How this book is useful?

Features

- Thoroughly revised chapters to include recent developments in theory and practice, as well as new drugs released in India.
- 'Problem directed study; a novel exercise which introduces the reader to the process of therapeutic decision making.
- Enriched illustrations, flow charts, tables and boxed point-wise summaries of important aspects.
- Comprehensive and systematic coverage of drugs, highlighting their therapeutic status.
- Text arranged under hierarchical headings, reorganization of some chapters and revised classification of certain classes of drugs makes the presentation highly user friendly.
Preface

Medical pharmacology is a unique synthesis of basic pharmacology with clinical pharmacology and pharmacotherapeutics. The subject is highly dynamic. Developments are occurring both in defining molecular targets for drug action and finding targeted drugs, as well as in accruing credible evidence regarding the impact of different treatment modalities on therapeutic outcomes. These efforts have begun to crystallize into evidence based medicine and clear cut therapeutic guidelines. The present edition endeavours to amalgamate the developments with the core content of the subject.

While the primary theme of the book outlined in the preface to the first edition is maintained, the successive editions have become more descriptive and more comprehensive. In preparing this edition, all chapters have been revisited and extensively updated. Latest therapeutic guidelines from authoritative sources like WHO, British National Formulary, National Formulary of India, as well as from eminent professional bodies have been incorporated, especially in areas like hypertension, dyslipidaemias, acute coronary syndromes, surgical prophylaxis, tuberculosis (including MDR-TB), MAC-infection, leprosy, HIV-AIDS, malaria, kala-azar, etc. Recent innovations have been highlighted, notably in antidiabetic drugs, psychopharmacological agents, antiplatelet drugs, treatment of inflammatory bowel disease, drugs affecting renin-angiotensin system, anticoagulants, antiviral (including anti-HIV) drugs, targeted anticaner drugs, etc.

New drugs released in India have been included. Infrequently used drugs and those not available in India are presented briefly in extract type. Important points are summarized in boxes. Use of distinctive headings in a hierarchical order makes the text highly systematic. Representative trade names of drugs with available dosage forms are mentioned. Due emphasis is given to diseases prevalent in India and similar tropical countries, alongwith their current drug therapy.

The most important objective of medical pharmacology is to train medical students in therapeutic decision making according to specific clinical problems in individual patients. A new feature ‘problem directed study’ has been included at the end of majority of chapters to give an exercise in therapeutic decision making for a realistic clinical scenario. The solutions provided in Appendix-1 explain how rational decisions could be arrived at.

I thank students and other readers of this text for their valuable feedback and suggestions. All credit for existence of this book, especially the present edition, goes to Mr. Jitendar Pal Vij, the untiring Group Chairman and Mr. Ankit Vij (Managing Director) of M/s Jaypee Brothers. Meticulous typesetting by Ms. Sunita Katla and proof reading by Ms. Geeta Srivastava deserves special mention. Credit for improving the illustrations goes to Mr. Manoj Pahuja. The cooperation and editorial management of my wife is acknowledged.

New Delhi
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KD Tripathi
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DRUGS FOR COUGH

Cough is a protective reflex, its purpose being expulsion of respiratory secretions or foreign particles from air passages. It occurs due to stimulation of mechano- or chemoreceptors in throat, respiratory passages or stretch receptors in the lungs. Cough may be useful or useless. Useless (nonproductive) cough should be suppressed. Useful (productive) cough serves to drain the airway, its suppression is not desirable, may even be harmful, except if the amount of expectoration achieved is small compared to the effort of continuous coughing. Apart from specific remedies (antibiotics, etc. see box), cough may be treated as a symptom (nonspecific therapy) with:

1. **Pharyngeal demulcents**  
   Lozenges, cough drops, linctuses containing syrup, glycerine, liquorice.

2. **Expectorants (Mucokinetics)**  
   (a) *Bronchial secretion enhancers*: Sodium or Potassium citrate, Potassium iodide, Guaiaphenesin (Glyceryl guaiacolate), balsam of Tolu, Vasaka, Ammonium chloride.  
   (b) *Mucolytics*: Bromhexine, Ambroxol, Acetyl cysteine, Carbocisteine

3. **Antitussives (Cough centre suppressants)**  
   (a) *Opioids*: Codeine, Ethylmorphine, Pholcodeine.  
   (b) *Nonopioids*: Noscapine, Dextromethorphan, Chlophedianol.  
   (c) *Antihistamines*: Chlorpheniramine, Diphenhydramine, Promethazine.  
   (d) *Peripherally acting*: Prenoxdiazine.

4. **Adjuvant antitussives**  
   *Bronchodilators*: Salbutamol, Terbutalin.

DEMULCENTS AND EXPECTORANTS

Pharyngeal demulcents sooth the throat and reduce afferent impulses from the inflamed/irritated pharyngeal mucosa, thus provide symptomatic relief in dry cough arising from throat.

Expectorants (Mucokinetics) are drugs believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

Sodium and potassium citrate are considered to increase bronchial secretion by salt action. Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa. Prolonged use can affect thyroid function and produce iodism. It is not used now. Guaiaphenesin, vasaka, tolu balsum are plant products which are supposed
to enhance bronchial secretion and mucociliary function while being secreted by tracheobronchial glands. Ammonium salts are nauseating—reflexly increase respiratory secretions. A variety of expectorant formulations containing an assortment of the above ingredients, often in combination with antitussives/antihistaminics are marketed and briskly promoted, but objective evidence of efficacy of these is non-conclusive. The US-FDA has stopped marketing of all expectorants, except guaiphenesin. Steam inhalation and proper hydration may be more helpful in clearing airway mucus.

**Mucolytics**

**Bromhexine** A derivative of the alkaloid vasicine obtained from Adhatoda vasica (Vasaka), is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes—network of fibres in tenacious sputum is broken. It is particularly useful if mucus plugs are present. Side effects are rhinorrhea and lacrimation, nausea, gastric irritation, hypersensitivity. *Dose:* adults 8 mg TDS, children 1–5 years 4 mg BD, 5–10 years 4 mg TDS. **BROMHEXINE** 8 mg tablet, 4 mg/5 ml elixir.

**Ambroxol** A metabolite of bromhexine having similar mucolytic action, uses and side effects.

**Acetylcysteine** It opens disulfide bonds in mucoproteins present in sputum—makes it less viscid, but has to be administered directly into the respiratory tract. **MUCOMIX** 200 mg/ml inj in 1,2,5 ml amps; injectable solution may be nebulized/instilled through trachiostromy tube.

**Carbocisteine** It liquefies viscid sputum in the same way as acetylcysteine and is administered orally (250–750 mg TDS). Some patients of chronic bronchitis have been shown to benefit. It may break gastric mucosal barrier; is contraindicated in peptic ulcer patients. Side effects are gastric discomfort and rashes. **MUCODYNE** 375 mg cap, 250 mg/5 ml syr.

It is available in combination with amoxicillin or cephalixin for treatment of bronchitis, bronchiectasis, sinusitis, etc. **CARBOMOX:** Carbocisteine 150 mg + amoxicillin 250 or 500 mg caps. **CARBICEF:** Carbocisteine 150 mg + cephalolin 250 or 500 mg caps. **ANTITUSSIVES**

These are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions. Because they aim to control rather than eliminate cough, antitussives should be used only for dry nonproductive cough or if cough is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).
Opioids

**Codeine** *(see Ch. 34)* An opium alkaloid, qualitatively similar to and less potent than morphine, but is more selective for cough centre. Codeine is regarded as the standard antitussive; suppresses cough for about 6 hours. The antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain. Abuse liability is low, but present; constipation is the chief drawback. At higher doses respiratory depression and drowsiness can occur, especially in children. Driving may be impaired. Like morphine, it is contraindicated in asthmatics and in patients with diminished respiratory reserve; should be avoided in children.

