The word *asthma* is derived from a Greek word meaning difficulty in breathing. The clinical expression of asthma varies from a mild intermittent wheeze or cough to severe chronic obstruction that can restrict normal activity. Acute asthma attacks are triggered by a variety of stimuli, including exposure to allergens or cold air, exercise, and upper respiratory tract infections. Recently, a number of genetic polymorphisms have been associated with an increased risk of developing asthma. Thus, genetic factors probably contribute to the exaggerated response of the asthmatic airway to various environmental challenges. The most severe exacerbation of asthma, *status asthmaticus*, is a life-threatening condition that requires hospitalization and must be treated aggressively. Unlike most exacerbations of the disease, status asthmaticus is by definition unresponsive to standard therapy.

The most important outcomes for successful therapy of asthma are as follows:

- Prevent chronic and troublesome symptoms
- Maintain (near) normal pulmonary function
- Maintain normal activity levels
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects

**Pathophysiology**

Asthma symptoms are produced by reversible narrowing of the airway, which increases resistance to airflow and consequently reduces the efficiency of movement of
air to and from the alveoli. In addition to airway obstruction, cardinal features of asthma include inflammation and hyperreactivity of the airway. In contrast to chronic obstructive pulmonary disease (emphysema and chronic bronchitis), the airway obstruction associated with asthma is generally reversible. However, severe long-standing asthma changes the architecture of the airway. These changes, including smooth muscle hypertrophy and bronchofibrosis, can lead to an irreversible decrement in pulmonary function. These structural changes are limited to the airways. The lung parenchyma is generally spared.

An aberrant immune response associated with allergy appears to underlie asthma in most children over age 3 years and in most young adults; allergy-induced asthma is also known as extrinsic asthma. In contrast, a large number of patients, especially those who acquire asthma as older adults, have no discernible immunological basis for their condition, although airway inflammation remains a characteristic of the disease; this type of asthma is termed intrinsic asthma. Other patients may have both allergic and nonallergic forms of asthma.

**Airway Obstruction**

Three factors contribute to airway obstruction in asthma: (1) contraction of the smooth muscle that surrounds the airways; (2) excessive secretion of mucus and in some, secretion of thick, tenacious mucus that adheres to the walls of the airways; and (3) edema of the respiratory mucosa. Spasm of the bronchial smooth muscle can occur rapidly in response to a provocative stimulus and likewise can be reversed rapidly by drug therapy. In contrast, respiratory mucus accumulation and edema formation are likely to require more time to develop and are only slowly reversible.

**Airway Inflammation**

The recognition that asthma is a disease of airway inflammation (Fig. 39.1) has fundamentally changed the

![Mediators of Bronchial Asthma](https://example.com/mediators.jpg)

**FIGURE 39.1**

Cellular pathophysiology of asthma. Top, Cross-section of the normal airway and the asthmatic airway. Mediators released during the inflammatory process associated with asthma cause bronchoconstriction, mucus secretion, and mucosal inflammation and edema. These changes reduce the size of the airway lumen and increase resistance to airflow, which leads to wheezing and shortness of breath. Bottom, The multitude of inflammatory cells (macrophages, eosinophils, mast cells, neutrophils) and neurotransmitters implicated in asthma pathophysiology.
manner in which the disease is treated. Thus, it is useful
to discuss the involvement of various mediators and in-
flammatory cells in antigen-induced asthma, an exten-
sively studied, albeit simplistic, model of the disease. In
this model, antigens, such as ragweed pollen or house
mite dust, sensitize individuals by eliciting the produc-
tion of antibodies of the immunoglobulin (Ig) E type.
These antibodies attach themselves to the surface of
mast cells and basophils. If the individual is reexposed
to the same antigen days to months later, the resulting
antigen–antibody reaction on lung mast cells will trigger
the release of histamine and the cysteinyl leukotrienes,
agents that produce bronchoconstriction, mucus secre-
tion, and pulmonary edema. Mast cells also release a va-
riety of chemotactic mediators, such as leukotriene B4
and cytokines. These agents recruit and activate addi-
tional inflammatory cells, particularly eosinophils and
alveolar macrophages, both of which are also rich
sources of leukotrienes and cytokines. Ultimately, re-
peated exposure to antigen establishes a chronic inflam-
matory state in the asthmatic airway.

TREATMENT STRATEGY
Clinical symptoms alone cannot be used as an accurate
assessment of the severity of physiological impairment
in the asthmatic patient, because a substantial degree of
impairment may persist even after symptoms are re-
lieved by treatment. Consequently, the overall objec-
tives of antiasthma therapy are to return lung function
to as near normal as possible and to prevent acute ex-
acerbations of the disease. For quality of life, the ideal
regimen permits normal activities, including exercise,
with minimal or no side effects.

