GIT Drugs

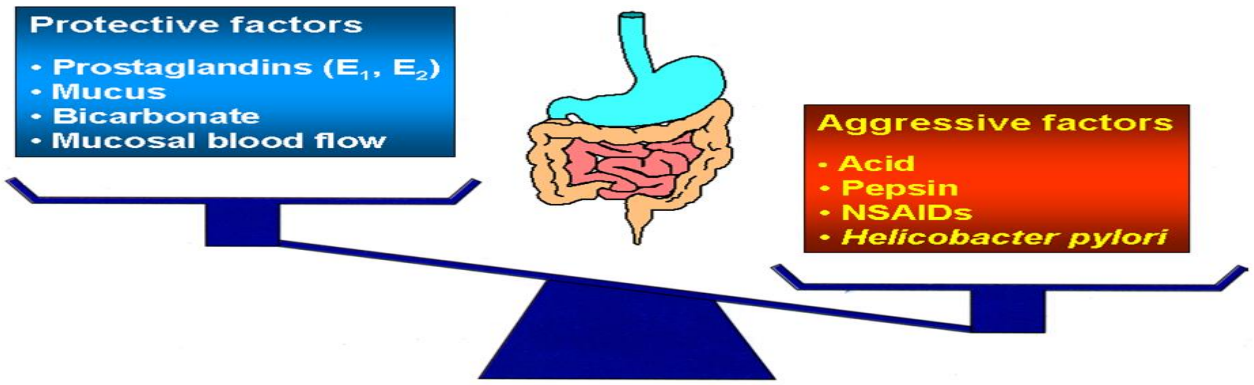
Drugs used to treat peptic ulcer disease and gastroesophageal reflux disease (GERD):

The main functions of GIT are **digestion**& **absorption**.

The stimulatory factors for acid secretion are:

1- Gastrin hormone which is a stimulating hormone.
2- Acetylcholine which is a stimulating neurotransmitter.
3- Histamine which is a local hormone.
4- PGI2, E2 hormones which decrease HCl secretion.

Peptic ulcer: A benign lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed to acid and pepsin. It results due to an imbalance between the aggressive and defensive factors.



The causes of peptic ulcer disease are 1) infection with gram negative ***Helicobacter pylori***, 2) the use of nonsteroidal anti-inflammatory drugs (NSAIDs), the gastrinoma (Zollinger-Ellison Syndrome) ((Tumors of the duodenum or pancreas and secrete abnormally high amounts of gastrin which

stimulates gastric acid)), 3) cigarette smoking, heredity, stress also Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role. Treatment approaches include:
1) Eradicating the H. pylori infection, **2) reducing secretion of gastric acid with the use of PPIs, H2 -receptor antagonists 3) neutralizing gastric acidity by antacids 4) providing agents that protect the gastric mucosa from damage, such** as misoprostol and sucralfate.

GERD **(gastroesophageal reflux disease)** is when acid and pepsin from the stomach flows backward up into the esophagus often called heartburn.

A. Antimicrobial agents:

Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with H. pylori require antimicrobial treatment. Successful eradication of H. pylori (80% to 90%) is possible with various combinations of antimicrobial drugs. Currently, triple therapy consisting of a PPI combined with amoxicillin (metronidazole may be used in penicillin-allergic patients) plus clarithromycin is the therapy of choice. Quadruple therapy of bismuth subsalicylate, metronidazole, and tetracycline plus a PPI is another option. Quadruple therapy should be considered in areas with high resistance to clarithromycin. Treatment with a single antimicrobial drug is much less effective, results in antimicrobial resistance, and is not recommended. The duration of treatment for 2 weeks. [Note: GERD (heartburn) is not associated with H. pylori infection and does not respond to antibiotics.]

B. H2 -receptor antagonists and regulation of gastric acid secretion:

These drugs include cimetidine, ranitidine, famotidine, and nizatidine. They are competitively blocking the binding of histamine to H2 receptors; these agents reduce the secretion of gastric acid. The histamine H2-receptor antagonists act

selectively on H2 receptors in the stomach, but they have no effect on H1 receptors. They are competitive antagonists of histamine and are fully reversible.

Cimetidine was the first histamine H -receptor antagonist. However, its utility is limited by its adverse effect profile and drug– drug interactions.

Therapeutic uses:

a. **Peptic ulcers:**
b. **Acute stress ulcers:** because tolerance may occur with these agents in this setting, PPIs have gained favor for this indication.
c. **Gastroesophageal reflux disease (GERD):** Low doses of H2 antagonists, currently available for over-the-counter sale, are effective for the treatment of heartburn (GERD) in only about 50% of patients. H2-receptor 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. For these reasons, PPIs are now used preferentially in the treatment of GERD, especially for patients with severe heartburn.