*Dose:* 10–30 mg; children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg, frequently used as syrup codeine phos. 4–8 ml. CODINE 15 mg tab, 15 mg/5 ml linctus.

**Ethylmorphine** It is closely related to codeine which is methylmorphine, and has antitussive, respiratory depressant properties like it, but is believed to be less constipating.

*Dose:* 10–30 mg TDS; DIONINDON 16 mg tab.

**Pholcodeine** It has practically no analgesic or addicting property, but is similar in efficacy as antitussive to codeine and is longer acting—acts for 12 hours; dose: 10–15 mg. COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

**Nonopioids**

**Noscapine (Narcotine)** An opium alkaloid of the benzoisoquinoline series *(see Ch. 34)*. It depresses cough but has no narcotic, analgesic or dependence inducing properties. It is nearly equipotent antitussive as codeine, especially useful in spasmodic cough. Headache and nausea occur occasionally as side effect. It can release histamine and produce bronchoconstriction in asthmatics.

*Dose:* 15–30 mg, children 2–6 years 7.5 mg, 6–12 years 15 mg. COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

**Dextromethorphan** A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist; the *d*-isomer has antitussive action while *l*-isomer is analgesic. Dextromethorphan does not depress mucociliary function of the airway mucosa and is practically devoid of constipating action. Though considered nonaddicting, some drug abusers indulge in it. The antitussive action of dextromethorphan has been rated equivalent to codeine, but some clinical studies have found it to be no better than placebo.

*Side effect:* Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.

*Dose:* 10–20 mg, children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg. It is a common ingredient of many proprietary cough formulations *(see antitussive combinations below)*.

**Chlophedianol** It is a centrally acting antitussive with slow onset and longer duration of action.

*Side effect:* Dryness of mouth, vertigo, irritability.

*Dose:* 20–40 mg; DETIGNON, TUSSIGON 20 mg/5 ml linctus with Ammon. chloride 50 mg and menthol 0.25 mg.

**Antihistamines**

Many H1 antihistamines have been conventionally added to antitussive/expectorant formulations *(see below)*. They afford relief in cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre. They have no expectorant property, may even reduce secretions by anticholinergic action. They have been specially promoted for cough in respiratory allergic states, though their lack of efficacy in asthma is legendary.

Chlorpheniramine (2–5 mg), Diphenhydramine (15–25 mg) and Promethazine (15–25 mg; PHENERGAN 5 mg/5 ml elixir) are commonly used. Second generation antihistamines like fexofenadine, loratadine, etc. are ineffective.

**Peripherally acting antitussives**

**Prenoxdiazine** In contrast to other antitussives, it acts peripherally; desensitizes the pulmonary stretch receptors and reduces tussal impulses originating in the lungs. It is indicated in cough of bronchial origin. Efficacy, however, is not impressive. Though an old drug developed in Hungary, it has been introduced recently in India.

*Dose:* 100–200 mg TDS-QID; PRENOXID 100, 200 mg tab.

**Bronchodilators** Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals with...
**DRUGS FOR COUGH AND BRONCHIAL ASThma**

Bronchial hyperreactivity. Bronchodilators relieve cough in such individuals and improve the effectiveness of cough in clearing secretions by increasing surface velocity of airflow during the act of coughing. They should be used only when an element of bronchoconstriction is present and not routinely. Their fixed dose combinations with antitussives are not satisfactory because of differences in time course of action of the components and liability for indiscriminate use.

Fixed dose combinations of a centrally acting antitussive with a bronchodilator or with an antihistaminic having high atropinic activity have been banned in India, but many are still marketed.

*Aeromatic chest rub* is widely advertised as a cough remedy. Though it has been shown to reduce experimentally induced cough in healthy volunteers, there is no evidence of benefit in pathological cough.

**SOME ANTI TUSSIVE-EXPECTORANT COMBINATIONS**

**ASTHALIN EXPECTORANT**: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syr; dose 10–20 ml.

**ASCORIL-C**: Codeine 10 mg, chlorpheniramine 4 mg per 5 ml syr.

**AXALIN**: Ambroxol 15 mg, guaiphenesin 50 mg, salbutamol 1 mg, menthol 1 mg per 5 ml syr.

**BRONCHOSOLVIN**: Guaiphenesin 100 mg, terbutaline 2.5 mg, bromhexine 8 mg per 10 ml susp.

**CADICOFF, GRILINCTUS**: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, Amm. chloride 60 mg per 5 ml syr.

**BENADRYL COUGH FORMULA**: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, ammon. chlor. 60 mg/5 ml syr; dose 5–10 ml, children 2.5–5 ml.

**BRO-ZEDEX**: Bromhexine 8 mg, guaiphenesin 100 mg, terbutaline 2.5 mg, menthol 5 mg per 10 ml syrup; dose 10 ml.

**CADISTIN EXPECTORANT**: Chlorpheniramine 2 mg, glycercyl guaiacolate 80 mg, ammon. chlor. 100 mg, sod. citrate 44 mg, menthol 0.8 mg, terpin hydrate 4 mg, tolu balsam 6 mg, Vasaka syrup 0.13 ml per 5 ml syrup; dose 10 ml.

**CHERICOF**: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg per 5 ml liq.

**CLISTIN**: Carbinoxamine 4 mg, ammon. chlor. 240 mg, sod. citrate 240 mg per 10 ml syrup.

**COREX**: Chlorpheniramine 4 mg, codeine phos. 10 mg, menthol 0.1 mg per 5 ml syrup; dose 5 ml, children 1.25–2.5 ml.

**COSCOPIN LINCTUS**: Noscapine 7 mg, chlorpheniramine 2 mg, citric acid 29 mg, sod. citrate 3 mg, ammon. chlor. 28 mg, per 5 ml syrup; dose 10–20 ml.

**COSOME**: Dextromethorphan 10 mg, phenylpropanolamine 25 mg, chlorpheniramine 4 mg per 10 ml syr; dose 10 ml.

**GRILINCTUS**: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, ammon. chlor. 60 mg/5 ml syr; dose 5–10 ml.

**GRILINCTUS SOFTCAPS**: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg softcaps.

**SOLVIN EXPECTORANT**: Bromhexine 4 mg, pseudoephedrine 30 mg tablet and in 10 ml liquid; dose 1 tablet/5 ml liquid.

**TOSSEX**: Codeine phos 10 mg, chlorpheniramine 4 mg, menthol 1.5 mg, sod. citrate 75 mg per 5 ml liquid; dose 5 ml.

**VENTORLIN EXPECTORANT**: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syrup; dose 10 ml, children 2.5–7.5 ml.

**ZEET LINCTUS**: Dextromethorphan 10 mg, guaiphenesin 50 mg, phenylpropanolamine 25 mg per 5 ml syr; dose 5 ml.

**DRUGS FOR BRONCHIAL ASThma**

Bronchial asthma is characterised by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion, mucosal edema and mucus plugging. Symptoms include dyspnoea, wheezing, cough and may be limitation of activity.

