After the student finishes studying this chapter, he will be able to:

- Classify the drugs used for hyperacidity, such as H2-receptor antagonists, proton pump inhibitors, antacids, etc., and the drugs used as antiemetic.
- Illustrate the mechanisms of actions of these drugs.
- Numerate the remarkable side effects and drug-drug interactions of these studied medications.
- Clarify the remarkable clinical aspects of these drugs indications.
- Explain the most remarkable points regarding the pharmacokinetic and pharmacodynamic parameters of these drugs.
The two main causes of peptic ulcer disease are:

- Infection with gram-negative *Helicobacter pylori*, also:
- The use of nonsteroidal anti-inflammatory drugs (NSAIDs).
- Increased hydrochloric acid (HCl) secretion.
- Inadequate mucosal defense against gastric acid.

Treatment approaches include:

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.
Gastrointestinal and Antiemetic Drugs

<table>
<thead>
<tr>
<th>ANTIMICROBIAL AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin  GENERIC ONLY</td>
</tr>
<tr>
<td>Bismuth compounds  PEPTO-BISMOL,</td>
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<tr>
<td>KAOPECTATE</td>
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<tr>
<td>Clarithromycin  BIAxin</td>
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<tr>
<td>Metronidazole  FLAGYL</td>
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<tr>
<td>Tetracycline  GENERIC ONLY</td>
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<thead>
<tr>
<th>H₂ – HISTAMINE RECEPTOR BLOCKERS</th>
</tr>
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<tbody>
<tr>
<td>Cimetidine  TAGAMET</td>
</tr>
<tr>
<td>Famotidine  PEPCID</td>
</tr>
<tr>
<td>Nizatidine  AXID</td>
</tr>
<tr>
<td>Ranitidine  ZANTAC</td>
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<tr>
<th>PROTON PUMP INHIBITORS</th>
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<tbody>
<tr>
<td>Dexamethasone  DEXILANT</td>
</tr>
<tr>
<td>Esomeprazole  NEXIUM</td>
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<tr>
<td>Lansoprazole  PREVACID</td>
</tr>
<tr>
<td>Omeprazole  PRILOSEC</td>
</tr>
<tr>
<td>Pantoprazole  PROTONIX</td>
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<tr>
<td>Rabeprazole  ACIPHEX</td>
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<tr>
<th>PROSTAGLANDINS</th>
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<tbody>
<tr>
<td>Misoprostol  CYTOTEC</td>
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<tr>
<th>ANTUSCARINIC AGENTS</th>
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<tbody>
<tr>
<td>Dicyclomine  BENTYL</td>
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<tr>
<th>ANTACIDS</th>
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<tbody>
<tr>
<td>Aluminum hydroxide  GENERIC ONLY</td>
</tr>
<tr>
<td>Calcium carbonate  TUMS</td>
</tr>
<tr>
<td>Magnesium hydroxide  MILK OF MAGNESIA</td>
</tr>
<tr>
<td>Sodium bicarbonate  ALKA-SLTZER</td>
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<tr>
<th>MUCOSAL PROTECTIVE AGENTS</th>
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<tbody>
<tr>
<td>Bismuth subsalicylate  PEPTO-BISMOL</td>
</tr>
<tr>
<td>Sucralfate  CARAFATE</td>
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</tbody>
</table>
AGENTS THAT REDUCE INTRAGASTRIC ACIDITY:

PHYSIOLOGY OF ACID SECRETION:

• The parietal cell contains receptors for gastrin (CCK-B), histamine (H₂), and acetylcholine (muscarinic, M₃).

Cholecystokinin- B receptors

- Dicyclomine blocks the cholinergic receptor.
- Ranitidine blocks the H₂-histamine receptor.
- Misoprostol stimulates the prostaglandin receptor.
- Omeprazole blocks proton pump.

Protein kinase (activated)

Gastric acid

LUMEN OF STOMACH

Proton pump

PARIELT CELL
Antimicrobial agents:

- Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with *H. pylori* require antimicrobial treatment.

- Eradication of *H. pylori* with various combinations of antimicrobial drugs results in rapid healing of active ulcers and low recurrence rates (less than 15%, compared with 60% to 100% per year for ulcers healed with acid-reducing therapy alone).

- Currently, quadruple therapy of bismuth subsalicylate, metronidazole, and tetracycline plus a PPI is a recommended first-line option.

