Histamine & antihistamine drugs

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Objectives

- What is histamine?
- Histamine releasers
- Clinical symptoms associated with histamine release
- Histamine receptors and its pharmacological actions
- Drugs antagonizing histamine actions
- What are meant by antihistamines?
- Clinical uses of antihistaminics
- Adverse effects of antihistaminics
- Classes of antihistaminics

Histamine

I am NOT a drug

- **Histamine is an endogenous substance (autacoid) (NOT a drug) synthesized, stored and released in**:

(a) Mast cells, which are abundant in the skin, GI, and the respiratory tract

(b) Basophils in the blood

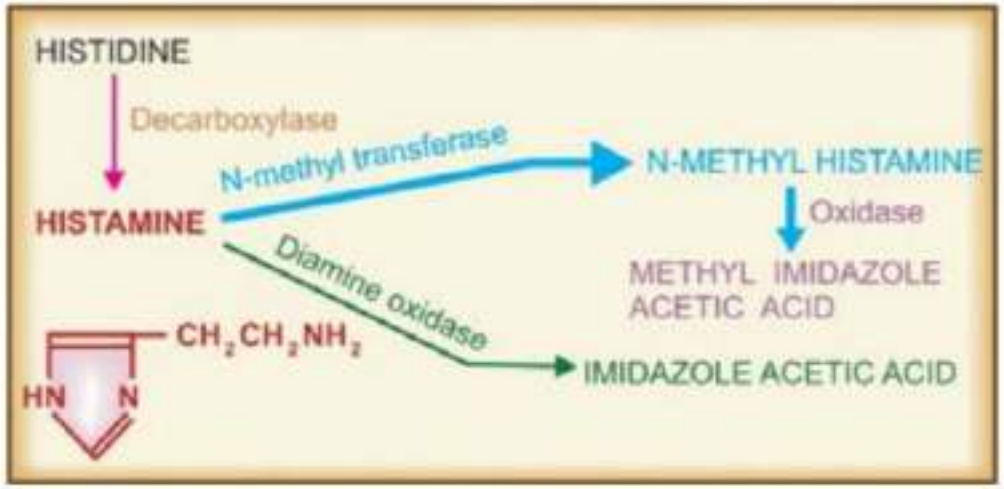
(c) Some neurons in the CNS and PNS

Histamine functions

- 1- Histamine is a critical mediator of IgE/mast cell-mediated anaphylaxis (**mediator of allergic inflammation**)
- 2- Neurotransmitter
- 3- Regulator of gastric acid secretion.

Histamine synthesis and metabolism

- Histamine is a **monoamine** synthesized from the amino acid **histidine** through a reaction catalyzed by the **enzyme histidine decarboxylase** (HDC), which removes carboxyl group from histidine.
- Histamine-N-methyltransferase (HNMT) and diamine oxidase (DAO) to degrade histamine, which is essential for preventing excessive allergic reactions to **harmless substances.**



Histamine Release

•Immunologic Release (IgE- mediated): Ca-dependent

• Mast cell & basophils are degranulated when exposed to the appropriate antigen (bacterial toxins, pollen, pet dander)

•Chemical Release (non- immunologic) : non-Ca- dependent

•Non-immunologic release of histamine from mast cells and basophils

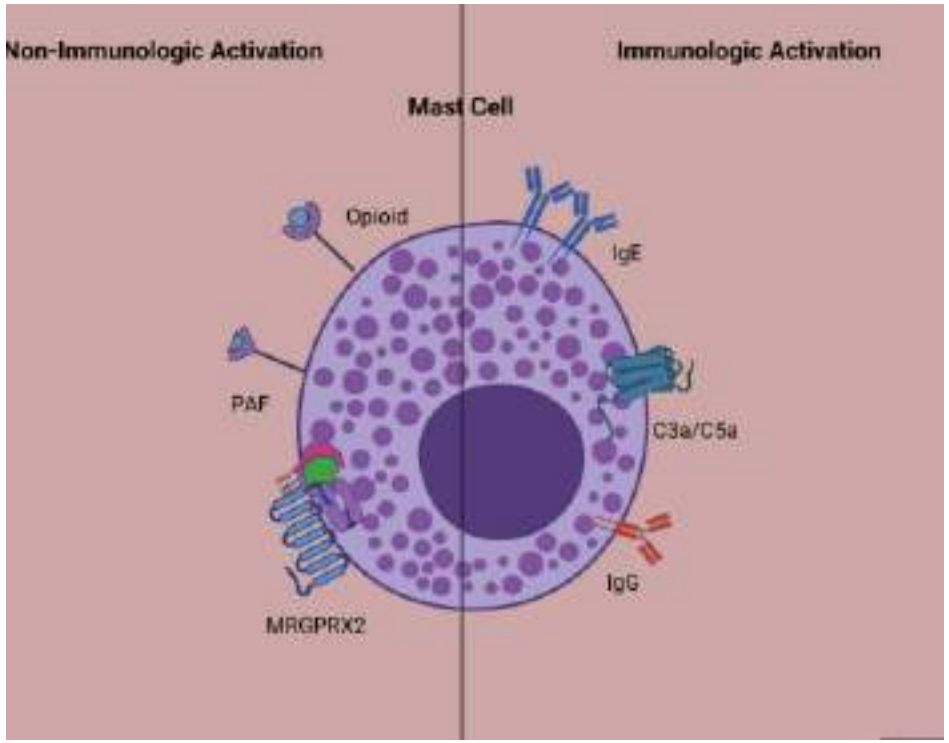
•**By direct cell activation** by various **chemical and physical stimuli**, including : neuropeptides, complement fragments, cytokines, certain foods and medications, extreme temperatures, and trauma.

