

Treatment of asthma

By

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Disorders of Respiratory Function

Classification

Main disorders of the respiratory system are :

- 1. Bronchial asthma**
- 2. Cough**
- 3. Allergic rhinitis**
- 4. Chronic obstructive pulmonary disease (COPD, also called emphysema)**

Asthma

is a chronic inflammatory disorder of airways that result in recurrent attack of airway obstruction in response to external stimuli

Airways of the asthmatic patients are characterized by:

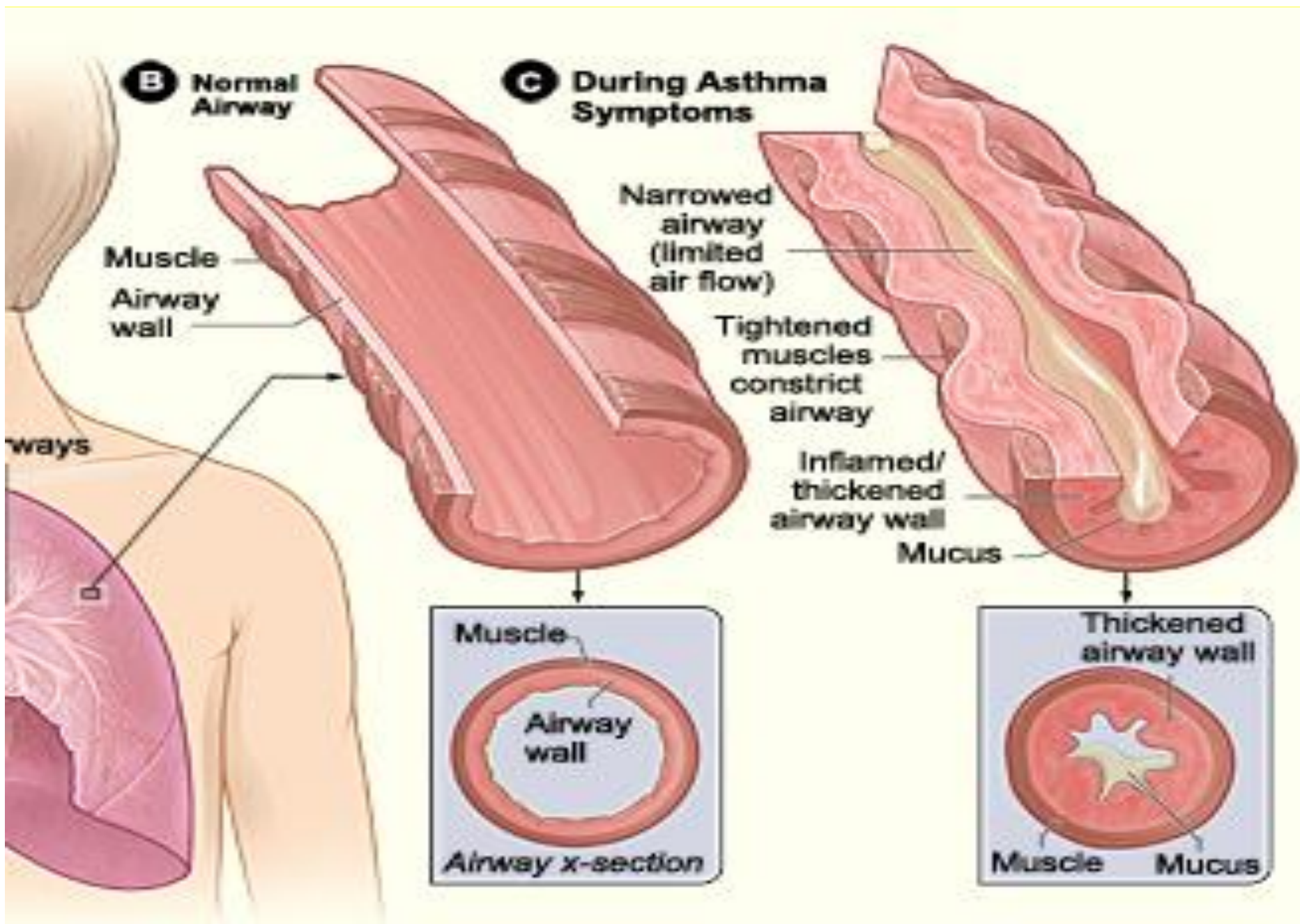
1. Airway hyper-reactivity: abnormal sensitivity of the airways to wide range of external stimuli as pollen, cold air and tobacco smoke.

2. Inflammation

- **Swelling**
- **Thick mucus production.**

3. Bronchospasm

- **constriction of the muscles around the airways, causing the airways to become narrow.**



Symptoms of asthma

Asthma produces recurrent episodic attack of

- **Acute bronchospasm (*immediate response*)**
- **Late response (*bronchospasm, inflammation, vasodilatation, Mucus secretions*).**
- **Shortness of breath**
- **Chest tightness**
- **Wheezing**
- **Rapid respiration**
- **Cough**

Symptoms can happen each time the airways are irritated.

Causes

- **Infection**
- **Emotional conditions**
- **Stress**
- **Exercise**
- **Pets**
- **Seasonal changes**
- **Some drugs as aspirin**

Airways Innervation

Efferent

1. Parasympathetic supply

- **M3 receptors in smooth muscles and glands.**

2. No sympathetic supply

- **B2 in smooth muscles and glands, mast cells**

Afferents

1. Irritant receptors (vagal fibres).

Upper airways

2. C-fiber receptors (sensory fibers)

Lower airways.

