Gut Instincts: Navigating Pharmacotherapy after Gastrointestinal Procedures

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Disclosure

The following individual has nothing to disclose concerning possible conflicts of interests related to this presentation

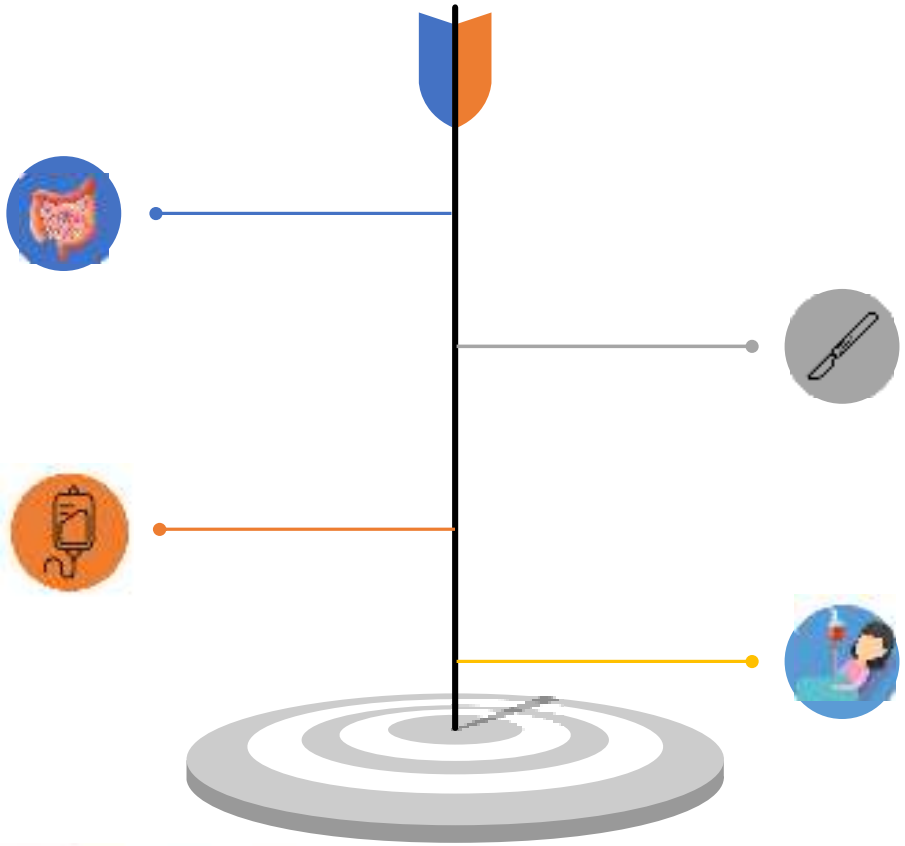
Objectives

Anatomy

Review the human gastrointestinal (GI) tract and physiology of absorption

Pharmacotherapy

Discuss strategies to enhance drug absorption and manage the complications following GI procedures



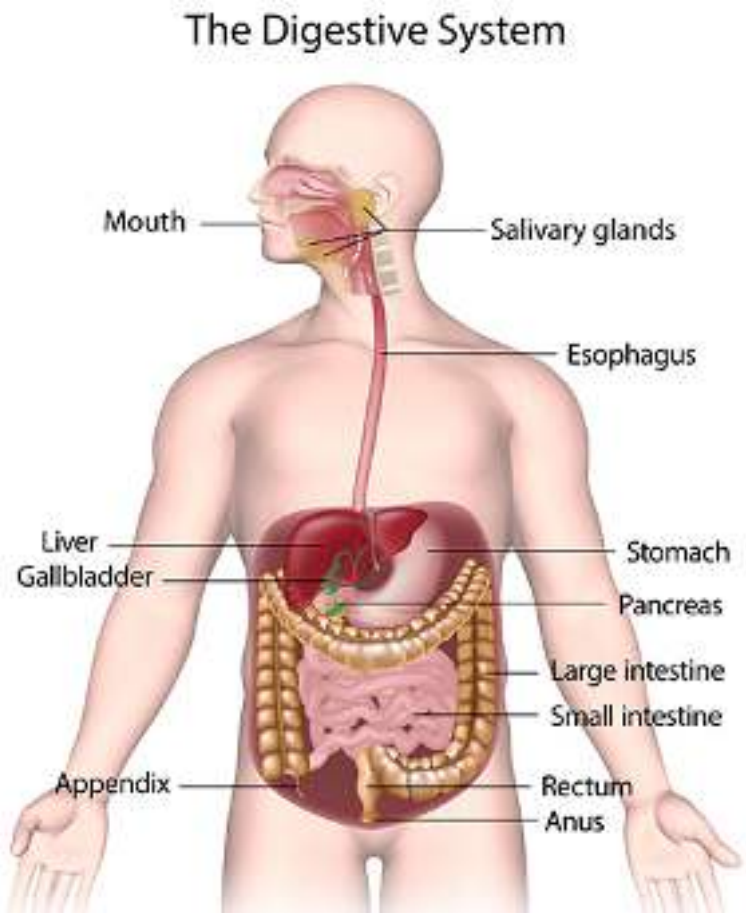
Pathophysiology

Assess the changes associated with various GI procedures

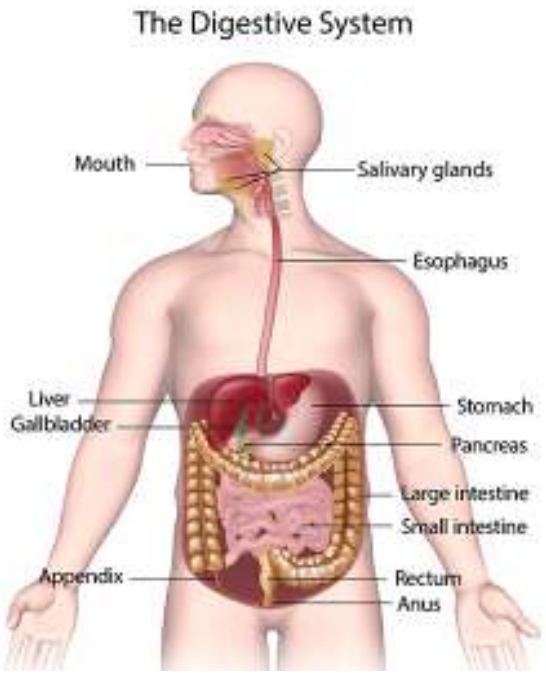
Patient Case

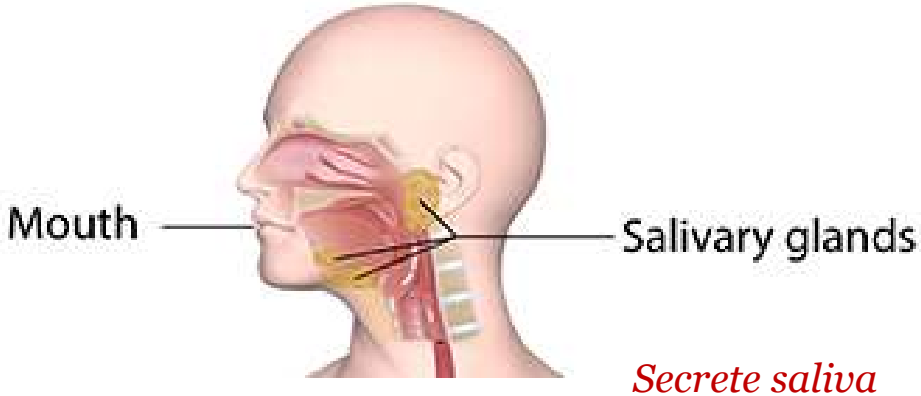
Apply evidence-based pharmacotherapy to develop an effective treatment plan

