

A 23-year-old woman comes to the physician due to acute nausea and vomiting. She recently returned from a vacation to Mexico and started to feel "queasy" on the last day of her trip. The patient then developed nausea with frequent vomiting and intermittent bouts of watery diarrhea. She has no visible blood in her stools. Her temperature is 36.8 C (98 F), blood pressure is 118/70 mm Hg, pulse is 86/min, and respirations are 12/min. Abdominal examination shows mild tenderness and increased bowel sounds. Improvement of this patient's vomiting would best be achieved by a medication targeting which of the following receptors?

- A. 5-HT<sub>3</sub> receptor
- B. μ-opioid receptor
- C. Dopamine receptor
- D. Histamine H<sub>1</sub> receptor
- E. Histamine H<sub>2</sub> receptor
- F. Muscarinic acetylcholine receptor
- G. Somatostatin receptor

This patient's nausea, vomiting, and watery diarrhea are typical symptoms of classic **travelers' diarrhea (TD)**. TD can be caused by a variety of organisms, including bacteria (eg, *Escherichia coli*), viruses (eg, rotaviruses), or occasionally, parasites (eg, *Cryptosporidium parvum*). In most cases, the illness is self-limited and treatment is symptomatic.

The choice of antiemetic therapy depends on the source of the emetogenic stimulus. Conditions that cause **gastrointestinal irritation** (eg, infections, chemotherapy, distention) result in increased mucosal **serotonin** release and activation of 5-HT<sub>3</sub> receptors on vagal and spinal afferent nerves. These then relay their impulses to the medullary vomiting center, inducing emesis. **5-HT<sub>3</sub> receptor antagonists** (eg, ondansetron) are well-tolerated medications that are very effective at reducing nausea and vomiting caused by gastrointestinal upset.

**(Choice B)** Loperamide is a  $\mu$ -opioid receptor agonist that functions as an antimotility agent. It is commonly used in TD to reduce diarrhea but can worsen nausea and vomiting due to colonic retention.

**(Choice C)** Dopamine receptor antagonists (eg, metoclopramide, prochlorperazine) are effective in treating central nausea (seen in acute migraines) and also reduce migraine headache pain. Dopamine antagonists have significant adverse effects including sedation and extrapyramidal symptoms; these are not the first-line treatment for nausea due to gastrointestinal upset.

**(Choices D and F)** First-generation H<sub>1</sub> receptor antagonists (eg, diphenhydramine, meclizine) and muscarinic acetylcholine receptor antagonists (eg, scopolamine) are frequently used to treat vestibular nausea (eg, motion sickness). Promethazine is a dopamine and H<sub>1</sub> receptor antagonist that can also treat vestibular nausea. All of these medications can cause significant sedation.

**(Choice E)** H<sub>2</sub> blockers (eg, ranitidine) reduce gastric acid secretion and can alleviate symptoms of gastroesophageal reflux but do not treat nausea and vomiting.

**(Choice G)** Somatostatin receptor agonists (eg, octreotide) inhibit bioactive amine release and are used to treat diarrhea in patients with carcinoid syndrome and vasoactive intestinal peptide-secreting tumors (ie, VIPoma). They are also used for treatment of acute esophageal variceal hemorrhage.

### Educational objective:

5-HT<sub>3</sub> receptor antagonists are useful for the treatment of visceral nausea due to gastrointestinal insults, such as gastroenteritis, chemotherapy, and general anesthesia. Antihistamines and anticholinergics are recommended for vestibular nausea. Dopamine antagonists are useful for nausea associated with migraine.



سرا ۲۰۳

A 57-year-old man with a history of alcoholic cirrhosis is brought to the emergency department due to altered mental status. Over the weekend, he ate a lot of smoked meats at a local barbecue competition. Since then, he has been sleeping most of the day and is confused and disoriented when awake. On examination, he has abdominal distension with shifting dullness. The patient answers correctly when asked for his name but does not know that he is in the hospital and says the year is "1997." When asked to extend his hands as if stopping traffic, the patient makes rhythmic flapping movements. He is started on rifaximin. Which of the following is the most likely mechanism of action of this drug when used to treat this patient's current condition?

- A. Binding of dietary phosphate
- B. Decreased intraluminal ammonia production
- C. Exchange of intraluminal sodium ions for potassium ions
- D. Formation of a nonabsorbable complex with bile acids
- E. Increased conversion of ammonia to ammonium ion

سرا ۲۰۳

This patient likely has **hepatic encephalopathy (HE)**, a neurologic complication of **cirrhosis** due in part to the liver's inability to convert **ammonia** (a neurotoxin) to urea. Excess ammonia is shunted past the liver and crosses the blood-brain barrier, leading to **altered mental status** (thought due to impaired neurotransmitter release, astrocyte dysfunction, neuroinflammation, and/or edema). Asterixis, the rhythmic flapping of dorsiflexed hands, is another common manifestation of HE.

A primary source of ammonia is degradation of nitrogen products by intestinal bacteria. Therefore, **gastrointestinal (GI) bleeding** can precipitate HE as hemoglobin breakdown leads to increased nitrogen products in the gut. **Excess dietary protein intake** (eg, large steak meal) is another common trigger. Others include infection, sedatives, and metabolic derangements (eg, hypokalemia).

**Rifaximin** is a nonabsorbable antibiotic that alters GI flora to decrease intestinal production and absorption of ammonia. In patients with HE, rifaximin is generally used in addition to **lactulose**, which is catabolized by intestinal bacterial flora to short chain fatty acids, lowering the colonic pH and increasing conversion of ammonia to ammonium (**Choice E**). Rifaximin is also sometimes used for traveler's diarrhea, as it inhibits bacterial RNA synthesis through binding with DNA-dependent RNA polymerase.

A 52-year-old postmenopausal woman comes to the office for evaluation of several months of episodic abdominal discomfort and nausea, especially after a fatty meal. She has no past medical history and does not use tobacco, alcohol, or illicit drugs. Her BMI is 33 kg/m<sup>2</sup>. Physical examination shows a soft, nontender abdomen with normal bowel sounds. Liver span is 8 cm. Murphy sign is negative. Abdominal x-ray reveals no calcifications, but abdominal ultrasound shows a small, non-obstructing gallstone. The patient prefers nonoperative management. Which of the following would best treat this patient's condition?

- A. Bile acid supplement
- B. Cholestyramine therapy
- C. Estrogen replacement therapy
- D. Fenofibrate therapy
- E. Iron chelation therapy
- F. Phosphate-binding agent
- G. Rapid weight loss

س. ٢٠٢٠

**Cholesterol gallstones** are the most common type of gallstone. They are primarily composed of cholesterol monohydrate crystals but can contain variable amounts of calcium salts, bilirubin, and mucin. Normally, bile acids and phospholipids solubilize the cholesterol to prevent stone formation. Decreased amounts of bile acids and phospholipids can cause the bile to become supersaturated with cholesterol, allowing it to crystallize and form cholesterol gallstones. Risk factors for stone formation include increasing age, obesity, excessive bile salt loss (eg, terminal ileum disease), and female sex.

Cholecystectomy is the preferred treatment for symptomatic gallstones. However, medical therapy is an option in patients refusing surgery or with high surgical risk. Administration of **hydrophilic bile acids** (eg, ursodeoxycholic acid) reduces cholesterol secretion and increases biliary bile acid concentration. This improves cholesterol solubility and **promotes gallstone dissolution**. Although the response to medical therapy is good in patients with mild symptoms and small stones, there is a high rate of gallstone recurrence.

**(Choice B)** Bile acid sequestrants (eg, cholestyramine) decrease enterohepatic recirculation of bile acids (increase gallstone risk). However, they also stimulate the conversion of cholesterol to bile acids and increase biliary motility (decrease gallstone risk). The net result is no significant change in the risk of gallstones.

**(Choice C)** Estrogen increases cholesterol secretion and progesterone reduces bile acid secretion, ultimately causing bile to become supersaturated with cholesterol. Progesterone also slows gallbladder emptying, which causes bile stasis and further promotes gallstone formation.

**(Choice D)** Fibrates increase cholesterol content in bile, which increases the risk of gallstones.

**(Choice E)** Iron chelation therapy is used to treat iron overload syndromes but has no significant effect on gallstones.

**(Choice F)** Phosphate-binding agents can lower serum phosphate in chronic kidney disease and dialysis patients but do not significantly affect gallstones.

**(Choice G)** Very low-calorie diets with decreased caloric intake and rapid weight loss can lead to bile stasis and increased cholesterol mobilization, increasing the risk of gallstone formation.

**Educational objective:**

Medical therapy to dissolve cholesterol gallstones is an option in patients refusing cholecystectomy or with high surgical risk. Hydrophilic bile acids (eg, ursodeoxycholic acid) improve cholesterol solubility by reducing the amount of cholesterol secreted into the bile and increasing biliary bile acid concentration.

