# Gastrointestinal and antiemetic drugs

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# GI drugs

- Drugs used for:
- Peptic ulcers and gastroesophageal reflux disease (GERD)
- Drugs used to control Chemotherapy-induced nausea and vomiting
- Antidiarrheals
- Constipation
- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)

# Peptic ulcer

- Causes of peptic ulcer:
- Infection with gram-negative Helicobacter pylori
- Use of nonsteroidal anti-inflammatory drugs  (NSAIDs)
- Increased hydrochloric acid secretion
- Inadequate mucosal defense against gastric acid
- Tumors (rare)

# Drugs for peptic ulcer

- Treatment of peptic ulcer
  1. Eradicating the H. pylori infection
  2. Reducing secretion of gastric acid with the use of proton pump inhibitors or H2-receptor antagonists
  3. Providing agents that protect the gastric mucosa from damage such as misoprostol and sucralfate
  4. Neutralizing gastric acid with nonabsorbable antacids

# Drugs for peptic ulcer/GERD

- Antimicrobials
- H2-receptor antagonists
- Proton pump inhibitors
- Potassium-competitive Acid Blockers
- Prostaglandins
- Antacids

- These medications can be used for GERD except antimicrobials which are not warranted

# Antimicrobial agents

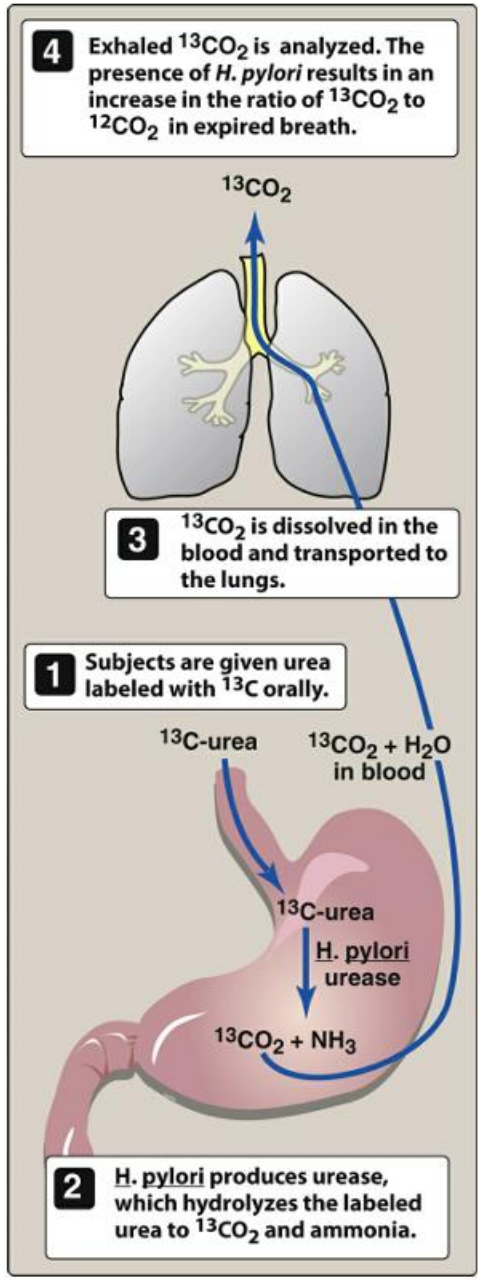
- Antimicrobial agents (For H. pylori): several medications can be used depending on resistance patterns and antibiograms. Other factors to consider include patient factors like hypersensitivity, exposure to antimicrobials, kidney and liver functions, etc

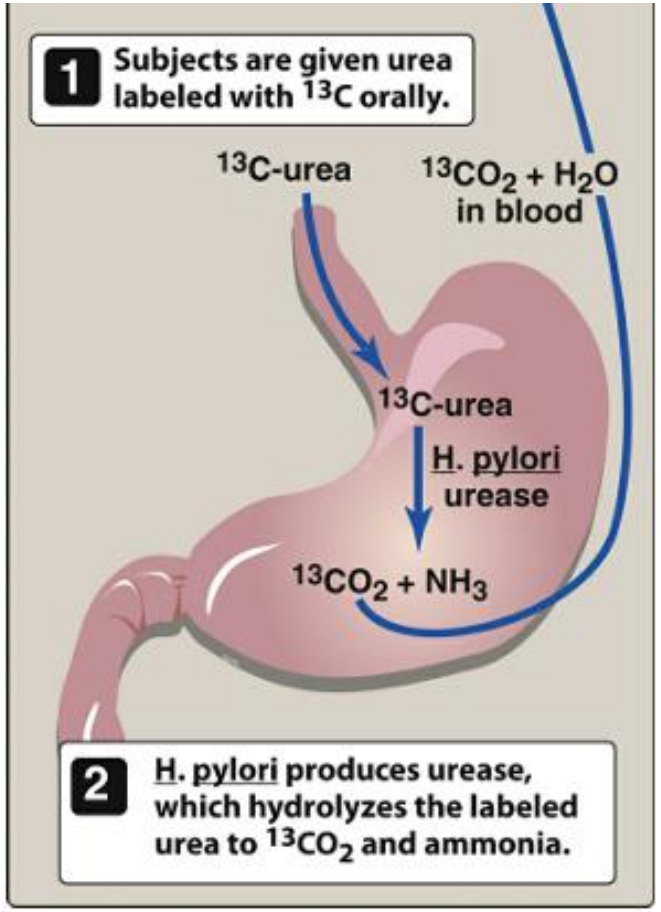
- Options include:
  - Metronidazole
  - Amoxicillin
  - Clarithromycin
  - Tetracyclines
  - Bismuth compounds

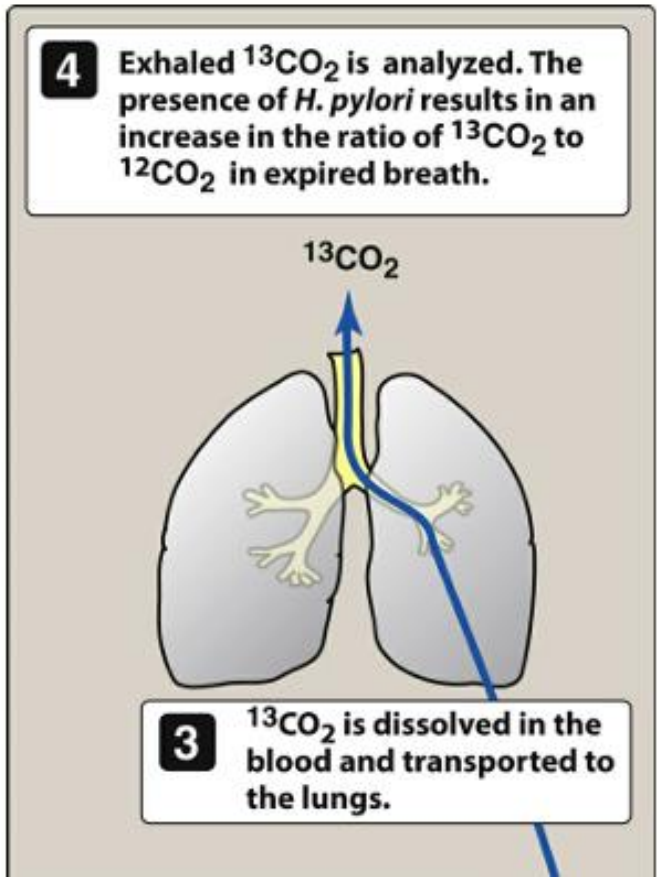
# Antimicrobial agents

- Optimal therapy for patients with peptic ulcer disease infected with H. pylori requires antimicrobial treatment
- Endoscopic biopsy of the gastric mucosa or various noninvasive methods are used, including serologic tests and urea breath tests to document infection with H. pylori
- Eradication of H. pylori results in rapid healing of  active peptic ulcers and low recurrence rates