Human GI Tract



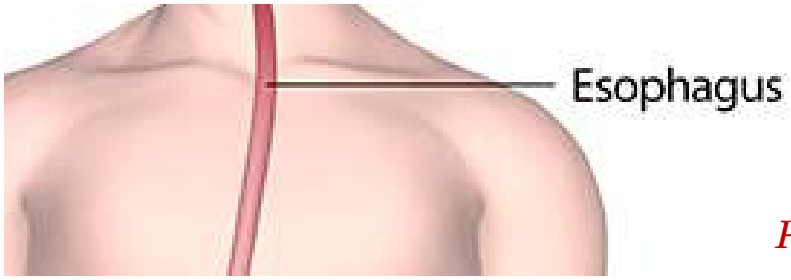
Human GI Tract





Mechanical breakdown of food

Secrete saliva
Initiate breakdown of carbohydrates

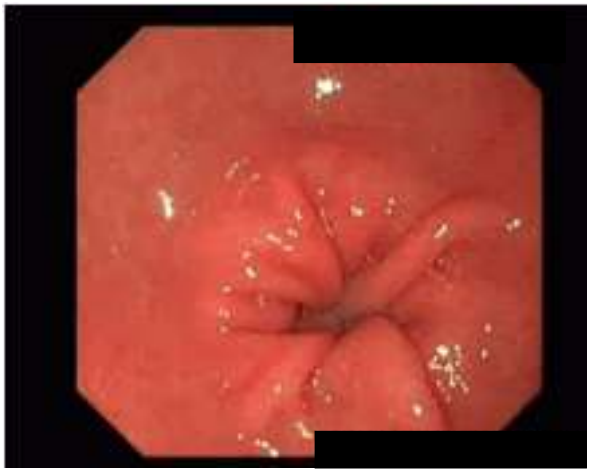


Peristalsis into stomach

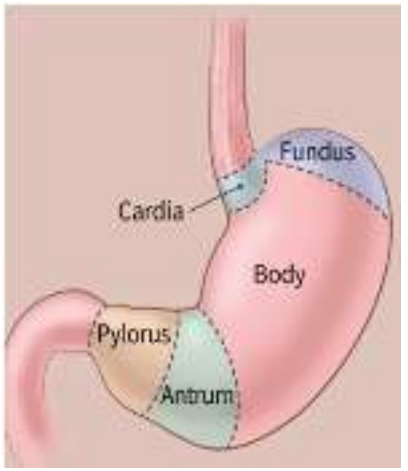
Dissolution

Hydrochloric acid

Peristalsis



Antral systole

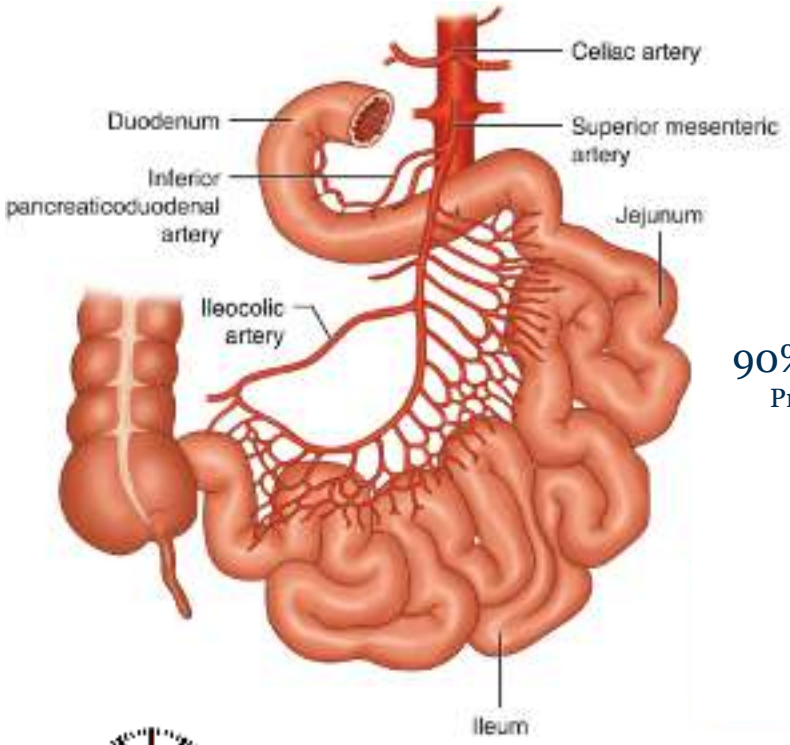


Transit time

- 45 min (glass of water)
- 4-6 hours (high caloric breakfast)

Abuhelwa AY, et al. Eur J Pharm Biopharm. 2017;112:234-248.
Stillhart C, et al. Eur J Pharm Sci. 2020;147:105280.