   Pharmacokinetics: *Cimetidine, ranitidine,* and *famotidine* are available in intravenous formulations. The half-life of all of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.

   Adverse effects: In general, the H2 antagonists are well tolerated. Cimetidine can have endocrine effects because it acts as a nonsteroidal antiandrogen. These effects include gynecomastia and galactorrhea (continuous release/discharge of milk). The other agents do not produce the antiandrogenic and prolactin-stimulating effects of *cimetidine. Cimetidine* inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many other drugs, such as *warfarin, phenytoin,* and *clopidogrel*. All H_2 antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as *ketoconazole.*

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailability	80	50	40	>90
Relative Potency	1	5 -10	32	5 -10
Half life (hrs)	1.5 - 2.3	1.6 - 2.4	2.5 - 4	1.1 -1.6
Duration of action (hrs)	6	8	12	8
Inhibition of CYP 450	1	0.1	0	0
Dose mg(bd)	400	150	20	150

C.PPIs: Inhibitors of the H+/K+-ATPase proton pump

PPIs include dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. The PPIs irreversibly inhibited of proton pump (H+/ K+ ATPase) that is responsible for final step in gastric acid secretion from the parietal cell.

Therapeutic uses: The PPIs are superior to the H_2 antagonists in suppressing acid production and healing ulcers. Thus, they are the preferred drugs for stress ulcer treatment and prophylaxis and for the treatment of GERD, erosive esophagitis, active duodenal ulcer, and pathologic hypersecretory conditions (for example, Zollinger- Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl). If an H_2-receptor antagonist is needed, it should be taken well after the PPI. H_2 antagonists reduce the activity of the proton pump, and PPIs require active pumps to be effective. PPIs also reduce the risk of bleeding from ulcers caused by *aspirin* and other NSAIDs and may be used for prevention or treatment of NSAID-induced ulcers.

Mechanism of Action: Prodrugs inactive at neutral pH

- **At pH < 5 rearranges to two charged cationic forms (sulfenamide + sulphenic acid) that bind covalently with SH groups of H^+K^+ ATPase and inactivate it irreversibly**
- **Also inhibits gastric mucosal carbonic anhydrase**

Pharmacokinetics: PPIs are Prodrugs requiring activation in acid environment. Activated forms binds irreversibly to H+/K+ATPase and inhibit it .All of these agents are effective orally. For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. [Note: *dexlansoprazole* has a dual delayed release formulation and can be taken with-out regard to food.].

Given as enteric coated granules in capsule or enteric coated tablets. Omeprazole, *Esomeprazole*, *lansoprazole*, and *pantoprazole* are also available in intravenous formulations. Although the plasma half-life of these agents is half life is very short and only 1-2 hrs, they have a long duration of action (still the action persists for 24 to 48 hrs after a single dose, Action lasts for 3-4days even after stoppage of the drug) due to covalent bonding with the H+/K+-ATPase enzyme((irreversible inhibition of PPI and new PP synthesis takes time (24 to 48 hour suppression of acid secretion, despite the much shorter plasma half-lives of the parent compounds).

Adverse effects: diarrhea, headache, Vitamin B12 deficiency, increased incidence of pneumonia. *Omeprazole* and *esomeprazole* may decrease the effectiveness of *clopidogrel* because they inhibit CYP450 and prevent the conversion of *clopidogrel* to its active metabolite. Concomitant use of these PPIs with *clopidogrel* is not recommended because of a possible increased risk of cardiovascular events. PPIs may increase the risk of fractures, particularly if the duration of use is1 year or greater. Dose reduction is required in severe liver failure.

Drug	Bioavailability	Half-Life (h)
Omeprazole	40–65%	0.5–1
Esomeprazole	50–89%	1.2
Lansoprazole	80–90%	1.5
Pantoprazole	77%	1.9
Rabeprazole	52%	0.7–2.0

D. Prostaglandins:

Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. Misoprostol is an analog of prostaglandin E, is approved for the prevention of NSAID-induced gastric ulcers. Prophylactic use of misoprostol should be considered in patients who are taking NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers. Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.

E. Antacids

Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity. Commonly used antacids are combinations of salts of aluminum and magnesium, such as *aluminum hydroxide* and *magnesium hydroxide* [Mg (OH) $_2$]. *Calcium carbonate* [$CaCO_3$]((non

systemic antacids)).while NaHCO3 considered as systemic antacid which Systemic absorption of it can produce transient metabolic alkalosis. Therefore, this antacid is not recommended for long-term use.

Therapeutic uses: Antacids are used for symptomatic relief of peptic ulcer disease and GERD, and they may also promote healing of duodenal ulcers. They should be administered after meals for maximum effectiveness.

