WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

DRUGS FOR DIARRHEA & CONSTIPATION

Skye McKennon, PharmD, BCPS, ACSM-GEI
Thread Director, Interprofessional Education & Pharmacology
Clinical Associate Professor
Elson S. Floyd College of Medicine
skye_mckennon@wsu.edu

DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify and describe the appropriate drugs and drug classes for managing diarrhea and constipation
2. Explain the mechanism of action of drug classes for managing diarrhea and constipation and correlate with underlying pathophysiology
3. Describe adverse effects and contraindications to drug classes for managing patients with diarrhea and constipation
4. Describe the clinically important drug interactions of each drug class for managing patients with diarrhea and constipation

AGENDA

- Connection to GI Physiology
- Constipation & Laxatives
- Diarrhea & Antidiarrheals

CONTROL MECHANISMS IN GI PHYSIOLOGY

Enteric Nervous System (ENS)

- Division of the Autonomic Nervous Systems (ANS)
- Large neural network located within the wall of the GI tract
- "Minibrain"
- Responsible for much of the moment-to-moment control of GI motility and secretion

ENS utilizes different neurotransmitters

- Acetylcholine: stimulates secretion and motility
- ATP and nitric oxide (NO): inhibits motility
- Peptide neurotransmitters
  - Vasoactive intestinal polypeptide
  - Opioid peptides (inhibits)
  - Substance P, 5-hydroxytriptamine (stimulates)

ACTIVE LEARNING

You learned the Enteric Nervous System (ENS) utilizes different neurotransmitters including, but not limited, to:

- Acetylcholine: stimulates secretion and motility
- ATP and nitric oxide (NO): inhibitory
- Peptide neurotransmitters (eg, vasoactive intestinal polypeptide, opioid peptides, substance P, 5-hydroxytriptamine)

Based on these neurotransmitters, list at least three drug classes you think could cause constipation or diarrhea.

CONTROL MECHANISMS IN GI PHYSIOLOGY

ENS can function independently

ENS is linked to the central nervous system (CNS)

- Parasympathetic Nervous System
  - Efferent innervation generally stimulatory (more secretion, more propulsive motility)
- Sympathetic Nervous System
  - Generally inhibitory (decreased propulsive motility)

CONSTIPATION

GI tract must extract water, minerals, and nutrients from the luminal contents, leaving behind a manageable pool of fluid for proper expulsion of waste material via the process of defecation

Water normally 70-85% total stool weight

Feces become too dry → condense into large, hard mass → difficult to pass → colon undergoes segmental contraction & pushes feces in both directions to mix with water

COMMON CAUSES OF CONSTIPATION

No specific causes found in most cases of constipation

- Poor diet or malfunction of GI tract
  - Lack of fiber
    - Fiber incorporates into stool → absorbs water → stool bulks (prevents hardening) → easier to pass
  - Decreased motility of the GI tract (IBS, medications such as opioids)
    - More time in the large intestine → more water removed → hardened stool

STRATEGIES FOR CONSTIPATION

1. Fiber-rich diet (20-35 grams daily)
2. Adequate fluid intake
3. Appropriate bowel habits and training
4. Avoidance of constipating drugs
   - Opioids
   - Antihypertensive agents
   - Tricyclic antidepressants
   - Iron preparations
   - Antiseizure medications
   - Anti-Parkinsonian agents (anticholinergic or dopaminergic)
   - Barium

LAXATIVE OVERVIEW

Softening of Feces Onset: 1-3 Days	Soft or Semifluid Stools Onset: 6-8 Hours	Watery Evacuation Onset: 1-3 Hours
Bulk-forming laxatives Psyllium preparations Methylcellulose Calcium polycarbophil	**Stimulant laxatives** Bisacodyl Senna	**Osmotic laxatives** *Saline* Magnesium sulfate Magnesium hydroxide (Milk of magnesia) Magnesium citrate Polyethylene glycol
Surfactant/Emollient Docusate		**Castor oil**
Osmotic laxatives Lactulose		

