Drugs Used in Gastrointestinal disorders Part 2

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B. Drugs That Promote Upper Gastrointestinal Motility

- Drugs that can selectively stimulate gut motor function (**prokinetic** agents) have significant potential clinical usefulness.
  - Agents that increase lower esophageal sphincter pressures may be useful for **GERD**.
  - Drugs that improve gastric emptying may be helpful for **gastroparesis** and **postsurgical gastric emptying delay**.
    - Gastroparesis: Paralysis of the muscles of the stomach and possibly other parts of the gastrointestinal tract due to damage to gastrointestinal nerves or muscle; common in advanced diabetes and advanced Parkinson's disease.

B. Drugs That Promote Upper Gastrointestinal Motility

1. Cholinomimetic agents
2. Metoclopramide and domperidone
3. Macrolide antibiotics

Cholinomimetic agents

- In the past, cholinomimetic agonists such as **bethanechol** were used for GERD and gastroparesis, but the availability of less toxic agents has supplanted their use.

- The acetylcholinesterase inhibitor **neostigmine** is still used for the treatment of hospitalized patients with acute large bowel distention.

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

Metoclopramide and Domperidone

- Metoclopramide and domperidone are dopamine D2 receptor antagonists.
- Within the **gastrointestinal tract** activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents.
- Metoclopramide and domperidone also block dopamine D2 receptors in the **chemoreceptor trigger zone**, resulting in potent anti-nausea and anti-emetic action.
- When used chronically, metoclopramide can cause symptoms of parkinsonism, other extrapyramidal effects, and hyperprolactinemia.
- Domperidone is less likely to cause CNS toxicity, because it does not cross the blood-brain barrier.

Metoclopramide and Domperidone

- **Clinical uses:**

1. Gastroesophageal reflux disease
2. Impaired gastric emptying
3. Nonulcer dyspepsia
4. Prevention of vomiting
5. Postpartum lactation stimulation

Metoclopramide and Domperidone

Domperidone use is associated with an increased risk of sudden cardiac death

Contraindications

Domperidone is now contraindicated in people:

1. with conditions where cardiac conduction is, or could be, impaired
2. with underlying cardiac diseases such as congestive heart failure
3. receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors (azole antifungals, macrolides antibiotics, grapefruit juice)
4. with severe hepatic impairment

Macrolides

- Macrolide antibiotics such as **erythromycin** directly stimulate motilin receptors on gastrointestinal smooth muscle.
  - **Motilin receptor** is a G protein-coupled receptor that binds motilin. Motilin in turn is an intestinal peptide that stimulates contraction of gut smooth muscle.

- Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops.

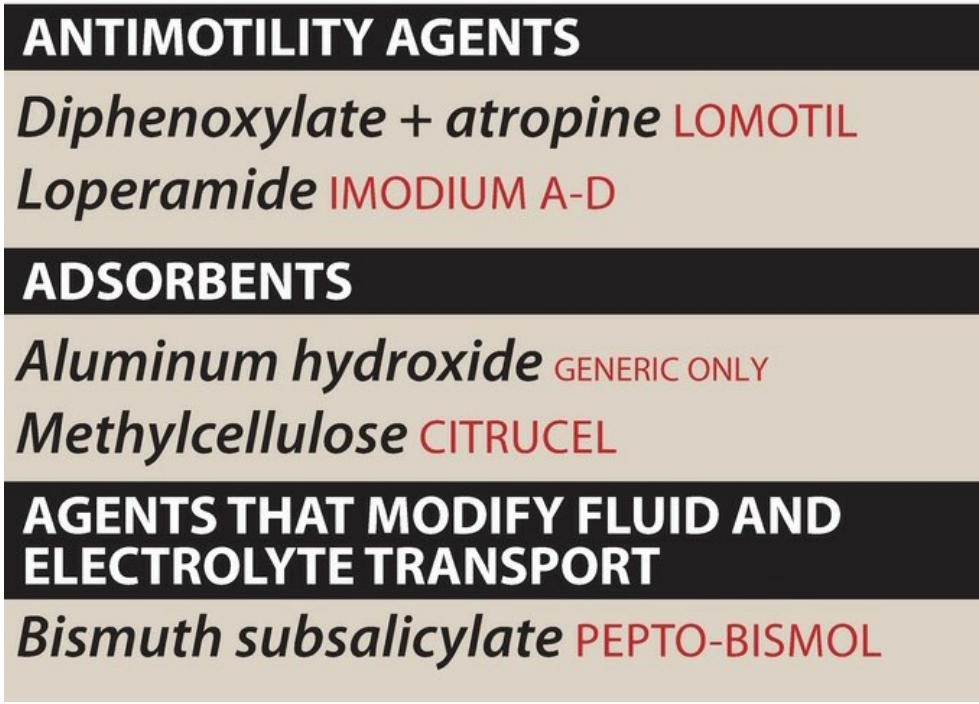
Antidiarrheal agents

Antidiarrheal Agents

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

- Antidiarrheal drugs include:

1. Antimotility agents
2. Adsorbents
3. Drugs that modify fluid and electrolyte transport



Antimotility agents

- **Loperamide** and **diphenoxylate** have opioid-like actions on the gut. They activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis.
  - At the usual doses, they lack analgesic effects.
  - Loperamide is used for the general treatment of acute diarrhea, including traveler's diarrhea.
  - Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

Antimotility agents

- Loperamide has no potential for addiction.
- **High doses of diphenoxylate** have central nervous system effects, and prolonged use can lead to opioid dependence.
- Commercial preparations commonly contain small amounts of atropine to discourage overdosage (2.5 mg diphenoxylate with 0.025 mg atropine). The anticholinergic properties of atropine may contribute to the antidiarrheal action.