Small Bowel

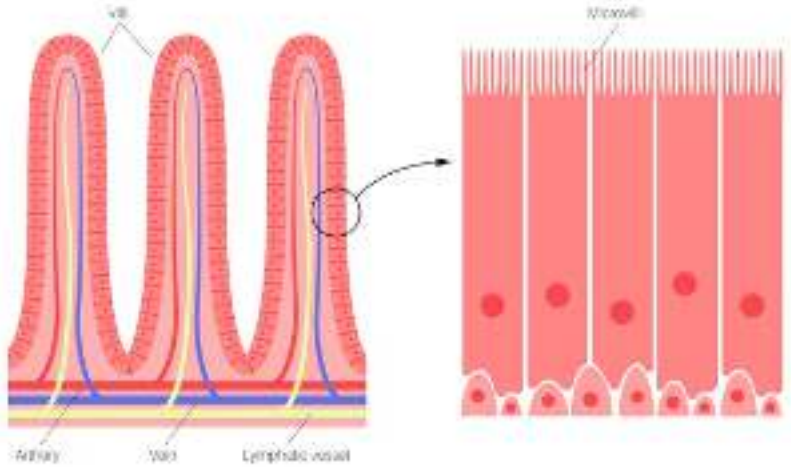


Transit time: ~ 4 hours

Absorption
Transport
Metabolism

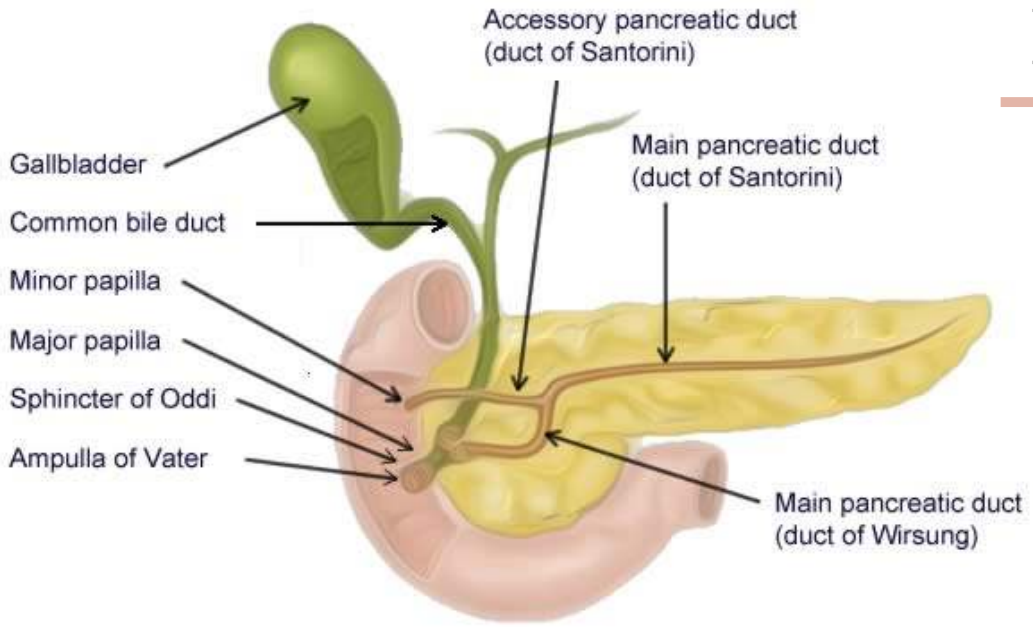
90% Absorption
Proximal jejunum

Jejunum has largest surface area: villi and microvilli



Thomas VH, et al. Expert Opin Drug Metab Toxicol. 2006 Aug;2(4):591-608.
Stillhart C, et al. Eur J Pharm Sci. 2020;147:105280.
Yang CH, et al. Small Intestine Disease (1-20). 2022.

Digestive Fluids and Enzymes



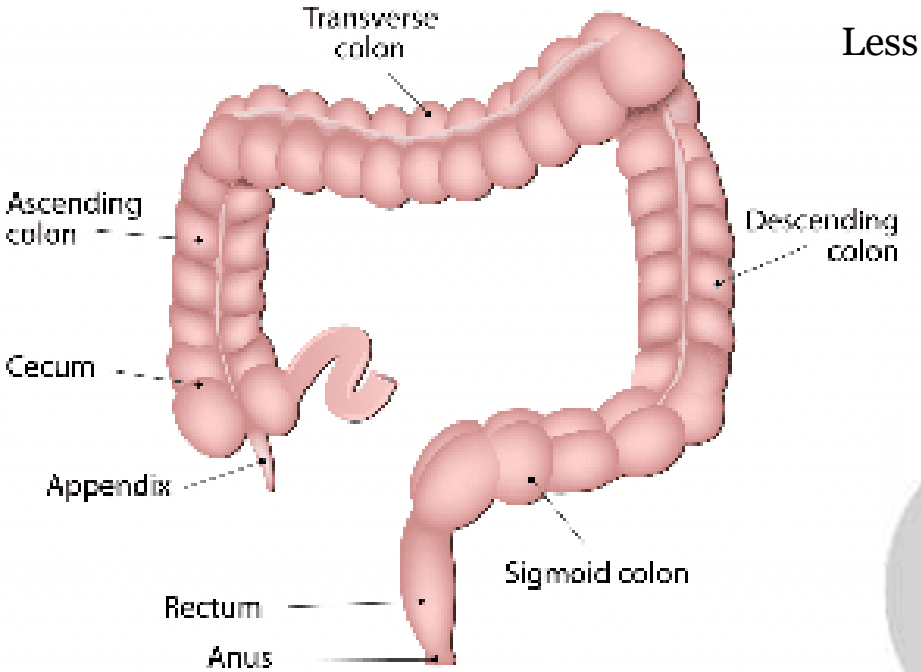
Duodenum & Jejunum

Cholecystokinin	→	*Bile and pancreatic enzyme release*
Secretin	→	*Bicarbonate secretion*
GLP-1	→	*Satiety signals*

Highly lipophilic drugs may depend upon bile acids to enhance solubility

DiGregorio N, et al. StatPearls; 2024 Jan.
Brown CS, et al. Epilepsy Behav Rep. 2021 Mar 22;16:100439.
Krieger JP, et al. Peptides. 2020 Sep, 131, 170342.