- **Bismuth subsalicylate:** an antacid medication used to treat temporary discomforts of the stomach and gastrointestinal tract, such as diarrhea, indigestion, heartburn and nausea {90% eradication rate}. 

Gastrointestinal and Antiemetic Drugs

Pharmacology-2/Dr. Y. Abusamra
• **Triple therapy:** consists of a PPI combined with amoxicillin (metronidazole may be used in penicillin-allergic patients) plus clarithromycin is a preferred treatment when rates of clarithromycin resistance are low and the patient has no prior exposure to macrolide antibiotics.

**H2 receptor antagonists:**

- Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin.
- The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H+/K+-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K+ into the lumen of the stomach.
• By competitively blocking the binding of histamine to H2 receptors, these agents reduce the secretion of gastric acid.

• The four drugs used in the US {cimetidine, famotidine, nizatidine, and ranitidine} inhibit basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately 70%.

• Cimetidine was the first H2 receptor antagonist.

• However, its utility is limited by its adverse effect profile and drug–drug interactions.

• They are reversible competitive inhibitors of H2 receptors.

• Their use has decreased with the advent (rising) of PPIs.
• All four agents are equally effective in promoting the healing of duodenal and gastric ulcers.

• Recurrence is common if *H. pylori* is present and the patient is treated with these agents alone.

• Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than do H2 receptor antagonists.

• PPIs are also used for acute stress ulcers.

• **Acute stress ulceration** often occurs in seriously ill patients who have an acute pathophysiological disturbance, such as hypotension, hypoxia, sepsis, uremia {high urea levels in the blood} or ischemia {restriction in blood supply to tissues}. 
GASTROESOPHAGEAL REFLUX DISEASE – (GERD):

- H2 receptor antagonists are effective for the treatment of heartburn or GERD.
- H2 receptor antagonists act by decreasing acid secretion; therefore, they may not relieve symptoms of heartburn for up to 45 minutes.
- Antacids more quickly and efficiently neutralize stomach acid, but their action is short lived.
- For these reasons, PPIs are now used preferentially in the treatment of GERD, especially for patients with severe and frequent heartburn.
Pharmacokinetics:

- After oral administration, the H2 receptor antagonists are rapidly absorbed.
- They distribute widely throughout the body (including into breast milk and across the placenta).
- They are excreted mainly in the urine.
- Cimetidine, ranitidine, and famotidine are also available in intravenous formulations.
- The half-life of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.
- Cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism resulting in a bioavailability of approximately 50%.
- Nizatidine has little first-pass metabolism.
Gastrointestinal and Antiemetic Drugs

- They are highly **selective** and do not affect H1 or H3 receptors (cognition disorders, modulate the release of other NT’s in the brain; histamine release in the CNS triggers excitatory NT’s release such as glutamate and acetylcholine by stimulation of H1 receptors in the cortex).
- H2 antagonists **reduce** acid secretion stimulated by histamine as well as by gastrin and cholinomimetic (cholinergic) agents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
<th>Dose to Achieve &gt; 50% Acid Inhibition for 10 Hours</th>
<th>Usual Dose for Acute Duodenal or Gastric Ulcer</th>
<th>Usual Dose for Gastroesophageal Reflux Disease</th>
<th>Usual Dose for Prevention of Stress-Related Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>1</td>
<td>400–800 mg</td>
<td>800 mg HS or 400 mg bid</td>
<td>800 mg bid</td>
<td>50 mg/h continuous infusion</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>4–10</td>
<td>150 mg</td>
<td>300 mg HS or 150 mg bid</td>
<td>150 mg bid</td>
<td>6.25 mg/h continuous infusion or 50 mg IV every 6–8 h</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>4–10</td>
<td>150 mg</td>
<td>300 mg HS or 150 mg bid</td>
<td>150 mg bid</td>
<td>Not available</td>
</tr>
<tr>
<td>Famotidine</td>
<td>20–50</td>
<td>20 mg</td>
<td>40 mg HS or 20 mg bid</td>
<td>20 mg bid</td>
<td>20 mg IV every 12 h</td>
</tr>
</tbody>
</table>

bid, twice daily; HS, bedtime.
H2 antagonists are especially effective at inhibiting nocturnal acid secretion (which depends largely on histamine).

They have a modest impact on meal-stimulated acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine).