Adsorbents

- Adsorbent agents, such as **aluminum hydroxide** and **methylcellulose**.
- These agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa.
- They are much less effective than antimotility agents, and they 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.

Laxatives

Laxatives

- The overwhelming majority of people do not need laxatives; yet they are self-prescribed by a large portion of the population.
- For most people, intermittent constipation is best prevented with a high-fiber diet, adequate fluid intake, regular exercise, and the heeding of nature's call.
- Patients not responding to dietary changes or fiber supplements should undergo medical evaluation before initiating long-term laxative treatment.
- Laxatives may be classified by their major mechanism of action, but many work through more than one mechanism.

TABLE 59–1 The major laxative mechanisms and some representative laxative drugs.

Mechanism	Examples
Bulk-forming	Psyllium, methylcellulose, polycarbophil
Stool-softening	Docusate, glycerin, mineral oil
Osmotic	Magnesium oxide, sorbitol, lactulose, magnesium citrate, sodium phosphate, polyethylene glycol
Stimulant	Aloe, senna, cascara, castor oil, bisacodyl
Chloride channel activator	Lubiprostone Linaclotide (*indirect* via cGMP)
Opioid receptor antagonists	Methylnaltrexone, alvimopan

1. Bulk-forming laxatives

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

- Common preparations include:
  1. Natural plant products (**psyllium, methylcellulose**)
  2. Synthetic fibers **(polycarbophil)**.

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

2. Stool surfactant agents (Stool softeners)

- Surface active agents that become emulsified with the stool produce softer feces and ease passage of stool.
- Common agents include **docusate**.
- It may take days to become effective and are often used for prophylaxis rather than acute treatment.
- It is commonly prescribed to hospitalized patients to prevent constipation and minimize straining.

3. Lubricant laxatives

Mineral oil and **glycerin suppositories** are lubricants and act by facilitating the passage of hard stools.

Mineral oil is a clear, viscous oil. It is not palatable but may be mixed with juices.

Aspiration can result in a severe lipid pneumonia. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid pneumonia.

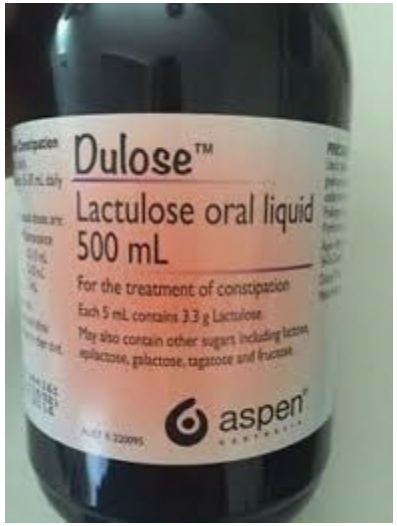
4. Osmotic laxatives

- Osmotic laxatives are soluble but nonabsorbable compounds that result in **increased stool liquidity** due to an obligate increase in fecal fluid.
  A. Nonabsorbable sugars or salts
  B. Balanced polyethylene glycol

4A. Nonabsorbable sugars or salts

- Saline laxative agents include:
- **magnesium citrate, magnesium hydroxide (milk of magnesia) , sodium phosphate, and magnesium sulfate.**

- **Sorbitol** and **lactulose** are nonabsorbable sugars.
- These sugars are metabolized by colonic bacteria, producing severe flatus and cramps.



4A. Nonabsorbable sugars or salts

- **High doses** of osmotically active agents produce prompt bowel evacuation **(purgation)** within 1–3 hours. The rapid movement of water into the distal small bowel and colon leads to a high volume of liquid stool followed by rapid relief of constipation.
- The most commonly used purgatives are **magnesium citrate** and **sodium phosphate**.
- When taking these agents, it is very important that patients maintain adequate hydration by taking increased oral liquids to compensate for fecal fluid loss.
- Sodium phosphate preparations should not be used in patients who are frail or elderly, have renal insufficiency, have significant cardiac disease (because they cause electrolyte imbalance), or are unable to maintain adequate hydration during bowel preparation.

4B. Balanced polyethylene glycol

- Lavage solutions (ingested rapidly (2–4 L over 2–4 hours)) containing **polyethylene glycol (PEG)** are used for complete colonic cleansing before gastrointestinal endoscopic procedures.
- These balanced, isotonic solutions are designed so that no significant intravascular fluid or electrolyte shifts occur. Therefore, they are safe for all patients.
- For treatment or prevention of chronic constipation, smaller doses of PEG powder may be mixed with water or juices (17 g/8 oz) and ingested daily.
- In contrast to sorbitol or lactulose, PEG does not produce significant cramps or flatus.

5. Stimulant laxatives

- **Stimulant laxatives** induce bowel movements through a number of poorly understood mechanisms. These include direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.

- Common agents include **senna**, **bisacodyl** and **castor oil.**

5. Stimulant laxatives

1. Senna

- This agent is a widely used stimulant laxative.
- It causes water and electrolyte secretion into the bowel.
- Taken orally, senna causes evacuation of the bowels within 6 to 12 hours.
- In combination products with a docusate-containing stool softener, it is useful in treating opioid-induced constipation.

2. Bisacodyl

- Available as suppositories and enteric-coated tablets.
- It is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.
- produce a bowel movement in 6–12 hours when given orally and within 2 hours when given rectally.

