

Respiratory System (Antihistamines)

Introduction

Histamine (HT) is a chemical messenger mostly generated in mast cells. As Histamine is present in practically all tissues {with significant amounts in the lungs, skin, blood vessels, and GI tract (and It is found at high concentration in mast cells and basophils)}, histamine mediates a wide range of cellular responses, including:

- 1- Allergic and inflammatory reactions.
- 2- 2- Gastric acid secretion.
- 3- 3- And neurotransmission in parts of the brain.

It is noteworthy to mention, that histamine is rapidly inactivated by the enzyme amine oxidase. Accordingly, it is mainly stored in granules found in mast cells. Histamine has no clinical applications, but agents that inhibit the action of histamine (antihistamines or histamine receptor blockers) have important therapeutic applications.

Most often, histamine is just one of several chemical mediators released in response to stimuli. The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma. Allergies and anaphylaxis can also trigger significant release of histamine. Actions of HT are summarized in **figure 1**.

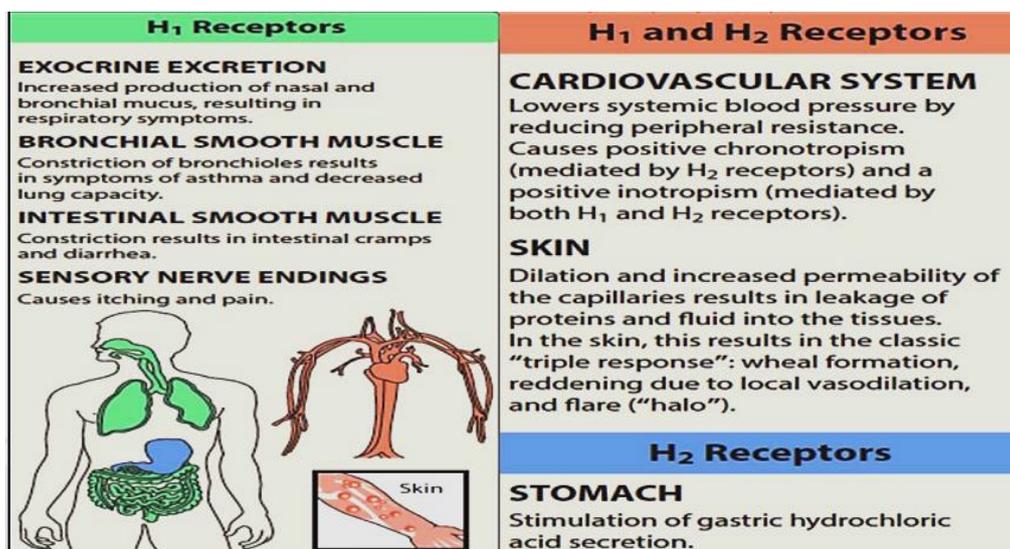


Figure1: Actions of histamine.

Role in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include:

- 1- Contraction of airway smooth muscle.
- 2- Stimulation of secretions.
- 3- Dilation and increased permeability of the capillaries.
- 4- And stimulation of sensory nerve endings.

Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, and leukotrienes.

In some cases, these mediators cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response.

It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results. However, if histamine release is too fast for efficient inactivation, a full-blown anaphylactic reaction occurs.

H1 ANTIHISTAMINES

- The term antihistamine refers primarily to the classic H1-receptor blockers. The H1-receptor blockers can be divided into first- and second-generation drugs (**Figure 2**).
- The older first-generation drugs are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the CNS and cause sedation.
- Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects.
- The second-generation agents are specific for peripheral H1 receptors and do not penetrate the CNS because they are prepared as polar drugs.
- Accordingly, the second-generation agents do not penetrate the blood–brain barrier, causing less CNS depression than the first-generation drugs.
- Among the second-generation agents, desloratadine, fexofenadine, and loratadine show the least sedation (Figure 2). Cetirizine and levocetirizine are partially sedating second-generation agents.

