disturbances.
- Chest tightness or pain. Initial chest tightness without any other symptoms may be an early indicator of a serious attack.
- Rapid heart rate
- Sweating

The end of an attack is often marked by a cough that produces thick, stringy mucus. After an initial acute attack, inflammation lasts for days to weeks, often without symptoms. (The inflammation itself must still be treated, however, because it usually causes relapse.)

## **Symptoms of a Life-Threatening Attack**

The following signs and symptoms may indicate a life-threatening situation:

- As the chest labors to bring enough air into the lungs, breathing often becomes shallow.
- Lacking enough oxygen, the skin becomes bluish.
- The flesh around the ribs of the chest appears to be sucked in.
- The patient may begin to lose consciousness.

Asthma often progresses very slowly to a serious condition or may develop to a fatal or near-fatal attack within a few minutes. It is very difficult to predict when an attack will become very serious.

## **Exercise-Induced Asthma**

Exercise-induced asthma (EIA) is a limited form of asthma in which exercise triggers coughing, wheezing, or shortness of breath. This condition generally occurs in children and young adults, most often during intense exercise in cold dry air. Symptoms are generally most intense about 10 minutes after exercising and then gradually resolve.

EIA is triggered only by exercise and is distinct from ordinary allergic asthma in that it does not produce a long duration of airway activity, as allergic asthma does. (However, some people have both forms of asthma.) People who have only EIA do not appear to need long-term maintenance therapy.

## **Nocturnal Asthma**

Asthma occurs primarily at night (nocturnal asthma) in as many as 75% of patients with asthma. Attacks often occur between 2 and 4 a.m. Some doctors believe that nocturnal asthma may actually be a unique form, with its own specific biologic mechanisms occurring only at night.

## **Diagnosis**

When asthma is suspected, the patient should describe for the doctor any pattern related to the symptoms and possible precipitating factors, including:

- Whether symptoms are more frequent during the spring or fall (allergy seasons).
- Whether exercise, a respiratory infection, or exposure to cold air has ever triggered an attack.
- Any family history of asthma or allergic disorders, such as eczema, hives, or hay fever.
- Any occupational or long-term exposure to chemicals. If symptoms improve on weekends and vacation and are worse at work, the job is the likely source of the asthma, although not always.

## **Ruling out Other Diseases**

A number of disorders may cause some or all of the symptoms of asthma:

- Asthma and chronic obstructive lung diseases (chronic bronchitis and emphysema) affect the lungs in similar ways and, in fact, may all be present in the same person. Unlike other chronic lung conditions, asthma usually first appears in patients younger than age 30 and with chest x-rays that are normal. Still, it may be difficult to distinguish among these disorders in some adults with late onset asthma.
- Panic disorder can coincide with asthma or be confused with it.
- Other diseases that must be considered during diagnosis are pneumonia, bronchitis, severe allergic reactions, pulmonary embolism, cancer, heart failure, tumors, psychosomatic illnesses, and certain rare disorders (such as tapeworm and trichomoniasis).

## **Pulmonary Function Tests**

If symptoms and a patient's history suggest asthma, the doctor will usually perform *pulmonary function tests* to confirm the diagnosis and determine the severity of the disease.

Using a spirometer, an instrument that measures the air taken into and exhaled from the lungs, the doctor will determine several values:

- Vital capacity (VC), the maximum volume of air that can be inhaled or exhaled.
- Peak expiratory flow rate (PEFR), commonly called the peak flow rate, the maximum flow rate that can be generated during a forced exhalation.
- Forced expiratory volume (FEV1), the maximum volume of air expired in one second.

Spirometry is a painless study of air volume and flow rate within the lungs. Spirometry is frequently used to evaluate lung function in people with obstructive or restrictive lung diseases such as asthma or cystic fibrosis.

If the airways are obstructed, these measurements will fall. Depending on the results, the doctor will take the following steps:

- If measurements fall, the doctor typically asks the patient to inhale a bronchodilator. This drug is used in asthma to open the air passages. The measurements are taken again. If the measurements are more normal, the drug likely has cleared the airways and a diagnosis of asthma is likely.
- If measurement results fail to show airway obstruction, but asthma is still suspected, the doctor may perform a *challenge test*. This involves administering a specific drug (histamine or methacholine) that usually increases airway resistance only when asthma is present. The challenge test may be quite useful in ruling out occupational asthma. It is not always accurate, particularly in patients whose only symptom is persistent coughing.
- Administering cold air is another method for inducing airway resistance. This test is very accurate for ruling out asthma, but it is not sensitive enough to accurately identify asthma in adults.

## **Allergy Tests**

The patient may receive skin or blood allergy tests, particularly if a specific allergen is suspected and available for testing. Allergy skin tests may help diagnose allergic asthma, although they are not recommended for people with year-round asthma.