5. Stimulant laxatives

3. Castor oil

- This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis.
- Pregnant patients should avoid castor oil because it may stimulate uterine contractions.
- Use of castor oil is generally not recommended due to poor palatability and potential for GI adverse effects.

6. Chloride Channel Activator

- **Lubiprostone** and **linaclotide**.
- They increase chloride-rich fluid secretion into the intestine, which stimulates intestinal motility and shortens intestinal transit time.
- Over 50% of patients experience a bowel movement within 24 hours of taking one dose.
- Both are approved for the treatment of chronic constipation and IBS with predominant constipation.

7. Opioid receptor antagonists

- Two selective antagonists of the μ-opioid receptor:

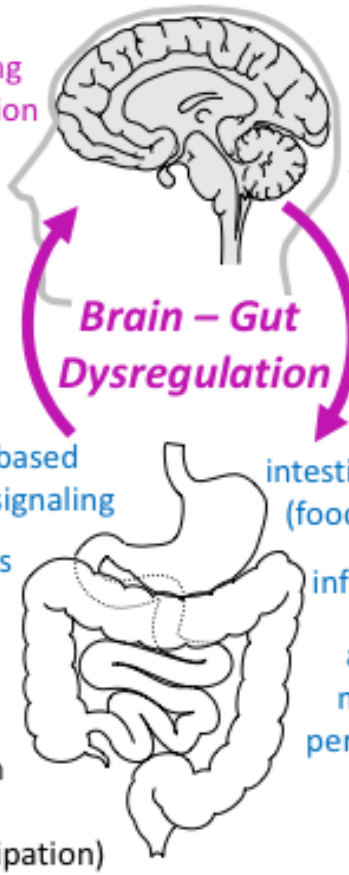
1. **Methylnaltrexone** bromide (S.C)
2. **Alvimopan** (P.O)

- Because these agents do not readily cross the blood-brain barrier, they inhibit peripheral μ-opioid receptors without impacting analgesic effects within the central nervous system.
- Approved for treatment of opioid-induced constipation.
- Because of possible cardiovascular toxicity, alvimopan currently is restricted to short-term use in hospitalized patients only.

Drugs Used In The Treatment Of Irritable Bowel Syndrome & Inflammatory Bowel Disease

Irritable Bowel Syndrome

MRI/PET studies:
↑central pain processing with colorectal distension in IBS vs normal



Risk Factors

Psychosocial stressors:
- *anxiety*
- *stress*
- *depression*

Subtypes

IBS w/ Constipation (IBS-C)
IBS w/ Diarrhea (IBS-C)
Unsubtyped IBS

Pathophysiology

visceral hypersensitivity (common)
- exagerrated response to cholecystokinin
- altered response to meal ingestion

Δ altered bowel motility (diarrhea or constipation)
low grade inflammation (in some IBS-D patients)

Treatments

Counseling / Stress Management / Diet

Physical activity (increased exercise)

Laxatives (IBS-C)
- osmotic laxatives (PEG)
- Cl-channel activator (lubiprostone)
- guanylate cyclase agonist (linaclotide)

Antidiarrheals (IBS-D)
- loperamide
- bile acid sequestrants (e.g. cholestyramine)
- 5-HT antagonists (alosetron)

Antibiotics (IBS-D)
- rifaximin

Abdominal Pain
- antispasmodics
- tricyclic antidepressants (low dose)
- SSRIs?

Drugs Used In The Treatment Of Irritable Bowel Syndrome (IBS)

- IBS is an idiopathic chronic, relapsing disorder characterized by abdominal discomfort (**pain, bloating, distention, or cramps**) in association with alterations in bowel habits **(diarrhea, constipation, or both).**

- With episodes of abdominal pain or discomfort, patients note a change in the frequency or consistency of their bowel movements.

- Pharmacologic therapies for IBS are directed at relieving abdominal pain and discomfort and improving bowel function.

Drugs Used In The Treatment Of Irritable Bowel Syndrome (IBS)

- For patients with predominant diarrhea:

1. Antidiarrheal agents, especially **loperamide**, are helpful in reducing stool frequency and fecal urgency
2. Other agents: **alosetron** (5-HT3 antagonist).

5-HT3 receptors in the gastrointestinal tract activate visceral afferent pain sensation.

Inhibition of gastrointestinal 5-HT3 receptors may reduce unpleasant sensations including nausea, bloating, and pain.

Drugs Used In The Treatment Of Irritable Bowel Syndrome (IBS)

- For patients with predominant constipation:

1. **fiber supplements** may lead to softening of stools and reduced straining; however, increased gas production may exacerbate bloating and abdominal discomfort.
2. Consequently, **osmotic laxatives, especially milk of magnesia**, are commonly used to soften stools and promote increased stool frequency
3. Other agents: **chloride-channel activators**, **lubiprostone** and **linaclotide.**