Asthma is now recognized to be a primarily inflammatory condition: inflammation underlying hyperreactivity. An allergic basis can be demonstrated in many adult, and higher percentage of pediatric patients. In others, a variety of trigger factors (infection, irritants, pollution, exercise, exposure to cold air, psychogenic) may be involved:

*Extrinsic asthma*: It is mostly episodic, less prone to status asthmaticus.

*Intrinsic asthma*: It tends to be perennial, status asthmaticus is more common.

Mast cells (present in lungs) and inflammatory cells recruited as a result of the initial reaction produce a multitude of mediators by the following processes:

- Release of mediators stored in granules *(immediate)*: histamine, protease enzymes, TNFα.
- Release of phospholipids from cell membrane followed by mediator synthesis (within minutes): PGs, LTs, PAF.
- Activation of genes followed by protein synthesis (over hours): Interleukins, TNFα. These mediators together constrict bronchial smooth muscle, cause mucosal edema, hyperemia and produce viscous secretions, all resulting in reversible airway obstruction. The inflammation perpetuates itself by cell-to-cell communication and recruitment of more and more inflammatory cells. Bronchial smooth muscle hypertrophy, increase in the population of mucus secreting cells and blood vessels occurs over time and damage to bronchial epithelium accentuates the hyper-reactivity. Vagal discharge to bronchial muscle is enhanced reflexly. Airway remodeling progressively worsens the disease.

Chronic obstructive pulmonary disease (COPD) is also an inflammatory disease of the lungs characterized by progressive emphysema (alveolar destruction) and broncholar fibrosis in variable proportions. Loss of bronchiolar elasticity leads to closure of smaller air tubes during expiration. The airway obstruction is accentuated during exercise causing shortness of breath. The expiratory airflow limitation does not fluctuate markedly over long periods of time, but there are exacerbations precipitated by respiratory infections, pollutants, etc. Smoking reduces the rate of decline in lung function. Bronchodilators prevent closure of peripheral air tubes during expiration and afford symptomatic relief in COPD patients, but improvement in forced expiratory volume in 1st second (FEV₁) following inhalation of a short-acting β₂ agonist is generally <15%. An increasing part of airway obstruction is irreversible.

APPROACHES TO TREATMENT
1. **Prevention of AG:AB reaction**—avoidance of antigen, hyposensitization—possible in extrinsic asthma and if antigen can be identified.
2. **Neutralization of IgE (reaginic antibody)**—Omalizumab.
3. **Suppression of inflammation and bronchial hyperreactivity**—corticosteroids.
4. **Prevention of release of mediators**—mast cell stabilizers.
5. **Antagonism of released mediators**—leukotriene antagonists, antihistamines, PAF antagonists.
6. **Blockade of constrictor neurotransmitter**—anticholinergics.
7. **Mimicking dilator neurotransmitter**—sympathomimetics.
8. **Directly acting bronchodilators**—methylxanthines.

CLASSIFICATION

I. **Bronchodilators**
   A. **β₂Sympathomimetics:** Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol, Ephedrine.
   B. **Methylxanthines:** Theophylline (anhydrous), Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Theophylline ethanolate of piperazine, Doxophylline.
   C. **Anticholinergics:** Ipratropium bromide, Tiotropium bromide.

II. **Leukotriene antagonists**
   Montelukast, Zafirlukast.

III. **Mast cell stabilizers**
   Sodium cromoglycate, Ketotifen.

IV. **Corticosteroids**
   A. **Systemic:** Hydrocortisone, Prednisolone and others.
   B. **Inhalational:** Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.

V. **Anti-IgE antibody**
   Omalizumab

**SYMPATHOMIMETICS** (see Ch. 9)

Adrenergic drugs cause bronchodilatation through β₂ receptor stimulation → increased cAMP formation in bronchial muscle cell → relaxation. In addition, increased cAMP in mast cells and other inflammatory cells decreases mediator release. Since β₂ receptors on inflammatory cells desensitize quickly, the contribution of this action to the beneficial effect of β₂ agonists in asthma where airway inflammation is chronic, is uncertain, and at best minimal. Adrenergic drugs are the mainstay of treatment of reversible airway obstruction.
obstruction, but should be used cautiously in hypertensives, ischaemic heart disease patients and in those receiving digitalis. They are the most effective and fastest acting bronchodilators when inhaled.

Though adrenaline (β₁+β₂+α receptor agonist) and isoprenaline (β₁+β₂ agonist) are effective bronchodilators, it is the selective β₂ agonists that are now used in asthma to minimize cardiac side effects.

Salbutamol (Albuterol) A highly selective β₂ agonist; cardiac side effects are less prominent. Selectivity is further increased by inhaling the drug. Inhaled salbutamol delivered mostly from pressurized metered dose inhaler (pMDI) produces bronchodilatation within 5 min and the action lasts for 2–4 hours. It is, therefore, used to abort and terminate attacks of asthma, but is not suitable for round-the-clock prophylaxis. Muscle tremors are the dose related side effect. Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. Hypokalaemia is a possible complication. Salbutamol undergoes presystemic metabolism in the gut wall, oral bioavailability is 50%. Oral salbutamol acts for 4–6 hours, is longer acting and safer than isoprenaline, but not superior in bronchodilator efficacy. Because of more frequent side effects, oral β₂ agonist therapy is reserved for patients who cannot correctly use inhalers or as alternative/adjuvant drugs in severe asthma.

**Dose:** 2–4 mg oral, 0.25–0.5 mg i.m./s.c., 100–200 μg by inhalation.

ASTHALIN 2, 4 mg tab., 8 mg SR tab., 2 mg/5 ml syrup, 100 μg metered dose inhaler; 5 mg/ml respirator soln., 200 μg rota caps; CROYSAL 0.5 mg/ml inj, SALOL 2.5 mg/3 ml inj; VENTORLIN 2 mg/5 ml syr, 4 mg, 8 mg CR caps; DERIHALER 100 μg metered dose inhaler.

Single enantiomer preparation of R(−) salbutamol has also been marketed, because it is the active β₂ agonist and more potent bronchodilator which may produce fewer side effects than the racemate.

Terbutaline It is similar to salbutamol in properties and use.

**Dose:** 5 mg oral, 0.25 mg s.c., 250 μg by inhalation.

Inhaled salbutamol and terbutaline are currently the most popular drugs for quick reversal or bronchospasm, but should not be used on any regular schedule. Regular use does not reduce bronchial hyperreactivity: may even worsen it. This may be responsible for the diminished responsiveness seen after long-term use of these drugs. Regular use also down regulates bronchial β₂ receptors. It is advised that patients requiring regular medication should be treated with inhaled steroids, with or without inhaled long acting β₂ agonists (e.g. salmeterol), while short acting β₂ agonist inhalers should be restricted to symptomatic relief of wheezing.

Bambuterol This bicsarbamate ester prodrug of terbutaline is slowly hydrolysed in plasma and lungs by pseudocholinesterase to release the active drug over 24 hours. Reversible inhibition of pseudocholinesterase occurs in a dose dependent manner. It is indicated in nocturnal and chronic asthma as a single evening dose of 10–20 mg oral.

Concurrent inhaled steroid appears to limit this risk. Excess mortality among asthmatics treated continuously with long acting β₂ agonist inhalations has been reported. However, clinical studies have shown sustained improvement in asthma symptoms and lung function in majority of patients. Concurrent use of inhaled salmeterol with inhaled glucocorticoid produces effects equivalent to double dose of the corticoid alone. It is
advocated that long-acting $\beta_2$ agonists should be used only in combination with an inhaled steroid; combined formulations are available.