Anti asthmatic drugs

I. Bronchodilators : (relievers)

are used to relieve acute attack of bronchoconstriction

- 1. β_2 - adrenoreceptor agonists**
- 2. Antimuscarinics**
- 3. Xanthine derivatives**

II- Anti - inflammatory Agents (controllers)

reduce the number of inflammatory cells in the airways and prevent blood vessels from leaking fluid into the airway tissues. By reducing inflammation, they reduce the spasm of the airway muscle

II- Anti - inflammatory Agents: (control medications)

Are used as prophylactic therapy

- 1- Mast cell stabilizers.**
- 2- Glucocorticoids.**
- 3- Anti-IgE monoclonal antibody
(omalizumab)**

III- Leukotrienes antagonists.

- a. 5-Lipoxygenase inhibitors**
- b. Leukotriene–receptor inhibitors**

Sympathomimetics

Mechanism of Action

- 1- direct β_2 stimulation \longrightarrow stimulate adenylyl cyclase \longrightarrow Increase cAMP \longrightarrow bronchodilation**
- 2- Inhibit mediators release from mast cells.**
- 3- Increase mucus clearance by (increasing ciliary activity).**

Classification

1-Non selective β agonists.

Epinephrine - Isoprenaline

2-Selective β_2 - agonists.

Salbutamol (albuterol)

Terbutaline

Metaproterenol.

Salmeterol

Formeterol

1-Non selective β agonists.

Epinephrine

- Potent**
- rapid action (maximum effect within 15 min).**
- S.C. or by inhalation via aerosol or nebulizer.**
- Duration of action 60-90 min**
- Drug of choice for acute anaphylaxis**

Disadvantages

- 1- Not effective orally.**
- 2- Hyperglycemia # in Diabetes.**
- 3- CVS side effects : Tachycardia, arrhythmia, hypertension # angina**
- 4- skeletal muscle tremor**

Isoprenaline

- Potent bronchodilator
- Given s.c. or via inhalation (aerosol- nebulizer)
- rapid action (maximum effect within 5 min)
- Duration of action 60-90 min

Disadvantages

As epinephrine

Nebulizer



Inhaler

Selective β_2 –agonists

- **are drugs of choice for acute attack of bronchospasm**
- **Have longer duration of action (3-4 h) or 12 hr (salmeterol - formoterol)**
- **Can be given orally, parenterally or by inhalation (metered dose inhaler or nebulizer)**
- **Minimal CVS side effects**
- **Suitable for asthmatic patients with hypertension or heart failure.**

Disadvantages

- 1- Skeletal muscle tremors.**
- 2- Tolerance (B-receptors down regulation).**
- 3- Tachycardia (B1 - stimulation).**

Selective β_2 –agonists are classified into

Short acting β_2 agonists

Salbutamol (albuterol)

Terbutaline

Metaproterenol.

Long acting β_2 agonists

Salmeterol

Formeterol

Short acting β_2 agonists

Salbutamol (albuterol) (inhalation, orally, I.V.)

Terbutaline (inhalation, S.C., orally)

Metaproterenol (inhalation)

- **have rapid onset of action (15-30 min), 5 min by inhalation**
- **duration of action (3 – 4 hr)**
- **used for acute attack of asthma**
- **salbutamol is used for premature labor.**

2. Long acting selective β 2 agonists

- **Salmeterol & formoterol:**

- **have slow onset of action**
- **Long acting bronchodilators (12 hours)**
- **high lipid solubility (creates a depot effect)**
- **are not used to relieve acute episodes**
- **used for nocturnal asthma (prophylaxis)**
- **combined with corticosteroids**

Muscarinic antagonists

Ipratropium – Tiotropium

Blocks all subtypes of muscarinic receptors.

Kinetics

Quaternary derivatives of atropine

Not absorbed orally

Given by aerosol inhalation (aerosol-nebulizer)

Do not enter CNS

delayed onset of action (30 min)

Duration of action 3-5 hr

Pharmacodynamics

Bronchodilator

No anti-inflammatory action

Less effective than B2-agonists.

Minimal systemic side effects.

Uses

- 1. Chronic obstructive pulmonary diseases.**
- 2. Adjuncts to B2 agonists & steroids for acute asthma**
- 3. Patients intolerant to B2 agonists**

Tiotropium

Longer duration (24 h)

Used for COPD

Methylxanthines

Theophylline (orally)

Aminophylline (theophylline + ethylene diamine) (orally-parenterally).

Mechanism of Action

1- are phosphodiesterase inhibitors

↑ cAMP → bronchodilation

2- Adenosine receptors antagonists (A₁).

3- Increase diaphragmatic contraction

4- Stabilization of mast cell membrane

Pharmacological Effects :

1- relaxation of bronchial smooth muscles

2- CNS stimulation.

*** stimulant effect on respiratory center.**

*** decrease fatigue & elevate mood.**

*** tremors, nervousness, insomnia,
convulsion**

3. ↑ contraction of diaphragm → improve ventilation

4. CVS:

+ ve Inotropic (↑ heart contractility)

+ ve chronotropic (↑ heart rate)

vasodilatation ↓ blood pressure

5. GIT : Increase gastric acid secretions

Kidney : weak diuretic action (↑ renal blood flow)

Pharmacokinetics

- Absorbed orally (given after meals)
- Metabolized in the liver by Cyt P450 enzymes ($t_{1/2} = 8 \text{ h}$)

$T_{1/2}$ is decreased by

Smoking, drinking, children.