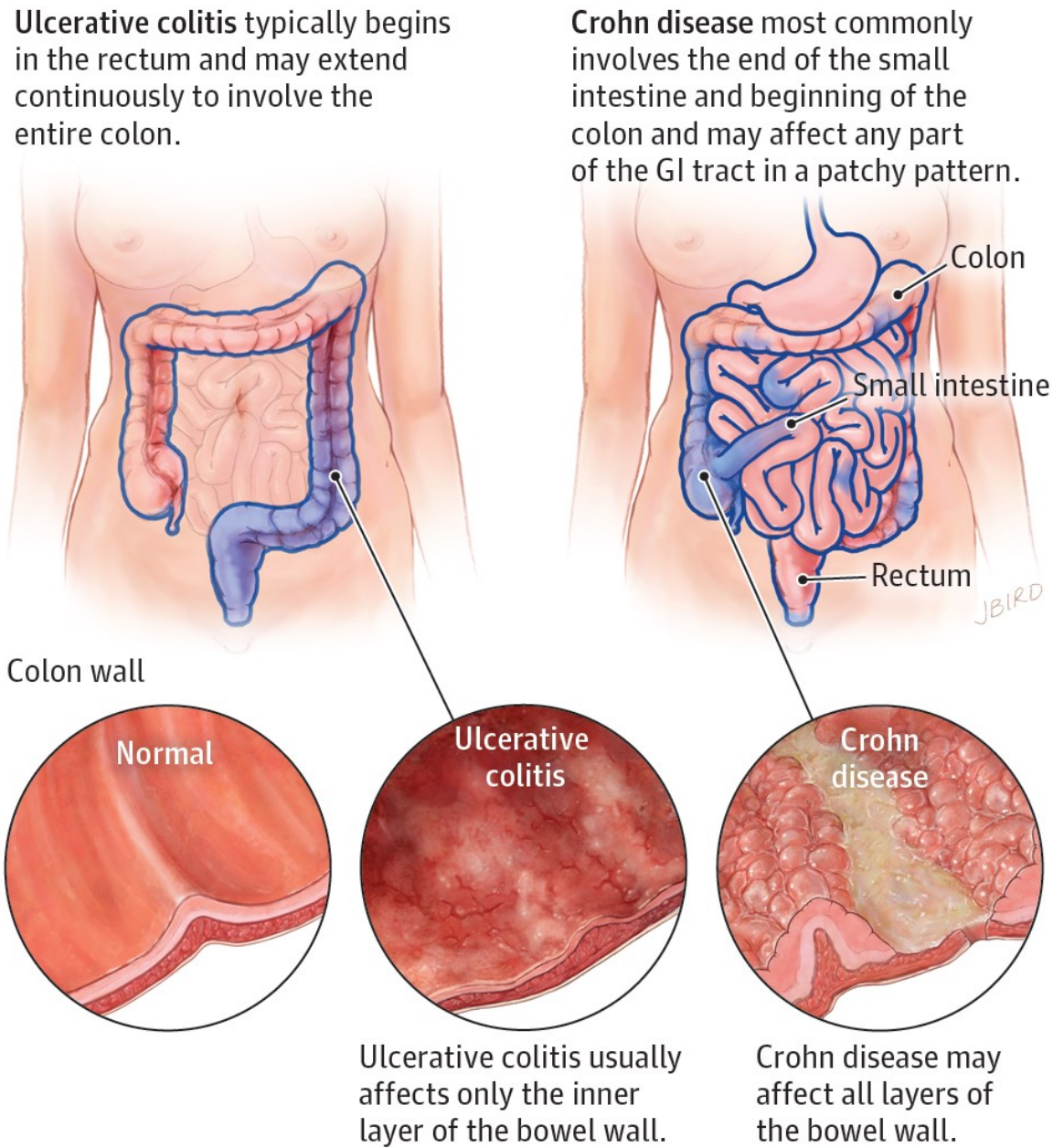
Drugs Used In The Treatment Of Irritable Bowel Syndrome (IBS)

- For chronic abdominal pain, **low doses of tricyclic antidepressants** (eg, amitriptyline or desipramine, 10–50 mg/d) appear to be helpful. At these doses, these agents have no effect on mood.

- For small or large bowel spasm, antispasmodics (anticholinergics) such as **dicyclomine** and **hyoscyamine** are used (However, small or large bowel spasm has not been found to be an important cause of symptoms in patients with IBS.)

Inflammatory Bowel Disease

- Inflammatory bowel disease (IBD) comprises two distinct disorders:
  - Ulcerative colitis
  - Crohn's disease.