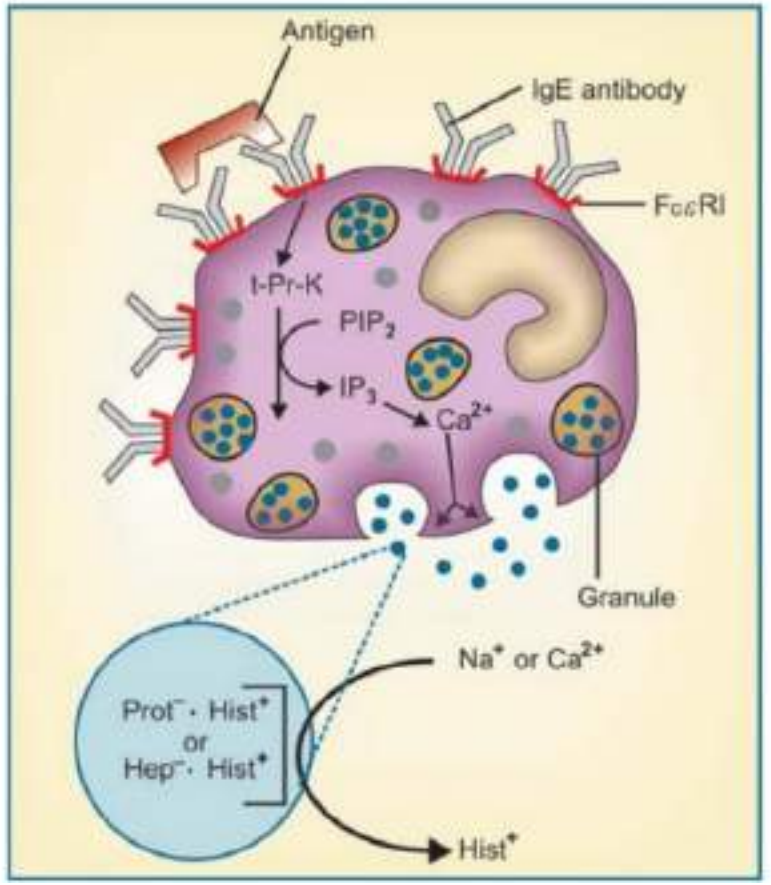
• This pathway **bypasses the need for IgE antibodies and specific antigen binding,** activating histamine release through different cellular mechanisms.

Drugs releasing histamine

- **1- Opioids**: morphine
- **2- Antibiotics**: vancomycin and polymyxin B
- **3- Anticancer drugs**: cyclophosphamide
- **4- Neuromuscular blockers**: d-tubocurarine
- **5- NSAIDs**: aspirin, naproxen