**COPD:** Long-acting $\beta_2$ agonists are superior to short-acting ones, and equivalent to inhaled anticholinergics in COPD. They reduce breathlessness by preventing expiratory closure of peripheral airways and abolishing the reversible component of airway obstruction.

SALMETER, SEROBID 25 $\mu$g per metered dose inhaler; 2 puffs BD; severe cases 4 puffs BD; also SEROBID ROTACAPS 50 $\mu$g; 1–2 caps BD by inhalation.

SEROFLO—100/250/500 ROTACAPS: Salmeterol 50 $\mu$g + fluticasone 100 $\mu$g/250 $\mu$g/500 $\mu$g per rotacap.

SEROFLO—125/250 INHALERS, COMBITIDE INHALER: Salmeterol 25 $\mu$g + fluticasone 125 $\mu$g/250 $\mu$g per puff.

**Formoterol** Another long-acting selective $\beta_2$ agonist which acts for 12 hrs when inhaled. In comparison to salmeterol, it has a faster onset of action. It is used on a regular morning-evening schedule for round-the-clock bronchodilatation.

Dose: 12–24 $\mu$g by inhalation twice daily.

FORATEC 12 $\mu$g rotacaps.

**Ephedrine** This oral sympathomimetic has $\alpha + \beta_1 + \beta_2$ actions; causes mild slowly developing bronchodilatation lasting for 3–5 hours. It is a constituent of older combination formulations and is used for mild to moderate chronic asthma. Because of low efficacy and frequent side effects, it is not preferred now.

**METHYL XANTHINES**

Theophylline and its compounds have been extensively used in asthma, but are not considered first line drugs any more. They are used more often in COPD. Theophylline is one of the three naturally occurring methylated xanthine alkaloids caffeine, theophylline and theobromine. The chemical relation between the three is depicted below:

They are consumed as beverages. The sources and average alkaloid contents of the beverages, as they are usually prepared are given below.

All three alkaloids have qualitatively similar actions, but there are marked quantitative (Table 16.1) and pharmacokinetic differences.

<table>
<thead>
<tr>
<th>Source</th>
<th>Alkaloid content in beverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thea sinensis (Tea leaves)</td>
<td>Caffeine 50 mg in an average 1 mg cup of tea</td>
</tr>
<tr>
<td>2. Coffea arabica (Coffee seeds)</td>
<td>Caffeine 75 mg in an average cup of coffee</td>
</tr>
<tr>
<td>3. Theobroma cacao (Cocoa, chocolate)</td>
<td>Theobromine 200 mg in an average 4 mg cup of cocoa</td>
</tr>
<tr>
<td>4. Cola acuminata (Guru nuts)</td>
<td>Caffeine 30 mg in 200 ml bottle of cola drink</td>
</tr>
</tbody>
</table>

**TABLE 16.1 Comparative pharmacological actions of caffeine and theophylline**

<table>
<thead>
<tr>
<th>ACTION</th>
<th>CAFF</th>
<th>THEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CNS—stimulation (low dose)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>—toxicity</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>2. Heart—stimulation</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>3. Blood vessel—relaxation</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>4. Bronchi—dilatation</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>5. Kidney—diuresis</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>6. Sk. muscle—increased contractility</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>7. Gastric mucosa—irritation</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>8. Phosphodiesterase inhibition</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>9. Adenosine antagonism</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

CAFF—Caffeine; THEO—Theophylline

Theobromine is of no therapeutic importance.

**Pharmacological actions**

1. **CNS** Caffeine and theophylline are CNS stimulants, primarily affect the higher centres. Caffeine 150–250 mg produces a sense of well-being, alertness, beats boredom, allays fatigue, thinking becomes clearer even when dullness has tended to prevail after a sustained intellectual effort. It tends to improve performance and increase motor activity. Caffeine is more active than theophylline in producing these effects. Higher doses cause nervousness, restlessness, panic, insomnia and excitement. Still higher doses produce tremors, delirium and convulsions.
Theophylline has greater propensity to produce these adverse effects at higher doses and is definitely more toxic than caffeine.

These alkaloids also stimulate medullary vagal, respiratory and vasomotor centres. Vomiting at high doses is due to both gastric irritation and CTZ stimulation.

2. **CVS**  Methylxanthines directly stimulate the heart and increase force of myocardial contractions. They tend to increase heart rate by cardiac action, but decrease it by causing vagal stimulation—net effect is variable. Tachycardia is more common with theophylline, but caffeine generally lowers heart rate. Cardiac output and cardiac work are increased. At high doses cardiac arrhythmias may be produced.

While consumption of > 9 cups of coffee per day has been found to be associated with increased incidence of arrhythmias, moderate ingestion of caffeine (upto 500 mg/day) does not increase frequency or severity of cardiac arrhythmias even in patients with ischaemic heart disease or preexisting ventricular extrasystoles. Methylxanthines, especially theophylline, dilate systemic blood vessels, including coronaries, by direct action: peripheral resistance is reduced. However, cranial vessels are constricted, especially by caffeine; this is one of the basis of its use in migraine.

Effect on BP is variable and unpredictable—
- Vasomotor centre and direct cardiac stimulation—tends to raise BP.
- Vagal stimulation and direct vasodilatation—tends to lower BP.

Usually a rise in systolic and fall in diastolic BP is observed.

3. **Smooth muscles**  All smooth muscles are relaxed, most prominent effect is exerted on bronchi, especially in asthmatics. Theophylline is more potent than caffeine. Slow and sustained dose-related bronchodilatation is produced, but the effect is much less marked compared to inhaled β₂ agonists. Vital capacity is increased. Biliary spasm is relieved, but effect on intestines and urinary tract is negligible.

4. **Kidney**  Methylxanthines are mild diuretics; act by inhibiting tubular reabsorption of Na⁺ and water as well as increased renal blood flow and g.f.r. Theophylline is more potent, but action is brief.

5. **Skeletal muscles**  Caffeine enhances contractile power of skeletal muscles. At high concentrations it increases release of Ca²⁺ from sarcoplasmic reticulum by direct action. At low doses, twitch response to nerve stimulation is augmented, while at toxic doses contracture is produced.

In addition, caffeine facilitates neuromuscular transmission by increasing ACh release. Its central action relieves fatigue and increases muscular work. Enhanced diaphragmatic contractility noted with theophylline in the therapeutic concentration range probably contributes to its beneficial effects in dyspnoea and COPD.

6. **Stomach**  Methylxanthines enhance secretion of acid and pepsin in stomach, even on parenteral injection. They are also gastric irritants—theophylline more than caffeine.

7. **Metabolism**  Caffeine and to a smaller extent theophylline increase BMR: plasma free fatty acid levels are raised. Release of endogenous catecholamines appears to be partly responsible for these effects.

8. **Mast cells and inflammatory cells**  Theophylline decreases release of histamine and other mediators from mast cells and activated inflammatory cells. This may contribute to its therapeutic effect in bronchial asthma.

**Mechanism of action**  Three distinct cellular actions of methylxanthines have been defined—
(a) Release of Ca²⁺ from sarcoplasmic reticulum, especially in skeletal and cardiac muscle.
(b) Inhibition of phosphodiesterase (PDE) which degrades cyclic nucleotides intracellularly.