BULK-FORMING AGENT MOA

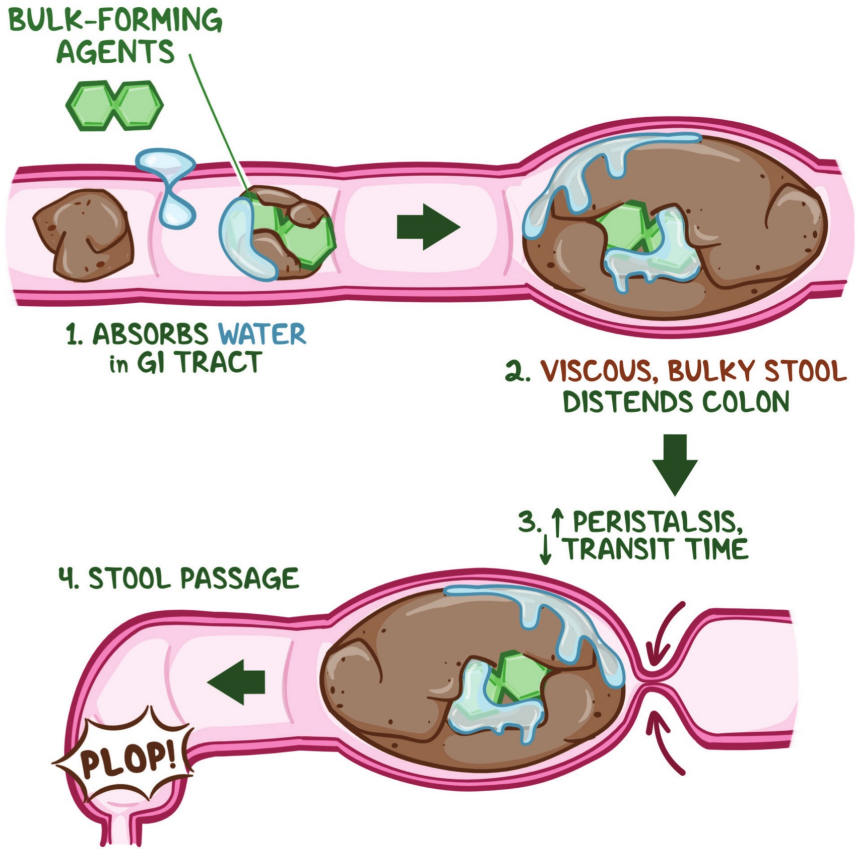
Indigestible, fibrous compounds

- Plant: methylcellulose, psyllium
- Synthetic: Polycarbophil

Not digested by GI tract enzymes

Incorporate in stool → attract/draw in water → stool swelling into soft, bulky mass → increase in stool size → stimulates gastric motility and makes stool easier to pass

Note: Can be administered PO



BULK-FORMING LAXATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Plant Methylcellulose Psyllium preparations	Intestinal obstruction	Fecal impaction (take with fluids) Bloating Flatulence	No known significant interactions
Synthetic Calcium polycarbophil			Decreases absorption of bisphosphonates, tetracyclines, phosphate supplements, quinolones Decreases therapeutic effect of calcium channel blockers, dobutamine, thyroid products Increases arrhythmogenic effect of cardiac glycosides Increased adverse/toxic effects of vitamin D analogs

