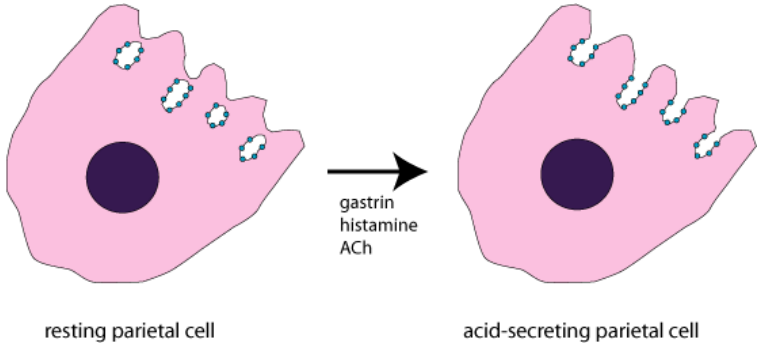
Drugs Used in the Treatment of Gastrointestinal Diseases.

Hamzeh Elayan, 2017.

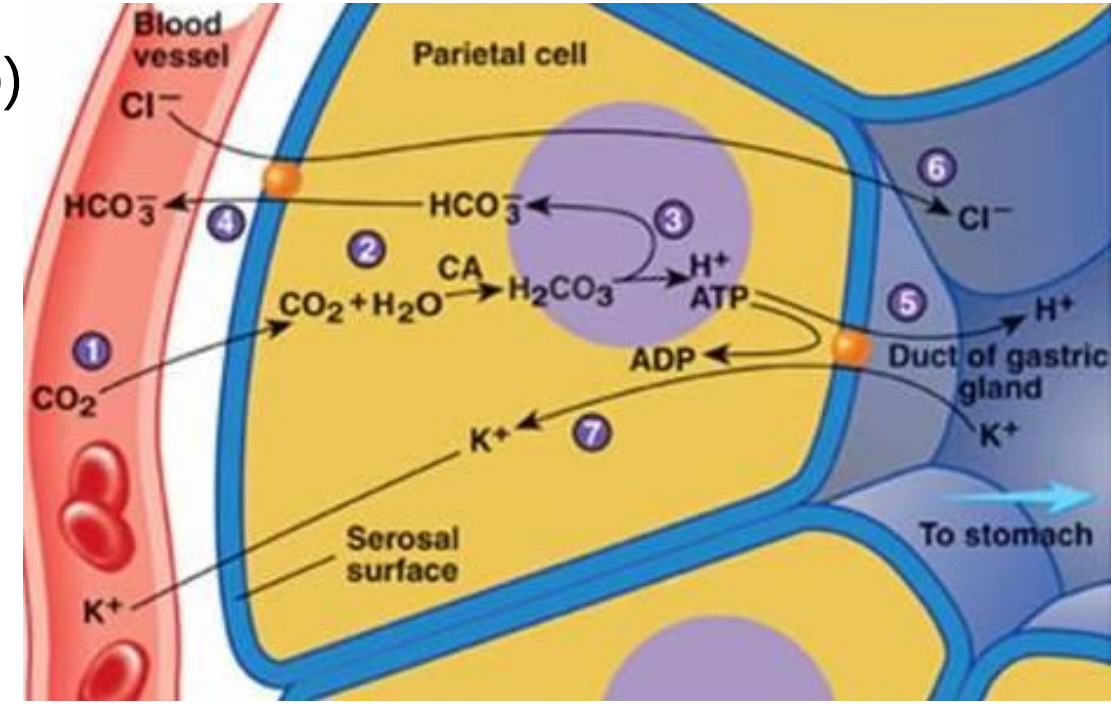
Physiology of gastric Secretion



Parietal cells secrete **2** liters of acid/ day.
Optimal pH (between **1.8-3.5**) for the function of the digestive enzyme pepsin.

Stimulation of acid secretion involves **translocation** of **H+/K+-ATPase** to the apical membrane of **parietal cell.**

H+/K+-ATPase (**proton pump**) uses the energy derived from ATP hydrolysis to pump H+ into the lumen in exchange for potassium ions.
Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi.

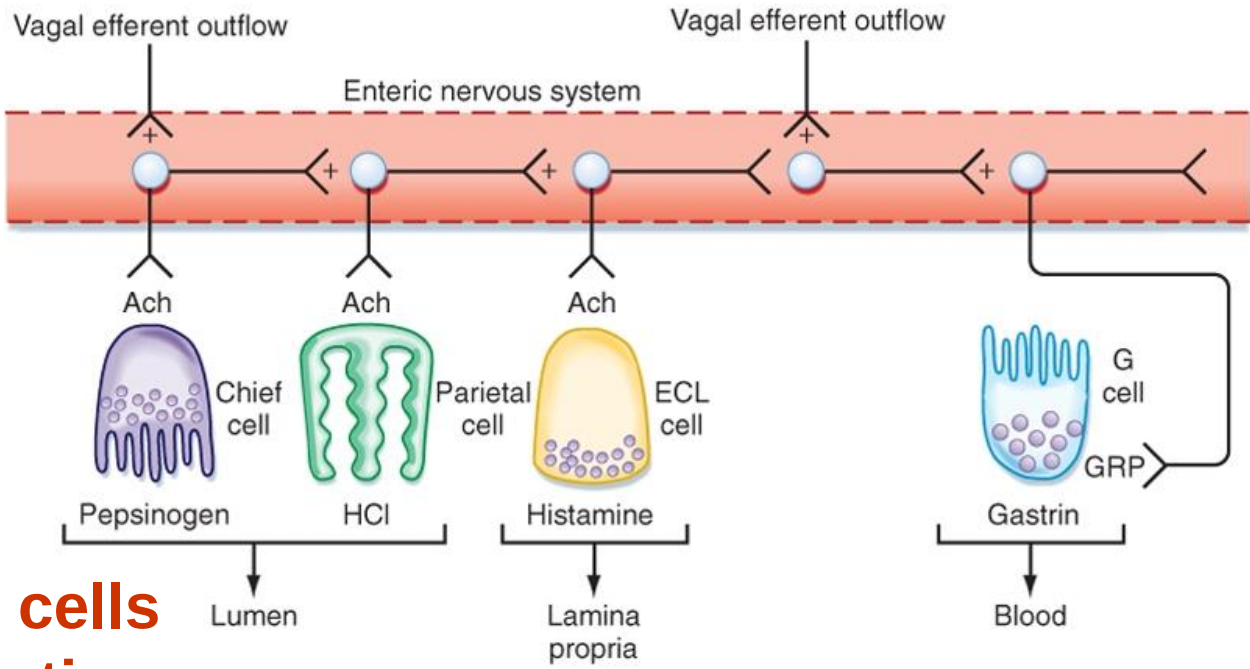


Stimulants of acid secretion:

1-**Ach** from **enteric neurons**.

2-Histamine from **ECL** (**enterochromaffin - like**) **cells**.

3-Gastrin released by **G cells.**



Somatostatin in **D cells inhibits acid secretion.**

Gastrin releasing peptide (**GRP**)

Gastric pH < 3 --> gastric D cells release somatostatin

It inhibits acid secretion by:

1-direct effects on parietal cells.

2- inhibiting release of histamine & gastrin.

Three phases in gastric acid secretion.

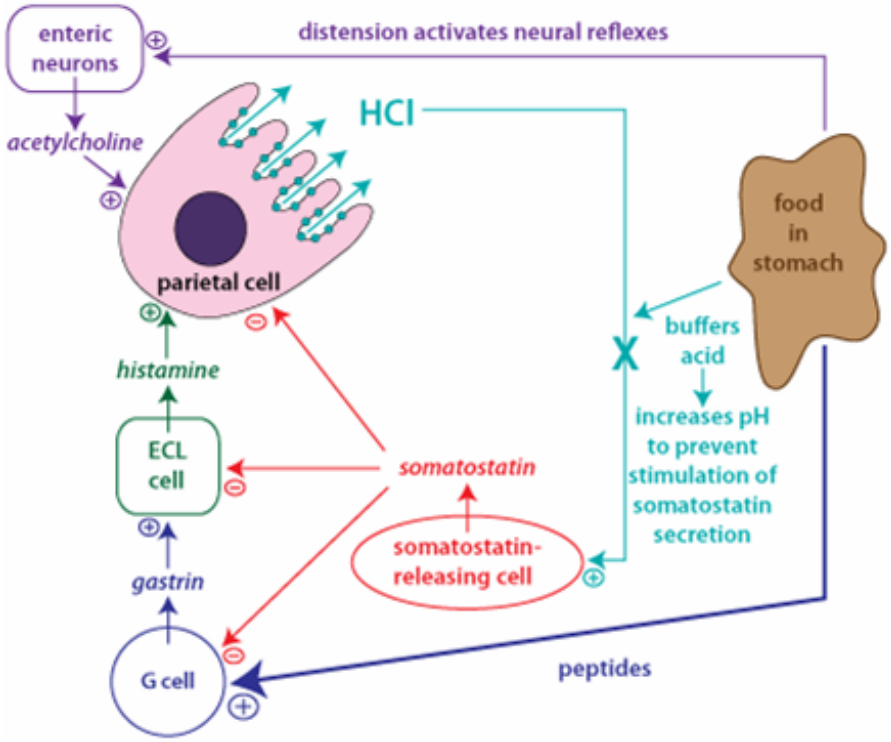
Cephalic Phase:

sight, smell, taste or thought of food,

activate enteric neurons via vagus. In humans, the major effect of **gastrin** is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.

Gastric Phase:

Food stretch stomach walls
activating a neural reflex
to stimulate acid secretion.
Peptides & amino acids stimulate
G cells to release gastrin.
Food acts as a buffer, raising the
pH & thus removing the stimulus
for somatostatin secretion .

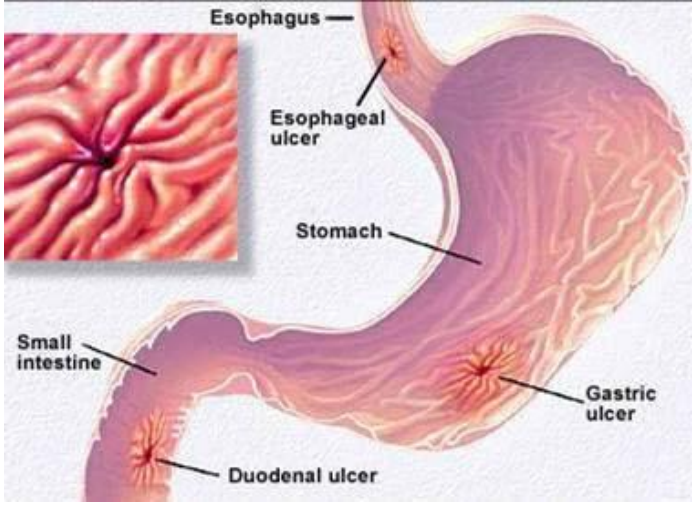


Intestinal Phase:

Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

Peptic ulcer

A defect in the lining of
the stomach or the duodenum.



Causes of Peptic Ulcer:

Helicobacter pylori (most common).

