Histamine & antihistamine drugs

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Objectives

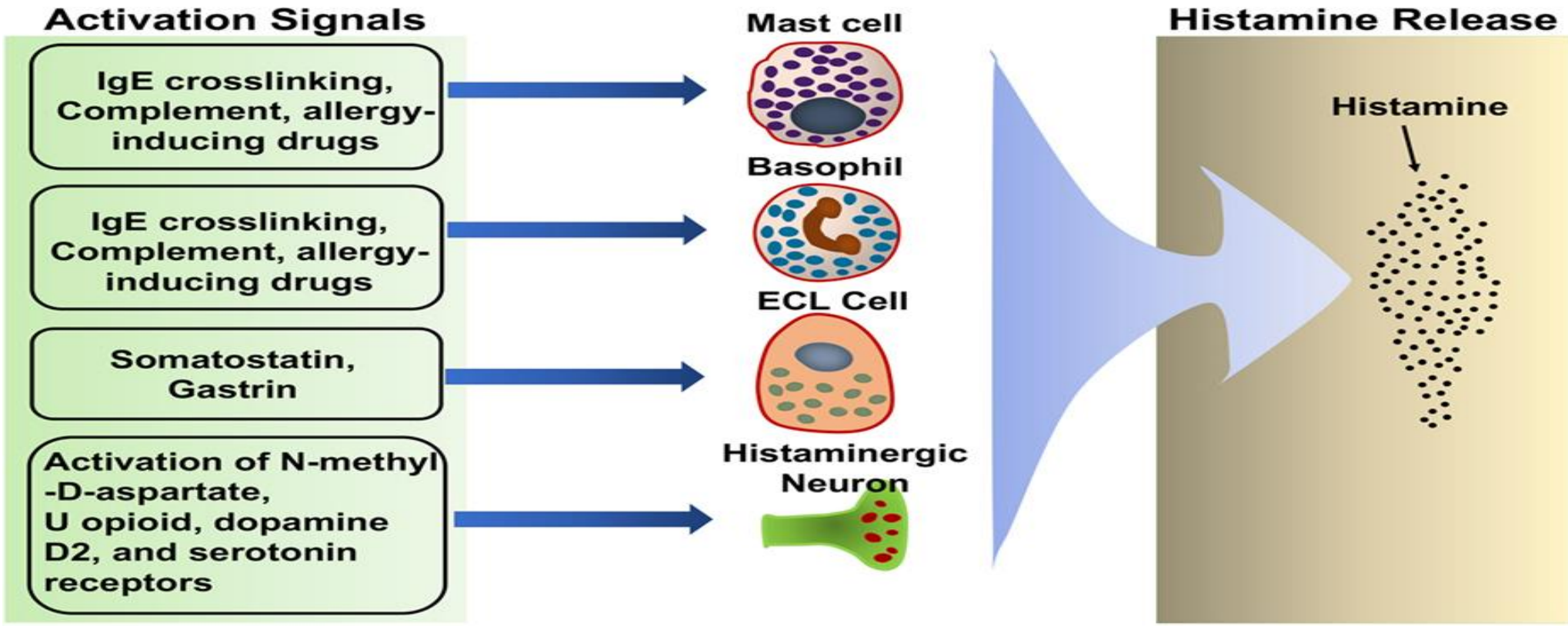
- What is histamine?
- Histamine releasers
- Clinical symptoms associated with histamine release
- Histamine receptors and its pharmacological actions
- Drugs antagonizing histamine actions
- What are meant by antihistamines?
- Clinical uses of antihistaminics
- Adverse effects of antihistaminics
- Classes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