The concentration of cyclic nucleotides is increased. Bronchodilatation, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells.
Several isoenzymes of the PDE superfamily exist in different tissues. Theophylline is a subtype nonselective and weak PDE inhibitor, but PDE4 inhibition is mainly responsible for bronchodilatation. However, some selective PDE4 inhibitors like Cilomilast and Roflumilast have been disappointing clinically in efficacy as well as side effects.

(c) Blockade of adenosine receptors: adenosine acts as a local mediator in CNS, CVS and other organs—contracts smooth muscles, especially bronchial; dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion. Methylxanthines produce opposite effects.

Action (a) is exerted only at concentrations much higher than therapeutic plasma concentrations of caffeine and theophylline (ranging from 5–20 μg/ml). Action (b) and action (c) are exerted at concentrations in the therapeutic range and appear to contribute to bronchodilatation. Raised cAMP levels in inflammatory cells may attenuate mediator release and promote eosinophil apoptosis adding to the therapeutic effect of theophylline in asthma. Adenosine A<sub>1</sub> receptor antagonism is considered responsible for cardiac arrhythmias and seizures occurring in theophylline toxicity.

Recent evidence suggests that low concentrations of theophylline enhance histone deacetylation in airway inflammatory cells, suppressing proinflammatory gene transcription. Thus, even sub-bronchodilator doses of theophylline may exert some beneficial effect in asthma.

(Pharmacokinetics, adverse effects and uses of caffeine are described in Ch. 35)

**Theophylline**

**Pharmacokinetics** Theophylline is well absorbed orally; rectal absorption from suppositories is erratic. It is distributed in all tissues—crosses placenta and is secreted in milk, (V 0.5 l/kg), 50% plasma protein bound and extensively metabolized in liver by demethylation and oxidation primarily by CYP1A2. Only 10% is excreted unchanged in urine. Its elimination rate varies considerably with age. At therapeutic concentrations, the t½ in adults is 7–12 hours. Children eliminate it much faster (t½ 3–5 hours) and elderly more slowly. In premature infants also the t½ is prolonged (24–36 hours). There are marked interindividual variations in plasma concentrations attained with the same dose.

Theophylline metabolizing enzymes are saturable, t½ is prolonged with higher doses (to as much as 60 hours) as kinetics changes from first to zero order. Plasma concentrations, therefore, increase disproportionately with dose.

Factors which need dose reduction are—age > 60 yr (× 0.6), CHF (× 0.6), pneumonia (× 0.4), liver failure (× 0.2–0.4).

**Adverse effects** Theophylline has a narrow margin of safety. Dose-dependent toxicity starts from the upper part of therapeutic concentration range (Fig. 16.1). Adverse effects are primarily referable to the g.i.t., CNS and CVS. Headache, nervousness and nausea are early symptoms. Children are more liable to develop CNS toxicity.

The irritant property of theophylline is reflected in gastric pain (with oral), rectal inflammation (with suppositories) and pain at site of i.m. injection. Rapid i.v. injection causes precordial pain, syncope and even sudden death—due to marked fall in BP, ventricular arrhythmias or asystole.

**Interactions**

1. Agents which enhance theophylline metabolism primarily by inducing CYP1A2 lower its plasma level: dose has to be increased by the factor given in parenthesis. Smoking (1.6), phenytoin (1.5), rifampicin (1.5), phenobarbitone (1.2), charcoal broiled meat meal.
2. Drugs which inhibit theophylline metabolism and increase its plasma level are—erythromycin, ciprofloxacin, cimetidine, oral contraceptives, allopurinol; dose should be reduced to 2/3.

3. Theophylline enhances the effects of—furosemide, sympathomimetics, digitalis, oral anticoagulants, hypoglycaemics.

4. Theophylline decreases the effects of—phenytoin, lithium.

5. Aminophylline injection should not be mixed in the same infusion bottle/syringe with—ascorbic acid, chlorpromazine, promethazine, morphine, pethidine, phenytoin, phenobarbitone, insulin, penicillin G, tetracyclines, erythromycin.

**Preparations and dose**

(i) **Theophylline (Anhydrous)** Poorly water soluble, cannot be injected. 100–300 mg TDS (15 mg/kg/day) THEOLOONG 100, 200 mg SR cap., DURALYN-CR 400 mg continuous release cap, UNICONTIN 400 mg, 600 mg CR tabs, THEOBID 200 mg, 300 mg SR tabs.

Only sustained release (SR) tab/caps. are used, because fast release tabs. produce high peak and low trough plasma concentrations.

Because solubility of theophylline is low, a number of soluble complexes and salts have been prepared, particularly for parenteral use.

(ii) **Aminophylline (Theophylline-ethylenediamine; 85% theophylline)** water soluble, can be injected i.v. but not i.m. or s.c.—highly irritating. 250–500 mg oral or slow i.v. injection; children 7.5 mg/kg i.v.; AMINOPHYLLINE 100 mg tab, 250 mg/10 ml inj.

(iii) **Hydroxyethyl theophylline (Etophylline, 80% theophylline)** water soluble; can be injected i.v. and i.m. (but not s.c.), less irritating; 250–500 mg oral or slow i.v. injection; CHOLIPHYLLINE 100 mg tab, 250 mg/10 ml inj.

(iv) **Choline theophyllinate (Oxtriphylline; 64% theophylline)** 250–500 mg oral, CHOLIPHYPYLINE 125 mg cap., 125 mg/5 ml elixir.

(v) **Theophylline ethanolate of piperazine** 250–500 mg oral or i.v.; CADIPHYLATE 80 mg/5 ml elixir, ETOPHYLATE 125 mg/5 ml syrup.

**Uses**

1. **Bronchial asthma and COPD**: Theophylline benefits by causing bronchodilatation as well as by decreasing release of inflammatory mediators, promoting eosinophil apoptosis, improved mucociliary clearance, stimulation of respiratory drive and by augmenting diaphragmatic contractility. However, because of narrow margin of safety and limited efficacy, its use has declined. Sustained release theophylline can be used in mild-to-moderately severe asthma, as a 3rd line or alternative/adjuvant drug, especially in patients with nocturnal asthma. It is more useful in COPD; is often added to other drugs.

2. **Apnoea in premature infant**: Theophylline reduces the frequency and duration of episodes of apnoea that occur in some preterm infants in the first few weeks of life. Closely monitored oral or i.v. treatment is employed for 1–3 weeks. Caffeine is equally effective.

**ANTICHOLINERGICS (see Ch. 8)**

Atropinic drugs cause bronchodilatation by blocking M3 receptor mediated cholinergic constrictor tone; act primarily in the larger airways (Fig. 16.2) which receive vagal innervation. However, some recent evidence points to presence of M3 receptors on peripheral bronchiolar muscles as well, though they are not vagally innervated.

**Ipratropium bromide** is a short acting (duration 4–6 hours) inhaled anticholinergic bronchodilator, while tiotropium bromide is long acting (duration 24 hours). Both are less efficacious than inhaled β2 sympathomimetics in bronchial asthma.
However, patients of asthmatic bronchitis, COPD and psychogenic asthma respond better to anticholinergics. They are the bronchodilators of choice in COPD. Reflex cholinergic tone appears to be the major reversible component of airway obstruction in COPD. Tiotropium is rated more effective than ipratropium in COPD; more suitable for severe cases (FEV₁<50% of predicted). No decline in its clinical efficacy has been noted over a period of 4 years. The inhaled anticholinergics produce slower response than inhaled $\beta_2$ sympathomimetics and are better suited for regular prophylactic use (ipratropium 2–4 puffs 6 hourly or tiotropium 1 rotacap OD) than for quick relief of breathlessness. Combination of inhaled ipratropium with $\beta_2$ agonist produces more marked and longer lasting bronchodilatation; since their effects are additive. This can be utilized in severe asthma or COPD. Nebulized ipratropium mixed with salbutamol is employed in refractory asthma. Combined formulations are available.