Colon

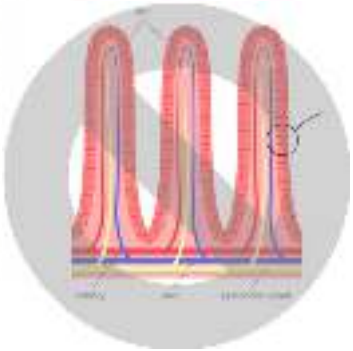


Water & electrolyte absorption
Metabolism
Formation/storage feces

Less enzymes involved in metabolism compared to small bowel

CYP450 | UDP glucosyltransferases | Sulfotransferases

Reduced absorption compared to small intestine

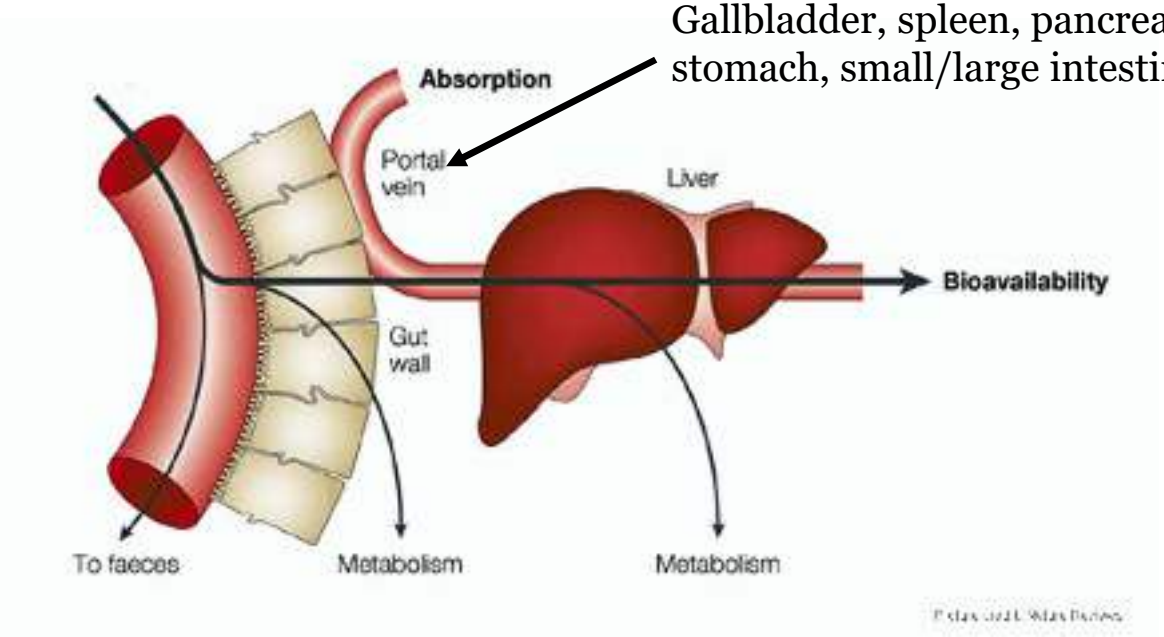


P-gp

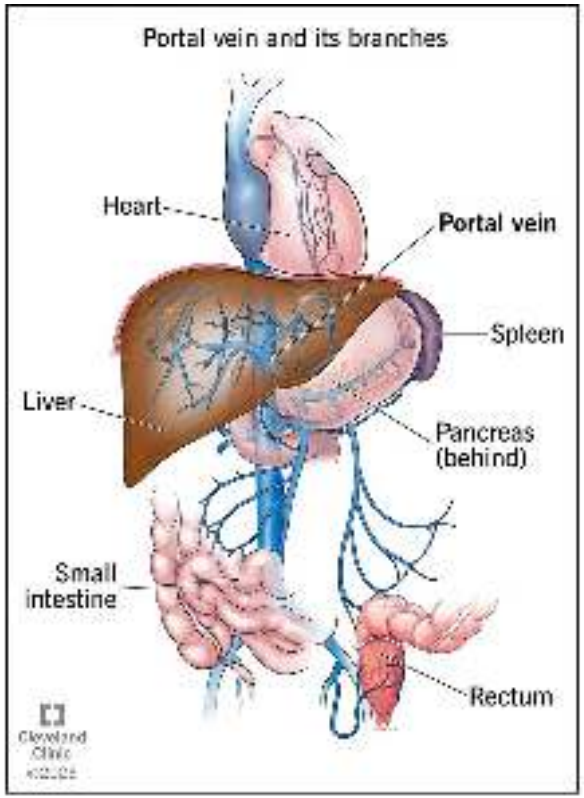
30% membrane permeability compared to small intestine

Transit time: 18-34 hours

First Pass Metabolism



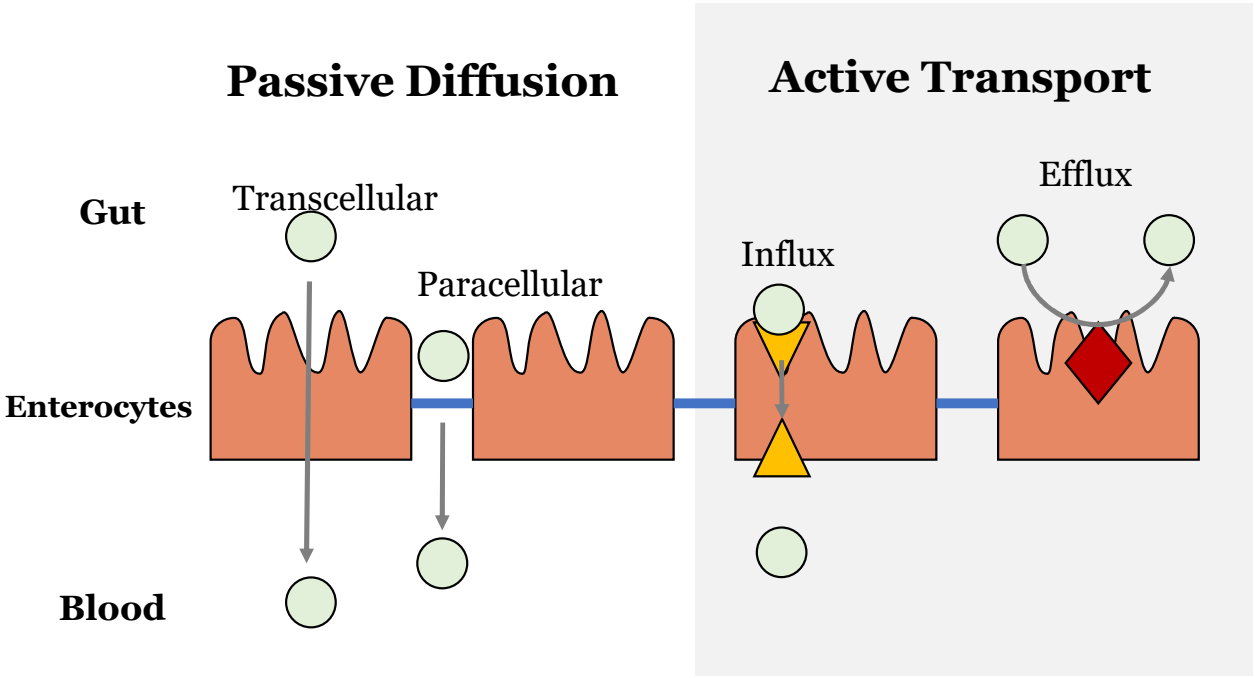
Gallbladder, spleen, pancreas, stomach, small/large intestines



Decreased first pass metabolism = ↑ bioavailability

Waterbeemd VD, et al. Nat Rev Drug Discov 2, 192-204 (2003).
Cleveland Clinic. (n.d.). Portal Vein. Cleveland Clinic. Retrieved January 6, 2025

Routes of Absorption



Transcellular: lipophilic
Paracellular: small, hydrophilic
Active transport: SGLT1, PEPT1, enterocytes

SGLT1: sodium glucose cotransporter 1
PEPT1: peptide transporter 1

Thomas VH, et al. Expert Opin Drug Metab Toxicol. 2006 Aug;2(4):591-608.
Stillhart C, et al. Eur J Pharm Sci. 2020;147:105280.
Yang CH, et al. Small Intestine Disease (1-20). 2022.

Role of pH

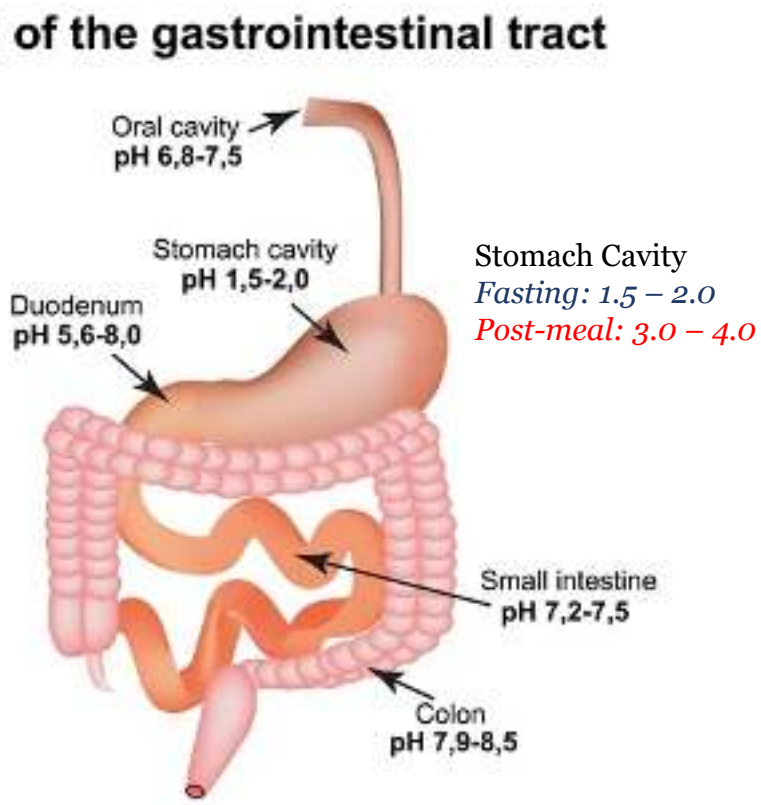


Image source: News Medical Life Sciences

Stomach Cavity
Fasting: 1.5 – 2.0
Post-meal: 3.0 – 4.0

Weak Acids	pKa	Weak Bases	pKa
Amoxicillin	2.4	Lidocaine	7.8
Aspirin	3.5	Codeine	8.2
Cephalexin	3.6	Atropine	9.7
Furosemide	3.9	Metoprolol	9.8
Warfarin	5.0	Epinephrine	8.7

