A: H1-receptor Antagonists

- The term antihistamine refers primarily to the classic H1-receptor blockers. The new classification of H1-receptor blockers: first-, second- and Third-generation.

First Generation (Sedating Antihistamines)

-The older first-generation drugs are still widely used because they are effective and inexpensive. Most of these drugs penetrate the CNS (lipophilic) and cause sedation. - Short duration of action (4 to 6 hours).
- Some of these drugs have another actions in addition of H1-blockers e.g. Anticholinergic, Antiemetic, Antiserotonin and local anesthetic effects.

Chlorpheniramine (Anallerge®)	**Brompheniramine (VaZol®)**	
Hydroxyzine (Atarax®)	**Triprolidine (Actifed®)**	**Dimethindene (Fenistil®)**
Clemastine (Tavegyl®)	**Pheniramine (Avil®)**	**Mequitazine (Primalan®)**

- Chlorpheniramine, Triprolidine ; slight sedation, common component of cold medication.
- Hydroxyzine : marked sedation.
- Brompheniramine , Dimethindene , Clemastine , Pheniramine and Mequitazine : slight sedation.

Diphenhydramine (Dramenex®)	**Cyclizine (Emetrex®)**	**Doxylamine (Donormyl®)**
Dimenhydrinate (Dramamine®)	**Meclizine (Navidoxine®)**	**Promethazine (Phenergan®)**

- Diphenhydramine , Dimenhydrinate, Cyclizine, Meclizine, Doxylamine and Promethazine are the most effective agents for prevention of the symptoms of motion sickness and vertigo (prevent nausea and vomiting). The antiemetic action; due to block central H1 and M1 muscarinic receptors.
- Diphenhydramine, Dimenhydrinate and Promethazine; marked sedation.
- Cyclizine and Meclizine; slight sedation.
- Doxylamine; strong sedation, used in the treatment of insomnia.

Cyproheptadine (Triactin®)

- Cyproheptadine also acts as a serotonin antagonist on the appetite center and is sometimes used off-label as an appetite stimulant.

Second Generation (Non-sedating Antihistamines)

- The newer second-generation drugs are expensive. - They are made polar mainly by adding carboxyl groups, the second-generation agents don't pass the BBB, causing less CNS sedation. - Long duration of action (12 to 24 hours). - More selective for H1-receptors (no anticholinergic, no antiemetic and no antiserotonin activity).

Cetirizine (Zyrtec®)	**Loratadine (Claritin®)**	**Acrivastine (Semprex®)**
Ebastine (Kestine®)	**Mizolastine (Zolim®)**	

- Cetirizine is a partially sedating second-generation agents.
- Loratadine, Acrivastine, Ebastine, Mizolastine; show the least sedation.

Ketotifen (Zaditen®)	**Alcaftadine (Lastacaft®)**	**Bepotastine (Talion®)**
Emedastine (Emadine®)	**Azelastine (Azelast®)**	**Olopatadine (Patanol®)**

[Ophthalmic Antihistamines]

Ketotifen , Alcaftadine , Bepotastine ,Emedastine , Azelastine and Olopatadine : ophthalmic formulations and used for the treatment of allergic conjunctivitis.
- Azelastine and Olopatadine have intranasal formulations, Ketotifen has oral formulations.
- Azelastine and Ketotifen; have mast cell stabilizing effects in addition to their H1-blocking effects.

Third Generation (Non-sedating Antihistamines)		
- Third-generation are the active enantiomer (Levocetirizine) or metabolite derivatives (Desloratadine & Fexofenadine) of second-generation drugs intended to have increased efficacy with fewer adverse drug reactions. - They are more expensive than second-generation. - Don't pass the BBB, causing no or less CNS sedation than second-generation. - Long duration of action (24 hours). - Pure selective for H1-receptors.		
Levocetirizine (Allear®)	**Desloratadine (Aerius®)**	**Fexofenadine (Telfast®)**
- Levocetirizine is the active enantiomer of Cetirizine, and cause partially sedation. - Desloratadine , Fexofenadine, are the least antihistamines sedation. - Desloratadine is an active metabolite of Loratadine. - Fexofenadine is an active metabolite of Terfenadine. - Terfenadine (Prodrug) is metabolized to Fexofenadine (Active drug), liver microsomal enzyme inhibitors (e.g. Erythromycin) inhibit this metabolism, lead to increase concentration of Terfenadine in the blood Block K+ channels in the heart cardiac arrhythmia (QT interval prolongation). (No cardiotoxicity with fexofenadine).		

Pharmacodynamics

1) Sedation:

- A common effect of first-generation antihistaminic is sedation, but the intensity of this effect varies among chemical structure and lipophilicity. This effect make them useful as "sleep aid".
- At very high toxic dose, marked stimulation, agitation and even convulsions may produce coma.
- Second-generation have little or no sedation or stimulant action.

