Treatment of Acute and Chronic Rhinitis and Cough

Learning objectives:

1. Definition of rhinitis and cough
2. To understand pharmacology of different drug group used in the treatment as, Antihistamines, leukotriene antagonists, corticosteroids, decongestants and anticholinergics.
3. An overview of the pharmacology of different expectorants and mucolytics used in the treatment of productive cough.
4. To understand pharmacology of antitussives(cough suppressants)

Rhinitis:

- Rhinitis is the irritation and/or inflammation of the mucous membranes inside the nose.

Types: 1. Allergic(seasonal, perennial)

2. infectious(infection with bacteria ,fungi and virus)

Rhinitis may be acute (7-14 days)

Rhinitis may be chronic(persistent more than 6 weeks)

Signs and symptoms of rhinitis:

Runny nose(Rhinorrhoea)

- Sneezing
- Nasal congestion/stuffy blocked nose
- Post nasal drip
- Systemic effects may be(fever, bodyache etc.).

Treatment of Rhinitis:

- A. Preventive Therapy:
    1. Environmental control
    2. Allergen immunotherapy

- B. **Pharmacotherapy:**
  1. Anti histamines(H_1- Receptor antagonists)
  2. Anti - allergics
     a) Cromolyn sodium(mast cell stabilizer)
     b) Leukotriene receptor antagonists(montelukast)
  3. Corticosteroids
  4. Decongestants (alpha- adrenergic agonists)
  5. Anticholinergics

6. Antibiotics(if bacterial infection occur).

what is histamine?

Histamine is a chemical messenger mostly generated in mast cell that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion and neurotransmission in parts of the brain.

Histasmine has no clinical application but antihistamines have important therapeutic applications.

1. Antihistamine (H_1 –Receptor antagonists):

The term antihistamine, without modifying objective, refers to the classic H_1 – receptor blockers. These drugs do not interfere the formation or release of histamine.

They block the receptor- mediated response of a target tissue.

1- ANTIHISTAMINES

H_1 receptor blockers

CLASSIFICATION [Chemical / Functional] → USES *vs* ADVERSE EFFECTS

	First GENERATION	Second GENERATION	Third GENERATION
1) ALKYLAMINES	Chlorpheniramine		
2) ETHANOLAMINES	Dimenhydrinate		
	Diphenhydramine		
3) ETHYLENEDIAMINES	Antazoline`		
4) PHENOTHIAZINES	Promethazine		
5) PIPERAZINE	Cyclizine	Cetirizine	→ Levocetirizine
6) PIPERIDINES	Azatidine		→ Fexofenadine
		Loratadine	→ Desoloratadine
	Ketotifen		
7) MISCELLANEOUS	Cyproheptadine		
	Short duration	*Longer duration = better control*	
	Interactions; with enzyme inhibitors *[macrolides, antifungals, calcium antagonists]* + additive pharmacodynamic ADRs	No drug interactions & minimal ADRs	

