Respiratory Pharmacology

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Agents used to treat cough

- Cough is one of the most common symptoms seen in clinical practice.
- The initial stimulus arises in the bronchial mucosa, where irritation results in stimulation of "Cough" receptors, which are specialized stretch receptors. Afferent impulses reach the cough center in the medulla via the vagus nerve and trigger a cough reflex.

Causes of cough:

- **Acute cough:** respiratory infection is the most common cause.
- **Chronic cough:**
  - Upper airway cough syndrome (post-nasal drip): due to allergic rhinitis, chronic sinusitis or tonsillitis. It is the most common cause of chronic cough.
  - Bronchial asthma: the 2nd most common cause.
  - Gastoesophageal reflux disease (GERD).
  - Other causes: ACEIs, lung tumors, CHF.

MANAGEMENT OF COUGH

- **Specific treatment:** directed to the cause of cough e.g. antibiotics for respiratory infections.
- **Non-specific treatment:**
  - **Antitussives:** are used to stop dry cough.
  - **Mucolytics and expectorants:** are used in productive cough to liquefy bronchial secretions and facilitate their removal.

COUGH SUPPRESSANTS (ANTITUSSIVES)

Definition: they are drugs that reduce the frequency or intensity of coughing.

Peripheral antitussives: they ↓ afferent impulses of the cough reflex.

- **Steam inhalation with menthol or tincture benzoin compound**

– It is one of the best and easy ways to relieve acute cough. Inhaling water steam with or without medications (e.g. menthol) helps flush out mucus and moisturizes dry, irritated air passages. The efficacy of added medication is not proved.

- **Benzonatate**

– It is a glycerol derivative chemically related to the local anesthetic **procaine**. It depresses peripheral cough receptors at the lung by local anesthetic effect.

Central antitussives: they inhibit cough center in the medulla.

- **Opioids: Codeine and hydrocodone**

– They are *natural* derivatives of morphine. They directly inhibit the cough center in the medulla at doses that are lower than those needed for analgesia.
– They are generally not recommended because of adverse effects.

Adverse effects

– Drowsiness and constipation.
– Drug dependence if used for long duration.
– Respiratory depression in large doses. Children less than 5 years old are more sensitive to respiratory depression so, codeine is not recommended to children < 5 years.

Opioid isomers: Dextromethorphan

- It is *synthetic* L-isomer of opioids.
- It has selective central antitussive action with **very few** opioid effects (i.e. **less** addiction liability, analgesic action, respiratory depression, or constipation).
- High doses can cause neuropsychiatric effects e.g. sedation and hallucinations.

MUCOLYTICS

Definition: they are agents that reduce viscosity of respiratory secretions without increasing their amount.

Bromhexine

- Bromhexine acts on the mucus at the formative stages within the mucus-secreting cells. It disrupts the structure of acid mucopolysaccharide fibers in mucoid sputum and produces a less viscous mucus, which is easy to expel.
- Because bromhexine can disrupt the gastric mucosal barrier, it should be avoided in patients with peptic ulcer.

- **Ambroxol**

– It stimulates synthesis and release of surfactant by type II pneumocytes. Surfactant acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall.

- ***N*-Acetylcysteine and carbocyseine**

– Acetylcysteine has free sulfhydryl (-SH) groups that break disulfide bonds in mucus and reduces its viscosity.

- **N.B.** Intravenous *N*-acetylcysteine is used as an antidote for acetaminophen (paracetamol) toxicity (quite apart from its mucolytic activity).

EXPECTORANTS

Definition: drugs that increase water content and amount of the respiratory secretions. This action facilitates the removal of respiratory secretions.

- **Potassium iodide**

– Iodides accumulates in the bronchial glands and stimulate secretion of low viscosity watery mucous.

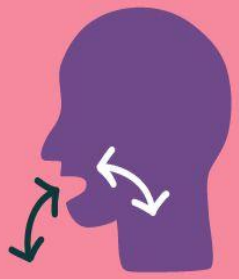
- **Guaifenesin**

– It is one of the most widely used over-the-counter (OTC) expectorants. It increases bronchial fluid secretions by unclear mechanism.

