

# **Drugs for Disorders of the Respiratory System**

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# Disorders of the Respiratory System



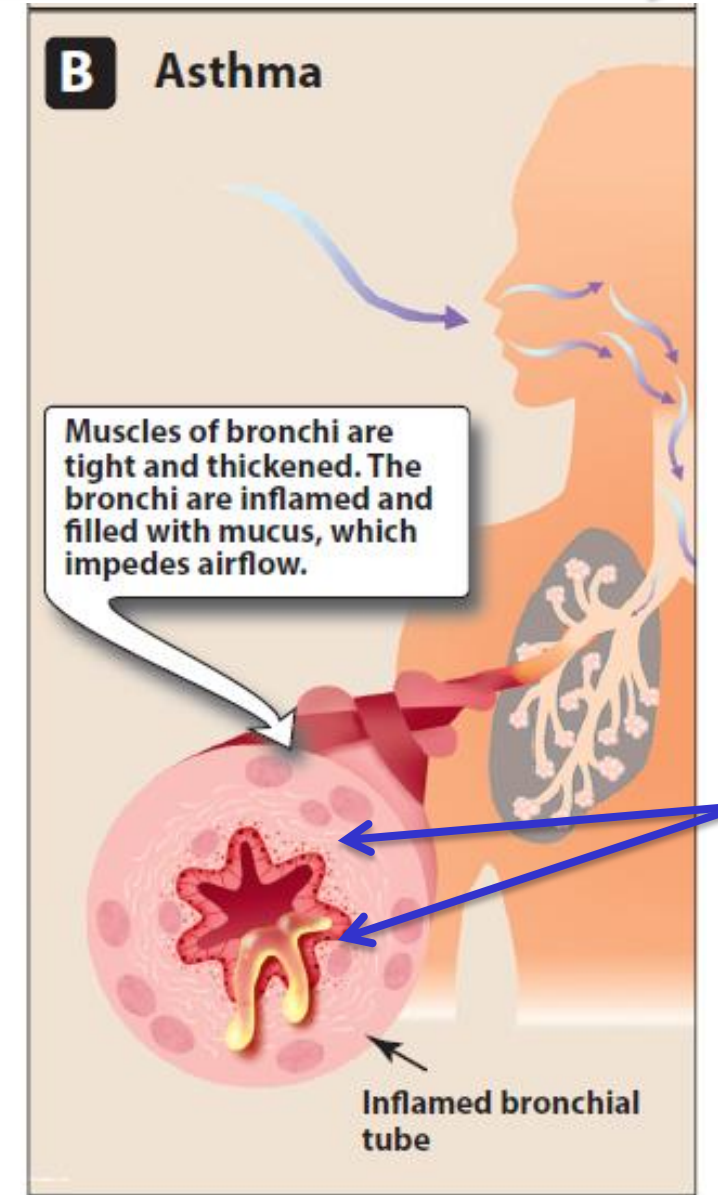
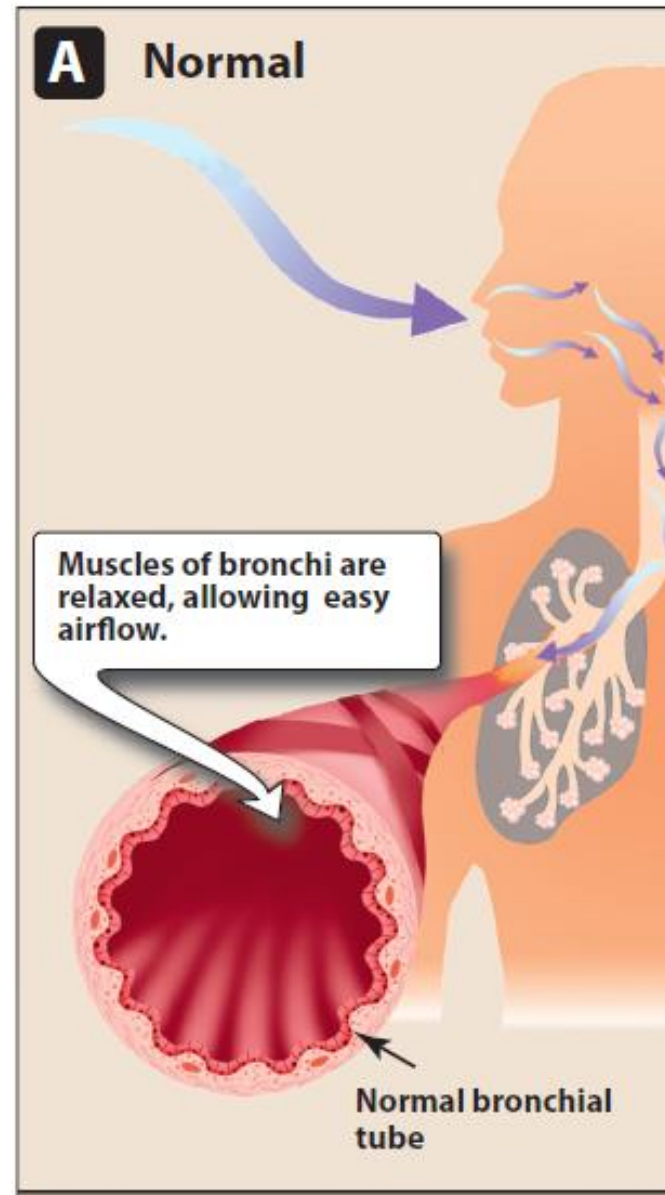
## Disorders of the Respiratory System:

- ✓ Asthma,
- ✓ Chronic obstructive pulmonary disease (COPD),
- ✓ Allergic rhinitis
- ✓ Cough

COPD is currently the fourth leading cause of death in the world.

# ASTHMA/ Pathophysiology of 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.



## A. 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.

However, if untreated, asthma may cause **airway remodeling**, resulting in increased severity and incidence of asthma exacerbations and/or death.

## B. 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.

Drug therapy for **long-term** control of asthma is designed to reverse and **prevent** airway inflammation.

## C. $\beta$ 2-Adrenergic agonists/ 1. Quick relief:



Inhaled  **$\beta$ 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.

Short-acting  $\beta$ 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.

$\beta$ 2 agonists have **no anti-inflammatory** effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma.

## C. $\beta$ 2-Adrenergic agonists/ 1. Quick relief:

However, monotherapy with SABAs may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm.

Direct acting  $\beta$ 2-selective agonists include **albuterol and levalbuterol**.

These agents provide significant bronchodilation with little of the undesired effect of  $\alpha$  or  $\beta$ 1 stimulation.

**Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia, are minimized with inhaled delivery versus systemic administration.**

These agents can cause  **$\beta$ 2-mediated skeletal muscle tremors**.

## C. $\beta$ 2-Adrenergic agonists/ 2. Long-term control:

**Salmeterol and formoterol** are long-acting  $\beta$ 2 agonists (**LABAs**) and chemical analogs of albuterol.

Salmeterol and formoterol have a long duration of action, providing bronchodilation for at least **12 hours**.

**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  $\beta$ 2 agonists.**



## C. $\beta_2$ -Adrenergic agonists/ 2. Long-term control:

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Intermittent	Less than 2 days per week	Near normal*	No daily medication	Short-acting $\beta_2$ agonist
Mild persistent	More than 2 days per week, not daily	Near normal*	Low-dose ICS	Short-acting $\beta_2$ agonist
Moderate persistent	Daily	60% to 80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting $\beta_2$ agonist
Severe persistent	Continual	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting $\beta_2$ agonist

ICS = inhaled corticosteroid. LABA = long-acting  $\beta_2$  agonist.

### Guidelines for the treatment of asthma

\*Eighty percent or more of predicted function.