Histamine

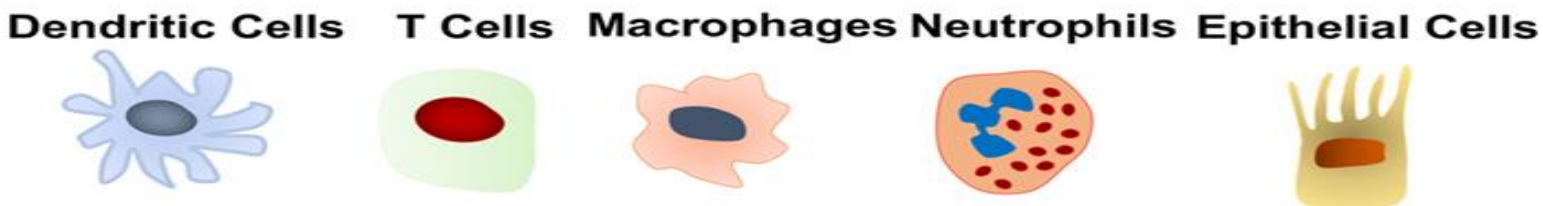
- **Histamine is an endogenous substance synthesized, stored and released in**:

(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 peripheral NS

Major Histamine-producing Cells



Minor Histamine-producing Cells



Histamine Release

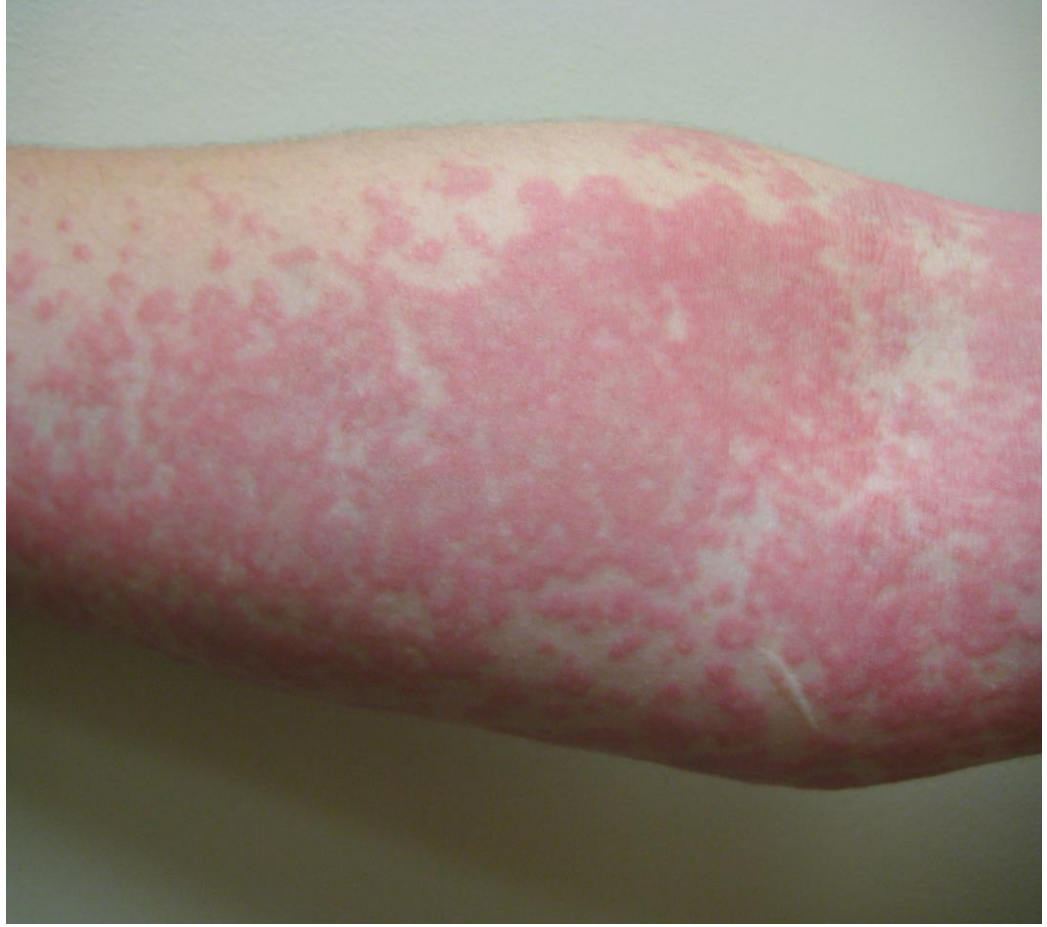
•**Immunologic Release (Cell destruction) (IgE- mediated):**

