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# Textbook of
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**Joginder Singh Pathania** MBBS, MD (Pharmacology), MD (Internal Medicine)

*Senior Medical Officer*

HP Government Hospital
Shimla, Himachal Pradesh

*Former Assistant Professor*

Indira Gandhi Medical College & Hospital (IGMC)
Shimla, Himachal Pradesh

**Rupendra Kumar Bharti** MBBS, MD (Pharmacology)

*Assistant Professor*

Government Medical College
Mahasamund, Chhattisgarh

**Vikas Sood** D Pharma, MSc, PhD

*Associate Professor*

Shivalik Institute of Nursing and Shimla Nursing College
Shimla, Himachal Pradesh



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Ph: +91-11-23289259, 23266861, 23266867 Website: www.cbspd.com
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# About the Authors

**Joginder Singh Pathania** MBBS, MD, is currently working as a Senior Medical Officer in Government Hospital, Shimla, Himachal Pradesh. He did his graduation and postgraduation in Pharmacology & Internal Medicine from Indira Gandhi Medical College (IGMC), Shimla, Himachal Pradesh. He has a vast experience of more than 20 years in medical practice. He is a former Assistant Professor in Department of Pharmacology in IGMC, Shimla, Himachal Pradesh. He has more than 8 years of teaching experience in medical college and published more than 10 national and international articles in the field of medical sciences. The author has been influential in the field of Pharmacovigilance and Disaster Management. He is an active member of Indian Pharmacological Society (IPS), Indian Medical Association (IMA), Disaster Management Cell (DMC) and Antibiotic Resistance Committee of the college. He is the recipient of "Best Oral Presentation Award" in IPS International Conference at Rajkot, Gujarat and "Pride of Himachal Award" at Shimla, Himachal Pradesh in 2015.

**Rupendra Kumar Bharti** MBBS, MD, is currently working as an Assistant Professor in the Department of Pharmacology at the Government Medical College Mahasamund, Chhattisgarh. He did his graduation from the International School of Medicine, Bishkek, Kyrgyzstan and MD Pharmacology from Indira Gandhi Medical College, Shimla, Himachal Pradesh. He has worked as a house surgeon in Sir Ganga Ram Hospital, New Delhi, Assistant Professor in Pharmacology at Raipur Institute of Medical Sciences and also as an Associate Professor at Balaji Institute of Medical Sciences, Raipur. He has served in the government as well as private medical colleges as an influential academician and has also published several articles related to the field of medical sciences in national and international journals.

**Vikas Sood** D Pharma, MSc, PhD, is presently working as an Associate Professor in Shivalik Institute of Nursing and Shimla Nursing College, Shimla, Himachal Pradesh. He has a considerable experience of 20 years in the medical field and more than 10 years' experience of teaching nursing students.

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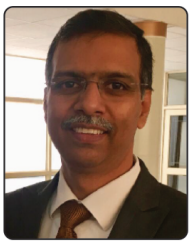

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**Vincent Jeyaraj**
MPT, MSW, FRCPT, PGDOSIM Wheelchair Prescription As per Who Knows
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MM Medical College and
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*Professor and HOD*
Department of Pharmacology
GMC, Nagpur, India

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# Preface

Pharmacology is the field of medicine which is dynamic in nature. Due to its immense value and importance, it is called the backbone of medicine. The knowledge of basic and clinical aspect of pharmacology is essential not only for students but also for practicing physicians. The idea for developing *Textbook of Pharmacology for Physiotherapy Students* originated after noticing the dearth of standard textbook conforming to the syllabus developed by physiotherapy council. We, the authors, keenly observed and felt this requirement made by the physiotherapy council, and developed this textbook in a way that students do not require any other resources to study Pharmacology. This textbook of Pharmacology is written in a very simple and understandable language, which will help readers to conceptualize the mechanism of drugs and their action in no time. Each chapter included *Clinical Aspect of Pharmacology*, *Must Know* and *Concept to Clinic* boxes, and also the responsibilities of the students while dealing with patients. We also included the chapters which were not required by Physiotherapy Council (e.g., Antibiotics, etc.) because they are essential for this textbook.

As in the field of medicine nothing is everlasting, we hope this book will help readers understand, conceptualize and reduce the difficulties while studying Pharmacology.

**Joginder Singh Pathania**
joginderpathania30@gmail.com
**Rupendra Kumar Bharti**
rbharti000@gmail.com
**Vikas Sood**
vikas_env@yahoo.co.in

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We are sincerely thankful to **Dr Ritu Shitak** (Associate Professor), **Dr Anamika Thakur** (Assistant Professor) Department of Pharmacology and **Dr Yogesh Diwan** (Assistant Professor) and **Dr Kunal Chawla** (Assistant Professor) Department of Anatomy for their positive attitude and valuable suggestions during this project.

We are also thankful to the Senior Residents **(Dr Ramesh, Dr Meenakshi, Dr Aanchal)** and Junior Residents **(Dr Navdha Sharma, Dr Sandeep Kaushik, Dr Vivek Thakur, Dr Sushma Sharma)** Department of Pharmacology for their support and sincere cooperation for completion of this book.

We cannot forget the cooperation we got from **Mr Rajan Bhimta**, **Mr Vijay Thakur**, **Ms Aditi**, **Ms Nalini** and all other staff members of the Department of Pharmacology, IGMC, Shimla.

We are sincerely thankful to **Ms Sampatti** for her sincere cooperation, constant encouragement and able guidance during the work.

I, **Dr JS Pathania**, express my profound gratitude to my parents, my wife **Dr Neelam Pathania**, **Siddharth Pathania** (loving son) and all family members for their patience, unfailing support and cooperation throughout this work period. Without their support and encouragement, this book could not have seen the light of the day.

I, **Dr RK Bharti**, express my profound gratitude to my mother **Smt Bangla Bai**, father **Shri Jagdish Bharti,** wife **Dr Pratima Koshewara**, son **Navyn** and all family members, for their showers of blessings, inspiration and encouragement at every stage of my life and career.

I, **Dr Vikas Sood**, express my profound gratitude to my parents, my wife **Mrs Babita Sood**, Daughter **Ms Vasvi Sood,** Son **Suryansh Sood** and all my family members for their patience, unfailing support and cooperation throughout this work period.

We all express our profound gratitude from the core of our heart to our families for their constant support and encouragement as they were the source of inspiration for us to accomplish this project.

We extend our special thanks to **Mr Satish Kumar Jain** (Chairman) and **Mr Varun Jain** (Managing Director), M/s CBS Publishers and Distributors Pvt Ltd for their wholehearted support in the publication of this book. We have no words to describe the role, efforts, inputs and initiatives undertaken by **Mr Bhupesh Aarora** [Sr Vice President – Publishing & Marketing (Health Sciences Division)] for helping and motivating me.

Our special thanks are due to the scientific editorial board of the CBS Physiobrid series, especially Dr Harshita Sharma, Dr Divya Gupta (PT) and Dr Surbhi Jain (PT) (Content Strategists cum Quality Check), and some senior faculties for their tireless efforts to provide valuable inputs throughout the project.

Last but not least, we sincerely thank the entire CBS team for bringing out the book with utmost care and attractive presentation. We would like to thank Ms Nitasha Arora (Publishing Head and Content Strategist – Medical and Nursing), Ms Annu Raina (Senior Manager – Publishing & Marketing), Dr Anju Dhir (Product Manager cum Commissioning Editor – Medical) for their support. We would also extend our thanks to Mr Shivendu Bhushan Pandey (Sr Manager and Team Lead), Mr Ashutosh Pathak (Sr Proofreader cum Team Coordinator) and all the production team members for devoting laborious hours in designing and typesetting the book.

# Special Features of the Book

## LEARNING OBJECTIVES

**This chapter is designed to enable the learner to understand:**

- Principles of pharmacodynamics, pharmacokinetics, classification and the principles of drug administration.
- Effects of microsomal enzymes.
- Types of drug formulations.
- Drug related adverse reactions.
- Rational use of drugs.

**Learning Objectives** given in the beginning of each chapter enable the student to know what he/she will learn after reading it.

Every chapter begins with a **Chapter Outline** to provide a glimpse of the content discussed.

## CHAPTER OUTLINE

- Introduction
- Definitions
- Sources of Drugs
- Systems of Measurement
- Types of Dosage Forms
- Classification of Drugs
- Routes and Principles of Administration of Drugs
- Pharmacokinetics
- Drug Interactions
- Pharmacodynamics
- Drug Potency and Efficacy

## KEY TERMS

**Addiction:** The physical and psychological dependence caused by drugs is called addiction.

**Anaphylaxis:** It is a hypersensitive reaction, which occurs due to ingestion of drugs or any foreign protein material.

**Antagonist:** The drug which opposes the action of other drugs, when given together or in combination is called antagonist.

Important terms of the respective chapters have been summarized in beginning of chapter under **Key Terms**.

Each and every topic starts with **Clinical Case Scenario** with explanation from theoretical and clinical integration point of view.

### Case Scenario 1

Parents came with a four-year-old child to the hospital with complaints of high-grade fever, cough and breathing difficulty. On examination, the child had tachycardia (HR >110/min), hyperventilation (RR >56/min), mild dehydration and hyperthermia with 104.3°F. On chest examination, the child had crepitation, wheezing and inspiratory chest indrawing.

### Case Scenario Explanation 1

As this child was diagnosed with acute pneumonia with indrawing of chest and increased respiratory rate, these are the red flag sign by Integrated Management of Neonatal and Childhood Illness (IMNC) and the treatment should be started as soon as possible with faster recovery which can be achieved by IV administration of antibiotics.

**MUST KNOW**

Absorption of the drug is 100% when given by intravenous route and always less than 100% when given by intramuscular, subcutaneous or oral route.

Principal facts have been covered under **Must Know** boxes.

**Concept to Clinic** box correlates the discussed topic with health care.

**CONCEPT TO CLINIC**

**Microsomal Enzymes Properties**

- All antifungal drugs are microsomal enzyme inhibitors except Griseofulvin.
- All antiepileptic drugs are microsomal enzyme inhibitors except Valproate.
- Acute alcoholism is a microsomal enzyme inhibitor, while chronic alcoholism is microsomal enzyme inducer.