These drugs are commonly given twice daily.

**CLINICAL USES:**

1. Gastroesophageal reflux disease (GERD):
   - Patients with infrequent heartburn or dyspepsia (fewer than three times per week) may take either antacids or intermittent H2 antagonists.
   - H2 antagonists may be taken prophylactically before meals in an effort to reduce the likelihood of heartburn.
Frequent heartburn is better treated with twice-daily H2 antagonists or PPIs.

2. Peptic ulcer disease:

- PPIs have largely replaced H2 antagonists in the treatment of acute peptic ulcer disease. Nevertheless, H2 antagonists are still sometimes used.

- **Nocturnal** acid suppression by H2 antagonists affords effective ulcer healing in most patients with uncomplicated gastric and duodenal ulcers (Once daily at bed time).

- For patients with ulcers caused by aspirin or other NSAIDs, the NSAID should be discontinued.

- If the NSAID must be continued for clinical reasons despite active ulceration, a PPI should be given instead of an H2 antagonist to more reliably promote ulcer healing.

- For patients with acute peptic ulcers caused by *H pylori*, H2 antagonists no longer play a significant therapeutic role.
3. Dyspepsia:

- They are sometimes prescribed in dyspepsia (indigestion; discomfort, pain nausea and bloating), yet the results compared with placebo are not that convincing.

4. Prevention of bleeding from stress-related gastritis:

- The agents that increase intragastric pH (H₂ antagonists or PPIs) reduce the incidence of clinically significant bleeding and should be administered to patients who are at high risk of gastrointestinal bleeding.

- For patients who are unable to receive enteral medications, either intravenous H₂ antagonists or PPIs may be administered.

- Continuous infusion of H₂ antagonists is preferred over bolus infusions.
Adverse effects:

In general, the H2 receptor antagonists are well tolerated (very safe).

- **Cimetidine** can have **endocrine** effects, such as **gynecomastia** and **impotence** in men, and **galactorrhea** (continuous release of milk) in women because it:
  - Inhibits binding of **dihydrotestosterone** to androgen receptors.
  - Inhibits metabolism of **estradiol**.
  - Increases serum **prolactin** levels.

  These effects are specific to **cimetidine**; don’t occur with other H2-antagonists.

- **CNS-related**: such as confusion and altered mentation occur primarily in elderly patients and after intravenous administration.
• H2 receptor antagonists may **reduce the efficacy** of drugs that require an acidic environment for absorption, such as ketoconazole {well dissolved in acidic media as it is a weak base}.

• **Cimetidine** inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many drugs, such as warfarin, phenytoin, and clopidogrel.

• H2 receptor blockers should **not** be administered to pregnant women unless necessary {**don’t have known harmful effects on the fetus**}.

• Secreted into breast milk; can affect nursing infants.

• **Rapid infusion** can **block cardiac H2** receptors; hypotension and bradycardia. Infuse over 30 minutes. (**stimulation**: increase in inotropic and chronotropic effects).
PROTON-PUMP INHIBITORS (PPIs):

• The PPIs bind to the H+/K+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen.

• The membrane-bound proton pump is the final step in the secretion of gastric acid; controls acid secretion apart from the source or the mechanism of the acid secretion.

• The available PPIs include:
  - Dexlansoprazole.
  - Esomeprazole.
  - Lansoprazole.
  - Omeprazole.
  - Pantoprazole.
  - Rabeprazole.
• 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 (unionized fraction) and transported to the parietal cell. There, it is converted to the active drug (sulfenamide; an isomer to omeprazole) and forms a stable covalent bond with the H⁺/K⁺-ATPase enzyme [see the figure, next slide].

• It takes about 18 hours for the enzyme to be resynthesized, and acid secretion is inhibited during this time.

