



PHARMACOLOGY

Treatment of Acute & Chronic Rhinitis and Cough

Objectives:

- Define rhinitis and cough
- Classify drugs used in the treatment of rhinitis
- Expand on the pharmacology of different drug groups used in the treatment as; antihistamines, leukotriene antagonists, corticosteroids, decongestants and anticholinergics.
- Describe the pharmacology of different expectorants and mucolytics used in the treatment of productive cough
- Describe the pharmacology of antitussives (cough suppressants)



Rhinitis

Rhinitis

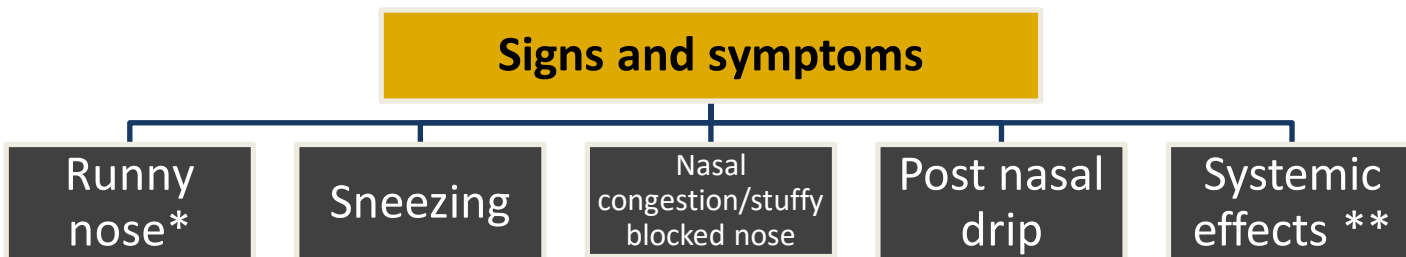
it is the irritation and/or inflammation of the mucous membranes inside the nose

It has two types:

1. **Allergic**: either seasonal (e.g. hay fever) or perennial "symptoms are present throughout the entire year".)
2. **infectious** (infection with bacteria, fungi and viruses)

Rhinitis may be:

- **Acute** (persist 7-14 days)
- **Chronic** (persistent more than 6 weeks)



* Runny nose: rhinorrhea; excess nasal secretion & discharge

** fever, body aches,....

Treatment Of Rhinitis

A. Preventive Therapy:

1- Environmental control
(dust control, pets)

2- Allergen immunotherapy.

B. Pharmacotherapy

1. Anti-histamines (H1- 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)

Histamine & antihistamines

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.

- Histamine has no clinical application but **antihistamines** have important therapeutic applications.

Antihistamines (H₁-receptor antagonists):

- The term antihistamine, without modifying objective, refers to the classic **H₁ – receptor blockers**. These drugs do not interfere with the formation or release of histamine, they only block the receptor-mediated **response** of a target tissue.
- **They are divided into 3 Generations:**
 - **The older first generation** drugs still widely used because they are effective and inexpensive. These drugs **penetrate the blood brain barrier (BBB)** and cause **sedation**. Furthermore, they tend to interact with other receptors (serotonin, adrenergic, cholinergic), producing a variety of **unwanted adverse effects**.
 - **Second generation (Non-sedating)** agents are specific for H₁ receptors and they carry polar groups, they **do not penetrate the BBB** causing less CNS depression

Antihistamines (H1 blockers)

1st Generation	2 nd Generation	3 rd Generation
Chlorpheniramine	Cetirizine	Levocetirizine
Dimenhydrinate		
Diphenhydramine		
Antazoline		
Promethazine	Loratadine	Fexofenadine
Cyclizine		
Azatidine		
Ketotifen		
Cyproheptadine		
<ul style="list-style-type: none"> • Short duration • Interactions; with enzyme inhibitors [as macrolides, antifungals, calcium antagonists] • Additive pharmacodynamic ADRs. 	<ul style="list-style-type: none"> • Long duration (better control) • No drug interactions & minimal ADRs, since they are more specific for H1 receptors. Unless if given in toxic dose, which will then cause ADRs similar to those of the first generation blockers. 	Desloratadine
All are used systemically or topically		