**Responsibilities of Medical Professionals**

- The different categories of drugs should be stored in different compartments. For example, tablets, liquids, powders, etc.
- The drugs for external use and that for internal use should be kept separately.
- The containers should be arranged alphabetically, so that it is easy to find the required drug.
- All poisonous drugs should be marked "poison" in red ink.

This section is very crucial as it provides valuable information regarding what a medical professional should do to perform his/her duty in a fair manner.

Numerous **Tables** are used to help students grasp the concepts quickly.

**Table 1.5:** List of prodrugs

| Prodrug | Active form |
|---|---|
| Prednisone | Prednisolone |
| Sulindac | Sulfide metabolite |
| Enalapril | Enalaprilat |
| Alfa-methyldopa | α-methyl norepinephrine |
| Fosphenytoin | Phenytoin |

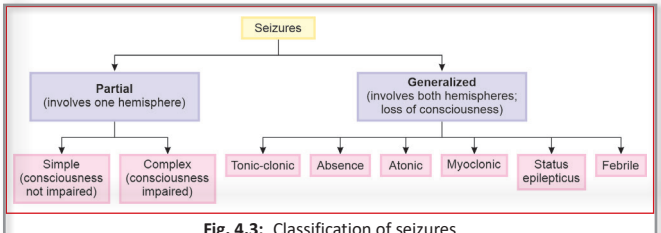


**Fig. 4.3:** Classification of seizures

Numerous **Figures** are used to make learning easy for students.

Each and every chapter ends with **Summarized one-liner** for quick revision of the chapter.

## SUMMARY

- The ideal anesthetic drug should be able to induce the unconsciousness smoothly and rapidly with prompt recovery from anesthesia whenever required. The drug, which is unable to produce the above effects, is not considered general anesthetic drug.
- The balanced anesthesia is made by keeping in view the advantage of the individual beneficial effects of different drugs and minimizing their individual toxic effects. This is usually made by making a combination of intravenous (IV) and inhaled drugs.

## ASSESS YOURSELF

**Long and Short Answer Questions**

1. What are benzodiazepines? Describe alprazolam and its uses.
2. Describe the stages of general anesthesia.
3. Describe the therapeutic uses of oxygen therapy.
4. Describe treatment and management of status epilepticus.
5. Why is adrenaline used with lignocaine in local anesthetics preparation?

**Multiple Choice Questions**

1. **Duration of action of flumazenil is:**
   a. 5 minutes b. 10 minutes
   c. 20 minutes d. 30 minutes
2. **Inverse agonist of benzodiazepine receptor is:**
   a. Phenobarbitone b. Flumazenil
   c. Beta carboline d. Gabapentin

At the end of every chapter, **Assess Yourself** section has been included to help the students assess their understanding of the discussed topics.

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# Syllabus

## PHARMACOLOGY

**Theory** **45 Hours**

### 1. General Pharmacology

Introduction, definitions, classification of drugs, sources of drugs, routes of drug administration, distribution of drugs, metabolism and excretion of drugs, pharmacokinetics, pharmacodynamics, drug potency and efficacy, combined effects of drugs, factors modifying drug response, adverse effects.

### 2. Autonomic Nervous System

- General considerations—the sympathetic and parasympathetic systems, receptors, somatic nervous system.
- Cholinergic and anticholinergic drugs, adrenergic and adrenergic blocking drugs, skeletal muscle relaxants.

### 3. Cardiovascular Pharmacology

- **Drugs used in the treatment of heart failure:** Digitalis, diuretics, vasodilators, ACE inhibitors antihypertensive drugs—diuretics, β-blockers, calcium channel blockers, central acting alpha agonists, peripheral alpha antagonists, direct acting vasodilators
- **Antiarrhythmic drugs**
- **Drugs used in the treatment of vascular disease and tissue ischemia:** Vascular disease, homeostasis lipid-lowering agents, antithrombotic, anticoagulants and thrombolytics, antiplatelets and fibrinolytics, hypolipidemic drugs, hematinics, plasma expanders; ischemic heart disease—nitrates, β-blockers, calcium channel blockers, cerebral ischemia peripheral vascular disease.

### 4. Neuropharmacology

- **Sedative-hypnotic drugs:** Barbiturates, benzodiazepines.
- **Antianxiety drugs:** Benzodiazepines, other anxiolytics.
- **Drugs used in treatment of mood disorders:** Monoamine oxidase inhibitors, tricyclic antidepressants, atypical antidepressants, lithium.
- Antipsychotic drugs or major tranquilizers or neuroleptic drugs.
- General and local anaesthetics.
- Drugs for deaddiction.
- CNS stimulants.

### 5. Disorders of Movement

- Drugs used in treatment of Parkinson's disease.
- Antiepileptic drugs.
- Spasticity and skeletal muscle relaxants.

## 6. Inflammatory/Immune Diseases

- **Non-narcotic analgesics and nonsteroidal anti-inflammatory drugs:** Acetaminophen, NSAIDs, aspirin, nonaspirin NSAIDs, drug interactins with NSAIDs.
- **Glucocorticoids:** Pharmacological uses of glucocorticoids, adverse effects, physiologic use of glucocorticoids.
- **Drugs used in treatment of arthritic diseases:** Rheumatoid arthritis, osteoarthritis, gout.
- **Drugs used in the treatment of neuromuscular immune/inflammatory diseases:** Myasthenia gravis, idiopathic inflammatory myopathies, systemic lupus erythematous, scleroderma, demyelinating disease.

## 7. Gastrointestinal Pharmacology

Peptic ulcer disease, constipation, diarrhea drugs, antihistamines, proton pump inhibitors, ulcer protectives, drug therapy for *Helicobacter pylori infection*, gastroesophageal reflux disease, antacids, antifoaming agents, purgatives and laxatives, emetics and antiemetics.

## 8. Respiratory Pharmacology

Obstructive airway diseases, drugs used in treatment of obstructive airway diseases, allergic rhinitis, antitussives, mucolytics.

## 9. Drugs Acting on Kidney

Diuretics and antidiuretics.

## 10. Endocrine Pharmacology

**Drugs used in treatment of diabetes mellitus:** Insulin, oral hypoglycaemic hormones, calcium salts, thyroid supplements and suppressants.

## 11. Chemotherapy

### General Principle of Chemotherapy

Antimicrobial, penicillin's, cephalosporins, aminoglycosides, macrolides, tetracyclines, quinolones, antiamoebic drugs, antimalarial drugs, antihelmentic drugs, antiviral agents, antifungal drugs, antitubercular therapy, antileprotic drugs, anticancer drugs.

## 12. Geriatrics

**Pharmacology and the geriatric population:** Adverse effects of special concern in the elderly, dementia, postural hypotension. Mucolytics, decongestants, expectorants, antitussives, bronchoconstrictors, antihistaminic.

## 13. Miscellaneous Topics

- Drugs for acne vulgaris
- Vaccines and sera
- Antisera and immunoglobulins
- Antidotes
- Antivenom
- Antiseptics and disinfectants
- Vitamins
- Minerals

# Contents

CHAPTER 7

# Drugs Acting on the Respiratory System

## LEARNING OBJECTIVES

**This chapter is designed to enable the learner to understand:**

- Principles of bronchodilators and their implications.
- Status asthmaticus.
- Role and handling of nebulizer, rotahalers.
- Corticosteroids in asthma.

## CHAPTER OUTLINE

- Asthma
- Antiasthmatics
- Mucolytics
- Decongestants
- Expectorants
- Antitussives
- Bronchoconstrictors
- Antihistaminics

## KEY TERMS

**Antitussives:** These drugs act directly on the cough center in the medulla of the brain to depress the cough reflex and raise the threshold of cough center or act peripherally in the respiratory tract to reduce cough impulses, or both these actions. The drugs used to control the dry cough are known as antitussives.

**Asthma:** It is a chronic inflammatory disease of the airways. It occurs due to hyper responsiveness of tracheobronchial tree to various allergic stimuli. These symptoms occur due to bronchospasm, increased bronchial secretions and edema of the bronchial mucosa.

**Bronchodilators:** These drugs have the ability to dilate the bronchi, which are in a state of bronchospasm. The bronchospasm is due to the contraction/constriction of bronchial smooth muscles which leads to decreased air entry into the tracheobronchial tree resulting into dyspnea and difficult respiration.

**Decongestants:** These drugs decrease the overproduction of secretions by causing local vasoconstriction in the nasal mucosa. These drugs provide relief from the discomfort of blocked nose by promoting drainage of secretions and thereby improving airflow.

**Mucolytics:** These drugs liquefy the sputum by breaking down the disulfide bonds in mucopolysaccharide strands. The thick tenacious sputum/secretions are very difficult to expel out in cough. These drugs help in easy expulsion of thick, tenacious secretions by decreasing the viscosity of sputum.

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# ASTHMA

## Case Scenario 1

A 55-year-old anxious female was recently diagnosed with stage 2 hypertension for which she was prescribed telmisartan 40 mg twice daily, and 25 mg propranolol for prophylaxis of anxiety. Two days later she was brought into the casualty with severe breathing difficulty. She was hyperventilating, and on examination bilateral wheezing of lungs was observed. The provisional diagnosis of acute asthmatic attack was made. Which of the drugs would you prescribe to attenuate this asthmatic attack?

Asthma is a chronic inflammatory disease of the airways. It occurs due to hyper responsiveness of tracheobronchial tree to various allergic stimuli. It is characterized by:

- Dyspnea
- Wheeze
- Dry cough

These symptoms occur due to bronchospasm, increased bronchial secretions and edema of the bronchial mucosa.

**MUST KNOW**

**Simplified View of Allergic Inflammation in the Airways**

Asthma is an episodic narrowing of the bronchi thought to be caused by an underlying chronic inflammatory disorder. In allergic asthma, inhaled allergen initiates the inflammatory response by interacting with IgE bound to basophils and mast cells. This leads to a cascade of events involving other immune cells and release of various inflammatory mediators into the interstitial space, where they influence the growth and function of cell types within the airway wall. The drugs available for the treatment of asthma are targeted at inhibiting the inflammatory responses and/or relaxing the bronchial smooth muscle (Fig. 7.1). The various classes of drugs used in treating asthma are $\beta_2$ adrenergic agonists; corticosteroids; leukotriene modifiers; muscarinic receptor antagonists; cromolyn; theophylline; anti-IgE therapy.

Asthma is divided into two categories: Extrinsic and intrinsic asthma (Table 7.1).