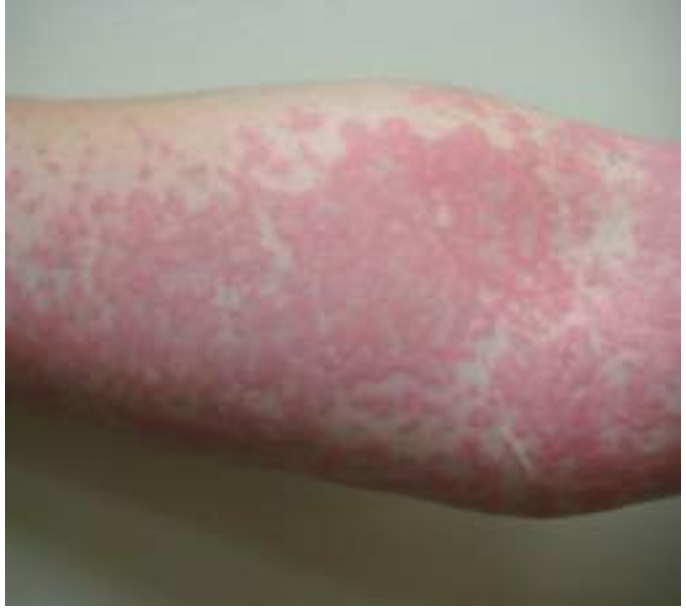
Histamine release

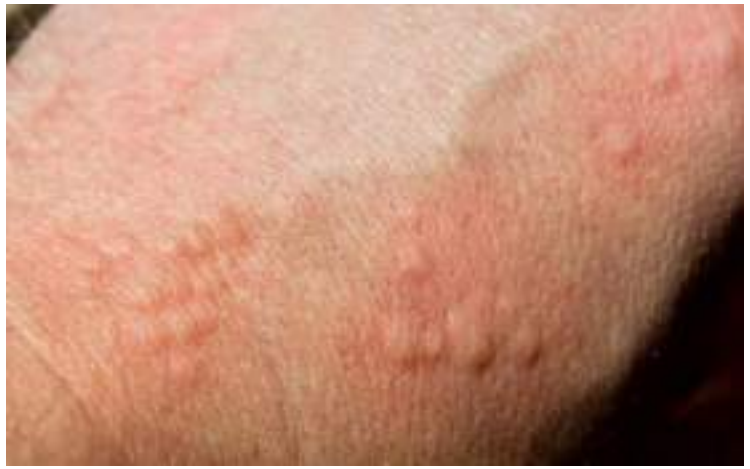


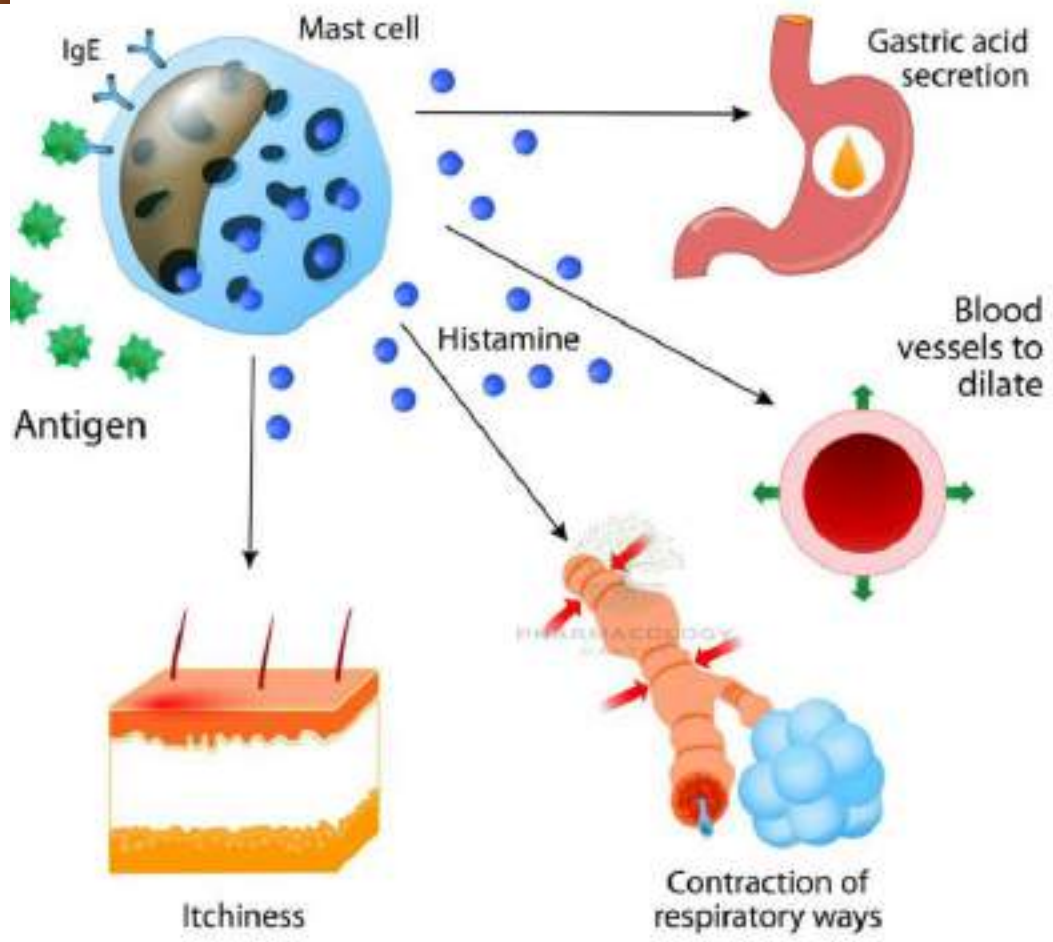


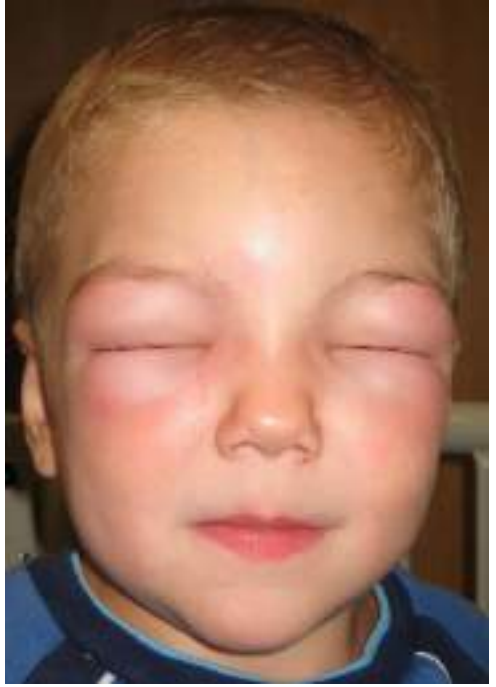
Clinical Manifestations Associated With Histamine Release (allergic manifestations)

•**Mild/cutaneous**	•Erythema, urticaria (red, itchy, swollen skin), and/or itching
•**Mild to moderate**	•**Skin reactions**: rashes, hives (urtecaria), itching, redness, flushing of the skin, and swelling, particularly of the **face, lips, or eyes** •**CVS:** Tachycardia, dysrhythmias, moderate hypotension, •**RS**: Mild respiratory distress
•**Sever/anaphylactic**	•Sever hypotension, ventricular fibrillations, cardiac arrest, bronchospasm, respiratory arrest






IgE
Mast cell
Gastric acid secretion
Histamine
Blood vessels to dilate
Antigen
Itchiness
Contraction of respiratory ways



Histamine Receptors: Distribution and Function

- Histamine has four histamine G-protein coupled receptors:
- H1, H2, H3, & H4
- **H1: (Responsible for most of allergic manifestations)**
- **Smooth muscle fibers, endothelium**: Bronchoconstriction, GI spasm, increasing exocrine glands secretions, vasodilation (relaxation of precapillary sphincters)
- **CNS, nerve endings (subcutaneous tissue):** motion sick, memory and wakefulness, sever itching

- **H2:**
- **Gastric parietal cell**: Regulate gastric acid secretion
- **Heart**: positive inotropic
- **Mast cell**: inhibition of IgE-dependent degranulation (negative feedback).

- **H3: CNS cells, and some in peripheral nerves Presynaptic**:
- Feedback inhibition of histamine synthesis and release. (**negative feedback**)
- Control release of DA, GABA, ACh, 5-HT & NE **(hetero-receptor)**