SURFACTANT/EMOLLIENT LAXATIVES

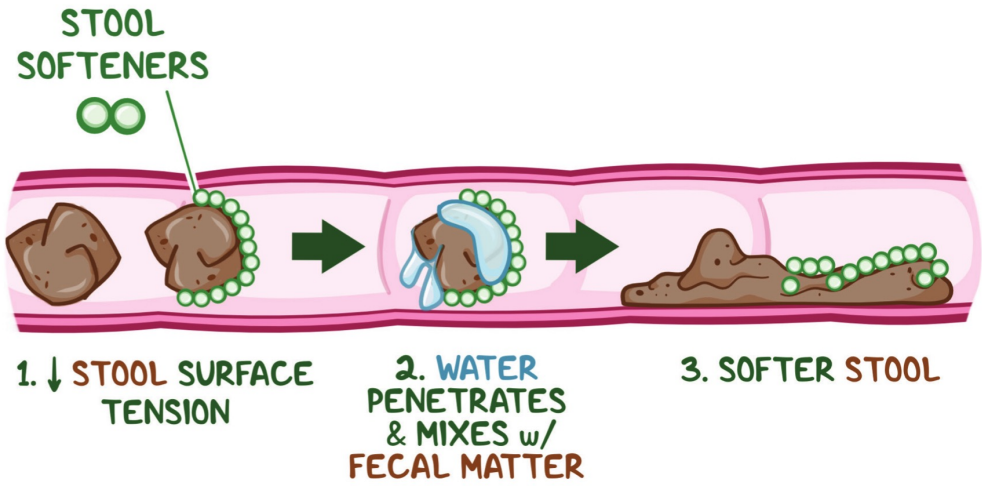
Anionic surfactants used to soften fecal matter

Decrease surface tension between water outside of stool and fat inside stool

Water penetrates and mixes with fecal matter

Softer, formed stool

Note: Can be administered PO or PR



SURFACTANT/EMOLLIENT LAXATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Docusate (Colace)	May contain benzyl alcohol, propylene glycol	Diarrhea	Increases systemic mineral oil absorption (leads to inflammation of intestinal mucosa, liver, spleen)

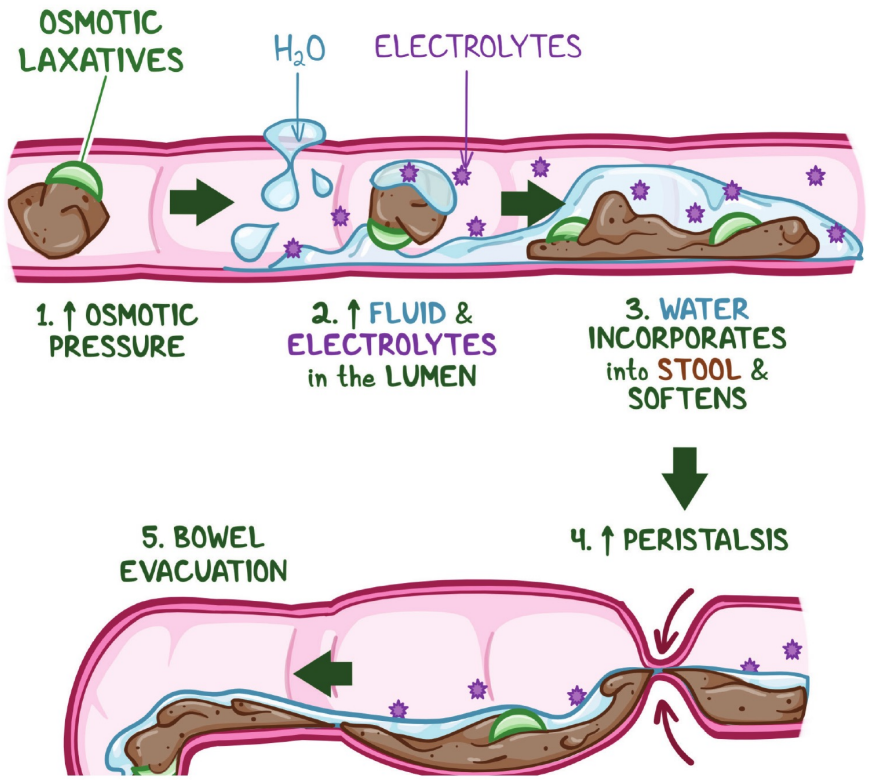
OSMOTIC LAXATIVE MOA

Poorly-absorbed salts, sugars

Stimulate colonic peristalsis

Increase osmotic pressure → increased fluids and electrolytes into bowel lumen → water incorporates into the stool → softens stool and increases peristalsis → bowel evacuation

Note: Can be administered PO or PR



ACTIVE LEARNING

Which contraindications/cautions and adverse effects would you expect from osmotic laxatives, based on their mechanism of action?