- Not indicated if no H.pylori infection is documented



# Antimicrobial agents

- GERD is not associated with H. pylori infection and does not respond to treatment with antibiotics
- Triple therapy consisting of a PPI combined with either metronidazole or amoxicillin plus clarithromycin for 2 weeks
  - (Amoxicillin, clarithromycin, omeprazole)
  - Peptipac®, Triopac®
- Quadruple therapy of bismuth subsalicylate and metronidazole plus tetracycline plus a PPI, administered for a 2-week course
- Treatment with a single antimicrobial drug is less effective, results in antimicrobial resistance, and is absolutely not recommended
- Switching antibiotics is not recommended
- Bismuth salts inhibit pepsin and increase the secretion of mucus

# Antimicrobial agents

- Currently, quadruple therapy of bismuth subsalicylate, metronidazole, and tetracycline plus a PPI is a recommended first-line option. This usually results in a 90% or greater eradication rate.

- Triple therapy consisting 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.

# $H_2$-receptor antagonists

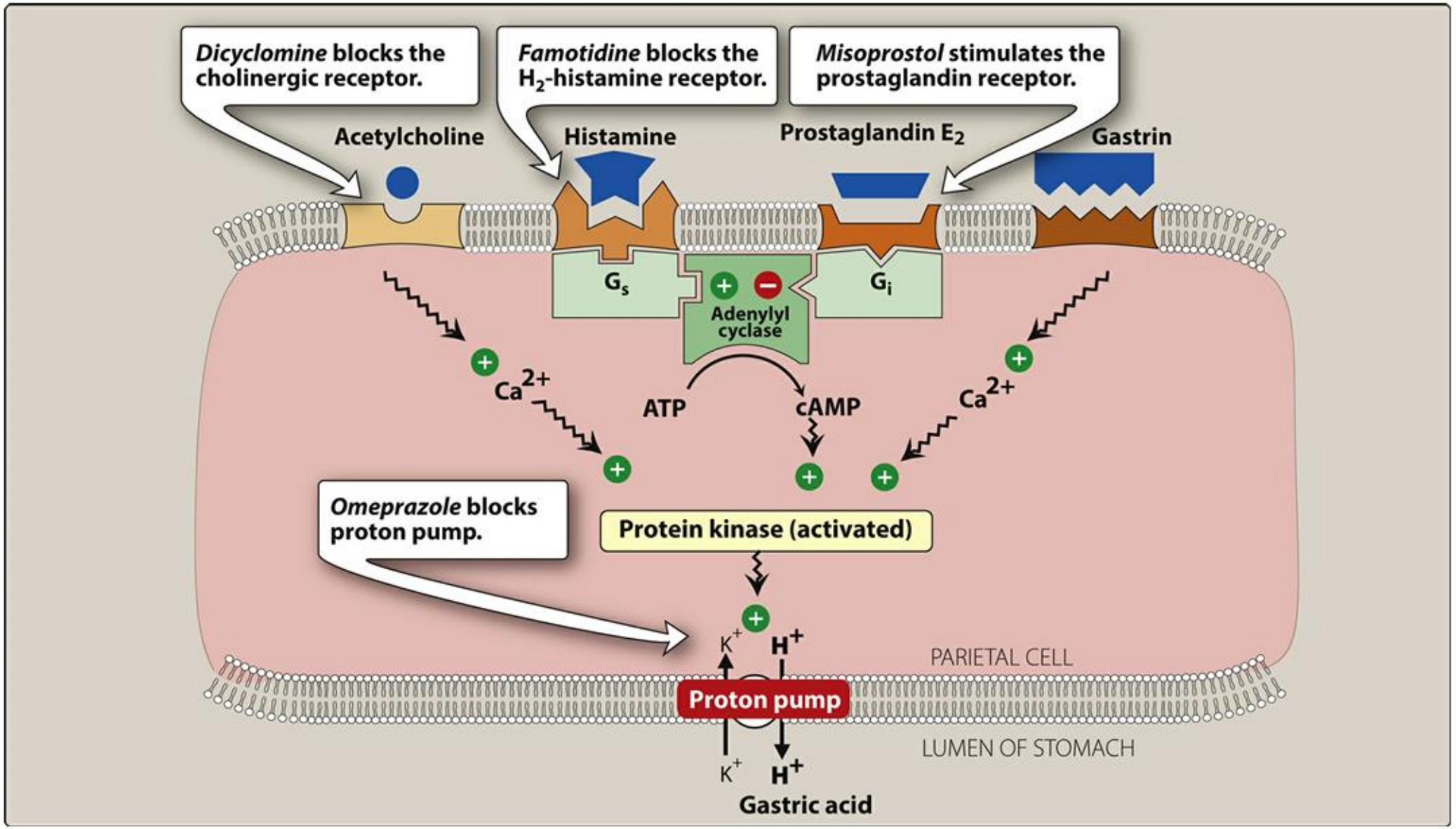
- Famotidine (Famodin®, Famo®, Gastrex®)
- Cimetidine (Cemidin®, Cimetag®, Tagamet®)
- Nizatidine

# $H_2$-receptor antagonists

- Gastric acid secretion by parietal cells of the gastric mucosa is stimulated by acetylcholine, histamine, and gastrin
- The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which stimulates the H+/K+– adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K+ into the lumen of the stomach
- Receptor binding of prostaglandin E2 and somatostatin diminish gastric acid production
- Histamine binding causes activation of adenylyl cyclase, whereas binding of prostaglandin E2 inhibits it
- Gastrin and acetylcholine act by inducing an increase in intracellular calcium levels

# $H_2$-receptor antagonists

- Antagonists of the histamine H2 receptor are used to inhibit gastric acid secretion
- By competitively blocking the binding of histamine to H2 receptors, these agents reduce the intracellular concentrations of cAMP and, secretion of gastric acid
- Inhibit basal, food-stimulated, and nocturnal  secretion of gastric acid after a single dose
- Cimetidine use is limited by its adverse effects and drug–drug interactions



# $H_2$-receptor antagonists therapeutic uses

- Peptic ulcer
- Acute stress ulcers
- Gastroesophageal reflux disease (GERD)

# $H_2$-receptor antagonists therapeutic uses

- Peptic ulcers:
- Effective in promoting the healing of duodenal and gastric ulcers
- Recurrence is common after treatment with H2 antagonists is stopped
- Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers better than H2 antagonists

# $H_2$-receptor antagonists therapeutic uses

- Acute stress ulcers
- H2 blockers are given as intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in intensive care units
- PPIs have gained favor for this indication because  tolerance may occur with these agents in this setting

