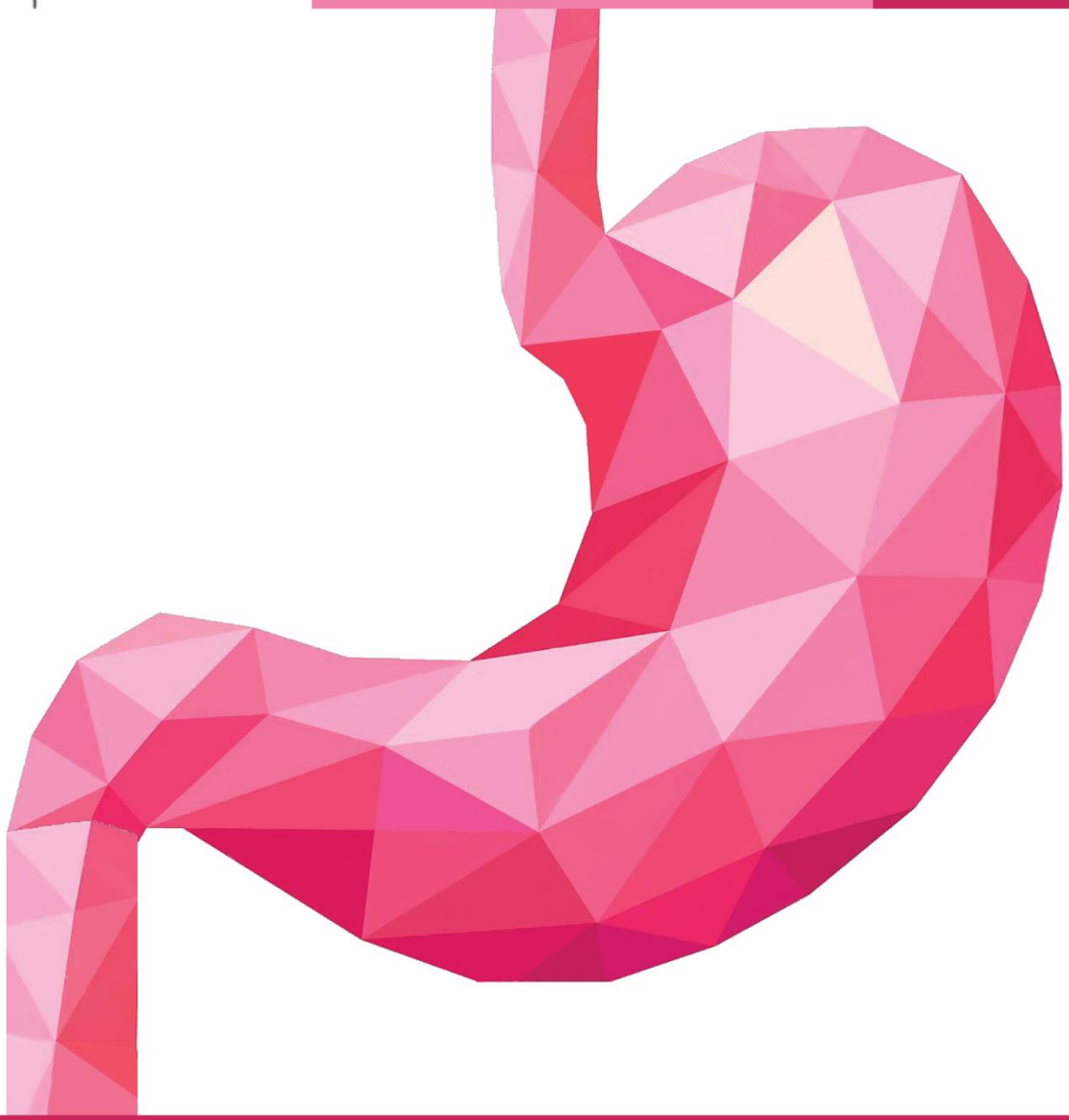
# GIS 4

## PHARMACOLOGY

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# Anti-diarrheal Agents

Diarrhea causes loss of fluids and electrolytes, and it's particularly dangerous in children, yet we have to be careful while using the antidiarrheal agents, because we first have to know the underlying conditions for their uses, for example antidiarrheal agents are **contraindicated** in patients suffering from **bloody diarrhea**, **high fever** or **systemic toxicity** because of the risk of worsening the underlying condition.