Drugs such as aspirin
& other NSAIDs

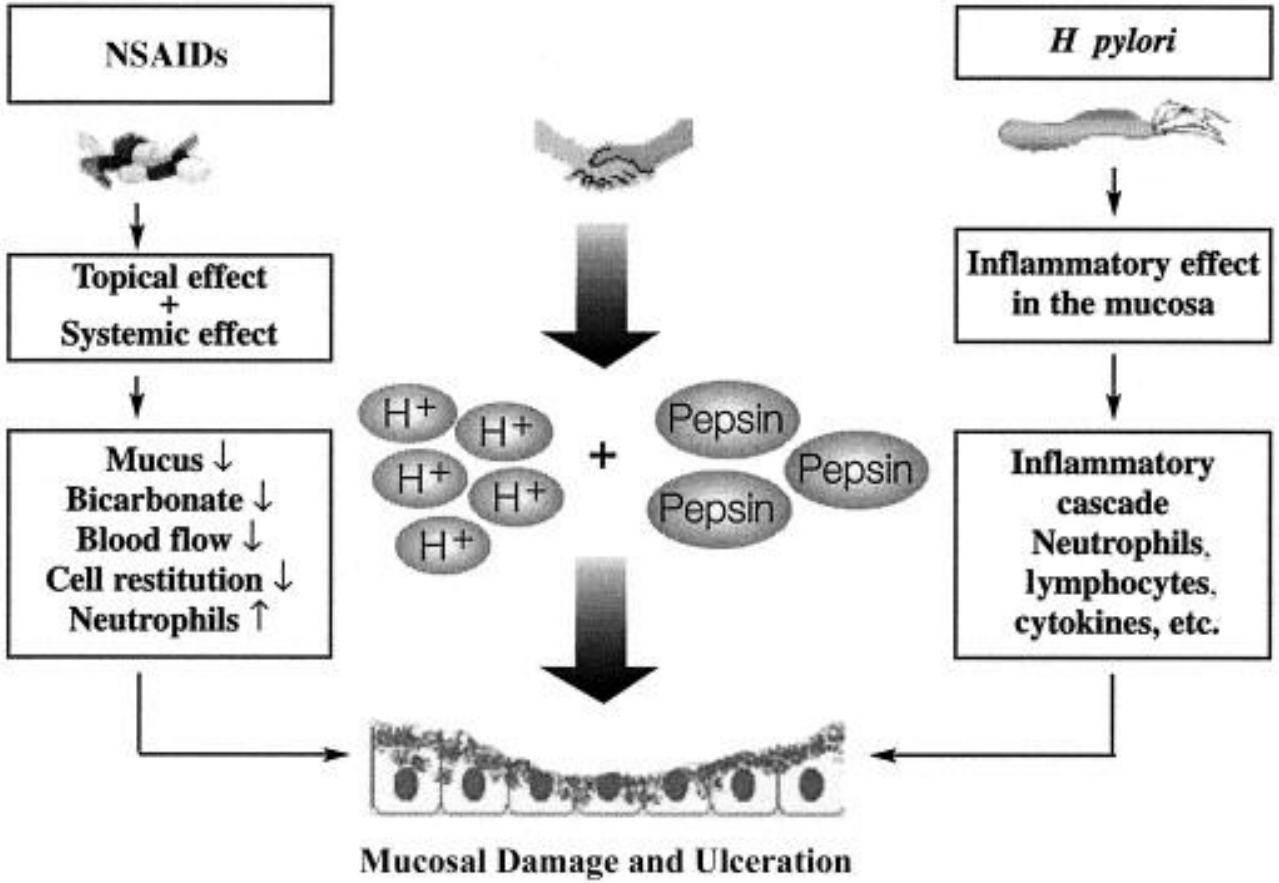
Other factors:

Smoking,
Stress,
alcohol.

Gastrinomas

Zollinger Elliso syndrome

a rare gastrin-secreting tumors

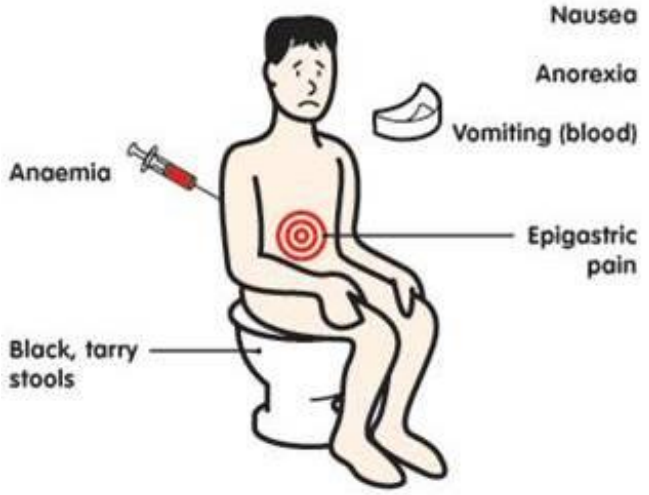


Symptoms:

burning pain in stomach between meals or at night, bloating, heartburn, nausea or vomiting.

In severe cases, symptoms include:

Dark or black stool (due to bleeding)
Vomiting blood
Weight loss & severe pain
in the mid to upper abdomen.



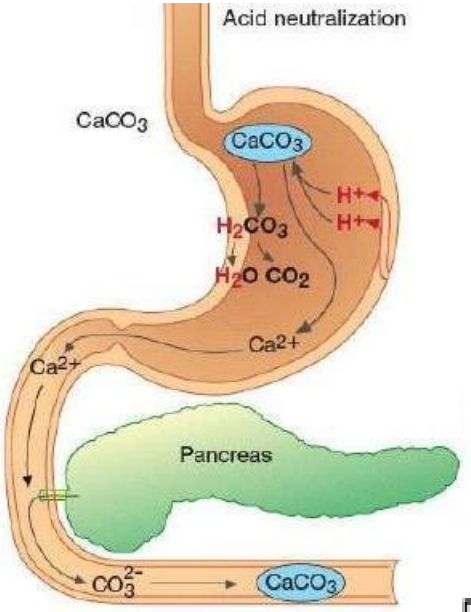
Complications of peptic ulcer

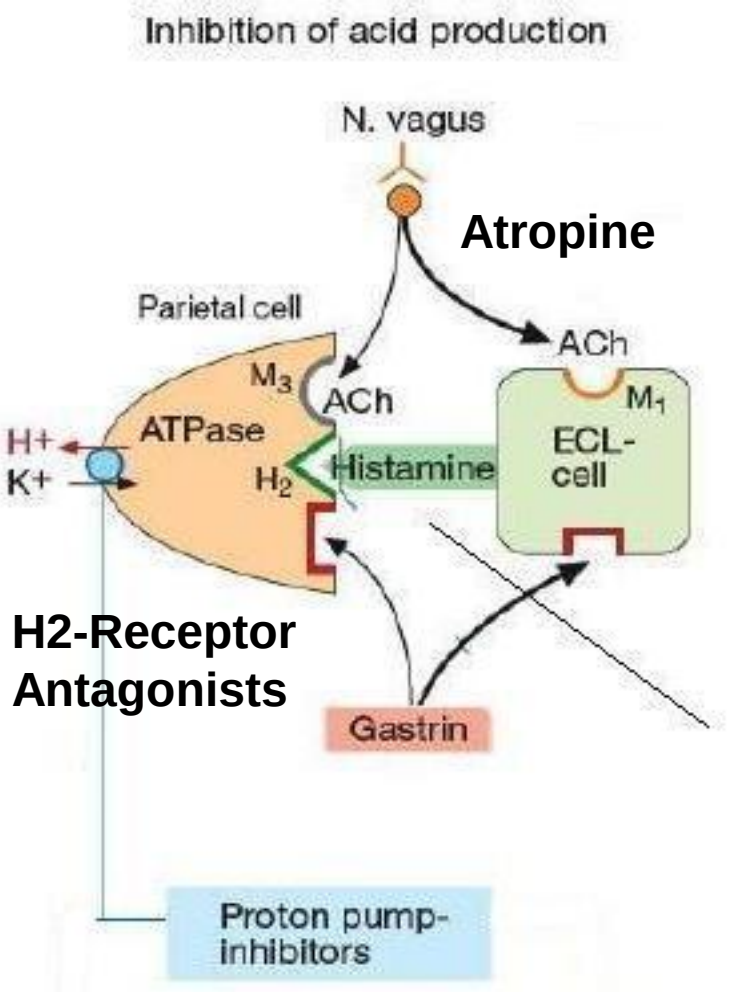
Gastrointestinal bleeding.
(Sudden large bleeding can be life threatening).
Cancer (Helicobacter pylori as the etiological factor)
Perforation (hole in the wall) Penetration.

Treatment options

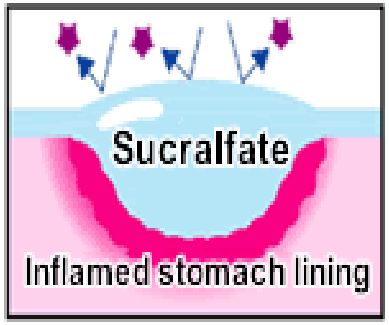
Reduce acid secretion or

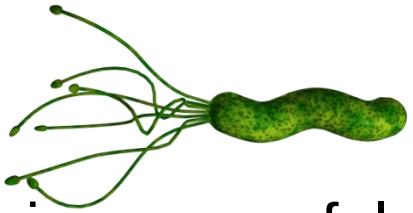
Neutralize acid in the lumen





Protect the mucosa from acid destruction





Antibiotics to eradicate *Helicobacter pylori.* If this is successful then the ulcer should begin to heal on its own.

Neutralization of acid (Antacids)

Nonprescription remedies for treatment of heartburn & dyspepsia.

Given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours.

$$AL(OH)3 + HCl \text{ -----> } ALCl3 + H2O$$
$$2HCl + Mg(OH)2 \text{ ----> } MgCl2 + 2H2O$$

Aluminum antacids cause constipation, interfere with absorption of many drugs.

Magnesium antacids have laxative action; diarrhea.

ionic magnesium stimulates gastric release (acid rebound)

Magnesium trisilicate slow-acting antacid

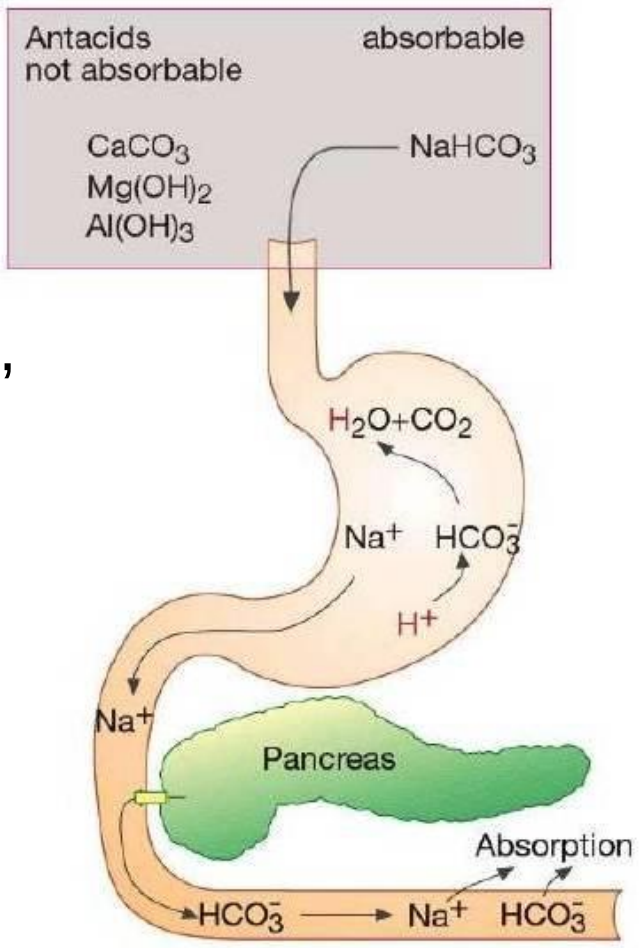
Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).