OSMOTIC LAXATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Magnesium sulfate Magnesium hydroxide (Milk of magnesia) Magnesium citrate	**All:** Pre-existing electrolyte imbalance Bowel obstruction **Magnesium-containing:** Renal impairment (increased risk of hypermagnesemia) Cardiac disease	Diarrhea Dehydration	Increased levels/effects of calcium channel blockers, calcium/sodium polystyrene sulfonate, gabapentin, misoprostol, penicillamine, quinine, raltegravir Decreased levels of bisphosphonates, captopril, chloroquine, fluoroquinolones, levothyroxine, tetracyclines
Polyethylene glycol Sorbitol			May decrease digoxin concentrations

OSMOTIC LAXATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Lactulose (Enulose)	Pre-existing electrolyte imbalance Bowel obstruction Diabetes (contains lactose and galactose)	Cramping Bloating Flatulence	May increase anticoagulant effect of warfarin

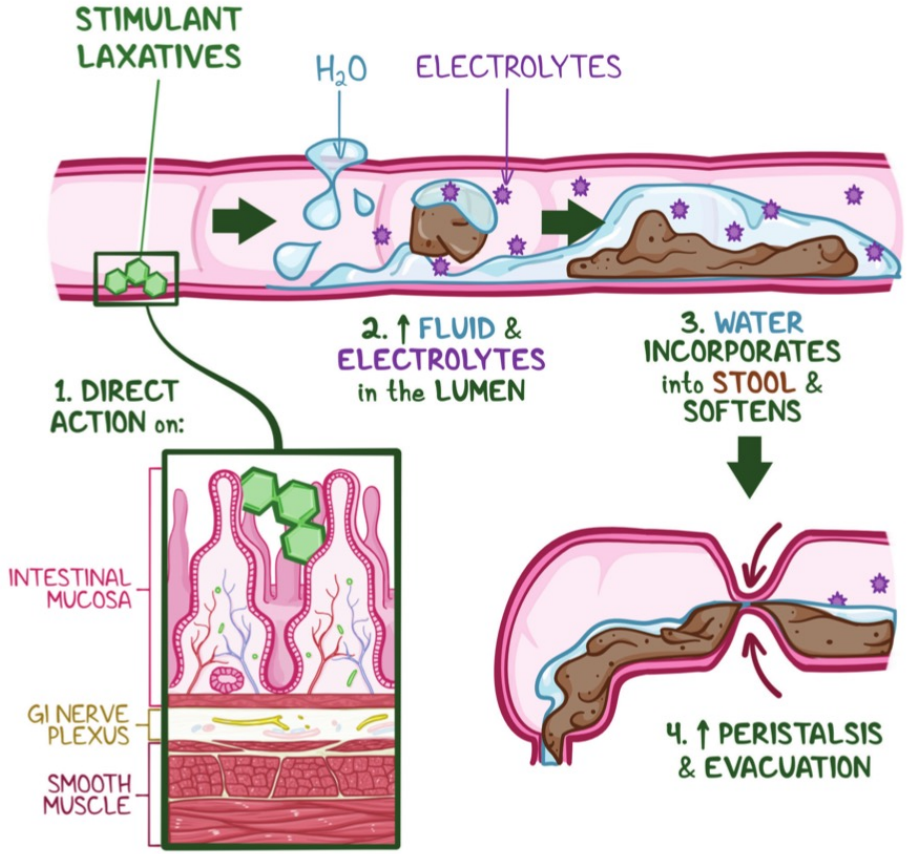
STIMULANT LAXATIVES

Irritant laxatives

Mild inflammations irritate small and large intestinal walls → increased electrolyte and water secretion into intestinal lumen