ANTIHISTAMINES

Actions	<p>The action of all the H₁ receptor blocker is qualitatively similar. They are much more effective in preventing symptoms than reversing them once they have occurred.</p> <p>Most of these drugs have additional effects unrelated to their blocking H1 receptors, which probably reflect binding of H1 antagonists to:</p> <ul style="list-style-type: none"> ▪Cholinergic, Adrenergic or Serotonin receptors
Therapeutic uses	<ol style="list-style-type: none"> 1. Allergic rhinitis: relieves rhinorrhea, sneezing, and itching of eyes and nasal mucosa 2. Common cold: dries out the nasal mucosa. Often combined with nasal decongestant and analgesics 3. Motion sickness . 4. Allergic dermatoses: can control <u>itching</u> associated with insect bites. 5. Nausea and vomiting (Promethazine)
Pharmacokinetics	<ul style="list-style-type: none"> • H₁ 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 • H₁- receptor blockers have high bioavailability and distributed to all tissues including CNS • Metabolized by the <u>hepatic</u> cytochrome P450 system • Excretion occur via <u>kidney</u> except fexofenadine excreted in feces unchanged
Adverse effects	Sedation, tinnitus "ear buzzing", fatigue, dizziness, blurred vision, dry mouth
Drug interaction	Interact with CNS depressants & cholinesterase inhibitors
Overdose	The most common and dangerous effects of acute poisoning are those on CNS; including hallucinations, excitement, ataxia and convulsions

INDICATIONS linked to H1 block	INDICATIONS not linked to H1 block		Side Effects & Interactions
	Receptor	Side effect interactions	
<ul style="list-style-type: none"> • Allergies : 1. GOOD CONTROL of Rhinitis, Conjunctivitis, Urticaria, Flu (cough & sneezing) 2. POOR CONTROL of Asthma, Otitis, Anaphylaxis, Sinusitis, Atopic dermatitis • ITCHING: Even if non-allergic • Others: Insomnia, Sleep aid, Vertigo, Anxiety, Cough 	serotonin	<ul style="list-style-type: none"> ↑ appetite 	
	α-adrenergic	<ul style="list-style-type: none"> ↑ Hypotension ↑ Dizziness ↑ Reflex tachycardia 	
	cholinergic	<ul style="list-style-type: none"> ↑ Dry mouth ↑ Urinary retention ↑ Sinus tachycardia 	

Anti-allergics & Corticosteroids

2- ANTI-ALLERGICS

	Mast cell stabilizers	Leukotriene receptor Antagonists
Example	Cromolyn & Nedocromyl	Zafirlukast, Montelukast, Pranlukast
Mech. Of action	only prophylactic: It does not antagonize histamine that is already released, but it decreases Histamine release from the beginning (by inhibiting Cl channels)	Block leukotriene actions
Uses	Used in children for prophylaxis of perennial allergic rhinitis. *Should be given on a daily basis and never stop abruptly.	<ul style="list-style-type: none"> - Prophylaxis of lower respiratory tract allergies - Acts on <u>lower</u> resp. tract allergies more than on <u>upper</u> resp. tract allergies. - E.g., acts on perennial allergen, exercise or aspirin-induced asthma (LRT allergies) more than on chronic rhinosinusitis (URT allergy)
ADRs	Induce cough, wheezes, headache, rash	As in asthma: Elevation of liver enzymes, headache, dyspepsia

3-Corticosteroids

examples	beclomethasone, budesonide, & fluticasone
Mech. of action	Anti-inflammatory → blocks phospholipase A ₂ → ↓ arachidonic acid synthesis → ↓ prostaglandins & leukotrienes
uses	Administered Topically as steroid spray ; Given in severe intermittent or moderate persistent symptoms
ADRs	Nasal irritation, fungal infection, hoarseness of voice

Decongestants & Anticholinergics

4- Decongestants (α -Adrenergic agonists)

