Gastrointestinal and Antiemetic Drugs
drugs used to treat four common medical conditions involving the gastrointestinal (GI) tract: • 1) peptic ulcers and gastroesophageal reflux disease (GERD), • 2) chemotherapy-induced emesis, • 3) diarrhea, • 4) constipation.
TREATMENT OF PEPTIC ULCER DISEASE AND GERD

The two main causes of peptic ulcer are:
- Infection with gram-negative Helicobacter pylori
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs)
Other risk factors

1-Increased hydrochloric acid (HCl) secretion
2-Inadequate mucosal defense against gastric acid also play a role
Treatment approaches

1) eradicating the H. pylori infection,
2) reducing secretion of gastric acid with the use of PPIs or H₂-receptor antagonists, and/or
3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate*

All effective in treating peptic ulcer disease.
Antimicrobial agents

Eradication of H. pylori • results in rapid healing of active ulcers and • low recurrence rates
(less than 15% compared with 60% to • 100% per year for initial ulcers healed with acid-reducing therapy alone) •
Successful eradication of H. pylori (80% to 90%)

triple therapy consisting of a PPI combined with **amoxicillin** •

(*metronidazole* may be used in *penicillin*-allergic patients)

plus **clarithromycin** is the therapy of choice
Successful eradication of H. pylori (80% to 90%)

Quadruple therapy of •

*bismuth subsalicylat, metronidazole, •
and *tetracycline* plus a PPI

is another option. Quadruple therapy •
should be considered in areas
with high resistance to *clarithromycin*. •
H 2- antagonists and regulation of gastric acid secretion

Gastric acid secretion is stimulated by • acetylcholine, • histamine, • gastrin • binding of acetylcholine, • histamine, or gastrin results in the activation of • protein kinases, • which in turn stimulates the H+/K+-adenosine (ATPase) proton pump to secrete H ions in exchange for K ions into the lumen of the stomach
II. Drugs Used to Treat Peptic Ulcer Disease and Gastroesophageal Reflux Disease

- **Dicyclomine** blocks the cholinergic receptor.
- **Cimetidine** blocks the $H_2$-histamine receptor.
- **Misoprostol** stimulates the prostaglandin receptor.

Diagram:
- Acetylcholine activates $G_s$ and stimulates adenyl cyclase to produce cAMP, which in turn increases $Ca^{2+}$ and $K^+$.
- Histamine activates $G_s$ and adenyl cyclase to produce cAMP, increasing $Ca^{2+}$.
- Prostaglandin $E_2$ activates $G_s$ and adenyl cyclase to produce cAMP, increasing $Ca^{2+}$.
- Gastrin activates $G_s$ and adenyl cyclase to produce cAMP, increasing $Ca^{2+}$.

- **Omeprazole** blocks the proton pump.
- **Proton pump** in the parietal cell releases protons into the lumen of the stomach.
- **Protein kinase** (activated) mediates the energy cascade.
H-2 antagonist drugs

cimetidine •
ranitidine , •
famotidine •
nizatidine •

competitively blocking the binding • of histamine to \( \text{H}_2 \) receptors, these agents • reduce the secretion of gastric acid. •
Therapeutic uses

Peptic ulcers •
Acute stress ulcers •
Gastroesophageal reflux disease (GERD)
pharmacokinetics

oral administration, the H2 antagonists • distribute widely throughout the body • (including into breast milk and across the placenta) and are excreted mainly in urine.

*Cimetidine, ranitidine, and famotidine* are also available in I.V formulations

The t 1/2 of all of these agents may be increased in patients with renal dysfunction •
Adverse effects

the H₂ antagonists are well tolerated. • *cimetidine* have endocrine effects because it acts as a nonsteroidal antiandrogen. These effects include • gynecomastia • galactorrhea • Other drugs not produce the antiandrogenic and prolactin-stimulating effects of *cimetidine* • •
Adverse effects

Other CNS effects
- confusion and altered mentation occur primarily in elderly
- *cimetidine* inhibits several cytochrome P450 isoenzymes
  - interfere with the metabolism of many drugs, such as *warfarin*, *phenytoin*, and *clopidogrel*

All H₂ antagonists may reduce the efficacy of drugs that require an acidic pH for absorption, like *ketoconazole*
PPIs: Inhibitors of the H+/K+-ATPase proton pump

The PPIs bind to the H+/K+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions $\text{H}^+$ into the gastric lumen. It takes about 18 hours for the enzyme to be resynthesized.
Proton Pump Inhibitors

dexlansoprazole •
esomeprazole •
lansoprazole •
omeprazole , •
pantoprazole •
rabeprazole •