[Note: *Calcium carbonate* preparations are also used as calcium supplements for the treatment of osteoporosis.]

Adverse effects: *Aluminum hydroxide* tends to cause constipation, whereas *magnesium hydroxide* tends to produce diarrhea. Absorption of the cations from antacids (Mg^{2+}, Al^{3+}, Ca^{2+}) is usually not a problem in patients with normal renal function; however, accumulation and adverse effects may occur in patients with renal impairment.

F. Mucosal protective agents:

Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

Sucralfate: By forming complex gels with epithelial cells, *sucralfate* creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal. Although *sucralfate* is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to the need for multiple daily dosing and drug-drug interactions. Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H_2 antagonists, or antacids. It does not heal gastric ulcers.

Bismuth subsalicylate: This agent is used as a component of quadruple therapy to heal peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.

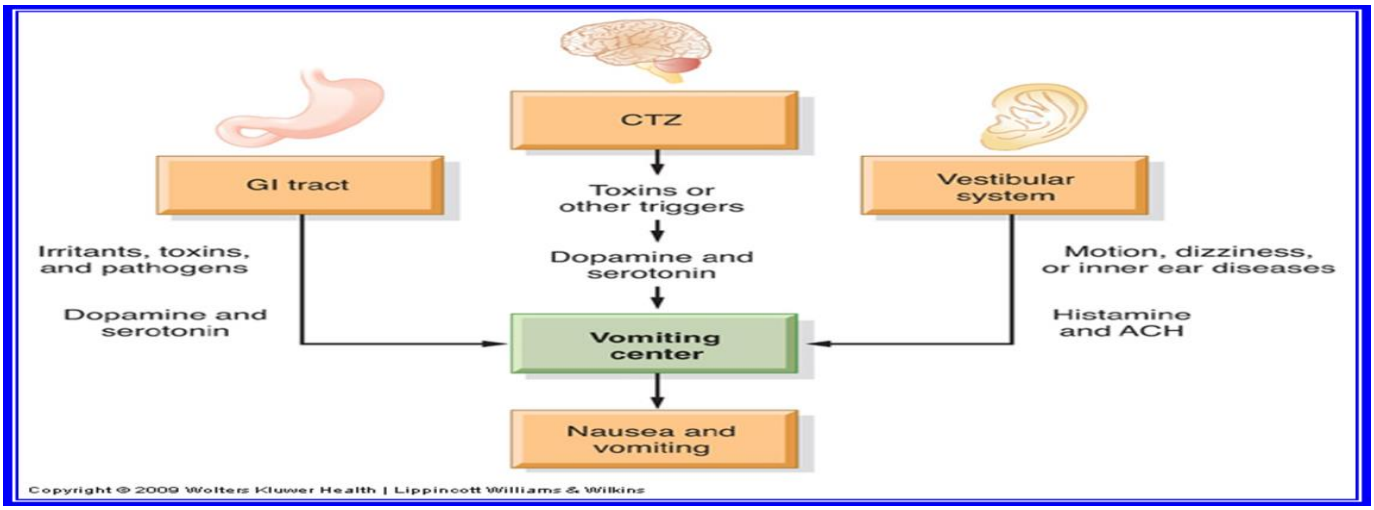
G. **Anti-Muscarinic Drugs**: Muscarinic receptor stimulation increases gastrointestinal motility and secretory activity. **Pirenzepine and telezepine are** relatively specific M1-receptor antagonists. They reduce acid production & Abolish gastrointestinal spasm.

ANTI-EMETICS:

Vomiting is defined as the ejection or expulsion of gastric contents through the mouth, often requiring a forceful event (reflexive).Vomiting can be lifesaving, physiological response to the ingested toxic substances. It also can be an adverse reaction of radiation and antineoplastic agents. Vomiting also occurs in early pregnancy, during migraine attack, in motion sickness, etc. uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

Mechanisms that trigger vomiting:

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone (CTZ). It can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting.



Emetic actions of chemotherapeutic agents:

Chemotherapeutic agents can directly activate the medullary CTZ or vomiting center. Several neuroreceptors, including dopamine receptor type 2 and serotonin type 3 (5-HT_3), play critical roles. Often, the color or smell of chemotherapeutic drugs (and even stimuli associated with chemotherapy) can activate higher brain centers and trigger emesis. Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and by releasing serotonin from the enterochromaffin cells of the small intestine. Serotonin activates 5-HT_3 receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

Antiemetic drugs:

The major categories of drugs used to control CINV include the following:

1- **Phenothiazines:** The first group of drugs shown to be effective antiemetic agents, phenothiazines, such as ***prochlorperazine***, act by blocking dopamine receptors. ***Prochlorperazine*** is effective against low or moderately emetogenic chemotherapeutic agents (for example, *fluorouracil* and *doxorubicin*).

