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Drugs acting on The Respiratory Disorders

- $Beta_2$ -Adrenergic Agonists.
- Methylxanthines
- Inhaled Anticholinergics
- Glucocorticoids
- Mast Cell Stabilizers
- Leukotriene Modifiers
- Antihistamines
- Decongestants
- Drugs for cough
- Cold remedies

1. Drugs for asthma

2. Drugs for allergic rhinitis and common cold

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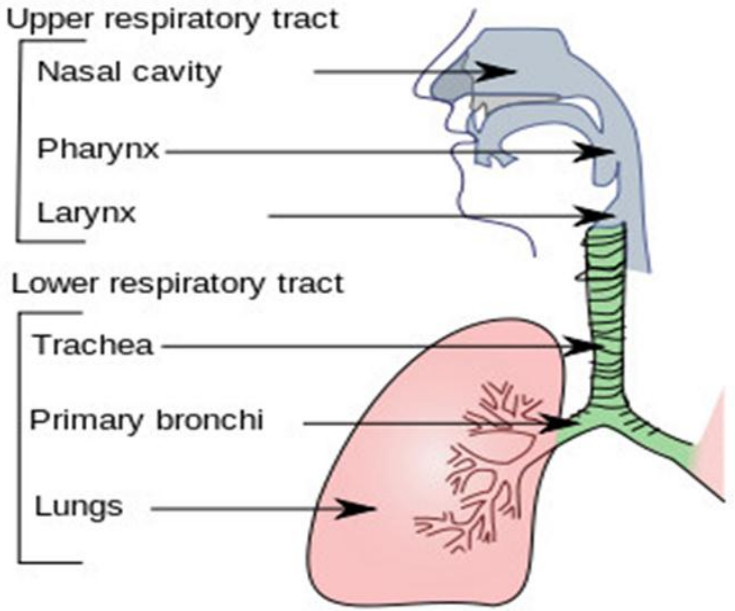
Drugs acting on the Respiratory System

- **Respiratory system** extending from the nose to the pulmonary capillaries and performs the essential function of gas exchange between the body and its environment.



- Drugs therapy used to treat respiratory tract disorders, is more effective in relieving respiratory symptoms than in curing the underlying disorders that cause the symptoms.