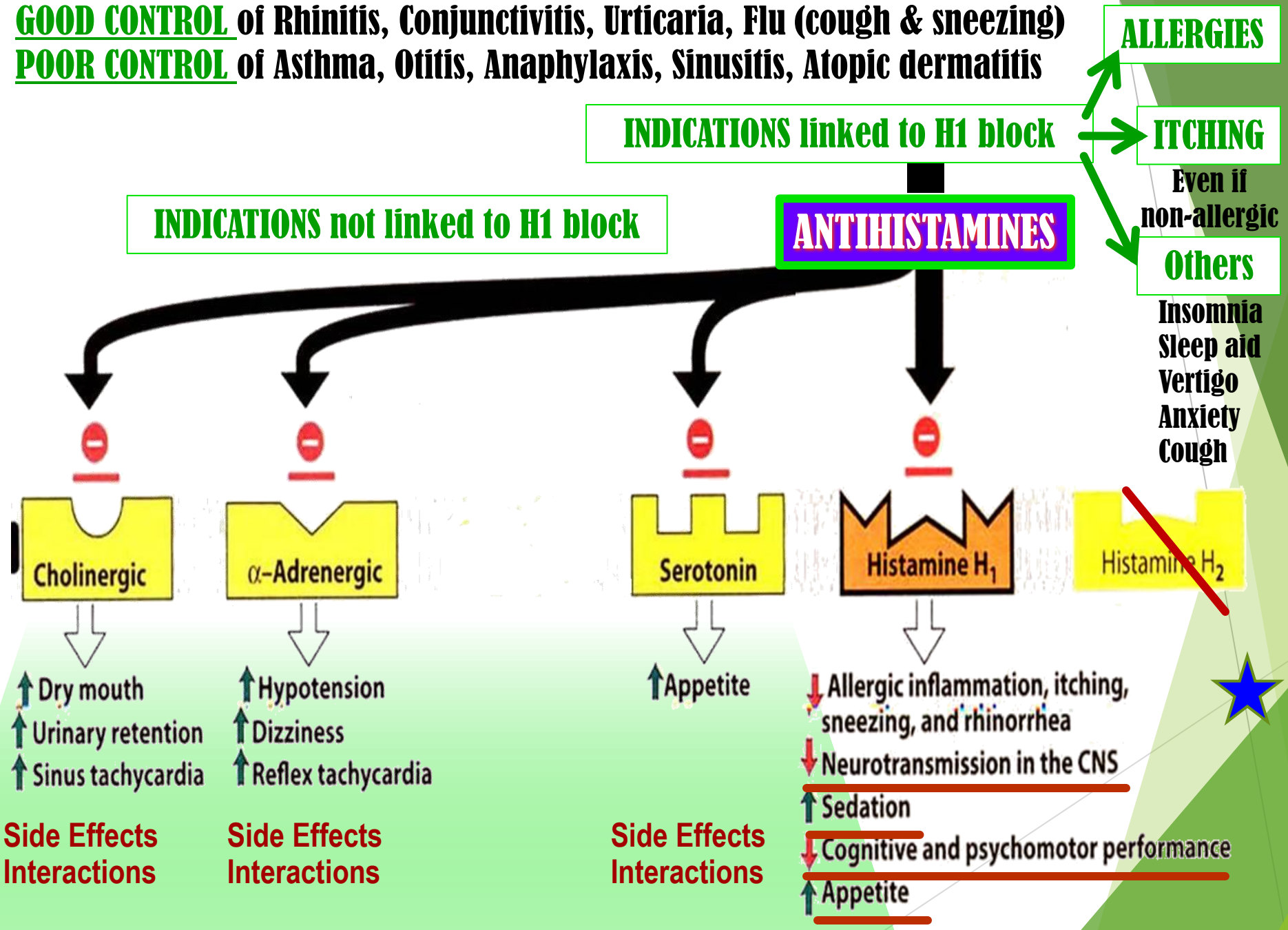
All are used systemic or topical

- The older first generation drugs still widely used because they are effective and inexpensive. These drugs penetrate the CNS and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects.
- Second generation agents are specific for H_1 receptors and they carry polar groups ,they do not penetrate the blood brain barrier causing less CNS depression.

Actions:

- The action of all the H_1 receptor blocker is qualitatively similar.
- they are much more effective in preventing symptoms than reversing them once they have occurred.
- Most of these drugs have additional effects unrelated to their blocking H_1 receptors, which probably reflect binding of H_1 antagonists to cholinergic, adrenergic or serotonin receptors.

GOOD CONTROL of Rhinitis, Conjunctivitis, Urticaria, Flu (cough & sneezing)
POOR CONTROL of Asthma, Otitis, Anaphylaxis, Sinusitis, Atopic dermatitis



Therapeutic uses:

1. Allergic and inflammatory (allergic rhinitis, urticaria)
2. Motion sickness
3. Nausea and vomiting

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- **Pharmacokinetics:**
- H_1 receptor blockers are well absorbed after oral administration
- Maximum serum levels occurring at 1-2 hours
- Average plasma half life is 4 to 6 hours
- H_1- receptor blockers have high bioavailability and distributed all tissues including CNS.
- metabolized by the hepatic cytochrome p450 system.
- Excretion occur via kidney except fexofenadine excreted in feces unchanged.

Adverse effects:

- 1. sedation, tinnitus, fatigue, dizziness blurred vision
- 2. Dry mouth
- Drug interaction: CNS depressants, cholinesterase inhibitors
- overdose: The most common and dangerous effects of acute poisoning are those on CNS, icluding hallucinations, excitement,ataxia and convulsions.

2-ANTI-ALLERGICS

CROMOLYN & NEDOCROMYL

↓ Histamine release [mast cell stabilizer by inhibiting Cl channels] i.e. can act only **prophylactic;** it does not antagonize released histamine

Used more **in children** for prophylaxis of perennial allergic rhinitis

Should be given on daily base and never stop abruptly.

Can induce cough, wheezes, headache, rash, …etc.