A 42-year-old woman comes to the office due to a 2-month history of an intermittent burning sensation in her chest with an occasional simultaneous acidic taste at the back of her throat. The symptoms occur soon after she eats a meal. The patient has no shortness of breath, lightheadedness, nausea, vomiting, or weight loss. She has no other medical conditions. The patient has smoked a pack of cigarettes daily for the last 10 years but does not use alcohol. Family history is unremarkable. Vital signs are within normal limits. BMI is 32 kg/m<sup>2</sup>. Physical examination shows no abnormalities. Urine pregnancy test is negative. Smoking cessation is discussed, and a medication is prescribed for treatment of her symptoms. The patient returns in 2 weeks for a follow-up visit and reports near-complete resolution of her symptoms. Which of the following is the most likely mechanism of action of this drug?

- A. Blockade of gastrin receptors
- B. Creation of a cytoprotective layer in the stomach
- C. Inhibition of H<sup>+</sup>/K<sup>+</sup> ATPase activity
- D. Inhibition of synthesis of gastrin
- E. Prostaglandin-mediated inhibition of acid secretion



This patient's heartburn is likely related to gastroesophageal reflux disease (GERD), a common disorder that occurs when gastric acid refluxes into the esophagus. Management consists of lifestyle and dietary modifications (eg, weight loss, avoidance of tobacco) as well as medications that suppress gastric acid secretion.

**Proton pump inhibitors** (PPIs) (eg, pantoprazole, omeprazole) are the most effective inhibitors of gastric acid secretion. They bind to and irreversibly **inhibit the  $H^+/K^+$  ATPase** on parietal cells. Side effects are related to elevated gastric pH and include an increased risk of *Clostridioides difficile* and nutritional deficiencies (eg, calcium, magnesium, iron).

Although less potent than PPIs, **histamine 2 receptor antagonists** (eg, famotidine, cimetidine) are also used as first-line therapy for GERD. They inhibit gastric acid secretion by targeting histamine receptors on parietal cells. These medications are less side effect-prone than PPIs; however, they have a slower onset of action, and tachyphylaxis is common.

**(Choice A)** Gastrin, a hormone released from G cells, binds to cholecystokinin (CCK) B receptors and stimulates gastric acid secretion both directly (through binding on parietal cells) and indirectly (through binding on enterochromaffin-like cells to increase histamine release). CCK receptor antagonists are not routinely used in clinical practice.

**(Choice B)** Sucralfate forms a viscous paste in the stomach, providing a cytoprotective layer that prevents the diffusion of gastric acid. It is less effective than PPIs and is typically used as an adjunctive medication for peptic ulcer disease.

**(Choice D)** Octreotide is a somatostatin analogue that inhibits gastrin synthesis (as well as many other gastrointestinal hormones). It is sometimes used in Zollinger-Ellison syndrome, but is not routinely used for GERD.

**(Choice E)** Misoprostol is a prostaglandin E1 analogue that binds prostaglandin receptors on parietal cells, reducing gastric acid production and inducing secretion of mucus and bicarbonate. Misoprostol can be used to prevent NSAID-induced gastric ulcers, but is less helpful for treating GERD; its significant uterotonic effects (eg, uterine contractions, cervical ripening) also limit its use in women of childbearing age.

#### **Educational objective:**

Management of gastroesophageal reflux disease includes lifestyle and dietary modifications (eg, weight loss, tobacco avoidance) and medications such as proton pump inhibitors (PPIs) (eg, pantoprazole, omeprazole) or histamine 2 receptor antagonists (eg, ranitidine). PPIs irreversibly inhibit the  $H^+/K^+$  ATPase on parietal cells, which decreases gastric acid secretion.

A 42-year-old woman comes to the office due to frequent episodes of burning in her chest and small amounts of regurgitation after meals and at nighttime. Medical history includes hypertension. Vital signs are within normal limits. BMI is 30 kg/m<sup>2</sup>. There is no abdominal tenderness and the remainder of the physical examination is normal. The patient shows the clinician an over-the-counter antacid that she has been taking to relieve her symptoms. The preparation contains a combination of magnesium and aluminum hydroxide. Which of the following is the most likely rationale for combining both mineral salts in this antacid preparation?

- ☐ A. Improve systemic absorption
- ☐ B. Minimize drug interactions
- ☐ C. Prevent rebound acid secretion
- ☐ D. Reduce adverse effects
- ☐ E. Reduce the risk of alkalosis and renal failure

Magnesium salts (eg, magnesium trisilicate, magnesium hydroxide) and aluminum hydroxide are **weak alkali mineral salts**. They temporarily **increase the gastric pH** by neutralizing hydrochloric acid, helping to **relieve gastroesophageal reflux** symptoms.

**Aluminum** hydroxide has a tendency to cause **constipation** due to interactions with intestinal secretions that form insoluble salts. In contrast, **magnesium** salts cause osmotic **diarrhea**. Therefore, the two medications are combined to offset the adverse effects of the individual medications. Patients with reflux symptoms and chronic constipation may benefit from magnesium salt monotherapy, whereas aluminum hydroxide monotherapy may be of value in patients with chronic diarrhea.

**(Choice A)** Aluminum, when absorbed in large doses, causes osteomalacia, bone pain, hypercalcemia, and dementia. Aluminum absorption in the gastrointestinal tract is minimal from the salt form, and toxicity tends to occur in patients with chronic kidney disease that limits renal excretion. Combination therapy does not alter systemic absorption.

**(Choice B)** Drug interactions are common with antacid medications, largely due to pH-related changes in protein binding, absorption, or elimination of the drugs. Combining multiple alkalinizing agents would not minimize their effects on other drugs.

**(Choice C)** Rebound acid hypersecretion can occur with calcium carbonate, magnesium hydroxide, aluminum hydroxide, and proton pump inhibitors. This is likely due to increased gastrin release as a result of gastric alkalinization or (in the case of calcium salts) direct ionic stimulation.

**(Choice E)** Milk-alkali syndrome is caused by excessive use of calcium carbonate antacids and is characterized by hypercalcemia, alkalosis, and renal dysfunction. Kidney injury occurs due to both hypercalcemia-induced renal vasoconstriction and calcium-induced diuresis. The resultant volume depletion, decreased glomerular filtration rate, and alkali intake lead to a metabolic alkalosis. However, severe alkalosis can occur with all antacids, and the combination of magnesium and aluminum would not decrease this risk.

#### **Educational objective:**

Magnesium salts and aluminum hydroxide are basic mineral salts used to neutralize gastric acid and relieve gastroesophageal reflux symptoms. Side effects include diarrhea and constipation, respectively. Therefore, these medications are often combined to offset the adverse effects of the individual medications.

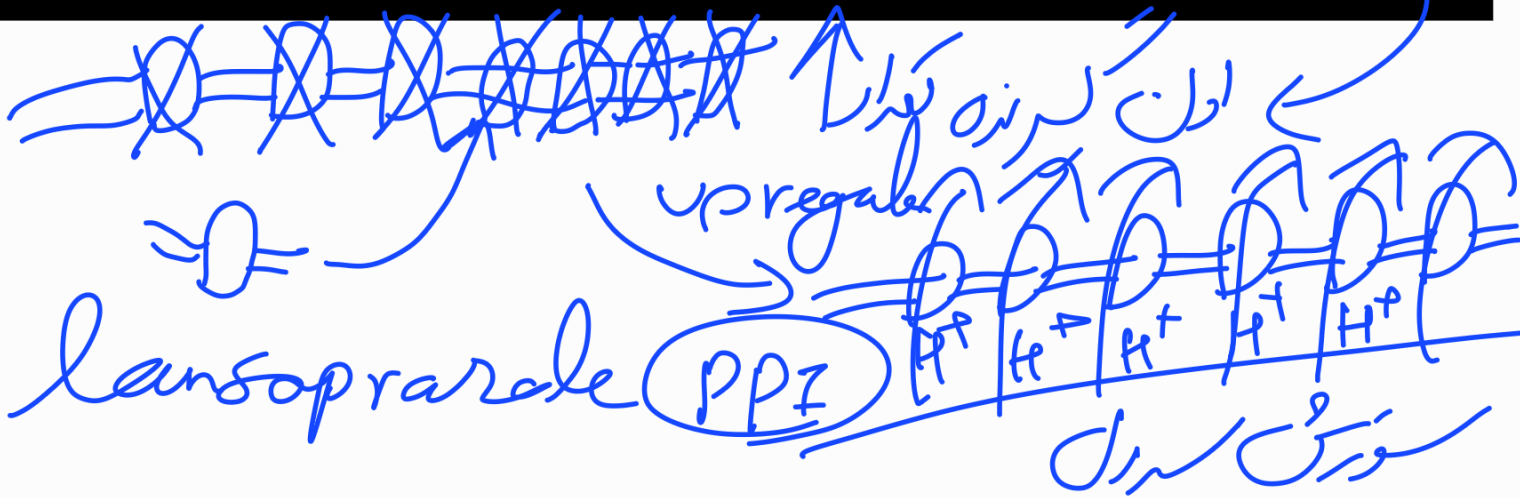
سوال 9:

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A 64-year-old woman is diagnosed with rheumatoid arthritis after coming to the office with symmetrical joint pain, swelling, and morning stiffness. The patient has a remote history of peptic ulcer disease and was treated with multidrug therapy for *Helicobacter pylori* eradication; a follow-up *H pylori* stool antigen test was negative and she had no recurrent symptoms. The patient is started on methotrexate and high-dose ibuprofen therapy. In addition, daily lansoprazole is prescribed for protection against the adverse gastrointestinal effects of ibuprofen. Three months later, joint symptoms were greatly improved. Ibuprofen and lansoprazole were discontinued. However, 2 weeks later, she begins experiencing heartburn after meals. Which of the following is the most likely cause of this patient's new gastrointestinal symptoms?