# $H_2$-receptor antagonists therapeutic uses

- Gastroesophageal reflux disease (GERD):
- Low doses of H2 antagonists is used for the prevention and treatment of heartburn (GERD)
- H2-receptor antagonists act by stopping acid secretion and may not relieve symptoms for at least 45 minutes
- Antacids more quickly and efficiently neutralize secreted acid already in the stomach, but their action is only temporary
- PPIs are now used preferentially in the treatment of GERD

# $H_2$-receptor antagonists

- The dosage of all these drugs must be decreased in patients with hepatic or renal failure
- Cimetidine can interfere in the metabolism of many drugs
- Cimetidine inhibits CYP450 and can slow metabolism and potentiate the action of several drugs resulting in serious adverse effects

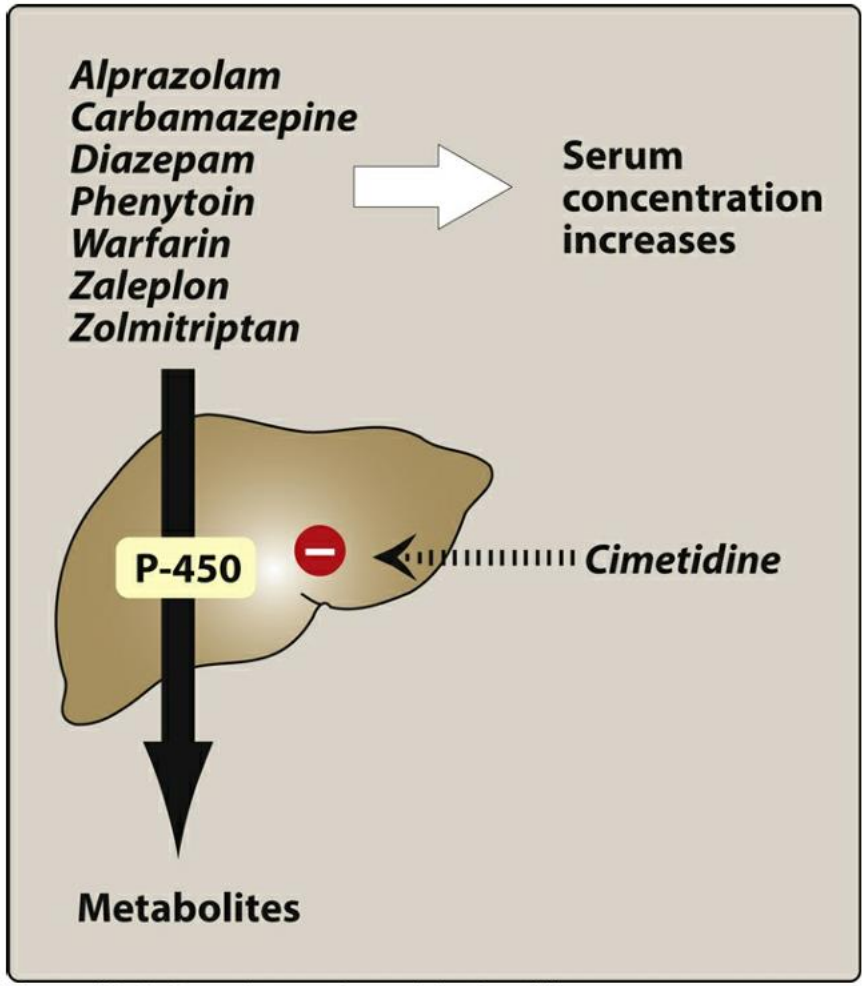



**Figure 42.5** Drug interactions with *cimetidine*.

# $H_2$-receptor antagonists

- Adverse effects:
  - Headache
  - Dizziness
  - Diarrhea
  - Muscular pain
  - Cimetidine can also have endocrine effects because it acts as a nonsteroidal antiandrogen
    - These effects include gynecomastia, and galactorrhea
- Drugs such as ketoconazole, which depend on an  acidic medium for gastric absorption, may not be efficiently absorbed if taken with H2 receptor antagonists

# Proton pump inhibitors

- Omeprazole (Locid®, Losec®, Marial®, Mepral®,  Pepticum®)
- Esomeprazole (Nexium®, Ezomax®)
- Lansoprazole (Lanso®, Lanton®, Zoton®)
- Dexlansoprazole
- Pantoprazole (Pantover®, Controloc®)
- Rabeprazole

# Proton pump inhibitors

- Bind to the H+/K+-ATPase enzyme system (proton pump) of the parietal cell and suppress the secretion of hydrogen ions into the gastric lumen, inhibiting gastric acid secretion
- The membrane-bound proton pump is the final step in the secretion of gastric acid
- More effective than H2 antagonists in suppressing gastric acid production and healing peptic ulcers

# Proton pump inhibitors

- PPIs 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 is absorbed and transported to parietal cells
- There, it is converted to the active form, which forms a stable covalent bond with H+/K+-ATPase
- It takes about 18 hours for the enzyme to be resynthesized
- At standard doses, all PPIs inhibit both basal and stimulated gastric acid secretion by ~90%

# Proton pump inhibitors therapeutic uses

- The superiority of the PPIs over the H2 antagonists for suppressing acid production and healing peptic ulcers has made them the preferred drugs for:
  - Stress ulcer treatment and prophylaxis
  - Treating erosive esophagitis and active duodenal ulcer
  - Long-term treatment of pathologic hypersecretory conditions (e.g. Zollinger-Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl)

# Proton pump inhibitors therapeutic uses

- Approved for the treatment of GERD and have gained favor over H2 antagonists
- PPIs reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs

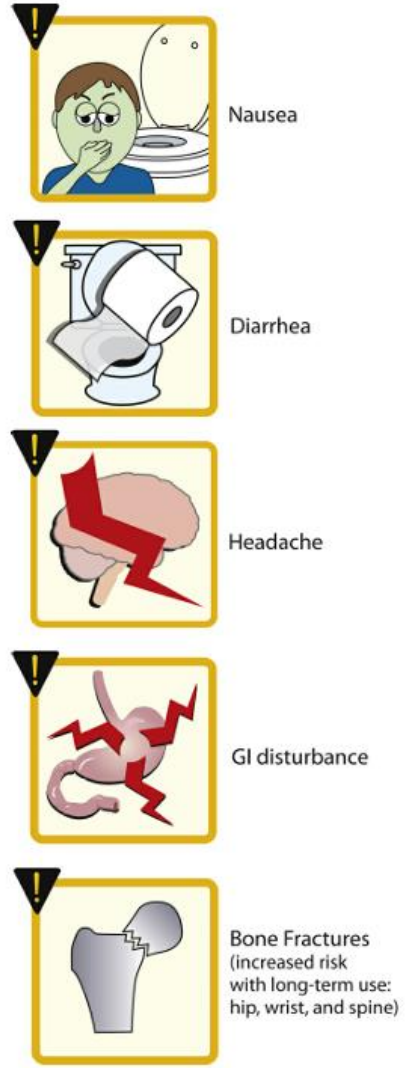
- Used with antimicrobial regimens to eradicate H. pylori

