

## Antiasthmatics (Antiasthmatic Drugs) — Definition and Classification

[See online here](#)

**Asthma is a chronic airway hyperresponsiveness (with acute exacerbations), which is widespread all over the world in both children and adults. In most cases, it is in response to environmental stimuli. The main pathological changes are bronchospasm, edema, and mucosal plugging, and the symptoms are wheezing, cough and breathlessness. Asthma therapy is directed against bronchospasms or inhibition of inflammation in general or their mediators such as leukotrienes. The most common drugs used are inhaled  $\beta_2$  agonists and inhaled corticosteroids.**

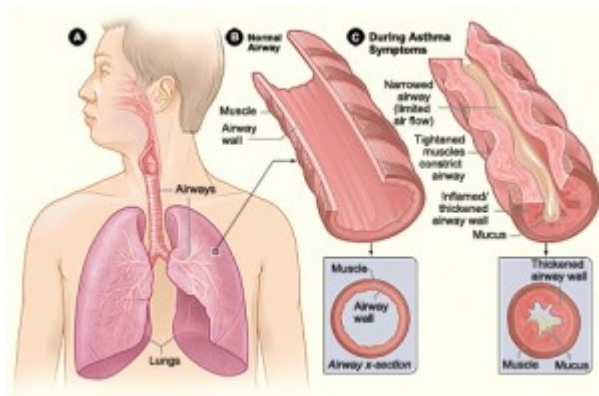


## Pathophysiology of Asthma

**Asthma** is a **chronic inflammatory disease** of the airway, involving airflow obstruction due to airway inflammation and bronchial hyperresponsiveness (manifesting as **bronchoconstriction**, **edema** and mucus plugging).

A variety of stimuli can lead to the increased sensitivity of asthma, which is typically an **IgE-mediated (type I) hypersensitivity reaction**; however, non-atopic and drug-induced asthma is also possible. Symptoms include **wheezing**, breathlessness, cough, particularly at night/early morning.

The pathology of chronic asthma additionally involves airway remodeling – airway wall thickening, membrane fibrosis, increase in the size and number of mucous glands and **hypertrophy/hyperplasia** of the bronchial wall.



**Image:** "Figure A shows the location of the lungs and airways in the body. Figure B shows a cross-section of a normal airway. Figure C shows a cross-section of an airway during asthma symptoms." by United States-National Institute of Health: National Heart, Lung, Blood Institute. License: [Public Domain](#)

The underlying pathophysiology is complex. The inflammatory mechanism is basically an exaggerated **T2 cell response** to normal environmental stimuli (e.g., pollen or dust). This leads to the secretion of cytokines such as interleukins and IgE.

While **interleukins** themselves promote inflammation, **IgE** acts on mast cells to release other **cytokines** and **inflammatory mediators**.

Although the list of mediators is huge, the ones that are definitely implicated, and against which pharmacology can be successfully directed, are **leukotrienes** (bronchoconstriction, increased vascular permeability, mucus secretion) and **acetylcholine** (direct smooth muscle constriction). All this combined leads to the hypersensitivity reaction of asthma.

**Exercise-induced asthma:** an asthma attack that is triggered by (aerobic) exercise. It lasts several minutes.

**Nocturnal asthma:** marked worsening of asthma symptoms during sleep.

## Antiasthmatic Drugs

### Classification

#### Bronchodilators

- $\beta_2$  adrenergic agonists;
- Short-acting (mnemonics: ALT): Albuterol (Salbutamol), Levalbuterol, Terbutaline;
- Long-acting (mnemonics: FoSa): Formoterol, Salmeterol;
- Methylxanthines: Theophylline;
- Muscarinic antagonists: Ipratropium, Tiotropium.

#### Anti-inflammatory agents

- Mast cell stabilizers: Cromolyn, Nedocromil;

- Antibodies (immunoglobulin E, IgE);
- Corticosteroids: Prednisone, Budesonide, Fluticasone, etc.

### Leukotriene antagonists

- Lipoxygenase inhibitors: Zileuton;
- Receptor antagonists: zafirlukast (Accolate®) and montelukast (Singulair®).

## β<sub>2</sub> adrenergic agonists

They act on the β<sub>2</sub> adrenergic receptors on the smooth muscles of the bronchial tree (via the G protein-adenylylcyclase pathway) to induce relaxation.