• An oral product containing omeprazole combined with sodium bicarbonate for faster absorption [in the alkaline medium] and to protect the non-enteric coated drug from degradation in the acidic medium.
Gastrointestinal and Antiemetic Drugs

Blood (pH 7.4) → Cytosol (pH 7.1) → Secretory Canaliculus (pH < 2.0)

Omeprazole ↔ Omeprazole → Omeprazole^+ → Sulfenamide^+ → S-S-Sulfenamide

\[ \text{H}^+ / \text{K}^+ - \text{ATPase} \]

Enzyme-SH → S-enzyme
Therapeutic uses:

- The PPIs are superior to the H2 antagonists in suppressing acid production and healing ulcers. Thus,
  - They are the preferred drugs for the {1} treatment of GERD, {2} erosive esophagitis, {3} active duodenal ulcer, and pathologic hypersecretory conditions such as {4} Zollinger-Ellison syndrome [GASTRINOMA: tumor in the duodenum or pancreas; secretes large amounts of GASTRIN; hyperacidity].
  - PPIs {5} reduce the risk of bleeding from ulcers caused by aspirin and other NSAIDs and may be used for {6} prevention or treatment of NSAID-induced ulcers.
  - PPIs are also used for {7} stress ulcer prophylaxis and management.
  - PPIs are {8} combined with antimicrobial regimens used to eradicate H. pylori.
Pharmacokinetics:

- 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.
- Dexlansoprazole has a dual delayed-release formulation and can be taken without regard to food. {2 different sets of enteric-coated granules, see the figure on the next slide}.
- Esomeprazole, lansoprazole, and pantoprazole are available in intravenous formulations.
- Although the 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.
Dual-delayed release of dexlanzoprazole

Immediate release enteric pellets
(Dissolve > pH 5.5)

Delayed release enteric pellets
(Dissolve > pH 6-7)
ADVERSE EFFECTS:

- The PPIs are generally well tolerated.

- Omeprazole and esomeprazole may **(1) decrease the effectiveness of** clopidogrel [anti-platelet; it has to be activated] because they inhibit CYP2C19 and prevent the conversion of clopidogrel to its active metabolite.

- In general, concomitant use of these PPIs with clopidogrel is **NOT recommended**.

- However, if PPIs have to be prescribed to patients taking clopidogrel, agents with **minimal CYP2C19 inhibition** (pantoprazole or rabeprazole) may be preferred (3-study report).

- PPIs may increase the risk of **(2) fractures**, particularly if the duration of use is **1 year** or greater.
Prolonged acid suppression with PPIs (and H2 receptor antagonists) may result in **low vitamin B12** because acid is required for its absorption in a complex with intrinsic factor [a glycoprotein produced by the parietal cells & is necessary for Vit B12 absorption].

Elevated gastric pH may also **impair the absorption of calcium carbonate**.

**Calcium citrate** is an effective option for calcium supplementation in patients on acid suppressive therapy, since absorption of the citrate salt is not affected by gastric pH.

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

**Hypomagnesenaemia** {↓Mg}.

Increased incidence of **pneumonia**.
Prostaglandins:

- Their cytoprotective effects include:
  - Inhibition of acid secretion.
  - Stimulation of mucus and bicarbonate secretion.

- A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. Misoprostol, an analog of prostaglandin E1, is approved for the prevention of NSAID-induced gastric ulcers.

- Prophylactic use of misoprostol should be considered in patients who take 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** is the most common adverse effect and limits the use of this agent.

• **Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.**

**Antacids:**

• Antacids are **(1) weak bases** that react with gastric acid to form water and a salt to diminish gastric acidity.

• Because pepsin (a proteolytic enzyme; **mucosal damage**) is **inactive** at a **pH greater than 4**, **(2) antacids also reduce pepsin activity.**

• Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, and palatability.
Commonly used antacids are combinations of salts of \textbf{ALUMINUM AND MAGNESIUM}, such as aluminum hydroxide and magnesium hydroxide [Mg(OH)$_2$].

\textbf{Calcium carbonate} [CaCO$_3$] reacts with HCl to form CO$_2$ and CaCl$_2$ and is also a \textbf{commonly used} preparation.

Systemic absorption of \textbf{SODIUM BICARBONATE} \textbf{transient metabolic alkalosis} and produce a \textbf{significant sodium load}. Therefore, this antacid is \textbf{not recommended}.

**Therapeutic uses:**

- Antacids are used for \textbf{symptomatic relief} of \textbf{peptic ulcer} disease, \textbf{heartburn}, and \textbf{GERD}.
- They should be administered \textbf{after meals} for maximum effectiveness.
- \textbf{Calcium carbonate supplements} preparations are also used as \textbf{calcium} for the prevention of osteoporosis.
Adverse effects:

- **Aluminum hydroxide** tends to cause **constipation**, whereas **magnesium hydroxide** tends to produce **diarrhea**, thus, preparations that combine these agents aid in normalizing bowel function.