- ☐ A. ~~Downregulation of vagal stimulation~~
- ☒ B. Gastrin-mediated rebound acid hypersecretion
- ☐ C. Increased prostaglandin production after ibuprofen discontinuation
- ☐ D. Recolonization with *Helicobacter pylori*
- ☐ E. Upregulation of ~~somatostatin~~ receptors

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Release of gastrin, a hormone produced by G cells in the gastric antrum, is stimulated by dietary protein intake, gastrin-releasing peptide (released in response to vagal stimuli), and increased gastric pH. Gastrin induces acid production directly by binding parietal cells and indirectly by binding enterochromaffin-like (ECL) cells and inducing histamine release.

**Proton pump inhibitors (PPIs)** (eg, omeprazole, lansoprazole) inhibit the hydrogen-potassium-ATPase pump and **decrease hydrochloric acid** production regardless of stimuli. The resultant increase in gastric pH leads to **increased gastrin** formation, which induces hypertrophy of the ECL and parietal cells. **Withdrawal** of the PPI results in overstimulation of the parietal cells with hyperfunctioning of the unblocked ATPase, leading to **rebound gastric acid hypersecretion** and reflux symptoms. PPIs can be slowly tapered to help prevent this adverse effect.

**(Choice A)** Acetylcholine (released with vagal stimulation) binds to parietal cell muscarinic (M3) receptors and promotes the secretion of hydrochloric acid. Downregulation of vagal tone would likely relieve, rather than cause, the patient's symptoms.

**(Choice B)** Prostaglandins decrease acid production by inhibiting the downstream messenger of histamine and increases bicarbonate formation from gastric epithelial cells. Nonsteroidal anti-inflammatory drugs (eg ibuprofen) inhibit prostaglandin formation and increase the risk of gastritis and peptic ulcer formation. Increased prostaglandin formation after drug withdrawal would be protective against gastritis.

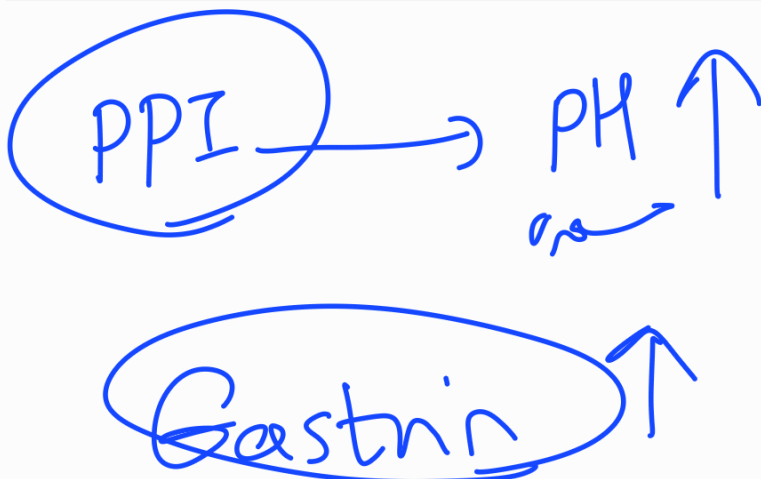
**(Choice C)** Prostaglandins decrease acid production by inhibiting the downstream messenger of histamine and increases bicarbonate formation from gastric epithelial cells. Nonsteroidal anti-inflammatory drugs (eg ibuprofen) inhibit prostaglandin formation and increase the risk of gastritis and peptic ulcer formation. Increased prostaglandin formation after drug withdrawal would be protective against gastritis.

**(Choice D)** Chronic *Helicobacter pylori* infection causes atrophic gastritis with parietal cell destruction. The effects of hypergastrinemia are masked in these patients due to the inability of the remaining parietal cells to create large volumes of acid. Reinfection is very rare, and the correlation with PPI withdrawal makes rebound hypersecretion more likely.

**(Choice E)** Somatostatin inhibits histamine and gastrin release; upregulation would lead to reduced gastric acid formation.

**Educational objective:**

Elevated gastric pH stimulates secretion of gastrin, a polypeptide hormone that increases gastric acid production. Proton pump inhibitors block gastric acid production by parietal cells; the resultant increase in pH leads to hypergastrinemia, which can cause rebound hypersecretion of gastric acid when the drug is withdrawn.



سوال : ✓

A 72-year-old man comes to the office due to watery diarrhea and abdominal cramps. The symptoms began several days after he started chemotherapy for metastatic colon cancer. He denies hematochezia, melena, or bulky, foul-smelling stools. Vital signs are within normal limits, and physical examination is unremarkable. Laboratory testing reveals no electrolyte abnormalities and no leukocytosis. Stool testing is negative for infection and fecal occult blood. The patient is advised to take a medication after each loose stool. The medication works by inhibiting the release of acetylcholine in the intestinal wall but does not cross the blood-brain barrier. Which of the following is the most likely medication prescribed for this patient?

A. Aprepitant

B. Bismuth subsalicylate

C. Fentanyl

D. Loperamide

E. Neostigmine

F. Octreotide

NK1

CC: Diarrhea + cramp

MOA: Inhibition ACh

→ ulcer  
→ AChEI → ACh ↑ → ↑ Peristalsis, ↓ cholinergic

hypersecretory

VIPoma

Carcinoma

Analogue

STT

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This patient with uncomplicated, chemotherapy-induced diarrhea was prescribed **loperamide**. Loperamide is an **opioid agonist** that exerts its antidiarrheal effects by binding to **mu opiate receptors** in the colonic myenteric plexus. This **inhibits acetylcholine release** from myenteric plexus neurons, decreasing activity of the intestinal smooth muscles and **slowing peristalsis**. Transit time within the intestine is prolonged, allowing for increased water absorption. In addition, the anticholinergic effects also result in decreased secretion from the intestinal epithelia, further reducing stool volume and increasing fecal consistency.

Unlike other opiates (eg, hydrocodone, fentanyl), loperamide undergoes **high first-pass metabolism** and **does not cross the blood-brain barrier**, allowing it to be used without opiate-related adverse events (eg, respiratory depression, sedation) or threat of abuse. The only side effect is constipation, which can be avoided with careful dose titration. Diphenoxylate, another opiate used for diarrhea, is less extensively metabolized and crosses the blood-brain barrier. To discourage abuse, diphenoxylate is typically combined with a small amount of atropine, an anticholinergic medication that results in dry mouth, flushing, pupil dilation, and urinary retention when used in large amounts.

**(Choice A)** Aprepitant is a neurokinin-1 receptor antagonist used for chemotherapy-related nausea and vomiting, not diarrhea.

**(Choice B)** Bismuth subsalicylate is frequently used for diarrhea and dyspepsia. Although its mechanism of action is not clearly understood, it stimulates the intestinal absorption of fluid (reducing diarrhea) and inhibits prostaglandin synthesis (reducing hypermotility). It does not inhibit acetylcholine release.

**(Choice C)** Fentanyl is an opiate commonly used as an analgesic and sedative. Although it causes constipation, it crosses the blood-brain barrier and therefore is not used for diarrhea due to the risk of systemic opiate-related adverse events (eg, respiratory depression, abuse).

**(Choice E)** Neostigmine is an acetylcholinesterase inhibitor that increases acetylcholine within the synapse. Its cholinergic effects would worsen this patient's diarrhea.

**(Choice F)** Octreotide is a somatostatin analogue that is sometimes used for refractory chemotherapy-induced diarrhea; however, it exerts its antidiarrheal effect by reducing secretion of pancreatic and gastrointestinal hormones (eg, secretin, gastrin, vasoactive intestinal peptide). ✓

#### **Educational objective:**

Loperamide is an opioid agonist that exerts its antidiarrheal effects by binding to mu opiate receptors in the colonic myenteric plexus, which inhibits acetylcholine release, decreases intestinal smooth muscle activity, and slows peristalsis. It undergoes high first-pass metabolism and does not cross the blood-brain barrier, thus avoiding systemic opiate-related adverse events (eg, sedation, respiratory depression).

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کوال ۸ :

سبوت

A 72-year-old man comes to the office for evaluation of constipation. His stools have been hard and pelletlike for as long as he can remember. The patient has a bowel movement every 3-4 days and frequently strains when using the bathroom. He has had associated abdominal discomfort but no hematochezia, melena, vomiting, or unexpected weight changes. The symptoms have not improved despite fiber supplementation. Vital signs are within normal limits. The abdomen is mildly distended with decreased bowel sounds. In addition to increasing water consumption, the patient is advised to try bisacodyl for constipation. What is the primary mechanism of action of this medication?