pKA: pH at which 50% of the drug is ionized

$$\mathrm{pH} = \mathrm{pK_a} + \log_{10}\left(\frac{[A^-]}{[HA]}\right)$$

pH < pKa: weak acids unionized, weak bases ionized

pH > pKa: weak acids ionized, weak bases unionized

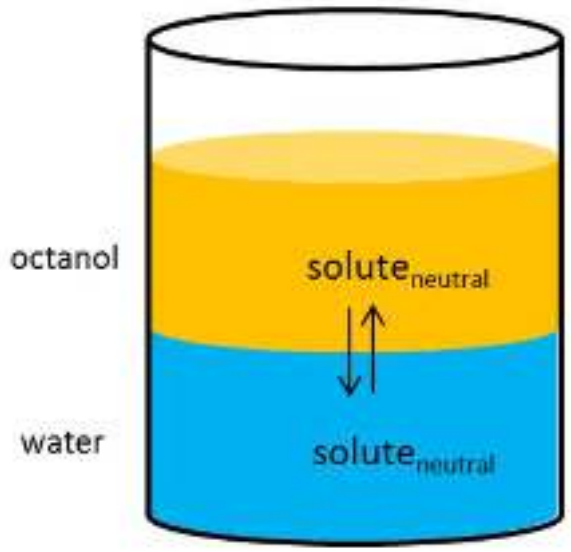
Ionized = ↑ Water solubility **Unionized = ↑ Diffusion**

Abuhelwa AY, et al. Eur J Pharm Biopharm. 2017;112:234-248.

Role of Lipophilicity

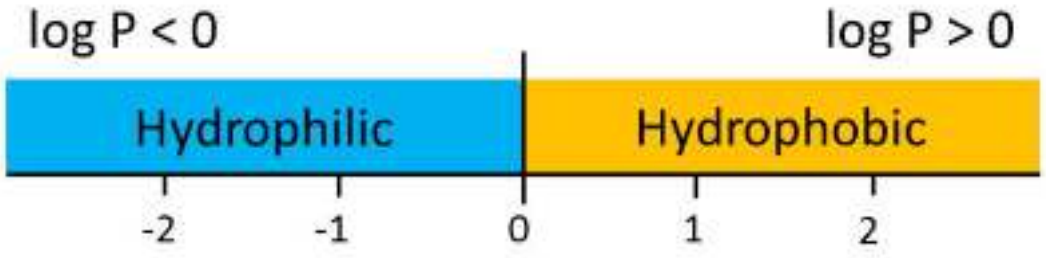
LogP: logarithm of partition coefficient (K) between n-octanol and water

$$K = \frac{[\text{Compound}]_{\text{octanol}}}{[\text{Compound}]_{\text{water}}} \qquad \text{LogP} = \log_{10}(K)$$



Vancomycin: - 3.1
Gentamicin: - 3.1

Fentanyl: 4.05
Midazolam: 2.73



Hydrophilicity
Plasma dissolution

Lipophilicity
Membrane penetration

Pharmacokinetics are Variable

Efflux transporters increases from proximal to the distal small intestine

Breast cancer resistance protein (BCRP)

P-glycoprotein (P-gp)

Multidrug-resistance-associated protein 2 (MDR2)

CYP450 enzymes highest in duodenum/jejunum

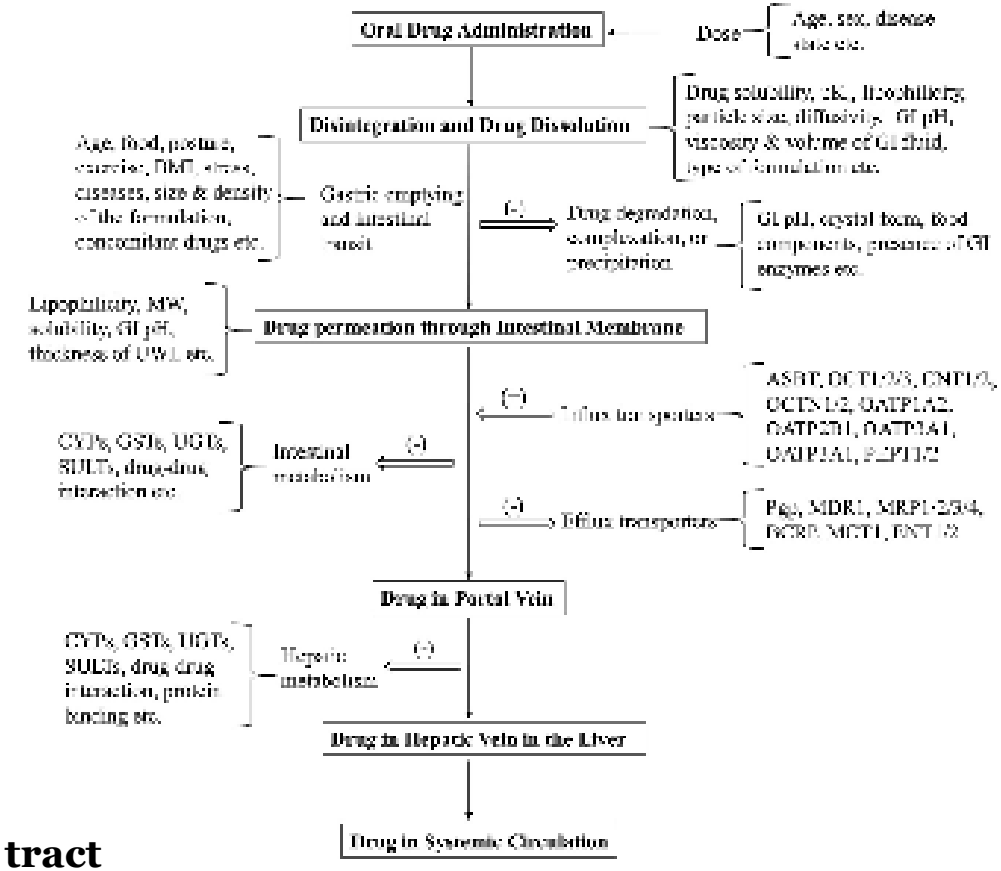
CYP2C

CYP3A4

Uptake transporters expressed throughout the GI tract

Monocarboxylate Transporter 1 (MCT1)

Organic Cation Transporter 1 (OCT1)