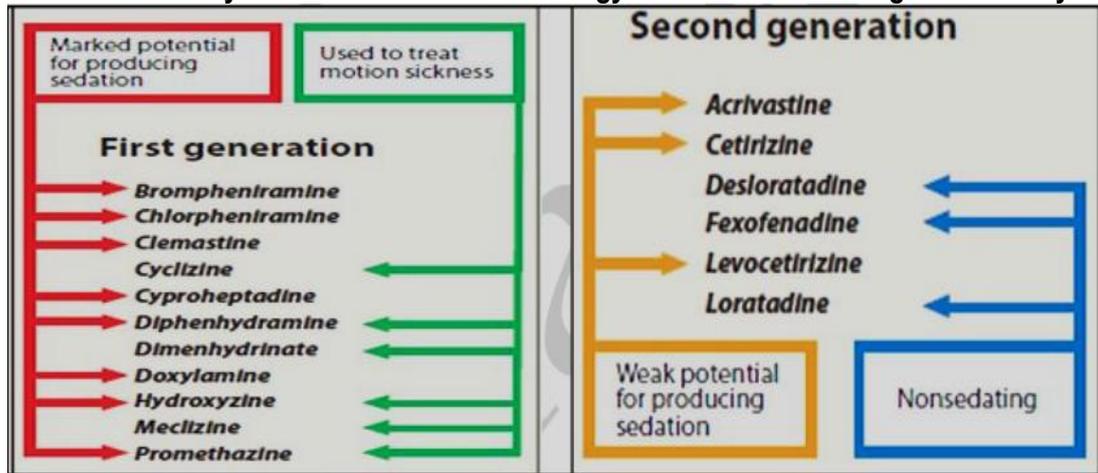


Figure 2: Summary of therapeutic advantages and disadvantages of some H1 histamine receptor–blocking agents.

Actions

- The action of all the H1-receptor blockers does not influence the formation or release of histamine. Rather, they block the receptor-mediated response of a target tissue.
- They are much more effective in preventing symptoms than reversing them once they have occurred.
- These agents have additional effects unrelated to their ability to block H1 receptors. These effects reflect binding of the H1-receptor antagonists to cholinergic, adrenergic, or serotonin receptors.
- Antihistamines such as azelastine and ketotifen also have mast cell– stabilizing effects in addition to their histamine receptor–blocking effects.

Therapeutic uses

1. Allergic and inflammatory conditions

H1-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E (IgE) antibody for example:

- Oral antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator released by mast cells.
- Ophthalmic antihistamines, such as azelastine, olopatadine, ketotifen, and others (Figure 2), are useful for the treatment of allergic conjunctivitis.
- The H1-receptor blockers are not indicated in treating bronchial asthma, because histamine is only one of several mediators that are responsible for causing bronchial reactions.

- Epinephrine has actions on smooth muscle that are opposite to those of histamine. Therefore, epinephrine is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.

2. Motion sickness and nausea:

Certain H₁-receptor blockers, such as diphenhydramine, and promethazine (Figure 2), are the most effective agents for prevention of the symptoms of motion sickness. They are usually not effective if symptoms are already present and, thus, should be taken prior to expected travel. The antiemetic action of these medications seems to be due to their blockade of central H₁ and M₁ muscarinic receptors.

3- Somnifacients: Although they are not the medications of choice, many first-generation antihistamines, such as diphenhydramine and doxylamine, have strong sedative properties and are used in the treatment of insomnia. These agents are available over-the-counter (OTC), or without a prescription. The use of first-generation H₁ antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical. The second-generation antihistamines have no value as somnifacients.

Pharmacokinetics

H₁-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average plasma half-life is 4 to 6 hours, except for that of meclizine and the second-generation agents, which is 12 to 24 hours allowing once-daily dosing.