Enzyme inducers (phenobarbitone-rifampicin)

$T_{1/2}$ is increased by

Enzyme inhibitor (cimetidine, erythromycin)

Uses

- 1. second line drug in asthma (theophylline is given orally as sustained-release preparation)**
- 2. For status asthmaticus (aminophylline is given as slow infusion)**

Side Effects

low therapeutic index narrow safety margin

monitoring of theophylline blood level is necessary

CNS side effects: seizures

CVS effects: hypotension, arrhythmia, cardiac arrest

Nausea & vomiting

II- Anti - inflammatory Agents

by reducing inflammation in airways, they reduce bronchial hyper-reactivity, spasm of the airways.

II- Anti - inflammatory Agents

1- Glucocorticoids.

2- Mast cell stabilizers.

3- Leukotrienes antagonists.

a. 5-Lipoxygenase inhibitors.

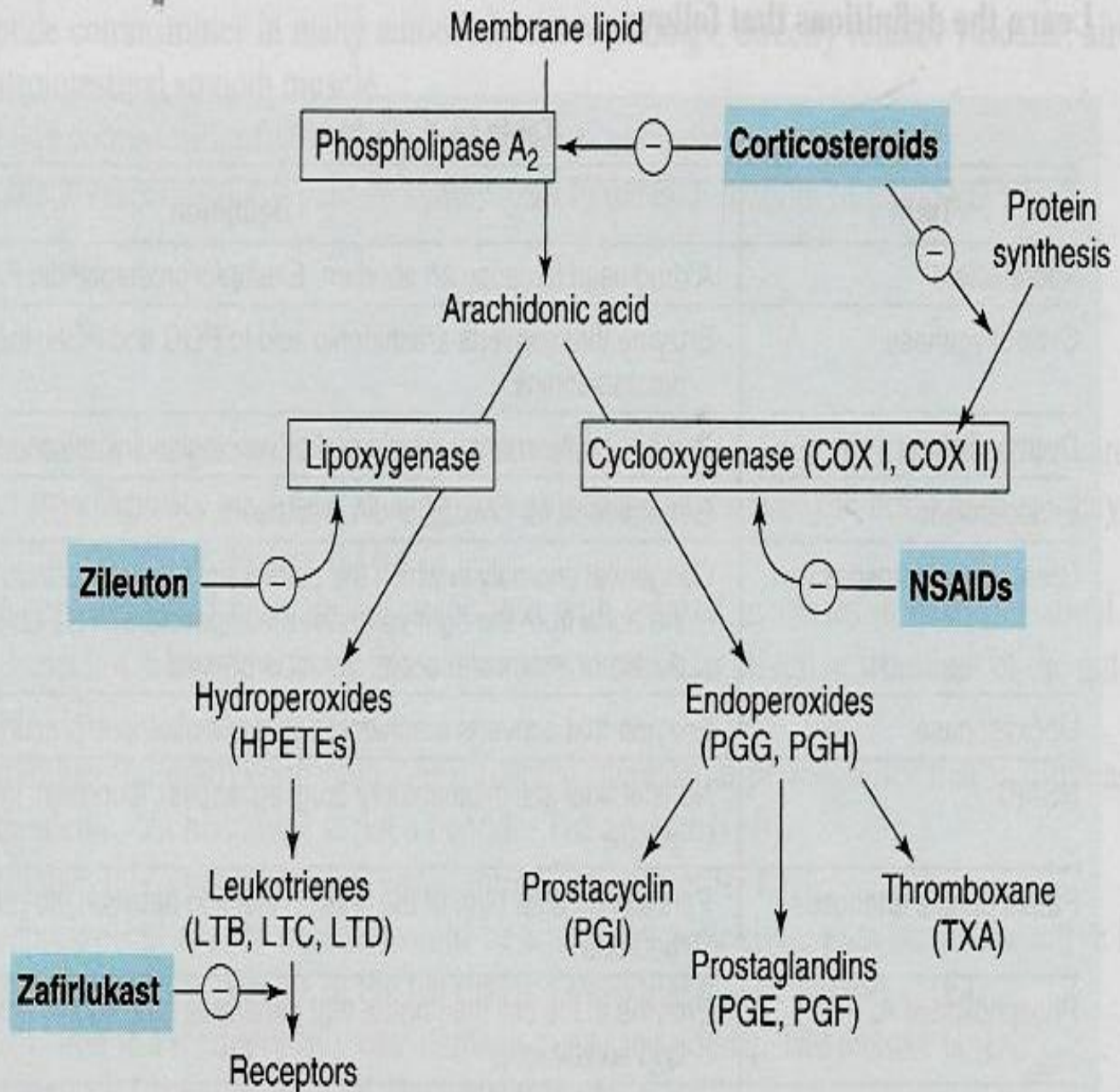
b. Leukotriene–receptor antagonists.