Special Populations

Age < 2 years

Increased CYP1A2 and CYP3A4 activity from formula feed

Higher post-prandial gastric pH from milk-based diet

Pregnant

Geriatric

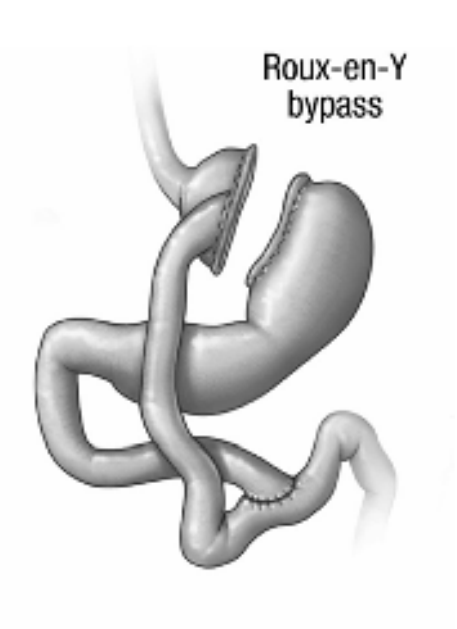
Increased gastric pH

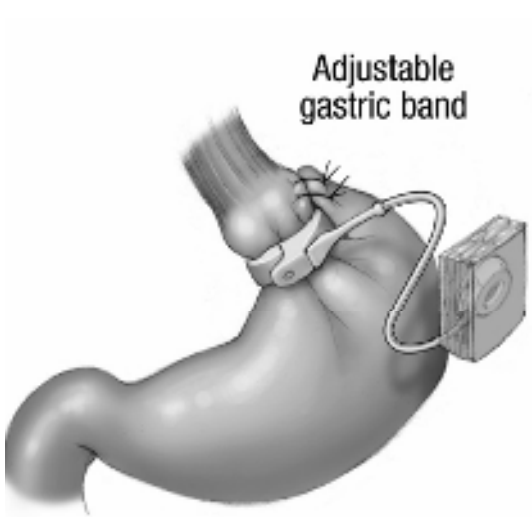
Delayed gastric emptying

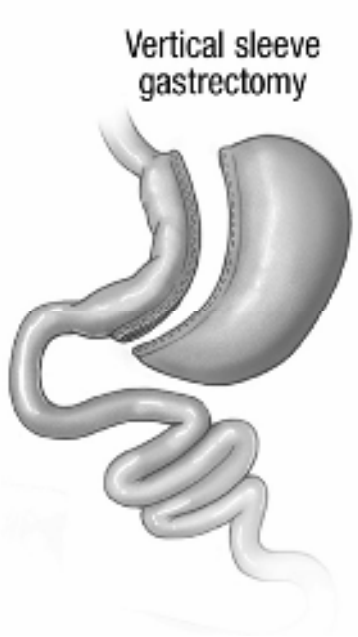
Slower intestinal transit time

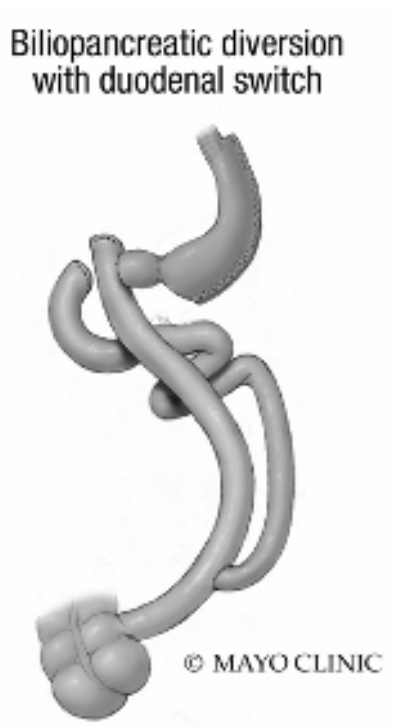
Heavner MS, et al. Pharmacotherapy. 2023;43:403-418.
Bonner JJ, et al. Biopharm. Drug Dispos 36, 245-257.