Calcium carbonate

associated with "acid rebound"

with excessive chronic use, it may cause milk-alkali syndrome with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels.

2HCl + CaCO3 ---> CaCl2 + **CO2** + H2O



Sodium bicarbonate

-Should be avoided as it aggravate CHF & counteracts diuretic therapy for hypertension

-Short duration of action, followed by acid rebound.

-Highly absorbed, potentially causing metabolic alkalosis.

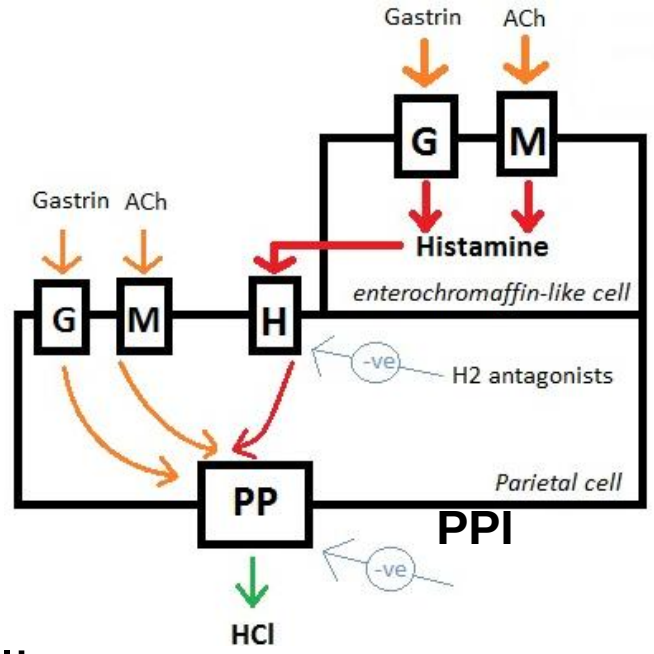
- CO2 results in gastric distention and belching.

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$

H2-Receptor Antagonists

Cimetidine, Ranitidine,

Famotidine Nizatidine.



Rapidly absorbed from intestine.

Cimetidine, ranitidine, famotidine

first-pass metabolism bioavailability %٥٠

Nizatidine has little first-pass metabolism.

Duration of action: 6–10 hours, given twice daily.

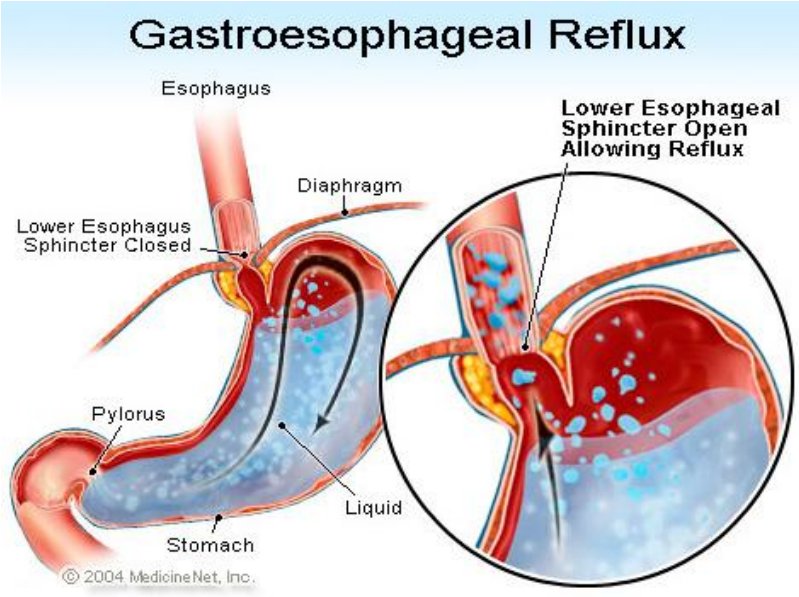
Inhibit 90% of nocturnal acid (depends on histamine).

Modest impact on meal-stimulated acid secretion (which is stimulated by gastrin, Ach and histamine).

Inhibit 60% of day-time, meal stimulated acid.

١٠ Inhibit 60-70% of total 24-h acid secretion.

Clinical Uses



Gastroesophageal Reflux Disease (GERD)

Taken prophylactically before meals.

In erosive esophagitis H2 antagonists healing is less than 50% hence **PPI** are preferred.

Non Ulcer Dyspepsia.

Over-the-counter agents for treatment of intermittent dyspepsia not caused by peptic ulcer.

Prevention of Bleeding from Stress-Related Gastritis

IV H2 antagonists are preferable over IV **PPI** because of their proven efficacy and lower cost.

Peptic Ulcer Disease:

Replaced by PPI.

- Healing rate more than 80-90% after 6-8 wks.
- Not effective in the presence of ***H. pylori.***
- Not effective if NSAID is continued.

Adverse Effects:

Extremely safe drugs. Diarrhea, headache, fatigue, myalgias, and constipation (3%).

Cimetidine may cause gynecomastia & impotence in men (antiandrogenic effects) and galactorrhea in women

Drug Interactions:

Cimetidine inhibits cytochrome P450 enzymes so can increase half life of many drugs.

Ranitidine binds 4-10 times less.

Nizatidine and famotidine binding is negligible

Proton Pump Inhibitors (PPIs)

Among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.

Omeprazole (oral).

Lanzoprazole (oral and IV).

Esomeprazole (oral and IV).

available as capsules of enteric-coated granules.

Rabeprazole (oral).

Pantoprazole (oral and IV).

are tablets with a pH-sensitive coating.

Prodrugs, released in the intestine (Destroyed by acid).

Immediate-Release Omeprazole

contains sodium bicarbonate to protect the drug from acid degradation results in rapid response.

Lipophilic weak bases, absorbed in small intestine and delivered to parietal cell through the blood.

Drug is protonated and “trapped” in acidic canaliculi.

Concentrated more than 1000-fold in the parietal cells.

Converted to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.

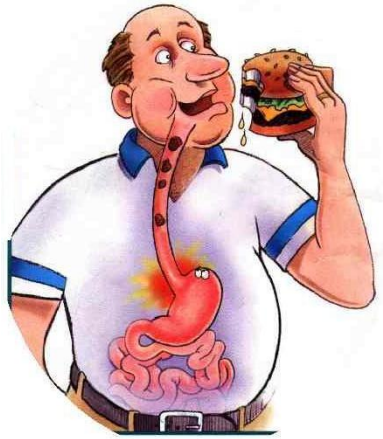
Have short half lives but effect lasts for 24 hours.

At least 18 hours are required for synthesis of new pump molecules.

Inhibit both fasting & meal-stimulated secretion

(90-98% of 24-hour secretion).

The full acid-inhibiting potential is reached in 3 to 4 days.



Clinical Uses of (PPIs) :

Gastroesophageal Reflux (GERD):

The most effective agents in all forms of GERD

Nonulcer Dyspepsia:

Modest activity.10-20% more beneficial than a placebo

Stress- Related Gastritis:

Oral immediate- release **omeprazole** administered by nasogastric tube.

For patients without a nasoenteric tube, **IV H_2- blockers** are preferred because of their proven efficacy.

Gastric acid hypersecretory states, including Zollinger -Ellison syndrome

Usually high doses of omeprazole are used.

Peptic Ulcer Disease:

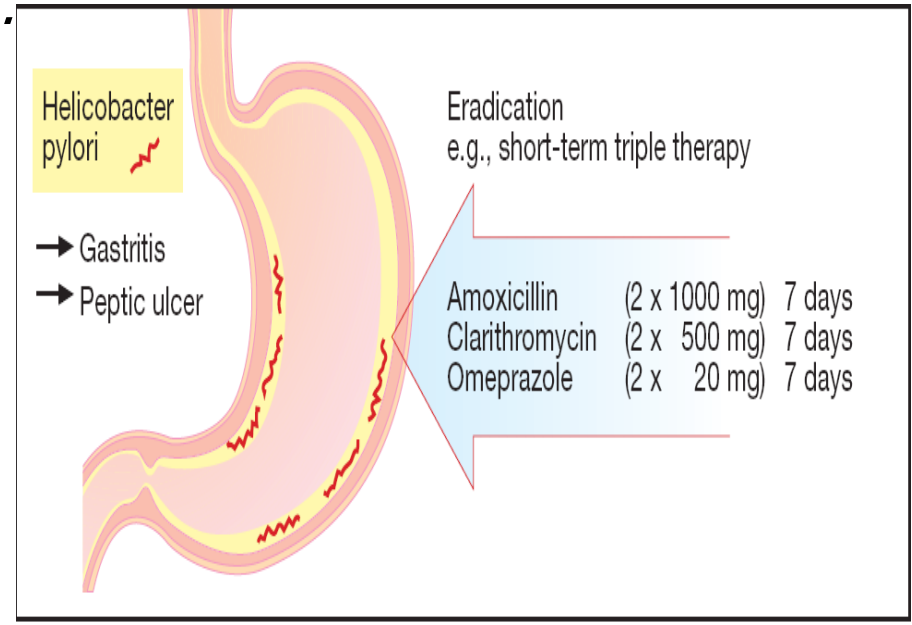
They heal more than 90% of cases within 4-6 weeks.

H. Pylori* - associated ulcers*:

PPI eradicate *H. pylori* by direct antimicrobial activity and by lowering MIC of the antibiotics.

***Triple Therapy*:**

PPI twice daily + Clarithromycin 500 mg twice daily +Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily.



C. Helicobacter eradication

NSAID-associated ulcers*:*

Healing despite continued NSAID use.

Also used to prevent ulcer of NSAIDs

Rebleeding peptic ulcer:

Oral or IV. High pH may enhance coagulation and platelet aggregation.

Adverse Effects of PPIs:

Well tolerated.

May cause headache, diarrhea, abdominal pain, nausea & dizziness

Reduction of cyanocobalamine absorption.

Increased risk of GI and pulmonary infection.