**Salbutamol + Ipratropium**

DUOLIN INHALER:  100 μg + 20 μg per metered dose

COMBIMIST INHALER

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**LEUKOTRIENE ANTAGONISTS**

Since it was realized that cysteinyl leukotrienes (LT-C₄/D₄) are important mediators of bronchial asthma, efforts were made to develop their antagonists and synthesis inhibitors. Two cysLT₁ receptor antagonists montelukast and zafirlukast are available.

**Montelukast and Zafirlukast**  Both have similar actions and clinical utility. They competitively antagonize cysLT₁ receptor mediated bronchoconstriction, airway mucus secretion, increased vascular permeability and recruitment of eosinophils. Bronchodilatation, reduced sputum eosinophil count, suppression of bronchial inflammation, mucus and hyperreactivity are noted in asthma patients. Parameters of lung function show variable improvement. Some studies have found that certain patients are ‘responders’ while others are ‘nonresponders’ to anti-LT therapy. This may reflect differing extent of involvement of LTs as asthma mediators.

Montelukast and zafirlukast are indicated for prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids. Though efficacy is low, they may obviate need for inhaled steroids, and may be more acceptable in children. In severe asthma, they have additive effect with inhaled steroids, may permit reduction in steroid dose and need for rescue $\beta_2$ agonist inhalations, but the additive effect of long-acting $\beta_2$ agonists is greater. They are not to be used for terminating asthma episodes. cysLT₁ antagonists are modestly effective in aspirin-induced asthma and exercise induced asthma, but are of no value in COPD.

Both montelukast and zafirlukast are very safe drugs; produce few side effects like headache and rashes. Eosinophilia and neuropathy are infrequent. Few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

They are well absorbed orally, highly plasma
protein bound and metabolized by CYP2C9 (montelukast by CYP3A4 as well). The plasma t½ of montelukast is 3–6 hours, while that of zafirlukast is 8–12 hours.

Montelukast: 10 mg OD; children 2–5 yr 4 mg OD, 6–14 y 5 mg OD; in the evening.
EMLUKAST, MONTAIR, VENTAIR 4 mg, 5 mg, 10 mg tabs
Zafirlukast: 20 mg BD; children 5–11 yr 10 mg BD;
ZUV AIR 10 mg, 20 mg tabs.

Zileuton It is a 5-LOX inhibitor, blocks LTC₄/D₄ as well as LTB₄ synthesis. It therefore has the potential to prevent all LT induced responses including those exerted by activation of cystLT receptor. However, clinical efficacy in asthma is similar to montelukast. The duration of action of zileuton is short and it has hepatotoxic potential. These limitations have restricted its use.

MAST CELL STABILIZERS
Sodium cromoglycate (Cromolyn sod.)
It is a synthetic chromone derivative which inhibits degranulation of mast cells (as well as other inflammatory cells) by trigger stimuli. Release of mediators of asthma like histamine, LTs, PAF, interleukins, etc. is restricted. The basis of this effect is not well understood, but may involve a delayed Cl⁻ channel in the membrane of these cells. Chemotaxis of inflammatory cells is inhibited. Long-term treatment decreases the cellular inflammatory response; bronchial hyperreactivity is reduced to variable extents. Bronchospasm induced by allergens, irritants, cold air and exercise may be attenuated. It is also not a bronchodilator, and does not antagonize constrictor action of histamine, Ach, LTs, etc. Therefore, it is ineffective if given during an asthmatic attack.

Pharmacokinetics Sod. cromoglycate is not absorbed orally. It is administered as an aerosol through metered dose inhaler delivering 1 mg per dose: 2 puffs 4 times a day. Only a small fraction of the inhaled drug is absorbed systematically; this is rapidly excreted unchanged in urine and bile.

Uses
1. Bronchial asthma: Sod. cromoglycate is a long-term prophylactic in mild-to-moderate asthma. Decrease in the frequency and severity of attacks is more likely in extrinsic (atopic) and exercise-induced asthma, especially in younger patients. Therapeutic benefit (when it occurs) develops slowly over 2–4 weeks and lasts 1–2 weeks after discontinuing. However, it is less effective than inhaled steroids and is seldom used now.
2. Allergic rhinitis: Cromoglycate is not a nasal decongestant, but regular 4 times daily use as a nasal spray produces some symptomatic improvement in many patients after 4–6 weeks. The need for nasal decongestants may be reduced.

3. Allergic conjunctivitis: Regular use as eye drops is beneficial in some chronic cases.

FINTEL inhaler: 1 mg and CROMAL 5 mg/puff metered dose inhaler; 2 puffs 4 times daily.
FINTEL nasal spray: 2% CROMAL AQ 2.8 mg/dose; 2 squeezes in each nostril QID.
FINTEL eye drops: 2% CROMAL 2% and 4% eye drops; 1 drop in each eye QID.

Adverse effects Because of poor aqueous solubility, absorption of cromoglycate is negligible; systemic toxicity is minimal. Bronchospasm, throat irritation and cough occurs in some patients, especially with fine powder inhalation. Rarely nasal congestion, headache, dizziness, arthralgia and rashes have been reported.

Ketotifen It is an antihistaminic (H1) with some cromoglycate like action: stimulation of immunogenic and inflammatory cells (mast cells, macrophages, eosinophils, lymphocytes, neutrophils) and mediator release are reduced. It is not a bronchodilator; produces sedation.

After prolonged use, modest symptomatic relief may occur in some patients of bronchial asthma, atopic dermatitis, perennial rhinitis, conjunctivitis, urticaria and food allergy. Thus, it may be tried in patients with multiple allergic disorders.

Adverse effects Generally well tolerated. Sedation and dry mouth are common. Other side effects are dizziness, nausea, weight gain.

Dose: 1–2 mg BD; children 0.5 mg BD.
ASTHAFEN, 1 mg tab, 1 mg/5 ml syrup; KETOVENT 1 mg tab, KETORID 0.25% eye drops.

CORTICOSTEROIDS
Glucocorticoids are not bronchodilators. They benefit by reducing bronchial hyperreactivity, mucosal edema and by suppressing inflammatory response to AG:AB reaction or other trigger stimuli. Their mechanism of action is detailed in Ch. 20.

The realization that asthma is primarily an inflammatory disorder which, if not controlled, accentuates with time, and the availability of inhaled steroids that produce few adverse effects has led to early introduction and more extensive use of glucocorticoids in asthma. Corticosteroids afford more complete and sustained symptomatic relief than bronchodilators or cromoglycate; improve airflow, reduce asthma exacerbations and may influence airway remodeling, retarding disease progression. They also increase airway
smooth muscle responsiveness to $\beta_2$ agonists and reverse refractoriness to these drugs. Inhaled corticosteroids have thus markedly changed the outlook on asthma therapy. However, long-term systemic steroid therapy has its own adverse effects which may be worse than asthma itself.

**SYSTEMIC STEROID THERAPY**

Systemic steroid therapy is resorted to in asthma under the following two situations:

(i) **Severe chronic asthma:** not controlled by bronchodilators and inhaled steroids, or when there are frequent recurrences of increasing severity; start with prednisolone 20–60 mg (or equivalent) daily; attempt dose reduction after 1–2 weeks of good control and finally try shifting the patient onto an inhaled steroid. Only few patients require long term oral steroids—in them dose should be kept at minimum.