2) Antinausea and antiemetic actions:

- Several first-generation antihistaminic have significant activity in prevention motion sickness.
- The antiemetic effects are not fully understood, but its central block H1 and M1 receptors properties are partially responsible and it may affect the medullary chemoreceptor trigger zone (CTZ).

3) Antiparkinsonism effects:

- Some of first-generation antihistaminic especially Diphenhydramine, have significant acute suppressant effects on certain the extrapyramidal symptoms associated with antipsychotic drugs (it given parenterally).

4) Anticholinoceptor actions:

Many first-generation have antihistaminic especially Diphenhydramine, Clemastine, Dimenhydrinate Doxylamine have significant atropine-like effects (dry mouth, urinary retention and blurred vision).

5) Adrenoceptor-blocking actions:

- α1-adrenoreceptor blocking effects can demonstrated for many first-generation antihistaminic especially Promethazine, this action may cause orthostatic hypotension.

6) Serotonin-blocking action:

- Strong blocking effects at serotonin receptors have been demonstrated for some first-generation antihistaminic especially Cyproheptadine, it is used off-label as an appetite stimulant.

7) Local anesthesia:

Several first-generation antihistaminic are potent local anesthetics especially Diphenhydramine and Promethazine they block Na+ channels in excitable membranes.

Therapeutic uses

1) Allergic Reactions: Antihistaminic agents are the first drugs used to prevent or treat symptoms of allergic reaction.

- Allergic rhinitis (hay fever): Antihistaminic agents are second line drugs after glucocorticoids administrated by nasal spray.

- Urticaria: Antihistaminic agents are first line (given before exposure). - Second-generation antihistaminic more preferred in chronic urticaria.

- Atopic dermatitis: First-generation antihistaminic such as Diphenhydramine used mostly due to sedative effects (decrease itching awareness).

- Bronchial asthma and angioedema: Antihistaminic agents are largely ineffective alone in bronchial asthma and angioedema due to in asthma and angioedema increase release of histamine and other mediator antihistaminic agents block only histamine action.

2) Motion Sickness and Vestibular Disturbance:

- Scopolamine and certain first-generation antihistaminic especially Diphenhydramine and Promethazine are the most effective agents available for prevention of motion sickness.

- Cyclizine and Meclizine also have significant activity in prevention of motion sickness and are less sedation than Diphenhydramine .

3) Nausea and Vomiting of Pregnancy (NVP):

- Meclizine, Cyclizine and Doxylamine are combined with Vitamin B6 to control of nausea and vomiting during pregnancy.

4) Somnifacient (Hypnotic):

- First-generation antihistaminic may use as sleep aid in insomnia especially Doxylamine and Diphenhydramine (Strong sedative).

CONTRAINDICATION

First-generation antihistaminic is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical such as drivers and worker in dangerous machines.

Toxicity

Systemic Acute Toxicity with first-generation antihistaminic is relatively common, especially in young children, including hallucinations, excitement, ataxia, and convulsions. So. **(Emetrex Ampoule)** is NOT recommended in CHILDREN younger than 6 years to prevent von (serotonin antagonists such as Ondansetron is safer).

Drug interaction

First generation antihistaminic interact;

- With anxiolytic and hypnotic drugs e.g. Benzodiazepines (BDZS) increase sedative effect (Additive effect).

- With MAO inhibitors increase anticholinergic effects.

- With cholinesterase inhibitors used in Alzheimer's disease decrease (Donepezil, Rivastigmine and galantamine) cholinergic effects.

Second generation Terfenadine interact;

- With Liver microsomal enzyme inhibitors (e.g. Erythromycin and Ketoconazole) inhibit metabolism of Terfenadine, lead to increase concentration of Terfenadine in the blood Block K+ channels in the heart cardiac arrhythmia (QT interval prolongation).

Histamine Antagonists
1) Physiological Antagonist of Histamine: - Adrenaline having apposite to those histamine on H1 receptor due to cause bronchodilatation (β2) and vasoconstriction (α1). **2) Mast Cell Stabilizers** (Inhibitors of histamine release): Decrease histamine release from mast cell used as prophylactics in asthma. A) Cromolyn (or Cromoglyeate), Nedocromil and Ketotifen. B) B2-adrenoceptor agonists e.g. Salbutamol. C) Methylxanthines e.g. Theophylline. **3) Histaminase Enzyme** (Diamine Oxidase): - Responsible for histamine metabolism. **4) Histamine Receptors Blockers:** A: H1-receptor blockers. B: H2-receptor blockers. C: H3-receptor blockers.

D: H4-receptor blockers.