- Usually, antidiarrheal drugs are used to control ***chronic diarrhea*** caused by irritable bowel syndrome (IBS) or inflammatory bowel disease.

## *i. Opioid Agonists*

We know that opioids, such as morphine, cause constipation. Based on that, they can be used as **antidiarrheal agents**. For instance, codeine is an opioid which is used for treating diarrhea. Opioids also increase colonic transit time, and this allows more water to be absorbed. As a result, feces become less watery (more solid). They also decrease mass colonic movements.

- The opioids effects on the CNS and their potential for causing addiction limit their usefulness as antidiarrheal agents.

Some of the opioids:

1. Loperamide: It doesn't cross the BBB, so it doesn't have any central effects. In other words, it doesn't cause **addiction** or **analgesia**.

2. Diphenoxylate: It doesn't have analgesic properties at standard doses, yet it can be used to treat diarrhea. However, at higher doses, it has CNS effects. This drug can also cause *dependence*.

Commercial preparations contain small amounts of *atropine* and low doses of *diphenoxylate*, forming a combination known as **Lomotil.** This drug can stop any form of diarrhea.

## *ii. Bile Salt Binding Resins*

Such as Cholestyramine, Colestipol and Colesevelam.

- Malabsorption of bile salts cause diarrhea, and this usually happens in Crohn's disease or after surgical resection. These drugs bind to bile salts and decrease the diarrhea caused by excess fecal bile acids.

Side-effects include bloating, flatulence, constipation and fecal impaction.

- **Cholestyramine** and **Colestipol** reduce the absorption of drugs and fats, but **Colesevelam** doesn't.

***Before talking about Octreotide, let's talk a little about somatostatins: (this is not written in our slides, but is included in the slides of the video)***

- **Somatostatin** is a hormone, an A14 amino acid peptide released in the GIT, pancreas as well as from the hypothalamus. It has so many actions such as:

1. *It inhibits the release of many hormones (gastrin, cholecystokinin, glucagon, growth hormone, insulin, secretin pancreatic polypeptide, vasoactive intestinal peptide and 5-HT (Serotonin or 5-hydroxytryptamine).*
2. *Reduces intestinal fluid and pancreatic secretions.*
3. *Slows GIT motility and gallbladder contraction.*
4. *Contracts blood vessels*
5. *Inhibits secretion of some anterior pituitary hormones.*

### *iii.* ***Octreotide***

- A synthetic octapeptide with actions similar to somatostatin.

**Clinical Uses** of Octreotide:

1. Inhibition of endocrine tumor effects like z and VIPoma (neuroendocrine tumors that secrete vasoactive intestinal polypeptide (VIP)), and can cause secretory diarrhea, flushing and wheezing.
2. Stop diarrhea due to vagotomy or dumping syndrome (ingested foods bypass the stomach too rapidly) or short bowel syndrome and AIDS.
3. To stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma (a disease affecting the skin and other organs that is one of the autoimmune rheumatic diseases)
4. It inhibits pancreatic secretion, so it's used in patients with pancreatic fistula which is a leakage of pancreatic secretions from damaged pancreatic ducts.
5. Treatment of pituitary tumors like acromegaly, which is caused by the excessive secretion of growth hormone. This tumor can be treated by somatostatin (analogues) and octreotide by inhibiting the secretion of Growth Hormone.
6. Sometimes used in gastrointestinal bleeding.

***Adverse effects*** *include:*

1. Impaired pancreatic secretion may cause **steatorrhea** (excessive fats in the fecal mass), which can lead to fat-soluble vitamin deficiency.
2. Nausea, abdominal pain, flatulence, and diarrhea.
3. Formation of sludge or **gallstones**, because of inhibition of gallbladder contractility and fat absorption.
4. Hyper or hypoglycemia due to hormonal imbalance which affects insulin secretion.
5. Hypothyroidism.
6. Bradycardia.