Glucocorticoids

Mechanism of action

- 1. Inhibition of phospholipase A2 decrease synthesis of arachidonic acid & prostaglandin and leukotrienes**
- 2. Decrease inflammatory cells in airways
e.g. macrophages, eosinophils**

- **Mast cell stabilization decrease histamine release**
- **decrease capillary permeability and mucosal edema.**
- **Inhibition of antigen-antibody reaction**
- **upregulate B2 receptors (**additive effect to B2 agonist**).**



Routes of administration

Inhalation (metered-dose inhaler):

Beclomethasone, fluticasone (high first pass effect in liver & low bioavailability)

orally:

prednisone

Injection:

hydrocortisone

Pharmacodynamics

- **not bronchodilators**
- **reduce bronchial inflammation**
- **reduce bronchial hyper-reactivity to stimuli**
- **Effective in allergic, exercise, antigen and irritant-induced asthma.**

- **effect usually attained after 2-4 weeks (delayed onset of action).**
- **maximum action at 9-12 months.**
- **given as prophylactic medications (to reduce frequency of asthma attacks)**

- **Abrupt stop of glucocorticoids should be avoided and dose should be tapered (*adrenal insufficiency syndrome*).**

Uses

Inhalation

- **relatively safe**
- **used as first-line treatment to control moderate to severe asthma in children and adults alone or in combination with beta-agonists**

**oral/parenteral corticosteroids
produce systemic effects and are
reserved for:**

- management of acutely ill patients**
- Status asthmaticus (i.v.).**

Side effects due to prolonged use of oral corticosteroids

- **Adrenal suppression**
- **Growth retardation**
- **Osteoporosis**
- **Fat distribution**
- **Hypertension**
- **Hyperglycemia**
- **fluid retention**

- weight gain**
- susceptibility to infections**
- Cataract**
- Glaucoma**
- wasting of the muscles**
- psychosis**

Inhalation has very less side effects.

- Oral candidiasis (thrush).**
- Dysphonia (voice hoarseness).**

Mast cell stabilizers

Sodium cromoglycate -nedocromil

act partially by stabilization of mast cell membrane.

Pharmacokinetics

- **Inhalation (aerosol, microfine powder, nebulizer).**
- **Poor oral absorption (10%)**
- **half life is 90 minutes.**

Pharmacodynamics

- **Not bronchodilators**
- **prophylactic anti-inflammatory drug**
- **Reduce bronchial hyper-reactivity.**
- **Effective in exercise, antigen and irritant-induced asthma.**
- **children respond better than adults**

Uses

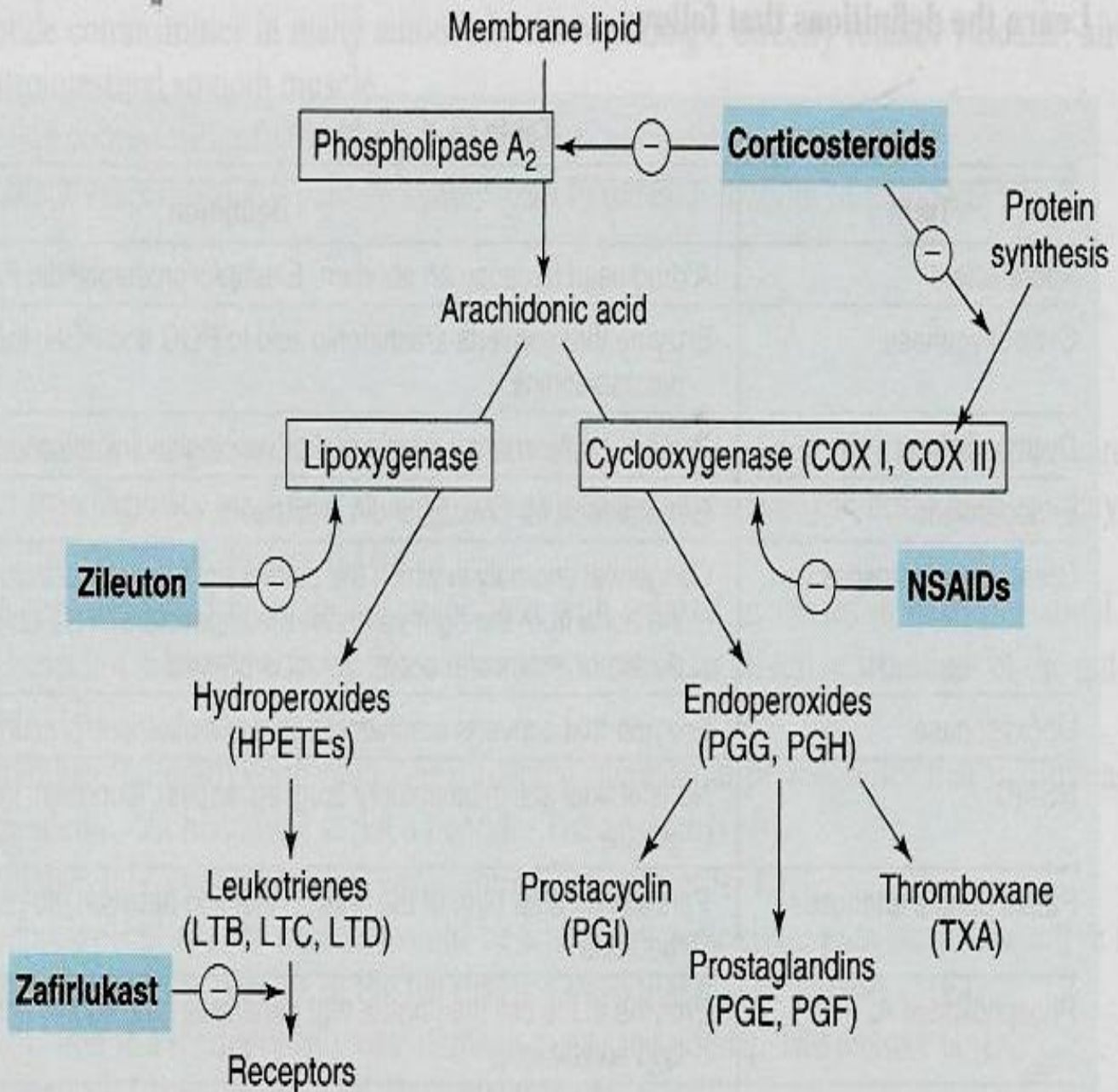
- **Prophylaxis in asthma especially in children.**
- **Allergic rhinitis.**
- **Conjunctivitis**