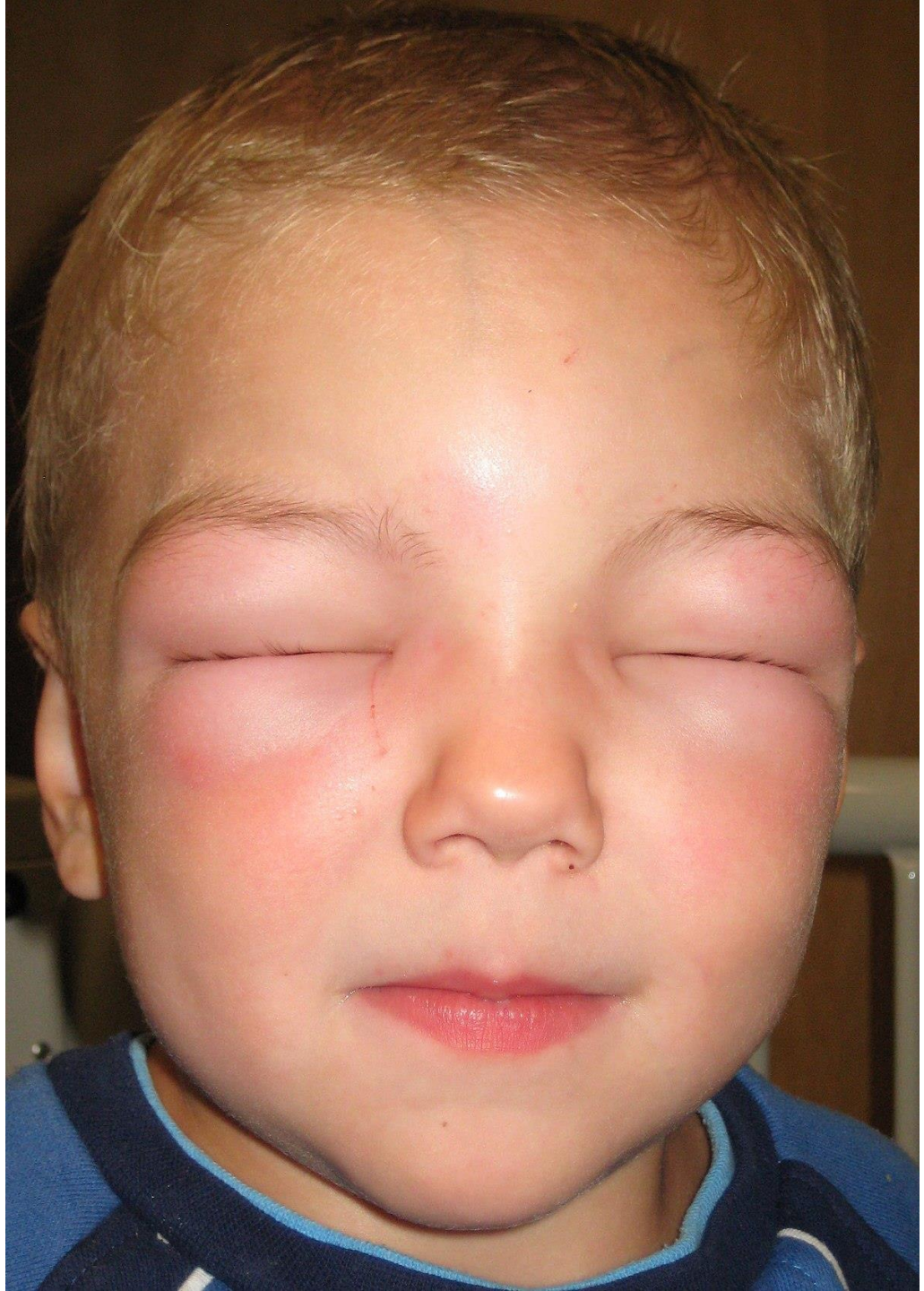
• mast cell & basophils are degranulated when exposed to the appropriate antigen (bacterial toxins, venom, cold, food, some drugs)