## Trigger Factors

- Upper respiratory tract infection (intrinsic asthma)
- Allergens. Examples: pollen grains, house dust or smoke, etc.
- Drugs such as aspirin, nonselective β-blocker (propranolol), opioids

**Table 7.1:** Differences between extrinsic and intrinsic asthma

| | Extrinsic asthma | Intrinsic asthma |
|---|---|---|
| time of onset | Childhood | Late/adulthood |
| Allergy | Personal history or strong family history | No H/O allergy |
| Level of IgE and eosinophils | Increased | Normal |
| External stimulus | Required | May or may not be required |
| Status asthmaticus | Less frequent | More frequent |

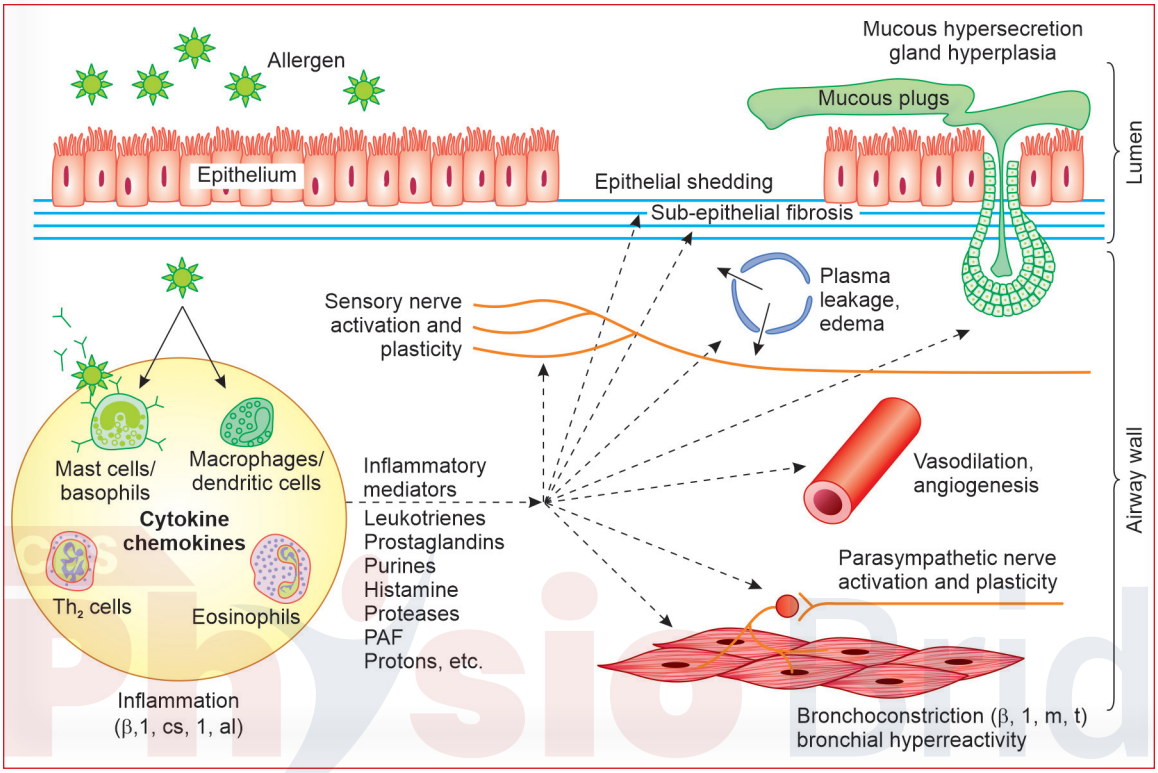


**Fig. 7.1:** Sites of action of various classes of drugs used in the treatment of asthma

- Cold or dry air
- Exercise induced (signs/symptoms develop when person takes rest after exercise)

## ANTIASTHMATICS

- The drugs used to treat the bronchial asthma are called antiasthmatics.
- **Bronchodilators**
  - ***Sympathomimetics:*** Salbutamol, terbutaline, salmeterol, formoterol, bambuterol and ephedrine.
  - ***Methylxanthines:*** Theophylline, aminophylline, doxophylline, acebrophylline
  - ***Anticholinergics:*** Tiotropium bromide and ipratropium bromide
- **Leukotriene antagonists:** Zafirlukast and montelukast.
- **Mast cell stabilizers:** Ketotifen and sodium cromoglycate.
- **Corticosteroids**
  - ***Systemic:*** Prednisolone, hydrocortisone and deflazacort, etc.
  - ***Inhalational:*** Budesonide, fluticasone, beclomethasone and ciclesonide.
- **Anti-IgE antibody:** Omalizumab

## Bronchodilators

Bronchodilators are the drugs that have the ability to dilate the bronchi, which are in a state of bronchospasm. The bronchospasm is due to the contraction/constriction of bronchial smooth muscles which leads to decreased air entry into the tracheobronchial tree resulting into dyspnea and difficult respiration.

There are various classes of drugs which act as bronchodilators such as:

- **Sympathomimetics:** Salbutamol, salmeterol, terbutaline, formoterol, bambuterol, ephedrine.
- **Methylxanthines:** Theophylline, aminophylline, doxophylline, acebrophylline
- **Anticholinergics:** Ipratropium bromide, tiotropium bromide.

### *Sympathomimetics (Mimicking Sympathetic System)*

These are the drugs which have actions similar to sympathetic stimulation. These drugs are potent bronchodilators.

#### Mechanism of Bronchodilatation of Sympathomimetics

- $\beta_2$-receptors are present in the bronchi.
- The stimulation of these $\beta_2$-receptors leads to bronchodilatory effect.
- The bronchodilatory effect is good in constricted bronchi.
- The main mechanism operating at cellular level is as follows:
  **Adrenergic drugs and $\beta_2$-receptor agonists → stimulation of $\beta_2$-receptor → increased cAMP formation in bronchial muscle cell → bronchodilatory effect.**
- In addition, the inflammatory mediator release is also decreased.
- These drugs are the drug of choice due to their effectiveness and rapid bronchodilatory effect in reversible airway obstruction. Preferably, these drugs are given in inhalational form for prompt relief. Details of the sympathomimetic drugs are given in Table 7.2.

**MUST KNOW**

**Adrenaline, ephedrine and isoprenaline:** Although these drugs are bronchodilators, but these are not preferred due to low efficacy, risk of adverse effects and availability of better drugs.

- **Doses of nebulizers:**
  - ***2–12 years:*** 0.63–1.25 mg every 4–6 hours.
  - ***Less than 4 years:***
    - ***For quick action:*** 0.63–2.5 mg every 4–6 hours.
    - ***Asthma exacerbation:*** 0.15 mg/kg 3 doses for every 20 minutes followed by 0.15–0.3 mg/kg for every 1–4 hours. In continuous nebulizer 0.5 mg/kg/hr.
- **5–11 years:**
  - ***For quick action:*** 1.25–5 mg every 4–8 hours.
  - ***Asthma exacerbation:*** 0.15 mg/kg 3 doses for every 20 minutes followed by 0.15–0.3 mg/kg for every 1–4 hours.
- **>12 years:**
  - ***For quick action:*** 1.25–5 mg every 4–8 hours.
  - ***Asthma exacerbation:*** 2.5–5 mg 3 dose for every 20 minutes followed by 2.5–10 mg for every 1–4 hours.

**Table 7.2:** Sympathomimetics

| Comparison | Salbutamol | Terbutaline | Salmeterol | Formoterol |
|---|---|---|---|---|
| Dosage and route of administration | • Adult and pediatric (>12 years): 2–4 mg TDS or BD orally. 100–200-mcg by inhalation<br>• Pediatric (2–6 years): 0.1 mg/kg TDS orally 6–12 years 2 mg TDS or QID orally. (Inhaled 15 minutes before exercise) | • Adult and pediatric (>15 years): 5 mg QID orally. 250-mcg by inhalation<br>• Pediatric (12–15 years): 2.5 mg TDS orally | • Adult and pediatric (≥12 years): 25-mcg pMDI two puffs 12 hourly<br>• Pediatric (4–12 years): one inhalation BD | • Adult and pediatric (>5 years): 12-mcg capsule 12 hourly, (Capsule inhaled using the aerolizer inhaler, at least 15 min before exercising) |
| Indications | • Long-acting treatment<br>• Prophylaxis of bronchospasm | Treatment and prophylaxis of bronchospasm in patients >12 years of age | • Prevention of asthma due to exercise<br>• As a maintenance therapy and nocturnal asthma<br>• COPD | • Prevention of asthma due to exercise<br>• As a maintenance therapy and nocturnal asthma<br>• COPD |
| Special points | • Inhaled salbutamol delivered mostly from pressurized metered dose inhaler (pMDI) produces broncho-dilatation within 5 minutes and the action lasts for 2–4 hours<br>• Levo-salbutamol has equal action at half dose | Use of inhalers should be restricted to symptomatic relief from wheezing | • Long-acting selective beta 2 agonist<br>• Onset of action is slow<br>• Mostly used in combination inhaled steroids | • Long-acting selective $\beta_2$ agonist<br>• It has faster onset of action than Salmeterol<br>• Specially used for round the clock bronchodilatation |

*Abbreviation:* COPD, chronic obstructive pulmonary disease

### Side Effects of Sympathomimetic Drugs

The side effects are commonly seen with the short acting $\beta_2$-receptor agonists such as salbutamol and terbutaline and less commonly with the long acting $\beta_2$-receptor agonists such as salmeterol and formoterol. Some commonly seen side effects are muscle tremors, palpitation, restlessness, nervousness, throat irritation, ankle edema and hypokalemia.

## Methylxanthines

The xanthines have been in use for the treatment of bronchospasm and asthma since ancient times. Theophylline and caffeine are methylxanthines obtained from natural sources. However, because they have a relatively narrow margin of safety and interact with many other drugs, they are no longer considered the first-choice bronchodilators. Xanthines are used to treat respiratory diseases and include theophylline, aminophylline, and doxophylline.