Increased serum gastrin levels causes:

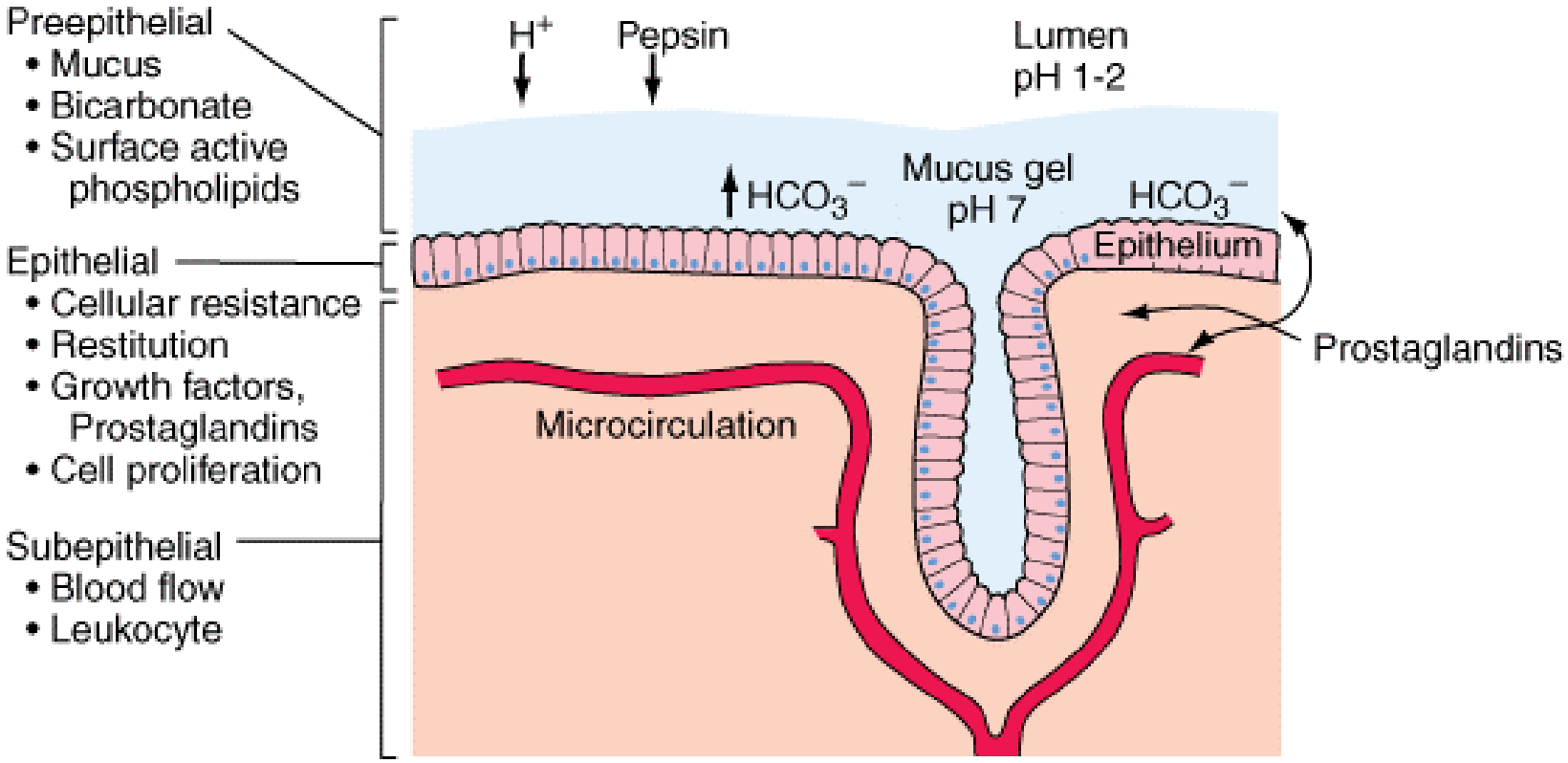
Chronic inflammation in gastric body.

Atrophic gastritis and intestinal metaplasia.

Drug Interactions:

May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.

Mucosal Protective Agents



1-Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.

2-Epithelial bicarbonate secretion

3-Blood flow carries bicarbonate

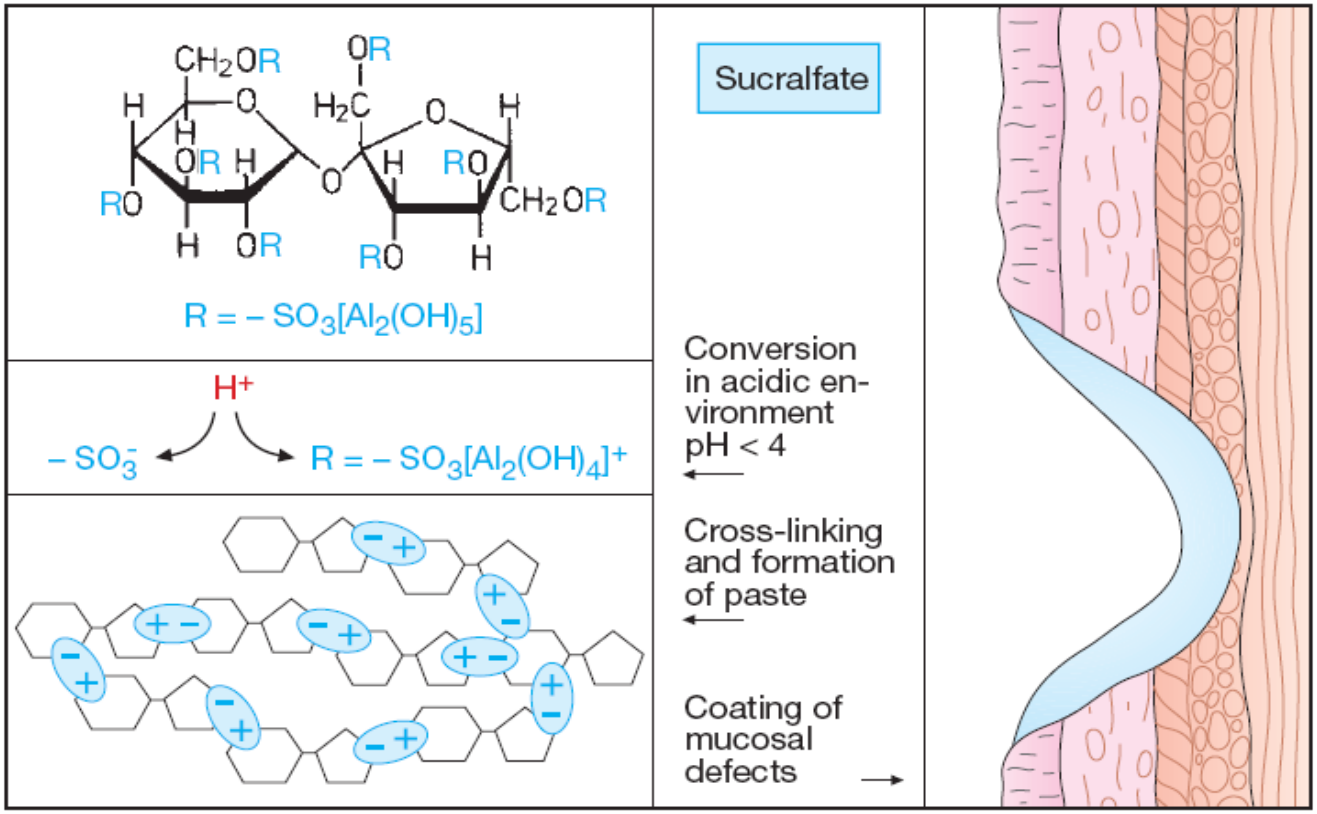
4- injured epithelium are repaired by **restitution**

5- Mucosal prostaglandins stimulates mucus and bicarbonate secretion and mucosal blood flow.

Sucralfate

A salt of sucrose complexed to sulfated aluminum hydroxide.

In the stomach, It breaks down into sucrose sulfate (strongly negatively charged) and an aluminum salt.



A. Chemical structure and protective effect of sucralfate

The **negatively** charged sucrose sulfate binds to **positively** charged proteins in the base of ulcers or erosion, forming a **physical barrier** that restricts further caustic damage and **stimulates mucosal prostaglandin and bicarbonate secretion**.

Acts for 6 hours.

Less than 3% of intact drug and aluminum is absorbed.

Clinical Uses

1 g four times daily on an empty stomach (through a nasogastric tube) reduces the incidence of upper GI bleeding in critically ill patients hospitalized in the intensive care unit.

Prevention of **stress-related bleeding** because acid inhibitory therapies may increase the risk of nosocomial pneumonia (an infection of the lungs that occurs during a **hospital** stay).

Adverse Effects

Not absorbed, so no systemic adverse effects.

Constipation (2%) due to the aluminum salt.

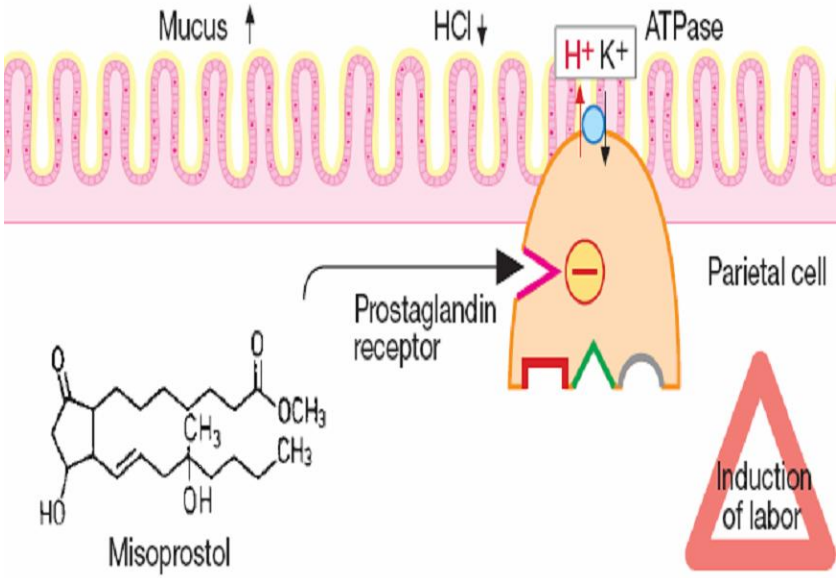
Caution in renal insufficiency.

Drug Interactions

Sucralfate may bind to other medications, impairing their absorption.

Prostaglandin Analogs

Misoprostol



A methyl analog of **PGE1.**

Half-life is less than 30 min

Administered 3-4 times daily.

1-Stimulates mucus & bicarbonate secretion.

2- Enhances mucosal blood flow.

3- Acts on parietal cells, reducing histamine-stimulated cAMP production and causing **modest acid inhibition**.

4- Stimulates **intestinal** electrolyte & fluid secretion,

5- Increase intestinal motility

6- **Uterine contractions**.

Clinical Uses of Prostaglandin Analogs:

Prevention of NSAID-induced ulcers in high-risk patients.

Not widely used for this purpose because of:

a- side effects.

b. need for multiple daily dosing.

c. **PPI** may be as effective and better tolerated.

d. Cyclooxygenase2-selective NSAIDs are an option for such patients**.**

Adverse Effects & Drug Interactions

Diarrhea and cramping abdominal pain (10–20%).

it should not be used during pregnancy

No significant drug interactions.

Colloidal Bismuth Compounds:

Bismuth subsalicylate.
Bismuth subcitrate.