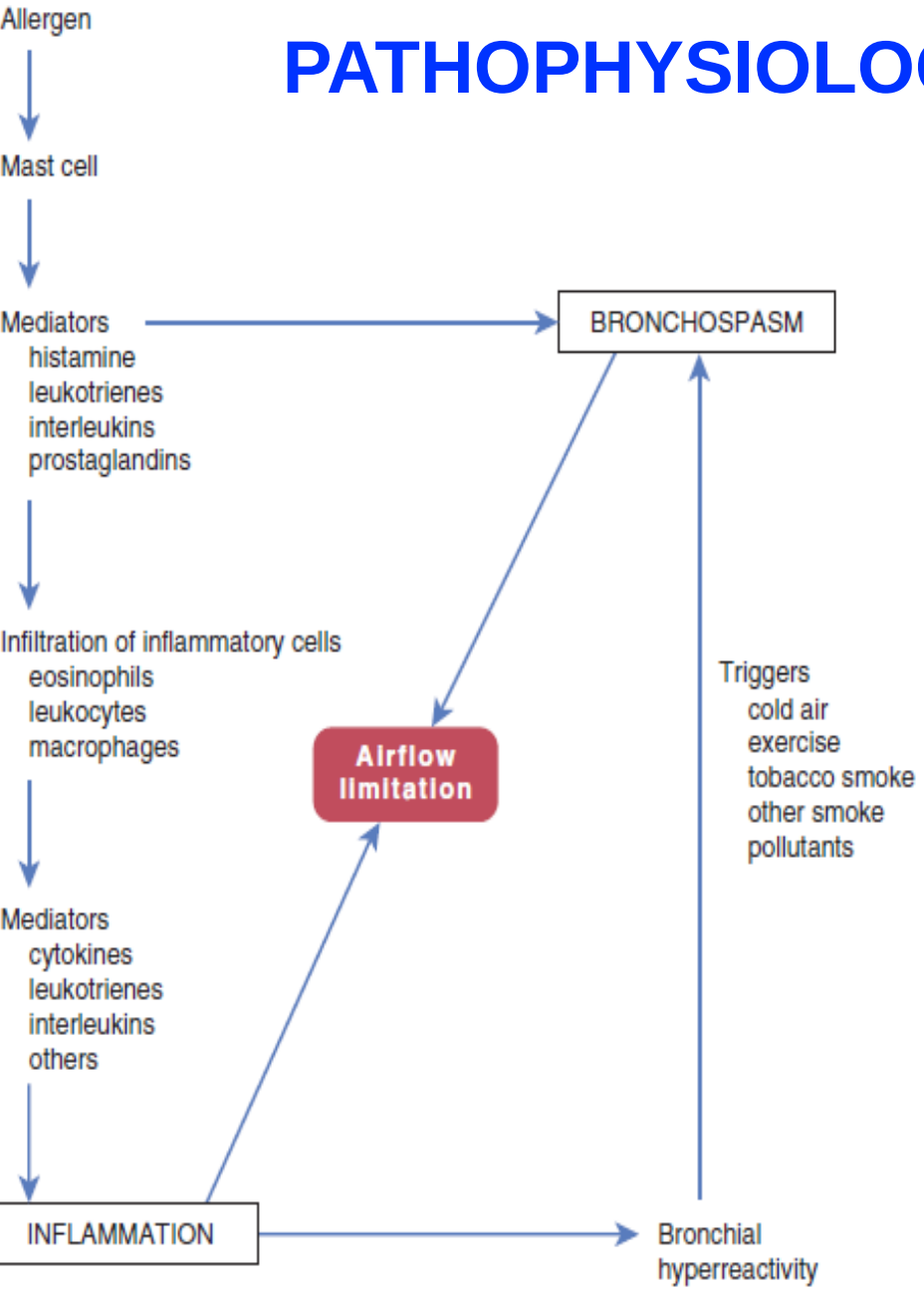
Treatment of Bronchial Asthma

- **Asthma** is a common, chronic inflammatory disorder of the airways that occurs in children and adult characterized by recurrent attacks of dyspnea (difficulty breathing) and wheezing caused by spasmodic constriction of the bronchi.

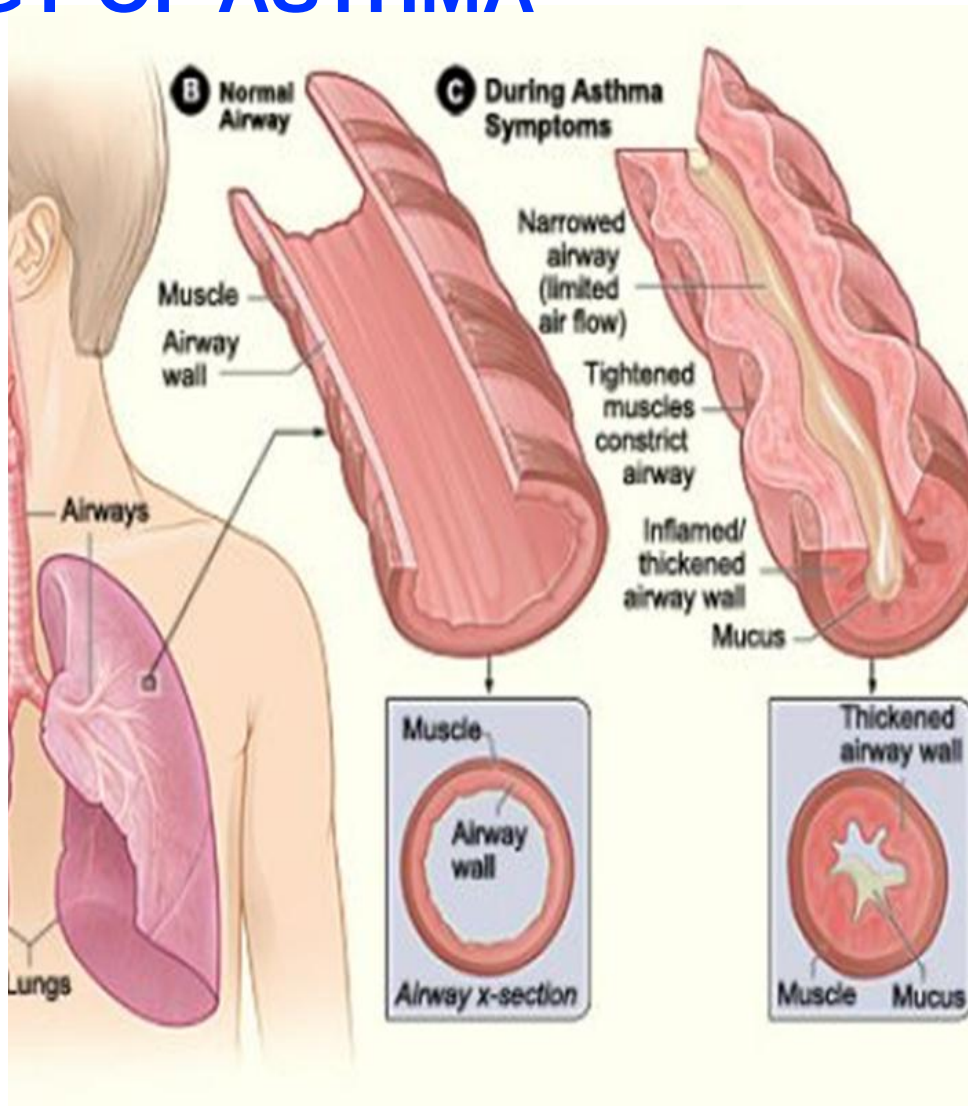
✓ Goals of asthma treatment

- **Relief the acute attack** (terminate acute bronchospasms in progress)
- **Prevent recurrence** (reduce the frequency of asthma attacks)

PATHOPHYSIOLOGY OF ASTHMA



re 76–1 ■ Allergen-induced inflammation and bronchospasm in asthma.