## D. Corticosteroids

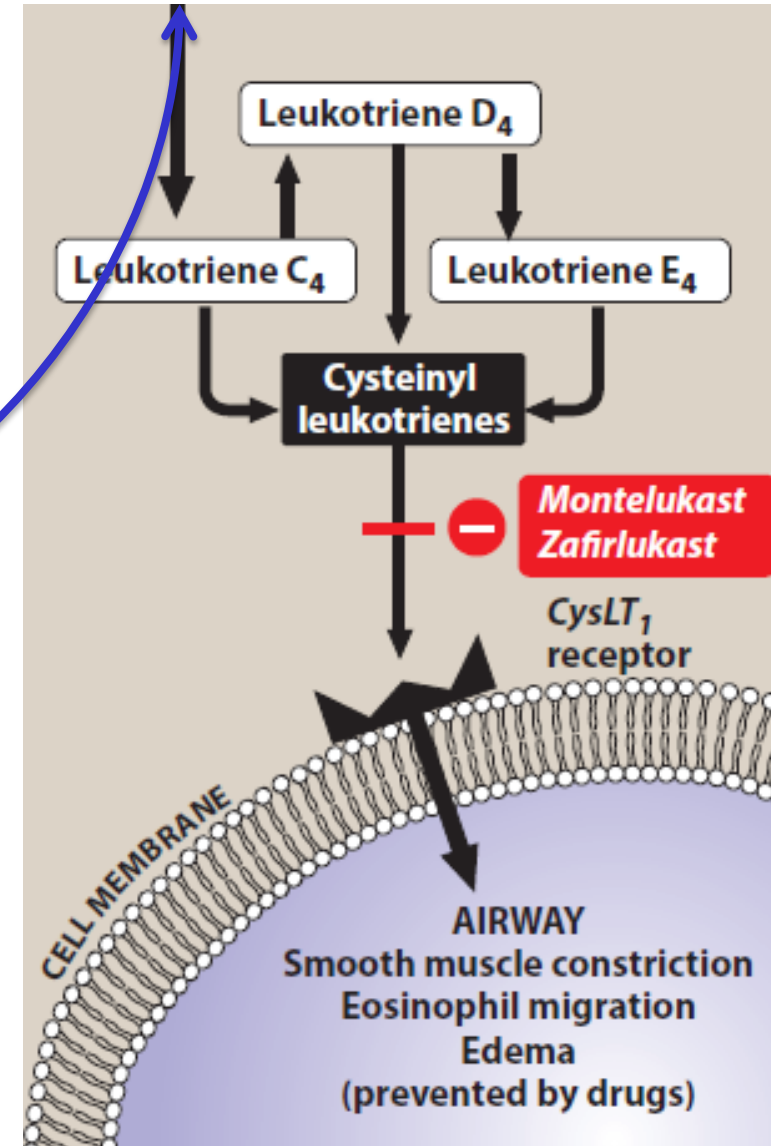
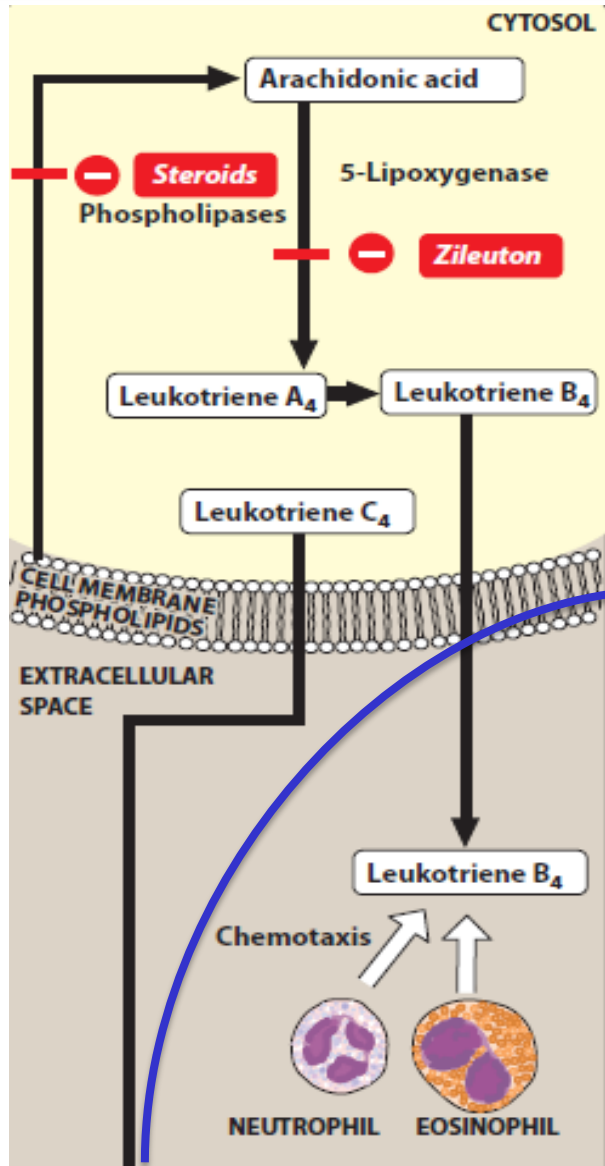