Adverse effects

The side effects of the antihistamine drugs vary according to the affinity of the drug to the receptors and the drug's structure. So, some side effects may be undesirable, and others may be of therapeutic value. First-generation H₁ antihistamines, such as chlorpheniramine, diphenhydramine, hydroxyzine, and promethazine, bind to H₁ receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation. Diphenhydramine may cause paradoxical hyperactivity in young children. Other central actions include fatigue, dizziness, lack of coordination, and tremors. Sedation is less common with the second-generation drugs, since they do not readily enter the CNS. Second-generation H₁ antihistamines are specific for peripheral H₁ receptors.

Other effects:

First-generation antihistamines exert anticholinergic effects, leading not only to dryness in the nasal passage but also to a tendency to dry out the oral cavity. They also may cause blurred vision and retention of urine.

The most common adverse reaction associated with second-generation antihistamines is headache. Topical formulations of diphenhydramine can cause hypersensitivity reactions such as contact dermatitis when applied to the skin.

Drug interactions:

Interaction of H1-receptor blockers with other drugs can cause serious consequences, such as potentiation of effects of other CNS depressants, including alcohol.

Overdoses: Although the margin of safety of H1-receptor blockers is relatively high, and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

HISTAMINE H2-RECEPTOR BLOCKERS

Histamine H2-receptor blockers (such as cimetidine and ranitidine) have little, if any, affinity for H1 receptors. Although antagonists of the histamine H2 receptor (H2 antagonists or H2-receptor blockers) block the actions of histamine at all H2 receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn.

Drugs for Disorders of the Respiratory System

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory disorders. Each of these conditions may be associated with a troublesome cough, which may be the only presenting complaint.

Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption. Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic side effects.

Asthma

Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing, and rapid respiration.

Pathophysiology of asthma

- Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus.

- The underlying inflammation of the airways contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.
- Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections.

Goals of therapy

The goals of asthma therapy are to decrease the intensity and frequency of asthma symptoms and the degree to which the patient is limited by these symptoms. All patients need to have a “quick-relief” medication to treat acute asthma symptoms while drug therapy for long-term control of asthma is designed to reverse and prevent airway inflammation.

Preferred drugs used to treat asthma

β 2-Adrenergic agonists

Inhaled β 2-adrenergic agonists directly relax airway smooth muscle. They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

Quick relief drugs

- Short-acting β 2 agonists (SABAs) have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. So, all patients with asthma should be prescribed a SABA inhaler.
- β 2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. However, monotherapy with SABAs may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm.
- Direct acting β 2-selective agonists (include albuterol and levalbuterol) can provide significant bronchodilation with little of the undesired effect of α or β 1 stimulation.
- Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia, are minimized with inhaled delivery versus systemic administration. These agents can cause β 2-mediated skeletal muscle tremors.

Long-term control drugs:

- Salmeterol and formoterol are long-acting β 2 agonists (LABAs). They have a long duration of action, providing bronchodilation for at least 12 hours. Neither salmeterol nor formoterol should be used for quick relief of an acute asthma attack.

- LABAs should be used only in combination with an asthma controller medication.
- Inhaled corticosteroids (ICS) remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining asthma control. Adverse effects of LABAs are similar to quick-relief β_2 agonists.

Corticosteroids

ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma.

Corticosteroids inhibit the release of arachidonic acid, thereby producing direct antiinflammatory properties in the airways.

No other medications are as effective as ICS in the long-term control of asthma in children and adults.

To be effective in controlling inflammation, glucocorticoids must be used regularly. Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.

Actions on lung: ICS do not directly affect the airway smooth muscle. Instead, ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes.

After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

Routes of administration

a. Inhalation: The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy.

Inhaler technique

Appropriate inhaler technique differs between metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), so assessing technique regularly is critical to the success of therapy. Metered-dose inhalers and dry powder inhalers

- MDIs have propellants that eject the active medication from the canister.

- Patients should be instructed to inhale slowly and deeply just before and throughout actuation of the inhaler to avoid impaction of the medication onto the laryngeal mucosa, rather than the bronchial smooth muscle.
- A large fraction (typically 80% to 90%) of inhaled glucocorticoids is either deposited in the mouth and pharynx or swallowed.
- The remaining 10% to 20% of a dose of inhaled glucocorticoids that is not swallowed is deposited in the airway.
- If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely.
- DPIs require a different inhaler technique. Patients should be instructed to inhale quickly and deeply to optimize drug delivery to the lungs.