- ☒ A. Decreases surface tension of stool
- ☒ B. Draws water into the stool by creating an osmotic gradient
- ☒ C. Draws water into the stool by directly activating chloride channels
- ☒ D. Improves peristalsis by blocking mu-receptors
- ☒ E. Improves peristalsis by stimulating enteric nerves

→ Docusate

Mg

→ Lubiprost

۱. فنی  
۲. بنالورین

{ Methylnaloxonium  
naloxone  
naldemide



$\frac{1}{2}$

**(Choice A)** Docusate reduces the surface tension of stool, enabling water and fat to enter and soften it.

**(Choice C)** Lubiprostone is an agonist of the ClC-2 chloride channel located on the apical membrane of the intestine, which increases chloride secretion into the intestinal lumen. Sodium and water follow chloride into the lumen, resulting in increased intestinal fluid content.

**(Choice D)** Methylnaltrexone is a mu-opioid receptor antagonist designed to treat opioid-induced constipation. It does not cross the blood-brain barrier, which allows it to be used without inducing opiate-withdrawal symptoms.

Uwandel USMLE + <sup>x</sup>Katzenung<sup>x</sup>

Bisacodyl is a commonly used stimulant laxative that stimulates the enteric neurons within the colonic myenteric plexus, thereby increasing peristaltic activity and enhancing colonic motility.

# DRUG SUMMARY TABLE: Gastrointestinal Drugs

| Subclass | Mechanism of Action | Clinical Applications | Pharmacokinetics | Toxicities | Interactions |
|----------|---------------------|-----------------------|------------------|------------|--------------|
|----------|---------------------|-----------------------|------------------|------------|--------------|

## Drugs used in acid-peptic diseases

|   |  |                                       |   |  |
|---|--|---------------------------------------|---|--|
| Proton pump inhibitors (PPIs; eg, omeprazole) | Irreversible blockade of $H^+/K^+$ ATPase in active gastric parietal cells | Peptic ulcer, GERD, erosive gastritis | Half-lives much shorter than duration of action | Low toxicity • reduction of stomach acid may reduce absorption of some drugs and increase that of others |
|---|--|---------------------------------------|---|--|

**Contraindication**

Other PPIs: esomeprazole, dexlansoprazole, lansoprazole, pantoprazole, rabeprazole

*H<sub>2</sub>-receptor blockers*: cimetidine, famotidine, nizatidine, ranitidine reduce nocturnal acid but less effective than PPIs against stimulated secretion; very safe, available over the counter (OTC). Cimetidine, but not other *H<sub>2</sub>* blockers, is a weak antiandrogenic agent and a potent P450 enzyme inhibitor

*Sucralfate*: polymerizes at site of tissue damage and protects against further damage; very insoluble with no systemic effects; must be given 4 times daily

*Antacids*: popular OTC medication for symptomatic relief of heartburn; not as useful as PPIs and *H<sub>2</sub>* blockers in peptic diseases

## Prokinetic agents

|                |   |  |                                  |  |
|----------------|---|--|----------------------------------|--|
| Metoclopramide | <i>D<sub>2</sub></i> receptor blocker<br>• increases gastric emptying and intestinal motility | Gastric paresis (eg, in diabetes) • antiemetic | Oral and parenteral formulations | Parkinsonian symptoms due to block of CNS <i>D<sub>2</sub></i> receptors |
|----------------|---|--|----------------------------------|--|

*Domperidone*: like metoclopramide but less CNS effect; not available in United States

*Cholinomimetics*: neostigmine used for colonic pseudo-obstruction in hospitalized patients

*Macrolides*: erythromycin useful in diabetic gastroparesis but tolerance develops

## Laxatives

|   |  |  |      |  |
|---|--|--|------|--|
| Magnesium hydroxide, other nonabsorbable salts and sugars | Osmotic agents increase water content of stool | Simple constipation<br>• bowel prep for endoscopy (especially PEG solutions) | Oral | Magnesium may be absorbed and cause toxicity in renal impairment |
|---|--|--|------|--|

*Bulk-forming*: methylcellulose, psyllium, etc; increase volume, stimulate evacuation

*Stool surfactants*: docusate, mineral oil; lubricate stool, ease passage

*Stimulants*: senna, cascara; stimulate activity; may cause cramping

*Chloride channel activators*: lubiprostone, a prostanoid acid derivative, stimulates chloride secretion into intestine, increasing fluid content; linaclotide, guanylyl cyclase-C agonist, stimulates chloride secretion by cystic fibrosis transmembrane conductance regulator

*Opioid receptor antagonists*: alvimopan, methylnaltrexone, block intestinal  $\mu$  opioid receptors but do not enter CNS, so analgesia is maintained



## DRUG SUMMARY TABLE: Gastrointestinal Drugs (*Continued*)

| Subclass  | Mechanism of Action  | Clinical Applications  | Pharmacokinetics  | Toxicities, Interactions   |
|---|--|--|---|--|
| <b>Antidiarrheal drugs</b>  |  |  |   |  |
| Loperamide  | Activates $\mu$ opioid receptors in enteric nervous system and slows motility with negligible CNS effects                  | Nonspecific, noninfectious diarrhea  | Oral; OTC   | Mild cramping but little or no CNS toxicity                        |
| <i>Diphenoxylate</i> : similar to loperamide, but high doses can cause CNS opioid effects and toxicity  |  |  |   |  |
| <i>Colloidal bismuth compounds</i> : subsalicylate and citrate salts available as OTC products; adsorption of toxins has some value in travelers' diarrhea  |  |  |   |  |
| <i>Kaolin + pectin</i> : adsorbent compounds available OTC in some countries  |  |  |   |  |
| <b>Drugs for irritable bowel syndrome (IBS)</b>   |  |  |   |  |
| Alosetron   | 5-HT <sub>3</sub> receptor antagonist of high potency and duration of binding • reduces smooth muscle activity in GI tract | Severe diarrhea-predominant IBS in women   | Oral  | Rare but serious constipation; ischemic colitis • bowel infarction |
| <i>Anticholinergics</i> : nonselective action on GI activity; associated with typical antimuscarinic toxicity   |  |  |   |  |
| <i>Chloride channel activator</i> : lubiprostone is useful in constipation-predominant IBS in women   |  |  |   |  |
| <b>Antiemetics</b>  |  |  |   |  |
| 5-HT <sub>3</sub> antagonists (eg, ondansetron)   | 5-HT <sub>3</sub> receptor block in GI and CNS   | Prevention of chemotherapy- or radiation-induced and postoperative nausea and vomiting | Oral and parenteral formulations  | May slow colonic transit   |
| <i>Other 5-HT<sub>3</sub> antagonist antiemetics</i> : dolasetron, granisetron, palonosetron; see Chapter 16  |  |  |   |  |
| <i>H<sub>1</sub> histamine-antagonist</i> : diphenhydramine; see Chapter 16   |  |  |   |  |
| <i>Corticosteroids</i> : mechanism not known but useful in antiemetic IV cocktails; see Chapter 39  |  |  |   |  |
| <i>Antimuscarinics (eg, scopolamine)</i> : effective in emesis due to motion sickness; no other types; see Chapter 8  |  |  |   |  |
| <i>Phenothiazines</i> : act primarily through block of D <sub>2</sub> and muscarinic receptors; see Chapter 29  |  |  |   |  |
| <i>Cannabinoids</i> : dronabinol is available for use in chemotherapy-induced nausea and vomiting, but is associated with CNS marijuana effects (see Chapters 32 and 60)  |  |  |   |  |
| <i>Aprepitant</i> : A neurokinin 1 (NK <sub>1</sub> ) antagonist available for use in chemotherapy-induced nausea and vomiting; associated with fatigue, dizziness, diarrhea, and P450 interactions. Netupitant, rolapitant similar with long half-lives (90 and 180 h) |  |  |   |  |
| <b>Drugs for inflammatory bowel disease (IBD)</b>   |  |  |   |  |
| Mesalamine (5-aminosalicylate)  | Mechanism uncertain, may be inhibition of eicosanoid inflammatory mediators  | Mild to moderately severe Crohn disease and ulcerative colitis                         | Various formulations designed to deliver drug to distal ileum and colon | Little or no toxicity  |
| <i>Azo compounds</i> : balsalazide, olsalazine, sulfasalazine; colonic bacterial azoreductase enzymes release 5-aminosalicylate in the colon; sulfasalazine can cause sulfonamide toxicity due to absorption of the sulfapyridine moiety                                |  |  |   |  |
| <i>Glucocorticoids</i> : see Chapters 39 and 55   |  |  |   |  |
| <i>Immunosuppressant antimetabolites</i> : see Chapters 54 and 55   |  |  |   |  |
| <i>Anti-TNF drugs</i> : see Chapters 36 and 55  |  |  |   |  |
| <i>Natalizumab</i> : antibody that blocks leukocyte integrins; may cause progressive multifocal leukoencephalopathy (PML)   |  |  |   |  |
| <i>Vedolizumab</i> : similar to natalizumab with very low risk of PML   |  |  |   |  |