•**Chemical Release (non- immunological)** : by drugs: like morphine, vancomycin & curare, X-ray contrast media

Clinical Symptoms Associated With Histamine Release

•mild/cutaneous	•erythema, urticaria, and/or itching
•mild to moderate	•skin reactions, tachycardia, dysrhythmias, moderate hypotension, mild respiratory distress
•severe/anaphylactic	•severe hypotension, ventricular fibrillations, cardiac arrest, bronchospasm, respiratory arrest





Histamine Receptors: Distribution and Function

- Histamine has four histamine H_1, H_2, H_3, & H_4 G-protein coupled receptors

- H1 – **Smooth muscle fibers, endothelium, CNS, nerve endings:**
  - Bronchoconstriction, vasodilation (relaxation of precapillary sphincters), motion sick, memory and wakefulness, increasing secretions of exocrine glands, sever itching

- H2 **– gastric parietal cell, heart, mast cell**:
  - Regulate gastric acid secretion, positive inotropic, inhibition of IgE-dependent degranulation (negative feedback).

- H3 **- CNS cells, and some in peripheral NS. Presynaptic**:
  - feedback inhibition of histamine synthesis and release. They also control release of DA, GABA, ACh, 5-HT & NE

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

Molecular biology of H1 receptors

❑**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+}

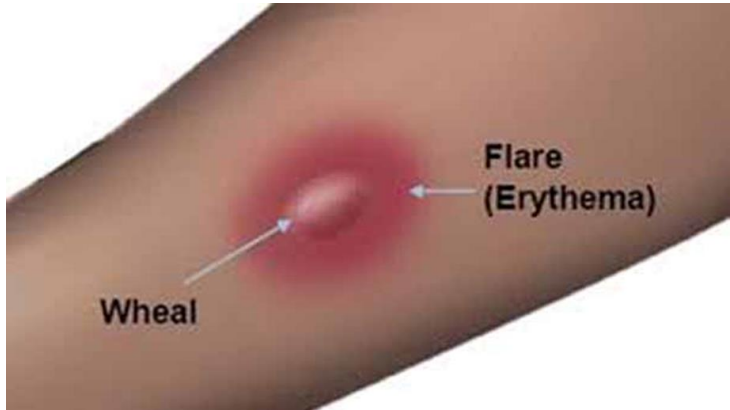
Triple Response of Willis

Subdermal histamine injection causes:

1.Red spot (few mm) in seconds: direct vasodilation effect , H1 receptor mediated

2.Flare (1cm beyond site): axonal reflexes, indirect vasodilation, and itching, H1 receptor mediated

3.Wheal (1-2 min) same area as original spot, edema due to increased capillary permeability, H1 receptor mediated



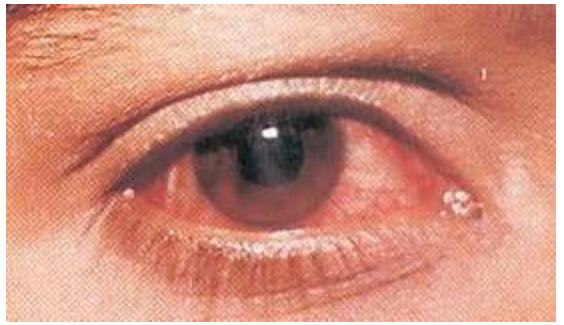
Drugs antagonizing histamine actions

- 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)

What is an antihistaminic?