Bismuth is minimally absorbed from GIT (< 1%).

A mucosal protective agent, provides coat on the ulcer.

Reduce the gastric HCL secretion.
Help in eradication of H. pylori.
Stimulates the PGE secretion.
Reduce pepsin secretion.
Decrease H+ ion back diffusion.

Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion.

Has direct antimicrobial effects & binds enterotoxins, so useful in preventing & treating **traveler's diarrhea**.

Widely used for the nonspecific treatment of dyspepsia and acute diarrhea.

Has direct antimicrobial activity against *H pylori and* used as second-line therapy for the eradication of *H pylori* infection

PPI with bismuth subsalicylate , tetracycline and metronidazole for 10–14 days).

Adverse Effects

Blackening of the stool and the tongue.

Prolonged usage may rarely lead to bismuth toxicity, resulting in **encephalopathy**.

Drugs Stimulating GI Motility

(**Prokinetic agents**)

Potential uses:

Increasing lower esophageal sphincter pressures, useful for GERD.

Improving gastric emptying, helpful for gastroparesis and postsurgical gastric emptying delay.

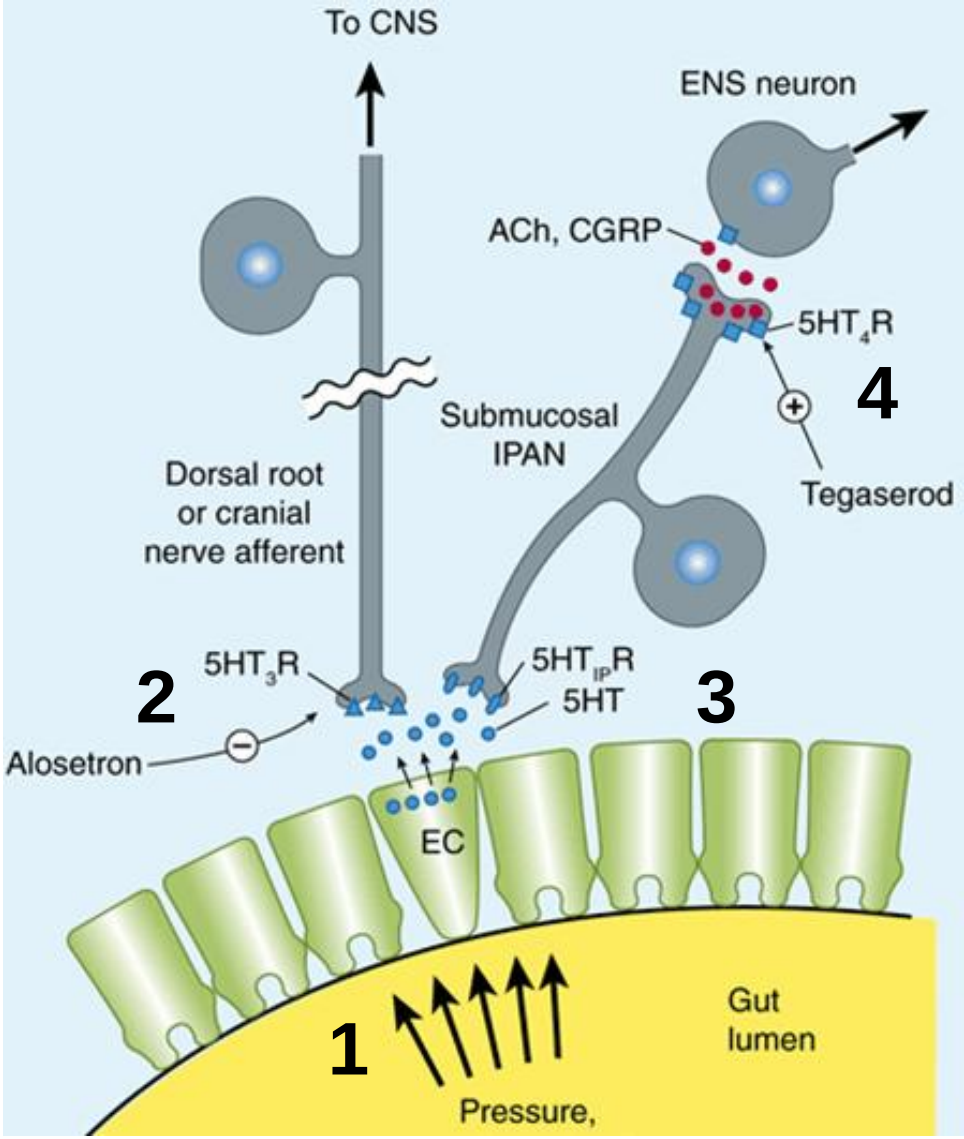
Stimulation of the small intestine useful for postoperative ileus.

Enhancing colonic transit, useful in the treatment of constipation.

1-Gut distention stimulates 5-HT release from EC cells.

2-Stimulation of **5-HT3** receptors on the extrinsic afferent nerves, stimulate **nausea, vomiting**, or **abdominal pain**.

3- 5-HT also stimulates **5-HT1P** receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for **peristaltic and secretory reflex activity.**



4- Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of **ACh** & calcitonin gene related peptide (**CGRP**), promoting reflex activity.

The enteric nervous system can independently regulate GI motility and secretion.

The myenteric interneurons control:

peristaltic reflex, promoting release of excitatory mediators proximally and inhibitory mediators distally.

Motilin may stimulate excitatory neurons or muscle cells directly.

Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal and gastric contractions.

Cholinomimetic Agents

Bethanechol

Stimulates muscarinic **M3** receptors on muscle cells and at myenteric plexus synapses .

Was used for the treatment of GERD and gastroparesis.

Neostigmine

AchE inhibitor enhances gastric, small intestine, and colonic emptying.

IV neostigmine used for the treatment of acute large bowel distention (**acute colonic pseudo-obstruction**).

Administration of 2 mg results in prompt colonic evacuation of flatus and feces.

Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.

Dopamine D2-receptor antagonists.

Metoclopramide & Domperidone

D2 Antagonists.

Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal & gastric contractions.

These agents block D2 receptors causing:

-increase esophageal peristaltic amplitude.

-increase lower esophageal sphincter pressure.

-enhance gastric emptying.

-have no effect on small intestine or colonic motility.

Also block dopamine **D2** receptors in the **chemoreceptor trigger zone of the medulla (area postrema),** resulting in potent **anti nausea and antiemetic actions.**

Clinical Uses

Gastroesophageal Reflux Disease

Not effective with **erosive esophagitis**.

Not superior to antisecretory agents.

Used mainly in combination with antisecretory agents in patients with **refractory heartburn**.

Impaired Gastric Emptying (Gastroparesis)

widely used in post surgical and diabetic gastroparesis

Nonulcer Dyspepsia

Prevention of Vomiting

Postpartum Lactation Stimulation.

Domperidone is used to promote postpartum lactation.

Adverse Effects:

Metclopromide crosses BBB so can cause: Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal symptoms (dystonia, akathisia, parkinsonian features) and tardive dyskinesia.

Domperidone does not cross the BBB, so

does not cause CNS effects

Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders.

Laxatives

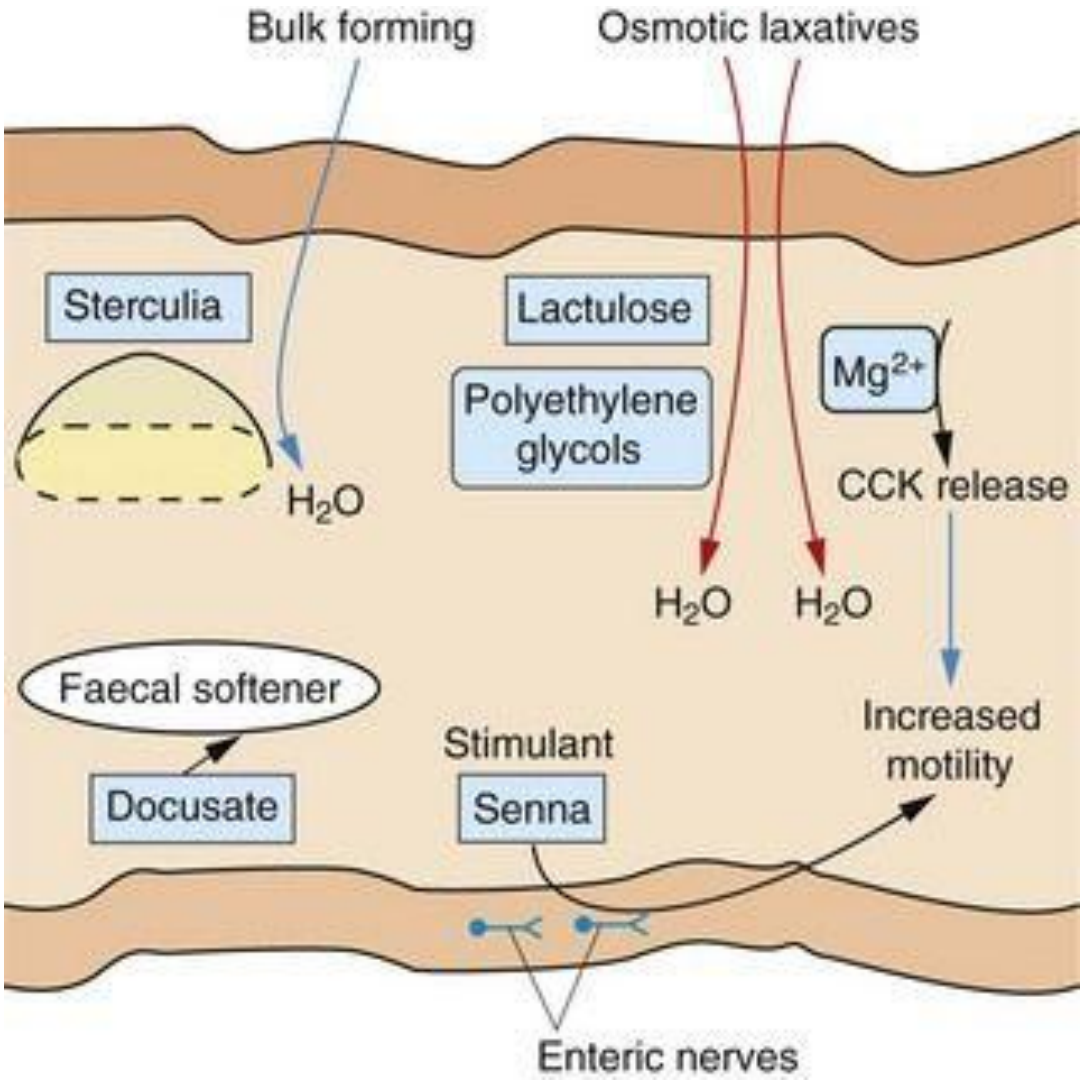
Intermittent constipation is best prevented with:

a high-fiber diet.