## **Treatment**

### **General Approach for Treating and Managing Asthma**

While medications play an essential role in the management of asthma, appropriate management of asthma involves much more:

- Identifying and avoiding allergens and other asthma triggers
- Following appropriate drug treatments
- Home monitoring performed by either patient or family

- Good communication between the doctor and patient
- Needed psychosocial support
- Treatment of asthma in all environments (school, work, exercise)

The severity of asthma is classified into four groups: Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent. Six specific components of severity are used to classify patients. These components are:

- Symptom frequency, ranging from fewer than 2 days per week to throughout the day
- Nighttime awakenings, ranging from none to nightly
- Short-acting beta2-agonist use for symptom control, ranging from 2 or fewer days per week to several times per day
- Interference with normal activity, ranging from none to extremely limited
- Lung function as measured by FEV1 and FEV1/FVC, measured with pulmonary function testing at the doctor's office
- Number of exacerbations (sudden worsening) requiring oral corticosteroids, ranging from none to two or more in the last 6 months

### **Treating Symptoms Versus Controlling the Disease**

Patients can greatly reduce the frequency and severity of asthma attacks by understanding the difference between coping with asthma attacks and controlling the disease over time.

Medications for asthma fall into two categories:

- *Rescue (Quick-Relief) Medication.* Medications that open the airways (bronchodilators, or inhalers) are used to quickly relieve any moderate or severe asthma attack. These drugs are usually short-acting beta-adrenergic agonists (beta2-agonists). Other drugs used in special cases include corticosteroids taken by mouth and anticholinergic drugs. Beta2-agonists and anticholinergics do not have any effect on the disease process itself. They are only useful for treating symptoms.
- *Long-Term Control (Maintenance) Medication.* Simply coping with asthma symptoms without also controlling the damaging inflammatory response is a common and serious error. For adults and children over age 5 with moderate-to-severe persistent asthma, doctors recommend inhaled corticosteroids sometimes with long-acting beta2-agonists.

Patients can greatly reduce the frequency and severity of asthma attacks by understanding the difference between coping with asthma attacks and controlling the disease over time.

Unfortunately, many patients do not understand the difference between medications that provide rapid short-term relief and those that are used for long-term symptom control. Many patients with moderate or severe asthma overuse their short-term medications and underuse their corticosteroid medications. The overuse of bronchodilators can have serious consequences; not using steroids can lead to permanent lung damage.

These are the signs of well-controlled asthma:

- Asthma symptoms occur twice a week or less
- Rescue bronchodilator medication is used twice a week or less
- Symptoms do not cause nighttime or early morning awakening



- Symptoms do not limit work, school, or exercise activities
- Peak flow meter readings are normal or the patient's personal best
- Both the doctor and the patient consider the asthma to be well controlled

## **Steps for Treating Asthma**

A stepwise approach is recommended for treating asthma. Medications and dosages are increased when needed, and decreased when possible. Based on severity of patients' asthma and their age, there are specific recommendations regarding whether to use long-term control medications and which ones to use. Patient education, environmental control measures, and management of any other conditions are also included. Doctors may always adjust these recommendations based on a specific patient.

In choosing therapy, doctors must also consider the risk an individual patient has for more severe exacerbations. Factors that may contribute to this include parental history of asthma, atopic dermatitis, and known sensitivity to different allergens or foods. Patients should be reevaluated within 2 - 6 weeks to assess response.

Key points regarding recommendations for adults include:

- Inhaled corticosteroids are the preferred long-term control therapy. Long-acting beta2-agonists and leukotriene antagonists are additional therapies usually used in addition to inhaled corticosteroids.
- Avoiding or managing environmental triggers is always important.

## **Devices Used for Administering Inhaled Drugs**

Most asthma drugs are taken with inhalers. In a hospital setting, or when a patient cannot use an inhaler, a nebulizer may be used. A nebulizer is a device that administers the drug in a fine spray that the patient breathes in. The two basic inhaler devices are the metered-dose inhaler (MDI) and dry powder inhalers (DPIs).

*Metered-Dose Inhaler.* The standard device for administering any asthma medication is the metered-dose inhaler (MDI). This device allows precise doses to be delivered directly to the lungs. They vary, however, in their ability to deliver medication. Often MDIs continue to deliver propellant after the drug has been used up. Patients should track their medicine and throw the device away when the last dose has been administered.

MDI-delivered drugs must be used regularly as prescribed, and the patient carefully trained in their use, for the drugs to be effective and safe. Some patients hold the MDI too close to their mouths, or even inside them. Others may exhale too forcefully before inhalation. A spacer, which is short tube attached to the mouthpiece, can help patients make sure they are getting the right amount of medication.