From therapeutic perspective, Symptoms of asthma result from a combination of:

- ✓ Bronchoconstriction
- ✓ Inflammation

****Accordingly, treatment must deal with both these components.**

👍 Approaches to treat asthma are :

1. **Prevention of exposure to allergen(s)** – determine precipitating factors and avoid them if possible
2. **Dilatation of narrowed bronchi** –**"Bronchodilators"** to reverse the bronchospasm
3. **Reduction of the bronchial inflammation and hyper - reactivity** –**"Anti-inflammatory drugs"** to inhibit or prevent the inflammatory components and the hyperactivity

- **DRUGS FOR ASTHMA: Prototype Drugs**
- The major drugs for treatment of asthma are fall into 2 main pharmacological classes:

1) Bronchodilators:

✓ **Beta2-Adrenergic Agonists**
  - Albuterol (inhaled, short acting)
  - Salmeterol (inhaled, long acting)

✓ **Methylxanthines:** Theophylline

✓ **Anticholinergic Drugs:** Ipratropium

2) Anti-inflammatory Drugs:

✓ **Glucocorticoids**
  - Beclomethasone (inhaled)
  - Prednisone (oral)

✓ **Mast cell stabilizer (Cromolyn, inhaled)**

✓ **Leukotriene modifier (Zafirlukast, oral)**

Administration of drugs

- Drugs used to prevent or treat pulmonary disorders are available in inhalation, oral and parenteral routes.
- **Drug therapy by inhalation: Aerosol therapy**
- Most of pulmonary drugs administered by inhalation, a route with 3 obvious advantages:

1. **Highly effective –**Increases therapeutic effects by delivering drugs directly to their site of action
2. **Relatively safe –** Reducing systemic adverse effects – the dose required is smaller than when the drug given orally resulting in ↓ drug's blood levels and thus ↓adverse effects.
3. **Faster –**Facilitates rapid relief of acute attacks.

   (immediate relief for bronchospasm)

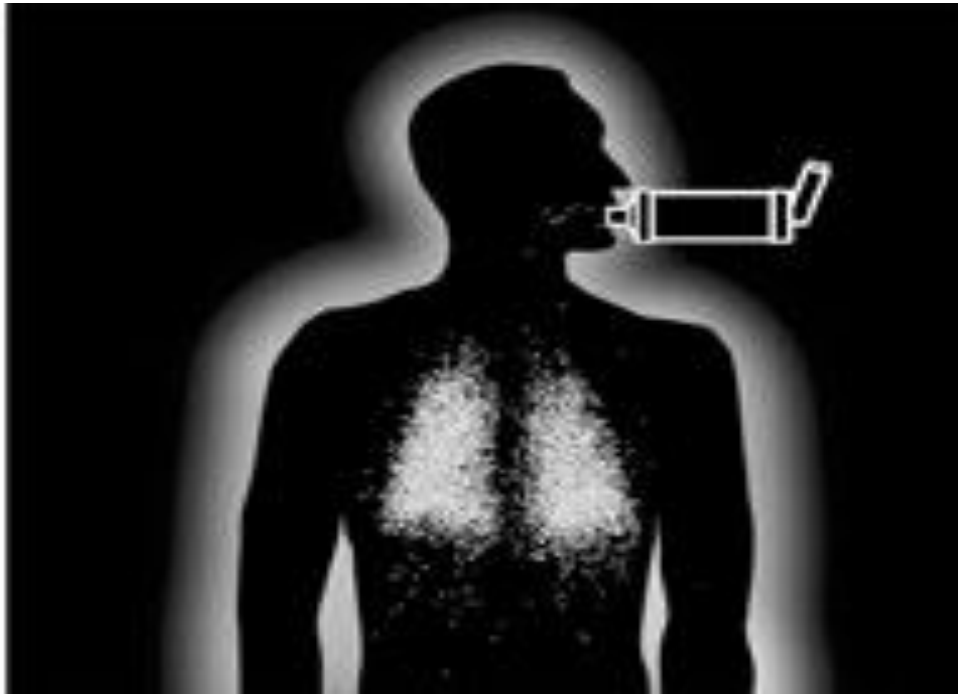
- Inhalation devices are employed in:

metered-dose inhalers, dry-powder inhalers, and nebulizers.