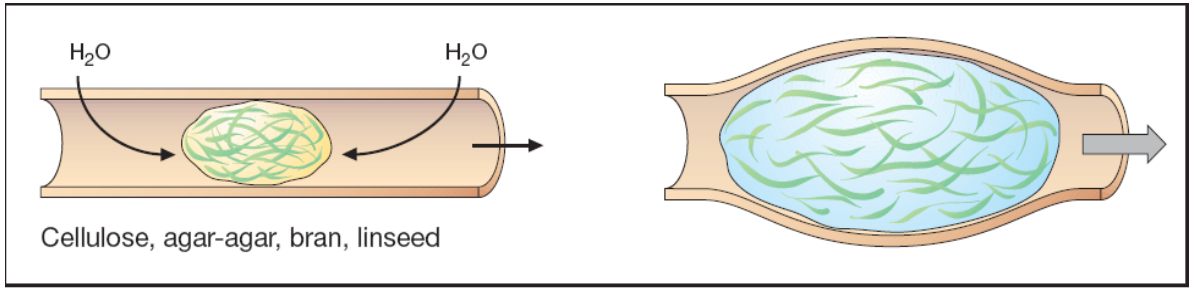
adequate fluid intake.

responding to nature's Call.

Regular exercise.



Bulk-Forming Laxatives



B. Bulk laxatives

Indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.

Effective within 1-3 days.

Common preparations include natural plant products (**psyllium, methylcellulose, bran**) and synthetic fibers **(polycarbophil).**

Bacterial digestion of plant fibers within the colon may lead to increased **bloating and flatus**.

Stool Surfactant Agents (Softeners)

Docusate

Detergents or surfactants that act as stool-wetting and stool-softening agents, allowing the mixing of water, lipids, and fecal matter.

Alters intestinal permeability and increases net water and electrolyte secretions in the intestine.

Orally: Softening of feces within **1-3 days**

Rectally: effective within **5 to 20 minutes.**

Used in symptomatic treatment of constipation & in painful anorectal conditions such as hemorrhoids and anal fissures.

Glycerin suppository.

works by irritating the lining of the intestine and increasing the amount of fluid, making it easier for stools to pass.

Lubricant/Emollient

Site of Action: **Colon.**

Onset of Action: 6 - 8 hours.

Causing lubrication of the stool & make it slippery, so that it slides through the intestine more easily.

It is not absorbed and increase the bulk of the intestinal contents as it reduces the water absorption

Liquid paraffin

Used to prevent and treat fecal impaction.

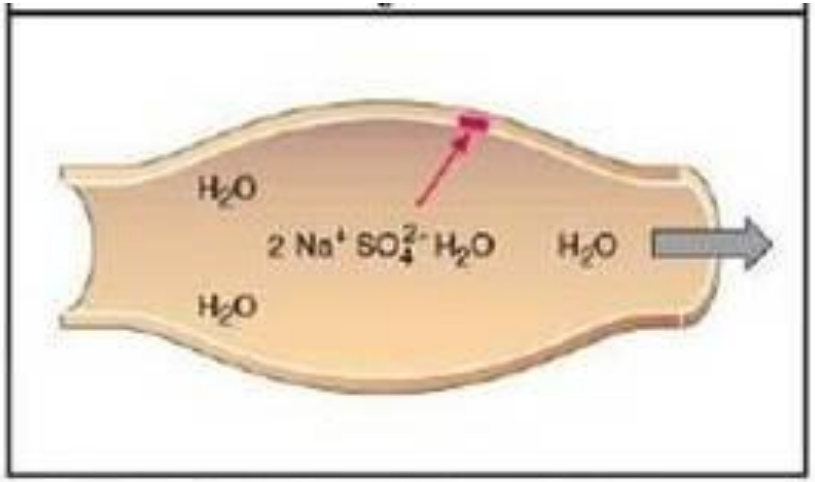
Aspiration can result in a severe lipid pneumonitis

Long-term use can impair absorption of fat-soluble vitamins.

Can slip out of anal sphincter and causes embarrassment. Not recommended for regular use.

Osmotic Laxatives

Soluble but nonabsorbable compounds that result in increased stool liquidity due to an increase in fecal fluid.



C. Osmotically active laxatives

Nonabsorbable Sugars or Salts

Magnesium hydroxide (milk of magnesia)

Not used for prolonged periods in renal insufficiency due to the risk of hypermagnesemia.

Large doses of **magnesium citrate** & **sodium phosphate** cause Purgation: rapid bowel evacuation within1-3 h. This might cause volume depletion.

Lactulose

Disaccharide, not absorbed causing retention of water through osmosis leading to softer, easier to pass stool.

in the **colon**, it is **fermented** by the gut flora producing osmotic metabolites causing severe flatus and cramps.

Drug of choice in hepatic encephalopathy to trap NH3.

Lactulose is converted into lactic acid, which decreases the luminal pH. So, NH3 is trapped and prevented from absorption.

Balanced Polyethylene Glycol:

Safe solution: no intrvascular fluid or electrolyte shifts.

Does not cause cramps or flatus.

It is a laxative solution that increases the amount of water in the intestinal tract to stimulate bowel movements.

PEG is an inert, nonabsorbable, cosmetically active sugar.

It also contains Sodium sulfate, bicarbonate and potassium chloride to replace electrolytes that are passed from the body in the stool

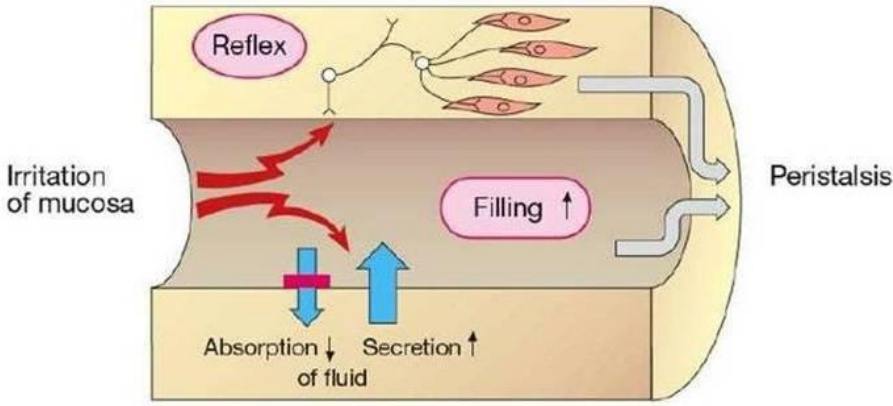
used to clean the bowel before colonoscopy, a barium x-ray or other intestinal procedures.

For colonic cleansing, it is ingested rapidly (4L over 2-4 h).

For chronic constipation, PEG powder is mixed with water or juice.

Stimulant Laxatives

Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.



Anthraquinone Derivatives:

Aloe, senna, and **cascara**

Occur naturally in plants.

Poorly absorbed & after hydrolysis in the colon, produce a bowel movement in 6–12 h when given orally and within 2 h when given rectally.

Chronic use leads to a brown pigmentation of the colon known as "**melanosis coli**.“

Bisacodyl

Tablet and suppository for treatment of acute and

chronic constipation

induces bowel movement within 6–10 h orally

and 30–60 minutes rectally.

Safe for acute and long-term use

Phenolphthalein

Removed from the market owing to concerns about possible cardiac toxicity.

Castor Oil

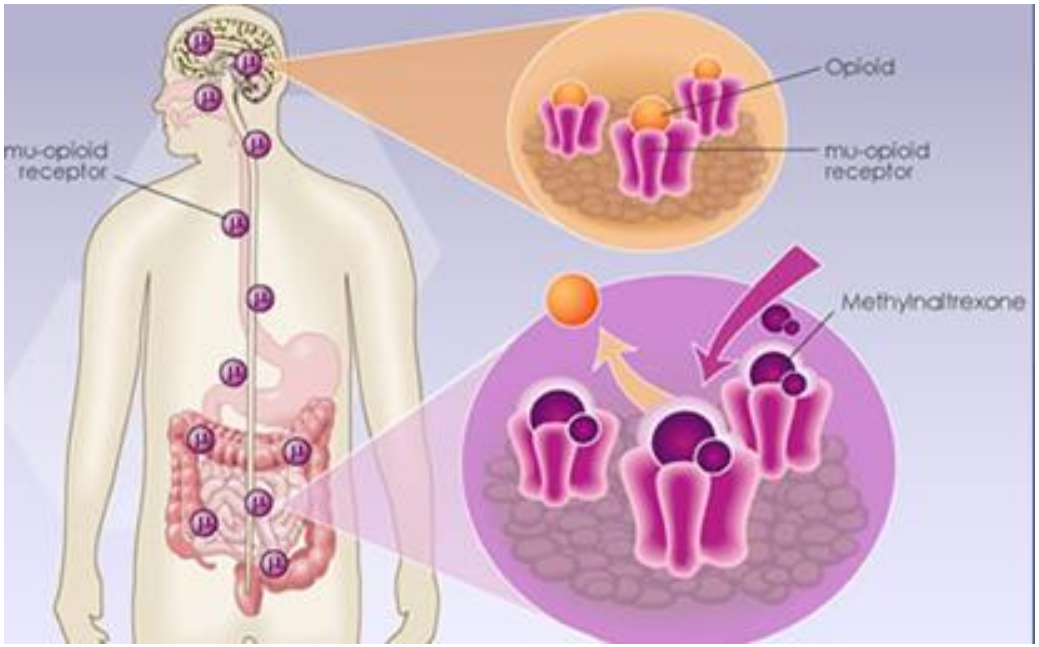
Hydrolyzed in upper intestine into ricinoleic acid which is a local irritant.

Was used as purgative to clean the colon before procedures.

Opioid Receptor Antagonists

Do not cross the BBB.

Block peripheral (**μ**) mu – opioid receptors without central analgesic effects.



Methylnaltrexone

Used for opioid - induced constipation in patients with advanced illness not responding to other agents. S.C. injection every 2 days.

Alvimopan

Short-term use for postoperative ileus in hospitalized patients.

Given orally within 5 hours before surgery and twice daily after surgery until bowel function has recovered, but for no more than 7 days, because of possible cardiovascular toxicity.

Antidiarrheal Agents

Should not be used in patients with **bloody diarrhea, high fever, or systemic toxicity** because of the risk of worsening the underlying condition.

Used to control chronic diarrhea caused by **irritable bowel syndrome (IBS)** or **inflammatory bowel disease.**

Opioid Agonists

Increase colonic transit time and fecal water absorption.

They also decrease mass colonic movements

CNS effects and potential for addiction limit the usefulness of most.

Loperamide

Does not cross BBB, so No analgesic or addiction potential.

Diphenoxylate

Not analgesic in standard doses.

Higher doses have CNS effects.

Can cause dependence.