Drugs Used To Treat Inflammatory Bowel Disease

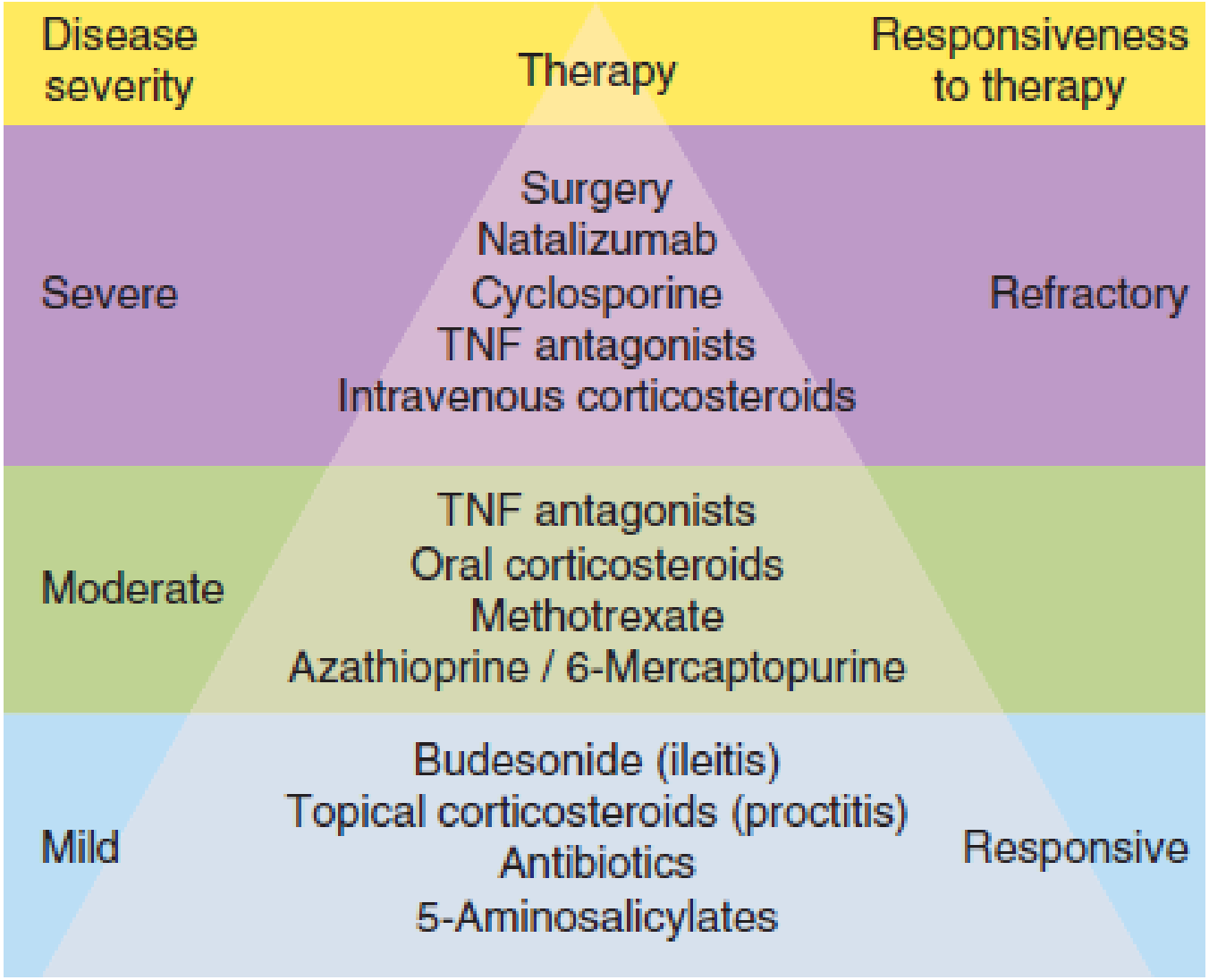
- The etiology and pathogenesis of these disorders remain unknown.

- For this reason, pharmacologic treatment of inflammatory bowel disorders often involves drugs that belong to different therapeutic classes and have different mechanisms of anti-inflammatory action.

- Drugs used in inflammatory bowel disease are chosen on the basis of:

1. Disease severity
2. Responsiveness
3. Drug toxicity.

Drugs Used To Treat Inflammatory Bowel Disease



Antiemetics

Antiemetics

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

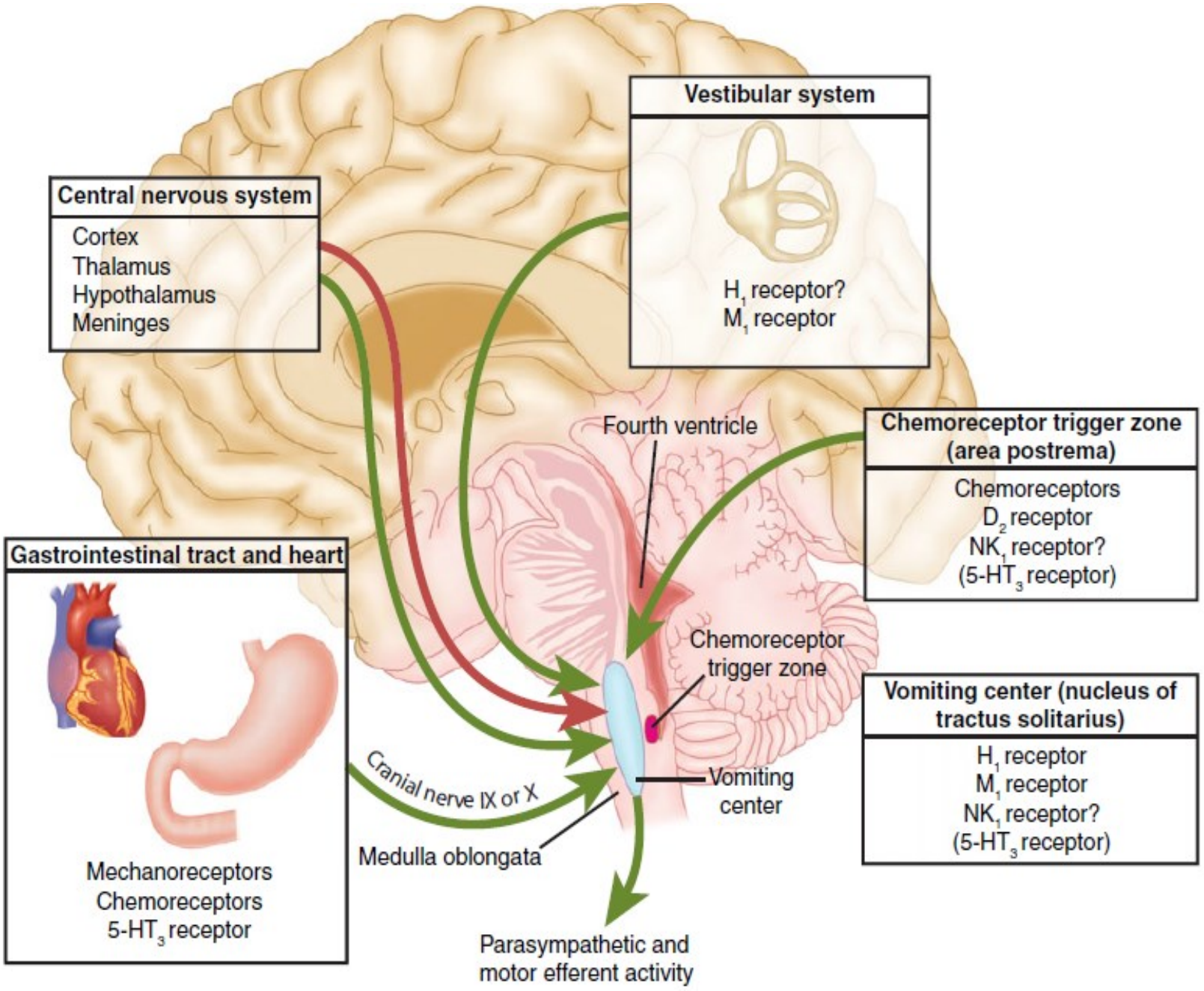
1. Adverse effects from medications
2. Systemic disorders or infections
3. Pregnancy
4. Vestibular dysfunction
5. Central nervous system infection or increased pressure
6. Peritonitis
7. Hepatobiliary disorders
8. Radiation or chemotherapy
9. Gastrointestinal obstruction
10. Dysmotility