ICS are the drugs of choice for **long-term control** in patients with any degree of **persistent** asthma.

Corticosteroids inhibit the release of **arachidonic acid** through phospholipase A2 inhibition, thereby producing direct anti-inflammatory properties in the airways.

Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.

## D. Corticosteroids



Sites of action for various respiratory medications. CysLT1 = cysteinyl leukotriene-1.

## D. Corticosteroids/ 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.

## D. Corticosteroids/ 2. 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.

**b. Oral/systemic:** Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous **methylprednisolone** or oral **prednisone** to reduce airway inflammation.

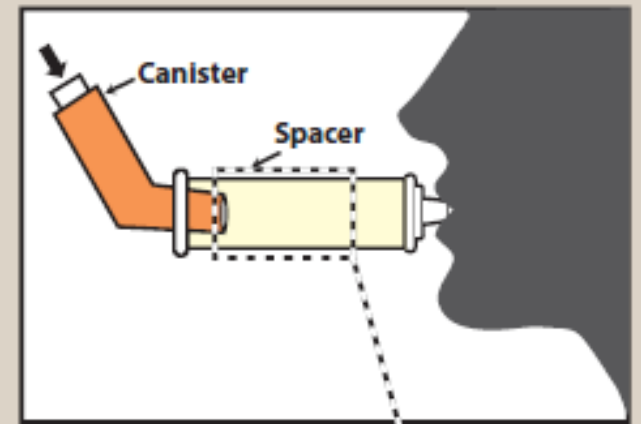
In most cases, suppression of the **hypothalamic–pituitary–adrenal cortex** axis will not occur during the short course of oral prednisone “burst” typically prescribed for an asthma exacerbation.

## D. Corticosteroids/ 3. Adverse effects:

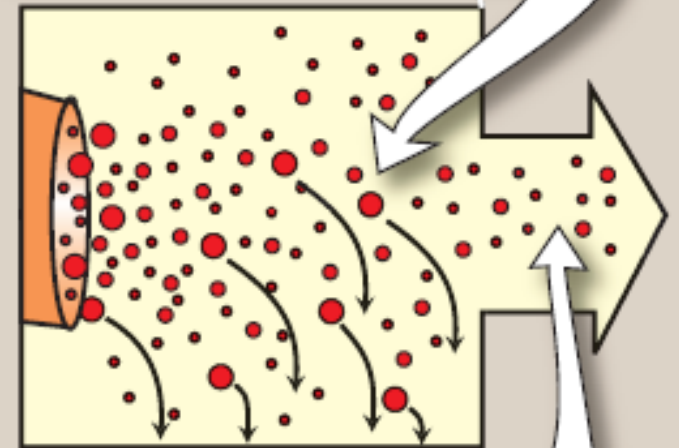
Oral or parenteral glucocorticoids have a variety of potentially serious side effects, whereas ICS, particularly if used with a **spacer**, have few systemic effects.

ICS deposition on the oral and laryngeal mucosa can cause adverse effects, such as **oropharyngeal candidiasis**.