A **Metered-dose Inhaler** (MDI)
commonly used, small, handheld, pressurized device that deliver a measured dose of drug with each actuation. Dosing is usually accomplished with 1 or 2 inhalations. Several kinds of spacers are available to use with MDI.

Spacers (holding chamber): are devices that attach directly to the MDI to

1. increase delivery of drug to the lungs (more drug reaches its site of action in the lung – thereby ↑ therapeutic effects)
2. decrease deposition of drug on the oropharyngeal mucosa (less drugs is deposited in the mouth and throat).



- **Dry-powder inhalers** (DPIs) are used to deliver drugs in the form of a dry, micronized powder directly to the lungs – activated by the process of inhalation to deliver a fine powder directly to the bronchial tree.
- Unlike MDIs, DPIs are breath activated.

- **A nebulizer** is a small machine used to convert a drug solution into a mist. The droplets in the mist are much finer than those produced by inhalers, resulting in less drug deposit on the oropharynx and increased delivery to the lung. Inhalation of the nebulized mist can be done through a face mask or through a mouthpiece held between the teeth.

Disadvantage of aerosol therapy

1. The precise dose received by the patient is difficult to measure because it depends on the patient's breathing pattern and the correct use of the inhaler device. **Even under optimal conditions, only 10% to 50% of the drug actually reaches the lower respiratory tract. Patients must be carefully instructed on the correct use of these devices.
2. Swallowing medication that has been deposited in the oral cavity may cause systemic adverse effects if the drug is absorbed in the gastrointestinal tract.
3. Patients should rinse their mouth thoroughly following drug use to reduce the potential for absorption of the drug across the oral mucosa.

- **Oral route** is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation.
- **Parenteral route:** drugs can be given by injection in acute severe pulmonary disorders – when administration by aerosol therapy is inadequate or inappropriate.

- **Bronchodilators** provide symptomatic relief in patients with Asthma but do not alter the underlying inflammation that is part of the disease process.
- **Beta$_2$ -adrenergic agonists: Sympathomimetic drugs**
- E.g., **Albuterol, Formoterol, Salmeterol, Terbutaline** administered by inhalation (preferable route - for quick relief), orally or by injection (for emergency)
- Beta$_2$-adrenergic agonists are effective bronchodilators also called **Relievers** because they provide rapid symptomatic relief.
- They are first-line drugs for the treatment of acute bronchoconstriction selectively by activating the beta$_2$-receptors in the bronchial smooth muscle, resulting in bronchodilation and relieve bronchospasm and making breathing easier for the patient.
- Beta$_2$ activation also stabilises mast cells and suppress histamine release in the lung and increase ciliary motility.
- Most patients with asthma carry an inhaler containing a rapid-acting beta agonist to terminate acute attacks if they occur.

Adverse Effects and Nursing Interventions --- Patient Education

Inhaled agents have minimal adverse effects.	
Oral agents can cause tachycardia and angina because of activation of $beta_1$ receptors in the heart	➤ Advise clients to observe for signs and symptoms (chest, jaw, or arm pain or palpitations) and to notify the provider if they occur. ➤ Dosage may need to be lowered.
Tremors caused by activation of $beta_2$ receptors in skeletal muscle	➤Tremors usually resolve with continued medication use. ➤Dosage may need to be reduced.

Inhaled Anticholinergics

Antimuscarinic bronchodilators

- Anticholinergic drugs are not effective as the adrenergic agonists but can provide some relief to those patients who cannot tolerate the other drugs (rarely used).
- Anticholinergic drugs improve lung function by blocking muscarinic receptors on bronchial smooth muscle thereby causing bronchodilation
- In clinical practice two agents are currently available: Both drugs are administered by inhalation. **Ipratropium and Tiotropium**. Tiotropium has a much longer duration of action, and so can be dosed less often. With both drugs, systemic effects are minimal.

Methylxanthines: theophylline and aminophylline

- The methylxanthines were considered drugs of choice for treating asthma 30 years ago. However, use of these drugs nowadays has declined largely because we now have safer and more effective medications.
- Methylxanthines are infrequently prescribed because they have a narrow safety margin (low TI), especially with prolonged use.
- The methylxanthines are bronchodilators chemically related to caffeine – produces bronchodilation by relaxing smooth muscle of the bronchi. Although the mechanism of bronchodilation has not been firmly established, the most probable is blockade of receptors for adenosine.
- Theophylline is currently used primarily for the long-term oral prophylaxis of asthma that is unresponsive to beta agonists or inhaled corticosteroids.
- Methylxanthines are administered by the PO or IV routes, rather than by inhalation (because it is not active by this route).
- Adverse effects such as nausea, vomiting, and CNS stimulation occur frequently, nervousness and insomnia, and dysrhythmias may be observed at high doses.