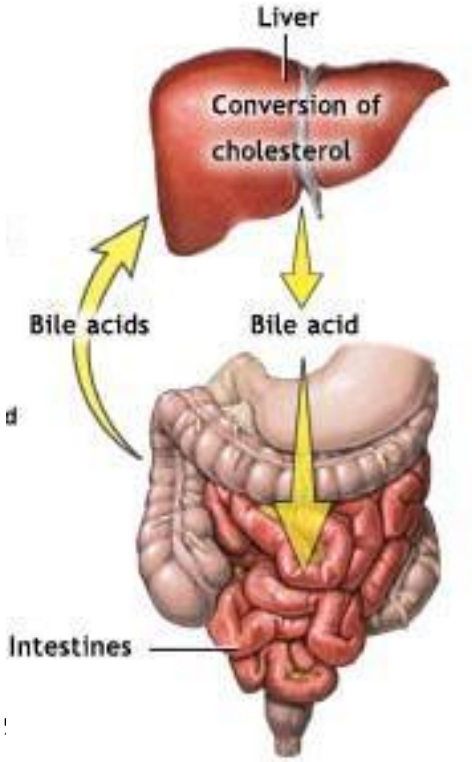
Commercial preparations contain small amounts of **atropine** **Lomotil** Diphenoxylate and Atropine which contribute to the antidiarrheal action.

Bile Salt-Binding Resins

Cholestyramine

Colestipol

Colesevelam



Malabsorption of bile salts cause diarrhea.

(Crohn's disease or after surgical resection)

They bind bile salts and decrease diarrhea

caused by excess fecal bile acids.

Can cause bloating, flatulence, constipation and fecal impaction.

Cholestyramine and **colestipol** reduce absorption of drugs and fat, but **Colesevelam** does not.

“

Octreotide:

Synthetic octapeptide with actions similar to somatostatin. **Clinical Uses:**

1. Inhibition of endocrine tumor effects:

Carcinoid and VIPoma (neuroendocrine tumors that secrete vasoactive intestinal polypeptide (VIP)) can cause secretory diarrhea, flushing and wheezing.

2. 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 used in patients with pancreatic fistula (leakage of pancreatic secretions from damaged pancreatic ducts).

5- treatment of pituitary tumors (e.g., acromegaly)

6- Sometimes used in gastrointestinal bleeding.

Adverse Effects:

Impaired pancreatic secretion may cause **steatorrhea** which can lead to fat-soluble vitamin deficiency.

Nausea, abdominal pain, flatulence, and diarrhea.

Formation of sludge or **gallstones**, because of inhibition of gallbladder contractility and fat absorption.

Hyper or hypoglycemia due to hormonal imbalance.

Hypothyroidism.

Bradycardia**.**

Drugs Used in the Treatment of Irritable Bowel Syndrome

IBS is an idiopathic chronic, relapsing disorder characterized by: Abdominal discomfort

pain, bloating, distention, or cramps with alterations in bowel habits

diarrhea, constipation, or both.

Pharmacologic therapies for **I**BS are directed at relieving abdominal pain and discomfort and improving bowel function.

Antispasmodics (Anticholinergics)

Dicyclomine and **Hyoscyamine** .

Block muscarinic receptors in the enteric plexus and on smooth muscle.

Their efficacy for relief of abdominal symptoms has never been convincingly demonstrated.

Low doses cause minimal autonomic effects.

Higher doses cause anticholinergic effects, including dry mouth, visual disturbances, urinary retention, and constipation.

For these reasons, antispasmodics are infrequently used.

Alosetron

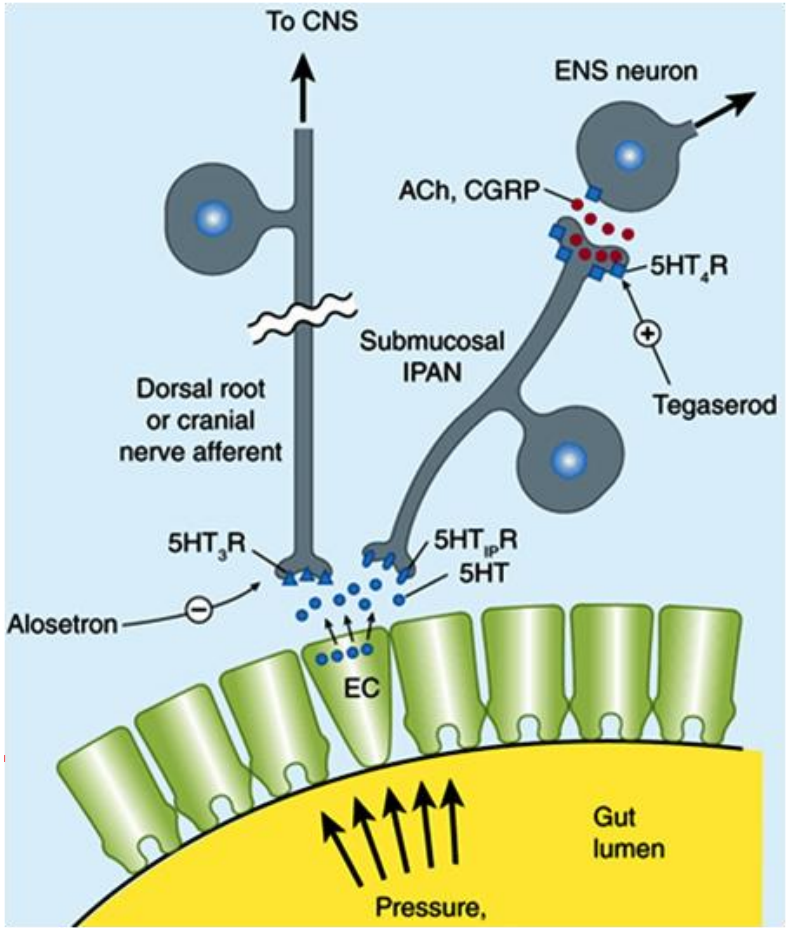
Potent & selective antagonist

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.



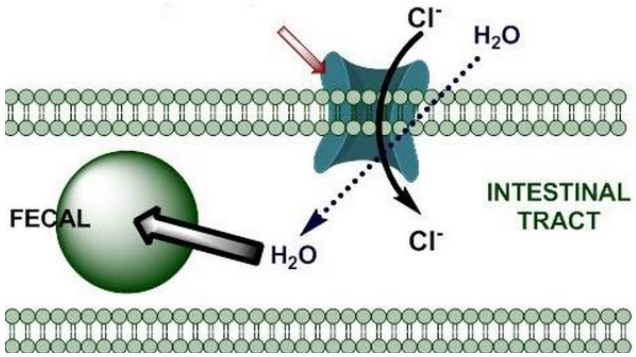
Prucalopride

High-affinity 5-HT4 agonist. No cardiovascular toxicity

Used for the treatment of chronic constipation in women.

Chloride Channel Activator

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



Lubiprostone

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 (30%) due to delayed gastric emptying.

Antiemetic Agents

Nausea and vomiting may be manifestations of a wide variety of conditions, including:

Adverse effects of medications.

systemic disorders or infections.

Pregnancy.

Vestibular dysfunction.

CNS infection or increased pressure.

Peritonitis.

Hepatobiliary disorders.

Radiation or chemotherapy.

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.

Vomiting center contains high concentrations of:

M1 receptors.

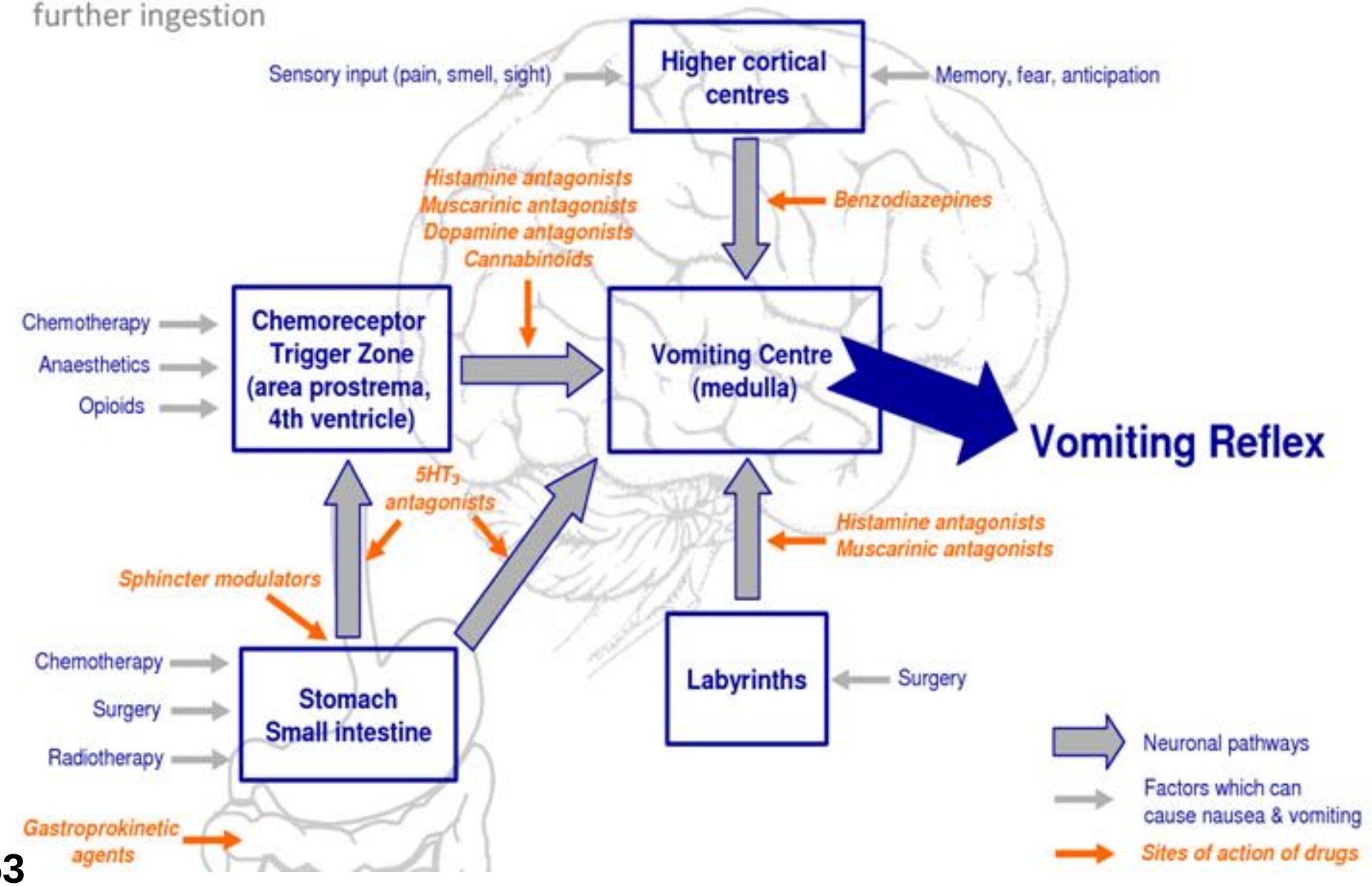
H1 receptors.

Neurokinin 1 (NK1) receptors.

5-HT3 receptors.

Antiemetic Agents

Vomiting :The act of vomiting and the sensation of nausea that accompanies it are protective reflexes that serve to rid the stomach and intestine of toxic substances and prevent their further ingestion



Serotonin 5-HT3 Antagonists

Ondansetron

Granisetron

Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.

Prevent emesis due to vagal stimulation and chemotherapy.

Other emetic stimuli such as motion sickness are poorly controlled.

Uses

Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting.

Their efficacy is enhanced by combination therapy with **dexamethasone** and **NK1-receptor antagonist.**

Adverse effects: Headache, dizziness, and constipation.