*Dry Powder Inhalers.* Dry powder inhalers (DPIs) deliver a powdered form of beta2-agonists or corticosteroids directly into the lungs. Some patients find that they are easier to manage than MDIs. Humidity or extreme temperatures can affect the performance of these inhalers, so they should not be stored in humid places (bathroom cabinets) or locations subject to high temperatures (glove compartments during summer months).

Dry-powder may cause tooth erosion, and children are advised to rinse their mouths out right after using a DPI and to brush twice a day with a fluoride toothpaste.

## Monitoring

People who self-manage their asthma with peak air flow measurements and adjust their medications as needed have fewer hospitalizations and unplanned doctors visits, and, generally, have a better quality of life than those who rely only on the occasional doctor or emergency room visit to control symptoms. Doctors recommend that patients with even mild asthma monitor their own conditions.

In general, monitoring involves the following steps:

- A peak flow meter is the standard monitoring device for measuring peak expiratory flow rate (PEFR).
- Patients with severe asthma should take PEFR readings two or three times a day. The overall goal should be to achieve less than a 20% (and ideally only 10%) variation in readings between evening and morning rates. For mild-to-moderate asthma, a single determination each morning usually suffices, but patients should check with their doctors.
- It is important to use the meter at the same times each day and to stand or sit in the same position to keep an accurate record.
- Patients should keep an ongoing record of their peak flow readings to help them detect worsening of their condition.
- They should also record attacks, exposure to any allergens or triggers, and medications taken.
- After about 2 months, patients and doctors can use the recorded data for administering medications effectively and to recognize problems before they become serious.

## Treatment of Asthma during Pregnancy

Guidelines from the National Asthma Education and Prevention Program (NAEPP) emphasize that most asthma medications are safe for pregnant women. The guidelines recommend that pregnant women with asthma have albuterol available at all times. Inhaled corticosteroids should be used for persistent asthma. Patients whose persistent asthma does not respond to standard dosages of inhaled corticosteroids may need a higher dosage or the addition of a long-acting beta-agonist to their drug regimen. For severe asthma, oral corticosteroids may be necessary. The NAEPP notes that while it is not clear if oral corticosteroids are safe for pregnant women, uncontrolled asthma poses an even greater risk for a woman and her fetus.

Medications for Treatment and Prevention of Asthma				
Medication Purpose	Drug Class	Generic Name	Brand Names	Administration
<i>Quick-Relief (Rescue) Medications (control acute attacks)</i>	<b>Short-Acting Beta2-Agonists</b>	Albuterol	Proventil, Ventolin, AccuNeb	Inhaler, nebulizer

Medications for Treatment and Prevention of Asthma				
Medication Purpose	Drug Class	Generic Name	Brand Names	Administration
		Levalbuterol	Xopenex	Nebulizer
		Metaproterenol	Alupent	Inhaler
		Pirbuterol	MaxAir	Inhaler
		Ipratropium/Albuterol	Combivent	Inhaler
	<b>Anticholinergics</b>	Ipratropium	Atrovent	Inhaler
		Tiotropium	Spiriva	Inhaler
	<b>Systemic Corticosteroids</b>	Cortisone	Cortone	Pill
		Dexamethasone	Decadron	Pill
		Hydrocortisone	Cortef	Pill
		Methylprednisolone	Medrol	Pill
		Prednisolone	Orapred, Prelone	Syrup
		Prednisone	Various	Pill
		Triamcinolone	Aristocort	Pill
<i>Long-Term Relief (Controller) Medications (prevent attacks and control chronic symptoms)</i>	<b>Inhaled Corticosteroids</b>	Beclomethasone	QVAR	Inhaler
		Budesonide	Pulmicort	Inhaler, nebulizer
		Budesonide/Formoterol	Symbicort	Inhaler
		Ciclesonide	Alvesco	Inhaler
		Flunisolide	AeroBid	Inhaler
		Fluticasone	Flovent	Inhaler
		Fluticasone/Salmeterol	Advair	Inhaler
		Mometasone	Asmanex	Inhaler
		Triamcinolone	Azmacort	Inhaler
	<b>Long-Acting Beta2-Agonists</b>	Formoterol	Foradil	Inhaler
	<i>Note: In 2008, FDA advisory panel voted</i>	Salmeterol	Serevent	Inhaler

Medications for Treatment and Prevention of Asthma				
Medication Purpose	Drug Class	Generic Name	Brand Names	Administration
	<i>to ban Foradil and Serevent.</i>			
	<b>Anti-inflammatory</b>	Cromolyn	Intal	Nebulizer
	<b>IgE-inhibitor</b>	Omalizumab	Xolair	Injectable
	<b>Leukotriene Modifiers</b>	Montelukast	Singulair	Pill
		Zafirlukast	Accolate	Pill
	<b>Methylxanthine</b>	Theophylline	Uniphyl, Quibron, Theo-24	Pill, syrup

## Quick-Relief Medications

These medications quickly control acute asthma attacks.