Mechanism that trigger vomiting

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

1. **The chemoreceptor trigger zone (CTZ)**. It is outside the blood–brain barrier. Thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid.
2. **Vomiting center**, which is located in the medulla, coordinates the motor mechanisms of vomiting.

- The vomiting center responds to afferent input from the vestibular system, the periphery (pharynx and GI tract), and higher brainstem and cortical structures.
- The vestibular system functions mainly in motion sickness.
- High concentrations of muscarinic M 1 , histamine H 1 , neurokinin 1 (NK 1), and serotonin 5-HT 3 receptors have been identified in the vomiting center.


Central nervous system
Cortex
Thalamus
Hypothalamus
Meninges
Vestibular system
H1 receptor?
M1 receptor
Fourth ventricle
Chemoreceptor trigger zone (area postrema)
Chemoreceptors
D2 receptor
NK1 receptor?
(5-HT3 receptor)
Gastrointestinal tract and heart
Mechanoreceptors
Chemoreceptors
5-HT3 receptor
Chemoreceptor trigger zone
Vomiting center (nucleus of tractus solitarius)
H1 receptor
M1 receptor
NK1 receptor?
(5-HT3 receptor)
Cranial nerve IX or X
Vomiting center
Medulla oblongata
Parasympathetic and motor efferent activity

Emetic actions of chemotherapeutic agents

1. Chemotherapeutic agents can **directly activate the medullary CTZ or vomiting center**. (dopamine receptor type 2 and serotonin type 3 (5-HT3), play critical roles).
2. Chemotherapeutic drugs can also **act peripherally** by:

a) causing cell damage in the GI tract

b) releasing serotonin from the enterochromaffin cells of the small intestine. Serotonin activates 5-HT3 receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

Chemotherapy-induced nausea and vomiting (CINV)

- Several factors influence the incidence and severity of CINV, including:

1. the specific chemotherapeutic drug
2. the dose, route, and schedule of administration
3. patient variables. For example, young patients and women are more susceptible than older patients and men, and 10% to 40% of patients experience nausea and/or vomiting in anticipation of chemotherapy (anticipatory vomiting).

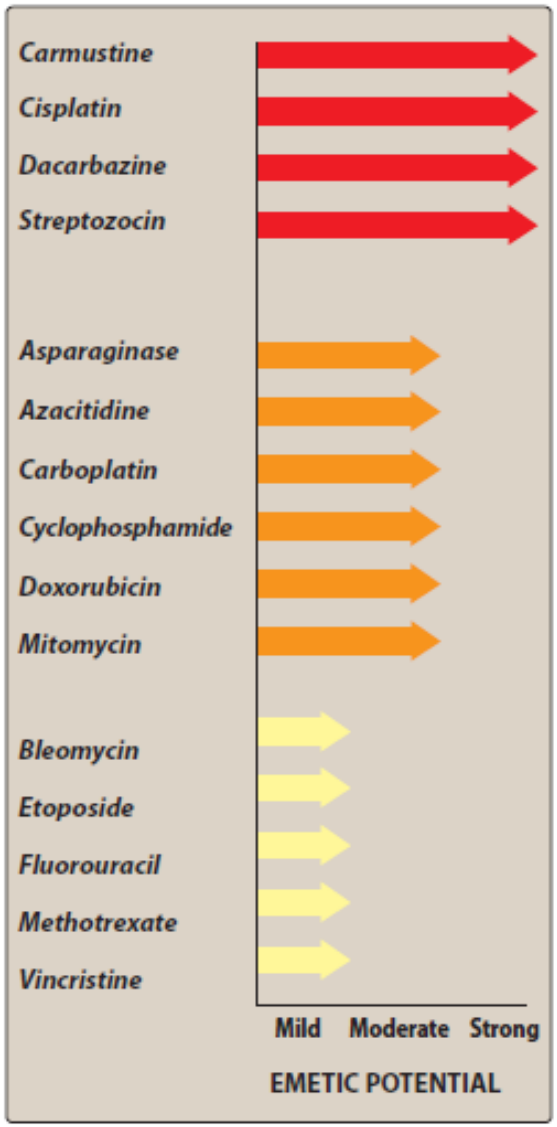


Figure 31.8
Comparison of emetic potential of anticancer drugs.