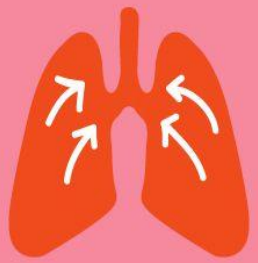
Drugs Used to Treat Asthma

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

Severe Asthma Symptoms



Rapid breathing

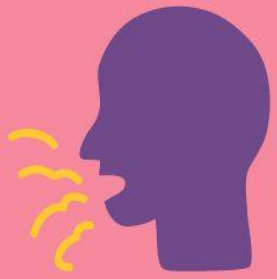


Shortness of breath

Chest tightness

Wheezing

Nighttime asthma episodes

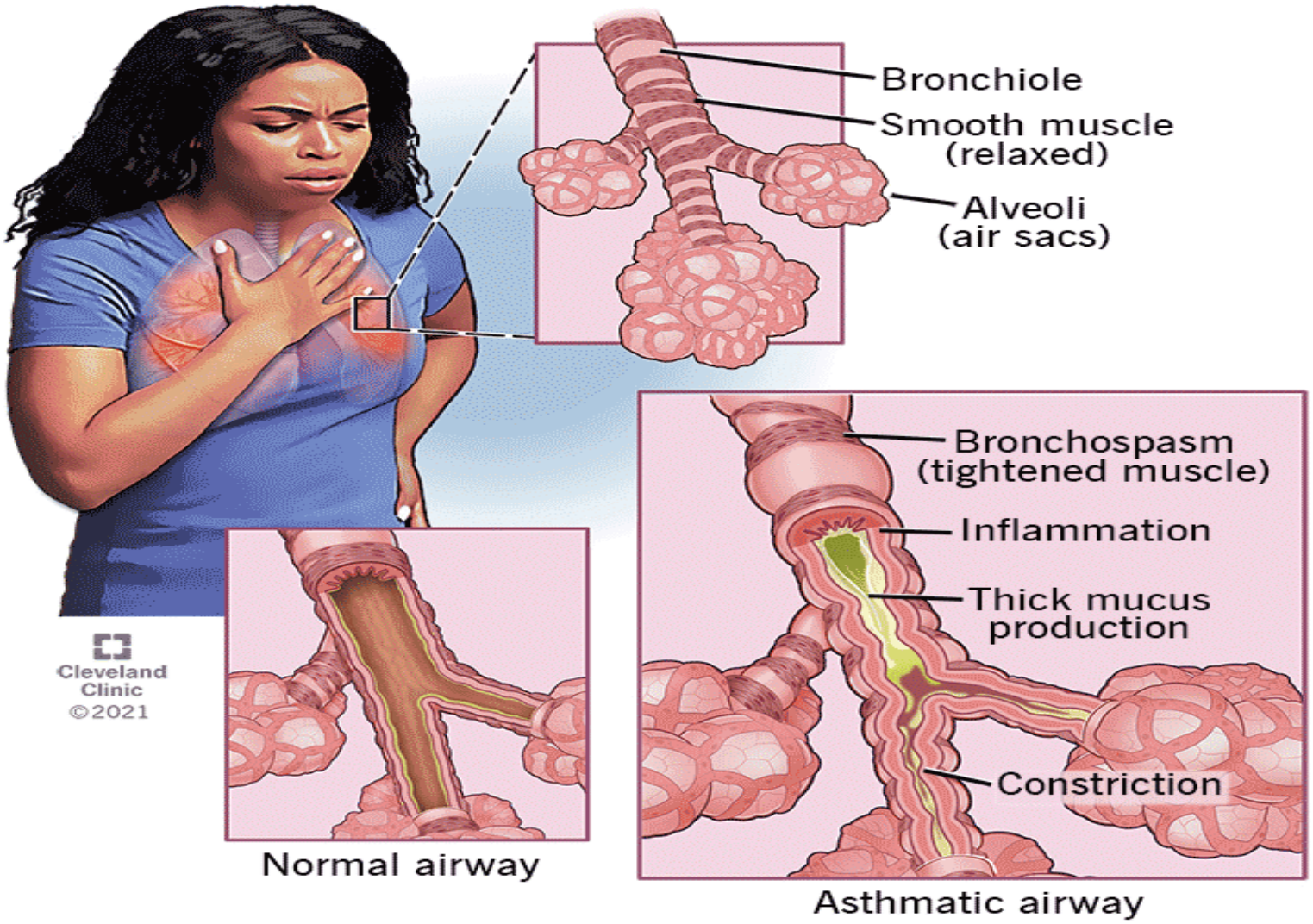


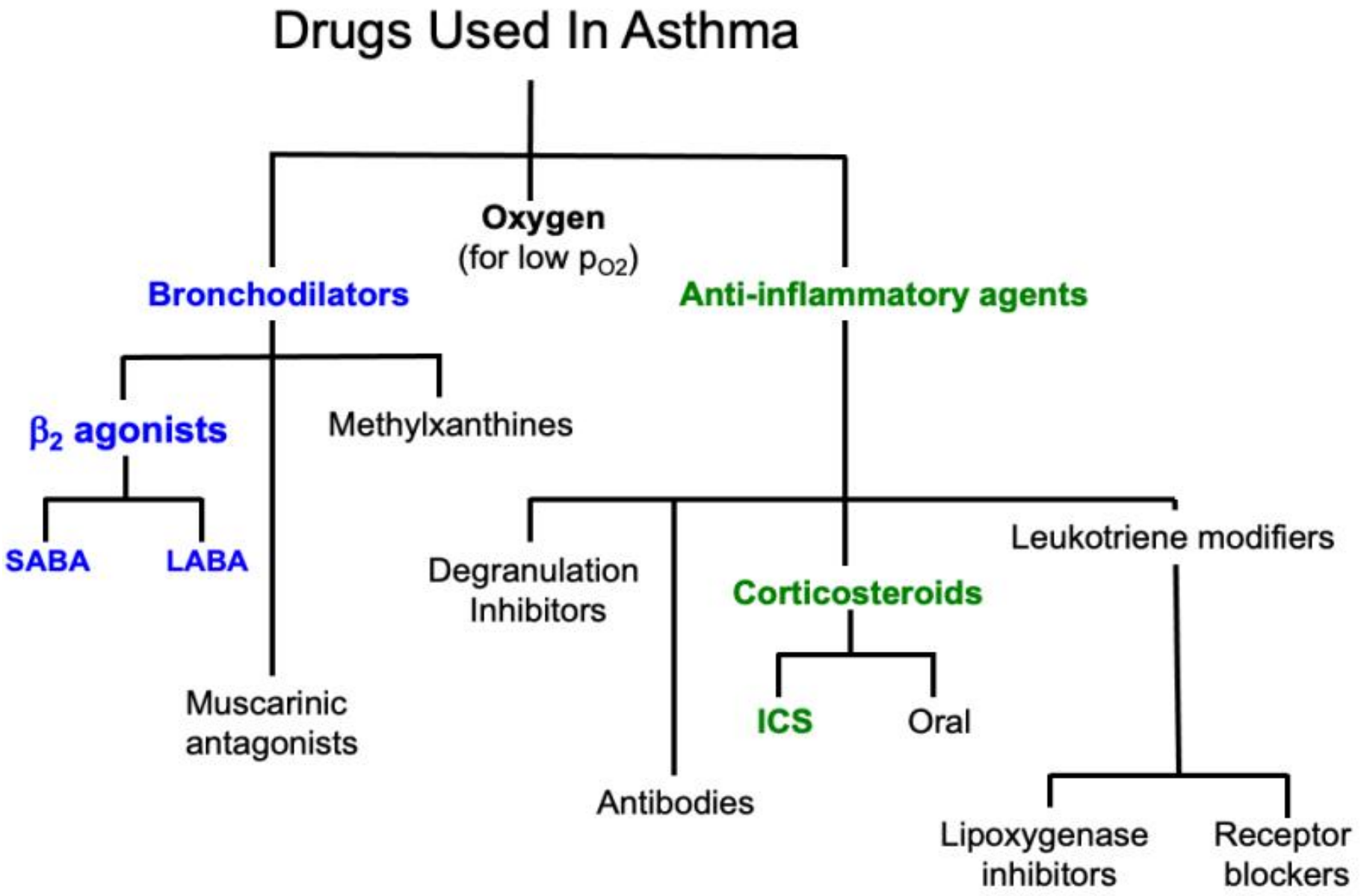
Chronic cough

Racing heartbeat

verywell

What is an Asthma Attack?




Drugs Used In Asthma
Oxygen
(for low p_{O2})
Bronchodilators
Anti-inflammatory agents
β_2 agonists
Methylxanthines
SABA
LABA
Muscarinic antagonists
Degranulation Inhibitors
Corticosteroids
Leukotriene modifiers
ICS
Oral
Antibodies
Lipoxygenase inhibitors
Receptor blockers

A- BRONCHODILATORS

β2-agonists

-Stimulates β2-adrenergic receptors of bronchi

Short-acting: salbutamol (quick relief)

Long-acting: salmeterol

Side effects:

Tremors
Tachycardia
Tolerance
Hypokalemia
Hyperglycemia
Hyperlipidemia
Constipation.

Anticholinergic drugs

-Block M3 receptors

Short-acting: Ipratropium

Long-acting: tiotropium

Side effects:

Tolerance

Methylxanthines