The primary classes of drugs used to treat asthma are
bronchodilators and antiinflammatory agents. Broncho-
dilators include theophylline, a variety of adreno-
mimetic amines, and ipratropium bromide. Antiinflam-
atory therapy consists of the corticosteroids. A
growing collection of drugs called alternative therapies
cannot be classified clearly as either bronchodilators or
antiinflammatory agents. These agents include the
leukotriene modulators, cromolyn sodium, and ne-
docromil sodium.

Bronchodilators are used both in maintenance ther-
apy and as needed to reverse acute attacks. These agents
are often referred to as relievers because they provide
rapid symptomatic relief but do not affect the funda-
mental disease process. Based on the underlying patho-
physiology of the disease, antiinflammatory therapy
must be used in conjunction with bronchodilators in all
but the mildest asthmatics. Antiinflammatory agents are
also called controllers because they provide long-term
stabilization of symptoms. In addition to drug therapy,
all treatment regimens should include patient education
focused on three key behaviors: (1) the appropriate use
of medications to control symptoms (e.g., proper tech-
nique for use of metered-dose inhalers), (2) recognition
of the signs of a deteriorating disease status (e.g., a
progressive increase in the use of bronchodilators),
and (3) prevention strategies (e.g., avoidance of anti-
genic material; influenza vaccination to forestall virus-
induced exacerbations).

Pharmacotherapy of asthma is managed in a step-
wise fashion according to the severity of the disease.
Recommendations for the stepwise treatment of
asthma in adults and children older than 5 years of age
are shown in Table 39.1.

BRONCHODILATORS
When administered in sufficient quantities by an appro-
priate route, bronchodilators will usually reduce the
work of breathing, relieve asthmatic symptoms, and im-
prove ventilation. Bronchodilators can produce a sub-
stantial increase in pulmonary function by relaxing
bronchial smooth muscle, thus dilating the airways.
Commonly used bronchodilators are discussed next.

Adrenomimetic Agents
Adrenergic drugs (Table 39.2) used for the manage-
ment of acute and chronic asthma are epinephrine
(Primatene), isoproterenol (Isuprel), and a group of
adrenoceptor agonists, including albuterol (Proventil,
Ventolin, Salbutamol), terbutaline (Brethine, Brethaire),
and salmeterol (Serevent), that are relatively selective
for β2-adrenoceptors (see Chapter 10). This class of
agents has become the mainstay of modern bronchodia-
lar therapy. These agents are used both as needed to re-
verse acute episodes of bronchospasm and prophylacti-
cally to maintain airway patency over the long term.

Basic Pharmacology
The general pharmacological actions of adrenomimetic-
s are described in detail in Chapter 10. The principal
pharmacological effects that may be observed in hu-
mans treated for bronchospasm are bronchodilation,
tachycardia, anxiety, and tremor. Stimulating β2-adreno-
ceptors produces all of these effects either directly or
indirectly.

Epinephrine activates both α- and β-adrenoceptors,
whereas isoproterenol is selective for β-adrenoceptors
but does not discriminate between β1- and β2-adreno-
ceptors. Much-improved selectivity is offered by agents
such as albuterol, terbutaline, and salmeterol. These
compounds have a higher affinity for β2-adrenoceptors,
the predominant subtype in the airway, than for β1-
adrenoceptors. Other β2-selective adrenomimetics used
as bronchodilators are bitolterol (Tornalate) and pir-
buterol (Maxair). Metaproterenol (Alupent), another β-adrenomimetic used as a bronchodilator, is less selective for β₂-adrenoceptors than is albuterol or terbutaline.

Epinephrine administered subcutaneously is used to manage severe acute episodes of bronchospasm and status asthmaticus. In addition to its bronchodilator activity through β-adrenoceptor stimulation, a portion of the therapeutic utility of epinephrine in these acute settings may be due to a reduction in pulmonary edema as a result of pulmonary vasoconstriction, the latter effect resulting from α-adrenoceptor stimulation. The effects
on pulmonary function are quite rapid, with peak effects occurring within 5 to 15 minutes. Measurable improvement in pulmonary function is maintained for up to 4 hours. The characteristic cardiovascular effects seen at therapeutic doses of epinephrine include increased heart rate, increased cardiac output, increased stroke volume, an elevation of systolic pressure and decrease in diastolic pressure, and a decrease in systemic vascular resistance. The cardiovascular response to epinephrine represents the algebraic sum of both α- and β-adrenoceptor stimulation. A decrease in diastolic blood pressure and a decrease in systemic vascular resistance are reflections of vasodilation, a β₂-adrenoceptor response. The increase in heart rate and systolic pressure is the result of either a direct effect of epinephrine on the myocardium, primarily a β₁ effect, or a reflex action provoked by a decrease in peripheral resistance, mean arterial pressure, or both. Overt α-adrenoceptor effects, such as systemic vasoconstriction, are not obvious unless large doses are used.