### Mechanism of Action of Methylxanthines

- **Inhibition of phosphodiesterase (PDE):** PDE enzyme degrades cyclic AMP and methylxanthines inhibit this enzyme, thereby increasing cAMP levels. This increase in cAMP causes bronchodilation.
- **Blockade of adenosine receptors:** Adenosine contracts smooth muscles by acting as a local mediator. Methylxanthines produce opposite effects.
- The calcium (in skeletal and cardiac muscle) from sarcoplasmic reticulum is released. This action is seen in higher dose only.
- At normal therapeutic doses, bronchodilation occurs due to mechanism 1 and 2.
- Action number 3 is observed only at toxic doses.

### Theophylline

#### Pharmacokinetics

- Theophylline is well-absorbed orally.
- It is widely distributed in all compartments of body.
- It also crosses the placental barrier and is secreted in milk.
- The metabolism occurs in liver and excretion occurs through kidneys.
- In higher doses, the kinetics of theophylline change from first order kinetics to zero order kinetics due to saturation of metabolizing enzyme of liver. Hence, accumulation of drugs occur which can lead to severe toxicity.

**Dose:** 100–300 mg orally, thrice daily.

**Side effects:** Theophylline has a narrow margin of safety. Side effect profile is different at different serum levels (Table 7.3).

### Aminophylline

It is a water-soluble drug. It is given by slow intravenous route in acute attack of asthma not responding to $\beta_2$ agonist. It should be given slow intravenously in a dose of 250 mg over 15–20 minutes. Rapid IV injection may cause hypotension and arrhythmia which may lead to convulsions, collapse and death. It is not given by IM/SC route due to its highly irritating nature. In children, the recommended dose is 7.5 mg/kg intravenously.

**Table 7.3:** Side effects of theophylline according to serum levels of theophylline

| Serum level (mcg/mL) | Side effects |
|---|---|
| ≤20 | Uncommon |
| >20–25 | Nausea, vomiting, diarrhea, insomnia, headache, irritability |
| >30–35 | Tachycardia, arrhythmias, hypotension, hyperglycaemia, seizures, brain damage, death |

**Hydroxyethyl theophylline (etophylline, 80% theophylline):** It is administered by intravenous, intramuscular and oral route in a dose of 250 mg. It has low irritating nature.

### Doxophylline

It is a methylxanthine with long duration of action and given by oral route. It neither interferes with sleep nor stimulates gastric secretion.

#### Dose

- **Adult:** 400 mg once or twice daily.
- **Children:** 12 mg/kg daily.

## Anticholinergics

These are the drugs which block the action of acetylcholine on muscarinic receptors. M3 cholinergic receptors are present in larger airways and their stimulation causes bronchoconstriction. Anticholinergic drugs block M3 receptors and cause bronchodilation. These drugs relax bronchial smooth muscles but response is slower than sympathomimetics. These drugs are given by inhalational route. These are the bronchodilators of choice in COPD. The anticholinergics show a good effect in patients of COPD, asthmatic bronchitis and psychogenic asthma. The synergistic effects are obtained by combining the ipratropium bromide with a $\beta_2$ agonist in the form of prolonged and potentiated bronchodilatation. Ipratropium bromide is a short acting (duration 4–6 hours), while Tiotropium bromide is long acting (duration 24 hours). Available in inhalers, rotacaps and solution forms.

# Leukotriene (LTs) Antagonists

**(Montelukast and Zafirlukast)**

- The pharmacological actions and uses of both these drugs are same.
- Both these agents exhibit competitive antagonism. They antagonize LTs receptor mediated broncho-constriction, airway mucous secretion, increased vascular permeability and recruitment of eosinophils.

## Pharmacokinetics

- These drugs have good oral absorption with high plasma protein binding.
- The metabolism occurs in liver.
- The plasma t½ of montelukast is 3–6 hours and zafirlukast is 8–12 hours.

## Indications

- Mild-to-moderate asthma as alternatives to inhaled glucocorticoids.
- Severe asthma (additive effect with inhaled steroids).
- Effective in aspirin-induced asthma and exercise-induced asthma.
- No value in chronic obstructive pulmonary disease (COPD).

## Side Effects

Headache, rashes and eosinophilia.

## Dose (Table 7.4)

**Table 7.4:** Dose of leukotriene antagonists

| Drugs | Dose |
|---|---|
| Montelukast | Adults: 10 mg once daily<br>Children: (age group 2–5 years): 4 mg once daily, (age group 6–14 years): 5 mg once daily<br>*To be given in the evening.* |
| Zafirlukast | Adults: 20 mg twice daily<br>Children (age group 5–11 years): 10 mg twice daily |



## Mast Cell Stabilizers

### Cromoglycate Sodium

It inhibits degranulation of mast cells and reduces the bronchial hyper reactivity. Bronchospasm induced by allergens, irritants, cold air and exercise is decreased. It does not have a therapeutic effect during an asthmatic attack. It is not a bronchodilator like salbutamol.

#### Pharmacokinetics

It is not absorbed orally. Hence, given by metered dose inhaler for direct effect on bronchi.

#### Uses

- **Bronchial asthma:** It is used for the prophylaxis of exercise-induced asthma and mild-to-moderate asthma.
- **Allergic rhinitis:** Some symptomatic improvement is seen after 4–6 weeks.
- Cromoglycate Sodium eye drops are given for the prophylaxis of chronic allergic conjunctivitis.

#### Dose

- Metered dose inhaler 1 mg and 5 mg/puff, 2 puffs 4 times daily.
- 2% nasal spray, two sprays in both nostrils QID.
- 2% and 4% eye drops: 1 drop in each eye QID.

#### Adverse Effects

- Systemic toxicity is minimal.
- Other side effects are dizziness, headache, nasal congestion, rashes, arthralgia, etc.

### Ketotifen

It is an antihistaminic (H1) and not a bronchodilator. It is given orally. It has some mast cell stabilizing effect also.

#### Indications

Bronchial asthma, urticaria, food allergy, conjunctivitis, perennial rhinitis and atopic dermatitis.

#### Adverse Effects

- Generally, well tolerated.
- The other side effects are dry mouth, nausea, sedation, dizziness, and increase in weight.

#### Dose

In adults, 1–2 mg twice daily and in children, 0.5 mg twice daily.

## Corticosteroids

- **Systemic:** Prednisolone, deflazacort, hydrocortisone, etc.
- **Inhalational:** Budesonide, fluticasone, beclomethasone, etc.

## Mechanism of Action

- Glucocorticoids do not have bronchodilatory effects.
- These agents decrease the bronchial tree hyper reactivity and mucosal edema by their potent anti-inflammatory actions.

## Systemic Steroids

The various indications of systemic steroidal therapy in asthma are as follows:

- **Severe chronic asthma:** Prednisolone is started in a dose of 20–60 mg (or equivalent) daily. (If the severe/recurrent episodic attacks of asthma are not controlled by steroidal inhaler and bronchodilator).
- Status asthmaticus/acute asthma exacerbation.
- **Chronic obstructive pulmonary disease (COPD):** Short-term (1–3 weeks) therapy of oral glucocorticoids can be beneficial during exacerbation of COPD.

## Inhalational Steroids

The following inhalational steroids are used frequently in the patients of asthma:

- **Beclomethasone dipropionate (available as):**
  - Inhaler 50 µg, 100 µg, 200 µg per metered dose.
  - Rotacaps (with rotahalers) 100, 200, 400 µg powder per cap.
  - Budesonide: 200–400 µg BD–QID by inhalation in asthma; 200-400 µg/day by intranasal spray for allergic rhinitis.
  - Fluticasone propionate: 100–250 µg BD inhalation in asthma.
  - Flunisolide: 25 µg per actuation nasal spray.
    - Ciclesonide: 80–160 µg by inhalation OD.
- These inhalational steroidal agents are used as an aerosol form as they have good topical activity on tracheobronchial tree. Their systemic action is poor because of high first pass metabolism.

### Adverse Effects

The common side effects are dysphonia, hoarseness of voice, oropharyngeal candidiasis, sore throat and oral thrush.

*(These above-mentioned side effects can be controlled by the use of a spacer device and normal saline gargling after every dose.)*

# Anti-IgE Antibody

## Omalizumab

- Omalizumab acts against IgE by binding and neutralizing the free IgE in blood circulation.
- It is a humanized monoclonal antibody and given by subcutaneous route with 62% of bioavailability.
- It does not activate mast cells and other inflammatory mediating cells.
- It is metabolized in liver and excreted through bile.
- The elimination t½ is 26 days.
- Omalizumab reduces the exacerbations and the requirement of steroidal therapy in severe allergic asthma; therefore, it is indicated in corticosteroid non-responsive asthma, and persistent allergic asthma.
- Side effects are injection site reaction, alopecia, headache, malaise, pruritus, dermatitis, arthralgia, sinusitis, cough, thrombocytopenia, bronchospasm.



- It is very costly. Therefore, reserved for resistant cases only.
- It should be given only after sensitivity test.

**MUST KNOW**

**Drugs Used by Inhalational Route for Asthma Treatment**

The following types of antiasthmatic drugs are available in inhalational forms.

- **Glucocorticoids** *(Beclomethasone, fluticasone, budesonide, ciclesonide)*
- **$\beta_2$ agonists** *(Salbutamol, terbutaline, salmeterol, etc.)*
- **Anticholinergics** *(ipratropium bromide, tiotropium bromide)*
- **Cromoglycate sodium**

Currently, inhalational agents are the preferred drugs for both short and long-term management of asthma.

Drugs given by inhalational route have following advantages over that given by oral route:

- The drug is delivered directly at the site of action.
- Prompt action is achieved.
- Minimal systemic side effects than oral anti-asthmatics.
- Inhalational doses are lower than oral doses of the same drug.

## Management of Asthma

The immediate treatment of asthma is guided by the severity of the signs and symptoms of patient. The main aim of the treatment is to relieve the bronchospasm and prevent the further damage to the respiratory tract. After the asthma is under control for 3–6 months, the medications are reduced in a stepwise manner (Table 7.5).