- **H4 - Highly expressed in immune cells**: immunity modulation

Effect of histamine on pre-capillary sphincters

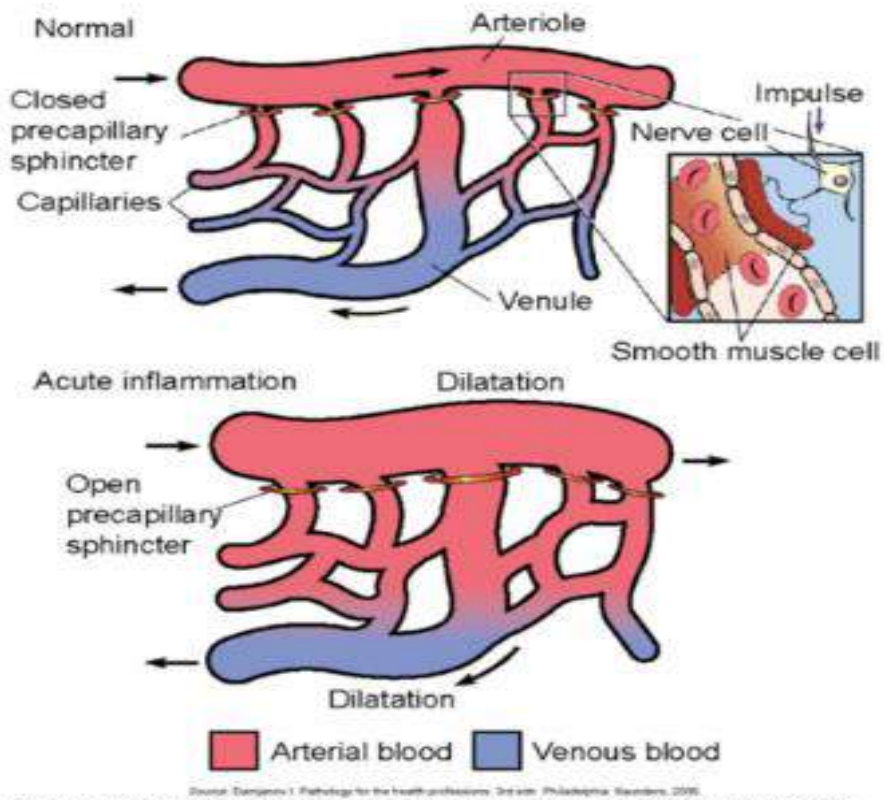


Fig. 13-7. Vasodilation of the capillary beds during inflammation induced by histamine and nitric oxide. Relaxation of the pre-capillary sphincter in the arterioles results in flooding of the capillary network and dilatation of the capillaries and post-capillary venules.

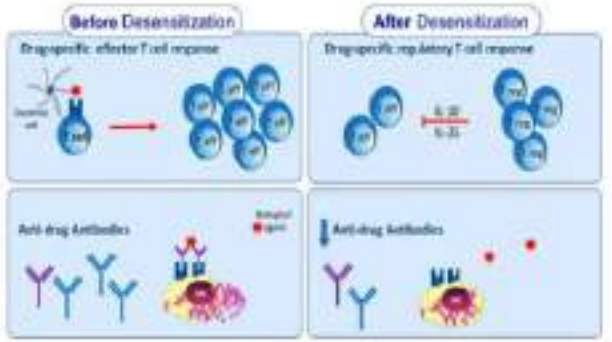
Pharmacological actions of H1 receptors on smooth muscle fibers

❑**Vasodilatation** is via endothelial H_1 receptors

•H_1 stimulation → Increased intracellular Ca^{2+} → Activation of PLA_2 → PGI_2 & NO production → Diffusion to smooth muscles → vasodilatation

❑**Contraction of bronchi, intestine and other smooth muscle fibers** occur via stimulation of *PLC-coupled H_1 receptors* followed by increased IP_3 & DAG: increasing intracellular Ca^{2+}

Drugs antagonizing histamine actions

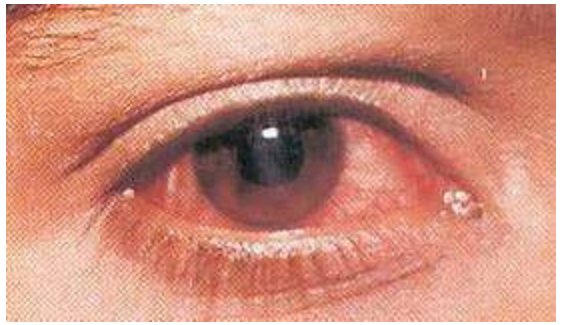


- **1- Physiologic antagonism?**
- **2- Mast Cell Stabilizers** (Cromolyn Na, ketotifen)
- **3- Receptor antagonism:**
- H1 Receptor Antagonists (1st and 2nd generation)
- H2 Receptor Antagonists (Ranitidine, Cimetidine)
- H3 Receptor Agonist and Antagonists (potential new drugs being developed)
- **4- Immunotherapy (desensitization): adaptive changes of immune system**
- Treatment for allergies that involves gradually exposing the immune system to increasing doses of an allergen, such as pollen or dust mites, to make it less sensitive and reduce allergic reactions

What is an antihistamine?