In patients requiring long-term glucocorticoid therapy, alternative treatment with immunosuppressants like methotrexate (low dose) or cyclosporine has been tried.

(ii) **Status asthmaticus/acute asthma exacerbation:** Asthma attack not responding to intensive bronchodilator therapy: start with high dose of a rapidly acting i.v. glucocorticoid which generally acts in 6–24 hours—shift to oral therapy for 5–7 days and then discontinue abruptly or taper rapidly.

**COPD** A short course (1–3 week) of oral glucocorticoid may benefit some patients of COPD during an exacerbation.

**INHALED STEROIDS**

These are glucocorticoids with high topical and low systemic activity (due to poor absorption and/or marked first pass metabolism). *Beclomethasone dipropionate*, *Budesonide* and *Fluticasone* have similar properties. *Ciclesonide* is a later addition. Because airway inflammation is present in early mild disease as well, and bronchial remodeling starts developing from the beginning, it has been advocated that inhaled steroids should be the ‘step one’ for all asthma patients. However, currently inhaled steroids are not considered necessary for patients with mild and episodic asthma. They are indicated in all cases of persistent asthma when inhaled $\beta_2$ agonists are required almost daily or the disease is not only episodic. Start with 100–200 $\mu$g BD, titrate dose upward every 3–5 days; max. 400 $\mu$g QID, beyond which no further benefit generally occurs.

Inhaled steroids suppress bronchial inflammation, increase peak expiratory flow rate, reduce need for rescue $\beta_2$-agonist inhalations and prevent episodes of acute asthma. However, they have no role during an acute attack or in status asthmaticus. Peak effect is seen after 4–7 days of instituting inhaled steroids and benefit persists for a few weeks after discontinuation. They can be started in patients who in the past have required oral steroids as well as in those with no such history. Patients who are to be switched over from oral steroid should receive inhaled steroid in addition for 1–2 weeks before oral steroid is tapered, otherwise steroid withdrawal may manifest (precipitation of asthma, muscular pain, lassitude, depression, hypotension). This confirms lack of systemic activity of inhaled steroids (at doses < 600 $\mu$g/day). Long-term experience has shown that efficacy of inhaled steroids is maintained and reinstitution of oral steroids is seldom needed. Short courses of oral steroids may be added during periods of exacerbation. Some patients who remain well controlled for long periods can even stop inhaled steroids without worsening of asthma.

**COPD:** The airway inflammation in COPD is not very responsive to corticosteroids. As such, only high dose inhaled steroids are beneficial in advanced COPD with frequent exacerbations; should not be used in early/mild cases. There is no proof that they slow disease progression.

**Adverse effects** Hoarseness of voice, dysphonia, sore throat, asymptomatic or symptomatic oropharyngeal candidiasis are the most common side effects. These can be minimized by the use of a spacer, gargling after every dose (to wash off the drug deposited on oral and pharyngeal mucosa) and prevented as well as treated by
topical nystatin/clotrimazole. There is no evidence of mucosal damage or increased incidence of chest infections, even on prolonged use.

Systemic effects of long-term inhaled glucocorticoids are clinically relevant only at doses > 600 µg/day. The significant ones are—mood changes, osteoporosis, growth retardation in children, bruising, petechiae, hyperglycaemia and pituitary-adrenal suppression; several reports of adrenal crisis have appeared, especially in children, during stress (of an infection, etc).

Inhaled steroids are safe during pregnancy.

**Beclometasone dipropionate**

BECLATE INHALER 50 µg, 100 µg, 200 µg per metered dose, 200 doses inhaler, BECORIDE 50, 100, 250 µg per puff inhaler.

BECLATE ROTACAPS (with rotahaler) 100, 200, 400 µg powder per cap.

AEROCORT INHALER 50 µg/metered aerosol dose with salbutamol 100 µg.

AEROCORT ROTACAPS 100 µg with salbutamol 200 µg rotacaps (with rotahaler).

Intranasal spray (50 µg in each nostril BD–TDS) is effective in perennial rhinitis.

**Budesonide** A nonhalogenated glucocorticoid with high topical: systemic activity ratio (greater first pass metabolism than beclometasone). Small fraction that is absorbed is rapidly metabolized; less systemic effects, may be preferred in more severe cases.

Dose: 200–400 µg BD–QID by inhalation in asthma; 200–400 µg/day by intranasal spray for allergic rhinitis.

PULMICORT 100, 200, 400 µg/metered dose inhaler, BUDECORT 100 µg/metered dose inhalation.

FORACORT: Formoterol 6 µg + Budesonide 100 µg/200 µg rotacaps.

RHINOCORT 50 µg per metered dose nasal spray; BUDENASE AQ 100 µg metered dose aqueous nasal spray; for prophylaxis and treatment of seasonal and perennial allergic or vasomotor rhinitis, nasal polyposis; initially 2 puffs in each nostril every morning, maintenance 1 puff in each nostril in the morning.

Nasal irritation, sneezing, crusting, itching of throat and dryness may occur, especially in the beginning. Contraindicated in presence of infection or nasal ulcers.

**Fluticasone propionate** This inhaled glucocorticoid has high potency (about double of beclometasone); longer duration and negligible oral bioavailability. The dose swallowed after inhalation has little propensity to produce systemic effects. At high doses, systemic effects may be due to absorption from the lungs. The inhalational dose is 100–250 µg BD (max 1000 µg/day). May be preferred in patients requiring higher doses.

FLOHALE INHALER 25 µg, 50 µg, 125 µg per actuation.

FLOHALE ROTACAPS 50 µg, 100 µg, 250 µg rotacaps.

FLOMIST 50 µg per actuation nasal spray.

**Flunisolide** This topical steroid is available for prophylaxis and treatment of seasonal and perennial rhinitis.

SYNTARIS 25 µg per actuation nasal spray; one spray in each nostril 2–3 times daily.

**Ciclesonide** This inhalational steroid utilizes a novel approach to improve topical: systemic activity ratio. It is a prodrug that is cleaved by esterases in the bronchial epithelium to release the active moiety. Though it is absorbed from the lungs, oral bioavailability is <1%. In the circulation it is extensively bound to plasma proteins, further minimizing exposure of tissue cells to the free and active drug.

Dose: 80–160 µg by inhalation OD, preferably in the evening.

CICLEZ 80 µg and 160 µg per metered dose inhaler with HFA propellant.

**ANTI-IgE ANTIBODY**

**Omalizumab** It is a humanized monoclonal antibody against IgE. Administered s.c., it neutralizes free IgE in circulation without activating mast cells and other inflammatory cells. On antigen challenge, little IgE is available bound to the mast cell surface receptors (FεR1) to trigger mediator release (see Fig. 11.2) and cause bronchoconstriction. In severe extrinsic asthma, omalizumab has been found to reduce exacerbations and steroid requirement. No benefit has been noted in nonallergic asthma. It is very expensive; use is reserved for resistant asthma patients with positive skin tests or raised IgE levels who require frequent hospitalization. It is being tried in other allergic diseases as well.

**inhaled asthma medication**

Four classes of antiasthma drugs, viz. β1 agonists, anticholinergics, cromoglycate and glucocorticoids are available for inhalational use. They are aimed at delivering the drug to the site of action so that lower dose is needed and systemic side effects are minimized. Faster action of bronchodilators can be achieved compared to oral administration. Most asthma patients are now maintained on inhaled medication only.
Aerosols are of two types:

(i) use drug in solution: pressurized metered dose inhaler (pMDI), nebulizers.