## DRUG SUMMARY TABLE: Gastrointestinal Drugs (*Continued*)

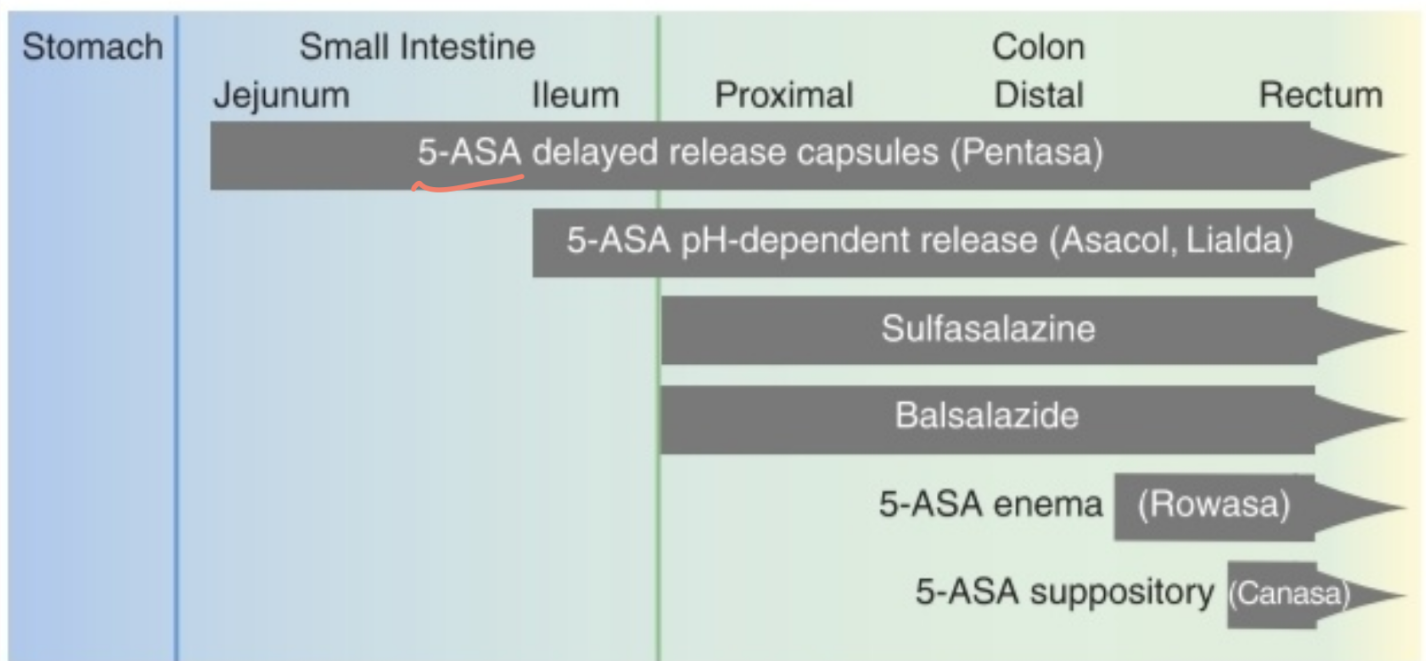
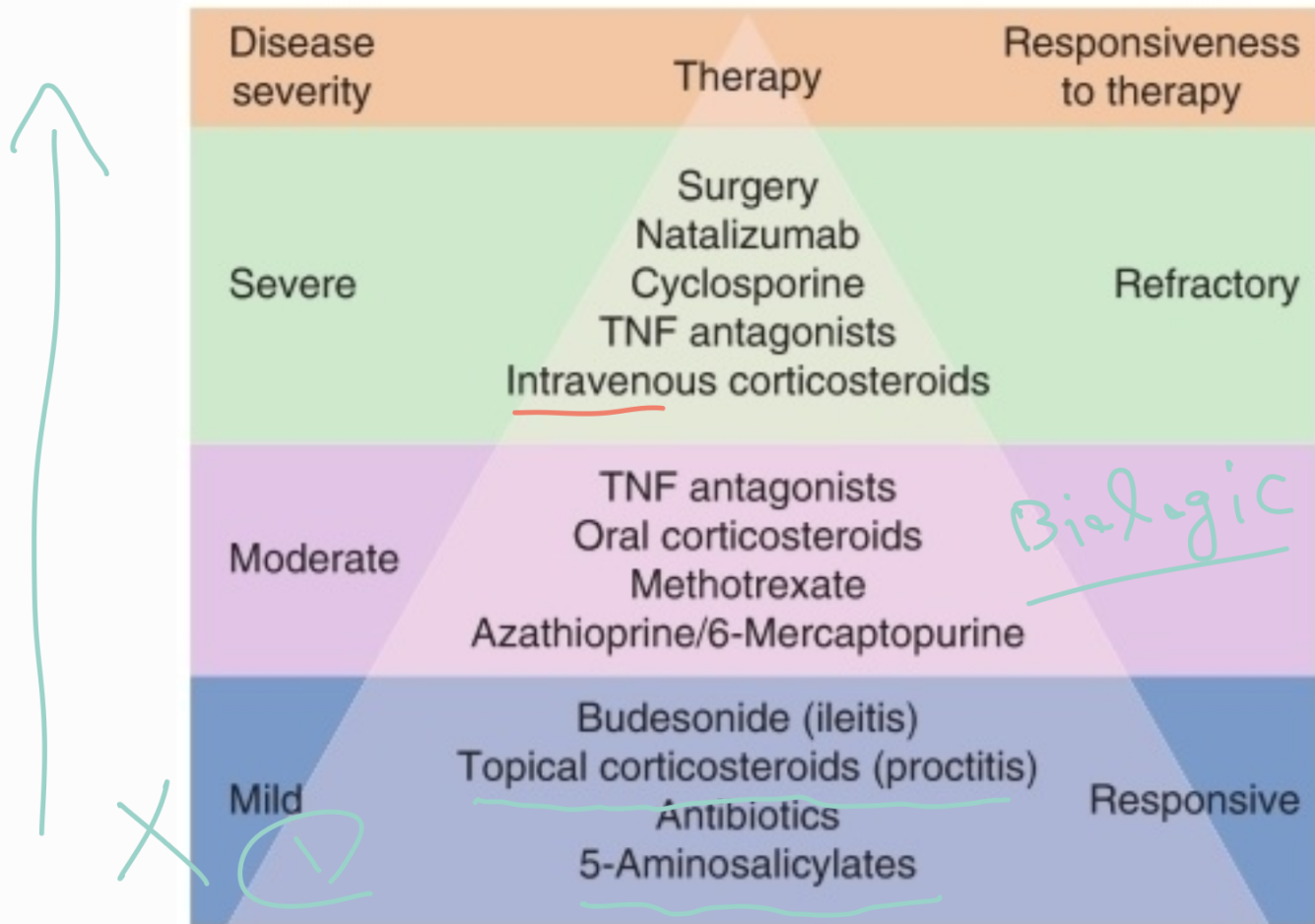
| Subclass  | Mechanism of Action  | Clinical Applications   | Pharmacokinetics      | Toxicities, Interactions         |
|---|--|---|-----------------------|----------------------------------|
| <b>Pancreatic supplements</b>   |  |   |                       |                                  |
| Pancrelipase  | Replacement enzymes from animal pancreatic extracts that improve digestion of fat, protein, and carbohydrate | Pancreatic insufficiency due to cystic fibrosis, pancreatitis, pancreatectomy | Taken with every meal | May increase incidence of gout   |
| <i>Pancreatin</i> : similar pancreatic extracts but much lower potency; rarely used |  |   |                       |                                  |
| <b>Bile acid therapy for gallstones</b>   |  |   |                       |                                  |
| Ursodiol  | Reduces cholesterol secretion into bile  | Gallstones in patients refusing or not eligible for surgery                   | Oral                  | Little or no toxicity            |
| <b>Drugs to treat variceal hemorrhage</b>   |  |   |                       |                                  |
| Octreotide  | Somatostatin analog  | Variceal bleeding   | IV                    | Hyper/hypoglycemia               |
| Propranolol   | Reduces variceal pressure  | Variceal bleeding   | Oral                  | Bradycardia, bronchoconstriction |

GERD, gastrointestinal reflux disease; PEG, pegylated.