Antiemetics

1. Dopamine receptor antagonists

A) Substituted banzamide: **metoclopramide**

Metoclopramide is effective at high doses against the emetogenic cisplatin, preventing emesis in 30% to 40% of patients and reducing emesis in the majority of patients.

Antidopaminergic adverse effects, including extrapyramidal symptoms, limit long-term high-dose use.

B) Phenothiazines: **Prochlorperazine**, promethazine, and thiethylperazine.

Prochlorperazine is effective against low or moderately emetogenic chemotherapeutic agents (for example, fluorouracil and doxorubicin).

C) Butyrophenone: **Droperidol**

moderately effective antiemetic

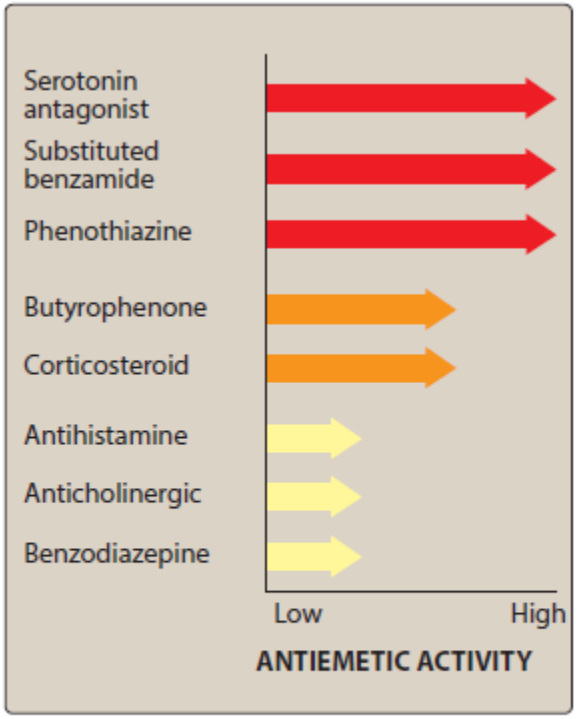


Figure 31.10
Efficacy of antiemetic drugs.

Antiemetics

2. Serotonin 5-HT 3 antagonists

Ondansetron, granisetron, **dolasetron**, and palonosetron.

A) This class of agents is important in treating CINV, because of their superior efficacy and longer duration of action

B) They are also useful in the management of postoperative nausea and vomiting.

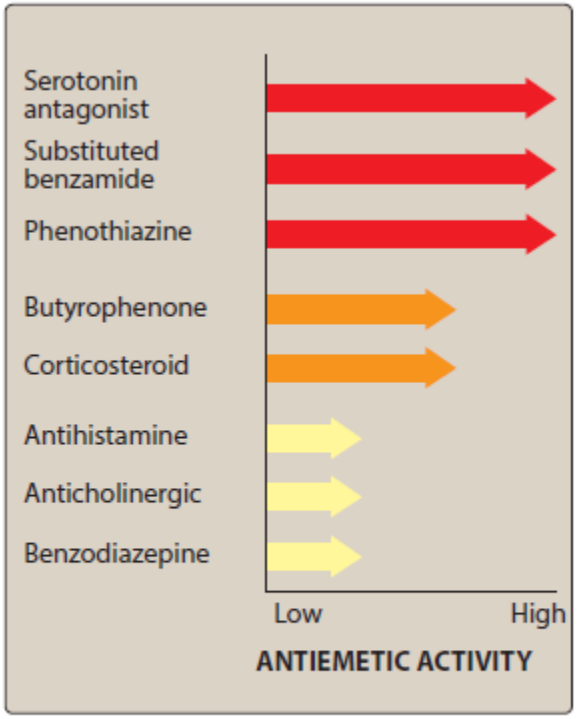


Figure 31.10
Efficacy of antiemetic drugs.

Antiemetics

3. Corticosteroids

Dexamethasone and **methylprednisolone** have antiemetic properties, but the basis for these effects is unknown.

Can be used alone for moderately emetogenic chemotherapy.

Most frequently, they are used in combination with other agents.

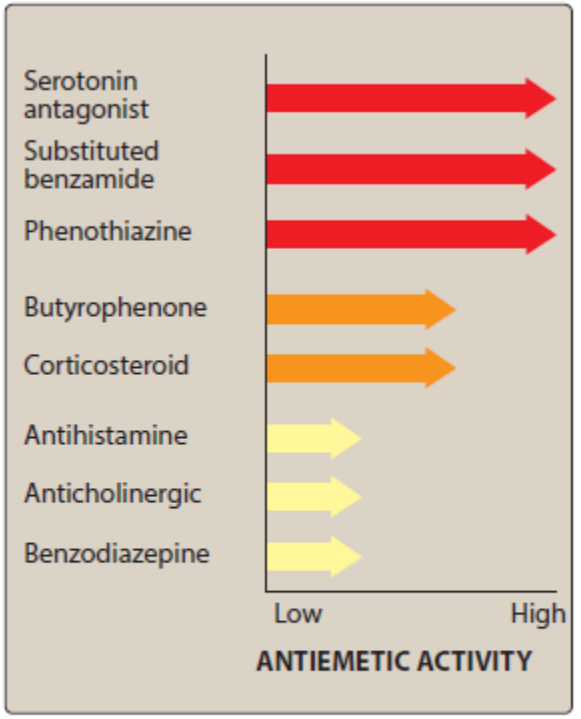


Figure 31.10
Efficacy of antiemetic drugs.