### Short-Acting Beta2-Agonists

Beta2-agonists do not reduce inflammation or airway responsiveness but serve as *bronchodilators*, relaxing and opening constricted airways during an acute asthma attack. They are used alone only for patients with mild and intermittent asthma. Patients with more severe cases should use them in combination with other drugs.

Asthma is a disease in which inflammation of the airways causes airflow into and out of the lungs to be restricted. When an asthma attack occurs, mucus production is increased, muscles of the bronchial tree become tight, and the lining of the air passages swells, reducing airflow and producing the characteristic wheezing sound.

Specific short-acting beta2-agonists include:

- Albuterol (Proventil, Ventolin), called salbutamol outside the U.S., is the standard short-acting beta2-agonist in America. Other similar beta2-agonists are isoproterenol (Isuprel, Norisodrine, and Medihaler-Iso), metaproterenol (Alupent, Metaprel), pirbuterol (Maxair), terbutaline (Brethine, Brethaire, and Bricanyl), and bitolterol (Tornalate).
- Newer beta2-agonists, including levalbuterol (Xopenex), have more specific actions than the standard drugs. Studies have indicated that levalbuterol is as effective as albuterol with fewer side effects.

Short-acting bronchodilators are generally administered through inhalation and are effective for 3 - 6 hours. They relieve the symptoms of acute attacks, but they do not control the underlying inflammation. If asthma continues to worsen with the use of these drugs, patients should discuss corticosteroids or other drugs to treat underlying inflammation.

*Side Effects of Beta2-Agonists.* Side effects of all beta2-agonists include:

- Anxiety
- Tremor
- Restlessness
- Headache
- Fast and irregular heartbeats. Notify a doctor immediately if this side effect occurs, particularly in people with existing heart conditions. Such patients face an increased risk for sudden death from cardiac related causes.

Beta2-agonists have serious interactions with certain other drugs, such as beta-blockers, and patients should tell the doctor about any other medications they are taking. Individuals with diabetes, heart disease, high blood pressure, hyperthyroidism, an enlarged prostate, or a history of seizures should take these drugs with caution.

*Loss of Effectiveness and Overdose.* There has been some concern that short-acting beta2-agonists become less effective when taken regularly over time, increasing the risk for overuse. Over time some patients may become tolerant to many effects of short-acting beta2-agonists. The degree to which this affects the airways is uncertain.

Patients who perceive beta2-agonists as being less effective may overuse them. Overdose can be serious and in rare cases even life threatening, particularly in patients with heart disease.

### **Anticholinergic Drugs**

Two inhaled drugs, ipratropium bromide (Atrovent) and tiotropium (Spiriva) act as bronchodilators over time. Neither is highly beneficial for acute asthma attacks. Moreover, the drugs are not approved specifically for asthma. They may, however, have some benefits:

- They may be useful for certain older patients with asthma who also have emphysema or chronic bronchitis.
- Combining them with a beta2-agonist might help patients who do not initially respond to treatment with a beta2-agonist alone.

### **Systemic Corticosteroids**

Common oral corticosteroids include prednisone, prednisolone, methylprednisolone, and hydrocortisone. They very effectively reduce inflammation. They are generally used for asthma flareups that do not respond to inhaler medications. In some severe cases, they may be used as maintenance therapy. Usually, the dosage starts out higher and is then gradually reduced over a 5 - 7 day period.

Adverse effects of prolonged use of oral steroids include cataracts, glaucoma, osteoporosis, diabetes, fluid retention, susceptibility to infections, weight gain, hypertension, capillary fragility, acne, excess hair growth, wasting of the muscles, menstrual irregularities, irritability, insomnia, and psychosis. Osteoporosis (bone thinning) is a common and particularly severe long-term side effect of prolonged steroid use.

Osteoporosis is a condition characterized by progressive loss of bone density, thinning of bone tissue, and increased vulnerability to fractures. Osteoporosis may result from disease, dietary or hormonal deficiency or advanced age. Regular exercise and vitamin and mineral supplements can reduce and even reverse loss of bone density.

Long-term use of oral steroid medications suppresses secretion of natural steroid hormones by the adrenal glands. After withdrawal from these drugs, this so-called adrenal suppression persists, and it can take the body a while (sometimes up to a year) to regain its ability to produce natural steroids again. There have been a few cases of severe adrenal insufficiency that occurred when switching from oral to inhaled steroids, which, in rare cases, has resulted in death.

No one should stop taking any steroids without consulting a doctor first. If the doctor orders steroids withdrawn, regular follow-up monitoring is necessary. Patients should talk to their doctor about ways to prevent adrenal insufficiency during withdrawal, particularly during stressful times when the risk increases.