Omeprazole, esomeprazole, and •
lansoprazole are available over-the-counter for short-term treatment of GERD. •
Proton Pump Inhibitors

**Actions:** These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum, and the prodrug, a weak base, is absorbed and transported to the parietal cell.
Proton Pump Inhibitors

Therapeutic uses:

1- treatment of stress ulcer
2- prophylaxis and treatment of GERD,
3- erosive esophagitis,
4- active duodenal ulcer,
5- pathologic hypersecretory conditions example, Zollinger- Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl
Pharmacokinetics

PPIs should be taken 30 to 60 minutes before • breakfast or the largest meal of the day. • dexlansoprazole • has a dual delayed release formulation and can be taken without regard to food. • Esomeprazole, lansoprazole, and pantoprazole • are also available in I.V formulations. • plasma half-life of these agents is only a few hours, • they have a long duration of action due to covalent bonding with the H+/K+ ATPase enzyme • Metabolites of these agents are excreted in urine and feces
Adverse effects

*esomeprazole* may decrease the effectiveness of *clopidogrel* because they inhibit CYP2C19. PPIs may:

- increase the risk of fractures
- Prolonged acid suppression with PPIs (and H2 antagonists) may result in low vitamin B12 because acid is required for its absorption in a complex with *intrinsic factor*.
- Elevated gastric pH may also impair the absorption of *calcium*. 
Adverse effects

Diarrhea and •
Clostridium difficile colitis may occur in •
community patients receiving •
PPIs. Patients must be counseled to •
discontinue PPI therapy •
and contact their physician if they have •
diarrhea for several days.

Additional adverse effects may include •
hypomagnesemia and an increased incidence •
of pneumonia
Prostaglandins

Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect)

Misoprostol

analog of prostaglandin E, approved for the prevention of NSAID-induced gastric ulcers
Antacids

Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids activity also reduce pepsin
Antacids

Commonly used antacids • *aluminum hydroxide and magnesium hydroxide* [Mg(OH)$_2$]. *Calcium carbonate* • [CaCO$_3$] reacts with HCl to form CO$_2$ and CaCl$_2$.

Systemic absorption of *sodium bicarbonate* [NaHCO$_3$] can produce transient *metabolic alkalosis*. •

is not recommended for long-term use. •
Antacids

Adverse effects: •

*Aluminum hydroxide* tends to cause • constipation,

*magnesium hydroxide* tends to produce • diarrhea.

Absorption of the cations from antacids (Mg • Al, Ca) • accumulation and adverse effects may occur • in patients with renal impairment
Mucosal protective agents

**Sucralfate**: complex of *aluminum hydroxide* and sulfated sucrose

binds to positively charged groups in proteins of both normal and necrotic mucosa. creates a physical barrier that protects the ulcer from pepsin and acid.
Mucosal protective agents

Because it requires an acidic PH for activation, **sucralfate** should not be administered with **PPIs**, **H 2 antagonists**, or **antacids**.
Mucosal protective agents

**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.
DRUGS USED TO CONTROL NAUSEA AND VOMITING

- motion sickness
- pregnancy
- Hepatitis
- Chemotherapy
- young patients and women are more susceptible than older patients and men,
- and 10% to 40% of patients experience nausea and/or vomiting in anticipation of chemotherapy
DRUGS USED TO CONTROL NAUSEA AND VOMITING

Mechanisms that trigger vomiting •

Two brainstem sites have key roles in the vomiting reflex pathway. •

Chemoreceptor trigger zone (CTZ) is located in the area postrema. •

It is outside the blood–brain barrier. •

It can respond directly to chemical stimuli in the blood or CSF fluid •
DRUGS USED TO CONTROL NAUSEA AND VOMITING

second important site, the vomiting center •
is located in the lateral reticular formation of •
the medulla
coordinates the motor mechanisms of •
vomiting. The vomiting center also responds •
to afferent input from the vestibular system •
And the periphery (pharynx and GI tract), and •
higher brainstem and cortical structures.
The vestibular system functions mainly in •
motion sickness.
Emetic actions of chemotherapeutic agents

Chemotherapeutic agents can directly activate the medullary CTZ or Vomiting Center

Several neuroreceptors, including D2 receptor and serotonin 5-HT3 receptor

Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and by releasing serotonin from enterochromaffin cells of the small intestine
Antiemetic drugs