4. Benzodiazepines

Lorazepam or **diazepam** are used before the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by anxiety.

Antiemetics

5. Neurokinin receptor antagonists

Aprepitant, **fosaprepitant** (a prodrug of aprepitant that is administered IV).

- are approved for use in combination with other antiemetics for prevention of the nausea and vomiting associated with highly emetogenic chemotherapeutic regimens.
- These agents are effective for the delayed phase of CINV, which occurs 24 hours or more after chemotherapy.

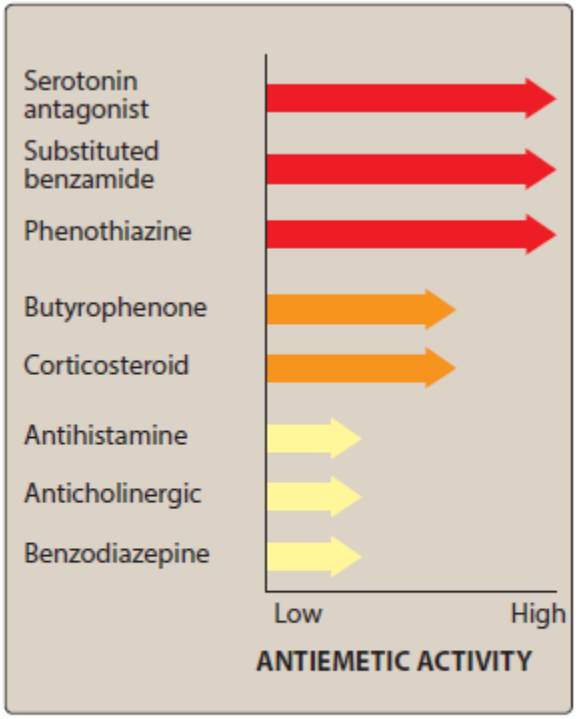


Figure 31.10
Efficacy of antiemetic drugs.

Antiemetics

6. H 1 antihistamines

Diphenhydramine, dimenhydrinate, meclizine

Antihistamines are often administered in combination with high-dose metoclopramide to reduce extrapyramidal reactions.

7. Anticholinergics

Hyoscine (scopolamine)

very useful in motion sickness but are ineffective against substances that act directly on the CTZ.

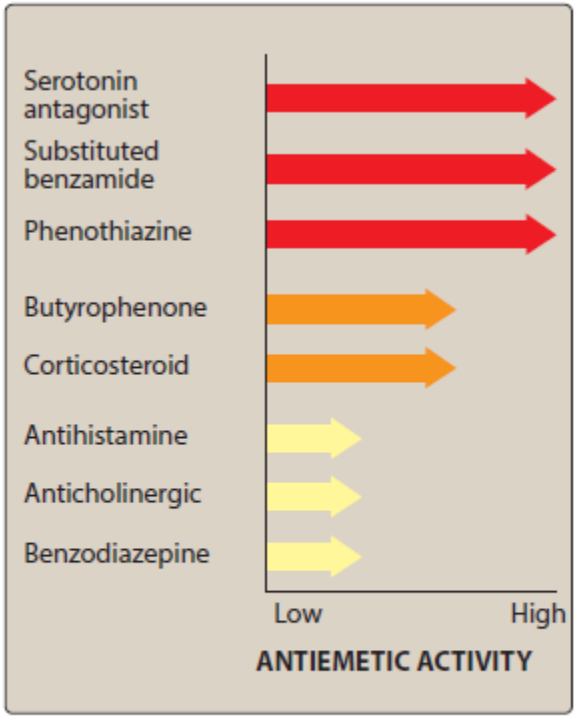


Figure 31.10
Efficacy of antiemetic drugs.

Chemotherapy-induced nausea and vomiting (CINV)

- Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity.
  - **Ondansetron** and **granisetron** prevent emesis in 50% to 60% of cisplatin-treated patients.
  - Corticosteroids, most commonly **dexamethasone**, increase antiemetic activity when given with the 5-HT3 antagonist.

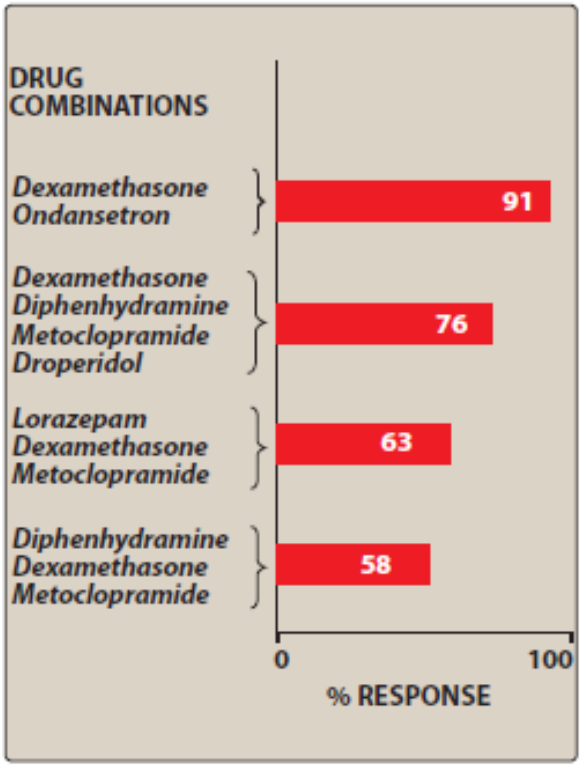


Figure 31.11
Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after *cisplatin* chemotherapy.

The End