Isoproterenol is administered almost exclusively by inhalation from metered-dose inhalers or from nebulizers. The response to inhaled isoproterenol and other inhaled adrenomimetics is instantaneous. The action of isoproterenol is short-lived, although an objective measurement of pulmonary function has shown an effective duration of up to 3 hours. When it is administered by inhalation, the cardiac effects of isoproterenol are relatively mild, although in some cases a substantial increase in heart rate occurs.

Terbutaline and albuterol are administered either orally or by inhalation, whereas salmeterol is given by inhalation only. All three agents are relatively selective for β₂-adrenoceptors and theoretically are capable of producing bronchodilation with minimal cardiac stimulation. However, the term β₂-selectivity is a pharmacological classification based primarily on the relative potency of an individual adrenomimetic to stimulate the pulmonary or the cardiovascular system. Indeed, β₂-agonists invariably produce a degree of tachycardia at large doses, either by activating sympathetic reflex pathways as a consequence of systemic vasodilation or by directly stimulating cardiac β₁-adrenoceptors. In addition, a significant number of β₂-adrenoceptors are present in the human heart, and stimulation of these receptors may contribute to the cardiac effects of β₂-adrenoceptor agonists.

Inhaled salmeterol has a pharmacological half-life in excess of 12 hours, much longer than either albuterol or terbutaline. The likely basis for this long half-life is that the long lipophilic tail of salmeterol promotes retention of the molecule in the cell membrane. Its long duration of action makes salmeterol particularly suitable for prophylactic use, such as in preventing nocturnal symptoms of asthma. Because of its relatively slow onset of action, salmeterol should not be used to treat acute symptoms.

The second messenger, cyclic adenosine monophosphate (cAMP), is thought to mediate the bronchodilator effects of the adrenomimetics. Adrenomimetics enhance the production of cAMP by activating adenyl cyclase, the enzyme that converts adenosine triphosphate (ATP) to cAMP. This process is triggered by the interaction of the adrenomimetics with β₂-adrenoceptors on airway smooth muscle.

Clinical Uses

Epinephrine is used in a variety of clinical situations, and although concern has been expressed about the use of epinephrine in asthma, it is still used extensively for the management of acute attacks.

Isoproterenol is used principally by inhalation for the management of bronchospasm. It is also used intravenously for asthma and as a stimulant in cardiac arrest.

Terbutaline, albuterol, salmeterol and other β₂-adrenoceptor agonists are used primarily in the management of asthma. Terbutaline and albuterol have very rapid onset of action and are indicated for acute symptom relief. Salmeterol, in contrast, has a slow onset of action but a long duration of action. Salmeterol is thus used as prophylactic therapy only, not to reverse acute symptoms.

In addition to its use as a bronchodilator, terbutaline is used extensively to control premature labor, since contractions of uterine smooth muscle are abolished by adrenomimetics (see Chapter 62).

Adverse Effects

Patients treated with recommended dosages of epinephrine will complain of feeling nervous or anxious. Some will have tremor of the hand or upper extremity and many will complain of palpitations. Epinephrine is dangerous if recommended dosages are exceeded or if the drug is used in patients with coronary artery disease, arrhythmias, or hypertension. The inappropriate use of epinephrine has resulted in extreme hypertension and cerebrovascular accidents, pulmonary edema, angina, and ventricular arrhythmias, including ventricular fibrillation.

At recommended dosages, adverse effects from inhaled isoproterenol are infrequent and not serious. When excessive dosages are used, tachycardia, dizziness, and nervousness may occur, and some patients may have arrhythmias.

The limiting side effect associated with orally administered β₂-adrenoceptor agonists is muscle tremor, which results from a direct stimulation of β₂-adrenoceptors in skeletal muscle. This effect is most notable on the initiation of therapy and gradually improves on continued use. β₂-Agonists also cause tachycardia and palpitations in some patients. When used by intravenous infusion for premature labor, β₂-agonists have been re-
ported to produce tachycardia and pulmonary edema in the mother and hypoglycemia in the baby. When administered by inhalation, the β2-agonists produce only minor side effects.