Direct stimulation of enteric nervous system → increased smooth muscle contraction → increased peristalsis

Note: Can be administered PO or PR



STIMULANT LAXATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Bisacodyl (Dulcolax)	**Do not use more than 10 consecutive days (atonic colon)**	**Atonic colon** Cramps N/V Diarrhea Fluid/electrolyte imbalances	May increase toxic effect of sodium sulfate
Senna (Senokot)		**Melanosis coli** Cramps N/V Diarrhea Fluid/electrolyte imbalances	May increase toxic effect of sodium sulfate May enhance adverse effects of digoxin

SENNA

Obtained from the dried leaflets on pods of *Cassia acutifolia* or *Cassia angustifolia*

CHLORIDE CHANNEL ACTIVATOR MOA

Prostanoid activator of chloride channels in epithelium of the GI tract → increased chloride-rich fluid secretion in the intestine → improved stool consistency and increased frequency by activating motility

- Thought to bind to the EP4 receptor for PGE2
- GPCR that couples to Gs → activation of adenylyl cyclase → enhanced chloride conductance

Bypasses the antisecretory effects of opioids

Note: Can be administered PO or PR

CHLORIDE CHANNEL ACTIVATOR

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Lubiprostone (Amitiza)	GI obstruction Severe diarrhea Hepatic impairment	Diarrhea Nausea Headache Chest pain/discomfort Abdominal pain Dizziness	Methadone may decrease effects

Also used for IBS

DIARRHEA

Background

Stool that contains fluid weight > 200 grams of fluid/day

Increased frequency of bowel movements

Acute or chronic

Infectious or non-infectious

Role of Antidiarrheals

Acute

- Cautiously (fever absent, non-bloody stool)

Chronic

- Diagnosis made, definitive treatment unavailable
- Diagnostic evaluation eluded