**Table 7.5:** Management of various types of asthma

| Type of asthma | Management |
|---|---|
| **Seasonal asthma** (Symptoms seen in particular seasons only due to allergens/cold climatic conditions) | • Inhaled short-acting $\beta_2$-receptor agonist<br>• Inhaled steroid in low-dose<br>• Cromoglycate sodium (should be given 3–4 weeks before the onset of seasonal attacks and continued till 3–4 weeks after the season is over) |
| **Mild episodic asthma** (Symptoms <1 per day, asymptomatic in between attacks) | • Inhaled short-acting $\beta_2$-receptor agonist at the onset of each episode |
| **Mild chronic (persistent)** (Acute exacerbation) | • Regular low-dose inhaled steroid<br>• Inhaled cromoglycate sodium<br>• Oral theophylline<br>• Episode treatment with inhaled short acting $\beta_2$-receptor agonist |
| **Moderate asthma** (Attacks occur >1 per day or mild baseline symptoms) | • Slightly higher dose of inhaled steroid + inhaled long-acting $\beta_2$-receptor agonist<br>• Sustained release theophylline may be used in addition<br>• Leukotriene receptor antagonist may be used in addition |
| **Severe asthma** (Continuous symptoms; activity limitation; frequent exacerbations/ hospitalization) | • High dose of inhaled steroid administered regularly by a large volume spacer device + inhaled long-acting $\beta_2$-receptor agonist (salmeterol) twice daily<br>• Leukotriene antagonist/sustained release oral theophylline/oral $\beta_2$-receptor agonist/inhaled ipratropium bromide<br>• Rescue treatment with short-acting inhaled $\beta_2$-receptor agonist<br>• Humidified oxygen inhalation |

**MUST KNOW**

**Aerosols**

These are the drug preparations which can be converted into vapor form for their maximum effect in the tracheobronchial tree.

Aerosols are of two types:

1. **Drug in solution:** Pressurized metered dose inhaler (pMDI), nebulizers.
   **Metered dose inhalers:** They are the small handy devices, which can be carried in pockets and used on 'as and when required' basis.
   **Nebulizer:** It is an electrical drug delivery device, which converts the nebulizing solution into aerosol forms for inhalation with the help of mask. It provides immediate local action on the tracheobronchial tree. It is used at bedside in patients of all age groups.
2. **Drug as dry powder:** Spinhaler, rotahalers.
   **Dry powder inhalers:** They are also portable handy drug delivery devices in which the drug-containing capsule is fitted in a pit. The rotation of the device breaks the capsule, which releases the aerosolized drug. The patient has to take deep inspiration through this device, which carries the aerosolized drug directly to the site of action.

## Status Asthmaticus/Refractory Asthma

Status asthmaticus is also known as acute severe asthma. It is a life-threatening condition and mostly occurs due to precipitation of chronic asthma by acute respiratory infection.

### Patient with signs/symptoms of:

- Unable to speak a sentence due to severe dyspnea.
- Severe cyanosis.
- Pulsus paradoxus (inspiratory fall in systolic blood pressure ≥10 mm Hg).
- Silent chest (No pathological sign during auscultation).
- Encephalopathy, seizure, coma and death if not treated appropriately within the golden period.

### Management of Status Asthmaticus

- Hydrocortisone 100 mg intravenously given stat, then 100–200 mg 4–8 hourly infusion (or equivalent dose of another glucocorticoid). The onset of action of hydrocortisone takes about 6 hours.
- 2.5–5 mg of nebulized salbutamol + 0.5 mg of ipratropium bromide.
- Administration of humidified oxygen in high flow.
- Salbutamol/terbutaline 0.4 mg intramuscularly or subcutaneously can be given for its better therapeutic effect.
- In severe respiratory distress, intubation and mechanical ventilation is advocated.
- Broad spectrum antibiotic therapy is required to control the chest infection.
- Correction of electrolyte imbalance.
- Correction of acidosis with sodium bicarbonate/lactate infusion.
- If hypokalemia is detected, correct with potassium chloride infusion.
- Recording and maintenance of vitals.

### Case Scenario Explanation 1

For the management of acute attack of bronchial asthma, inhaled $\beta_2$ agonists such as salbutamol are the main line of drugs, since the patient on propranolol, which is nonselective β-blocker, the effect of $\beta_2$ agonists will be ineffective.

In this situation, bronchodilators other than $\beta_2$ agonists such as theophylline (methylxanthines) or ipratropium bromide (anticholinergic) are given.

## Drug Interactions

- The metabolism of theophylline is enhanced by smoking, phenytoin and rifampicin by microsomal enzyme induction; hence, either dose of theophylline should be increased or the combination should be avoided.
- The metabolism of theophylline is decreased by allopurinol, ciprofloxacin, erythromycin and oral contraceptives; hence, either dose of theophylline should be decreased or the combination should be avoided.
- The effects of oral anticoagulants, digitalis, furosemide and oral hypoglycemic are enhanced by theophylline.
- Injection of aminophylline interacts with phenytoin, insulin, erythromycin, tetracyclines, etc. Hence, mixing in the same infusion bottle should be avoided.
- Sodium cromoglycate potentiates the effect of sedatives, hypnotics, antihistaminics and alcohol.

### Responsibilities of Medical Professionals

- Obtain complete medical and personal history related to the diseases prior to admission. That includes history of cerebrovascular, cardiovascular, respiratory, metabolic diseases, drug history, drug/food allergy, OTC/herbal drugs, and symptoms that are associated with any food, seasons or environmental changes.
- Monitor the therapeutic effects of drugs such as improvement in breathlessness, PFT, nocturnal sleep with better peripheral oxygen perfusion and feeling of well-being.
- Continuously monitor the therapeutic aim as the drug is given for improvement in breathlessness, PFT, nocturnal sleep with better peripheral oxygen perfusion, reduction in additional breath sounds, and improvement in feeling of well-being.
- Always keep inhaler bronchodilator (short acting) in case of acute asthmatic attack. Health care professional should be aware of the proper route of drug delivery and onset of action of various bronchodilators.
- During aminophylline infusion, keep a check on heart rate as HR >120/min is a sign of toxicity.
- Health care professional should know the appropriate technique to deliver inhaler/MDIs/Rotahalers (especially while administering inhalational corticosteroids), and after administering these agents; to avoid the drug must not come back to the pharynx. Always wash mouth after delivery of inhalational agent to prevent opportunistic infections such as candida or oral thrust and ulcers.
- Teach the use of inhalers to patients. Advise the patient to brush the teeth after using inhalers to prevent infections in mouth (steroid inhaler causes fungal infection in mouth).
- It is utmost important to know the proper administration guidelines for inhalational agent (inhaler or MDIs or rotahalers) as the drug should reach the bronchi for proper therapeutic effect.
  - Advise patient to shake/load the inhaler with tablet/powder as instructed.
  - When corticosteroid and bronchodilator inhalational agents are prescribed; patient should inhale bronchodilator first; and after 10–15 minutes, patient should take corticosteroid.
  - Instruct patient to wash mouth every time after using inhalers.
  - Also, wash the inhaler and spacer with water on a daily basis and dry in air.

## MUCOLYTICS

**(*Muco*- mucous; *lytic*- to break)**

Mucolytics are the drugs, which liquefy the sputum by breaking down the disulfide bonds in mucopolysaccharide strands. The thick tenacious sputum/secretions are very difficult to expel out in cough. These drugs help in easy expulsion of thick, tenacious secretions by decreasing the viscosity of sputum.

The drugs that act as mucolytics are bromhexine, ambroxol, acetylcysteine, carbocysteine, dornase alfa.

## Bromhexine

- It is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion.
- It is given orally.
- It breaks down the network of fibers in tenacious sputum by depolymerizing mucopolysaccharides and also by liberating lysosomal enzymes.

### Dose

- Adults: 8 mg thrice daily.
- For children (1–5 years), 4 mg twice daily and for 5–10 years, 4 mg thrice daily.

### Side Effects

- Rhinorrhea
- Lacrimation
- Nausea and gastric irritation
- Hypersensitivity

## Ambroxol

- It is a metabolite of bromhexine.
- It is given orally.
- Its mucolytic action, uses and side effects are similar to bromhexine.

### Dose

15–30 mg thrice daily.

## Acetylcysteine

- Acetylcysteine/N-acetylcysteine (NAC) is a mucolytic and antioxidant drug that may also influence several inflammatory pathways.
- Acetylcysteine's sulfhydryl groups hydrolyze disulphide bonds within mucin, breaking down the oligomers, and making the mucin less viscid.
- These sulfhydryl groups also act as a precursor of reduced glutathione and as a direct reactive oxygen species (ROS) scavenger; hence, they regulate the redox status in the cells for their antioxidant effect.
- It is a good mucolytic, available in solution and tablet form.
- It is administered directly into the respiratory tract by injectable solution, which is given by nebulization or by instilling through tracheostomy tube.
- It opens disulfide bonds in mucoproteins present in sputum and makes it less viscid.
- It is also used as antidote in paracetamol poisoning.

### Dose

- By nebulization, 2–20 mL of 10% solution 2–6 hourly.
- By direct instillation in lungs, 1–2 mL of 10–20% solution 1–4 hourly.
- Tablet: 600 mg thrice daily.



## Carbocysteine

- It liquefies viscid sputum in the same way as acetylcysteine.
- It is administered orally.
- Specially given in patients of chronic bronchitis.
- Most effective in smoker's cough.

### Dose

250–750 mg thrice daily.

### Side Effects

- Rashes
- Gastric discomfort, hence, contraindicated in peptic ulcer

### Other Uses

Bronchitis, bronchiectasis, sinusitis, etc.

## Dornase Alfa

- It is a mucolytic prepared by recombinant DNA technique.
- It selectively breaks down respiratory tract mucus by separating extracellular DNA from proteins.
- Dornase alfa has a long duration of action.
- It is used in Cystic fibrosis, which is characterized by thick, tenacious mucous production.
- It is also used in postoperative patients such as patients with tracheostomy to facilitate airway clearance and suction.
- Clearing of secretions for diagnostic tests (e.g., diagnostic bronchoscopy).

### Dose

About 2.5 mg once daily inhaled through nebulizer, may be increased to 2.5 mg twice daily if needed.

### Contraindications and Cautions

- In patients of acute bronchospasm, the increased secretions can aggravate the problem. Hence, contraindicated.
- Cautious use in patients suffering from peptic ulcer and esophageal varices, because these drugs can break the gastric mucosal barrier.

# DECONGESTANTS

- Decongestants are the drugs, which decrease the overproduction of secretions by causing local vasoconstriction in the nasal mucosa.
- These drugs provide relief from the discomfort of blocked nose by promoting drainage of secretions and thereby improving airflow.

- Topical decongestants are sympathomimetics, meaning that they imitate the effects of the sympathetic nervous system to cause vasoconstriction.
- They are available as nasal drops and nasal sprays.
- These are used to relieve the discomfort of nasal congestion that accompanies the common cold, sinusitis, and allergic rhinitis.