- Accumulation and adverse effects may occur in patients with **renal impairment**.

**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.
1. Sucralfate:

- This complex of **aluminum hydroxide** and **sulfated sucrose** binds to positively charged groups in proteins of both normal and necrotic mucosa forming complex gels which act as 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.
  - Drug–drug interactions.
  - The availability of more effective agents.

- Because it requires an **acidic pH for activation**, sucralfate should **not** be administered with **PPIs**, **H2 antagonists**, or **antacids**.

- Sucralfate is well tolerated {constipation due to Al}.

- It can bind to other drugs and **interfere with their absorption**.
2. Bismuth subsalicylate:
• It is a component of quadruple therapy to heal *H. pylori*-related peptic ulcers.
• In addition to its {1} antimicrobial actions, {2} it inhibits the activity of pepsin, {3} increases secretion of mucus, {4} and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.

ADVERSE EFFECTS:
• All bismuth formulations have excellent safety profiles.
  ○ Bismuth causes harmless blackening of the stool, which may be confused with gastrointestinal bleeding.
  ○ Harmless darkening of the tongue.
  ○ Prolonged usage of some bismuth compounds may rarely lead to bismuth toxicity, resulting in encephalopathy (ataxia, headaches, confusion, seizures).
ANTIEMETIC AGENTS:

- Nausea and vomiting may be manifestations of a wide variety of conditions, including adverse effects from medications; systemic disorders or infections; pregnancy; vestibular dysfunction; central nervous system infection or increased pressure; peritonitis; hepatobiliary disorders; radiation or chemotherapy; and gastrointestinal obstruction, dysmotility (related to the muscles of the GIT), or infections.

- Uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

- 10% to 40% of patients experience nausea and/or vomiting in anticipation of chemotherapy (anticipatory vomiting).

- Anticipatory vomiting: triggered by talking or thinking about the medication.
Pathophysiology:

- **Vomiting center**, brain stem neuronal region, coordinates the complex act of vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers.

- High concentrations of **muscarinic M1**, **histamine H1**, **neurokinin 1 (NK1)**, and **serotonin 5-HT3** receptors have been identified in the **vomiting center**.

- There are **four** important sources of afferent input to the vomiting center:
  1. The **chemoreceptor trigger zone**:
     - Outside the BBB.
     - D2 receptors, opioid receptors, 5-HT3 and NK1 receptors.
Gastrointestinal and Antiemetic Drugs

**Central nervous system**
- Cortex
- Thalamus
- Hypothalamus
- Meninges

**Vestibular system**
- H1 receptor?
- M1 receptor

**Chemoreceptor trigger zone (area postrema)**
- Chemoreceptors
- D2 receptor
- NK1 receptor?
- (5-HT3 receptor)

**Gastrointestinal tract and heart**
- Mechanoreceptors
- Chemoreceptors
- 5-HT3 receptor

**Chemoreceptor trigger zone**
- Cranial nerve IX or X
- Medulla oblongata
- Parasympathetic and motor efferent activity

**Vomiting center (nucleus of tractus solitarius)**
- H1 receptor
- M1 receptor
- NK1 receptor?
- (5-HT3 receptor)

**Pharmacology**

**Abbreviations:**
- NK: neurokinin
- M: muscarine
- D: dopamine
- 5-HT: serotonin
2. The **vestibular system** {of the inner ear}:

- A sensory system that is responsible for providing the brain with information about **motion**, **head position**, and **spatial orientation**.
- Important in **motion sickness** via cranial nerve VIII.
- It is rich in **muscarinic M1** and **histamine H1** receptors.

3. **Vagal and spinal afferent nerves**:

- From the gastrointestinal tract.
- Rich in **5-HT3** receptors.
- Irritation of the gastrointestinal mucosa by **chemotherapy**, **radiation** therapy, **distention**, or acute **infectious gastroenteritis** leads to release of mucosal **serotonin** and activation of these receptors.
4. The central nervous system:

- Vomiting due to psychiatric disorders, stress, and anticipatory vomiting prior to cancer chemotherapy.

- Due to the complexity of the mechanisms involved in emesis, the antiemetics represent a variety of classes.