## **Long-Term Relief Medications**

These medications are taken on a regular basis to prevent asthma attacks and control chronic symptoms.

### **Inhaled Corticosteroids**

Corticosteroids, also called glucocorticoids or steroids, are powerful anti-inflammatory drugs. Steroids are not bronchodilators (they do not relax the airways) and have little effect on symptoms. Instead, they work over time to reduce inflammation and prevent permanent injury in the lungs. They can also help prevent asthma attacks from occurring. The use of inhaled corticosteroids in patients with moderate-to-severe asthma reduces the rate of rehospitalizations and deaths from asthma.

Receiving corticosteroids using an inhaler makes it possible to provide effective local anti-inflammatory activity in the lungs with very few side effects elsewhere in the body. (By contrast, steroids taken by mouth have considerable side effects throughout the body.) Inhaled corticosteroids are recommended as the primary therapy for any patient needing long-term control medications for persistent asthma.

Examples of inhaled corticosteroids:

- The most recent generation of inhaled steroids include fluticasone (Flovent), budesonide (Pulmicort), triamcinolone (Azmacort and others), flunisolide (AeroBid), mometasone furoate (Asmanex), and ciclesonide (Alvesco). These steroids are sometimes combined with a long-acting beta2-agonist in a single inhaler, such as budesonide-formoterol (Symbicort) and fluticasone-salmeterol (Advair)..
- The older corticosteroid inhalants are beclomethasone (Beclovent, Vanceryl) and dexamethasone (Decadron Phosphate Respihaler and others).

Optimal timing of the dose is important and may vary depending on the medication.

Inhaled steroids are generally considered safe and effective and only rarely cause any of the more serious side effects reported with prolonged use of oral steroids. The following are side effects of inhaled steroids:

- The most common side effects are throat irritation, hoarseness, and dry mouth. Using a spacer device and rinsing the mouth after each treatment can minimize or prevent these effects.
- Rashes, wheezing, facial swelling (edema), fungal infections (thrush) in the mouth and throat, and bruising are also possible but not common with inhalators.
- Inhaled corticosteroids are associated with a higher risk for cataracts in patients over age 40, particularly with higher dosages. (No higher risk is observed in younger people.)
- Some studies report a higher risk for bone loss in patients who take inhaled steroids regularly, a side effect known to occur with oral steroids.

### **Long-Acting Beta2-Agonists**

Long-acting beta2-agonists are used for preventing an asthma attack (not for treating attack symptoms). These drugs can be dangerous when used alone, because they can mask asthma symptoms, and they can increase the risk of asthma death unless paired with an inhaled steroid. In 2008, an FDA advisory panel voted to ban the use of salmeterol (Serevent) and formoterol (Foradil) for treatment of asthma in children and adults. The FDA panel decided that salmeterol-fluticasone (Advair) and formoterol-budesonide (Symbicort), long-acting beta2 agonists products that are combined with a steroid in a single inhaler, can continue to be used for treatment of moderate-to-severe asthma.

Doctors are still trying to determine when long-acting beta2-agonists should be added to an asthma treatment plan. If your symptoms do not improve or if symptoms worsen with this type of drug, your doctor will recommend discontinuing it. Do not, however, stop taking this drug or other asthma medications without first talking with your doctor.

### **Cromolyn**

Cromolyn sodium (Intal) is both an anti-inflammatory drug and has antihistamine properties that block asthma triggers, such as allergens, cold, or exercise. A cromolyn nasal spray called NasalCrom has been approved for over-the-counter purchase, but only to relieve nasal congestion caused by allergies. Patients should not use it for self-medication without the advice of a doctor.

*Candidates.* Cromolyn is a treatment option for exercise-induced asthma (EIA) in all age groups, for pregnant women, and possibly for preventing allergic asthma in adults as well as children. Cromolyn may be used as an alternative to inhaled corticosteroids, inhaled corticosteroids are considered the preferred choice for long-term control of persistent asthma.

*Side Effects.* Side effects of cromolyn include nasal congestion, coughing, sneezing, wheezing, nausea, nosebleeds, and dry throat.

## Leukotriene Antagonists

Leukotriene antagonists (also called anti-leukotrienes or leukotriene modifiers) are pills that block leukotrienes. Leukotrienes are powerful immune system factors that, in excess, produce a battery of damaging chemicals that can cause inflammation and spasms in the airways of people with asthma. As with other anti-inflammatory drugs, leukotrienes are used for prevention, NOT for treating acute asthma attacks.

Leukotriene antagonists include montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo). These drugs are considered an alternative for long-term control of asthma, but inhaled corticosteroids should always be used first. Other potential uses include preventing exercise-induced asthma.

*Side Effects and Complications.* Gastrointestinal distress is the most common side effect of leukotriene antagonists. Other concerns are indications of liver injury in patients when taking zafirlukast at higher than standard doses. No adverse effects on the liver have been reported to date with montelukast.