- A drug that **reduces or eliminates** the effects mediated by histamine
- The term antihistamine **only refers to H_1 receptor antagonists**
- Antihistamines **compete with histamine for binding sites at the receptors (antagonism??)**
- Antihistamine **cannot remove the histamine if it is already bound**
- More effective in **preventing** the actions of histamine rather than **reversing** them
- Should be given **early in treatment**, before all the histamine binds to the receptors

Clinical Uses of Antihistamines

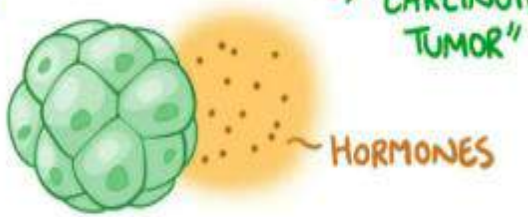


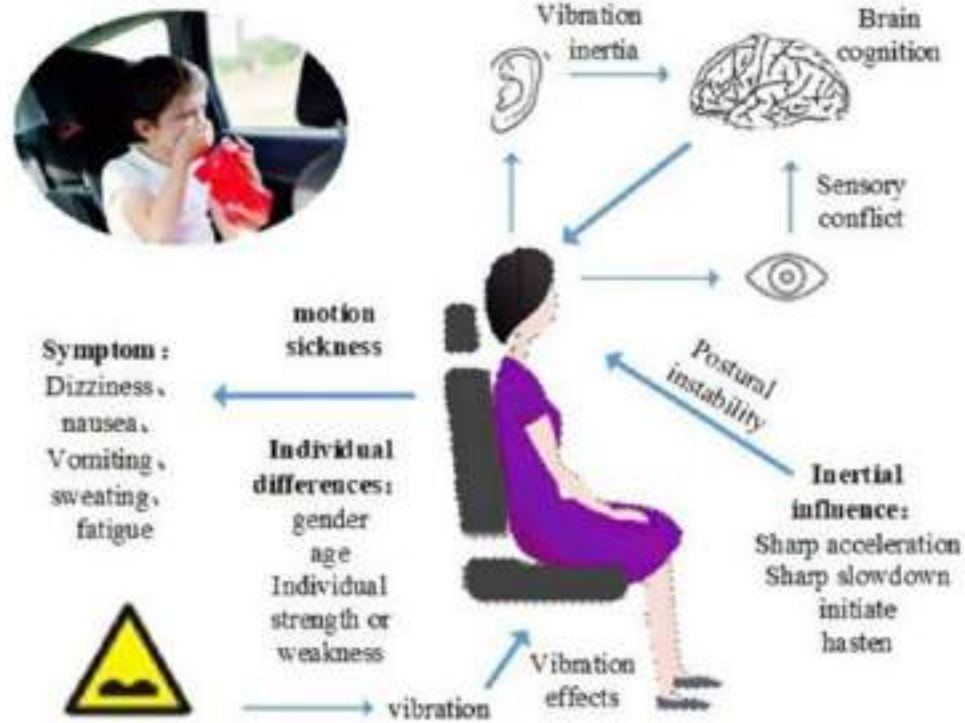
- **1- Allergy**: (both 1st and 2nd generations)
- Allergic rhinitis (common cold)
- Allergic conjunctivitis (pink eye)
- Anaphylactic reactions (severe allergies)
- Allergic dermatological conditions:
- A- Urticaria (hives)
- B- Angioedema (swelling of the skin)
- C- Pruritus (atopic dermatitis, insect bites)
- **2- Motion sickness, vertigo** (first generation H_1-antihistamines)
- **3- Sedative/sleep aid** (1st generation)
- **4- Carcinoid syndrome**: Cyproheptadine