2- **5-HT_3 receptor blockers:** The 5-HT_3 receptor antagonists include ondansetron, granisetron, palonosetron, and dolasetron. These agents selectively block 5-HT3 receptors in the periphery and in the brain (CTZ). These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against all grades of emetogenic therapy. *Ondansetron* and *granisetron* prevent emesis in 50% to 60% of *cisplatin*-treated patients. These agents are also useful in the management of postoperative nausea and vomiting. 5-HT3 antagonists are extensively metabolized by the liver; however, only *ondansetron* requires dosage adjustments in hepatic insufficiency. Elimination is through the urine. Headache is a common side effect.
3- **Substituted benzamides (dopamine antagonists):** One of several substituted benzamides with antiemetic activity, *metoclopramide* is effective at high doses against the emetogenic *cisplatin*, preventing emesis in 30% to 40% of patients and reducing emesis in the majority of patients. Antidopaminergic side effects, including extrapyramidal symptoms, limit long-term high-dose use.
4- **Butyrophenones:** Droperidol and haloperidol act by blocking dopamine receptors. Droperidol had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines. High-dose haloperidol was found to be nearly as effective as high-dose metoclopramide in preventing cisplatin-induced emesis.
5- **Corticosteroids:** Dexamethasone and methylprednisolone, used alone, are effective against mildly to moderately emetogenic chemotherapy. Most frequently, however, they are used in combination with other agents. Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins.
6- **Substance P/neurokinin-1 receptor blocker:** Aprepitant is indicated only for highly or moderately emetogenic chemotherapy regimens. It is usually administered orally with dexamethasone and a 5-HT antagonist. It may

affect the metabolism of other drugs such as warfarin and oral contraceptives.

- **Note:** for tx of emesis-motion sickness, we used drugs: **H1 antagonists** such as diphenhydramine, cyclizine, meclizine, cinnarazine also can be used **Anticholinergics** such as Hyoscine. While in case of emesis-morning sickness (Vomiting during pregnancy) during 1st trimester of pregnancy due to effect of increased oestrogen levels on CTZ so we can be used cyclizine, meclizine, vitamin B6 (pyridoxine).

Antidiarrheals:

Increased motility of the GI tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport.

A. Antimotility agents

Two drugs that are widely used to control diarrhea are *diphenoxylate* and *loperamide*. Both are analogs of *meperidine* and have opioid-like actions on the gut. Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

B. Adsorbents

Adsorbent agents, such as *aluminum hydroxide* and *methylcellulose*, are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa.

C. Agents that modify fluid and electrolyte transport

Bismuth subsalicylate, used for traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include black tongue and black stools.

LAXATIVES

Laxatives are commonly used for constipation to accelerate the movement of food through the GI tract. Laxatives increase the potential for loss of pharmacologic effect of poorly absorbed, delayed-acting, and extended-release oral preparations by accelerating their transit through the intestines. They may also cause electrolyte imbalances when used chronically.

A. Irritants and stimulants

1. Senna: This agent is a widely used stimulant laxative. Taken orally, *senna* causes evacuation of the bowels within 8 to 10 hours. It also causes water and electrolyte secretion into the bowel. In combination products with a *docusate*-containing stool softener, it is useful in treating opioid-induced constipation.

2. Bisacodyl: Available as suppositories and enteric-coated tablets, *bisacodyl* is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.

3. Castor oil: This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid *castor oil* because it may stimulate uterine contractions.

B. Bulk laxatives

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and

intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by *methylcellulose*, psyllium seeds, and bran. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction.

C. Saline and osmotic laxatives

Saline cathartics, such as *magnesium citrate* and *magnesium hydroxide,* are non-absorbable salts (anions and cations) that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few hours. Electrolyte solutions containing *polyethylene glycol* (*PEG*) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. *Lactulose* is a semisynthetic disaccharide sugar that acts as an osmotic laxative. It cannot be hydrolyzed by GI enzymes. Oral doses reach the colon and are degraded by colonic bacteria into lactic, formic, and acetic acids. This increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation. *Lactulose* is also used for the treatment of hepatic encephalopathy, due to its ability to reduce ammonia levels.

D. Stool softeners (emollient laxatives or surfactants)

These include docusate sodium and docusate calcium. They may take days to become effective and are often used for prophylaxis rather than acute treatment.

E. Lubricant laxatives

Mineral oil and glycerin suppositories are lubricants and act by facilitating the passage of hard stools. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia

F. Chloride channel activators

Lubiprostone, currently the only agent in this class, works by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stools and causes little change in electrolyte balance. Lubiprostone is used in the treatment of chronic constipation, particularly because tolerance or dependency has not been associated with this drug.