B: H2-receptor Antagonists

- The H2 receptor antagonists (H:RA) are a class of drugs used to block the action of histamine on parietal cells (specifically the histamine H2 receptors) in the stomach, decreasing the production of acid by these cells.

Cimetidine (Tagamet®) | Ranitidine (Zantac®)
Nizatidine (Ulcefree®) | Famotidine (Antodine®)

- Cimetidine, Ranitidine , Famotidine , and Nizatidine are reduces the secretion of gastric acid by blocking H2 receptors.
- Cimetidine is largely replaced by other H2 receptor blocker due to side effects.

Pharmaco -kinetics

- All four agents are rapidly absorbed from the intestine.
- Cimetidine, Ranitidine and Famotidine first-pass hepatic metabolism (bioavailability = approximately 50%), Nizatidine has tittle first-pass hepatic metabolism.
- Half-life of four agents approximately 1.1 to 4 hours, duration of action depend on the dose given.
- Dose reduction is required in moderate to severe renal dysfunction and severe hepatic impairment.

Drug	Relative potency	Usual dose	Parenteral form
Cimetidine	1	400 mg twice or 800 mg at bedtime	50mg
Ranitidine	4-10	150 mg twice or 300 mg at bedtime	50mg
Nizatidine	4-10	150 mg twice or 300 mg at bedtime	Not available
Famotidine	20-50	20 mg twice or 40mg at bedtime	20mg

Mechanism Of action

~Histamine released from enterochromaffin-like (ECL) cells in the fundus of the stomach by gastrin or vagal parasympathetic stimulation (acetylcholine).
~H2 receptor antagonists block the actions of histamine at parietal cell H2 receptors and supress basal and meal stimulated acid secretion.
~H2 receptor antagonists inhibit 60-70% of total 24- hours acid secretion.

Therapeutic uses

1) Peptic Ulcer Disease (PUD):

- All four agents are equally effective in promoting the healing of duodenal and gastric ulcers.
- Proton pump inhibitors have largely replaced H2-antagonists in the treatment of acute peptic ulcer (NSAID-induced ulcers and ulcer caused by H.pylori), because these agents heal and prevent recurrence.
- H2-antagonists used in Zollinger-Ellison Syndrome (ZES), ZES is a gastrin-secreting tumor of the pancreas that stimulates the acid- secreting cells of the stomach, cause mucosal ulceration.

2) Gastroesophageal Reflux Disease (GERD):

- Is a chronic symptom which stomach acid coming up from the stomach into the esophagus Heartburn.
- H2-antagonists act by stopping acid secretion. Therefore, they may not relieve symptoms for at least 45 minutes.
- Antacids more quickly and efficiently neutralize stomach acid, but their action is

	only temporary. - PPIS are now used preferred in the treatment of GERD. **3) Non-ulcer Dyspepsia:** - Commonly used for dyspepsia not caused by peptic ulcer. **4) Acute Stress Ulcers:** - Given as an IV infusion to prevent and manage acute stress ulcers. - PPIS are favor for this indication.
Side effects	- H2-antagonists are extremely safe drugs. Side effects occur in less than 3% of patient include diarrhea, headache and fatigue. - Cimetidine inhibits binding of dihydrotestosterone to androgen receptors (Anti-androgenic effect) and↑ serum prolactin, long term use may cause: - Impotence in male (Anti-androgenic effect). - Gynecomastia in male (Increase prolactin). - Galactorrhea and amenorrhea in female (Increase prolactin). Rapid IV infusion of H2-antagonists may rarely cause bradycardia and hypotension by blocking cardiac H2-receptors. - H2-antagonists in pregnancy FDA category B.
Drug Interactions	-Cimetidine inhibits several cytochrome P450 isoenzymes (is a LME inhibitor) and can interfere with the metabolism of many other drugs, such as Warfarin and Phenytoin. - All of H2-antagonists except Famotidine inhibit gastric first pass metabolism of Ethanol especially in women resulting in increased bioavailability of ethanol increase blood ethanol level. - H2-antagonists compete with Creatinine and certain drugs (e.g. Procainamide) for renal tubular secretion.

C: H3-& H4 receptor Antagonists
Although no selective H3 or H4 ligands are presently available for general clinical uses.
Betahistine (Betaserc®)
- Betahistine is an anti-vertigo drug used in balance disorders or relieve vertigo symptoms associated with Ménière's disease . **{MECHANISM OF ACTION}** - Betahistine has a very strong affinity as an antagonist for histamine H3- receptors and a weak affinity as an agonist for histamine H1-receptors. - Betahistine seems to dilate the blood vessels within the inner ear which can relieve pressure from excess fluid and act on the smooth muscle. - Ménière's disease is a disorder of the inner ear that causes spontaneous episodes of vertigo, fluctuating hearing loss, ringing in the ear (tinnitus) and affects only one ear. **N.B:** Tiprolisant is a selective H3-receptor inverse agonist/antagonist, It is currently in clinical trials for schizophrenia and Parkinson's disease.