# Proton pump inhibitors therapeutic uses

- PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day
- If an H2-receptor antagonist is also needed, it should be taken well after the PPI for best effect because the H2 antagonists will reduce the activity of the proton pump
- In patients with GERD in whom a once-daily PPI is only partially effective, increasing to a twice-daily regimen or keeping the PPI in the morning and adding an H2 antagonist in the evening may improve symptom control

# Proton pump inhibitors adverse effects

- Diarrhea
- Clostridium difficile colitis
- Patients must be counseled to discontinue PPI therapy if they have diarrhea for several days and to contact their physicians
- Possible increased risk of fractures of the hip,  wrist, and spine
- The greatest risk is associated with patients taking the PPIs for one year or greater
- Acute interstitial nephritis
- Hypomagnesemia
- Increased incidence of pneumonia



# Proton pump inhibitors drug interactions

- Omeprazole, esomeprazole inhibit CYP2C19, resulting in significantly reduced antiplatelet activity of clopidogrel.
- Omeprazole inhibits the metabolism of warfarin, phenytoin, diazepam, and cyclosporine through competitive inhibition of CYP450 enzymes
- Prolonged therapy may result in low vitamin B12, because acid is required for its absorption
- Prolonged elevation of gastric pH can cause incomplete absorption of calcium carbonate products
- Use calcium citrate as a source of calcium for patients taking acid-suppressing medications

# Potassium-competitive Acid Blockers

- Vonoprazan
- Bind competitively and reversibly to the potassium binding site of the H+/K+-ATPase following protonation and suppress the secretion of hydrogen ions into the gastric lumen, inhibiting gastric acid secretion.

- Therapeutic uses
  - Peptic ulcer
  - GERD

- Adverse effects: diarrhea, nasopharyngitis, dyspepsia, headache, and abdominal pain.

# Prostaglandins

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

- A deficiency of prostaglandins is involved in the pathogenesis of peptic ulcers

# Prostaglandins

- Misoprostol (Cytotec®)
  - A stable analog of prostaglandin approved for the prevention of gastric ulcers induced by NSAIDs
  - Less effective than H2 antagonists and the PPIs for acute treatment of peptic ulcers
  - Has cytoprotective actions, but is clinically effective only at higher doses that diminish gastric acid secretion
  - Routine prophylactic use of misoprostol may not be justified except in patients who are taking NSAIDs and are at high risk of NSAID-induced ulcers such as elderly patients and those with ulcer complications

# Prostaglandins

- Misoprostol (Cytotec®)
  - Like other prostaglandins, misoprostol produces uterine contractions, dislodging of the fetus, and is contraindicated during pregnancy
  - Adverse effects: diarrhea and nausea

# Antacids

- Weak bases that react with gastric acid to form  water and a salt to diminish gastric acidity
- Antacids also reduce pepsin activity because  pepsin is inactive at a pH greater than 4

# Antacids

- Aluminum hydroxide
- Magnesium hydroxide
- Calcium carbonate
- Systemic absorption of sodium bicarbonate can produce transient metabolic alkalosis and is not recommended for long-term use
- Food delays stomach emptying allowing more time for the antacid to react

# Antacids

- Aluminum hydroxide + Magnesium hydroxide (Maalox®)
- Calcium carbonate + Magnesium carbonate (Rennie®)
- Calcium carbonate (Tums®)

# Antacids therapeutic uses

- Aluminum- and magnesium-containing antacids are used to:
  - Provide symptomatic relief of peptic ulcer disease and GERD
  - Promote healing of duodenal ulcers
  - Used as last-line therapy for acute gastric ulcers

- Calcium carbonate preparations are also used as calcium supplements for the treatment of osteoporosis

# Antacids adverse effects

- Aluminum hydroxide causes constipation
- Magnesium hydroxide causes diarrhea
- The binding of phosphate by aluminum-containing antacids can lead to hypophosphatemia
- Sodium bicarbonate
  - Can cause systemic alkalosis
  - Liberates CO2, causing belching and flatulence
  - The sodium content of antacids can be an important consideration in patients with hypertension or congestive heart failure

# Mucosal protective agents

- Cytoprotective compounds
- Enhance mucosal protection mechanisms,  preventing mucosal injury, reducing inflammation, and healing existing ulcers.
  - Sucralfate (Ulsanic®)
  - Bismuth subsalicylate (Pink Bismuth®, Kalbeten®)

# Sucralfate

- A complex of aluminum hydroxide and sulfated sucrose
- Binds to positively charged groups in proteins of both normal and necrotic mucosa
- Forms complex gels with epithelial cells creating a physical barrier that impairs diffusion of HCl and prevents degradation of mucus by pepsin and acid
- Stimulates prostaglandin release, mucus and bicarbonate output
- Inhibits peptic digestion
- By these mechanisms, sucralfate effectively heals duodenal ulcers and is used in long-term maintenance therapy to prevent their recurrence
- Does not prevent NSAID-induced ulcers, and does not heal gastric ulcers

# Sucralfate

- Requires an acidic pH for activation and should not be administered with PPIs, H2 antagonists, or antacids
- Little of the drug is absorbed systemically
- Very well tolerated, but it can interfere with the absorption of other drugs by binding to them

# Bismuth subsalicylate

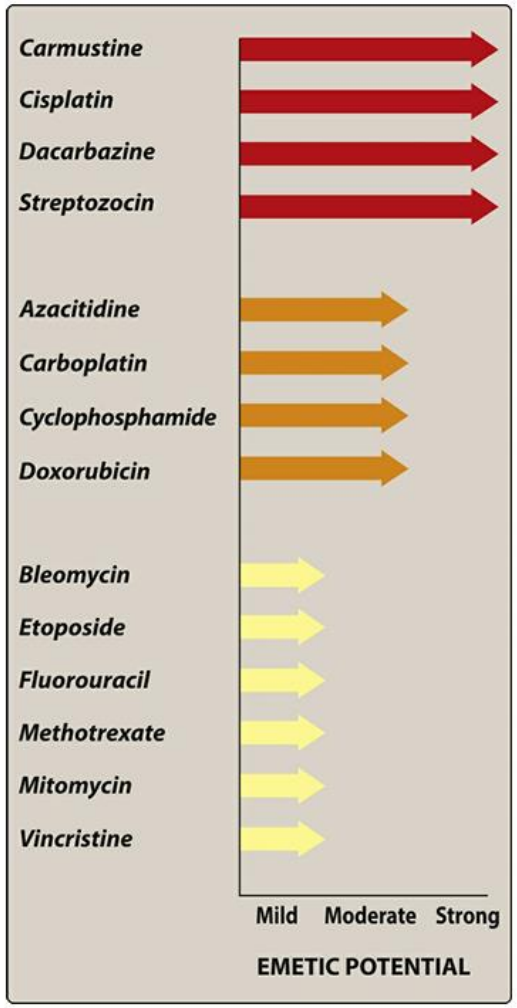
- Effectively heals peptic ulcers
- Has antimicrobial actions
- Inhibits the activity of pepsin
- Increases secretion of mucus, and interact with  glycoproteins in necrotic mucosal tissue to coat and protect the ulcer crater

# Drugs used to control chemotherapy induced emesis

- Nausea and vomiting may occur in a variety of conditions (motion sickness, pregnancy, and hepatitis) and are always unpleasant for the patient
- The nausea and vomiting produced by many chemotherapeutic agents demands especially effective management
- 70% -80% percent of all patients who undergo chemotherapy experience nausea or vomiting