Nursing Interventions -Patient Education

- **Methylxanthine has narrow therapeutic index therefore we must:**

✓ Before administered these drugs I.V., always ask if the patient is already taking theophylline orally. Don't combine oral and I.V and dosage must be carefully controlled

✓ Monitor for signs of toxicity: vomiting, tachycardia, tremor, headache and CNS excitation

✓ Serum drug levels should be monitored to help regulate dosage and avoid adverse effects

✓ Advise clients to take the medication as prescribed. If a dose is missed, the following dose should not be doubled.

✓ Instruct clients not to chew or crush sustained-release preparations. These medications should be swallowed completely.

Anti-inflammatory drugs also called **Controllers** because they provide long– term stabilization of symptoms, they are the foundation of asthma therapy

The principal anti-inflammatory drugs are the Corticosteroids

Corticosteroids are available in inhaled and systemic forms.

Inhalation	Oral	Parenteral steroids
Beclomethasone Budesonide Fluticasone	Prednisone Prednisolone Dexamethasone	Hydrocortisone Methylprednisolone Dexamethasone

Mechanism of Antiasthma Action

1. Glucocorticoids reduce asthma symptoms by suppressing Inflammation. Specific anti-inflammatory effects include:

✓ Decreased synthesis and release of inflammatory mediators (eg, leukotrienes, histamine, prostaglandins)

✓ Decreased infiltration and activity of inflammatory cells (eg, eosinophils, leukocytes)

✓ Decreased edema of the airway mucosa (secondary to a decrease in vascular permeability).

☼ ☼ Beneficial effects of suppressing airway inflammation include decreased mucus secretion, decreased edema of airway mucosa, and repair of damaged epithelium, with subsequent reduction of airway hyper-reactivity.

2. There is also some evidence that glucocorticoids may increase the number of bronchial $beta_2$ receptors as well as their responsiveness to $beta_2$ agonists.

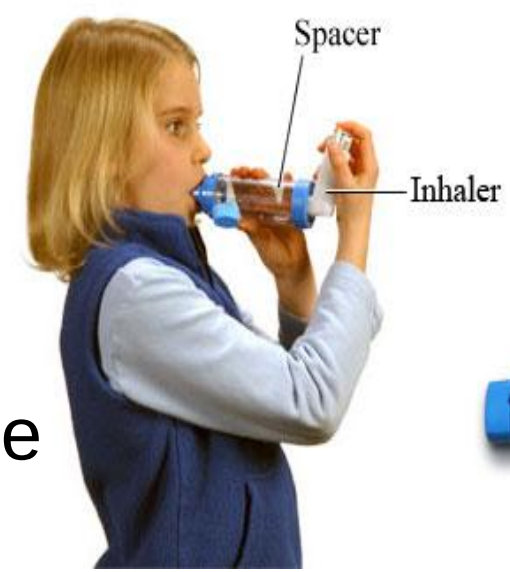
- Corticosteroids may be given systemically or by inhalation.

Inhaled corticosteroids

- Highly effective drugs – first-line therapy for asthma.
- Glucocorticoids are used for prophylaxis of chronic asthma. Accordingly, dosing must be done on a fixed schedule daily– because therapeutic effects develop slowly.
- Glucocorticoids do not alter the natural course of asthma, even when used in young children.
- Safe – corticosteroids suppress inflammation without producing major adverse effects, even when used in high doses.
- Reduces the need for systemic steroids in many cases, thus reducing the patient's risk of developing serious long-term adverse reactions.

The most common adverse reactions to inhaled corticosteroids are: (result from local deposition of inhaled corticosteroids)

- Oropharyngeal candidiasis
- Dysphonia
- Mouth irritation



To reduce the risk of these adverse effects, the patient should

1. use the lowest possible dosage to maintain control,
2. gargle after each administration (rinse out his mouth),
3. employ a spacer device during administration (which will greatly ↓drug deposition in the oropharynx)

**If candidiasis develops, it can be treated with antifungal drug.

Systemic corticosteroids

- Systemic forms are usually reserved for moderate to severe attacks, but they're also used in the patient with milder asthma that fails to respond to or control with other safer medications (inhaled corticosteroids and inhaled B_2-agonists) – because of their potential toxicity.

**When used acutely (less than 10 days), even in very high doses, oral glucocorticoids do not cause significant adverse effects. However, prolonged therapy, even in moderate doses, can be hazardous.