A few epidemiological studies suggest that the overuse of β-adrenoceptor agonists is associated with an overall deterioration in disease control and a slight increase in asthma mortality. This apparent trend may be caused by several factors, the most likely of which is that patients rely too heavily on bronchodilator therapy to control acute symptoms at the expense of antiinflammatory therapy to control the underlying disease process.

**Theophylline**

Twenty years ago theophylline (Theo-Dur, Slo-bid, Uniphyl, Theo-24) and its more soluble ethylenediamine salt, aminophylline, were the bronchodilators of choice in the United States. Although the β2-adrenoceptor agonists now fill this primary role, theophylline continues to have an important place in the therapy of asthma because it appears to have antiinflammatory as well as bronchodilator activity.

**Basic Pharmacology**

Smooth muscle relaxation, central nervous system (CNS) excitation, and cardiac stimulation are the principal pharmacological effects observed in patients treated with theophylline. The action of theophylline on the respiratory system is easily seen in the asthmatic by the resolution of obstruction and improvement in pulmonary function. Other mechanisms that may contribute to the action of theophylline in asthma include antagonism of adenosine, inhibition of mediator release, increased sympathetic activity, alteration in immune cell function, and reduction in respiratory muscle fatigue. Theophylline also may exert an antiinflammatory effect through its ability to modulate inflammatory mediator release and immune cell function.

Inhibition of cyclic nucleotide phosphodiesterases is widely accepted as the predominant mechanism by which theophylline produces bronchodilation. Phosphodiesterases are enzymes that inactivate cAMP and cyclic guanosine monophosphate (GMP), second messengers that mediate bronchial smooth muscle relaxation.

**Clinical Uses**

The principal use of theophylline is in the management of asthma. It is also used to treat the reversible component of airway obstruction associated with chronic obstructive pulmonary disease and to relieve dyspnea associated with pulmonary edema that develops from congestive heart failure.

**Adverse Effects, Drug Interactions, and Contraindications**

Theophylline has a narrow therapeutic index and produces side effects that can be severe, even life threatening. Importantly, the plasma concentration of theophylline cannot be predicted reliably from the dose. In one study, the oral dosage of theophylline required to produce therapeutic plasma levels (i.e., between 10 and 20 μg/mL) varied between 400 and 3,200 mg/day. Heterogeneity among individuals in the rate at which they metabolize theophylline appears to be the principal factor responsible for the variability in plasma levels. Such conditions as heart failure, liver disease, and severe respiratory obstruction will slow the metabolism of theophylline.

The most frequent complaints of patients taking theophylline are nausea and vomiting, which occur most frequently in patients receiving theophylline for the first time and when the plasma level approaches 20 μg/mL but rarely occur at plasma concentrations below 15 μg/mL. The fact that patients who receive the drug intravenously also have the same complaint suggests that the nausea and vomiting result from an action in the CNS.

When serum concentrations exceed 40 μg/mL, there is a high probability of seizures. Nausea will not always be a premonitory sign of impending toxicity. For instance, in children, restlessness, agitation, diuresis, or fever can occur even when nausea does not. A rapid intravenous injection of theophylline can cause arrhythmias, hypotension, and cardiac arrest. Thus, extreme caution should be used when giving the drug by this route. Since it is not possible to predict blood levels on the basis of dosage, toxicity is fairly common by any route of administration. Consequently, plasma concentrations of theophylline should be determined when a patient begins therapy and then at regular intervals of 6 to 12 months thereafter.

Theophylline should be used with caution in patients with myocardial disease, liver disease, and acute myocardial infarction. The half-life of theophylline is prolonged in patients with congestive heart failure. Because of its narrow margin of safety, extreme caution is warranted when coadministering drugs, such as cimetidine or zileuton, that may interfere with the metabolism of theophylline. Indeed, coadministration of zileuton with theophylline is contraindicated. It is also prudent to be careful when using theophylline in patients with a history of seizures.

**Anticholinergics**

The parasympathetic cholinergic pathway emanating from the vagus nerve exerts the main neuronal control in human airways. The cholinergic efferent nerves synapse in ganglia within the airways, and from there,
short postganglionic fibers innervate the end organs, including the airway smooth muscle and mucous glands. Stimulation of these nerve fibers, with the resultant release of acetylcholine and activation of muscarinic cholinoreceptors, elicits bronchoconstriction, mucous secretion, and bronchial vasodilation. Thus, the cholinergic pathways play a key role in the maintenance of the caliber of the airways and contribute to the airway obstruction in both asthma and chronic obstructive pulmonary disease.

**Basic Pharmacology**

The airway effects of released acetylcholine are mediated via activation of three distinct muscarinic receptor subtypes: M₁, in parasympathetic ganglia, mucous glands and alveolar walls; autoinhibitory M₂, in parasympathetic nerve terminals; and M₃, in airway smooth muscle, mucus glands, and airway epithelium.