# Drugs used to control chemotherapy induced emesis

- Several factors influence the incidence and severity of chemotherapy-induced emesis including
- The specific chemotherapeutic drug
- The dose
- Route and schedule of administration
- Patient variables
  - Young patients and women are more susceptible than older patients and men



# Drugs used to control chemotherapy induced emesis

- 10% - 40% of patients experience nausea or vomiting in anticipation of their chemotherapy (anticipatory vomiting)
- Emesis not only affects the quality of life but can also lead to rejection of potentially curative antineoplastic treatment
- Uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion

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# Mechanisms that trigger vomiting

- Two brainstem sites have key roles in the  vomiting reflex pathway
  - Chemoreceptor trigger zone
    - Found outside the blood-brain barrier, thus can respond directly to chemical stimuli in the blood or CSF
  - The vomiting center
    - Located in the lateral reticular formation of the medulla
    - Coordinates the motor mechanisms of vomiting
    - Responds to afferent input from the vestibular system, the periphery (pharynx and gastrointestinal tract), and higher brainstem and cortical structures
    - The vestibular system functions mainly in motion sickness

# Emetic actions of chemotherapeutic agents

- Chemotherapeutic agents can activate the medullary chemoreceptor trigger zone, or vomiting center
- Several neuroreceptors, including dopamine receptor Type 2 (D2) and serotonin Type 3 (5-HT3), play critical roles
- The color or smell of chemotherapeutic drugs and even stimuli associated with chemotherapy can activate higher brain centers and trigger emesis
- Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and releasing serotonin from the enterochromaffin cells of the small intestinal mucosa
- Released serotonin activates 5-HT3 receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response

# Antiemetic drugs

- Antiemetics represent a variety of classes with  various efficacies
- Anticholinergic drugs like the muscarinic receptor  antagonist scopolamine and H1-receptor antagonists, such as dimenhydrinate, meclizine, and cyclizine are very useful in motion sickness but are ineffective against substances that act directly on the chemoreceptor trigger zone

# Antiemetic drugs

- Scopolamine
- Dimenhydrinate (Dramine®)
- Cyclizine
- Meclizine (Meclozine)
    - Meclozine + pyridoxine (Ancozine®, Paravomine®)

# Antiemetic drugs

- Phenothiazines
- 5-HT3 receptor blockers
- Substituted benzamides
- Butyrophenones
- Benzodiazepines
- Corticosteroids
- Substance P/neurokinin-1 receptor blocker

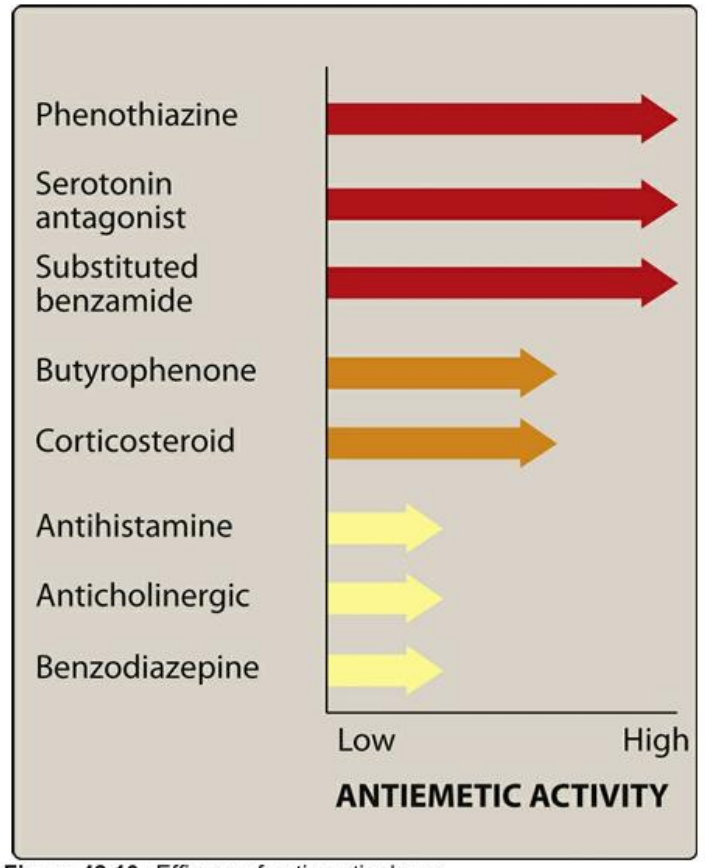


**Figure 42.10** Efficacy of antiemetic drugs.

# Phenothiazines

- Prochlorperazine
- Act by blocking dopamine receptors
- Effective against low or moderately emetogenic chemotherapeutic agents (e.g. fluorouracil and doxorubicin)
- Side effects:
  - Hypotension and restlessnes (Dose limiting)
  - Extrapyramidal symptoms
  - Sedation

# 5-HT3 receptor blockers

- Ondansetron
- Granisetron
- Palonosetron
- Dolasetron

# 5-HT3 receptor blockers

- Important in treating emesis linked with chemotherapy,  because of their longer duration of action
- Selectively block 5-HT3 receptors in the periphery (visceral  vagal afferent fibers) and in the brain (chemoreceptor trigger zone)
- Can be administered as a single dose prior to chemotherapy  (intravenously or orally)
- Efficacious against all grades of emetogenic therapy
- Extensively metabolized by the liver, doses should be  adjusted in patients with hepatic insufficiency
- Side Effects:
  - Headache
  - Electrocardiographic changes, such as a prolonged QT interval, can occur with dolasetron

# Substituted benzamides

- Metoclopramide (Emistop®, Pramin®)
- Effective at high doses against the emetogenic  cisplatin, preventing emesis in 30%-40% percent of patients and reducing emesis in the majority
- Antidopaminergic side effects like sedation,  diarrhea, and extrapyramidal symptoms, limit its high-dose use

# Butyrophenones

- Droperidol
- Haloperidol
- Act by blocking dopamine receptors
- Moderately effective antiemetics
- Droperodol may prolong the QT interval, and is reserved for patients with inadequate response to other agents
- High-dose haloperidol was found to be nearly as effective as high-dose metoclopramide in preventing cisplatin-induced emesis

# Benzodiazepines

- Lorazepam (Lorocare®, Lorivan®)
- Alprazolam (Xanax®, Xanagis®, Prazolex®)
- The antiemetic potency of lorazepam and  alprazolam is low
- Their beneficial effects may be due to their  sedative, anxiolytic, and amnesic properties
- These same properties make benzodiazepines  useful in treating anticipatory vomiting

# Corticosteroids

- Dexamethasone
- Methylprednisolone
- Effective against mildly to moderately emetogenic chemotherapy
- Most frequently used in combination with other agents
- Their antiemetic mechanism is not known
- Can cause insomnia and hyperglycemia in patients with diabetes mellitus

# Substance P/neurokinin-1 receptor blocker

- Aprepitant
- Targets the neurokinin receptor in the brain and blocks the actions of the natural substance
- Aprepitant administered orally with dexamethasone and palonosetron
- Undergoes extensive metabolism, primarily by CYP3A4
- Affect the metabolism of other drugs
- Induce CYP3A4
  - Concomitant use with warfarin can shorten its half life
- Side effects: constipation and fatigue
- Only indicated for highly or moderately emetogenic chemotherapy regimens