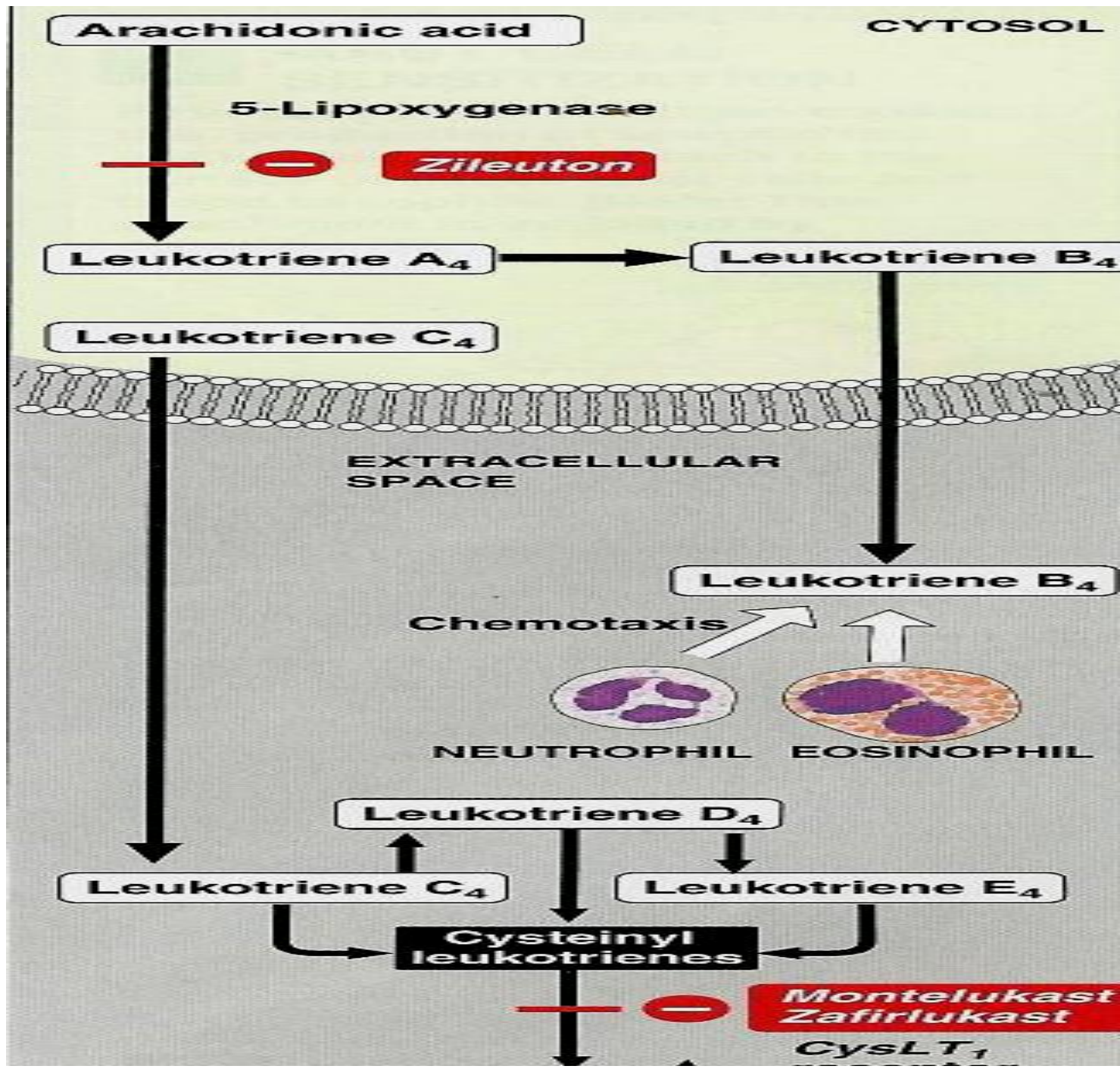
Side Effects are mild

- **Bitter taste**
- **minor upper respiratory tract irritation (burning sensation, nasal congestion)**

Leukotrienes antagonists

- **5-Lipoxygenase inhibitors.**
- **Leukotriene–receptor antagonists.**





- **Leukotrienes**
- **synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells)**
- **Products of 5-lipo-oxygenase action on arachidonic acid**
- **Leukotriene B4:**
chemotaxis of neutrophils , eosinophils

Cysteinyl leukotrienes C4, D4 & E4:

- bronchoconstriction**
- increase bronchial hyper-reactivity**
- mucosal edema**
- mucus hyper-secretion**