The FDA is evaluating reports of suicidal tendencies associated with these medications. Patients who take a leukotriene antagonist drug should be monitored for signs of behavioral and mood changes.

## Theophylline

*Theophylline.* Theophylline (Theo-Dur, Theolair, Slo-Phyllin, Slo-bid, Constant-T, and Respid) relaxes the muscles around the bronchioles and also stimulates breathing. The use of inhaled corticosteroids and long-acting beta2-agonists has dramatically reduced the need to use theophylline in most patients with asthma. It may be useful for treating nocturnal asthma. Available in tablet, liquid, and injectable forms, some theophylline sustained-release tablets and capsules work for a long time and can, therefore, be taken once or twice a day with good results.

If theophylline is not taken exactly as prescribed, an overdose can easily occur. Toxicity can cause nausea, vomiting, headache, insomnia, and, in rare cases, disturbances in heart rhythm and convulsions. Contact a doctor immediately if any of these side effects occur.

The risks for these adverse effects are small if the drug is taken exactly as prescribed, but patients should note the following precautions:

- Chronic smokers metabolize theophylline much more quickly and need higher doses of the drug than nonsmokers; prolonged-release versions are helpful for such people.
- Too much caffeine can increase the concentration of this drug and the amount of time it stays in the body.
- Theophylline also interacts with many other drugs that are taken for other common medical conditions, including asthma. Use caution when taking beta2-agonists and theophylline together.
- No one with a peptic ulcer should take theophylline. The elderly and anyone with heart disease, liver disease, hypertension, seizure disorders, or heart failure should take theophylline with caution. People with heart conditions who take theophylline by mouth have an increased risk for sudden death from heart-related problems.



## **Omalizumab**

Omalizumab (Xolair) is FDA-approved for patients age 12 and older who have moderate-to-severe persistent asthma related to allergies. The presence of allergies must generally be proven by increased levels in the blood of a certain antibody called immunoglobulin E (IgE). The first drug of this type to be approved for asthma, omalizumab is a monoclonal antibody (MAb), a genetically developed drug designed to attack very specific targets. Omalizumab is given by injection every 2 - 4 weeks. It is used only to treat patients who have moderate-to-severe persistent asthma related to allergies whose symptoms are not controlled by inhaled corticosteroids.

Omalizumab prevents IgE from triggering the inflammatory events that lead to asthmatic attacks. Studies have shown excellent benefits of the drug, including a reduced need for corticosteroids, fewer hospitalizations, and significant symptomatic improvements.

However, about 1 in 1,000 patients who take omalizumab develop anaphylaxis (a life-threatening allergic reaction). Patients can develop anaphylaxis after any dose of omalizumab, even if they had no reaction to a first dose. Anaphylaxis may occur up to 24 hours after the dose is given.

Omalizumab should always be injected in a doctor's office and health care providers should observe patients for at least 2 hours after an injection. Patients should also carry emergency self-treatment for anaphylaxis (such as an Epi-Pen) and know how to use it. With an Epi-Pen, or similar auto-injector device, patients can quickly give themselves a life-saving dose of epinephrine.

Anaphylaxis symptoms include:

- Difficulty breathing
- Chest tightness
- Dizziness
- Fainting
- Itching and hives
- Swelling of the mouth and throat

## **Other Treatments**

### **Immunizations**

Patients with asthma should receive the flu vaccine annually, and they should receive the vaccination against pneumococcal pneumonia at least once. [For more information, see *In-Depth Report #94: Colds and influenza.*]

### **Treating Seasonal Allergies and Sinusitis**

Patients with asthma and chronic allergic rhinitis may need to take medications daily. Patients with severe seasonal allergies may need to start medications a few weeks before the pollen season, and to continue medicine until the season is over.

Immunotherapy ("allergy shots") may help reduce asthma symptoms, and the use of asthma medications, in patients with known allergies. They may also help prevent the development of asthma in children with allergies. Immunotherapy poses some risk for severe allergic reactions, however, especially for children with poorly controlled asthma.

Treatment of allergies and sinusitis can help control asthma.

[For more information, see *In-Depth Reports* #77: Allergic rhinitis, #5: Asthma in children and adolescents, and #62: Sinusitis.]

## **Preventing and Treating Respiratory Infections**

Respiratory infections, including the common cold, can act with allergies to worsen asthma. People with asthma should try to minimize their risk for respiratory tract infections. Washing hands is a very simple but effective preventive measure.

## **Treating Gastroesophageal Reflux Disease (GERD)**

Patients with obvious symptoms of reflux may consider the following lifestyle changes:

- Avoiding heavy meals and meals with fried food
- Avoiding caffeine
- Avoiding eating or drinking at least 3 hours before bedtime
- Elevating the head of the bed by 6 inches
- Taking medications treating gastroesophageal reflux. Be sure to talk to your doctor before taking these medicines.