Neurokinin 1 Receptor (NK1) Antagonists

Block central **NK1receptors** in the area postrema.

Aprepitant

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

Cannabinoids

Dronabinol, Nabilone

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.

Antipsychotic drugs

Prochlorperazine

Promethazine

Droperidol

Antiemetics due to blocking dopamine and muscarinic receptors.

Sedative effects due to antihistamine activity.

Benzodiazepines

Lorazepam

Diazepam

Reduce anticipatory vomiting caused by anxiety.

H1 Antihistamines & Anticholinergic Drugs

Particularly useful in **motion sickness**.

May cause dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention.

Diphenhydramine, **Dimenhydrinate**

Have significant anticholinergic properties.

Meclizine

Minimal anticholinergic properties and less sedating.

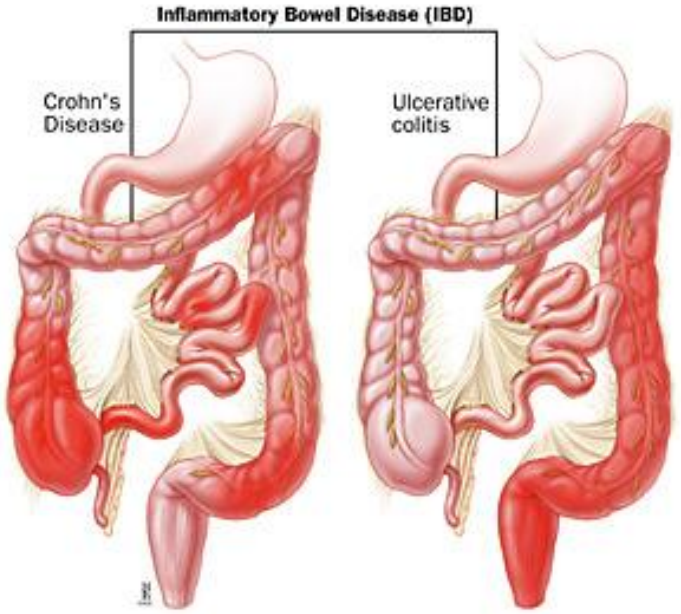
Used for the prevention of motion sickness and the treatment of **vertigo due to labyrinth dysfunction.**

Hyoscine (scopolamine)

Very high incidence of anticholinergic effects.

It is better tolerated as a transdermal patch.

Drugs Used to Treat Inflammatory Bowel Disease



Inflammatory bowel disease (**IBD**):
Ulcerative colitis
& **Crohn's disease.**
Etiology & pathogenesis are unknown.

Crohn's can affect any part of the GIT.
Most cases start in the terminal ileum.
Ulcerative colitis is restricted to the colon and the rectum.
ulcerative colitis is restricted to the mucosa,
while Crohn's disease affects the whole bowel wall.

Crohn's disease and ulcerative colitis present with extra-intestinal manifestations (such as liver problems, arthritis, skin manifestations and eye problems) in different proportions.

Aminosalicylates

5-aminosalicylic acid (5-ASA)

Aminosalicylates work topically (not systemically) in areas of diseased gastrointestinal mucosa.

Up to 80% of unformulated 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon.

A number of formulations deliver 5-ASA to various distal segments of the small bowel or the colon.

Azo Compounds

Sulfasalazine, Balsalazide, Olsalazine

5-ASA bound by an **azo (N=N) bond** to an inert compound or to another 5-ASA molecule

The azo structure markedly **reduces absorption** of the parent drug from the small intestine.

In the terminal ileum and colon, resident bacteria cleave the azo bond by an **azoreductase enzyme**, releasing **5-ASA**.

Mesalamine Compounds

Pentasa:

Timed-release microgranules that release 5-ASA throughout the small intestine .

Asacol :

5-ASA coated in a pH-sensitive resin that dissolves at the pH of the distal ileum and proximal colon).

5-ASA also delivered as:

Enema **(Rowasa)**

Suppositories **(Canasa).**

The mechanism of action of 5-ASA is not certain.

Several mechanisms were proposed, including:

1- Inhibition of cytokine synthesis

2- Inhibition of prostaglandin and leukotriene synthesis

3- Free radical scavenging

4- Immunosuppressive activity

5-ASA inhibits both T-cell proliferation and subsequent activation and differentiation.

5- Impairment of white cell adhesion and function.

Clinical Uses

5-ASA drugs are **first-line agents** for treatment of mild to moderate active **ulcerative colitis**.

Their efficacy in Crohn's disease is unproven, although used as first-line therapy for mild to moderate disease involving the colon or distal ileum.

Adverse Effects:

Due to systemic absorption: especially in slow acetylators:

Nausea, headache, arthralgia, myalgia, bone marrow suppression, and malaise.

Also allergic reactions, oligospermia, and folate deficiency.

Glucocorticoids

-Inhibit production of inflammatory cytokines and chemokines.

-Reduce expression of inflammatory cell adhesion molecules.

- inhibit gene transcription of nitric oxide synthase, phospholipase A2, cyclooxygenase-2, and NF- B.

Clinical Uses:

Moderate to severe active IBD. Not useful for maintenance.

Prednisolone Orally or IV.

Hydrocortisone Rectally for rectal and sigmoid involvement.

Budesonide

A controlled-release oral formulation ,releases the drug in the distal ileum and colon for ileal and proximal colon involvement.

Antimetabolites:

Azathioprim, 6-Mercaotopurine.

Are purine analogs; which produce thioguanine nucleotides (Active form).

Immunosuppressants.

Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis.

Clinical Use:

Onset delayed for 17 weeks.

Used in induction and maintenance of remission.

Allow dose reduction or elimination of steroids.

Adverse Effects:

Nausea, vomiting, bone marrow suppression, hepatic toxicity and allergic reactions(fever, rash, pancreatitis, diarrhea and hepatitis).

Allopurinol increases levels of the drugs.

Methotrexate:

Antimetabolite, Used in cancer chemotherapy, rheumatoid arthritis and psoriasis.

Mechanism of action:

Inhibition of dihydrofolate reductase enzyme which is important in the synthesis of thymidine and purines.

- At high doses it inhibits cellular proliferation.
- At low doses used in IBD, it interferes with the inflammatory actions of interleukin-1, stimulates adenosine release, apoptosis and death of activated T lymphocytes.

Uses

Induction and maintenance of remissions of Crohn's Disease.

Adverse effects:

At high doses, can cause:

bone marrow depression,

megaloblastic anemia,

alopecia and mucositis.

Renal insufficiency may increase risk of hepatic accumulation and toxicity.

Side effects counteracted by **folate** supplementation.

Anti-Tumor Necrosis Factor Therapy

Moderate to severe **Crohn's disease.**

Also **TNF-α** is one of the principal cytokines mediating the TH1 (helper T cell type 1) immune response characteristic of **Crohn's disease**.

Infliximab

A chimeric immunoglobulin (25% mouse, 75% human) that binds to and neutralizes **TNF-α** .

Infliximab binds to both soluble & transmembrane forms of TNF- α and inhibits their ability to bind to TNF receptors and may cause lysis of these cells.

Given by IV infusion.

Half life 8-10 days with persistence of antibodies in plasma for 8-12 weeks

Used in acute and chronic treatment of patients with for **refractory ulcerative colitis.**

Response might be lost due to development of antibodies to infliximab.

Side Effects:

Acute:

fever, chills, urticaria, or even anaphylaxis

Delayed :

serum sickness–like reactions may develop after infliximab infusion, but **lupus-like syndrome** occurs only rarely.

Antibodies to infliximab can decrease its clinical efficacy.

Therapy is associated with increased incidence of **respiratory infections; reactivation of TB.**

Infliximab also is contraindicated in patients with severe congestive heart failure.

Adalimumab

Fully humanized IgG antibody, given SC.

Certolizumab

Polyethylene glycol Fab fragment of humanized anti- TNF-α, also given SC.

immunogenicity appears to be less of a problem than that associated with infliximab.

Natalizumab

Humanized IgG4 monoclonal antibody against the cell adhesion molecule α 4-integrin subunit.

Prevents binding of several integrins on circulating inflammatory cells to vascular adhesion molecules

Used for patients with moderate to severe Crohn's disease who have failed other therapies

Given by IV infusion every 4 weeks, and patients should not be on other immune suppressants to prevent the risk of progressive multifocal leukoencephalopathy (rare and usually fatal viral disease)

Adverse effects include acute infusion reactions &

a small risk of opportunistic infections.

Pancreatic Enzyme Supplements

Contain a mixture of **amylase, lipase, and proteases.**

Used to treat pancreatic enzyme insufficiency.

Pancrelipase.

Available in both non-enteric-coated (given with acid suppression therapy) & enteric-coated preparations.

Administered with each meal and snack.

Excessive doses may cause diarrhea and abdominal pain.

The high purine content of pancreas extracts may lead to hyperuricosuria and renal stones.

Drugs Used to Treat Variceal Hemorrhage

Portal hypertension most commonly occurs as a consequence of chronic liver disease.

Portal hypertension is caused by increased blood flow within the portal venous system and increased resistance to portal flow within the liver.

Splanchnic blood flow is increased in patients with cirrhosis.

The extra blood flow causes the veins in the esophagus to balloon outward.

Varices can rupture, leading to massive upper GI bleeding.

Somatostatin & Octreotide

In patients with cirrhosis and portal hypertension, intravenous somatostatin or octreotide reduces portal blood flow and variceal pressures.

They inhibit the release of glucagon and other gut peptides that alter mesenteric blood flow.

They promote initial homeostasis from bleeding esophageal varices.

They are generally administered for 3–5 days.

Vasopressin (antidiuretic hormone)

Is a potent arterial vasoconstrictor.

IV infusion causes splanchnic arterial vasoconstriction that leads to reduced splanchnic perfusion and lowered portal venous pressures.

Vasopressin was commonly used to treat acute variceal hemorrhage. Because of its high adverse-effect profile, it is no longer used for this purpose.

Patients with acute gastrointestinal bleeding from small bowel or large bowel vascular ectasias or diverticulosis, vasopressin may be infused—to promote vasospasm—into one of the branches of the superior or inferior mesenteric

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 artery through an angiographically placed catheter.

Adverse effects:

Are common. hypertension, myocardial ischemia or infarction, or mesenteric infarction.

Other common adverse effects are nausea, abdominal cramps, and diarrhea (due to intestinal hyperactivity).

vasopressin promotes retention of free water, which can lead to hyponatremia, fluid retention, and pulmonary edema.

Terlipressin is a vasopressin analog that have similar efficacy to vasopressin with fewer adverse effects.

Beta-Receptor-Blocking Drugs

Beta-receptor antagonists reduce portal venous pressures via a decrease in portal venous inflow.

This decrease is due to a decrease in cardiac output (β1 blockade) and to splanchnic vasoconstriction (β2 blockade) caused by the unopposed effect of systemic catecholamines on α receptors.

Thus, nonselective blockers such as **propranolol** and **nadolol** are more effective than selective β1 blockers in reducing portal pressures.

Nonselective β blockers significantly reduce the rate of recurrent bleeding.