- 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
- 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

Adverse effects

•**Associated with the first generation H_1-antihistamines and due to their lack of selectivity for the H_1:**

•**1- Sedation:** lipophilic: pass BBB

•**EXCITATION** in children under 6 years age (atropine-like)

•2- **Atropine-like action:**

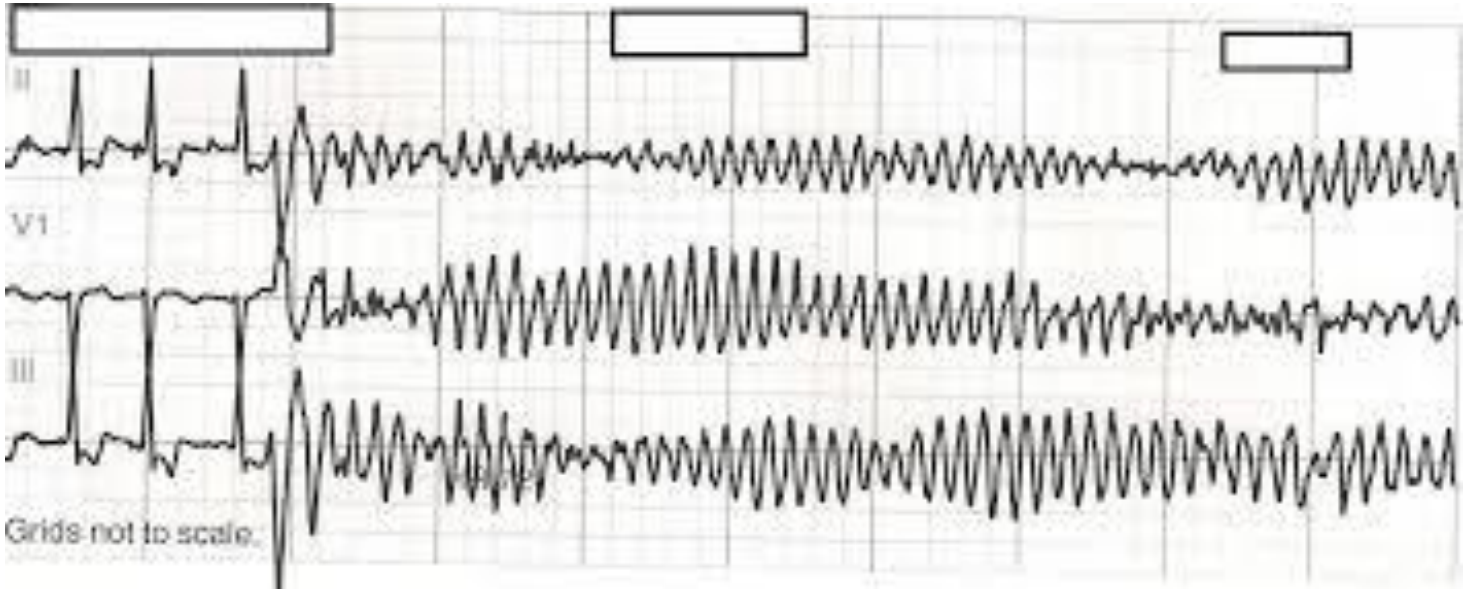
•Blurred vision, dry mouth, urine retention (esp. old age), glaucoma (old age)

• **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 and have less side effects, BUT