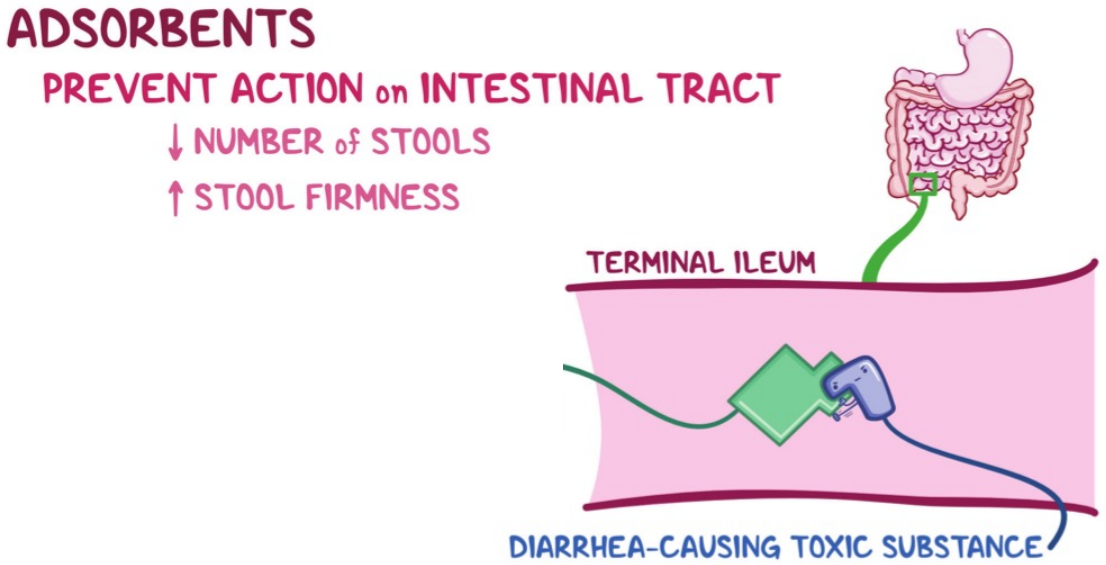
ADSORBENTS

Bind diarrhea-causing toxins and water

Bismuth

- Antisecretory
- Anti-inflammatory
- Antimicrobial

Note: Can be administered PO



ADSORBENTS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Bismuth subsalicylate (Pepto-Bismol)	Aspirin/ salicylate allergy Neurotoxic at large doses	Bismuth component **Black tongue** **Stool discoloration** Salicylate component **Ototoxicity** **Reye's syndrome**	Decreased effect of ACE inhibitors, loop diuretics, probenecid, tetracyclines Increased risk of bleeding with anticoagulants Increased hypoglycemic effect of glucose-lowering drugs Increased toxic effect of salicylates and carbonic anhydrase inhibitors Increased risk of ulceration and bleeding with corticosteroids Decreased effect of loop diuretics Increased methotrexate concentrations

May also be used in *H. pylori* management regimens

TONGUE DISCOLORATION

Adverse effect of bismuth subsalicylate use

Hypothesized from formation of bismuth sulfide (from reaction between bismuth subsalicylate and bacterial sulfides in GI tract)

May also turn stool black

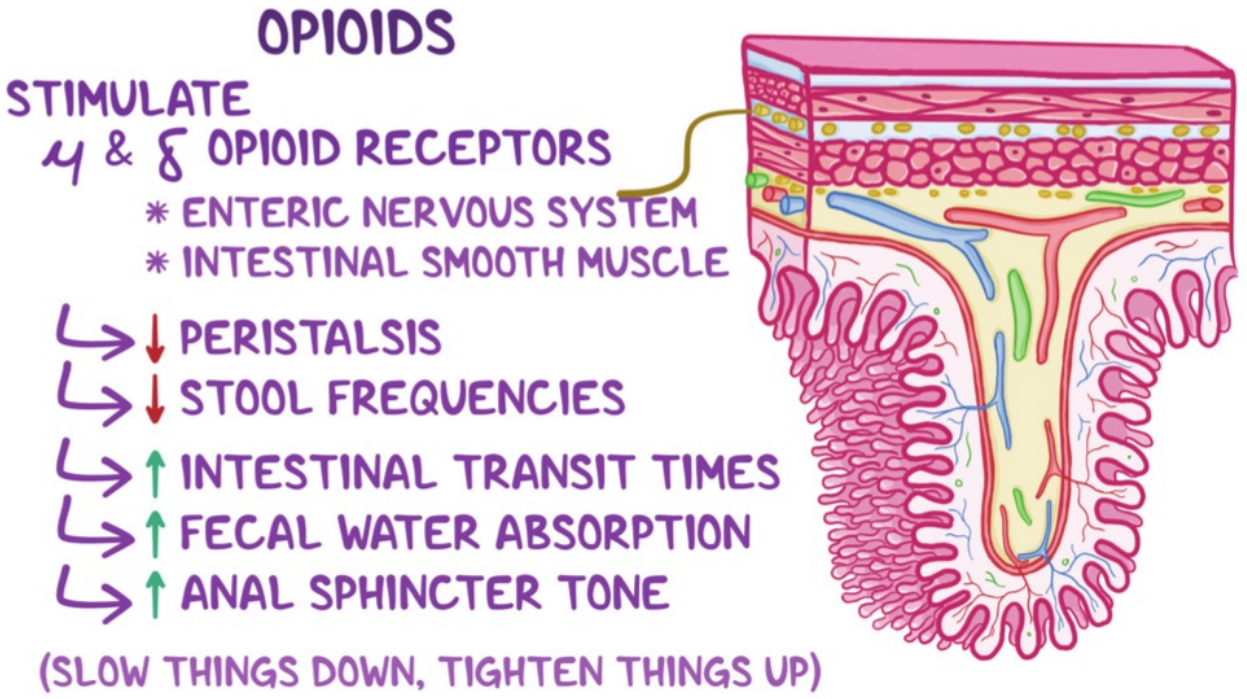
OPIOID DERIVATIVES

Meperidine analogs

Stimulate mu/delta opioid receptors in enteric nervous system, intestinal smooth muscle → decreased peristalsis → decreased stool frequency