Although atropine and related compounds possess bronchodilator activity, their use is associated with the typical spectrum of anticholinergic side effects (see Chapter 13), and they are no longer used in the treatment of asthma. To improve the clinical utility of anticholinergics, quaternary amine derivatives of atropine were developed. By virtue of their positive charge, these drugs are absorbed poorly across mucosal surfaces and thus produce fewer side effects than atropine, especially when given by inhalation.

**Clinical Uses**

Ipratropium bromide (Atrovent) is a quaternary amine derivative that is used via inhalation in the treatment of chronic obstructive pulmonary disease and to a lesser extent, asthma. Ipratropium has a slower onset of action (1–2 hours for peak activity) than β₂-adrenoceptor agonists and thus may be more suitable for prophylactic use. Compared with β₂-adrenoceptor agonists, ipratropium is generally at least as effective in chronic obstructive pulmonary disease but less effective in asthma. Ipratropium has greater effectiveness than β₂-adrenoceptor agonists in two settings: in psychogenic asthma and in patients taking β₂-adrenoceptor antagonists. A fixed combination of ipratropium and albuterol (Combivent) is approved for use in chronic obstructive pulmonary disease.

**Adverse Effects**

Ipratropium is virtually devoid of the CNS side effects associated with atropine. The most prevalent peripheral side effects are dry mouth, headache, nervousness, dizziness, nausea, and cough. Unlike atropine, ipratropium does not inhibit mucociliary clearance and thus does not promote the accumulation of secretions in the lower airways.

### Antiinflammatory Agents

The medical and scientific communities have recognized that asthma is not simply a disease marked by acute bronchospasm but rather a complex chronic inflammatory disorder of the airways. On the basis of this knowledge, antiinflammatory agents, particularly corticosteroids, are now included in the treatment regimens of an ever-increasing proportion of asthmatic patients.

**Corticosteroids**

A major breakthrough in asthma therapy was the introduction in the 1970s of aerosol corticosteroids. These agents (Table 39.3) maintain much of the impressive therapeutic efficacy of parenteral and oral corticosteroids, but by virtue of their local administration and markedly reduced systemic absorption, they are associated with a greatly reduced incidence and severity of side effects. The success of inhaled steroids has led to a substantial reduction in the use of systemic corticosteroids. Inhaled corticosteroids, along with β₂-adrenoceptor agonists, are front-line therapy of chronic asthma.

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Trade Name</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral corticosteroids</td>
<td>Prednisone</td>
<td>Deltasone</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Medrol</td>
<td>Oral</td>
</tr>
<tr>
<td>Parenteral corticosteroids</td>
<td>Methylprednisolone</td>
<td>Depo-Medrol</td>
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<td></td>
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<td>Solu-Medrol</td>
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</tr>
<tr>
<td>Inhaled corticosteroids</td>
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<tr>
<td></td>
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<td>Azmacort</td>
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<td></td>
<td></td>
<td>Flovent</td>
<td>Inhalation</td>
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</tbody>
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**TABLE 39.3 Corticosteroids Used in Asthma**
Basic Pharmacology

All corticosteroids have the same general mechanism of action; they traverse cell membranes and bind to a specific cytoplasmic receptor. The steroid-receptor complex translocates to the cell nucleus, where it attaches to nuclear binding sites and initiates synthesis of messenger ribonucleic acid (mRNA). The novel proteins that are formed may exert a variety of effects on cellular functions. The precise mechanisms whereby the corticosteroids exert their therapeutic benefit in asthma remain unclear, although the benefit is likely to be due to several actions rather than one specific action and is related to their ability to inhibit inflammatory processes. At the molecular level, corticosteroids regulate the transcription of a number of genes, including those for several cytokines.

The corticosteroids have an array of actions in several systems that may be relevant to their effectiveness in asthma. These include inhibition of cytokine and mediator release, attenuation of mucus secretion, up-regulation of β-adrenoceptor numbers, inhibition of IgE synthesis, attenuation of eicosanoid generation, decreased microvascular permeability, and suppression of inflammatory cell influx and inflammatory processes. The effects of the steroids take several hours to days to develop, so they cannot be used for quick relief of acute episodes of bronchospasm.