5-Lipoxygenase inhibitors

Zieluton

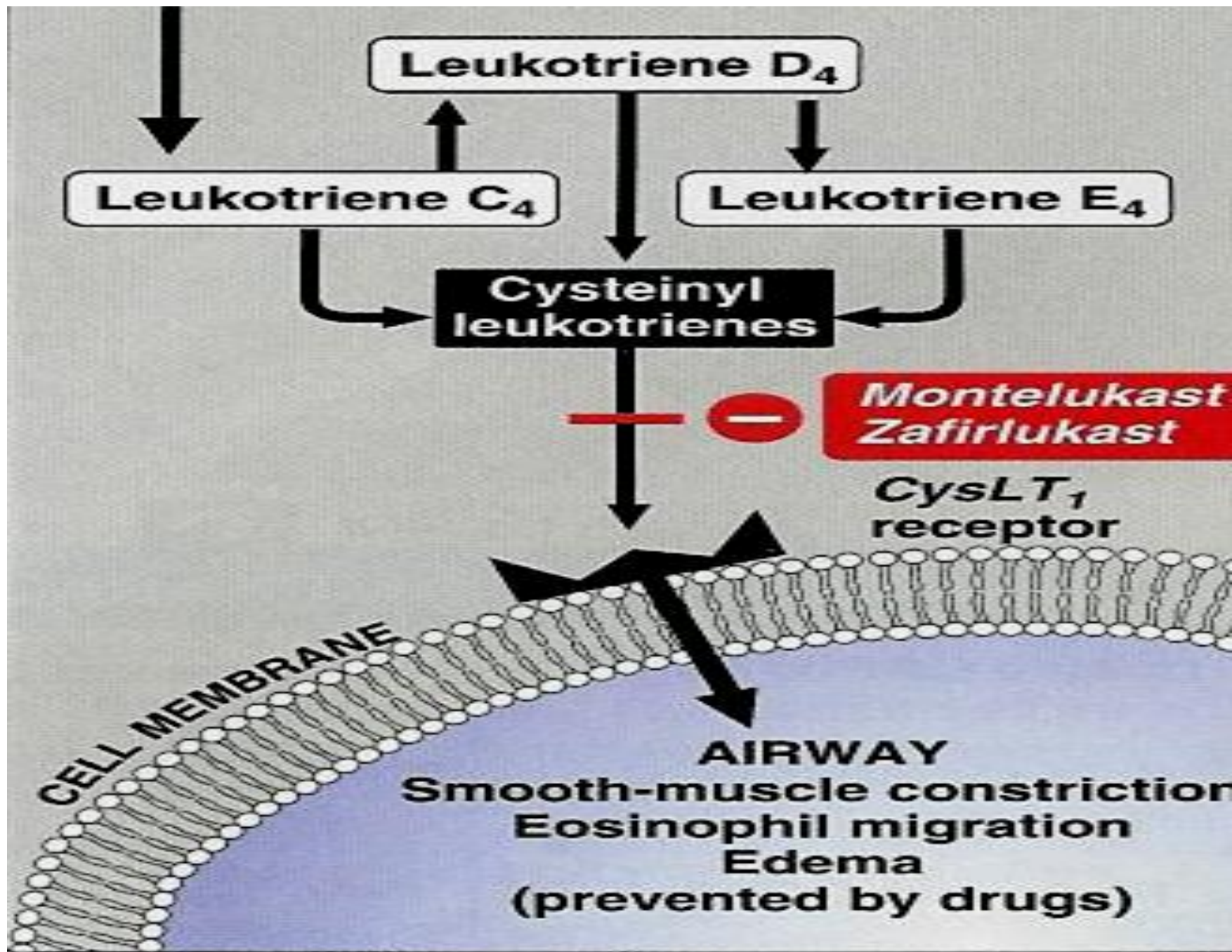
- **is a selective inhibitor of 5-lipoxygenase**
- **inhibits synthesis of leukotrienes (LTB₄ , LTC₄, LTD₄& LTE₄).**
- **Given orally**
- **Short duration of action.**
- **Is given (3-4 times/ day).**

Leukotriene receptor antagonists

Zafirlukast, Montelukast

Pranlukast, Cinalukast

- **are selective, reversible inhibitors of cysteinyl leukotriene (LTD₄) on Cys LT₁ receptors.**
- **Taken orally.**



Uses of antileukotriene drugs

- **Used for prophylaxis of mild to moderate asthma**
- **Aspirin-induced asthma**
- **Prevention of antigen and exercise-induced asthma**
- **Are not effective to relieve acute attack of asthma**