## Commonly Used Nasal Decongestants

- **Topical Nasal Decongestants:** Ephedrine, Xylometazoline, Phenylephrine, Oxymetazoline, etc. (Table 7.6).
- **Oral Decongestants:** Pseudoephedrine (Table 7.7).
- **Topical Steroid Nasal Decongestants:** Beclomethasone, Flunisolide, Dexamethasone, Budesonide, Triamcinolone, etc. (Table 7.8).

**Table 7.6:** Topical nasal decongestants

| Drugs | Dosage |
|---|---|
| Ephedrine | • Instil solution in each nostril 4 hourly<br>• Do not use for children <6 years unless advised by physician |
| Xylometazoline | • Adult: Two to three sprays or two to three drops in each nostril 8 hourly (0.17% solution)<br>• Pediatric (2–12 years): Two to three drops of 0.05% solution 8–12 hourly |
| Phenylephrine | • Adult and pediatric (>6 years): One to two sprays in each nostril 3–4 hourly<br>• Pediatric (2–6 years): Two to three drops of 0.125% solution in each nostril 4 hourly |
| Oxymetazoline | • Adult and pediatric (>6 years): Two to three sprays or drops in each nostril 12 hourly<br>• Pediatric (2–5 years): Two to three drops of 0.05% solution in each nostril 12 hourly |

**Table 7.7:** Oral decongestants

| Drug | Dosage |
|---|---|
| Pseudoephedrine | • Adult: 60 mg 4–6 hourly<br>• Pediatric:<br>▪ 6–12 years 30 mg 4–6 hourly<br>▪ 2–5 years: 15 mg 4–6 hourly<br>▪ 1–2 years: 0.02 mL/kg 4–6 hourly<br>▪ 3–12 months: Three drops/kg 4–6 hourly |

**Table 7.8:** Topical steroid nasal decongestants

| Drug | Dosage |
|---|---|
| Beclomethasone | • Adult: One to two inhalations in each nostril 12 hourly<br>• Pediatric (6–11 years): One inhalation in each nostril 12 hourly |
| Flunisolide | • Adult: Two sprays in each nostril 12 hourly<br>• Pediatric (6–14 years): One spray in each nostril 8 hourly to two sprays in each nostril 12 hourly |
| Dexamethasone | • Adult: Two sprays in each nostril BD to TDS<br>• Pediatric: One to two sprays in each nostril 12 hourly |
| Budesonide | Adult and pediatric (>6 years): Two sprays in each nostril morning and evening or four sprays in each nostril in the morning |
| Triamcinolone | Adult: Two sprays in each nostril every day |

## Indications

- Nasal congestion related to the common cold, sinusitis, and allergic rhinitis.
- To relieve the pain and congestion of otitis media.

## Pharmacokinetics

- **Topical nasal decongestants:** The onset of action is almost immediate. These are not generally absorbed systemically. The metabolism occurs in the liver and excretion through kidneys, if the drug is absorbed.
- **Oral decongestants:** Pseudoephedrine is well absorbed and attains peak levels quickly in 20–45 minutes. The metabolism occurs in the liver and excretion is through kidneys.
- **Topical steroid nasal decongestants:** The onset of action is not immediate. These drugs may require up to 1 week to produce their effect. The drug should be discontinued, if no effects are seen after 3 weeks. These drugs are not generally absorbed systemically. The absorbed drug (if any) is metabolized in the same way as other steroids.

The contraindications and adverse effects of various decongestants are given in Tables 7.9 and 7.10, respectively.

**Table 7.9:** Contraindications and cautions of decongestants

| Drug class | Contraindications and cautions |
|---|---|
| Topical nasal decongestants | • Erosion in the mucous membranes.<br>• Glaucoma, diabetes, coronary disease, hypertension, thyroid disease, or prostate hypertrophy |
| Oral decongestants | Glaucoma, diabetes, coronary disease, hypertension, thyroid disease, or prostate hypertrophy |
| Topical steroid nasal decongestants | • Active infection such as tuberculosis<br>• Chicken pox or measles |

# EXPECTORANTS

**(Mucokinetics: muco-mucous, kinetics-movement)**

- Expectorants are also called mucokinetics.
- Expectorants are the drugs which increase the bronchial secretions.
- These drugs also reduce the viscosity of these secretions thereby helping in easy expulsion of the sputum.
- These are included in expectorant formulations in combination with antitussives and antihistaminics.

Examples are:

- Bronchial secretion enhancers: Guaifenesin, sodium or potassium citrate, potassium iodide, ammonium chloride, vasaka.
- Mucolytics: Acetyl cysteine, ambroxol, bromhexine, carbocisteine.

**Table 7.10:** Adverse effects of decongestants

| Drugs class | Adverse effects |
|---|---|
| Topical nasal decongestants | • Local stinging and burning<br>• Rebound congestion<br>• Sympathomimetic effects (e.g., increased pulse rate and BP; urinary retention) seen in some patients only |
| Oral decongestants | • Rebound congestion<br>• Sympathomimetic effects such as anxiety, restlessness, tremors, hypertension, arrhythmias, sweating, and pallor |
| Topical steroid nasal decongestants | • Local irritation, headache and dryness of the mucosa<br>• Delayed healing in nasal surgery or trauma |

## Mechanism of Action (Table 7.11)

**Table 7.11:** Expectorants

| Drug | Dosage | Mechanism of action |
|---|---|---|
| Sodium and Potassium citrate | 1–2 g | Increase bronchial secretion by salt action |
| Ammonium chloride | 300 mg | Reflexly increase respiratory secretions |
| Potassium iodide | 200–300 mg | Irritate the airway mucosa as it is secreted by bronchial glands |
| Guaifenesin (most commonly used) | Adult and pediatric (>12 years): 200–400 mg PO 4 hourly<br>Pediatric:<br>• 6–12 years 100–200 mg 4 hourly<br>• 2–6 years 50–100 mg 4 hourly | Enhance mucociliary excretory function as these are secreted by tracheobronchial glands |

## Indications

In the treatment of productive cough accompanied with excessive, thick and difficult to remove secretion/sputum.

## Adverse Effects

- GI symptoms such as nausea, vomiting, and anorexia (most common).
- Headache, dizziness or both.

## Precautions

- The most important consideration in the use of these drugs is identifying the exact cause of the underlying cough.
- Prolonged use of the OTC (cough syrup) preparations could result in the masking of important symptoms of a serious underlying disorder.
- These drugs should not be used for more than 1 week; if the cough persists, encourage the patient to seek health care.

The various drugs, their classes and their sites of action on respiratory tract are given in Figure 7.2.

# ANTITUSSIVES

- The drugs used to control the dry cough are known as antitussives.
- These drugs act directly on the cough center in the medulla of the brain to depress the cough reflex and raise the threshold of cough center or act peripherally in the respiratory tract to reduce cough impulses, or both these actions.

**The aim of giving antitussives is to control rather than eliminate cough.**

**Antitussives can be classified into:**

- **Opioids:** Codeine, pholcodeine, ethyl morphine.
- **Nonopioids:** Noscapine, dextromethorphan, chlophedianol.

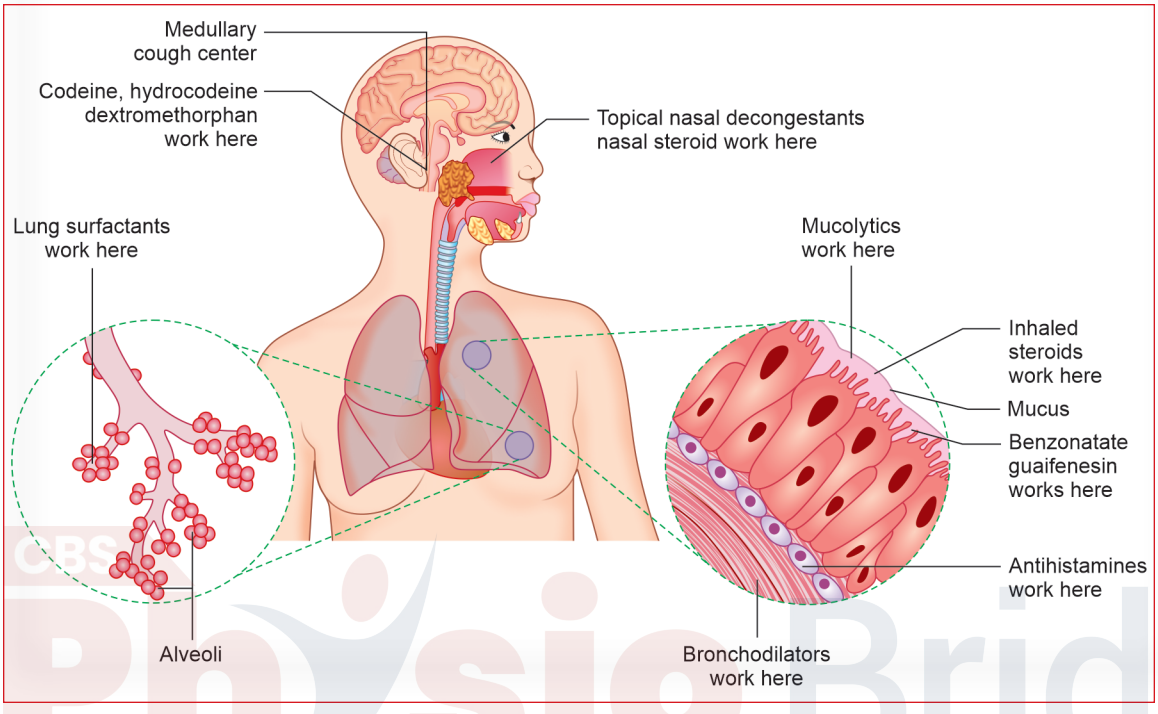


**Fig. 7.2:** Site of action of various drugs on respiratory tract

## Opioids

### *Codeine (Methyl Morphine)*

- An opium alkaloid, similar to but less potent than morphine.
- More selective for cough center.
- Codeine is regarded as the standard antitussive.
- Suppresses cough for about 6 hours.
- Abuse liability is low, but present.