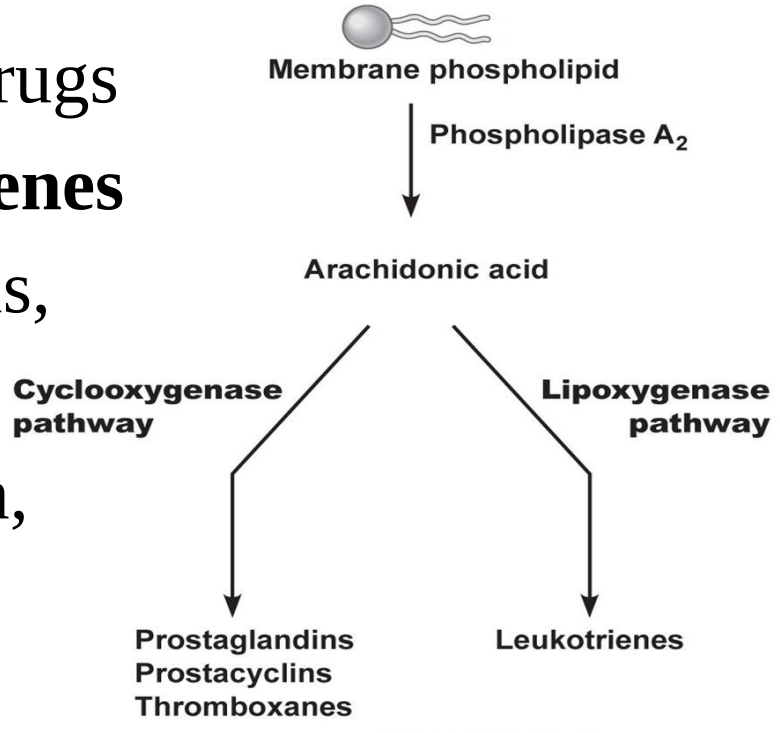
** If taken for longer than 10 days, systemic corticosteroids can produce significant adverse effects. (Potential adverse effects include adrenal suppression, osteoporosis, hyperglycemia, peptic ulcer disease, and, in young patients, growth Suppression).

- **Other Anti-inflammatory drugs, include**

Leukotriene Modifiers :

Mast Cell Stabilizers:

- **Leukotriene Modifiers:** drugs that suppress the effects of **leukotrienes** (compounds released from mast cells, eosinophils, and basophils that promote smooth muscle constriction, blood vessel permeability, and inflammatory responses).



- **Leukotrienes** formed by the lipoxygenase pathway of arachidonic acid metabolism in response to cellular injury.
- In patients with asthma, these drugs can decrease inflammatory responses, bronchoconstriction, airway edema and mucus secretion.

❍❍Leukotriene modifiers include two types: All are dosed orally.

1. **Leukotriene-receptor antagonists**, block leukotriene receptors, such as **Montelukast** and **Zafirlukast**
2. **Leukotriene synthesis inhibitors**, such as **zileuton**, blocks leukotriene synthesis by block the enzyme, 5-lipoxygenase, which is necessary for the formation of leukotrienes.

- **Indications**

– Prophylaxis of asthma: The drugs help to prevent acute asthma attacks but not effective in relieving acute attacks.
– Seasonal allergic rhinitis

Mast Cell Stabilizers: e.g., Cromolyn sodium and Nedocromil sodium

Expected mechanism of action

- These medications stabilize the cytoplasmic membrane of mast cells → impair the immediate response of mast cells to allergen → thereby preventing the release of histamine and other inflammatory mediators from mast cells.
- ⋆Mast cell stabilizers used for prophylaxis – not quick relief of symptoms.
- **Therapeutic Uses**

– Management of chronic asthma by inhalation
– Prophylaxis of exercise–induced asthma and prevention of allergen–induced attack
– Allergic rhinitis by intranasal route

- **Pharmacokinetics:** Cromolyn is poorly absorbed from the GIT but is well absorbed from the lung, and it is administered by inhalation only; it is eliminated unchanged in the urine and bile. Cromolyn also available as a nasal solution for prevention and treatment of allergic rhinitis.
- **Nursing Interventions**

– Teach the patients carefully about the drug therapy for accurate administration.
– Instruct the patients to take the leukotriene modifiers on an empty stomach, 1 hour before or 2 hours after meals; the bioavailability of these drugs is decreased markedly by the presence of food, and advise the patients to take mast cell stabilizers 15 min before exercise or exposure to allergen drug.

- Caution the patient that these drugs are not to be used during an acute asthmatic attack or bronchospasm; instead, regular emergency measures will be needed.

- Caution the patient to take the leukotriene modifiers continuously and not to stop the medication during symptom-free periods to ensure that therapeutic levels are maintained.