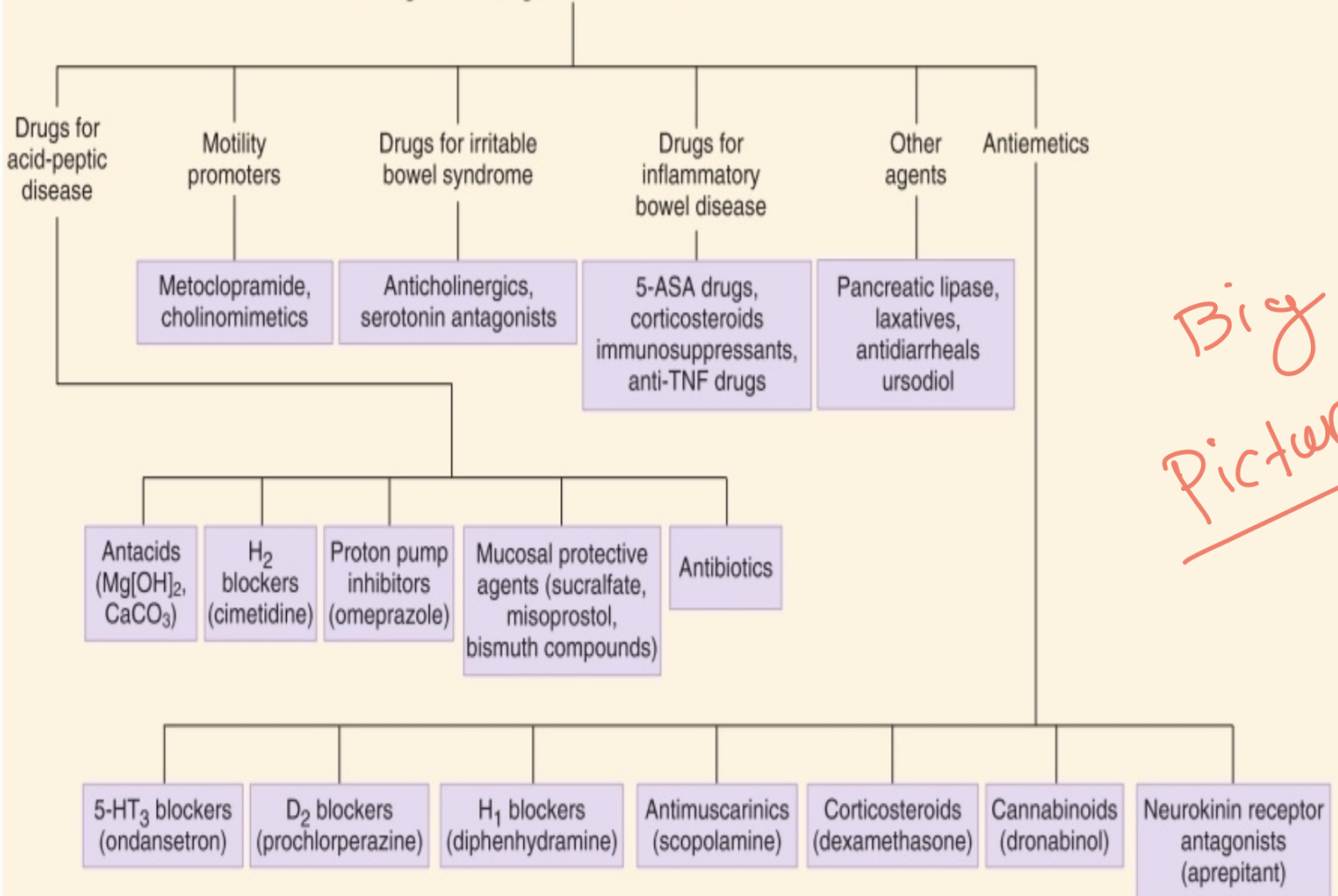
Anfi Diarrhea

| 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<br>Linaclotide ( <i>indirect</i> via cGMP)  |
| Opioid receptor antagonists | Methylnaltrexone, alvimopan  |





## Drugs used for gastrointestinal disorders



*Big Picture*

1. A 55-year-old woman with type 1 diabetes of 40 years' duration complains of severe bloating and abdominal distress, especially after meals. Evaluation is consistent with diabetic gastroparesis. Which of the following is a prokinetic drug that could be used in this situation?
- (A) Alosetron → 5HT<sub>3</sub> IBS-D  
 (B) Cimetidine → H<sub>2</sub>RA Ulcer, GERD  
 (C) Loperamide → opioid agonist Diarrhea  
 ✓ (D) Metoclopramide → D<sub>2</sub> blocker → prokinetic  
 (E) Sucralfate → Cytoprotective → PUD
2. A patient who is taking verapamil for hypertension and angina has become constipated. Which of the following drugs is an osmotic laxative that could be used to treat the patient's constipation?
- (A) ✗ Aluminum hydroxide → بوسنت - Osmotic  
 (B) ✗ Diphenoxylate → بوسنت - μ agonist  
 ✓ (C) Magnesium hydroxide  
 (D) Metoclopramide  
 (E) Ranitidine H<sub>2</sub>RA - GERD, PUD
3. A 40-year-old male CEO came to the emergency department ED with severe burning chest pain radiating to his neck. His electrocardiogram was normal and test for troponin was negative. MI  
 A diagnosis of GERD was made and he was sent home with a prescription for a drug that inhibits stomach acid. Which of the following is a drug that irreversibly inhibits the H<sup>+</sup>/K<sup>+</sup> ATPase in the parietal cells? ECG  
 (A) Cimetidine  
 (B) Diphenoxylate  
 ✓ (C) Esomeprazole  
 (D) Metoclopramide  
 (E) Sulfasalazine → 5ASA, IBD, ~~Sulfapyridine~~



4. A 25-year-old college student went to student health care center for severe cramps, diarrhea, fever, and weight loss. She was diagnosed with Crohn disease. Which drug is most likely to be useful in the treatment of her inflammatory bowel disease?

(A) Diphenhydramine X

(B) Diphenoxylate X

(C) Mesalamine ✓ → 5ASA, IBD

(D) Ondansetron 5HT<sub>3</sub> N&V

(E) Ursodiol X → شش صفراوی

IBD

5. A 34-year-old woman has irritable bowel syndrome with diarrhea that is not responsive to conventional therapies. Despite the small risk of severe constipation and ischemic colitis, the patient decides to begin therapy with alosetron. Alosetron has which of the following receptor actions?

✓ (A) 5-HT<sub>3</sub> receptor antagonist

(B) 5-HT<sub>4</sub> receptor agonist → Tegaserod

(C) D<sub>2</sub> receptor antagonist

(D) NK<sub>1</sub> receptor antagonist

(E) Muscarinic receptor antagonist

IBS-D

IBS-C

6. On your way to an examination, you experience the vulnerable feeling that an attack of diarrhea is imminent. If you stopped at a drugstore, which one of the following antidiarrheal drugs could you buy without a prescription even though it is related chemically to the strong opioid analgesic meperidine?

(A) Aluminum hydroxide X

(B) Diphenoxylate X → ~~OTC~~

✓ (C) Loperamide

(D) Magnesium hydroxide X

(E) Metoclopramide X

OTC

7. A 45-year-old man with a duodenal ulcer was treated with a combination of drugs intended to heal the mucosal damage and to eradicate *Helicobacter pylori*. Which of the following antibacterial drugs is used commonly to eradicate intestinal *H. pylori*?

(A) Cefazolin

(B) Ciprofloxacin

✓ (C) Clarithromycin

(D) Clindamycin

(E) Vancomycin

Tetracycline

metv / Amoxicilline

clarithromycin

8. A patient is receiving highly emetogenic chemotherapy for metastatic carcinoma. To prevent chemotherapy-induced nausea and vomiting, she is likely to be treated with which of the following?

(A) Levodopa

(B) Methotrexate

(C) Misoprostol

✓ (D) Ondansetron

(E) Sucralfate

3

5HT<sub>3</sub>

NK1

Corticoids

Dacarbazine

Cisplatin

Cyclophosphamide

Mild

Moderate



**Questions 9 and 10.** The following matching questions consist of a list of lettered options followed by several numbered items. For each numbered item, select the ONE option that is most closely associated with it.

- (A) Aluminum hydroxide → Antacid
- (B) Balsalazide → 5-ASA
- (C) Castor oil → laxative
- (D) Cimetidine → H<sub>2</sub>RA
- (E) Dexamethasone → corticosteroid
- (F) Methotrexate → Anti-metabolite IBD
- (G) Metoclopramide
- (H) Mineral oil → laxative
- (I) Omeprazole
- ✓ (J) Linaclotide → CF
- (K) Pancrelipase → پانکریاس (Amylase, -)
- (L) Sucralfate →

9. Which drug stimulates chloride secretion into the gut lumen and is used for irritable bowel syndrome? J IBS-C
10. This is a small molecule that polymerizes in stomach acid and coats the ulcer bed, resulting in accelerated healing and reduction of symptoms. Sucralfate

**Questions 9 and 10.** The following matching questions consist of a list of lettered options followed by several numbered items. For each numbered item, select the ONE option that is most closely associated with it.

- (A) Aluminum hydroxide  
(B) Balsalazide  
(C) Castor oil  
(D) Cimetidine  
(E) Dexamethasone  
(F) Methotrexate  
(G) Metoclopramide  
(H) Mineral oil  
(I) Omeprazole  
(J) Linacotide  
(K) Pancrelipase  
(L) Sucralfate
9. Which drug stimulates chloride secretion into the gut lumen and is used for irritable bowel syndrome?
10. This is a small molecule that polymerizes in stomach acid and coats the ulcer bed, resulting in accelerated healing and reduction of symptoms.