Loperamide: anti-secretory effect

Note: Can be administered PO



ACTIVE LEARNING

The antidiarrheal opioid derivative drug diphenoxylate is available only in combination with atropine. List two reasons why diphenoxylate would be combined with atropine.

COMBINATION WITH ATROPINE

Diphenoxylate is a Schedule V drug

Combined with atropine to reduce the likelihood of abuse

- Crosses blood-brain barrier
- Potential CNS side effects (ie, euphoria, CNS depression)

Loperamide lower abuse potential (OTC)

- Does not cross blood-brain barrier

OPIOID DERIVATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Diphenoxylate /atropine (Lomotil)	Obstructive jaundice CNS depression Renal and hepatic impairment Diarrhea associated with pseudomembranous enterocolitis or other enterotoxin-producing bacteria	Flushing Tachycardia Confusion Drowsiness Euphoria Hallucination Urinary retention	Anticholinergic agents Opioid agonists (increased CNS depression)

OPIOID DERIVATIVES

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Loperamide (Imodium)	< 2 years of age Acute ulcerative colitis Diarrhea associated with pseudomembranous enterocolitis or other enterotoxin-producing bacteria Hepatic impairment (reduced first-pass metabolism)	Torsades de pointes and sudden cardiac death Dizziness (CNS effects) Constipation	Agents that prolong QTc-interval (ie, antipsychotics, antiarrhythmics, fluoroquinolones, macrolides,, antidepressants, methadone, sumatriptan, ondansetron, cisapride)

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

ANY QUESTIONS?

REFERENCE LIST

Drugs That Affect the GI Tract. In: Stringer JL. eds. Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, 5e. McGraw Hill; 2017. Accessed October 26, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=2147&sectionid=161352543

Gastrointestinal Physiology. In: Kibble JD, Halsey CR. eds. Medical Physiology: The Big Picture. McGraw Hill; 2014. Accessed October 28, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=1291&sectionid=75577353

Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept. 2009 Jun 5;155(1-3):11-7. doi: 10.1016/j.regpep.2009.03.012. Epub 2009 Apr 2. PMID: 19345246; PMCID: PMC3163293.

McQuaid KR. Drugs Used in the Treatment of Gastrointestinal Diseases. In: Katzung BG, Vanderah TW. eds. Basic & Clinical Pharmacology, 15e. McGraw Hill; 2021. Accessed October 27, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250604938

Nemeth V, Pfleghaar N. Diarrhea. [Updated 2022 Nov 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448082/

Schumacher MA, Basbaum AI, Naidu RK. Opioid Agonists & Antagonists. In: Katzung BG, Vanderah TW. eds. Basic & Clinical Pharmacology, 15e. McGraw Hill; 2021. Accessed October 24, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250599194

Sharkey KA, MacNaughton WK. Gastrointestinal Motility and Water Flux, Emesis, and Biliary and Pancreatic Disease. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed October 20, 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172483503

Sizar O, Genova R, Gupta M. Opioid-Induced Constipation. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493184/

Zhao Q, Chen YY, Xu DQ, Yue SJ, Fu RJ, Yang J, Xing LM, Tang YP. Action Mode of Gut Motility, Fluid and Electrolyte Transport in Chronic Constipation. Front Pharmacol. 2021 Jul 27;12:630249. doi: 10.3389/fphar.2021.630249. PMID: 34385914; PMCID: PMC8353128.