-inhibit phosphodiesterase increase cAMP

theophylline & aminophylline

Used in patients whose asthma does not respond to β2- agonists

Side effects:

narrow therapeutic window

Dysrhythmia (IV administration), which can be fatal.

GIT disturbance

β-adrenergic agonists

Classification

- **Non-selective β-receptor agonists:** e.g. adrenaline, isoprenaline and ephedrine. They are rarely used as bronchodilators.
- **Selective β2 agonists:**
  Short acting: salbutamol, terbutaline, fenoterol (duration 3-4 hrs).
  Long acting: salmeterol and formoterol (duration 12 hrs).

Mechanism of action

- Stimulation of bronchial β_2 receptors → ↑ cAMP → bronchodilatation.
- Stimulation of β_2 receptors in the mast cells → ↓ histamine release
- They ↓ bronchial inflammation and wall edema.

Use of LABA monotherapy is contraindicated, and LABAs should be used only in combination with an asthma controller medication, such as an inhaled corticosteroid (ICS). ICS remain the long-term choice in asthma, and LABAs are controllers of considered to be useful adjunctive therapy for attaining control in moderate to severe asthma.

Adverse effects

– Tachycardia and arrhythmia

- Tremors of skeletal ms and nervousness.
- Tolerance with prolonged use *(requiring temporary cessation of the drug)*.
- Hypokalemia *(due to shift of K^+ from blood to cells)*.

Muscarinic antagonists: Ipratropium bromide

- **Atropine** blocks M_3 receptors in airway ms leading to bronchodilatation through unopposed β_2 action, but it is **not used for treatment of asthma** because:
  - It is non-selective M_3 blocker leading to many side effects e.g. dry mouth and urine retention.
  - It can cross BBB and causes CNS side effects e.g. sedation.
  - It causes excessive dryness of bronchial secretions making it difficult to expel

- **Ipratropium is more preferred than atropine because:**
  - It is more selective muscarinic blocker than atropine.
  - It is quaternary ammonium compound that can't cross BBB.
  - Does not cause excessive dryness of bronchial secretions.

- **Ipratropium is not sufficient alone for bronchodilatation.** It is usually combined with **β_2 agonists** to get synergistic effect.