CARCINOID SYNDROME

* DIARRHEA
* SHORTNESS OF BREATH
* FLUSHING

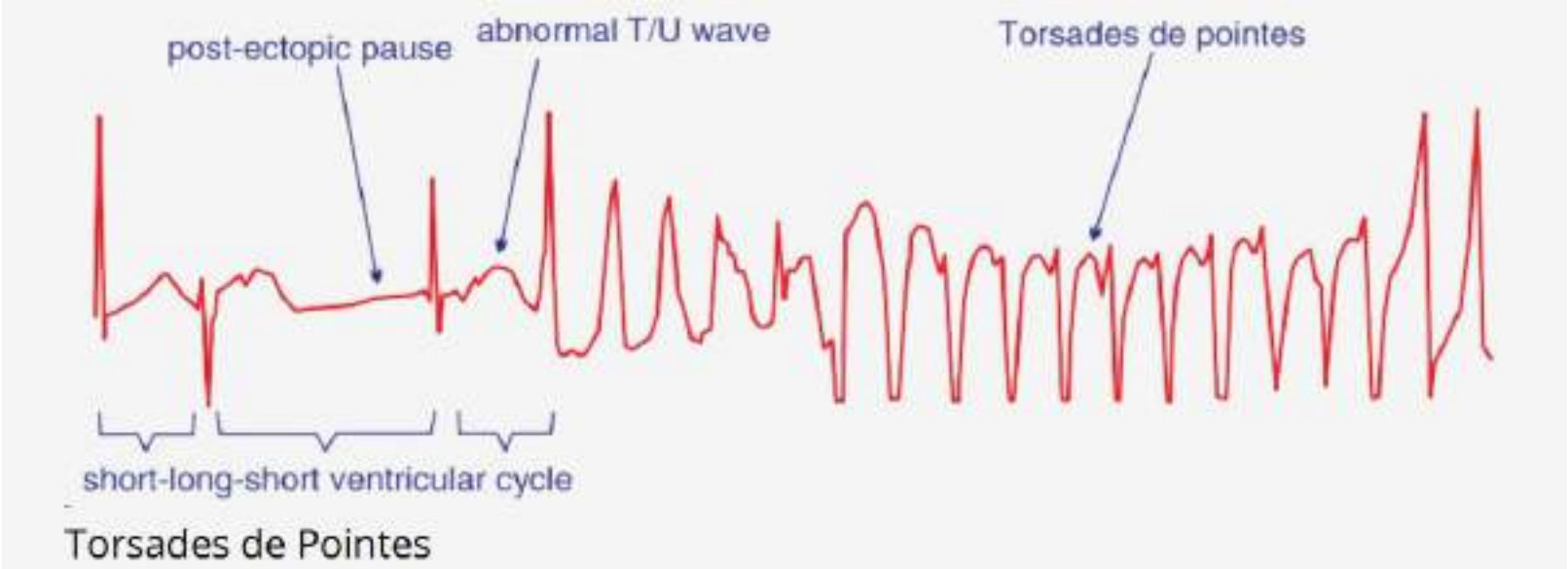
NEUROENDOCRINE TUMOR
↳ "CARCINOID TUMOR"