Drugs for Allergic Rhinitis

- Allergic rhinitis is the most common an inflammatory disorder that affects the upper airway.
- Major symptoms are sneezing, rhinorrhea (runny nose), pruritus (itching), and nasal congestion caused by dilation and increased permeability of nasal blood vessels. In addition, some patients experience associated conjunctivitis, sinusitis, and even asthma.
- Symptoms are triggered by airborne allergens, which bind to immunoglobulin E (IgE) antibodies on mast cells, and thereby cause release of inflammatory mediators, including histamine, leukotrienes, and prostaglandins.
- Allergic rhinitis has two major forms: seasonal (also known as hay fever) and perennial.
- Drug therapy is frequently necessary to control symptoms and to prevent secondary complications.

- The **therapeutic goals** of treating allergic rhinitis are to prevent its occurrence and to relieve symptoms. Thus, drugs used to treat allergic rhinitis may be grouped into two simple categories:

✓ Preventers are used for prophylaxis and include antihistamines, intranasal corticosteroids, and mast cell stabilizers.

✓ Relievers are used to provide immediate relief of acute allergy symptoms once they have occurred –include the oral and intranasal decongestants, usually drugs from the sympathomimetic class and usually used in conjunction with other agents to help relieve nasal congestion.

- In addition to treating allergic rhinitis with drugs, nurses should help patients identify sources of the allergies and recommend appropriate interventions.

- The **therapeutic goals** of treating allergic rhinitis are to prevent its occurrence and to relieve symptoms.

TABLE 77–1 ▪ Overview of Drugs for Allergic Rhinitis

Drug or Class	Route	Actions	Adverse Effects
Glucocorticoids	Nasal	Prevent inflammatory response to allergens and thereby reduce all symptoms.	Nasal irritation; possible slowing of linear growth in children
Antihistamines	Oral/nasal	Block H_1 receptors and thereby decrease itching, sneezing, and rhinorrhea; do *not* reduce congestion.	*Oral:* Sedation and anticholinergic effects (mostly with first-generation agents) *Nasal:* Bitter taste
Cromolyn	Nasal	Prevents release of inflammatory mediators from mast cells, and thereby can decrease all symptoms. However, benefits are modest.	None
Sympathomimetics	Oral/nasal	Activate vascular alpha$_1$ receptors and thereby cause vasoconstriction, which reduces nasal congestion; do *not* decrease sneezing, itching, or rhinorrhea.	*Oral:* Restlessness, insomnia, increased blood pressure *Nasal:* Rebound nasal congestion
Anticholinergics	Nasal	Block nasal cholinergic receptors and thereby reduce secretions; do *not* decrease sneezing, nasal congestion, or postnasal drip.	Nasal drying and irritation
Antileukotrienes	Oral	Block leukotriene receptors and thereby reduce nasal congestion.	Rare neuropsychiatric effects

Intranasal Corticosteroids e.g., **Beclomethasone, Fluticasone**……. intranasal spray devices.

- Intranasal steroids (have anti-inflammatory effects) are the most effective and safe drugs for prevention (prophylaxis) and treatment of allergic rhinitis (have to be used regularly to be effective). With proper use, over 90% of patients respond.
- **Adverse effects** are mild.
- Local side-effects include dryness, irritation of nose and throat, and epistaxis. Systemic effects are possible, but are rare at recommended dose.

Oral antihistamine

- 1st Generation e.g., **Chlorpheniramine, Diphenhydramine**
- 2nd Generation e.g., **Cetirizine, Fexofenadine, Loratadine, Claritin, Desloratadine**

- Drugs can be taken orally to control most of symptoms. However, they do not reduce nasal congestion (pharm. and adverse effects (previous lec.)
- For therapy of allergic rhinitis, antihistamines are most effective when taken *prophylactically*, and less helpful when taken after symptoms appear therefore they should be administered on a regular basis throughout the allergy season, even when symptoms are absent to prevent an initial histamine receptor activation.

- **Intranasal antihistamines**
- **e.g., Azelastine, Olopatadine** – supply in metered – nasal spray devices – indicated for adult and children over 12 years old.
- Benefits are equal to those of oral antihistamines. The usual dosage is 2 sprays in each nostril twice daily.
- The most common side effects – irritation of nasal mucosa; a bitter taste in the mouth – occur in 20 % of patients (if applied incorrectly). Although these drugs are considered a non-sedative antihistamine, some of patients experience somnolence.

- **Mast cell stabilizers and Leukotriene Modifiers**
- **Intranasal Cromolyn Spray (NasalCrom)**
- **Montelukast (Singulair)**
- These drugs reduce symptoms by suppressing release or effects of histamine and other inflammatory mediators. Accordingly, the drug is best suited for prophylaxis – not treatment – most effective when given before symptoms start.
- Beneficial effects may take a week or 2 to develop; patient should be informed for this delay.
- Adverse effects are minimal, less than with any other drug for allergic rhinitis.