# Drugs Used in the Treatment of Irritable Bowel Syndrome

- **IBS** is an *idiopathic chronic, relapsing (comes and goes) disorder* characterized by: Abdominal discomfort, abdominal pain, bloating, distention, or cramps with alterations in bowel habits. Diarrhea, constipation, or both might also take place.
  - ➢ Pharmacologic therapies for IBS are directed *at relieving abdominal pain & discomfort and improving bowel function.*

## *i. Antispasmodics (Anticholinergics)*

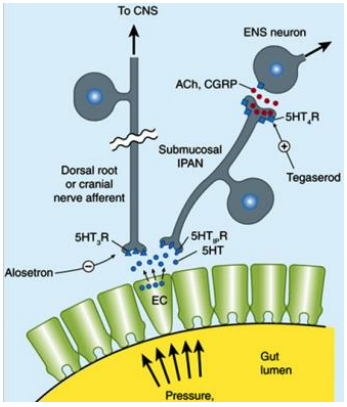
Such as **1.**Dicyclomine and **2.**Hyoscyamine: are used to relieve the spasm or abdominal pain, although they are not very effective (their efficacy for relief of abdominal symptoms has never been convincingly demonstrated. Low doses cause minimal autonomic effects & don't produce efficacy to stop the spasm).

- ➢ They are only effective if were given in high doses, but when so, side effects (anticholinergic effects) might occur. These effects include dry mouth, visual disturbances, urinary retention, and constipation. *For these reasons, antispasmodics are infrequently used.*
- They block muscarinic receptors in the enteric plexus and on smooth muscle.

*(The Alosteron and Prucalopride part wasn't explained due to an error in the video)*

**3.** Alosetron

- Potent & selective antagonist of the 5-HT3 receptor
- ➢ Rapidly absorbed, half-life of 1.5h, but has a much longer duration of effect. **Restricted to women with severe diarrhea-predominant IBS not responding to conventional therapies.**
- ➢ **Its efficacy in men has not been established**.




**4.** Prucalopride: high-affinity 5-HT4 agonist.

- No cardiovascular toxicity.
- Used for the treatment of chronic constipation in women.

## *ii. Chloride Channel Activator*

Chloride channels are critical to the digestive process because they promote fluid to release into the intestines.

**1.** Lubiprostone**:** a **PG analog** stimulates type 2 chloride channel (ClC-2) in the small intestine & this increases liquid secretion in the intestine, which stimulates intestinal motility & bowel movement within 24 hours of taking one dose.

- Used in the treatment of chronic constipation. Approved for the treatment of women with IBS with predominant constipation. Its efficacy for men with IBS is unproven. Should be avoided in women of child-bearing age.
- Causes nausea (in 30% patients) due to delayed gastric emptying.

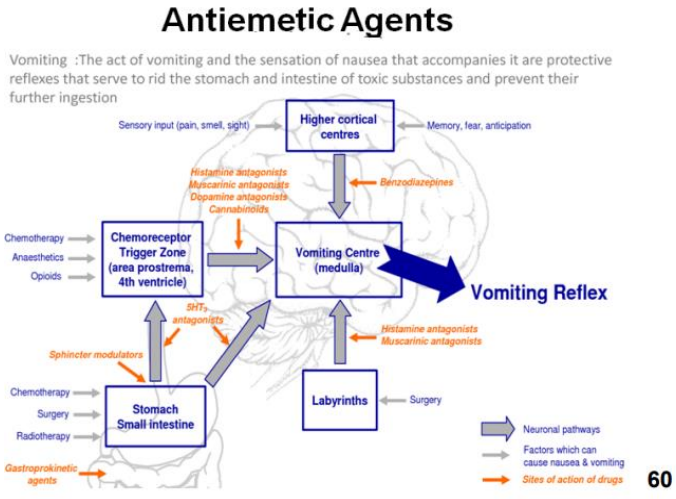
## iii. Antiemetic Agents

- Nausea and vomiting may be manifestations of a wide variety of conditions, including:
    a. Adverse effects of medications.
    b. Systemic disorders or infections.
    c. Pregnancy (pregnancy cravings).
    d. Vestibular dysfunction.
    e. CNS infection or increased pressure.
    f. Peritonitis.
    g. Hepatobiliary disorders.
    h. Radiation or chemotherapy (cause severe vomiting).
    i. GIT obstruction, dysmotility, or infections.

### *Pathophysiology*

- The brainstem "vomiting center" coordinates vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor centers.
- The act of vomiting includes many actions: contraction of the diaphragm to push the opening of the esophagus sphincter in order for the contents to go up, proceeding with nausea and increased secretions so lots of coordination occurring in the vomiting center.
    - Vomiting center contains high concentrations of: M1 cholinergic receptors, H1 histamine receptors, Neurokinin 1 (NK1) receptors and 5-HT3 serotonin receptors.