1. Phenothiazines •
   *prochlorperazine* •
   is a dopamine (D$_2$) receptor blocking •
   it effective against low or moderately emetogenic chemotherapeutic agents •
   example, *fluorouracil* and *doxorubicin* •
Antiemetic drugs

2. 5-HT₃ receptor blockers •

ondansetron •

granisetron •

palonosetron •

dolasetron •

selectively block 5-HT₃ receptors in the periphery (visceral vagal afferent fibers) and in the brain (CTZ).
Antiemetic drugs

these drugs are important in treating • emesis linked with chemotherapy, because of their longer duration of action and superior efficacy
.Electrocardiographic changes, such as a • prolonged QT interval, occur with
dolasetron and high dose of ondansetron.
Antiemetic drugs

3. Substituted benzamides •

*Metoclopramide* •
dopamine D$_2$ receptors antagonist •
it effective at high doses against the emetogenic *cisplatin*, preventing emesis in 30% to 40% of patients •
Antidopaminergic side effects, •
including *extrapyramidal symptoms*, limit •
long-term high-dose use
Antiemetic drugs

4. Butyrophenones: •

*Droperidol and Haloperidol* •
.a potent $D_2$ (dopamine receptor) antagonist •
The butyrophenones •
are moderately effective antiemetics •
used most often for sedation in endoscopy •
and surgery, in combination with opioids or
benzodiazepines. •
Antiemetic drugs

side effect of Droperidol • may prolong the QT interval • lengthened QT interval is a marker • for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.
Antiemetic drugs

5. Benzodiazepines •

*Alprazolam and Lorazepam* •
effects may be due to their sedative, •
anxiolytic, and amnesic properties
Concomitant use of alcohol should •
be avoided due to additive CNS depressant •
effects.
Antiemetic drugs

6. Corticosteroids: •

Methylprednisolone •

Dexamethasone  •

antiemetic mechanism is not known, but it may involve blockade of prostaglandins
Antiemetic drugs

7. Substance P/neurokinin-1 receptor blocker:

*Aprepitant* •

targets the *neurokinin receptor* in the brain and blocks the actions of the natural substance. Usually administered orally with *dexamethasone and 5-HT 3 antagonist*. 
Combination regimens

Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity. *Dexamethasone,* increase antiemetic activity when given with high-dose metoclopramide, a 5-HT3 antagonist, phenothiazine, butyrophenone, or a benzodiazepine.

Antihistamines, such as *diphenhydramine,* are often in combination with high-dose metoclopramide to reduce extrapyramidal reactions or with corticosteroids to counter *metoclopramide induced* diarrhea.
ANTIDIARRHEALS

Increased motility of the GI tract and decreased absorption of fluid are major factors in diarrhea.

Antidiarrheal drugs include antimotility agents, adsorbents drugs, and drugs that modify fluid and electrolyte transport.
ANTIDIARRHEALS

Antimotility agents •

*diphenoxylate* •

*loperamide* •

activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine (Ach) release and decrease peristalsis.
ANTIDIARRHEALS

Adsorbents •

*aluminum hydroxide* •
*methylcellulose* •

act by adsorbing (coating) intestinal toxins • or microorganisms

And / or by coating or protecting the intestinal mucosa.
ANTIDIARRHEALS

Agents that modify fluid and electrolyte transport

*Bismuth subsaliclylate* •
decreases fluid secretion in the bowel •
LAXATIVES

A. Irritants and stimulants •

Senna •

*senna* causes evacuation of the bowels within 8 to 10 hours. It also causes secretion into the bowel water and electrolyte

Bisacodyl •

a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.

Castor oil •

broken down in the small intestine to *ricinoleic acid*, which is very irritating to the stomach and promptly increases peristalsis.
LAXATIVES

B. Bulk laxatives •
hydrophilic colloids •
methylcellulose, •
psyllium seeds, •
bran •

They form gels in the large intestine, •
causing water retention and intestinal •
distension, thereby increasing peristaltic activity.
LAXATIVES

C. Saline and osmotic laxatives •

* magnesium citrate •
and * magnesium hydroxide, •
are nonabsorbable salts •

* polyethylene glycol •

* Lactulose •
LAXATIVES

D. Stool softeners (emollient laxatives or surfactants)

- docusate sodium
- docusate calcium
LAXATIVES

E. Lubricant laxatives •

Mineral oil and glycerin •

F. Chloride channel activators •

Lubiprostone •

activating chloride channels to increase fluid secretion in the intestinal lumen.