Decongestants (Sympathomimetics)

- Decongestants are drugs that relieve nasal congestion by activating alpha1-adrenergic receptors on nasal blood vessels. This causes vasoconstriction, which in turn causes shrinkage of swollen membranes followed by nasal drainage.
- With topical (drops, spray) administration, vasoconstriction is both rapid and intense with rapid symptom relief and minimal adverse reactions – e.g., **Naphazoline, Oxymetazoline**.
- With oral administration, responses are delayed, moderate, and prolonged – e.g., **Phenylephrine, Pseudoephedrine**.
- Sympathomimetics do not reduce sneezing, rhinorrhea or itching. In addition to their use in allergic rhinitis they can reduce congestion associated with sinusitis and colds.

- **Adverse effects:**
- Intranasal sympathomimetics produce few systemic effects .
- ✘ **Rebound congestion:** The most serious, limiting side effect of the intranasal preparations is rebound congestion, a condition characterized by hypersecretion of mucus and worsening nasal congestion once the drug effects wear off.
- Once established, it can lead to a cycle of escalating congestion and increased drug use.
- The cycle can be broken by abrupt decongestant withdrawal, other option is to discontinue the drug in one nostril at a time but the better option is to use an intranasal glucocorticoid (in both nostrils) for 2 to 6 weeks, starting 1 week before discontinuing the decongestant.
- Development of rebound congestion can be minimized by limiting topical application to 3 to 5 days. Accordingly, topical sympathomimetics are not appropriate for individuals with chronic rhinitis.

- Other reactions include: burning and stinging of the nasal mucosa, sneezing, mucosal dryness or ulceration.
- When administered orally, decongestants do not produce rebound congestion. Their onset of action by this route, however, is much slower than when administered intranasal, and they are less effective at relieving severe congestion.
- The possibility of systemic adverse effects is also greater with the oral drugs (Discuss previously).

Cold remedies
Combination preparation

- The common cold is a viral infection of the upper respiratory tract that produces a characteristic array of annoying symptoms. It is fortunate that the disorder is self-limiting, because there is no cure or effective prevention for colds.
- Because no single drug can relieve all of the symptoms of a cold, the pharmaceutical industry has formulated a vast number of cold remedies that contain mixtures of ingredients.
- Many combination products are available for treating symptoms of the common cold.
- Many of the products contain 2 or more of the following ingredients: (1) chlorpheniramine (antihistamine),
  (2) pseudoephedrine (adrenergic nasal decongestant),
  (3) acetaminophen (analgesic and antipyretic),
  (4) drugs that suppress cough and loosen bronchial secretions,
  (5) caffeine.
- Many cold remedies are over-the-counter (OTC) formulations.

Drugs used to treat cough

(Antitussives, Expectorants, Mucolytics)

- Cough is a complex reflex involving the CNS, the peripheral nervous system, and the muscles of respiration.
- **Antitussives:** are drugs that suppress cough through its action on the CNS. The major clinical indication for use of antitussives is a dry, hacking, nonproductive cough that interferes with rest and sleep. It is not desirable to suppress a productive cough because the secretions need to be removed. Antitussives include:

➢ **Opioid** e.g., codeine, hydrocodone – in very low doses – act to elevate cough threshold

➢ **Non-opioid** e.g., dextromethorphan, Benzonatate.

- **Codeine** is the most effective cough suppressant available (Hydrocodone is somewhat more potent than codeine but carries a greater liability for abuse). The drug is active orally and decreases both the frequency and intensity of cough. Doses are low, about one-third those needed to relieve pain. At those doses, the risk of physical dependence is small.
- Care must be taken when using these medications in patients with asthma, because bronchoconstriction may occur.

- **Dextromethorphan** is the most effective of the non-opioid centrally acting antitussives.
- Dextromethorphan is chemically similar to the opioids and acts on the CNS to raise the cough threshold.
- Although it does not have the same level of abuse potential as the opioids, large amounts of dextromethorphan produce symptoms that include hallucinations, slurred speech, dizziness, drowsiness, euphoria, and lack of motor coordination.
- Nurses should be aware of the potential for abuse of this drug, especially among teens, and should counsel patients to not exceed the recommended dose.

- **Expectorant** is a drug that renders cough more productive by stimulating the flow of respiratory tract secretions.
- The most effective OTC expectorant is **Guaifenesin** – effective in treating patients with productive cough. Like dextromethorphan, guaifenesin produces few adverse effects and is a common ingredient in many OTC multi-symptom cold and flu preparations.
- **Mucolytics:** act directly on mucus, breaking down sticky, thick secretions, make it more watery and easily eliminated, e.g., **Acetylcysteine** by the inhalation route and used in patients who have cystic fibrosis, chronic bronchitis, or other diseases that produce large amounts of thick bronchial secretions.