**Side Effects and Precautions**

- Constipation.
- Respiratory depression (at higher dosage).
- It causes drowsiness. Hence, advised caution for drivers.
- It is contraindicated in asthmatics.
- It should be avoided in children.
- Not to be used in head injury patients.

**Dose**

- **Adult:** 10–20 mg orally 4–6 hourly.
- **Pediatric (6–12 years):** 5–10 mg orally 4–6 hourly.
- **Pediatric (2–6 years):** 2.5–5 mg orally 4–6 hourly.

### Pholcodeine

- It is similar to codeine in efficacy as antitussives.
- It is longer acting and acts for 12 hours.
- It has no analgesic or addictive property.

**Dose**

10–15 mg 12 hourly.

### Ethyl Morphine

It is similar to codeine in all actions except constipation, which is less with it.

**Dose**

10–30 mg 8 hourly.

## Nonopioids

### Noscapine (Narcotine)

- It is nearly equipotent antitussive as codeine.
- It depresses the cough center.
- It has no narcotic, analgesic or dependence inducing properties.
- Useful in spasmodic cough.

**Side Effects**

- Headache and nausea
- Bronchoconstriction in asthmatics

**Dose**

- **Adults:** Given in a dose of 15–30 mg 3–4 times daily.
- **Children (2–6 years):** Given in a dose of 7.5 mg 3–4 times daily.
- **Children (6–12 years):** Given in a dose of 15 mg 3–4 times daily.

### Dextromethorphan

- The antitussive action of dextromethorphan is similar to codeine.
- It is a synthetic and centrally acting NMDA (N-methyl D-aspartate) receptor antagonist.
- Constipation not seen.
- Nonaddicting.

**Side Effects**

- Dizziness
- Nausea
- Drowsiness
- Ataxia and hallucinations (at high doses)

**Dose**

- **Adult:** 10–30 mg 4–8 hourly; 60 mg 8 hourly for sustained action
- **Pediatric (6–12 years):** 5–10 mg 4 hourly; 30 mg 8 hourly for sustained action
- **Pediatric (2–6 years):** 2.5–7.5 mg 4–8 hourly; 15 mg 8 hourly for sustained action

### Chlophedianol

- It is an antitussive having central action.
- It has slow onset of action with longer duration.

**Side Effects**

The common side effects are vertigo, irritability, sedation and dryness of mouth.

**Dose**

20–40 mg 2–3 times daily.

**Pharmacokinetics**

- All antitussives are rapidly absorbed orally.
- The metabolism occurs in liver, and excretion is through kidneys.
- It crosses the placenta barrier and secreted in breast milk.

**Contraindications and Cautions**

- In patients with asthma and emphysema because cough suppression in these patients could lead to an accumulation of secretions.
- In patients who are hypersensitive to or have a history of addiction to narcotics.
- During driving, as these drugs can cause sedation and drowsiness.
- In pregnancy and lactation as these drugs have potential for adverse effects on the fetus or baby, including sedation and CNS depression.

## BRONCHOCONSTRICTORS

- The drugs which cause constriction of bronchi (bronchospasm) are called bronchoconstrictors.
- Bronchoconstriction is never induced as a part of any treatment, except in experimental animals to check the effectiveness of bronchodilators.
- In experimental animals, histamine is commonly used as bronchoconstriction inducing agent.
- Some other bronchoconstrictors are 5HT, LTC4, LTD4, PGF2α, PGD2, PAF and TXA2.
- Bronchoconstriction due to histamine causes symptoms of dyspnea, which are antagonized with antihistaminics and adrenaline, which act as physiological antagonist.

## ANTIHISTAMINICS

The drugs which competitively antagonize the actions of histamine on histaminic receptors are called antihistaminic drugs.

### Histamine

- A major amount of histamine is present in the mast cells.
- The tissues containing maximum histamine are skin, gastric mucosa, intestinal mucosa, liver, placenta and lungs.
- Brain, gastric mucosa, epidermis and growing regions contain non-mast cell histamine.
- Some other sites where histamine is found are body secretions, blood, pathological fluids and venoms of snake and scorpions.
- Histamine acts through various receptors known as histaminic receptors.

**Table 7.12:** Histamine receptors

| Receptor | Distribution in body | Actions |
|---|---|---|
| $H_1$ receptor | Airway, intestinal and uterine smooth muscle | Contractions |
| | Blood vessels | Vasodilatation due to release of nitrous oxide |
| | Larger blood vessels (smooth muscles) | Vasoconstriction |
| $H_2$ receptor | Gastric glands | Increase of acid secretion |
| | Blood vessels | Vasodilatory effect |
| | Brain | Increase of synapse transmission |
| $H_3$ receptor | Brain | Sedation |
| | Lung, spleen, skin and gastric mucosa | Reduction of histamine release |
| $H_4$ receptor | Eosinophil, mast cells and basophils | Chemotaxis effect |

## Histamine Receptors

The histamine receptors are of four types: *$H_1$, $H_2$, $H_3$ and $H_4$* (Table 7.12).

- The antihistaminic term is conventionally used for $H_1$ antagonists only.
- The drugs which antagonize $H_2$ receptors are called $H_2$ receptor blockers. $H_2$ receptor blockers are specifically used for acid suppression in gastric mucosa and are studied in detail with GIT system.
- $H_3$ and $H_4$ antagonists have not been ascribed for any specific clinical utility yet.

## Antihistaminics ($H_1$ Antagonists)

- The $H_1$ antagonistic drugs act at $H_1$ receptors and antagonize the actions of histamine competitively.
- The $H_1$ antihistaminics have many common properties except that they differ in mainly their sedative actions.

**Antihistaminics are classified as:**

- First Generation: mild, moderate and highly sedative
- Second Generation or nonsedative

## First Generation Antihistaminics (Table 7.13)

The first compound of this group was introduced in the late 1930s. These were very frequently used before introduction of less sedating/nonsedating 2nd generation antihistaminics. Some of these drugs are still used for a variety of purposes.

### Pharmacological Actions

- **Histaminic antagonizing effects:** The bronchoconstriction and the triple response due to histamine are antagonized. The triple response consists of wheal, flare and itch.
- **Antiallergic effects:** The manifestations of immediate hypersensitivity (type I reactions) are suppressed. They are having a good role in the treatment of urticaria, itching and angioedema.
- **Anticholinergic effects:** The acetylcholine produces muscarinic effects through $H_1$ receptor, which are antagonized by these drugs.



**Table 7.13:** First generation of antihistaminics

| Drugs | Dose and route of administration |
|---|---|
| **Mild sedatives** | |
| • Chlorpheniramine | • 2–4 mg orally and intramuscularly |
| • Dexchlorpheniramine | • 2 mg by oral route |
| • Triprolidine | • 2.5–5 mg by oral route |
| • Clemastine | • 1–2 mg by oral route |
| **Moderate sedatives** | |
| • Pheniramine | • 20–50 mg orally and intramuscularly |
| • Cinnarizine | • 25–50 mg by oral route |
| • Cyproheptadine | • 4 mg by oral route |
| **Highly sedatives** | |
| • Diphenhydramine | • 25–50 mg by oral route |
| • Promethazine | • 25–50 mg orally and intramuscularly |
| • Hydroxyzine | • 25–50 mg by oral route |

- **CNS effects:** The older antihistaminics show sedative effects whereas these effects are rarely or not at all seen with the newer second generation antihistaminic drugs.
- **CVS effects:** No CVS effects are seen on oral administration. Fast IV administration of these drugs can produce sudden hypotension.

### Pharmacokinetics

- By both oral and parenteral routes, the absorption of these drugs is optimal.
- The metabolism occurs in liver and excretion occurs through urine.
- These agents show wide distribution in the body tissues and also penetrate the blood brain barrier.

### Side Effects

Side effects of first generation $H_1$ antihistaminics are frequent, but generally mild.

- Some tolerance to side effects develops on repeated use.
- The common side effects are sedation, reduced alertness and ability to concentrate, tendency to fall asleep, headache, listlessness.
- Regular use of conventional antihistamines may interfere with learning due to CNS depressant property, hence, not advisable in children.
- Some other side effects due to anticholinergic activity are xerostomia, visual disturbance, GI disturbances and urinary hesitation.

## *Second Generation Antihistaminics (Table 7.14)*

The $H_1$ receptor blockers which were marketed after 1980 are called second generation antihistaminics (SGAs). The 2nd generation agents have poor or absent penetration of blood brain barrier. Hence, have minimal or no sedative effect.

These have one or more of the following properties:

- No sleepiness due to absence of CNS depression.
- No anticholinergic side effects due to high $H_1$ selectivity.

**Table 7.14:** Second generation antihistaminics

| Drug | Dosage | Specific points |
|---|---|---|
| **Fexofenadine** | 120–180 mg orally, once daily | Safe in cardiac patients, doesn't cross blood brain barrier |
| **Loratadine** | 10 mg orally, once daily | Fast acting, with longer t½ of 17 hours |
| **Desloratadine** | 5 mg orally, once daily | Effective at half the dose of loratadine |
| **Cetirizine** | 10 mg orally, once daily | • Metabolite of hydroxyzine<br>• Mild sedation in some recipients<br>• Attains high concentration in skin |
| **Levocetirizine** | 5–10 mg orally, once daily | • It is the active enantiomer of cetirizine<br>• Effective at half the dose of cetirizine<br>• Less sedative |
| **Azelastine** | 4 mg orally, once daily; 0.28 mg intranasally | • Good topical activity antagonizes LT and PAF<br>• Provide quick symptomatic relief when given by intranasal route |
| **Rupatadine** | 10 mg orally, once daily | Additional PAF antagonistic property |

- Additional antiallergic mechanisms such as antagonizing leukotrienes and PAF.
- Poor, antipruritic, antiemetic and antitussive actions.

### Major Indications

- **Nose:** Allergic rhinitis, pollinosis, (to control sneezing, runny but not blocked nose).
- **Eye:** Conjunctivitis, red, watering and itchy eyes.
- **Skin:** Atopic eczema, urticaria, dermographism, hay fever.
- **General:** Drug and food allergy.