### 1. Short-acting β<sub>2</sub> agonists (e.g., Albuterol)



- **Image:** "Salbutamol metered dose inhaler commonly used to treat asthma attacks." by James Heilman, MD. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

**Onset of action:** 5–30 min

- **Duration of action:** 4–6 hours
- Albuterol has a high first-pass metabolism (oral bioavailability 50 %)
- Albuterol and levalbuterol are β<sub>2</sub> selective. Albuterol has β<sub>2</sub>:β<sub>1</sub> action ratio of approximately 650:1

**Route(s) of administration:** Inhalation, oral

#### Clinical uses:

- Quick, symptomatic treatment of bronchospasms and acute bronchoconstriction
- As an inhaler for asthma (attacks)
- Oral β<sub>2</sub> agonist therapy is reserved for those who cannot use inhalers or tolerate other drugs

#### Adverse effects/toxicity:

- Because of high β<sub>2</sub> selectivity, side effects due to α or β<sub>1</sub> stimulation is minimal
- **Tachycardia**, hyperglycemia, hypokalemia, and hypomagnesemia (minimized with intranasal administration)
- β<sub>2</sub>-mediated skeletal muscle tremors

**Contraindications:** Cardiovascular disorders

### 2. Long-acting β<sub>2</sub> agonists (e.g., Salmeterol)



- **Image:** "Previously Used Metered Dose inhaler of Serevent brand salmeterol." License: Public Domain

**Onset of action:** slow (formoterol has a slightly faster onset of action than salmeterol)

**Duration of action:** approximately 12 hours

Salmeterol is highly  $\beta_2$  selective— $\beta_2 : \beta_1$  action ratio = 50,000 : 1

**Route(s) of administration:** Inhalation

**Clinical uses:**

- Maintenance therapy
- Nocturnal asthma
- Round-the-clock bronchodilation (asthma prophylaxis)

**Adverse effects/toxicity:**

- Tachycardia, hyperglycemia, hypokalemia and hypomagnesemia (minimized with intranasal administration)
- $\beta_2$ -mediated skeletal muscle tremors

**Contraindications:**

- Monotherapy: should be only used in combination with inhaled corticosteroids
- Tachyarrhythmias

### 3. Methylxanthines: Theophylline



[Image](#): "Theophylline extended-release tablets in Japan."  
License: Public Domain

Other methylxanthines include caffeine (coffee) and theobromine (cocoa).

**Route(s) of administration:** Oral (prompt-release and slow-release formulations)

**Mechanism of action:** Bronchodilation, which is achieved by two possible mechanisms: inhibition of phosphodiesterase, which degrades cyclic AMP (and other cyclic nucleotides) and blocking of adenosine receptors in the central nervous system and elsewhere.

**Clinical uses:**

- Asthma
- [Chronic obstructive pulmonary disease](#) (COPD)
- Nocturnal asthma (slow-release preparation)

**Adverse effects/toxicity:**

- Gastrointestinal symptoms (nausea, vomiting), tremor, insomnia
- At high doses: hypotension, [cardiac arrhythmias](#), and seizures
- Very high doses can be lethal
- [Beta-blockers](#) (e.g., esmolol) should be administered in cases of methylxanthine (theophylline) toxicity

**Drug interactions:**

- Theophylline is metabolized by hepatic cytochrome P450. Therefore, drugs that inhibit this (e.g., erythromycin, fluoroquinolones, ketoconazole, [antidepressants](#) such as fluvoxamine and paroxetine, etc.) can increase blood theophylline levels
- Increases renal clearance of lithium

**Contraindications:** To be used with caution in patients with neurological and

cardiovascular conditions

#### 4. Muscarinic antagonists: Ipratropium & Tiotropium

- Ipratropium and tiotropium are quaternary antimuscarinic agents for aerosol use; they have little systemic action
- Tiotropium is longer-acting (duration of action: 24 hours)
- Tiotropium has recently (September 2015) been approved for use in the long-term maintenance treatment of asthma by the US FDA in people ages 12 and over

**Route(s) of administration:** Aerosol

#### **Mechanism of action:**

- Competitively block muscarinic receptors, thereby preventing vagal discharge-induced bronchoconstriction
- On systemic administration (not approved), they act like other short-acting muscarinic antagonists
- No effect on the inflammation involved in asthma

#### **Clinical uses:**

- Some patients with asthma (to reverse bronchoconstriction)
- Acute [COPD](#) episodes
- COPD maintenance therapy - daily inhalation of tiotropium