## **Managing Hormonal-Related Asthma**

Women who suspect that menstrual-related changes may influence asthma severity should keep a diary of their menstrual dates and times of asthma attacks. Sometimes, adjusting medications in anticipation of menstruation may help prevent attacks.

## **Other Treatments**

Children, adolescents, and adults with asthma are widely using alternative therapies. In one study, nearly half of asthma or allergy sufferers resorted to alternative treatments. To date, however, evidence does not support any value from most alternative therapies, including high-dose vitamins, urine injections, homeopathic remedies, and most herbal remedies.

*Relaxation and Stress-Reduction Techniques.* Some patients report benefits from many stress reduction techniques, such as acupuncture, hypnosis, breathing relaxation techniques, massage therapy, and meditation practices. There have been very few well-conducted studies supporting their use, however.

Acupuncture, hypnosis and biofeedback are all alternative ways to control pain. Acupuncture involves the insertion of tiny sterile needles, slightly thicker than a human hair, at specific points on the body.

*Breathing Exercises.* Breathing exercises may help improve patients' quality of life even if they do not have a major impact on medication reduction.

*Probiotics.* Probiotics are beneficial microbes that some believe may help protect against allergies and asthma. Probiotics can be obtained in active yogurt cultures and supplements, which are being studied for protection. However, evidence to date does not support efficacy in preventing or treating asthma.

*Herbal Remedies.* Few rigorous studies have evaluated herbal remedies for asthma. Manufacturers of herbal remedies and dietary supplements do not need FDA approval to sell their products. Just like a drug, herbs and supplements can affect the body's chemistry, and therefore have the potential to produce side effects that may be harmful. There have been a number of reported cases of serious and even lethal side effects from herbal products. Always check with your doctor before using any herbal remedies or dietary supplements.

## **Managing Asthma at Home**

### **Asthma Action Plans**

Asthma action plans create a written document for patients to manage asthma during stable times and to more easily identify when asthma is worsening. Important components of a home program include:

- A clearly written plan for taking asthma medications when condition is stable
- A complete education regarding the difference between long-term control medications and quick-relief medications
- Monitoring of asthma on a daily basis. Symptom monitoring is adequate for patients with intermittent or mild persistent asthma. Peak flow monitoring should be performed in patients with moderate or severe persistent asthma or those with a history of more severe exacerbations (sudden worsening or increase in severity of symptoms).
- A list of environmental control measures that need to be taken
- When to seek medical care

*Managing Asthma Exacerbations.* Always refer to the written action plan from your doctors and nurses. Treatment approaches generally include:

- Recognizing symptoms and measuring peak flow
- Using for the first time or increasing usage of short-acting medications
- Eliminating or withdrawing from any triggers or irritants that may be responsible for increase in severity of symptoms
- Depending on written instructions from doctor, begin oral corticosteroids if available
- Monitoring response to treatments and communicating with doctor if symptoms worsen or if severe symptoms occur. [See: "Symptoms" section.]

Follow-up generally depends on the severity of asthma, how recently asthma was diagnosed, patient compliance, and whether recent changes in treatment were made.

### **Avoiding Environmental Triggers**

Avoiding and controlling triggers that lead to asthma attacks are as much a priority as treatment of the disease.

*Controlling Pets.* Patients who already have pets and are not allergic to them probably have a low risk for developing allergies. If pets trigger asthma, take the following precautions:

- If possible, keep pets outside
- If this isn't possible, confine pets to carpet-free areas outside the bedroom. Cats harbor significant allergens, which can even be carried on clothing. Dogs usually cause fewer problems.
- Wash animals once a week to reduce allergens. Dry shampoos, available for both cats and dogs, can remove allergens from the skin and fur and are easier to administer than wet shampoos.

*Controlling for Dust.* Spray furniture polish is very effective for reducing both dust and allergens. Air cleaners, filters for air conditioners, and vacuum cleaners with High Efficiency Particle Arresting (HEPA) filters can help remove particles and small allergens found indoors. Neither vacuuming nor the use of anti-mite carpet shampoo, however, is effective in removing mites in house dust. In fact, vacuuming stirs up both mites and cat allergens. If possible, avoid carpets and rugs.

A High Efficiency Particle Arresting (HEPA) filter can remove the majority of harmful particles, including mold spores, dust, dust mites, pet dander and other irritating allergens from the air. Along with other methods to reduce allergens, such as frequent dusting, the use of a HEPA filtration system can help control the amount of allergens circulating in the air. HEPA filters can be found in most air purifiers, which are usually small and portable.