LEUKOTRIENE RECEPTOR ANTAGONISTS

Block leukotriene actions

For **prophylaxis** of lower respiratory [i.e perennial allergen, exercise or aspirin-induced asthma] > upper respiratory allergies [chronic rhinosinusitis]

ADRs; as in asthma

3-CORTICOSTERIODS

Anti-inflammatory → blocks phospholipase A_2 → ↓arachedonic a. synthesis → ↓ prostaglandins & leukotrienes

Topical; steroid **spray**; beclomethasone, budesonide, & fluticasone

Given if severe intermittent or moderate persistent symptoms

ADRs; Nasal irritation, fungal infection, hoarseness of voice

4. DECONGESTANTS

α-Adrenergic agonists → For treatment of nasal stuffiness

SYSTEMIC

- PSEUDOEPHEDRINE

TOPICAL

PHENYLETHYLAMINES

- Phenylephrine
- Methoxamine

IMIDAZOLINE

- Naphazoline
- Oxymetazoline HCl
- Xylometazoline HCl

Can cause nervousness, insomnia, tremors, palpitations, hypertension.
Better avoided in hypertension, heart failure, angina pectoris, hyperthyroidism,glaucoma

But can cause **Rebound nasal stuffiness** (repeated administration (10 days -2 weeks)

5. ANTICHOLINERGICS

Ipratropium

Given as nasal drops to **control rhinorrhea** (excess nasal secretion & discharge)
So very effective **in vasomotor rhinitis** (watery hyper-secretion).
Its indication as bronchiodilator in asthma and ADRs → see asthma

Effectiveness of different drug groups in controlling symptoms of RHINITIS

Drug Groups	Main Symptom		
	Sneezing	Blockage Stuffiness	Secretions Rhinorrhea
Anti-histamines	++	-	+
Anti-allergics (cromolyns)	+	+	+
Topical corticosteroids	++	++	++
Decongestant	-	++	-
Anticholinergics	-	-	++

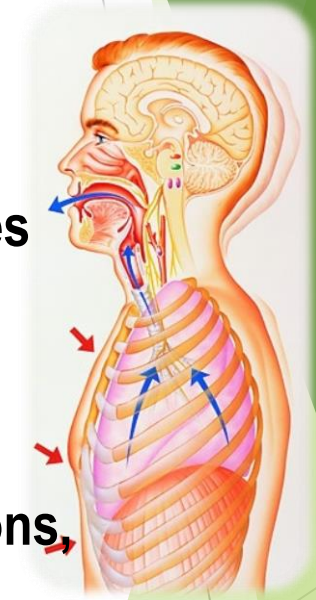
DRUGS USED

IN TREATMENT OF COUGH

The respiratory tract is protected mainly by➔

1. **MUCOCILIARY CLEARANCE** ➔ ensures optimum tracheobronchial clearance ➔ by forming sputum (in optimum quantity & viscosity) exhaled by ciliary movement s.
2. **COUGH REFLEX** ➔ exhales sputum out, if not optimally removed by the mucociliary clearance mechanisms

Coughing is sudden expulsion of air from the lungs through the epiglottis at an amazingly fast speed (~100 miles/ hr) to rid breathing passage ways of unwanted irritants. Abdominal & intercostal muscles contract, against the closed epiglottis ➔ pressure ↑ ➔ air is forcefully expelled to dislodge the triggering irritant.



Cough is **meant to be useful** ➔ *"wet or productive"*
May not be useful & annoying 2ndry to irritant vapors, gases, infections, cancer➔ *"dry or irritant"*

TREATMENT

- EXPECTORANTS, MUCOLYTICS ➔ For Productive Cough
- ANTITUSSIVE AGENTS ➔ For Non-productive (dry) Cough

EXPECTORANTS

Act by removal of mucus through

Reflex stimulation Irritate GIT → stimulate gastropulmonary vagal reflex → loosening & thinning of secretions → **Guaifenesin**

ADRs ; Dry mouth, chapped lips, risk of kidney stones(↑uric a. excretion)

Direct stimulation Stimulate secretory glands → ↑ respiratory fluids production → **Iodinated glycerol, Na or K iodide / acetate , Ammonium chloride, Ipecacuahna**

ADRs; Unpleasant metallic taste, hypersensitivity, hypothyroidism, swollen of salivary glands(overstimulation of salivary secretion), & flare of old TB.

INDICATIONS ← Final outcome is that cough is indirectly diminished

- Common cold
- Bronchitis
- Pharyngitis
- Chronic paranasal sinusitis

MUCOLYTICS

Act by altering biophysical quality of sputum → becomes easily exhaled by mucociliary clearance or by less intense coughing

MECHANISM OF ACTIONS

Mucolysis occurs by one or more of the following;

- ↓ Viscoelasticity by ↑water content; **Hypertonic Saline & $NaHCO_3$**
- ↓ Adhesivness; **Steam inhalation**
- Breakdown S-S bonds in glycoproteins by reducing its SH Gp → less viscid mucous; **N-Acetyl Cysteine**
- Synthesize serous mucus (sialomucins of smaller-size) so it is secretolytic + activate ciliary clearance & transport; **Bromohexine & Ambroxol**
- Cleavage of extracellular bacterial DNA, that contributes to viscosity of sputum in case of infection; **rhDNAase (Pulmozyme)**