(ii) use drug as dry powder: spinhaler, rotahaler

Pressurized metered dose inhalers use chlorofluorocarbon (banned now for their effect on ozone layer) or hydrofluoroalkane (HFA) propellants and deliver a specified dose of the drug in spray form per actuation. Device actuation has to be properly coordinated with deep inspiration, which many patients are unable to learn. A large volume ‘spacer’ (chamber interposed between the inhaler and the patient’s mouth) can be used to improve drug delivery by obviating the need for precise coordination. Moreover, larger particles settle on the walls of the spacer reducing the fraction that deposits in the throat and is later swallowed. Local complications (candidiasis with inhaled steroids) as well as systemic exposure are reduced. Jet nebulizers produce a mist of the drug solution generated by pressurized air or oxygen which can be inhaled through a mouth piece, face mask or in a tent. Ultrasonic nebulizers use electrically vibrated crystals; pressurized air/oxygen is not needed. Metered dose inhalers are convenient hand-held devices which can be carried along, while nebulizers are used at patient’s bed side. Nebulizers are preferred for severe episodes of asthma as well as for children and elderly. More than one drug can be nebulized simultaneously.

Dry powder inhalers are also portable devices in which the capsule (rotacap) containing the drug is punctured/cut across and the powder is aerosolized by the inspiratory air flow of the patient. It requires high velocity inspiration which children, elderly and the very sick may not be capable of. The dry powder is also more likely to irritate the air passages—producing cough and bronchospasm.

Efficacy of aerosolized drug depends on the particle size: 1–5 μm diameter particles deposit on the bronchioles and effectively deliver the drug. Larger particles settle on the oropharynx, while very fine particles do not settle anywhere and are exhaled out. On an average only ~10% of the inhaled drug reaches the site of action. A considerable fraction is swallowed. Therefore, to minimize systemic action, the drug should have low oral bioavailability. Spacer devices improve inhaled to swallowed drug ratio. Slow and deep inbreathing after device actuation and holding the breath after inhalation also enhance efficacy of the inhaler. Greater proportion of smaller particles in a relatively narrow band width of 1–2 μM can be generated using the newer HFA propellant based pMDIs. This improves delivery of the drug to the smaller bronchioles. However, systemic absorption from the peripheral lungs is also more.

**CHOICE OF TREATMENT**

The severity of asthma symptoms ranges from transient respiratory difficulty to incapacitating breathlessness and characteristically fluctuates over time. A stepwise guideline to the treatment of asthma as per needs of the patient has been recommended. After the asthma is under control for 3–6 months, an attempt to reduce medication should be made in stepwise manner.

1. **Mild episodic asthma** (symptoms less than once daily, normal in between attacks) Inhaled short-acting β₂ agonist at onset of each episode. Since asthma is intermittent, it does not require continuous prophylactic therapy (Step-1).

2. **Seasonal asthma** Start regular low-dose inhaled steroid (200–400 μg/day) or cromoglycate 3–4 weeks before anticipated seasonal attacks and continue till 3–4 weeks after the season is over. Treat individual episodes with inhaled short-acting β₂ agonist.

3. **Mild chronic (persistent) asthma with occasional exacerbations** (symptoms once daily or so, subnormal ventilatory performance). Regular low-dose (100–500 μg/day) inhaled steroid (Step-2). Alternatively, inhaled cromoglycate or oral theophylline, but these are less effective. Episode treatment with inhaled short-acting β₂ agonist.

4. **Moderate asthma with frequent exacerbations** (attacks affect activity, occur >1 per day or mild baseline symptoms) Increasing doses of inhaled steroid (up to 800 μg/day) + inhaled long-acting β₂ agonist (Step-3). In view of the potential risk of prolonged treatment with long-acting β₂ agonists, attempt should be made to discontinue it after maintaining asthma control over few months. Leukotriene antagonists may be tried in place of long-acting β₂ agonists, but their additive effect is less marked. Sustained release theophylline may be used as alternative additional drug to long-acting β₂ agonists, especially in nocturnal asthma.

5. **Severe asthma** (continuous symptoms; activity limitation; frequent exacerbations/hospitalization) Regular high dose inhaled steroid (800–2000 μg/day) through a large volume spacer device + inhaled long-acting β₂ agonist
(salmeterol) twice daily. Additional treatment with one or more of the following (Step-4):

Leukotriene antagonist/sustained release oral theophylline/oral β₂ agonist/inhaled ipratropium bromide.

Rescue treatment with short-acting inhaled β₂ agonist.

In patients not adequately controlled or those needing frequent emergency care—institute oral steroid therapy (Step-5). Efficacy of oral steroids is proven, but should be the last resort. Attempt to withdraw it should be made periodically. The British guidelines recommend continuing high dose inhaled steroids along with oral steroids.

6. Status asthmaticus/Refractory asthma

Any patient of asthma has the potential to develop acute severe asthma which may be life-threatening. Upper respiratory tract infection is the most common precipitant.

(i) Hydrocortisone hemisuccinate 100 mg (or equivalent dose of another glucocorticoid) i.v. stat, followed by 100–200 mg 4–8 hourly infusion; may take up to 6 hours to act.

(ii) Nebulized salbutamol (2.5–5 mg) + ipratropium bromide (0.5 mg) intermittent inhalations driven by O₂.

(iii) High flow humidified oxygen inhalation.

(iv) Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added, since inhaled drug may not reach smaller bronchi due to severe narrowing/plugging with secretions.

(v) Intubation and mechanical ventilation, if needed.

(vi) Treat chest infection with intensive antibiotic therapy.

(vii) Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion.

Aminophylline 250–500 mg diluted in 20–50 ml glucose (5%) solution injected i.v. over 20–30 min had been routinely used, but recent evidence shows that it does not afford additional benefit; may even produce more adverse effects; use is restricted to resistant cases.

Some antiasthma combinations

BRONKOURUS: Bromhexine 8 mg, salbutamol 2 mg tab., also syrup—bromhexine 4 mg, salbutamol 2 mg per 5 ml.

TERPHYLIN: Terbutaline 2.5 mg, etophylline 100 mg tab, and per 10 ml syr.

THEOASTHALIN: Salbutamol 2 mg, theophylline anhydrous 100 mg tab, and per 10 ml syr.

THEOASTHALIN-SR: Salbutamol 4 mg, theophylline 300 mg SR tab.

DURASALYN-CR: Salbutamol 4 mg, theophylline 200 mg CR cap.

16.1 A 60-year-old male patient of moderately severe chronic obstructive pulmonary disease (COPD) with FEV₁ 45% of predicted, who has quit smoking for the last 5 years, and is maintained on—Ipratropium br. 20 μg/puff metered dose inhaler, 2 puffs 3 times a day, and Theophylline 400 mg SR tab. twice a day, developed sore throat and fever. He was prescribed—

Tab Erythromycin 250 mg, one tab 4 times a day for 5 days

Tab Paracetamol 500 mg 3 times a day till fever persists.

After 3 days he presented with pain in epigastrium, restlessness, irritability, inability to sleep, palpitation, tremor of fingers and hand, and had vomited twice. His fever had subsided and throat was better.

(a) What could be the reason for his recent illness?

(b) Could this illness be prevented, if so, how?

(see Appendix-1 for solution)