#### *Bedding, Curtains, and Bedroom Environment.*

- Replace curtains with shades or blinds, and wash bedding using the highest temperature setting.
- Encase mattress and pillow in special dust mite proof covers (synthetic pillows may pose a higher risk for asthma attacks than feather pillows, or no pillow at all).
- Wash pillow in water hotter than 150° F, or in cooler water with detergent and bleach.
- Wash sheets and blankets weekly in hot water.
- Avoid sleeping or lying on cushions or furniture that are cloth covered.

*Reducing Humidity in the House.* Living in a damp house is counterproductive. Dust mites thrive in humidity and damp houses increase the risk for mold. Humidity levels should not exceed 30-50%:

- Fix all leaky faucets and pipes, and eliminate collections of water around the outside of the house.

- Dehumidify basements, but empty humidifiers and clean them daily with a vinegar solution.
- Clean often any moldy surfaces in the basement or in other areas of the home.
- Avoid prolonged use of vaporizers to manage symptoms during asthma attacks.

*Gas Stoves, Kerosene, and Cooking.* People with asthma should choose electric ovens. Gas ovens release nitrogen dioxide, a substance that can aggravate asthma symptoms. Even smoky cooking can worsen asthma. Kerosene (used in space heaters and lamps) may also produce allergic reactions.

*Exterminating Pests (Cockroaches and Mice).*

- Use a professional exterminator to eliminate cockroaches. (One study reported that ridding a home of cockroaches and cleaning the house using standard housecleaning techniques failed to eliminate the cockroach allergens themselves.)
- Exterminate mice and attempt to remove all dust, which might contain mouse urine and dander.
- Keep food and garbage in closed containers.
- Keep food out of bedrooms.

*Avoiding Cigarette Smoke.* Cigarette smoke can accelerate the decline in lung function related to asthma. Even exposure to secondhand smoke can double the risk of asthma-related emergency room visits. Everyone should quit smoking and encourage others around them to quit. [For help quitting, see *In-Depth Report #41: Smoking.*]

*Avoiding Outdoor Allergens.*

- Avoid scheduling camping and hiking trips during times of high pollen count (generally, May and June for grass pollen and mid-August to October for ragweed).
- Avoid strenuous activity when ozone levels are highest, which usually occur in early afternoon, particularly on hot hazy summer days. Levels are lowest in early morning and at dusk.
- Asthma attacks are often higher during thunderstorms. It is not clear why. Some evidence points to a build-up of ozone that accompanies such storms.
- Patients who are allergic to mold should avoid barns, hay, raking leaves, and mowing grass. Exposure to automobile fumes may worsen asthma. Fungi in car air conditioners can also be a problem.
- Air pollution can worsen asthma.

## **Exercise**

Asthma is no reason to avoid exercise. Historically, about 10% of Olympic athletes have asthma. Some studies indicate that long-term exercise even helps control asthma and reduce hospitalization. Exercise can help control weight, which can help with asthma symptoms. Patients should consult their doctors before starting any exercise program, however. Uncontrolled asthma can be dangerous and, rarely, fatal for athletes, even some with mild asthma. Using an inhaler is extremely important.

People who enjoy running should probably choose an indoor track to avoid pollutants. Swimming is excellent for people with asthma. Yoga, which uses stretching, breathing, and meditation techniques, may have particular benefits.

*Hints for Reducing Exercise Induced Asthma (EIA).* EIA occurs only after exercise and is more likely to happen during regular paced activities in cold, dry air. The following are some suggestions for reducing its impact:

- Comply with long-term control medications, particularly inhaled corticosteroids, when prescribed.
- Warm-up and cool-down before and after exercise.
- Participate in activities with short bursts of exercise (such as tennis and football) over exercises involving long-duration pacing (such as cycling, soccer, and distance running).
- Breathe through a scarf or through the nose. This helps warm up the airways when exercising in cold air.

*Medications.*

- Short-acting beta2-agonists taken before exercise are generally considered the first choice, and they last for 2 - 3 hours.
- Cromolyn is another option but it is not as effective.
- Leukotriene antagonists are another option, but they generally take hours to be effective.

### **Preventing and Treating Respiratory Infections**

People with asthma should try to minimize their risk for respiratory tract infections. Washing hands is a very simple but effective preventive measure.

### **Resources**

- [www.lungusa.org](http://www.lungusa.org) -- The American Lung Association
- [www.aaaai.org](http://www.aaaai.org) -- American College of Allergy, Asthma & Immunology
- [www.aaaai.org](http://www.aaaai.org) -- American Academy of Allergy, Asthma & Immunology
- [www.nhlbi.nih.gov](http://www.nhlbi.nih.gov) -- National Heart, Lung, and Blood Institute
- [www.aafa.org](http://www.aafa.org) -- Asthma and Allergy Foundation of America
- [www.aarc.org](http://www.aarc.org) -- American Association for Respiratory Care