#### **Adverse effects/toxicity:**

- Little systemic effects, because of poor absorption into the [circulation](#)
- Minor atropine-like effects with high doses

**Drug interactions:** Pramlintide (synergistic action with tiotropium for decreasing gastrointestinal motility)

#### **Contraindications:**

- To be avoided or used with caution in patients with narrow-angle glaucoma and urinary retention as they can worsen these conditions
- Tiotropium - lactose allergy and hypersensitivity to milk proteins (as milk proteins can be a part of the powder in the capsule)
- Ipratropium - some cases of severe [anaphylaxis](#) have been reported in patients with allergy to soy and peanuts (due to soy lecithin as one of the ingredients)

#### 5. Mast cell stabilizers: Cromolyn & Nedocromil

Nedocromil is no longer available in the U.S.

**Route(s) of administration:** Aerosol, oral

#### **Mechanism of action:**

- Unknown; possibly a decrease in the release of asthma inflammation mediators, e.g., leukotrienes, histamine, interleukins, etc., perhaps by interfering with chloride channel; possible inhibition of chemotaxis of inflammatory cells.
- No bronchodilation
- Prevent allergy-induced bronchoconstriction

**Clinical uses:**

- Asthma (but the use is on the decline in the U.S.), but ineffective during an asthma attack (as bronchoconstriction has already occurred)
- Oral cromolyn can, to an extent, prevent food allergy
- Topical administration to the conjunctiva (allergic conjunctivitis) and nasopharynx also has some allergy-prevention effects (e.g., hay fever, allergic rhinitis)

**Adverse effects/toxicity:**

- **Cough and airway irritation** with aerosol
- As they are generally insoluble, even high doses lead to very small systemic levels and are very rapidly excreted

**Contraindications:**

- [Hypersensitivity](#)
- Acute asthma (as they cannot reverse bronchospasm, only prevent it)

**6. IgE antibodies (Omalizumab)**

- Omalizumab is a monoclonal antibody
- Very expensive

**Route(s) of administration:** Parenteral (intravenous or subcutaneous)

**Mechanism of action:** Selectively binds to IgE; decreases binding of IgE to its receptor on mast cells and basophils – thus, it prevents mast cell degranulation and subsequent release of inflammatory mediators, thereby decreasing the allergic response

**Clinical uses:**

- Asthma prophylaxis and to reduce asthma exacerbation (administration for 10 weeks significantly reduces IgE levels, bronchospastic responses to antigen and asthma severity, as well as reduces corticosteroid requirement)
- Generally, reserved for refractory patients with positive skin tests or raised IgE levels and those with frequent exacerbations (requiring hospitalization)

**Adverse effects/toxicity:** Minor injection side effects

**Contraindications:** Known hypersensitivity to the drug

**7. (Inhaled) Corticosteroids**

Corticosteroids (particularly systemic administration) have many uses and side effects, but this section will focus mainly on inhaled corticosteroids

**Route(s) of administration:** Inhalation – surface-active corticosteroids (e.g., beclomethasone, budesonide, dexamethasone, flunisolide, fluticasone, mometasone), oral (prednisone)

**Mechanism of action:**

- They induce their anti-inflammatory action by inhibiting the release of arachidonic acid (via phospholipase A2 inhibition)
- Decrease airway mucosal edema, capillary permeability, leukotriene release
- Regular, long-term use (several months) leads to reduced airway hyperresponsiveness

**Clinical uses:**

- Inhaled corticosteroids – drug of choice (very effective) for long-term control of asthma, e.g., persistent asthma
- Inhaled corticosteroids + short course of oral corticosteroids – severe persistent asthma.
- Systemic corticosteroids – severe chronic asthma, acute severe asthma attack, status asthmaticus
- Systemic corticosteroids – [COPD](#) exacerbation

**Adverse effects/toxicity:**

- Inhaled corticosteroids have much fewer systemic adverse effects. Local side effects include hoarseness and dysphonia
- Long-term administration in children can affect growth, adrenal function, and bone mass
- Long-term high doses can lead to [adrenal insufficiency](#) in both children and adults and cataract in adults

**Drug interactions:** Caution is required with coadministration of CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir as this can increase the risk of adrenal insufficiency

**8. Lipoxygenase inhibitor - Zileuton**

Less effective than corticosteroids in severe asthma

**Route(s) of administration:** Oral

**Mechanism of action:** Selective inhibition of 5-lipoxygenase; this inhibits the conversion of arachidonic acid to leukotrienes