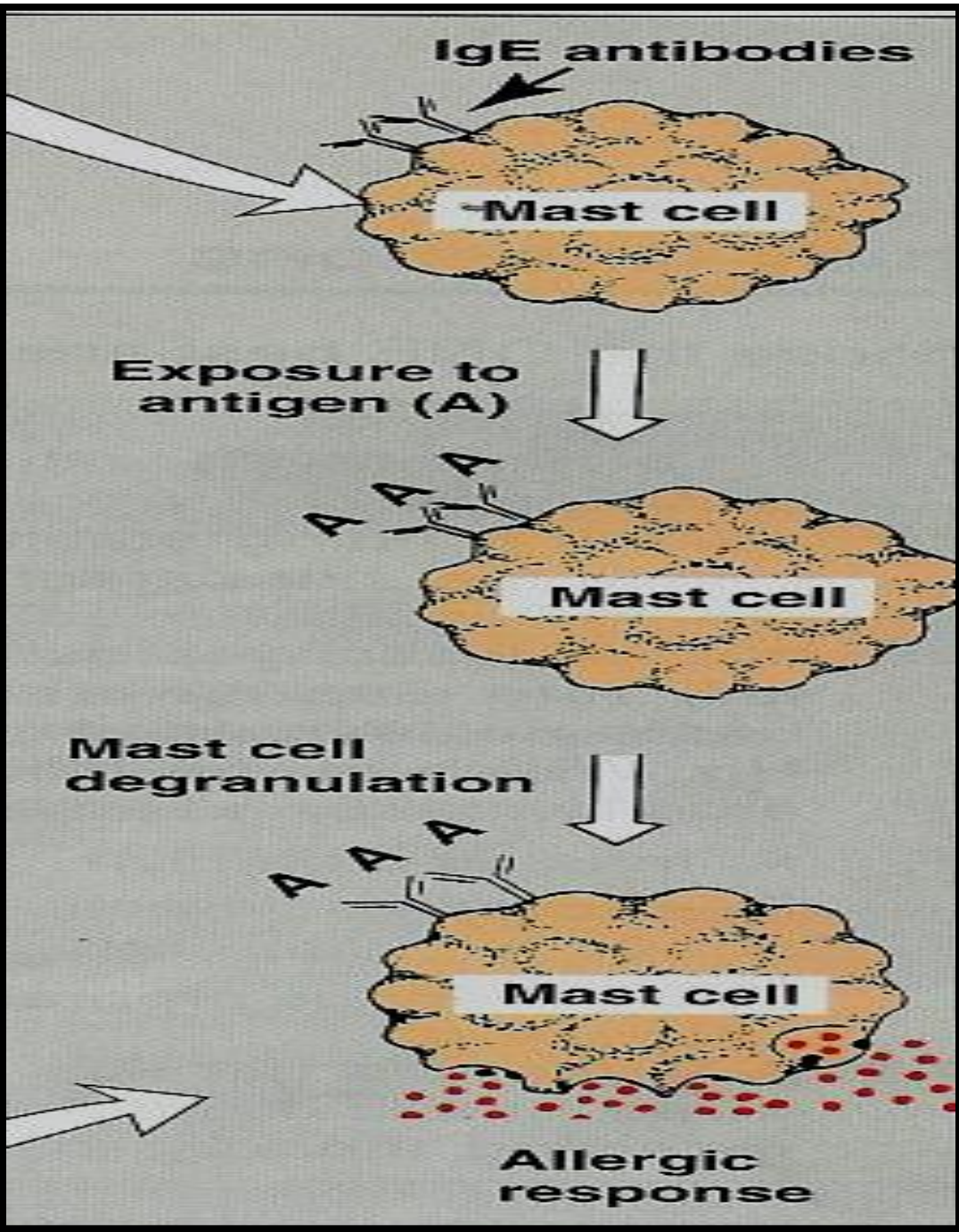
- **All antileukotriene drugs**
- **Are bronchodilators**
- **Have anti-inflammatory action**
- **less effective than inhaled corticosteroids**
- **potentiate corticosteroid actions**
(*has corticosteroid sparing effect*
low dose of corticosteroid can be given).

Side effects of Leukotriene antagonists

- **Elevation of liver enzymes.**
- **Headache**
- **Dyspepsia.**
- **Rare: Churg-Strauss syndrome (eosinophilic vasculitis).**

Omalizumab

- **is a monoclonal antibody directed against human IgE**
- **prevents IgE binding with its receptors on mast cells & basophils**
- **Decrease release of allergic mediators**
- **Used to treat allergic asthma**
- **Expensive-not first line therapy**



Treatment of COPD

- **Chronic irreversible airflow obstruction**
- **Smoking is a high risk factor**
- **Inhaled bronchodilators**
 - **Inhaled antimuscarinics (main drug)**
 - **Short acting bronchodilators**
 - **these drugs can be used either alone or combined**