## ANSWERS

- Of the drugs listed, only metoclopramide is considered a prokinetic agent (ie, one that increases propulsive motility in the gut). The answer is **D**. Alosetron is a 5-HT<sub>3</sub> receptor blocker, cimetidine is a H<sub>2</sub> receptor blocker, loperamide is an opioid, and sucralfate forms a protective layer over an ulcer.
- A laxative that mildly stimulates the gut would be most suitable in a patient taking a smooth muscle relaxant drug such as verapamil. By holding water in the intestine, magnesium hydroxide provides additional bulk and stimulates increased contractions. A helpful mnemonic is magnesium “magnifies” stool, aluminum hALts the stool. The answer is **C**. Diphenoxylate is an opioid receptor agonist, metoclopramide is a prokinetic agent, ranitidine is a H<sub>2</sub> receptor blocker.
- Esomeprazole, the (S) isomer of omeprazole, is a prodrug converting spontaneously in the parietal cell canaliculus to a sulfonamide that irreversibly inactivates the proton pump. The answer is **C**.
- Mesalamine is a form of 5-aminosalicylic acid that is active in the large intestine and thereby provides a local anti-inflammatory effect that is useful in Crohn disease, a form of inflammatory bowel disease. The answer is **C**.
- Serotonin plays a major regulatory role in the enteric nervous system, and the potent 5-HT<sub>3</sub> receptor antagonist alosetron has shown efficacy in treating women with IBS that is accompanied by diarrhea. The answer is **A**.
- Aluminum hydroxide is constipating but is not related chemically to meperidine; magnesium hydroxide is a strong laxative. The 2 antidiarrheal drugs that are structurally related to opioids are diphenoxylate and loperamide. Loperamide is available over the counter; diphenoxylate is mixed with atropine alkaloids, and the product (Lomotil, others) requires a prescription. The answer is **C**.
- The macrolide antibiotic clarithromycin is commonly used in antibiotic regimens designed to treat duodenal ulcers caused by *H. pylori*. The other antibiotics that are used include amoxicillin, tetracycline, and metronidazole. Bismuth also has an antibacterial action. The answer is **C**.
- The 5-HT<sub>3</sub> receptor antagonists are highly effective at preventing chemotherapy-induced nausea and vomiting, which can be a dose-limiting toxicity of anticancer drugs. The answer is **D**.
- Linacotide is approved for the treatment of chronic constipation and IBS with predominant constipation. Linacotide activates guanylyl cyclase-C on the luminal intestinal epithelial surface, which leads to activation of the cystic fibrosis transmembrane conductance regulator (CFTR) leading to increased chloride-rich secretion and acceleration of intestinal transit. The answer is **J**.
- Sucralfate is a small molecule that polymerizes in stomach acid and forms a protective coat over the ulcer bed. The answer is **L**.

## SKILL KEEPER ANSWER: 5-HT AGONISTS & ANTAGONISTS (SEE CHAPTERS 16 AND 30)

The only serotonin agonists in common use are the 5-HT<sub>1D</sub>-selective agonists such as sumatriptan and its congeners (see Chapter 16) that are used in migraine. Ergot alkaloids are partial agonists at several 5-HT receptors and are also used in migraine and other conditions. Several valuable antidepressants are inhibitors of the serotonin reuptake pump in neurons (see Chapter 30). Serotonin antagonists include cyproheptadine (also an H<sub>1</sub> blocker), phenoxybenzamine (also an  $\alpha$  blocker), and several of the atypical antipsychotic drugs (eg, olanzapine, aripiprazole; see Chapter 29), which have high affinity for 5-HT<sub>2A</sub> receptors. Cyproheptadine is used for pruritus and sometimes for carcinoid tumor. Phenoxybenzamine is used for carcinoid tumor as well as for pheochromocytoma. 5-HT<sub>3</sub> receptors are blocked by ondansetron and its congeners. These drugs are extremely useful in preventing postoperative and cancer chemotherapy-induced nausea and vomiting.

A 64-year-old woman comes to the emergency department due to intractable nausea and vomiting. She has not been able to keep anything down and feels weak and tired. The patient has had no diarrhea, constipation, or abdominal pain. She was diagnosed with breast cancer 4 weeks ago and received her first cycle of chemotherapy 1 week ago. Vital signs are within normal limits. Mucous membranes are dry. Cardiopulmonary examination is normal. Bowel sounds are normal. Which of the following agents would be most helpful in treating this patient's symptoms?

- A. Histamine H<sub>1</sub> blocker
- B. Motilin receptor agonist
- C. Mu opioid receptor agonist
- D. Muscarinic M<sub>1</sub> receptor antagonist
- ✓ E. Serotonin 5-HT<sub>3</sub> receptor antagonist

سوال ۹



The **vomiting reflex** can be activated by either humoral or neuronal stimuli. The **area postrema** in the fourth ventricle has a **chemoreceptor trigger zone** that can respond to many neurotransmitters, drugs, or toxins. The **nucleus tractus solitarius** (NTS) in the medulla receives information from the area postrema, gastrointestinal (GI) tract via the vagus nerve, vestibular system, and central nervous system (eg, meninges, hypothalamus). Neurons from the NTS project to other medullary nuclei and coordinate the vomiting process. The 5 major receptors involved in stimulating the vomiting reflex in the area postrema and adjacent vomiting center nuclei are M<sub>1</sub> muscarinic, D<sub>2</sub> dopaminergic, H<sub>1</sub> histaminic, 5-HT<sub>3</sub> serotonergic, and neurokinin 1 (NK1) receptors.

**5-HT<sub>3</sub> receptor antagonists** (eg, ondansetron, granisetron, dolasetron) are highly effective in preventing **chemotherapy-induced vomiting**. These agents act by 2 primary mechanisms: blocking **vagus**-mediated nausea and vomiting (from the GI tract stimuli) and blocking central **serotonin** receptors in the area postrema and the NTS. Other agents useful for chemotherapy-induced vomiting include **NK1 receptor antagonists** (eg, aprepitant), which inhibit substance P and help prevent both acute vomiting and delayed emesis; and dopamine receptor antagonists (eg, metoclopramide), which are associated with drowsiness and dystonic reactions.

**(Choices A and D)** Histamine blockers and antimuscarinic/anticholinergic agents are most helpful for vestibular nausea and vomiting.

**(Choice B)** Motilin regulates interdigestive migrating contractions. Erythromycin is a motilin receptor agonist used for gastroparesis.

**(Choice C)** Mu opioid receptor agonists (eg, morphine) are useful for cancer-related pain control but often have side effects such as nausea and vomiting.

### **Educational objective:**

Ondansetron inhibits serotonin (5-HT<sub>3</sub>) receptors and is used primarily to treat nausea and vomiting following chemotherapy. 5-HT<sub>3</sub> receptors are located peripherally in the presynaptic nerve terminals of the vagus nerve in the gastrointestinal tract. These receptors are also present centrally in the chemoreceptor trigger zone and the solitary nucleus and tract.



A 72-year-old man comes to the office due to constipation. His stools have become increasingly hard, small-volume, and difficult to pass. This has been associated with bloating but not vomiting. Symptoms have not improved despite fiber supplementation, polyethylene glycol, and bisacodyl. The patient was recently diagnosed with metastatic pancreatic cancer and was prescribed palliative chemotherapy 2 months ago. His cancer causes severe abdominal pain, which requires high-dose oxycodone to control. Vital signs are within normal limits. The abdomen is mildly distended with decreased bowel sounds. Which of the following medications acts as a  $\mu$ -opioid receptor antagonist that could alleviate this patient's constipation without inducing withdrawal symptoms? \*

- ☐ A. Diphenoxylate
- ☐ B. Loperamide
- ☐ C. Lubiprostone
- ☒ D. Methylnaltrexone
- ☐ E. Naloxone

BBB

→ withdrawal

\*All constipation medications can cause diarrhea at high doses.

This patient has **opioid-induced constipation (OIC)**. Opiates (eg, oxycodone) exert their analgesic effects by binding to opiate receptors in the central and peripheral nervous systems, reducing nociceptive transmission and the perception of pain. Constipation, the most common side effect of opiate therapy, occurs due to the activation of  **$\mu$ -opiate receptors** in the gastrointestinal tract. This results in decreased intestinal peristaltic activity and inhibition of ion and fluid secretion, leading to desiccated, pellet-like stool. Unlike many other opiate side effects, tolerance to constipation does not readily occur. Therefore, all patients on opiate therapy should be considered for prophylactic laxative therapy (eg, docusate, polyethylene glycol, bisacodyl).

Those with refractory OIC may benefit from **methylnaltrexone**, a peripherally acting  **$\mu$ -opioid receptor antagonist** that reverses the anti-peristaltic effect of opiates. It does not cross the blood-brain barrier; therefore, it **does not induce** opiate-related **withdrawal symptoms**, allowing for treatment of OIC without disrupting analgesic effects.

**(Choices A and B)** Diphenoxylate and loperamide are both opiate-based medications designed to inhibit peristalsis in the gastrointestinal tract. These medications are used to treat diarrhea and would worsen this patient's constipation.

**(Choice C)** Lubiprostone is a chloride channel agonist that increases intestinal secretions. Although it is not a  $\mu$ -opioid receptor antagonist, it can be used to treat OIC and would not put patients at risk for opiate-related withdrawal.

**(Choice E)** Naloxone is also an opioid receptor antagonist; however, unlike methylnaltrexone, naloxone crosses the blood-brain barrier. It induces symptoms of withdrawal and reversal of analgesia and is used to treat acute opioid toxicity (eg, respiratory depression, somnolence).