	Systemic	Topical
Ex.	Pseudoephedrine	- Phenylethylamines (Phenylephrine, Methoxamine) - Imidazoline (Naphazoline, Oxymetazoline HCl, Xylometazoline HCl)
uses	For treatment of nasal stuffiness	
ADRs	<ul style="list-style-type: none"> nervousness, insomnia, tremors, palpitations, hypertension. Better avoided in hypertension, heart failure, angina pectoris, hyperthyroidism, Glaucoma. 	Rebound nasal stuffiness Due to repeated administration (10 days -2 weeks)

5- Anticholinergics

Example	Ipratropium
Uses	-nasal drops to control rhinorrhea. -very effective in vasomotor rhinitis (watery hyper-secretion). -bronchodilator in asthma .
ADRs	minimal systemic side effects (wheezing, bladder pain, cough producing mucous)

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

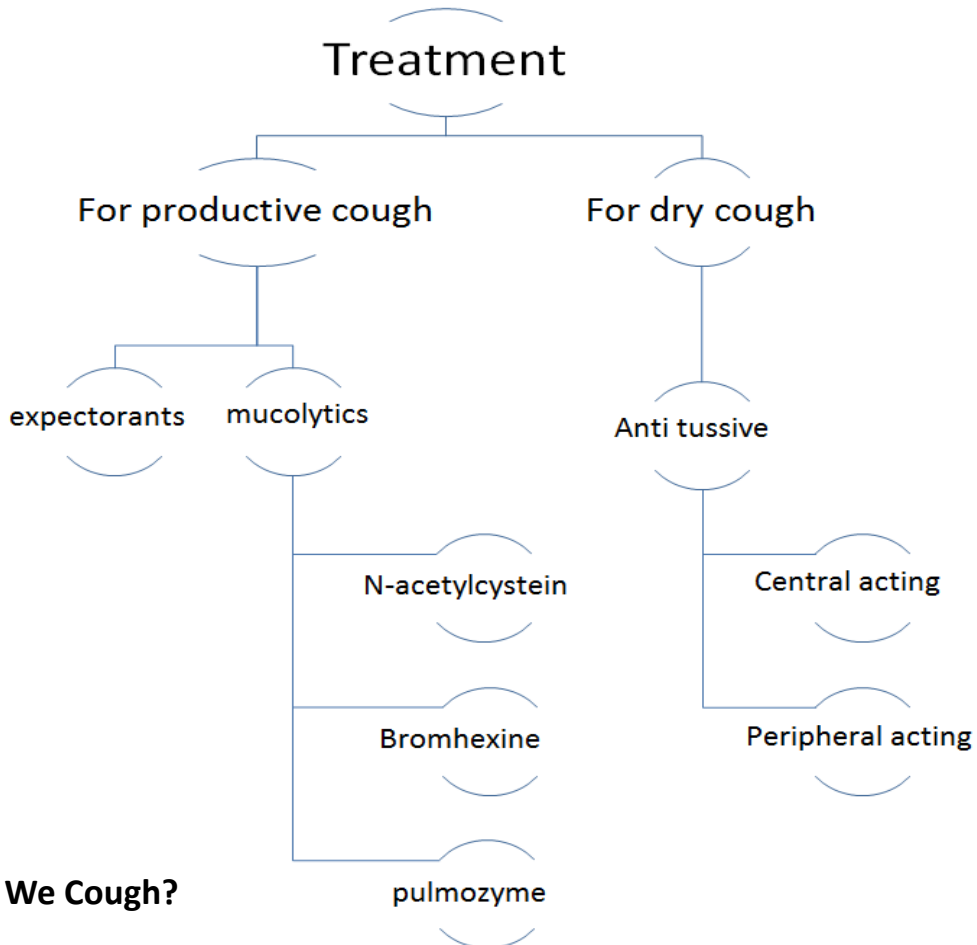
Treatment of cough

Respiratory system is protected mainly by 2 mechanisms:

1. **Mucociliary:** clearance ensures optimum tracheobronchial clearance → by forming sputum (in optimum quantity & viscosity) exhaled by ciliary movements.
2. **cough reflex:** exhales sputum out, if not optimally removed by the mucociliary clearance mechanism.