Spacers

- A spacer is a large-volume chamber attached to an MDI. The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device.
- The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue.
- Spacers improve delivery of inhaled glucocorticoids and are advised for virtually all patients. Patients should be advised to wash and/or rinse spacers to reduce the risk of bacterial or fungal growth that may induce an asthma attack.

b. Oral/systemic:

Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous methylprednisolone or oral prednisone to reduce airway inflammation. In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis will not occur during the short course of oral prednisone “burst” typically prescribed for an asthma exacerbation. Therefore, prednisone dose taper is unnecessary prior to discontinuation.

Due to the increased incidence of adverse effects with oral therapy, chronic maintenance with systemic administration of corticosteroids should be reserved for patients who are not controlled on an ICS.

Adverse effects:

Oral or parenteral glucocorticoids have a variety of potentially serious side effects, whereas ICS, particularly if used with a spacer, have few systemic effects. ICS

deposition on the oral and laryngeal mucosa can cause adverse effects, such as oropharyngeal candidiasis (due to local immune suppression) and hoarseness. Patients should be instructed to rinse the mouth in a “swish-and-spit” method with water following use of the inhaler to decrease the chance of these adverse events.

Alternative drugs used to treat asthma

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment. These drugs should be used in conjunction with ICS therapy for most patients, not as monotherapy.

A. Leukotriene modifiers

- Leukotrienes (LT) B₄ and the cysteinyl leukotrienes, are important materials in the inflammatory cascade as LTB₄ is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion.
- Zileuton is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB₄ and the cysteinyl leukotrienes.
- Because zafirlukast and montelukast are selective antagonists of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes. All three drugs are approved for the prevention of asthma symptoms.
- They should not be used in situations where immediate bronchodilation is required. Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise induced bronchospasm.
- All three drugs are orally active and highly protein bound.

Adverse effects

Elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal.

B. Cromolyn

- Cromolyn is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine. It is an alternative therapy for mild persistent asthma. However, it is not useful in managing an acute asthma attack, because it is not a bronchodilator.
- Cromolyn is available as a nebulized solution for use in asthma.
- Due to its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use. Adverse effects are minor and include cough, irritation, and unpleasant taste.

C. Cholinergic antagonists

- The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion.
- Inhaled ipratropium, a quaternary derivative of atropine, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with concomitant COPD.
- Ipratropium also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department.
- Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

D. Theophylline

- Theophylline is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. It may also possess anti-inflammatory activity, although the mechanism of action is unclear.
- Previously, the mainstay of asthma therapy, theophylline has been largely replaced with β_2 agonists and corticosteroids due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions.
- Overdose may cause seizures or potentially fatal arrhythmias.
- Serum concentration monitoring should be performed when theophylline is used chronically.

Drugs used to treat chronic obstructive pulmonary disease

- COPD is a chronic, irreversible obstruction of airflow that is usually progressive.
- Symptoms include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue.
- Although symptoms are similar to asthma, the characteristic irreversible airflow obstruction of COPD is one of the most significant differences between the diseases.
- Smoking cessation and/or continued avoidance should be recommended regardless of stage/ severity of COPD and age of patient. Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression.

Used drugs:

- Inhaled bronchodilators, including the β_2 -adrenergic agonists and anticholinergic agents (ipratropium and tiotropium), are the foundation of therapy for COPD.

- These (above mentioned) drugs increase airflow, alleviate symptoms, and decrease exacerbation rates.
- The long-acting agents, LABAs and tiotropium, are preferred as first-line treatment of COPD for all patients except those who are at low risk with less symptoms.
- Combination of both an anticholinergic and a β_2 agonist may be helpful in patients who have inadequate response to a single inhaled bronchodilator.
- The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function and quality of life in some COPD patients. However, the use of an ICS is associated with an increased risk of pneumonia, and therefore, use should be restricted to these patients.