#### **Educational objective:**

Constipation is the most common side effect of opiate therapy and occurs due to the binding of  $\mu$ -opioid receptors in the gastrointestinal tract, which decreases intestinal motility and inhibits ion and fluid secretion.

Methylnaltrexone, a peripherally acting  $\mu$ -opioid receptor antagonist that does not cross the blood-brain barrier, can alleviate opioid-induced constipation without inducing opiate-related withdrawal symptoms.

A 34-year-old man is evaluated for several months of epigastric pain that is worse at night and is relieved by eating. The patient has no significant medical history and takes no medications. He does not use tobacco, alcohol, or illicit drugs. The patient immigrated to the United States from China 4 years ago. Vital signs are within normal limits. Physical examination shows mild epigastric tenderness to deep palpation. Upper gastrointestinal endoscopy reveals a 1-cm ulcer in the first portion of the duodenum. Additional testing is pending. In addition to proton pump inhibitor therapy, which of the following therapies would most likely prevent ulcer recurrence in this patient?

- A. Antibiotics
- B. Gastric cytoprotectants
- C. Glucocorticoids
- D. Histamine 2 receptor blockers
- E. Prokinetic agents
- F. Prostaglandin analogues

سوال ۱۱  
ع رابو  
ع رابو

This patient's symptoms and endoscopic findings are consistent with **duodenal peptic ulcer disease** (PUD). Up to 90% of duodenal ulcers are caused by *Helicobacter pylori* infection. The remaining cases are typically associated with nonsteroidal anti-inflammatory drug (NSAID) use, which is unlikely in this patient who takes no medications. Over 50% of the world population is colonized with *H pylori*, with a particularly high prevalence in resource-limited countries, including much of Africa, Western Asia, and South America.

To reduce the likelihood of PUD recurrence after ulcer healing, *H pylori* infection must be eradicated. Effective regimens typically involve a combination of **antibiotics** (eg, tetracycline, metronidazole) and proton pump inhibitors (eg, omeprazole), often with bismuth subsalicylate (ie, quadruple therapy). The antibiotic regimen can be tailored based on local resistance patterns.

**(Choice B)** Gastric cytoprotectants (eg, sucralfate) bind to the base of mucosal ulcers and protect them against gastric acid. This can help duodenal ulcers heal but would be less effective in preventing ulcer recurrence than eradication of *H pylori*.

**(Choice C)** Glucocorticoids should be avoided in patients with PUD as they can promote peptic ulcer formation, especially when combined with NSAIDs.

**(Choice D)** Proton pump inhibitors suppress gastric acid secretion to a greater extent than histamine H<sub>2</sub>-receptor blockers (eg, ranitidine), allowing for superior ulcer healing during PUD treatment. However, neither medication would prevent ulcer recurrence (which requires *H pylori* eradication).

**(Choice E)** Metoclopramide is a dopamine antagonist with prokinetic and antiemetic properties that can be used to treat gastrointestinal motility disorders (eg, gastroparesis) and nausea/vomiting; however, it does not have a significant effect on PUD.

**(Choice F)** Prostaglandin analogues such as misoprostol are used to prevent NSAID-induced peptic ulcers.

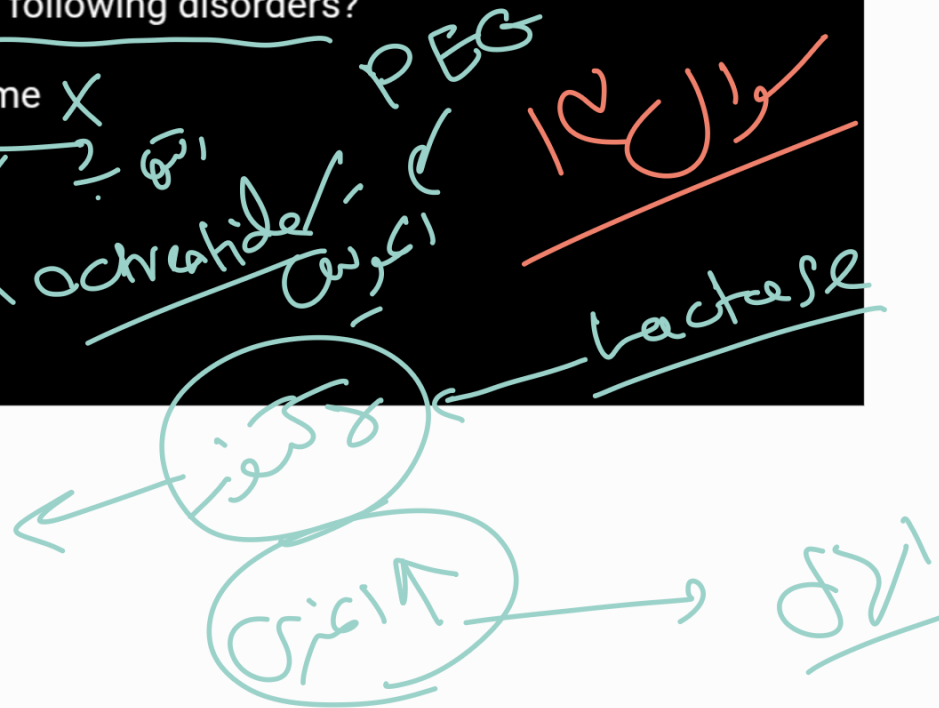
### **Educational objective:**

Most duodenal peptic ulcers are caused by *Helicobacter pylori* infection. The most effective method to prevent disease recurrence is to eradicate the infection with antibiotics (eg, tetracycline, metronidazole), typically in combination with proton pump inhibitors (eg, omeprazole) and, often, bismuth subsalicylate (quadruple therapy).



A 78-year-old male nursing home resident is brought to the physician because of abdominal pain and discomfort. He has a history of advanced dementia and is only partially able to verbalize his symptoms. He has had intermittent abdominal discomfort for years, with no other related symptoms. He denies diarrhea and rectal bleeding but has not had a bowel movement in approximately 5 days. The patient is largely bed-bound, and only has minimal activity with the help of nurses and physical therapists. Past regular colonoscopies have shown only benign lesions. His other medical problems include dementia, coronary artery disease, hypertension, spinal stenosis, and osteoarthritis of his hips and knees. Abdominal examination does not show tenderness, masses, or hepatosplenomegaly, although fullness is appreciated. The remainder of the examination shows no abnormalities. Polyethylene glycol is administered and produces a bowel movement within 24 hours. The mechanism of action of polyethylene glycol in this patient is most similar to the pathophysiology of which of the following disorders?

- ☐ A. Irritable bowel syndrome X
- ☐ B. Crohn's disease X
- ✓ ☒ C. Lactase deficiency ✓
- ☐ D. Carcinoid syndrome X
- ☐ E. Rectal prolapse X



## Explanation:

Constipation is common in elderly, debilitated patients as well as those on chronic opiate therapy. Because lifestyle changes are not an option in patients such as this one, constipation in this population is commonly treated with osmotic laxatives (e.g., magnesium citrate, polyethylene glycol), stool softeners, and enemas.

Osmotic laxatives are nonabsorbable or poorly absorbable substances that attract water into the intestinal lumen, thus distending the intestinal wall and increasing peristalsis. The laxative effect is usually fairly rapid. Magnesium hydroxide (and other magnesium-containing compounds, such as magnesium citrate) is another osmotic laxative that is often used, although its efficacy is questionable and there is not enough evidence to support its widespread use.

Lactase deficiency is a disease state characterized by osmotic diarrhea. Inherited or acquired deficiency of the intestinal brush border enzyme lactase (i.e., disaccharidase) causes inability to break down lactose into glucose and galactose. Undigested lactose is a nonabsorbable osmotic substance, and its accumulation in the small intestine leads to an increase in the secretion of water and electrolytes into the intestinal lumen. Lactase deficiency (i.e., lactose intolerance) presents with abdominal pain and distension and watery diarrhea. Abdominal pain and distention result from the metabolism of lactose by normal gut flora through fermentation, which causes the production of gas. The symptoms resolve when milk-containing products are eliminated from the diet.

**(Choice A)** Irritable bowel syndrome is a functional intestinal disorder that presents with diarrhea alternating with constipation, abdominal pain, and distention without organic cause. Fecal water and electrolyte content are normal.

**(Choice B)** Diarrhea in Crohn's disease is of the secretory type, which is characterized by high electrolyte content due to poor absorption and increased losses from the inflamed intestinal mucosa.

**(Choice D)** Diarrhea in carcinoid syndrome is secretory and high in electrolytes.

**(Choice E)** Rectal prolapse is a protrusion of rectal mucosa through the anus associated with pregnancy and constipation; it can also be seen in severe diarrhea. Another important cause of rectal prolapse is cystic fibrosis, particularly in children.

## Educational objective:

Polyethylene glycol is an osmotic laxative. Diarrhea associated with lactase deficiency is also osmotic and occurs due to accumulation of nonabsorbable lactose in the intestinal lumen. Magnesium hydroxide (and other magnesium-containing compounds, such as magnesium citrate) is another osmotic laxative that is often used, although its efficacy is questionable and there is not enough evidence to support its widespread use.