# Antiemetic drugs

- Combination regimens:
- Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity
- Corticosteroids, most commonly 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 administered in combination with high-dose metoclopramide to reduce extrapyramidal reactions or with corticosteroids to counter metoclopramide induced diarrhea

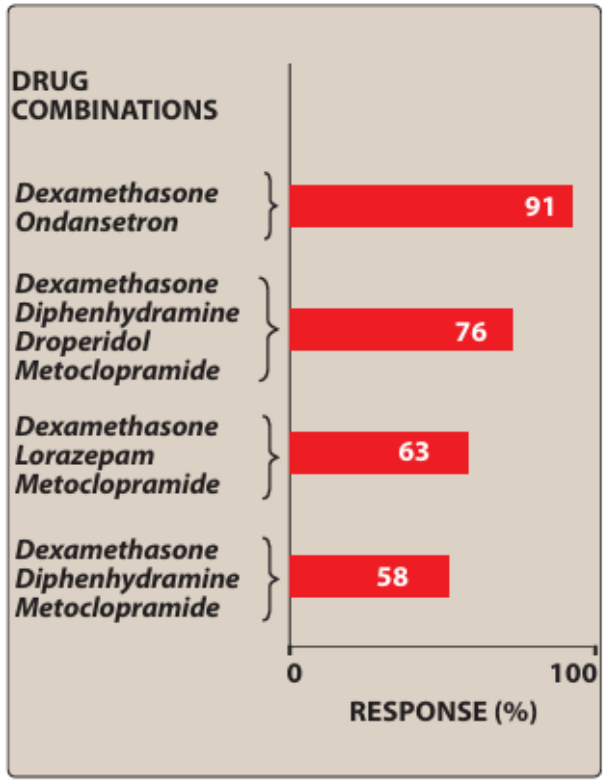


**Figure 42.12**
Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after *cisplatin* chemotherapy.

# Antidiarrheal drugs

- Increased motility of the gastrointestinal tract and decreased absorption of fluid are major factors in diarrhea
- Antidiarrheal drugs used to treat acute diarrhea include
  - Antimotility agents
  - Adsorbents
  - Agents that modify fluid and electrolyte transport

| DRUGS USED IN DIARRHEA |
| --- |
| *Oral rehydration therapy (ORS)* |
| *Probiotics* |
| *Zinc* |
| **ANTIMOTILITY AGENTS** |
| *Diphenoxylate + atropine* |
| *Loperamide* |
| **ADSORBENTS** |
| *Aluminum hydroxide* |
| *Methylcellulose* |
| **AGENTS THAT MODIFY FLUID AND ELECTROLYTE TRANSPORT** |
| *Bismuth subsalicylate* |

**Figure 42.13**
Summary of drugs used to treat diarrhea.

# Antimotility agents

- Diphenoxylate
- Loperamide (Diacare®, Imodium®)
- Both are analogs of meperidine and have opioid-like actions on the gut
- Activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis
- At the usual doses, they lack analgesic effects
- Side effects: drowsiness, abdominal cramps, and dizziness
- Contribute to toxic megacolon and should not be used in young children or in patients with severe colitis

# Adsorbents

- Aluminum hydroxide
- Methylcellulose
- Used to control diarrhea
- Act by adsorbing intestinal toxins or  microorganisms and/or by coating or protecting the intestinal mucosa
- Much less effective than antimotility agents and
- Can interfere with the absorption of other drugs

# Agents that modify fluid and electrolyte transport

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

# Constipation

- Common condition caused by
- Diminished fluid intake
- Slow motility of waste material through large intestine
- Certain foods, medications, diseases

# Laxatives

- Laxatives are commonly used for constipation to accelerate the movement of food through GIT
- Increase the potential for loss of pharmacologic effect of poorly absorbed, delayed acting, and extended-release oral preparations by accelerating their transit through the intestines
- May cause electrolyte imbalances when used chronically
- All of these drugs, except for the chloride channel activator lubiprostone, have a risk of dependency for the user

# Laxatives

- Irritants and stimulants
- Bulk laxatives
- Saline and osmotic laxatives
- Stool softeners
  - (emollient laxatives or surfactants)
- Lubricant laxatives
- Chloride channel activators


**Figure 42.12** Summary of drugs used to treat constipation.

# Irritants and stimulants

- Senna
- Bisacodyl
- Castor oil

# Irritants and stimulants: Senna

- Senna (Laxikal Forte®, Agiolax®)
- Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides
- Taken orally, senna causes evacuation of the bowels within 8 to 10 hours
- Also causes water and electrolyte secretion into the bowel
- In combination products with a docusate-containing stool softener, it is useful in treating opioid-induced constipation

# Irritants and stimulants: Bisacodyl

- Bisacodyl (Dilax®, Laxadin®)
- Potent stimulant of the colon
- Acts directly on nerve fibers in the mucosa of the colon
- Adverse effects include abdominal cramps and the potential for atonic colon with prolonged use
- Milk and drugs that may increase the gastric pH, such as antacids, PPIs, and H2-receptor antagonists, should not be taken at the same time as the enteric-coated tablets
  - These agents may cause the enteric coating to dissolve prematurely in the stomach, resulting in stomach irritation and pain

# Irritants and stimulants: Castor oil

- Castor oil
- Broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and increases peristalsis
- Pregnant patients should avoid castor oil because it may stimulate uterine contractions

# Bulk laxatives

- The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables)
- Form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity
- Similar actions are produced by methylcellulose, psyllium seeds, and bran
- Should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction

# Saline and osmotic laxatives

- Magnesium citrate
- Magnesium hydroxide
- Sodium phosphate
  - Nonabsorbable salts that hold water in the intestine by osmosis
  - This distends the bowel, increasing intestinal activity and producing defecation in a few hours
- Electrolyte solutions containing PEG are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures
  - PEG powder for solution is available as a laxative
- Lactulose is a semisynthetic disaccharide sugar that also acts as an osmotic laxative
  - It cannot be hydrolyzed by intestinal enzymes
  - Oral doses are degraded in the colon by colonic bacteria into lactic, formic, and acetic acids
  - This increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation

# Stool softeners

- Stool softeners (emollient laxatives or surfactants)
  - Docusate sodium
  - Docusate calcium
  - Docusate potassium
- Surface-active agents that become emulsified with the stool produce softer feces and ease passage
- May take days to become effective and are often used for prophylaxis rather than acute treatment

# Lubricant laxatives

- Include mineral oil and glycerin suppositories
- Act by facilitating the passage of hard stools
- Mineral oil should be taken orally in an upright  position to avoid its aspiration and potential for lipid or lipoid pneumonia

# Chloride channel activators

- Lubiprostone
- Activate chloride channels to increase fluid  secretion in the intestinal lumen
- This eases the passage of stools and causes little change in electrolyte balances
- Used in the treatment of chronic constipation
- Minimal drug–drug interactions because  metabolism occurs quickly in the stomach and jejunum
- Side effect: Nausea, Diarrhea