Clinical Uses

The corticosteroids are effective in most children and adults with asthma. They are beneficial for the treatment of both acute and chronic aspects of the disease. Inhaled corticosteroids, including triamcinolone acetonide (Azmacort), beclomethasone dipropionate (Beclovent, Vanceril), flunisolide (AeroBid), and fluticasone (Flovent), are indicated for maintenance treatment of asthma as prophylactic therapy. Inhaled corticosteroids are not effective for relief of acute episodes of severe bronchospasm. Systemic corticosteroids, including prednisone and prednisolone, are used for the short-term treatment of asthma exacerbations that do not respond to β2-adrenoceptor agonists and aerosol corticosteroids. Systemic corticosteroids, along with other treatments, are also used to control status asthmaticus. Because of the side effects produced by systemically administered corticosteroids, they should not be used for maintenance therapy unless all other treatment options have been exhausted.

A fixed combination of inhaled fluticasone and salmeterol (Advair) is available for maintenance antiinflammatory and bronchodilator treatment of asthma.

Adverse Effects and Contraindications

The side effects of corticosteroids range from minor to severe and life threatening. The nature and severity of side effects depend on the route, dose, and frequency of administration, as well as the specific agent used. Side effects are much more prevalent with systemic administration than with inhalant administration. The potential consequences of systemic administration of the corticosteroids include adrenal suppression, cushingoid changes, growth retardation, cataracts, osteoporosis, CNS effects and behavioral disturbances, and increased susceptibility to infection. The severity of all of these side effects can be reduced markedly by alternate-day therapy.

Inhaled corticosteroids are generally well tolerated. In contrast to systemically administered corticosteroids, inhaled agents are either poorly absorbed or rapidly metabolized and inactivated and thus have greatly diminished systemic effects relative to oral agents. The most frequent side effects are local; they include oral candidiasis, dysphonia, sore throat and throat irritation, and coughing. Special delivery systems (e.g., devices with spacers) can minimize these side effects. Some studies have associated slowing of growth in children with the use of high-dose inhaled corticosteroids, although the results are controversial. Regardless, the purported effect is small and is likely outweighed by the benefit of control of the symptoms of asthma.

Care should be taken in transferring patients from systemic to aerosol corticosteroids, as deaths due to adrenal insufficiency have been reported. In addition, allergic conditions, such as rhinitis, conjunctivitis, and eczema, previously controlled by systemic corticosteroids, may be unmasked when asthmatic patients are switched from systemic to inhaled corticosteroids. Caution should be exercised when taking corticosteroids during pregnancy, as glucocorticoids are teratogenic. Systemic corticosteroids are contraindicated in patients with systemic fungal infections.

ALTERNATIVE THERAPIES

A number of medications useful in the treatment of asthma are neither strictly bronchodilators nor antiinflammatory agents. They are classified as alternative asthma therapies (Table 39.4). These drugs, used prophylactically to decrease the frequency and severity of asthma attacks, are not indicated for monotherapy. They are used along with adrenomimetic bronchodilators, corticosteroids, or both.

Leukotriene Modulators

Until the late 1990s, nearly 3 decades had passed since the introduction of a truly new class of antiasthma drugs having a novel mechanism of action. This situation changed with the introduction of zafirlukast (Accolate) and montelukast (Singulair), cysteinyl leukotriene (CysLT)
receptor antagonists, and zileuton (Zyflo), a leukotriene synthesis inhibitor. CysLTs include leukotrienes C₄, D₄, and E₄. These mediators are products of arachidonic acid metabolism and make up the components of slow-reacting substance of anaphylaxis.

**Basic Pharmacology**

The cysteinyl leukotrienes are generated in mast cells, basophils, macrophages, and eosinophils. These mediators have long been suspected of being key participants in the pathophysiology of asthma. In particular, the powerful bronchoconstrictor activity of these leukotrienes has implicated them as major contributors to the reversible component of airway obstruction. Additional evidence suggests that their pathophysiologic role extends beyond their ability to elicit bronchoconstriction. Thus, it is now believed that these substances stimulate mucus secretion and microvascular leakage, both of which contribute to airway obstruction. The relative importance of the various actions of the cysteinyl leukotrienes in the complex pathophysiology of asthma is not clear.

The biological actions of the cysteinyl leukotrienes are mediated via stimulation of CysLT₁ receptors. Montelukast and zafirlukast are competitive antagonists of these receptors. In contrast, zileuton suppresses synthesis of the leukotrienes by inhibiting 5-lipoxygenase, a key enzyme in the bioconversion of arachidonic acid to the leukotrienes. Zileuton also blocks the production of leukotriene B₄, another arachidonic acid metabolite with proinflammatory activity. The CysLT₁-receptor antagonists alter neither the production nor the actions of leukotriene B₄.

**Clinical Uses**

Montelukast, zafirlukast, and zileuton are indicated for the prophylaxis and chronic treatment of asthma. They should not be used to treat acute asthmatic episodes. All three agents are administered orally.