INDICATIONS

- Most mucolytics → effective as adjuvant therapy in COPD, asthma, bronchitis, …etc. (when there is excessive &/or thick mucus….)
- In bronchiectasis, pneumonia & TB → they are of partial benefit
- *Hardly any benefit in cystic fibrosis & severe infections → Give* rhDNAase

1. N-Acetylcysteine

➔It is also a free radical scavenger ➔ used in acetaminophen overdose

ADRs; Bronchospasm, stomatitis, rhinorrhea, rash, nausea & vomiting

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2. Bromhexine & its metabolite Ambroxol

They also ↑immuno defence so ↓ antibiotics usage
They also ↓ pain in acute sore throat

ADRs; Rhinorrhea, lacrymation, gastric irritation, hypersensitivity

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3. Pulmozyme (Dornase Alpha or DNAse)

➔ A recombinant human deoxyribo-nuclease-1 enzyme that is neubilized

➔Full benefit appears within 3-7 days

ADRs;
Voice changes, pharyngitis, laryngitis, rhinitis, chest pain, fever, rash

ANTITUSSIVE AGENTS

Stop or reduce cough by acting either primarily on the peripheral or CNS components of cough reflex.

1. PERIPHERALLY ACTING ANTITUSSIVES

A. Inhibitors of airway stretch receptors

In Pharynx ➔ Use Demulcents ➔ form a protective coating
Lozenges & Gargles

In Larynx ➔ Use Emollients ➔ form a protective coating
menthol & eucalyptus.

In Tracheobronchial Airway ➔ Use aerosols or inhalational of hot steam
tincture benzoin compound & eucalyptol

During bronchoscopy or bronchography ➔ Use local anaesthetic aerosols, as lidocaine, benzocaine, and tetracaine

B. Inhibitors of pulmonary stretch receptors in alveoli

Benzonatate ➔ ↓ sensitivity (numbing) of receptors by local anesthetic action.
ADRS; drowsiness, dizziness, dysphagia, allergic reactions
Overdose ➔ mental confusion, hallucination, restlessness & tremors

ANTITUSSIVE AGENTS

2. CENTRALLY ACTING ANTITUSSIVES

A. OPIOIDS activating μ opioid receptors
e.g. Codeine & Pholcodine

B. NON-OPIODS → Antihistaminics (>sedating)

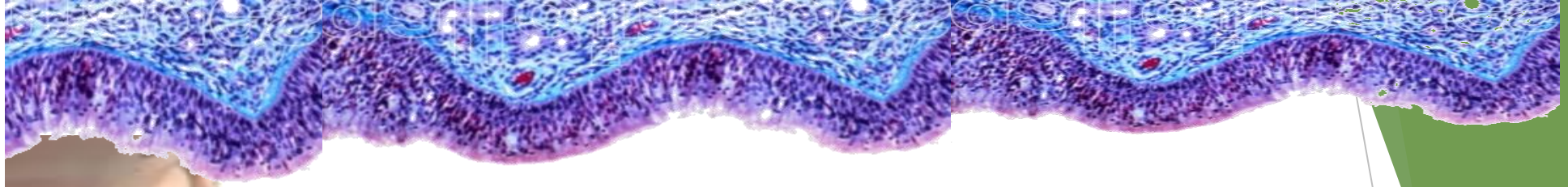
Dextromethorphan

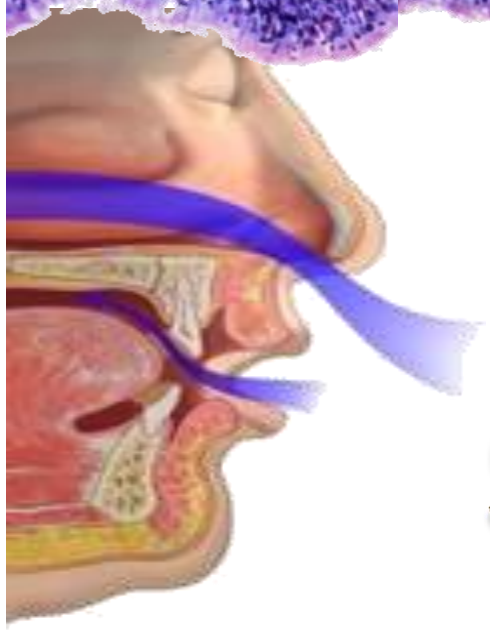
It ↑ threshold at cough center. It has benefits over opiods in being →

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

ADRs

Nausea, vomiting, dizziness, rash & pruritus in normal doses
In high doses, hallucinations + opiate like side effects on respiration & GIT





GOOD LUCK