Drugs used to treat allergic rhinitis

- Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes, a nonproductive cough.
- An attack may be precipitated by inhalation of an allergen (such as dust). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure. The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration.
- Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis

A. Antihistamines (H1-receptor blockers)

- Antihistamines are useful for the management of symptoms of allergic rhinitis caused by histamine release (sneezing, watery rhinorrhea, itchy eyes/nose). However, they are more effective for prevention of symptoms, rather than treatment once symptoms have begun.
- Ophthalmic and nasal antihistamine delivery devices are available for more targeted tissue delivery.
- First-generation antihistamines, such as diphenhydramine and chlorpheniramine, are usually not preferred due to adverse effects, such as sedation, performance impairment, and other anticholinergic effects.

- The second-generation antihistamines (such as loratadine, desloratadine and intranasal azelastine) are generally better tolerated.
- Combinations of antihistamines with decongestants are effective when congestion is a feature of rhinitis.

B. Corticosteroids

- Intranasal corticosteroids, such as beclomethasone and fluticasone are the most effective medications for treatment of allergic rhinitis. They improve sneezing, itching, rhinorrhea, and nasal congestion.
- Systemic absorption is minimal, and side effects of intranasal corticosteroid treatment are localized. These include nasal irritation, nosebleed, sore throat, and, rarely, candidiasis.
- To avoid systemic absorption, patients should be instructed not to inhale deeply while administering these drugs because the target tissue is the nose, not the lungs or the throat. For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy.

C. α -Adrenergic agonists

- Short-acting α -adrenergic agonists (“nasal decongestants”), such as phenylephrine, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Longer-acting oxymetazoline is also available.
- When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects. Unfortunately, the α adrenergic agonist intranasal formulations should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa).
- For this reason, the α -adrenergic agents have no place in the long-term treatment of allergic rhinitis.
- Administration of oral α -adrenergic agonist formulations results in a longer duration of action but also increased systemic effects.
- As with intranasal formulations, regular use of oral α -adrenergic agonists (phenylephrine and pseudoephedrine) alone or in combination with antihistamines is not recommended.

Other agents

- Intranasal cromolyn may be useful in allergic rhinitis, particularly when administered before contact with an allergen.
- To optimize the therapeutic effect, dosing should begin at least 1 to 2 weeks prior to allergen exposure. A nonprescription (over-the-counter) nasal formulation of cromolyn is available.
- Some LT antagonists are effective for allergic rhinitis as monotherapy or in combination with other agents. They may be a reasonable option in patients who also have asthma.

Drugs used to treat cough

- Coughing is an important defence mechanism of the respiratory system to irritants and is a common reason for patients to seek medical care.
- A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease.
- In some cases, cough may be an effective defence reflex against an underlying bacterial infection and should not be suppressed.
- Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate. The priority should always be to treat the underlying cause of cough when possible.

A. Opioids and Benzonatate

- Codeine, an opioid, decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion.
- These therapeutic effects occur at doses lower than those required for analgesia. However, common side effects, such as constipation, dysphoria, and fatigue, still occur. In addition, it has addictive potential.
- Dextromethorphan is a synthetic derivative of morphine that has no analgesic effects in antitussive doses. In low doses, it has a low addictive profile. However, it is a potential drug of abuse, since it may cause dysphoria at high doses.
- Dextromethorphan has a significantly safer side effect profile than codeine and is equally effective for cough suppression.
- Guaifenesin, an expectorant, is available as a single-ingredient formulation and is also a common ingredient in combination products with codeine or dextromethorphan.

- Unlike the opioids, benzonatate suppresses the cough reflex through peripheral action. Side effects include dizziness, numbness of the tongue, mouth, and throat. These localized side effects may be particularly problematic if the capsules are broken or chewed and the medication comes in direct contact with the oral mucosa.

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