**Adverse Effects, Drug Interactions, and Contraindications**

Dyspepsia is the most common side effect of zileuton. Liver transaminase levels are elevated in a small percentage of patients taking zileuton. Serum liver transaminase levels should be monitored and treatment halted if significant elevations occur. Zileuton inhibits the metabolism of theophylline. Thus, when these agents are used concomitantly, the dose of theophylline should be reduced by approximately one-half, and plasma concentrations of theophylline should be monitored closely. Caution should also be exercised when using zileuton concomitantly with warfarin, terfenadine, or propranolol, as zileuton inhibits the metabolism of these agents. Zileuton is contraindicated in patients with acute liver disease and should be used with caution in patients who consume substantial quantities of alcohol or have a history of liver disease.

Zafirlukast and montelukast are well tolerated. Zafirlukast increases plasma concentrations of warfarin and decreases the concentrations of theophylline and erythromycin. In rare cases, treatment of patients with CysLT receptor antagonists is associated with the development of Churg-Strauss syndrome, a condition marked by acute vasculitis, eosinophilia, and a worsening of pulmonary symptoms. Because these symptoms often appear when patients are given the leukotriene receptor antagonists when they are being weaned from oral corticosteroid therapy, it is not clear whether they are related to the action of the antagonists or are due to a sudden reduction in corticosteroid therapy.

**Cromolyn Sodium and Nedocromil Sodium**

Cromolyn sodium (Intal) and nedocromil sodium (Tilade) are chemically related drugs called chromones that are used for the prophylaxis of mild or moderate asthma. Both are administered by inhalation and have
very good safety profiles, making them particularly useful in treating children.

**Basic Pharmacology**

The precise mechanism or mechanisms whereby cromolyn sodium and nedocromil sodium exert their antiasthmatic activities is unknown. Early work suggested that these agents act by “stabilizing” mast cells, preventing mediator release. However, several other compounds exhibit greater potency for stabilization of mast cells yet possess no clinical efficacy in asthma. This suggests that the therapeutic activity of cromolyn sodium and nedocromil sodium in asthma is related to one or more other pharmacological mechanisms. Postulates include inhibitory effects on irritant receptors, nerves, plasma exudation, and inflammatory cells in general.

Cromolyn sodium and nedocromil sodium attenuate bronchospasm induced by various stimuli, including antigen, exercise, cold dry air, and sulfur dioxide. They suppress inflammatory cell influx and chemotactic activity along with antigen-induced bronchial hyperreactivity. Also inhibited is C-fiber sensory nerve activation in animal models, which may in turn suppress reflex-induced bronchospasm.

**Clinical Uses**

*Cromolyn sodium and nedocromil sodium are used almost exclusively for the prophylactic treatment of mild to moderate asthma and should not be used for the control of acute bronchospasm.* These agents are effective in about 60 to 70% of children and adolescents with asthma. Unfortunately, there is no reliable means to predict which patients will respond. They are less effective in older patients and in patients with severe asthma. It may take up to 4 to 6 weeks of treatment for cromolyn sodium to be effective in chronic asthma, but it is effective after a single dose in exercise-induced asthma. With respect to clinical efficacy, cromolyn sodium and nedocromil sodium do not differ in a substantial way.

**Adverse Effects**

Cromolyn sodium and nedocromil sodium are the least toxic of available therapies for asthma. Adverse reactions are rare and generally minor. Those occurring in fewer than 1 in 10,000 patients include transient bronchospasm, cough or wheezing, dryness of throat, laryngeal edema, swollen parotid gland, angioedema, joint swelling and pain, dizziness, dysuria, nausea, headache, nasal congestion, rash, and urticaria.

**STATUS ASTHMATICUS**

Status asthmaticus is a life-threatening exacerbation of asthma symptoms that is unresponsive to standard therapy. It must be treated very aggressively, and hospitalization may be necessary. A provocative factor such as prolonged allergen exposure or a respiratory infection often precedes status asthmaticus. A rapid increase in the daily use of bronchodilators to control acute symptoms is a danger sign of an impending crisis. Treatment includes oxygen, inhaled short-acting \( \beta_2 \)-agonists, and oral or parenteral corticosteroids. Subcutaneous \( \beta_2 \)-agonists can be given to those who respond poorly to inhaled adrenomimetics. Inhaled ipratropium may be effective in some patients.

**Study Questions**

1. The underlying pathophysiology of asthma is best described by which of the following statements?
   (A) Asthma is a psychosomatic disorder.
   (B) Asthma is caused by an aberrant response to vaccinations.
   (C) Asthma is a disease of airway inflammation.
   (D) Asthma is a disorder of the lung parenchyma.
   (E) Asthma is an infectious disease.