Bariatric Procedures

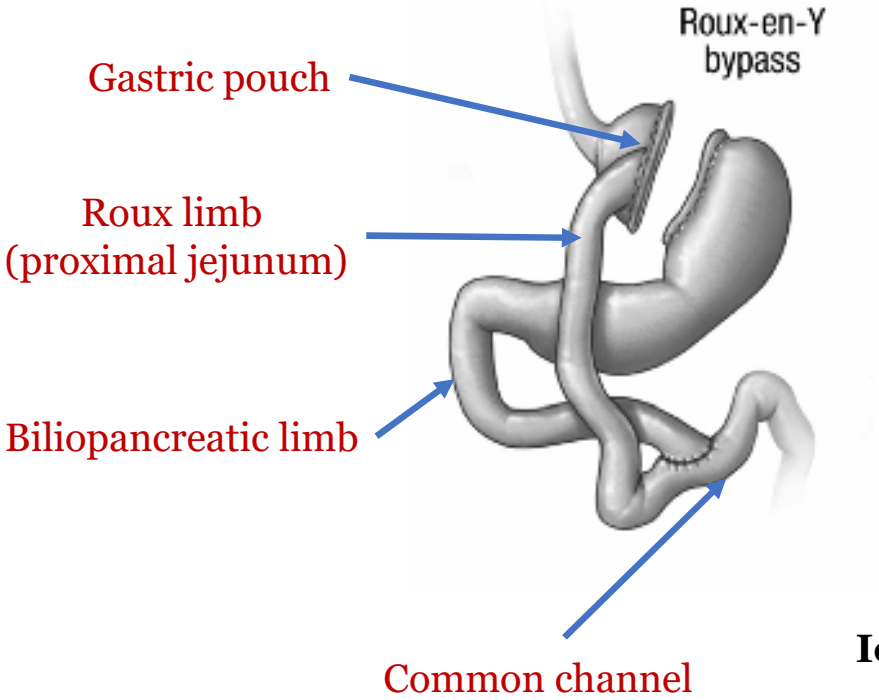


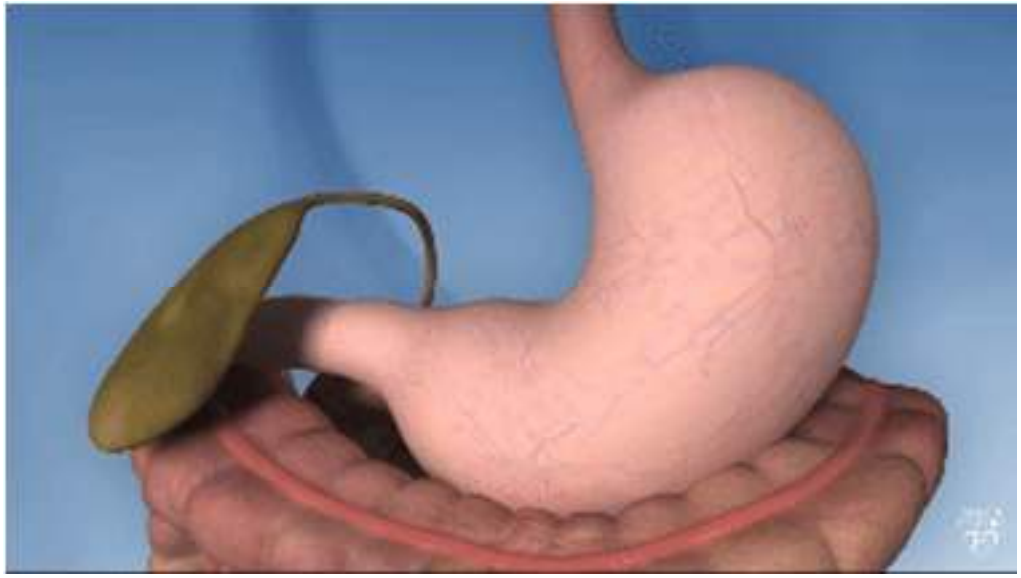






Roux-en-Y Gastric Bypass





1. Reduced parietal cells = increased pH

   Decreased solubility (ionization) of basic drugs

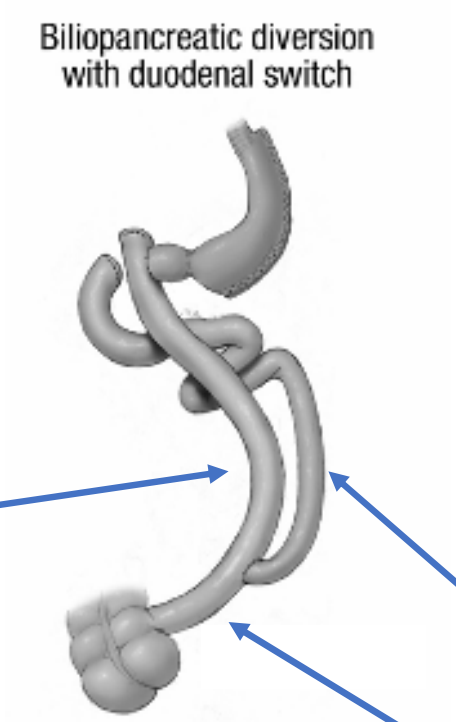
   Increased solubility (ionization) of acidic drugs

Ionization limits membrane penetration and absorption

2. Decreased absorptive surface

3. Decreased bile/pancreatic enzyme mixing

Biliopancreatic Diversion-Duodenal Switch



Alimentary limb (ileum)

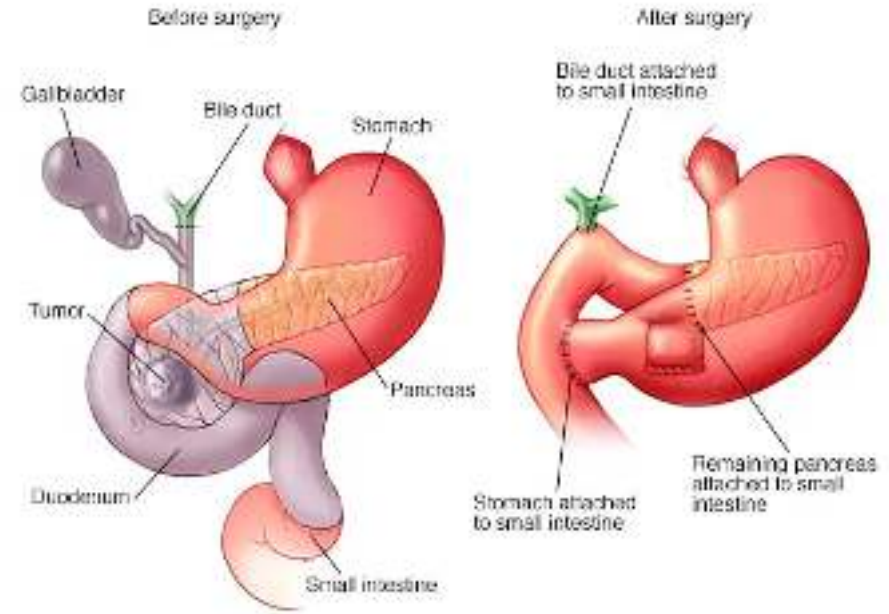
Biliopancreatic limb

Common channel

Shorter common channel = increased malabsorption of fats and nutrients

Nucleus Medical Media. (2015, May 19). *Biliopancreatic diversion with duodenal switch animation* [Video]. YouTube. https://www.youtube.com/watch?v=EX68RG6faUo

Pancreaticoduodenectomy (Whipple)



1. Decreased bicarbonate secretion

2. Potential loss of pylorus = ↑ acidic chime into jejunum

3. Sphincter of Oddi removal = ↑ bile flow into jejunum

Weak bases more likely ionized

↓ passive diffusion **↑ dissolution**

Weak acids less likely ionized

↑ passive diffusion **↓ dissolution**

Phillips ME. Gastroenterology, March 2016.

The Small Bowel Can Still Compensate

Int J Clin Pharmacol Ther. 2024 Jul;62(7):319-325. doi: 10.5414/CP204502.

Pharmacokinetics of apixaban in patients undergoing pancreaticoduodenectomy (PAP-UP)

Richard Zheng, Edwin Lam, Peter Altshuler, Madison Crutcher, Harish Lavu, Charles J Yeo, Douglas Stickle, Benjamin Leiby, Walter K Kraft