- ✓ The following diagram shows that higher cortical centers are involved in the vomiting reflex by the stimulation of sensory input (pain, smell, sight), memory (when you remember something bad you might vomit 😋), fear and anticipation.
- ✓ Chemoreceptor trigger zone stimulation by chemotherapy, anesthetics and opioids leads to the activation of the vomiting center, and so initiates the vomiting reflex.
- ✓ Labyrinths in the ear surgery can also cause vomiting.
- ✓ Stomach and small intestines irritation, chemotherapy, surgery and radiotherapy may also cause vomiting.





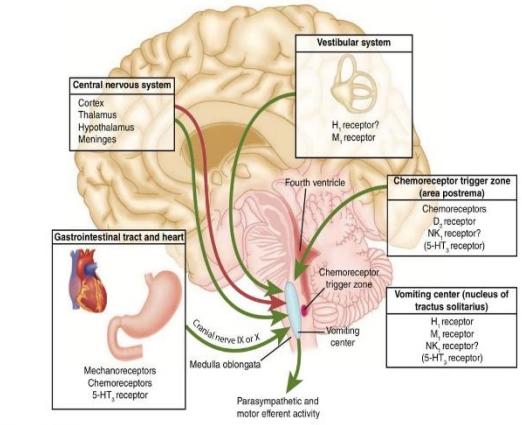




FIGURE 62–6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Adapted, with permission, from Krakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817. Copyright copy; 2005 Massachusetts Medical Society. Reprinted, with permission, from Massachusetts Medical Society.)

## A. *Serotonin 5-HT3 Antagonists*

Such as **Ondansetron, Granisetron:** they block central 5-HT3 and peripheral (main effect in the intestines) 5-HT3 receptors.

*(Cell damage in the GIT -> releasing serotonin from the ECL cells of the small intestines -> activating 5-HT3 receptors on the vagal afferent fibers which carry sensory signals to the medulla)*

- Prevent emesis due to vagal stimulation and chemotherapy (the stimulation of the peripheral 5-HT3 receptors on the sensory vagal nerve can cause nausea and vomiting).

Other emetic stimuli such as motion sickness are poorly controlled, and they are better controlled by antihistamine drugs.

- Uses: prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting. Their efficacy is enhanced by combination therapy with dexamethasone steroid and NK1-receptor antagonist.

Adverse effects: headache, dizziness, and constipation.

## B. *Neurokinin 1 Receptor (NK1) Antagonists*

- They block central NK1 receptors in the area postrema which is the chemoreceptor trigger zone.

  Aprepitant is used in combination with 5-HT3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from chemotherapy.

## C. *Cannabinoids* (cannabis weed derived)

Dronabinol, Nabilone (synthetic cannabinoids) are psychoactive agents.

- Used for chemotherapy-induced vomiting. Mechanisms for these effects are not understood. Adverse effects Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite.

## D. *Antipsychotic drugs*

Prochlorperazine, Promethazine and Droperidol (dopamine antagonists)

- Antiemetics due to blocking dopamine and muscarinic receptors. *Sedative effects due to antihistamine activity.*

## E. *Benzodiazepines*

Lorazepam and Diazepam (valium)

- Reduce anticipatory vomiting caused by anxiety (when a patient is going to have a major surgery, they anticipate pain and this can cause nausea and vomiting, so these drugs prevent this effect).

## *F. H1 Antihistamines & Anticholinergic Drugs*

- ✓ Particularly useful in the prevention of motion sickness.

Side effects: may cause dizziness, sedation, confusion, dry mouth, cycloplegia *(paralysis of the ciliary muscle of the eye)*, and urinary retention. All these are anticholinergic side effects. Remember that the first-generation antihistamines have antihistamine as well as anticholinergic effects.

Diphenhydramine, Dimenhydrinate

Have significant anticholinergic properties.

Meclizine

Minimal anticholinergic properties and less sedating. Used for the prevention of motion sickness and the treatment of vertigo due to labyrinth dysfunction.

Hyoscine (scopolamine)

Very effective in motion sickness but has very high incidence of anticholinergic effects. It is better tolerated as a transdermal patch and can be effective for 72 hours.