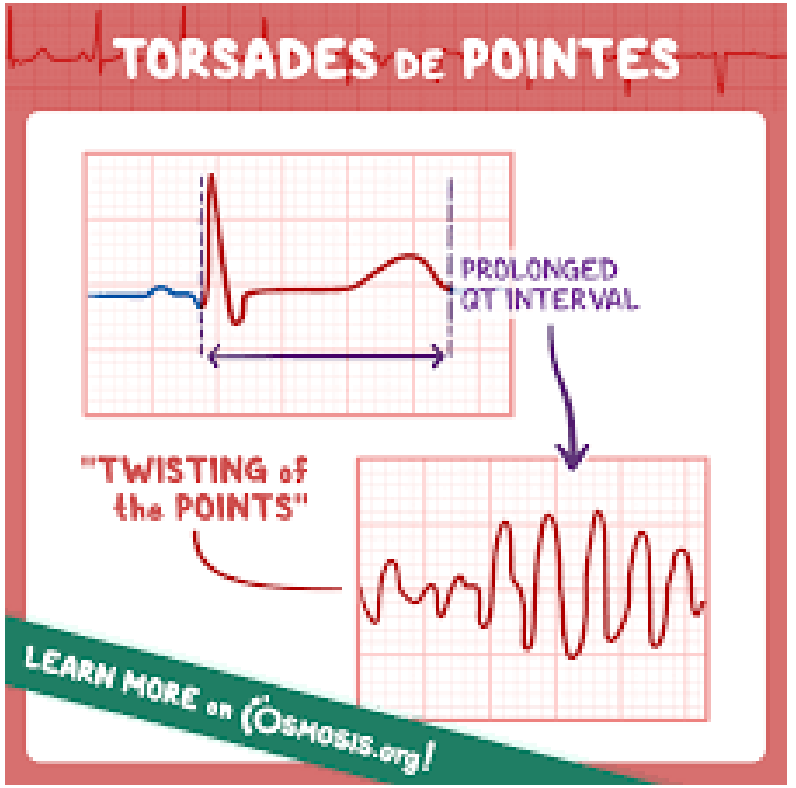


Adverse effects

- **Associated with the first generation H_1-antihistamines and due to their lack of selectivity for the H_1: (central & peripheral receptors)**
- **1- Sedation:** lipophilic: pass BBB
- **EXCITATION** in children under 6 years age
- **2- Atropine-like action☹: muscarinic receptor blocker**
- Blurred vision, dry mouth, urine retention (esp. old age), glaucoma (old age), tachycardia
- **3- Alpha blocking action:** orthostatic hypotension and tachycardia
- **4- Serotonin blocking action** (cyproheptadine): weight gain, dry mouth, drowsiness
- **5- Newer second generation H1-antihistamines are more selective** for the peripheral histamine receptors than central histamine receptors and have **less side effects**, **BUT!!!**
- **Serious types of arrhythmias(fatal)**: (Torsade de pointes) prolongation of QT-interval: **astemizole**



Torsades de Pointes

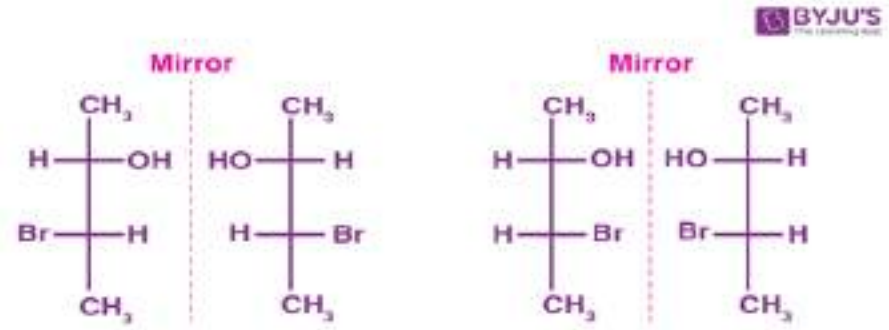


First generation H_1 receptor antagonist

- **Mepyramine**
- **Diphenhydramine:**
- Oldest
- Available over the counter
- Because it induces **sedation**, it's used in nonprescription sleep aids
- **Dimenhydrinate**: **Anti-emetic**
- **Cyclizine: motion sickness**
- **Cetirizine (Zyrtec):** allergies and is safe to use in **Children as young as 2 years old**
- **Kitotifen: mast cell stabilizer**
- **Cyproheptadine: serotonin receptor blocker (Carcinoid syndrome)**

Levocetirizine

- **Levocetirizine (2nd generation):** is a newer, more potent, and less sedating form of the older antihistamine cetirizine
- It is the **active "mirror image" (enantiomer)** of cetirizine.
- Similar effects of cetirizine **at half the dose**, with a lower incidence of drowsiness.
- Both medications are effective **for 24 hours** and are considered **relatively low-risk during pregnancy.**



Second generation H_1-receptor antagonists

•These are the newer drugs and they are **much more selective for the peripheral H1-receptors** involved in allergies than to the H1-receptors in the CNS.

•Therefore, these drugs provide the **same relief with many fewer adverse side effects**

•They are **less lipophilic** than the first generation drugs, therefore they do not cross the BBB.

Second generation H_1-receptor antagonists

- Astemizole & Terfenadine
- Have been **taken off the market** in most countries because of adverse **interactions with erythromycin and ketoconazole** (microsomal enzyme inhibitors) and **effects on cardiac potassium channels**
- Loratidine, desloratidine (active form of loratidine)

Third generation H_1-receptor antagonists

- These drugs are **derived from second generation antihistamines**
- **Highly selective H1-receptor antagonists**
- They are either the **active enantiomer or metabolite of the second generation drug** designed to have increased efficacy and fewer side effects: **NOT** readily crossing the blood-brain barrier
- **Fexofenadine** (the active metabolite of terfenadine: without cardiotoxicity)

Contraindications

- **First generation:**
- 1- Driving and daily activities (students, workers)
- 2- Children less than 6 years old
- 3- Old age (glaucoma & prostatic hypertrophy)
- 4-Hypotension
- **Second generation:**
- 1- Cardiac patients
- 2- Concurrent administration with ketoconazole and erythromycin
- 3- Liver diseases

Comparison between first and second generations

	First generation	Second generation
Sedation	Yes: interfering with driving or daily tasks	No
Potency	Less	More
Duration of action	4-6 hrs.: 3 times daily	24 hrs.: once daily
Cost	Cheap	Expensive
Receptor blocking	MAS	No
Children	Not recommended less than 6 years **(under 2 years old #)**	Recommended 6-12 years
Side effects	More	Less

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Thank you