• Cough clearance mechanism:

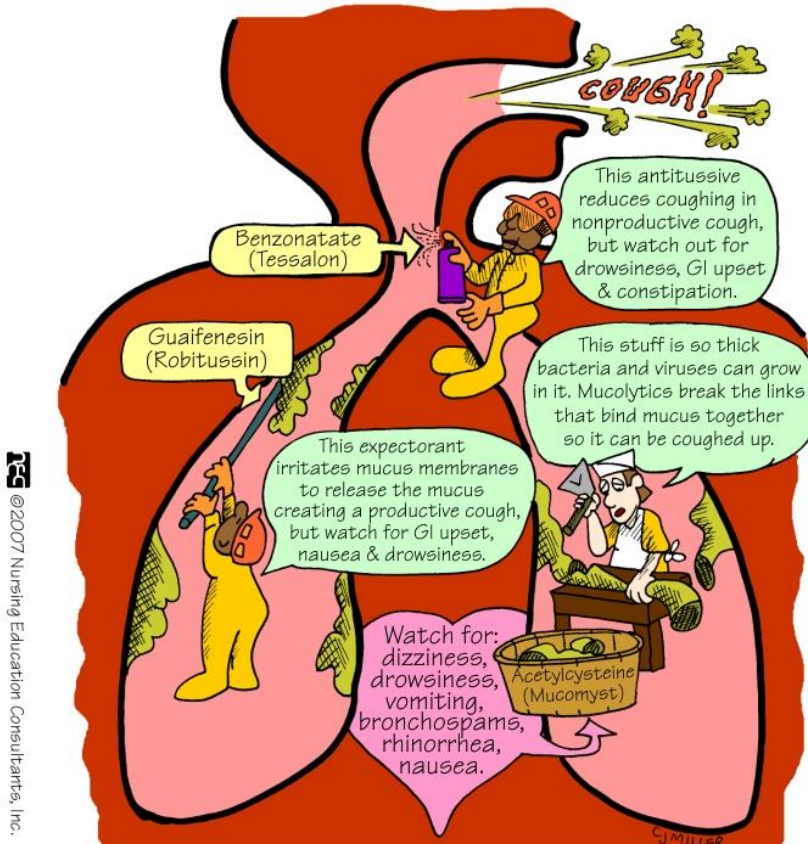
Coughing is a sudden expulsion of air from the lungs through the epiglottis at an amazingly fast speed (~100 miles/ hr) to get rid of unwanted irritants. Abdominal & intercostal muscles contract, against the closed epiglottis → pressure ↑ → air is forcefully expelled to dislodge the triggering irritant. (Cough is meant to be useful “wet or productive”. Sometimes, it may not be useful & annoying 2ndry to irritant vapors, gases, infections, cancer “dry or irritant”)



1. Expectorants

Expectorants (act by removal of mucus through):		
	Reflex stimulation	Direct stimulation
Examples	Guaifenesin.	Iodinated glycerol, Na or K iodide / acetate , Ammonium chloride, Ipecacuahna.
Mechanism of action	Irritate GIT → stimulate gastropulmonary vagal reflex → loosening & thinning of secretions .	Stimulate secretory glands → ↑ respiratory fluids production. They increase the amount or hydration of secretions, resulting in more yet clearer secretions and as a byproduct lubricating the irritated respiratory tract.
ADRs	Dry mouth, chapped lips, risk of kidney stones(↑ uric acid excretion).	Unpleasant metallic taste, hypersensitivity, hypothyroidism, swollen salivary glands (overstimulation of salivary secretion), & flare of old TB.
Indications	Common cold, Bronchitis, Pharyngitis, Chronic paranasal sinusitis. <u>-Final outcome is that cough is indirectly diminished</u>	