2. Status asthmaticus is best described by which of the following statements?
   (A) Status asthmaticus is well-controlled asthma.
   (B) Status asthmaticus is a life-threatening exacerbation of asthma.
   (C) Status asthmaticus is best treated with inhaled controller medication, such as cromolyn sodium or a leukotriene modulator.
   (D) Status asthmaticus always resolves without drug treatment.
   (E) Status asthmaticus occurs without warning in patients whose asthma symptoms are stable and well controlled.

3. Which one of the following \( \beta_2 \)-adrenoceptor agonists has such a slow onset of action that it is not indicated for the relief of acute asthma symptoms?
   (A) Salmeterol
   (B) Albuterol
2. B. Status asthmaticus is a dangerous exacerbation of asthma symptoms. It requires immediate and aggressive treatment with oxygen, inhaled bronchodilators, and systemic corticosteroids. Hospitalization of the patient is often indicated. By definition, status asthmaticus is not a condition in which symptoms are well controlled. Neither cromolyn sodium nor a leukotriene modulator is indicated for the treatment of status asthmaticus, as their onset of action is too slow. Status asthmaticus often does not resolve without aggressive intervention. Indeed, the patient’s condition can deteriorate rapidly to death. Upper respiratory tract infection or excessive exposure to an allergen often precedes status asthmaticus, as does increased use of inhaled bronchodilators.

3. A. The other agents have rapid onset and are appropriate for acute symptomatic relief of asthma.

4. D. In all asthma treatment regimens, inhaled β₂-adrenoceptor agonists are used as bronchodilators as needed to relieve acute symptoms. As asthma is an inflammatory disease of the airway, inhaled corticosteroids are also used as standard therapy to control symptoms in all but the mildest cases. The potential for dangerous side effects and drug interactions has relegated theophylline, once a mainstay of asthma treatment, to add-on therapy for hard to control symptoms. Inhaled β₂-adrenoceptor agonists or inhaled corticosteroids are not typically used as monotherapy, although the former class of agent can be used alone for patients with very mild symptoms. Because of extensive systemic side effects, oral corticosteroids are not typically used to treat asthma except when symptoms cannot be controlled by standard therapy.

5. A. Tachycardia, dizziness, and nervousness are often produced by larger doses of inhaled β-agonists. Dysphonia, candidiasis, and sore throat are associated with the use of inhaled corticosteroids. The emergence of Churg-Strauss syndrome, though uncommon, is associated with the use of oral leukotriene modulators. Theophylline produces a range of side effects, including nausea, agitation, and life-threatening convulsions. Muscle tremor and palpitations are frequently observed with oral β₂-adrenoceptor agonists but rarely occur when these agents are administered via inhalation.

SUPPLEMENTAL READING

Bisgaard H. Pathophysiology of the cysteinyl leukotrienes and effects of leukotriene receptor antagonists in asthma. Allergy 2001;56 Suppl 66:7–11.


Kelly HW. Asthma pharmacotherapy: Current practices and outlook. Pharmacotherapy 1997;17:135–21S.


Williams DM. Clinical considerations in the use of inhaled corticosteroids for asthma. Pharmacotherapy 2001;21:38S–48S.
A 67-year-old man arrives at the emergency department complaining of excessive bleeding from minor shaving cuts and bruising for no apparent reason. Although the signs are alarming to the patient, the intern on duty does not view them as particularly serious. Upon taking the patient’s history, the intern learns that for the last 5 years the patient has been taking warfarin for atrial fibrillation. In addition, the patient has had asthma since childhood. About 3 weeks ago the asthma symptoms were increasing in frequency and severity, prompting his pulmonologist to prescribe oral theophylline on top of the inhaled corticosteroid and β-adrenoceptor agonist that the patient was already taking. This new regimen seems to be controlling the asthma well. What is the most appropriate treatment for this patient?

**ANSWER:** The key event in this patient’s recent history is the addition of theophylline to his asthma regimen. Theophylline interferes with the metabolism of warfarin, and elevated warfarin levels can cause bleeding. Moreover, orally administered theophylline is notorious for producing widely variable plasma concentrations. Warfarin levels should be monitored in this patient, and his warfarin dosages should be adjusted accordingly. Withdrawing warfarin completely or administering vitamin K is not necessary, as the bleeding complications are not severe. Moreover, these actions could precipitate adverse clotting events (e.g., transient ischemic attack). Withdrawing asthma medication could impair asthma control. Pulmonary function tests are not necessary, as the patient’s asthma symptoms are adequately controlled.