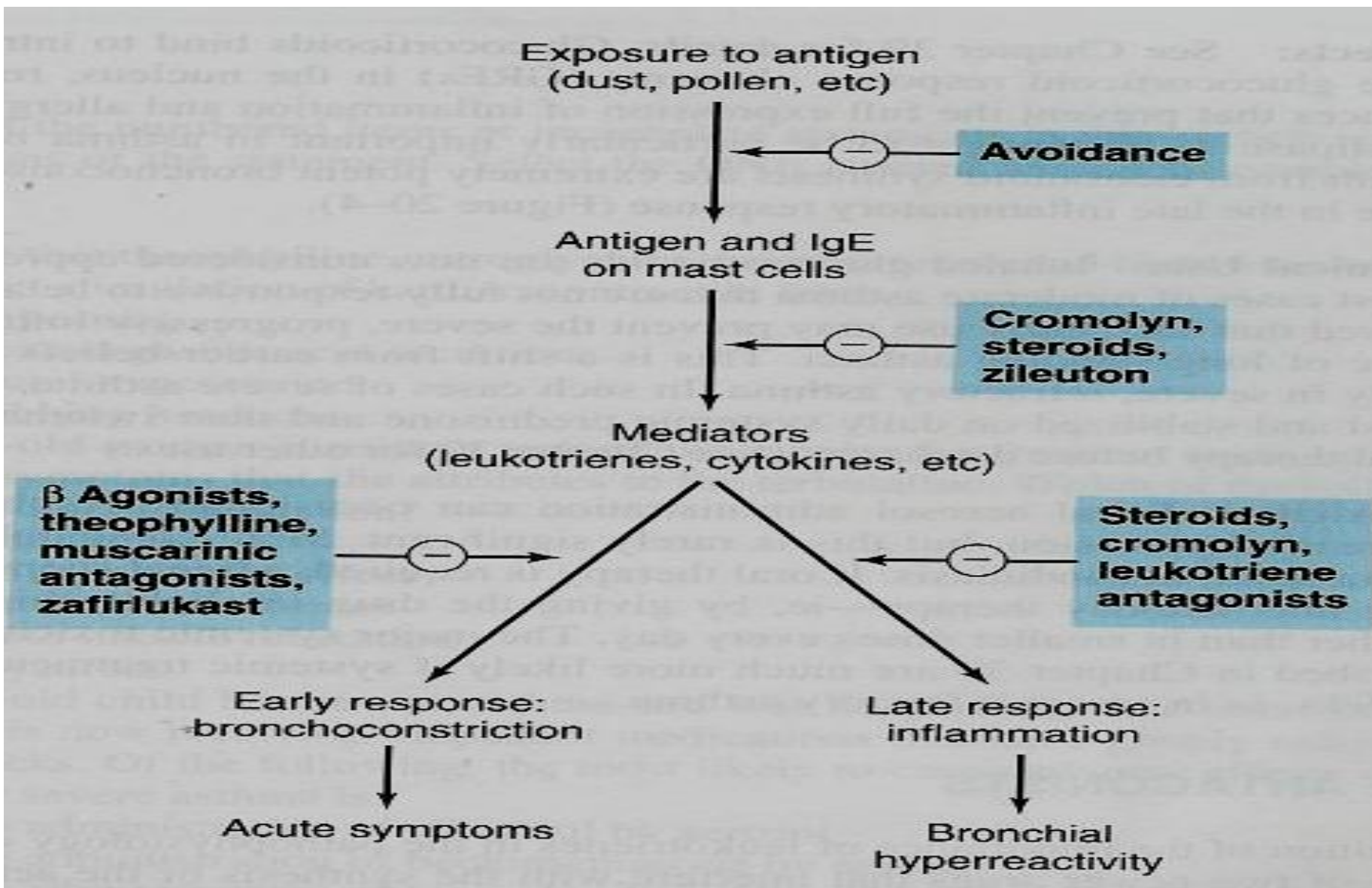
Examples

- salbutamol + ipratropium**
- Salmeterol + Tiotropium (long acting-less dose frequency)**

For severe COPD

- Bronchodilators**
- Inhaled glucocorticoids**
- Oxygen therapy**
- Antibiotics**

Summary for treatment of asthma



Bronchodilators (relievers for bronchospasm)

Drugs		
B2 agonists Salbutamol, terbutaline	<ul style="list-style-type: none"> – Short acting – main choice in acute attack of asthma – Inhalation 	↑ Adenyl cyclase ↑ cAMP
Salmeterol, formoterol	Long acting, Prophylaxis Nocturnal asthma	
Antimuscarinics Ipratropium (Short) Tiotropium (long)	Main drugs For COPD Inhalation	Blocks M receptors
Xanthine derivatives Theophylline Aminophylline	(orally) (orally- parenterally)	•Inhibits phosphodiesterase ↑ cAMP

Anti-inflammatory drugs (prophylactic)

Corticosteroids Beclomethasone, Fluticasone	Inhibits phospholipase A2 inhalation
prednisone	Orally
Hydrocortisone	parenterally
Mast stabilizers Cromoglycate, nedocromil	Inhalation Prophylaxis in children
Cysteinyl antagonists Zileuton (5 lipoxygenase inhibitor) Zafirlukast (block LTD4 effect)	(orally) (orally)
Omalizumab	Injection SC Anti IgE antibody

Cough

Physiological Cough (Productive Cough)

Is a protective reflex mechanism that removes foreign material and secretions from the bronchi and bronchioles.

Unproductive Cough

occurs due to exposure to irritant vapors or gases or due to pathological conditions as chronic bronchitis.

Antitussives

Are drugs used to suppress dry cough

1. Peripheral antitussives : e.g. Benzonatate
2. Central antitussives.
 - a. **Narcotic analgesics**
 - Morphine
 - Codeine
 - Methadone
 - Hydrocodone
 - b. **Synthetic narcotic analgesics**
 - c. **Antihistaminics (H1-Blockers)**

Narcotic analgesics

Codeine

- 1. opiate with less addiction liability.**
- 2. Potent antitussive**
- 3. Weak analgesic.**

Side Effects

- 1- Constipation.**
- 2- Inhibition of mucociliary clearance (thick sputum).**
- 3- Decrease secretions in the bronchioles**
- 4- Drowsiness & mild respiratory depression**
- 5- Dependence.**
- 6- Dry mouth.**

Synthetic narcotic analgesics

dextromethorphan - levopropoxyphene.

Dextromethorphan

- 1- As potent as codeine.**
- 2- No drowsiness.**
- 3- Less constipating effect.**
- 4- No respiratory depression.**
- 5- No inhibition of mucociliary clearance.**
- 6- No addiction.**

Antihistaminics (H1-Blockers)

**Diphenhydramine
Triprolidine.**

Side Effects

- **Anticholinergic actions**
- **Sedation**
- **Drowsiness.**

NOTES

- **Antitussives are used for dry cough.**
- **Contraindicated in**
 - **chronic bronchitis**
 - **cough associated with asthma**
(**harmful sputum thickening and retention**).

Expectorants

Are drugs used to facilitate expulsion of secretions and exudates from the respiratory passages by cough

They increase the fluidity of sputum and its expulsion by cough.

- **Potassium citrate**
- **Potassium acetate**
- **Ammonium chloride**
- **Ipecacuanha**
- **Na and K iodide.**
- **guaiacol.**

These drugs are used in chronic inflammation of respiratory mucosa (chronic bronchitis).

Mucolytics

acts by reducing the viscosity of sputum.

- 1. Acetyl cysteine (interfering with disulphide bonds in mucus).**
- 2. Bromohexine (destroy mucopolysaccharide structure of mucus).**
- 3. Steam inhalation**

Uses

- 1. Acute and chronic bronchitis**
- 2. Asthma**