Antitussives, Expectorants, & Mucolytics



2. Mucolytics

Mucolytics

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

Drug	Hypertonic saline and NaHCO ₃	Steam inhalation	
Mechanism of action	↓ Viscoelasticity by ↑ water content	↓ Adhesiveness	
Drug	N-acetylcysteine	Bromhexine and its metabolite(ambroxol)	Pulmozyme (Dornase Alpha or rhDNAase)
Over view	A free radical scavenger used in acetaminophen over dose	They increase immune defense: - ↓ antibiotics usage - ↓ pain in acute sore throat	A recombinant of human deoxyriboneuclease-1 that is nebulized. Full benefit appears within 3-7 days
Mechanism of action	Breakdown S-S bonds in glycoproteins by reducing its SH Gp → less viscid mucous	Synthesize serous mucus (sialomucins of smaller-size) so it is secretolytic + activate ciliary clearance & transport	Cleavage of extracellular bacterial DNA, that contributes to viscosity of sputum in case of infection
ADRs	Bronchospasm, stomatitis, rhinorrhea, rash, nausea & vomiting	Rhinorrhea, lacrimation, gastric irritation, hypersensitivity	Voice changes, pharyngitis, laryngitis, rhinitis, chest pain, fever, rash
Indication	<ul style="list-style-type: none"> - Most mucolytics are effective as adjuvant therapy 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 		

3. Antitussive agents

antitussive agents are drugs used in dry cough to Stop or reduce cough by acting either primarily on the peripheral or CNS components of cough reflex

Act	Types	Drug(s)	Use in	Form a protective coating:	
Peripherally inhibitors	Inhibitors of Airway stretch receptor	Demulcent	Pharynx	Lozenges & gargles	
		Emollients	Larynx	Menthol & eucalyptus	
		Eucalyptol & tincture benzoin compound	Tracheobronchial	Use aerosols or inhalational of hot steam	
		Lidocaine, benzocaine & tetracaine	Bronchoscopy OR bronchography	Use local anesthetic aerosols	
	Types	Drug(s)	Mechanism	ADVs	
Inhibitors of pulmonary stretch receptor in Alveoli	Benzonatate	↓ sensitivity (numbing) of receptors by local anesthetic action.	Drowsiness, Dizziness, Dysphagia allergic reaction	OVERDOSE: Tremors, Hallucination, Mental confusion, Restlessness.	
Centrally	Opioids (activating μ receptor)	Codeine & pholcodine			
	Non-opioids	Anti-Histamine	(sedating)		
		Dextromethrophan	<p>↑ Threshold at cough center.</p> <p>It has benefits over opioids in being:</p> <ol style="list-style-type: none"> As potent as codeine But no drowsiness Less constipating No respiratory depression. No inhibition of mucociliary clearance No addiction. 	<p>In normal doses:</p> <p>Nausea Vomiting Dizziness Rash Pruritus (Pruritus is severe itching of the skin)</p>	<p>OVERDOSE:</p> <p>Opiat-like ADRs on RT & GIT Hallucination</p>