## Uses of Antihistaminics

- **Allergic disorders** of eye (allergic conjunctivitis, angioedema of eyelids, etc.), nose (rhinitis, sneezing, etc.) and skin (angioedema of lips, itching urticaria, hay fever, etc.) and other general allergic disorders.
- **Pruritis:** Antihistaminics like chlorpheniramine, diphenhydramine and cyproheptadine are very commonly used in idiopathic pruritic cases.
- **Common cold:** Second generation antihistaminics are less effective in this respect. First generation antihistaminics provide only symptomatic relief by anticholinergic (reduce rhinorrhea) effect, but do not alter the course of the illness.
- **Motion sickness:** Promethazine, diphenhydramine and dimenhydrinate. These drugs should be taken at least one hour before starting journey to get the best effects.
- **Vertigo:** Cinnarizine is commonly used in Meniere's disease and other types of vertigo.

## Responsibilities of Medical Professionals

- Provide other measures to help relieve cough (e.g., humidity, cool temperature, fluids, use of topical lozenges) as appropriate.
- Some antihistaminics cause sedation, advise patient to take these drugs at bedtime only.
- Avoid combining the mucolytic agents with other drugs in the nebulizer to avoid the formation of precipitates and potential loss of effectiveness of either drug.
- Monitor patient's rate and depth of respiration, adventitious breath sounds if any, abnormal pulmonary secretion with cough; these symptoms are responsible for poor tissue perfusion and can cause hypoxia, anxiety, syncope, confusion; it could be sign of ineffective drug therapy.
- Educate patient to practice nonpharmacological measures such as steam inhalation, increase fluid intake to liquefy and mobilize mucus.
- **Cough suppressants:** Syrup should be taken with/without water; coated on the throat and take fluids only after 30–60 minutes.
- **Antihistamines:** Tablet/syrup can be taken with water to alleviate allergic symptoms.
- **Nasal decongestants:** Apply on the nose; clears nasal passage by blowing followed by nasal spray.
- **Expectorants:** Syrups can be taken with water; and increase water intake throughout the day for reducing thickening of mucus production.

## SUMMARY

- The bronchospasm is due to the contraction/constriction of bronchial smooth muscles which leads to decreased air entry into the tracheobronchial tree resulting into dyspnea and difficult respiration.
- M3 cholinergic receptors are present in larger airways and their stimulation causes bronchoconstriction. Anticholinergic drugs block M3 receptors and cause bronchodilation.
- Montelukast and Zafirlukast antagonize LTs receptor mediated bronchoconstriction, airway mucous secretion, increased vascular permeability and recruitment of eosinophils.
- Omalizumab is a humanized monoclonal antibody that acts against IgE by binding and neutralizing the free IgE in blood circulation and is given subcutaneously.
- Acetylcysteine/N-acetylcysteine (NAC) is a mucolytic and antioxidant drug that may also influence several inflammatory pathways.
- Decongestants decrease the overproduction of secretions by causing local vasoconstriction in the nasal mucosa, provide relief from the discomfort of blocked nose by promoting drainage of secretions and thereby improving airflow.
- Antitussives act directly on the cough center in the medulla of the brain to depress the cough reflex and raise the threshold of cough center or act peripherally in the respiratory tract to reduce cough impulses.
- Bronchoconstrictors are 5HT, LTC4, LTD4, PGF2α, PGD2, PAF and TXA2.

# ASSESS YOURSELF

## Long and Short Answer Questions

1. Classify the drugs used for the treatment of bronchial asthma.
2. Explain pharmacological management of status asthmaticus.
3. What do you understand by the nasal decongestants? Describe their uses and side effects.
4. Write short notes on:
   a. Omalizumab
   b. Salbutamol
   c. Inhalational steroids
   d. Theophylline
   e. Codeine

## Multiple Choice Questions

**1. To prevent exercise-induced bronchial asthma, drug used is:**
   a. Sodium cromoglycate
   b. Ipratropium bromide
   c. Terbutaline
   d. Epinephrine

**2. All of the following drugs can precipitate acute attack of asthma; except:**
   a. Phenylbutazone
   b. Naproxen
   c. Glucocorticoids
   d. Aspirin

**3. Omalizumab is administered in bronchial asthma by which route?**
   a. Oral
   b. Intravenous
   c. Subcutaneous
   d. Aerosol

**4. Advantage of salmeterol over salbutamol is its:**
   a. Shorter duration of action
   b. More potency
   c. Longer duration of action
   d. Lesser cardiac effects

**5. Which of the following antiasthma drugs is not a bronchodilator?**
   a. Ipratropium bromide
   b. Theophylline
   c. Formoterol
   d. Sodium cromoglycate

**6. Which of the following actions is not exhibited by methylxanthines?**
   a. Intracellular release of $Ca^{2+}$
   b. Antagonism of adenosine
   c. Inhibition of phosphodiesterase
   d. None of these

**7. Zileuton is:**
   a. 5 lipooxygenase inhibitor
   b. TX A2 inhibitor
   c. Leukotriene receptor antagonist
   d. Prostaglandin synthesis inhibitor

### Answer Key

**1.** a **2.** c **3.** c **4.** c **5.** d **6.** d **7.** c

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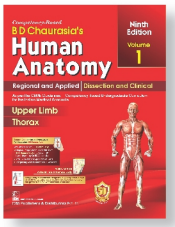


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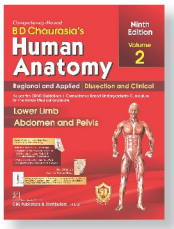


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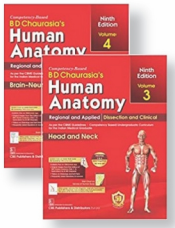


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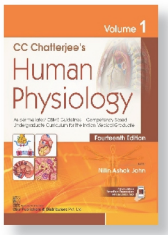


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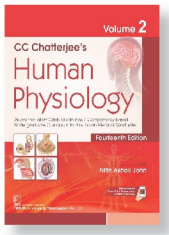


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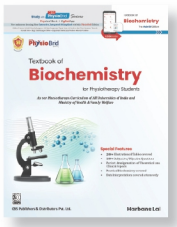


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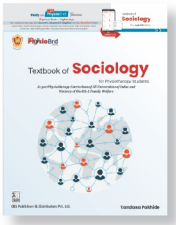


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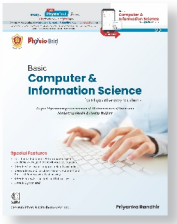


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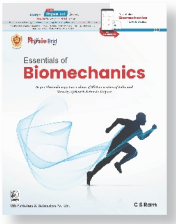


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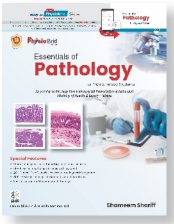


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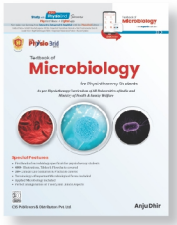


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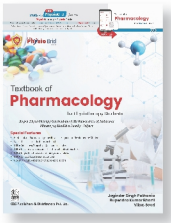


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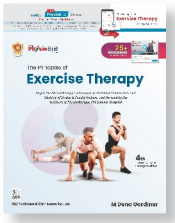


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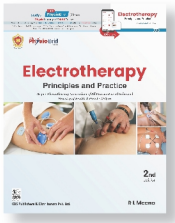


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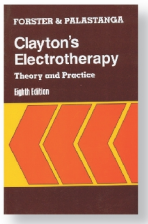


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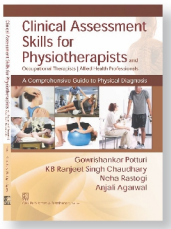


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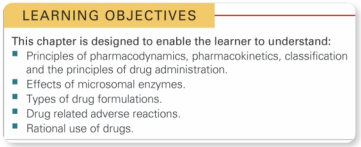
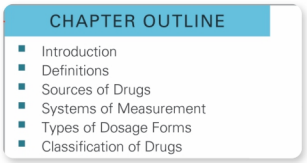
# Pharmacology for Physiotherapy Students

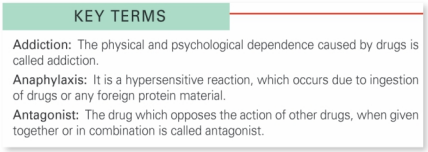
**Learning Objectives** in the beginning of every chapter help readers understand the purpose of the chapter.



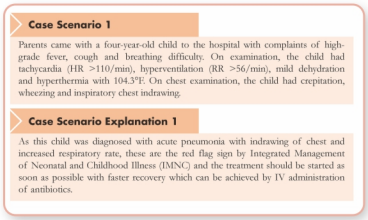

**Chapter Outline** provides a glimpse of the content covered in the chapter.



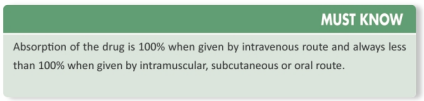

Important terms of the respective chapters have been summarized in the beginning of each chapter under **Key Terms**.

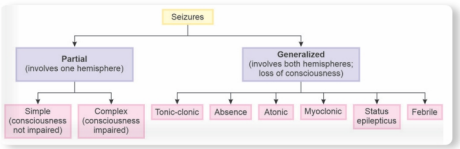



Each and every topic has been started with **Clinical Case Scenario** with explanation from theoretical and clinical integration point of view.



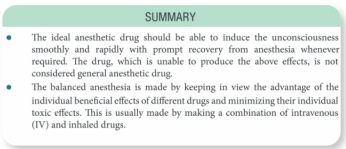

**Must Know** boxes provide the overview of important facts and terms of the concerned topic.

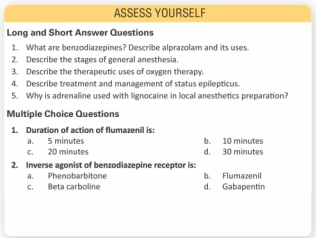



**Colorful Figures** are well illustrated in the book.

Each and every chapter ends with **Summarized one-liner** for quick glance of the chapter.




**Assess Yourself** section contains frequently asked questions and multiple choice questions to help students attain mastery over the subject.

## About the Authors


**Joginder Singh Pathania** MBBS, MD, is currently working as a Senior Medical Officer in Government Hospital, Shimla, Himachal Pradesh.

**Rupendra Kumar Bharti** MBBS, MD, is currently working as an Assistant Professor in the Department of Pharmacology at the Government Medical College Mahasamund, Chhattisgarh.

**Vikas Sood** D Pharma, MSc, PhD, is presently working as an Associate Professor in Shivalik Institute of Nursing and Shimla Nursing College, Shimla, Himachal Pradesh.



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