Methylxanthines

Classification

- **Natural:** e.g. caffeine, theophylline, and theobromine.
- **Semisynthetic:** e.g. aminophylline (salt of theophylline).

For asthma, the most commonly used xanthine is **theophylline.**

Mechanism and pharmacological effects

- Xanthines are adenosine **A receptor antagonists** leading to:
  - Bronchodilatation (block bronchoconstrictor effect of adenosine).
  - CNS stimulation (block the inhibitory effect of adenosine on the CNS)
  - ↓ mediator release from mast cells.
  - ↑ AV conduction.

- They inhibit **phosphodiestrase** enzyme (PDE3 and PDE4) → ↑ cAMP leading to:
  - Bronchodilatation (PDE4).
  - ↑ cardiac contractility and arrhythmogenic action (PDE3).
  - VC of cerebral and VD of peripheral vessels.
  - Relaxation of most smooth muscles (GIT, biliary, ureteric, etc).
  - Diuresis.

Therapeutic uses

- **Respiratory uses:**

  - Acute severe asthma:

- **CNS uses:**

  - To reverse CNS depression.
  - To delay physical and mental fatigue (caffeine).
  - Treatment of migraine (caffeine + ergotamine): to increase VC of cerebral blood vessels and increase absorption of ergotamine from GIT.
  - Neonatal apnea syndrome: caffeine is the agent of choice.

- **CVS uses:**

  - Acute pulmonary edema due to acute left sided HF.

REDUCTION OF BRONCHIAL INFLAMMATION

Corticosteroids

Mechanism of action

Corticosteroids can effectively ↓ bronchial inflammation and **hyperreactivity** through:

- They inhibit B cell function → ↓ antigen-antibody reaction.
- They inhibit T cell functions → ↓ mediators and cytokine release.

- They inhibit phospholipase A2 enzyme →↓ synthesis of PGs & LTs.
- Corticosteroids cause up-regulation of β2 receptors.

PROPHYLACTIC TREATMENT

The following classes of drugs are not bronchodilators but are used to reduce frequency of asthma exacerbations.

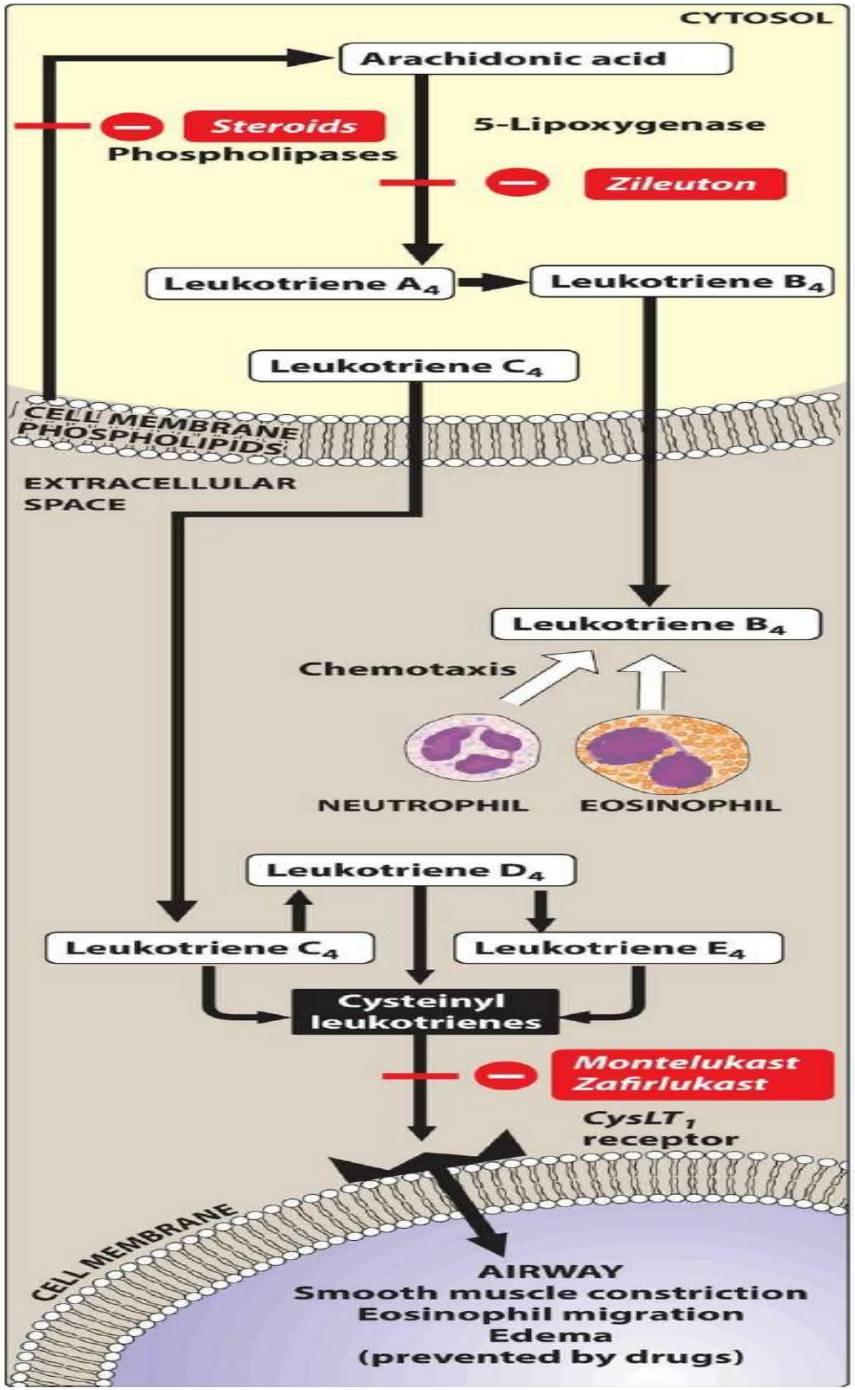
Leukotriene inhibitors:

Zafirlukast and montelukast

- They **block leukotriene (LTD4) receptors.**
- Zafirlukast is given twice daily but montelukast is given once daily.

Leukotriene modifiers

Leukotrienes (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. 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. ***Zafirlukast*** **and** ***montelukast*** are selective antagonists of the cysteinyl leukotriene-1 receptor, and they block the effects of cysteinyl leukotrienes . These agents are approved for the prevention of asthma symptoms. They should not be used in situations where immediate bronchodilation is required.


CYTOSOL
Arachidonic acid
Steroids
Phospholipases
5-Lipoxygenase
Zileuton
Leukotriene A4
Leukotriene B4
Leukotriene C4
CELL MEMBRANE PHOSPHOLIPIDS
EXTRACELLULAR SPACE
Leukotriene B4
Chemotaxis
NEUTROPHIL
EOSINOPHIL
Leukotriene D4
Leukotriene C4
Leukotriene E4
Cysteinyl leukotrienes
Montelukast
Zafirlukast
CysLT1 receptor
CELL MEMBRANE
AIRWAY
Smooth muscle constriction
Eosinophil migration
Edema
(prevented by drugs)

Zileuton

- It inhibits 5-lipooxygenase enzyme →↓ leukotriene synthesis.
- Zileuton is microsomal P450 inhibitor and can inhibit the metabolism of many drugs e.g. warfarin and theophylline.

- In clinical trials, leukotriene inhibitors reduced frequency of asthma exacerbations as equal to corticosteroids.
- Montelukast is approved to control asthma in children.

- **Anti-IgE monoclonal antibodies: Omalizumab**
  - Omalizumab is a new drug that inhibits the binding of IgE to mast cells and prevents mast cell degranulation. It may also inhibit IgE synthesis by B cells.
  - It reduces frequency and severity of asthma even when the dose of corticosteroids is reduced.

Thanks


عندما أحزن .. أغني
فأكتشف أن صوتي أسوأ
من مشاكلي .. فأبتسم !!
جورج برناردشو