Drugs summary

Drugs for rhinitis

Drugs for rhinitis							
Anti-histamines generations	1 st	e.g. Chlorpheniramine Diphenhydramine Promethazine (used for Nausea and vomiting)	short duration, drug interactions, ADRs (sedation)	Clinical uses: 1. Allergic rhinitis: relieves rhinorrhea, sneezing, and <u>itching</u> of eyes and nasal mucosa 2. Common cold 3. Motion sickness. 4. Allergic dermatoses	Metabolized in the liver Excretion via <u>kidney</u> except fexofenadine	ADRs: Sedation, tinnitus, fatigue, dizziness, blurred vision, dry mouth, CNS effects at overdose	Drugs interaction: Interact with CNS depressants & cholinesterase inhibitors
	2 nd	Cetirizine Loratadine	short duration, no drug interaction, minimal ADRs, specific for H1 receptors	H1 block actions: Conjunctivitis, Urticaria, Flu (cough & sneezing) Itching Insomnia, Sleep aid, Vertigo, Anxiety, Cough	serotonin	appetite	
	3 rd	Levocetirizine Fexofenadine Desloratadine		POOR CONTROL of Asthma, Otitis, Anaphylaxis, Sinusitis, Atopic dermatitis.	α -adrenergic cholinergic	Hypotension Dizziness Reflex tachycardia Dry mouth Urinary retention Sinus tachycardia	
			Clinical use	ADRs			
ANTI-ALLERGI CS		Mast cell stabilizers: Cromolyn & Nedocromyl	Used in children for prophylaxis of perennial allergic rhinitis. *Should be given on a daily basis and never stop abruptly.	Induce cough, wheezes, headache, rash			
		Leukotriene receptor Antagonists: Zafirlukast, Montelukast, Pranlukast	Prophylaxis of lower respiratory tract allergies	Elevation of liver enzymes, headache, dyspepsia			
topical Corticosteroids		beclomethasone, budesonide, & fluticasone	Given in severe intermittent or moderate persistent symptoms	Nasal irritation, fungal infection, hoarseness of voice			
Decongestants (α -Adrenergic agonists)		Systemic: Pseudoephedrine	For treatment of nasal stuffiness	<ul style="list-style-type: none"> nervousness, insomnia, tremors, palpitations, hypertension. Better avoided in hypertension, heart failure, angina pectoris, hyperthyroidism, Glaucoma. 			
		Topical: Phenylethylamines & Imidazoline		Rebound nasal stuffiness Due to repeated administration (10 days -2 weeks)			
Anticholinergics		Ipratropium	nasal drops to control rhinorrhea. -very effective in vasomotor rhinitis (watery hyper-secretion). -bronchodilator in asthma.	wheezing, bladder pain, cough producing mucous			

Drugs summary

Drugs for cough				
For Reproductive cough	Expectorants	Reflex stimulation (Guaifenesin)	ADRs: Dry mouth, chapped lips, risk of kidney stones (↑ uric acid excretion).	
		Direct stimulation (e.g. Iodinated glycerol)	ADRs: Unpleasant metallic taste, hypersensitivity, hypothyroidism, swollen salivary glands & flare of old TB.	
			Mechanism	ADRs
	Mucolytics	Hypertonic saline and NaHCO ₃	↓ Viscoelasticity by ↑ water content	Use: Most mucolytics are used as adjuvant therapy when there is excessive &/or thick mucus
		Steam inhalation	↓ Adhesiveness	
		N-acetylcysteine	Breakdown S-S bonds (used in acetaminophen over dose)	Bronchospasm, stomatitis, rhinorrhea, rash, nausea & vomiting
Bromhexine and its metabolite (ambroxol)		Synthesize serous mucus & activate ciliary clearance	Rhinorrhea, lacrimation, gastric irritation, hypersensitivity	
	Pulmozyme (Dornase Alpha or rhDNAase)	Cleavage of extracellular bacterial DNA (used in severe infections)	Voice changes, pharyngitis, laryngitis, rhinitis, chest pain, fever, rash	
		Drug	Target	
For dry cough: Antitussive agents	Peripherally inhibitors	Inhibitors of Airway stretch receptor	Demulcentm coated as Lozenges & gargles	Pharynx
			Emollients, coated by Menthol & eucalyptus	Larynx
		Inhibitors of pulmonary stretch receptor in Alveoli: Benzonatate	aerosols or inhalational of hot steam: Eucalyptol & tincture benzoin compound	Tracheobronchial
			Use local anesthetic aerosols: <i>Lidocaine</i> , <i>benzocaine</i> & <i>tetracaine</i>	Bronchoscopy OR bronchography
	Centrally	Opioids: Codeine & pholcodine		ADRs: Drowsiness, Dizziness, Dysphagia allergic reaction CNS effects when overdosed
		Non-opioids: Anti-Histamine & Dextromethrophan	↑ Threshold at cough center. It has benefits over opioids 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.	

QUIZ

THANK YOU FOR CHECKING OUR WORK
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