**CLASSES OF THE ANTIEMETIC AGENTS:**

1. Phenothiazines:

- Such as prochlorperazine.
- Act by blocking dopamine receptors in the CTZ.
- Prochlorperazine is effective against low or moderately emetogenic chemotherapeutic agents (e.g. fluorouracil and doxorubicin).
2. **5-HT3 receptor blockers:**

- The 5-HT3 receptor antagonists include dolasetron, granisetron, ondansetron, and palonosetron.
- They are important in treating chemotherapy-induced nausea and vomiting (CINV), because of their superior **efficacy** and **longer duration of action**.
- These drugs can be administered as a single dose prior to chemotherapy (i.v. or orally).
They are efficacious against all grades of emetogenic therapy.

**Ondansetron** and **granisetron** prevent emesis in 50% to 60% of **cisplatin**-treated patients.

Extensively metabolized by the liver, excreted in the urine.

**QT prolongation** can occur with high doses of ondansetron and dolasetron.

**Pharmacology**

**QT prolongation**: is a measure of delayed ventricular repolarisation, which means the heart muscle takes longer than normal to recharge between beats.

Excessive QT prolongation can trigger **tachycardias** such as Torsades de Pointes (TdP) {ventricular tachycardia}. 
3. Substituted benzamides:

- **Metoclopramide**, is effective at high doses against the emetogenic cisplatin.
- Metoclopramide accomplishes this through **inhibition of dopamine in the CTZ {blocking D2 receptors}**.
- **Antidopaminergic adverse effects**, including extrapyramidal symptoms [Spasm of tongue, neck, face and back / tremors, heavy gait / repetitive motion and agitation] limit long-term and high-dose use.
- Metoclopramide **enhances gastric motility** and is useful for patients with **gastroparesis** [motility is slowed down or doesn't work at all, preventing the stomach from emptying properly].
4. Butyrophenones:

- **Droperidol** and **haloperidol** act by **blocking dopamine receptors**.
- The butyrophenones are **moderately effective antiemetics**.
- Droperidol had been used most often for **sedation in endoscopy and surgery**, usually in combination with **opioids** or **benzodiazepines**.
- However, it may **prolong the QT-interval** and should be reserved for patients with inadequate response to other agents.

5. Benzodiazepines:

- The antiemetic potency of **lorazepam** and **alprazolam** is **LOW**.
- Their beneficial effects may be due to their **SEDATIVE**, **ANXIOLYTIC**, and **AMNESTIC** properties.
6. Corticosteroids:

- **Dexamethasone** and **methylprednisolone**, used alone, are effective against **mildly to moderately emetogenic chemotherapy**.
- Most frequently, they are used **in combination with** other agents.
- Their antiemetic mechanism is not known, but **it may involve blockade of prostaglandins**.

7. Substance P/neurokinin-1 receptor antagonists:

- It is a neuropeptide (11 amino acids), acting as a NT and as a neuromodulator.
- **Aprepitant**, **netupitant** and **rolapitant** target the **neurokinin receptor** in the vomiting center and block the actions of **substance P**, {that is related to **neurokinin A = substance K**}. 

Pharmacology-2/Dr. Y. Abusamra
• **Fosaprepitant** is a prodrug of **aprepitant** that is administered intravenously.

• These oral agents are indicated for **highly or moderately** emetogenic chemotherapy regimens.

• They are usually administered with **dexamethasone** and a **5-HT3 antagonist**.

• Unlike most 5-HT3 antagonists, these agents are **effective** for the **delayed** phase of CINV, which occurs 24 hours or more after chemotherapy. {**CINV**: chemotherapy-induced nausea and vomiting}

• Aprepitant and rolapitant undergo hepatic metabolism, primarily by CYP3A4.

• Coadministration with strong **inhibitors** or **inducers** of CYP3A4 (for example, **clarithromycin** or **St. John’s wort**, respectively) should be avoided.
Aprepitant is an inducer of CYP3A4 and CYP2C9, and it also exhibits dose-dependent inhibition of CYP3A4.

Rolapitant is a moderate inhibitor of CYP2D6.

Adverse Effects:
- Fatigue, diarrhea, abdominal pain, and hiccups [an involuntary spasm of the diaphragm and respiratory organs, with a sudden closure of the glottis and a characteristic sound like that of a cough].

Combinations of antiemetic agents aim to:
1. Increase efficacy.
2. Decrease toxicity and side effects.
Gonadal hormones and inhibitors
REFERENCES:

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