Patients should be instructed to **rinse** the mouth with water following use of the inhaler to decrease the chance of these adverse events.



Large particles of aerosol are deposited in the chamber before the patient inhales.



Inhaled aerosol is enriched in small particles that more readily travel to the small airways.

# ALTERNATIVE DRUGS USED TO TREAT ASTHMA



**Why do we need to use alternative drugs for treating asthma?**

## ALTERNATIVE DRUGS USED TO TREAT ASTHMA/ A. Leukotriene modifiers

**Leukotrienes** (LT) B<sub>4</sub> and the **cysteinyl leukotrienes**, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.

5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils.

**LTB<sub>4</sub> is a 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 LTB<sub>4</sub> and the cysteinyl leukotrienes.

Because **zafirlukast and montelukast** are selective antagonists of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes.



## ALTERNATIVE DRUGS USED TO TREAT ASTHMA/ A. Leukotriene modifiers



### Pharmacokinetics:

All three drugs are orally active and highly protein bound. Food impairs the absorption of zafirlukast. The drugs are metabolized extensively by the liver. Zileuton and its metabolites are excreted in urine, whereas zafirlukast, montelukast, and their metabolites undergo biliary excretion.

### 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. Other effects include headache and dyspepsia.

## ALTERNATIVE DRUGS USED TO TREAT ASTHMA/ 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.

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.

## ALTERNATIVE DRUGS USED TO TREAT ASTHMA/ 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.

**Why do we need to use ipratropium for treating asthma?**

Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

## ALTERNATIVE DRUGS USED TO TREAT ASTHMA/ 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  $\beta_2$  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.**

## ALTERNATIVE DRUGS USED TO TREAT ASTHMA/ E. Omalizumab

Omalizumab is a recombinant DNA-derived monoclonal **antibody** that selectively binds to human immunoglobulin E (**IgE**).

**This leads to decreased binding of IgE to its receptor on the surface of mast cells and basophils.**

Reduction in surface-bound IgE limits the release of mediators of the allergic response.

Omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients who are poorly controlled with conventional therapy.

**Its use is limited, why??**

**Adverse effects include serious anaphylactic reaction (rare), arthralgias, fever, and rash. Secondary malignancies have been reported.**

## 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 is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function.

## DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE



### A. Bronchodilators

Inhaled bronchodilators, including the  **$\beta$ 2-adrenergic agonists and anticholinergic** agents (ipratropium and tiotropium), are the foundation of therapy for COPD.

These 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  $\beta$ 2 agonist may be helpful in patients who have inadequate response to a single inhaled bronchodilator.

## DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE



### B. Corticosteroids

The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function and quality of life.

However, the use of an ICS is associated with an increased risk of **pneumonia**, and therefore, use should be restricted to these patients.

Although often used for acute exacerbations, oral corticosteroids are **not recommended** for long-term treatment.



## 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, pollen, or animal dander).

**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.

## DRUGS USED TO TREAT 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.

**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 (for example, fexofenadine, loratadine, desloratadine, cetirizine, and azelastine) are generally better tolerated.

## DRUGS USED TO TREAT ALLERGIC RHINITIS



### B. Corticosteroids

Intranasal corticosteroids, such as beclomethasone, budesonide, fluticasone, ciclesonide, mometasone, and triamcinolone, 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.**

## DRUGS USED TO TREAT ALLERGIC RHINITIS



### C. $\alpha$ -Adrenergic agonists

Short-acting  $\alpha$ -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  $\alpha$ -adrenergic agonist intranasal formulations should be used no longer than 3 days due to the risk of rebound nasal congestion (**rhinitis medicamentosa**).

Administration of oral  $\alpha$ -adrenergic agonist formulations results in a longer duration of action but also increased systemic effects.

## DRUGS USED TO TREAT COUGH



Coughing is an important **defense 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 defense reflex against an underlying bacterial infection and should not be suppressed.

## DRUGS USED TO TREAT COUGH

### A. Opioids

**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.

**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.