**Clinical uses:**

- Prevention of exercise- and antigen-induced bronchospasm
- Aspirin allergy (i.e., aspirin-induced bronchospasm)
- Prophylaxis and chronic treatment of asthma – but [liver](#) toxicity and availability of other safer drugs have reduced this use

**Adverse effects/toxicity:** Liver toxicity – elevation of liver enzymes

**Drug interactions:** Zileuton is a cytochrome P450 3A4 inhibitor and a substrate for 1A2 so it may increase the levels of drugs that are metabolized by those pathways, e.g., terfenadine, theophylline, cisapride, etc., and so careful monitoring is required

**Contraindications:** Liver dysfunction

**9. Leukotriene receptor inhibitors: Zafirlukast and Montelukast**

Less effective than corticosteroids in severe asthma

**Route(s) of administration:** Oral

**Mechanism of action:** Inhibit LTD<sub>4</sub>, as well as LTE<sub>4</sub>, leukotriene receptors

**Clinical uses:**

- Prevention of aspirin-, exercise- and antigen-induced bronchospasm
- Because they can be taken orally, they are used frequently in children (over 6

years of age) who have low compliance with inhalers. Also, montelukast can be taken irrespective of meals and only once a day

**Adverse effects/toxicity:**

- Usually well tolerated
- Rarely, Churg–Strauss syndrome (systemic vasculitis with asthma, pulmonary infiltrates and eosinophilia) is reported, but the association seems coincidental as it is usually due to unmasking of the syndrome when corticosteroids are withdrawn
- Rarely, allergic granulomatous angiitis

**Drug interactions:** Zafirlukast may increase prothrombin time, especially in combination with warfarin

**Contraindications:**

- Acute asthma
- Severe hepatic impairment

## Choice of Treatment Based On the Type of Asthma

Form	Treatment
Mild episodic asthma	Inhaled short-acting β2 agonist at the onset of the asthmatic episode; no prophylaxis <b>(Step 1)</b> .
Seasonal asthma	Regularly inhaled corticosteroids from 3–4 weeks before to 3–4 weeks after the anticipated seasonal attack.
Mild chronic asthma with occasional exacerbations	Regularly inhaled low-dose corticosteroid + inhaled short-acting β2 agonist at the onset of the episode <b>(Step 2)</b> .
Moderate asthma with frequent exacerbations	Regularly inhaled low-dose corticosteroid + regular inhaled long-acting β2 agonist <b>(Step 3)</b> . + inhaled short-acting β2 agonist at the onset of the episode. Alternatives: Zafirlukast, Montelukast, Theophylline
Severe asthma	Regularly inhaled high-dose corticosteroid + regularly inhaled long-acting β2 agonist + additional episodic asthma one of the following: Leukotriene antagonist or sustained release theophylline or oral β2 agonist or inhaled ipratropium <b>(Step 4)</b> + Inhaled short-acting β2 agonist at the onset of the episode If not controlled, oral steroid therapy <b>(Step 5)</b> .

## Review Questions

The correct answers can be found below the references.

**1. Which of the following antiasthmatic drugs is not available in an aerosol form?**

- A. Ipratropium
- B. Salbutamol
- C. Fluticasone
- D. Montelukast
- E. None of the above

**2. An 11-year-old boy was diagnosed with asthma and was prescribed an inhaled antiasthmatic drug. However, he could not use the inhaler well and was switched to an oral antiasthmatic. Two weeks later, the boy presented again with low-grade fever, cough and breathlessness, ankle edema with a rash, polyarthralgia, numbness over fingers and heels and general malaise. C-reactive protein and eosinophil count were elevated. Which of the following antiasthmatic drugs could most likely be responsible?**



- A. Montelukast
- B. Prednisone
- C. Theophylline
- D. Salmeterol
- E. Beclomethasone

3. **A patient with a chronic obstructive pulmonary disease is prescribed slow-release theophylline. Theophylline is a methylxanthine antiasthmatic that has many interactions. Which of the following will have to be ruled out in order to require no change in theophylline dosage?**

- A. History of congenital heart surgery with cardiopulmonary bypass;
- B. Concomitant ketoconazole use;
- C. Concomitant salmeterol use;
- D. History of neurological disease;
- E. Concomitant zileuton use.

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**Correct answers:** 1D, 2A, 3C

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