•**Serious types of arrhythmias(fatal)**: (Torsade de pointes) prolongation of QT-interval: astemizole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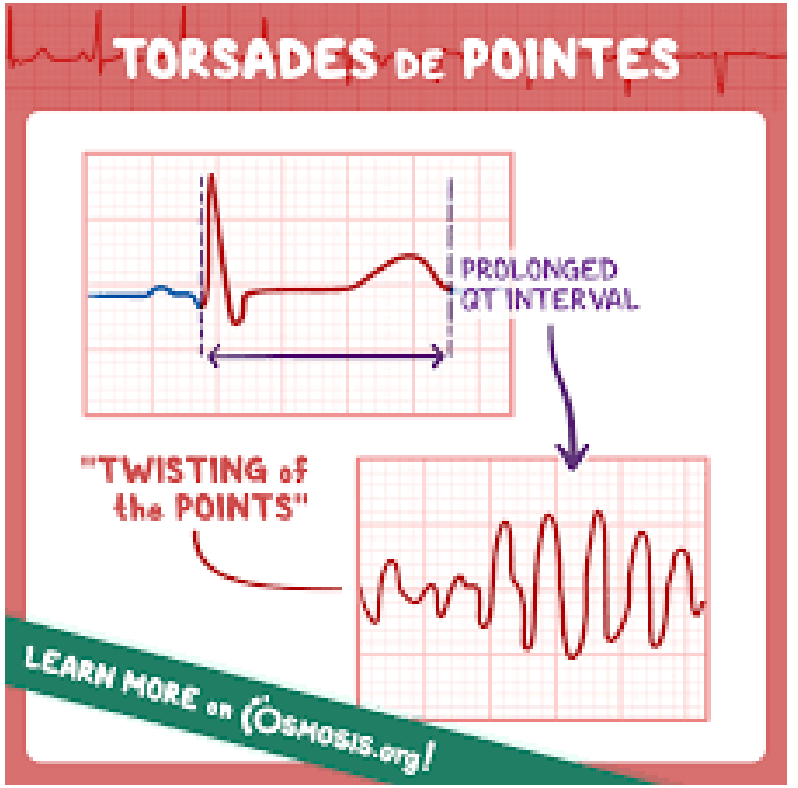
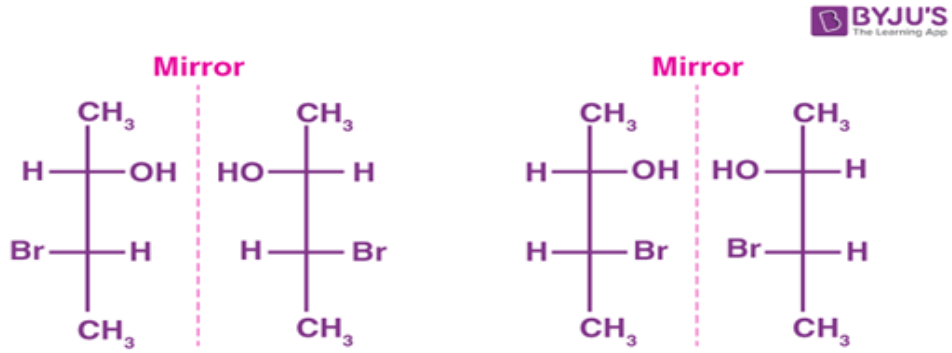

TORSADES DE POINTES
PROLONGED QT INTERVAL
"TWISTING of the POINTS"
LEARN MORE on OSMOSIS.org!

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
- **Kitotifen**
- **Cyproheptadine**

- **Levocetirizine:**
- This drug is the active enantiomer of cetirizine
- Also it is not metabolized and is likely to be safer than other drugs due to a lack of possible drug interactions.
- It does not cross the BBB and does not cause significant drowsiness



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 as readily

1st generation	2nd generations
• Short to intermediate action	• Long acting
• BBB cross	• Poor penetration
• Sedative action	• No
• Produce anti muscurnic side effects	• No
• Also block auonomic receptors	• No
• Cheap	• Relatively expensive

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

Third generation H_1-receptor antagonists

- These drugs are derived from second generation antihistamines
- They are either the active enantiomer or metabolite of the second generation drug designed to have increased efficacy and fewer side effects
- **Fexofenadine** (the active metabolite of terfenadine), was approved in July 1996

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Thank you