# Irritable Bowel Syndrome (IBS)

- IBS is characterized by chronic abdominal pain and altered bowel habits in the absence of an organic cause.
- IBS may be classified as constipation predominant (IBS-C), diarrhea predominant (IBS-D), or a combination of both.
- Diet and psychosocial modifications play an important role in management of the disease, as well as drug therapy


**Figure 42.13** Summary of drugs used to treat irritable bowel syndrome.IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea.

| DRUG | INDICATION | MECHANISM OF ACTION | ADVERSE EFFECTS |
|---|---|---|---|
| *Linaclotide*<br>*Plecanatide* | IBS-C* | Guanylate cyclase-C agonist | Diarrhea<br>Do not use in GI obstruction |
| *Lubiprostone* | Women with IBS-C*^ | Chloride channel activator | Nausea and vomiting, diarrhea<br>Do not use in GI obstruction |
| *Tegaserod* | Women with IBS-C and < 65 years old | 5-$HT_4$ partial agonist | Diarrhea<br>Do not use in GI obstruction or history of MI, stroke, or angina |
| *Tenapanor* | IBS-C | Sodium/hydrogen exchanger 3 (NHE3) inhibitor | Diarrhea<br>Do not use in GI obstruction |
| *Alosetron* | Women with severe IBS-D | 5-$HT_3$ antagonist | Constipation, nausea and vomiting, heartburn, ischemic colitis (rare) |
| *Eluxadoline* | IBS-D | μ-Opioid receptor agonist | Constipation, abdominal pain, nausea, pancreatitis (rare)<br>Avoid use in pancreatitis or alcoholism |
| *Rifaximin* | Short-term use in IBS-D | Decreases bacterial load (structural analog of *rifampin*) | Nausea, fatigue, headache, dizziness, peripheral edema, and risk of Clostridium difficile infection |
| *Dicyclomine* | IBS-C and IBS-D | Antimuscarinic; decreases GI spasms and motility | Anticholinergic effects such as drowsiness and dry mouth |
| *Hyoscyamine* | IBS-C and IBS-D | Antimuscarinic; decreases GI spasms and motility | Anticholinergic effects such as drowsiness and dry mouth<br>Overdose may produce hallucinations, arrhythmias, and nausea and vomiting |

# Drugs used for Irritable Bowel Disease (IBD)

- IBD is a group of idiopathic chronic intestinal conditions characterized by immune-mediated GI tract inflammation in response to bacterial antigens in the intestinal lumen.
- Most common subtypes of IBD are Crohn disease (CD) and ulcerative colitis (UC).
- CD can affect any portion of the GI tract from the mouth to the anus in a noncontinuous fashion and is characterized by transmural inflammation.
- UC usually affects the rectum. It may extend continuously to affect other parts of the colon and is characterized by inflammation limited to the mucosal layer
- Severity, extent of disease, and risk of complications guide treatment of IBD.

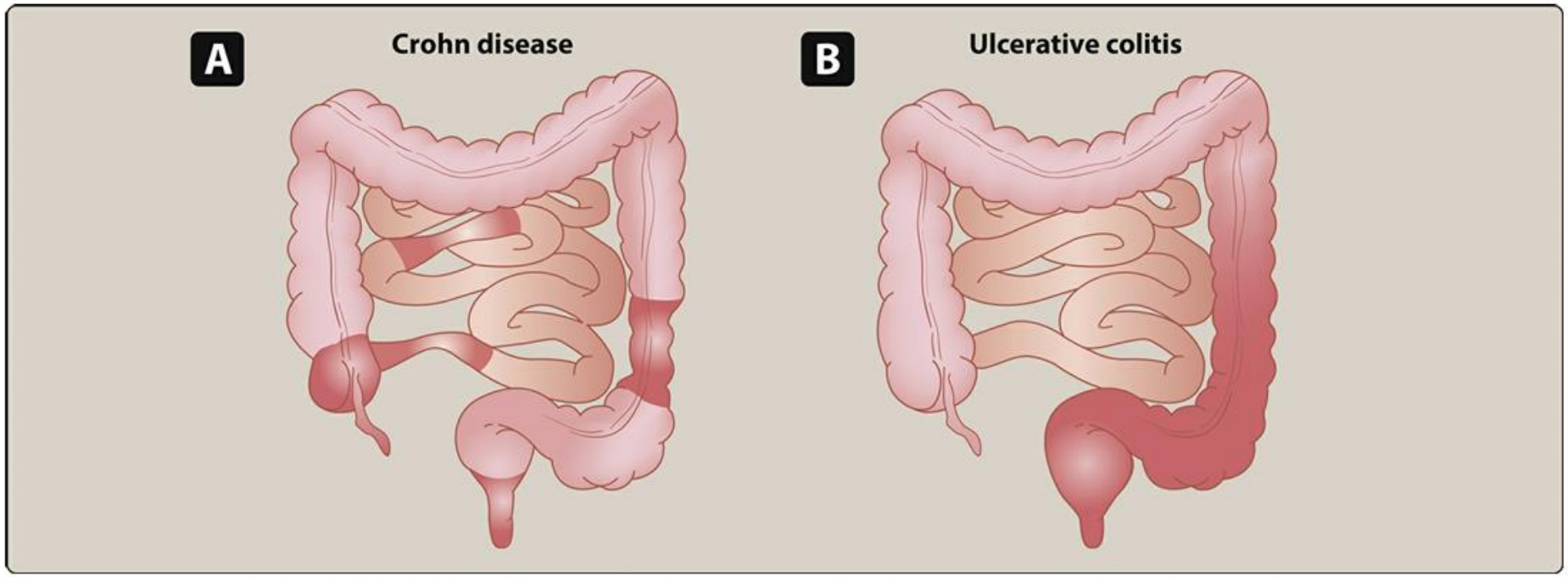


**Figure 42.15** Distribution patterns of disease with **(A)** skip lesions in Crohn disease and **(B)** continuous involvement of the colon, beginning with the rectum, in ulcerative colitis.

# Drugs used for Irritable Bowel Disease (IBD)

- Remission of IBD can be induced with the use of:
  - Rectal and oral 5-aminosalicylates (5-ASAs)
  - Corticosteroids (rectal, oral locally delivered, and systemic)
  - Biologic agents
    - TNF-α inhibitors
    - α-4 integrin inhibitors
    - IL-12/23 inhibitor: ustekinumab
  - Janus kinase inhibitor: tofacitinib.
  - Immunomodulators are additional agents used in the maintenance of remission in IBD
    - Azathioprine
    - 6-mercaptopurine
    - Methotrexate
- Drugs used to maintain remission are the same as those used for induction

**5-AMINOSALICYLATES**

Oral Formulation
- *Balsalazide* COLAZAL
- *Mesalamine* ASACOL HD, PENTASA
- *Olsalazine* DIPENTUM
- *Sulfasalazine* AZULFIDINE

Rectal Formulation
- *Mesalamine enema* ROWASA
- *Mesalamine suppository* CANASA

**CORTICOSTEROIDS**

Oral Formulation
- *Budesonide delayed-release* ENTOCORT EC
- *Budesonide extended-release* UCERIS
- *Hydrocortisone* CORTEF
- *Prednisone* DELTASONE
- *Methylprednisolone* MEDROL

Intravenous Formulation
- *Hydrocortisone* SOLU-CORTEF
- *Methylprednisolone* SOLU-MEDROL

Rectal Formulation
- *Budesonide foam* UCERIS RECTAL
- *Hydrocortisone suppository* ANUCORT-HC
- *Hydrocortisone enema* CORTENEMA
- *Hydrocortisone foam* CORTIFOAM

**BIOLOGIC AGENTS**

TNF-α Inhibitors
- *Adalimumab* HUMIRA
- *Certolizumab* CIMZIA
- *Golimumab* SIMPONI
- *Infliximab* REMICADE

α4-Integrin Inhibitors
- *Vedolizumab* ENTYVIO

IL-12/23 Inhibitor
- *Ustekinumab* STELARA

**JANUS KINASE INHIBITORS**

- *Tofacitinib* XELJANZ

**IMMUNOMODULATORS**

- *Azathioprine* IMURAN
- *6-Mercaptopurine* GENERIC ONLY
- *Methotrexate* VARIOUS

# 5-Aminosalicylates

- 5-ASA agents include:
  - Sulfasalazine
  - Mesalamine
  - Balsalazide
  - Olsalazine

# 5-Aminosalicylates

- The 5-ASAs exhibit anti-inflammatory and immunosuppressive properties that are the main determinants of their efficacy in IBD.
- The exact mechanism of action of 5-ASA is unknown but is thought to be due to
  - inhibition of cytokine and prostaglandin synthesis
  - inhibition of leukotriene release
  - scavenging of free radicals
  - inhibition of T-cell proliferation, activation, and differentiation
  - impairment of leukocyte adhesion and function.
  - 5-ASA is thought to act via topical interaction with the intestinal mucosa
- Mechanisms are the same with both oral and rectal administration.

# 5-Aminosalicylates therapeutic uses

- The 5-ASA drugs are the mainstay of treatment in UC for induction and maintenance of remission.
- Current guidelines recommend mesalamine, balsalazide, or olsalazine as first line for mild–moderate disease.
- Patients with moderate–severe UC may require use of biologic agents and immunomodulators.
- Use of 5-ASA drugs in CD is limited due to a general lack of efficacy.

# 5-Aminosalicylates adverse effects

- Sulfasalazine (due to the sulfapyridine component)
  - Headache, nausea, and fatigue (most common, dose related)
  - Serious reactions include hemolytic anemia, myelosuppression, hepatitis, pneumonitis, nephrotoxicity, fever, rash, and Stevens–Johnson syndrome.
  - Treatment should be discontinued at the first sign of skin rash or hypersensitivity.
  - Sulfasalazine reversibly impairs male fertility.
  - Sulfasalazine inhibits folate absorption
  - Folate supplementation is recommended with chronic use.
- Mesalamine (well tolerated)
  - Headache and dyspepsia are the most common adverse effects
  - Acute interstitial nephritis (Rare); renal function should be monitored
- Olsalazine: Watery diarrhea
- Coadministration of drugs that increase pH (PPIs, H2 receptor antagonists, and antacids) may result in increased systemic absorption of mesalamine
    - Olsalazine, balsalazide are non-pH dependent

# Corticosteroids

- Corticosteroids are used in IBD for their anti-inflammatory effects
- Very effective at inducing remission in IBD, but longterm maintenance with corticosteroids should be avoided due to the deleterious effects of chronic use.
- Rectal formulations (hydrocortisone enema and budesonide foam) have fewer adverse effects than systemic steroids, but use is limited to left-sided disease in UC.
- Enteric-release preparations of oral budesonide deliver corticosteroid to a portion of inflamed intestine.
- This agent has minimal systemic adverse effects due to low bioavailability resulting from extensive first-pass hepatic metabolism.

# Biologic agents

- Biologic agents used in the management of IBD.
  - TNF-α inhibitors
  - α-4 integrin inhibitors
  - IL-12/23 inhibitor: ustekinumab
- Associated with an increased risk for infection.
  - Patients should be evaluated for tuberculosis, and treatment for latent TB should be considered prior to use of these drugs.
- Many have other indications such as rheumatoid  arthritis or psoriasis

# TNF-α inhibitors

- Infliximab
- Adalimumab
- Certolizumab
- Golimumab
- Parenteral monoclonal antibodies effective for both induction and maintenance of remission in IBD.
- Indicated for moderate–severe CD and UC
- Second-line agents in patients with UC who have failed 5-ASAs, unresponsive to or dependent on corticosteroids, or who present with more severe disease.
- In CD, the TNF-α inhibitors have a first-line role in patients with moderate–severe disease and those at higher risk of progression and worse outcomes.
- Associated with the development of immunogenicity and antidrug antibodies that can result in loss of response

# α-4 integrin inhibitors

- Vedolizumab
- A humanized monoclonal to α-4/β-7 integrin
- Indicated in moderate–severe UC and CD for induction of remission and maintenance.
- α-4 Integrins are adhesion molecules that promote leukocyte migration to sites of inflammation.
- α-4 integrin inhibitors reduce lymphocyte migration into the intestinal mucosa and inflammation
- Adverse effects: headache, arthralgia, nausea, fatigue, and musculoskeletal pain.

# IL12/23 inhibitors

- Ustekinumab
- Inhibits IL-12 and IL-23 involved in lymphocyte activation.
- Indicated for psoriasis, psoriatic arthritis, and induction and maintenance of remission in CD in patients refractory to or intolerant of TNF-α inhibitors, immunomodulators, or corticosteroids.
- Adverse effects: headache, arthralgia, infection, nausea, and nasopharyngitis.

# Janus Kinase inhibitors

- Tofacitinib
- Recommended as monotherapy in moderate–severe UC in patients who are refractory to or intolerant of TNF-α inhibitors.
- Also used for rheumatoid arthritis, psoriasis
- Interference with the JAK-STAT signaling pathway result in decreased proliferation and differentiation of macrophage and T cells.
- Can be used for induction and maintenance of remission
- As with the use of biologic drugs, tofacitinib is associated with increased risk for infection, including a specific increased risk of herpes zoster infection.
- Patients should be evaluated for herpes zoster immunization prior to beginning therapy with tofacitinib.
- Adverse effects: nasopharyngitis, arthralgia, and headache.

# Immunomodulators in IBD

- Methotrexate
- Azathioprine
- 6-mercaptopurine (6-MP)

# Methotrexate (MTX)

- Also used in cancer, rheumatoid arthritis, psoriasis
- A structural analogue of folic acid that inhibits the production of folinic acid.
- The exact mechanism of action in CD is unknown.
- Only intramuscular or subcutaneous administration of MTX has efficacy in CD.
- MTX is a recommended monotherapy option for maintenance of remission in CD but is not recommended in maintenance for UC.
- Adverse effects: headache, nausea, vomiting, abdominal discomfort, serum aminotransferase elevations, and rash.
  - Administration of folic acid is effective at reducing the incidence of GI adverse effects and is recommended in patients receiving MTX.

# Thiopurines

- Azathioprine
- 6-mercaptopurine (6-MP)

- Oral medications that have corticosteroid-sparing effects in patients with UC and CD.
- They are considered first line as monotherapy for maintenance of remission.
- Use is limited by concerns of toxicity, including: bone marrow suppression and hepatotoxicity
  - Monitoring of complete blood counts and liver function tests is recommended