PMID: 38660886 DOI: 10.5414/CP204502

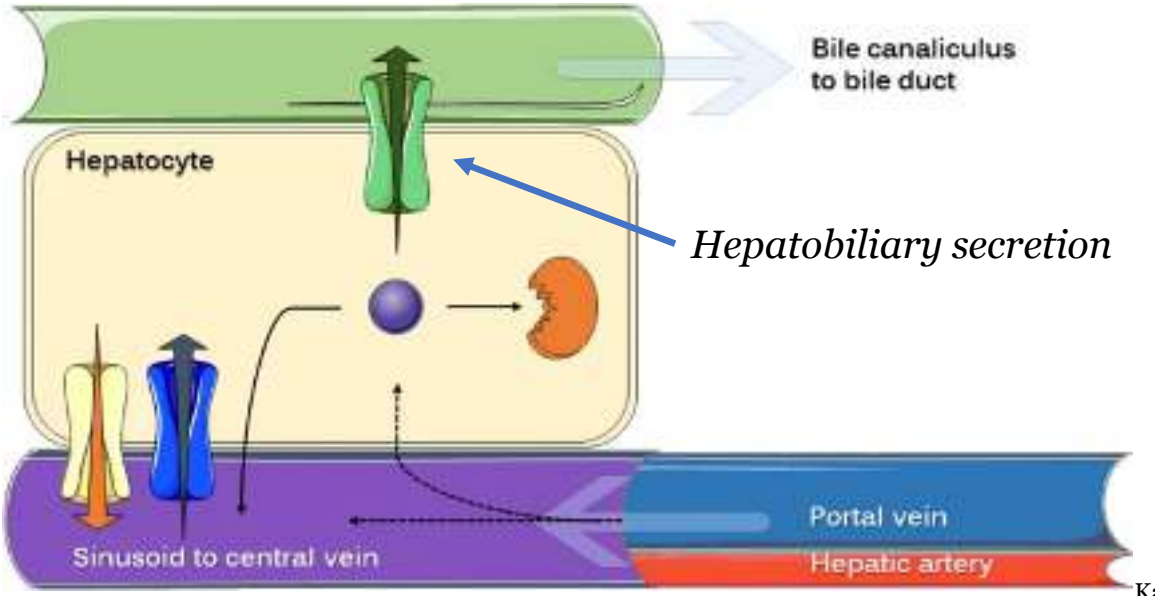
N = 4

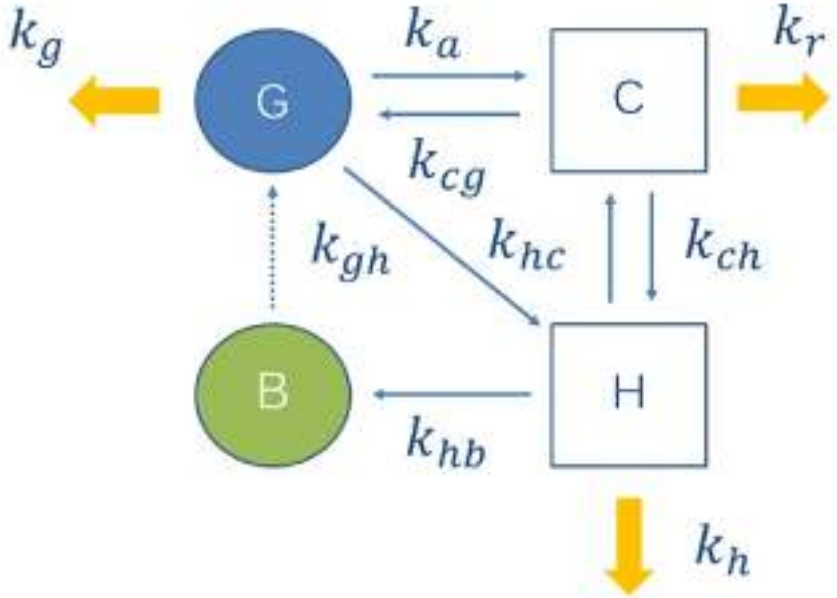
Apixaban 10 mg x 1
Pancreaticoduodenectomy at least 6 months prior

No difference in pharmacokinetic characteristics compared to health controls

Enterohepatic Recirculation

Drugs re-enter the duodenum for repeated absorption after circulating through the liver





G = gut, B = gallbladder, C = central compartment, H = hepatocyte

Kg = intestinal elimination, Kh = hepatic elimination, Kr = renal elimination

Ka = gut absorption
Kcg = systemic circulation to the gut
Kch = central compartment to hepatocyte
Khc = hepatocyte to central compartment

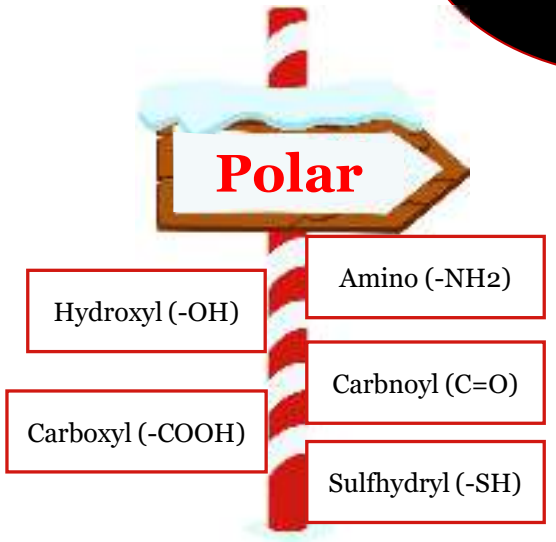
Khb = hepatobiliary secretion
Kgh = hepatic uptake from gut through portal venous blood

Ibarra M, et al. Sci Rep 2021 Mar 11;11(1):5794.

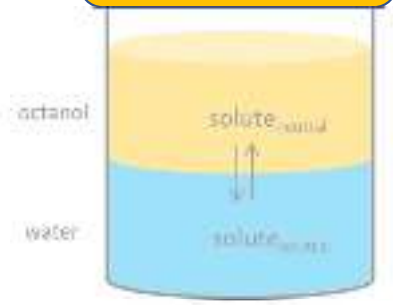
Enterohepatic Recirculation Drugs

- Apixaban
- Carbamazepine
- Digoxin
- Estrogens
- Phenobarbital
- Phenytoin
- Valproic acid
- Warfarin

MW > 300 Da



LogP > 2



Other Surgical Resection

Trauma

Malignancy

Mesenteric ischemia

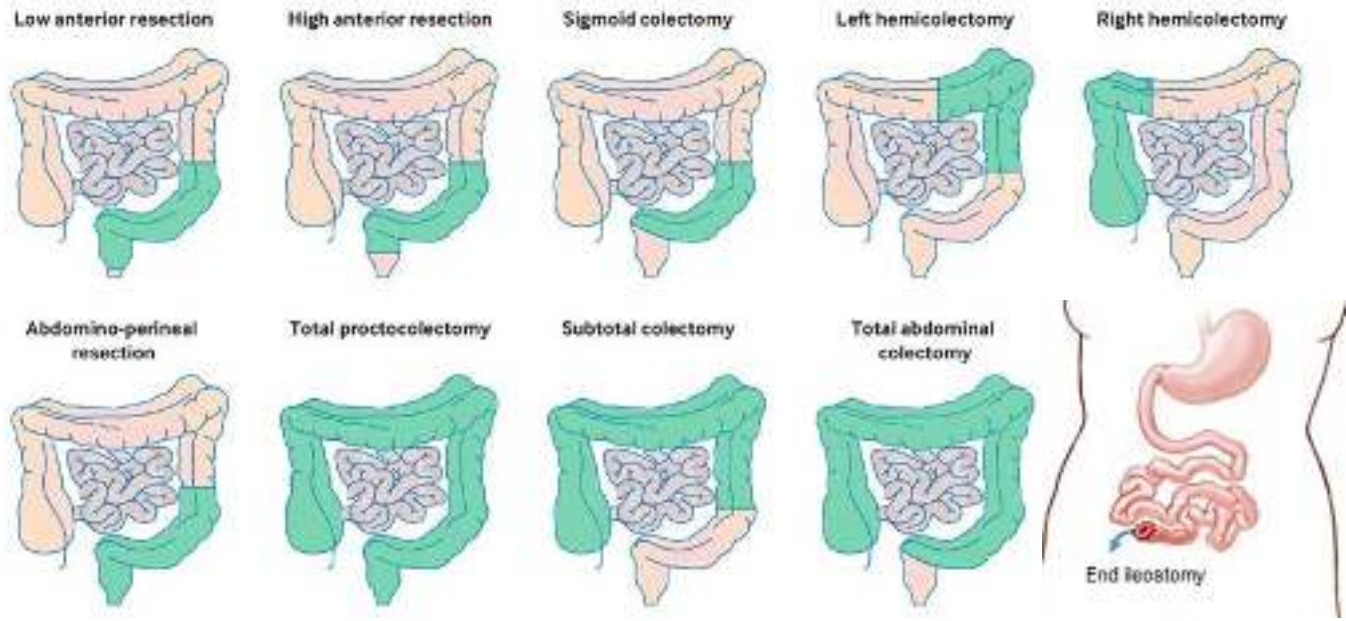
Radiation enteritis

Crohn's disease

Diverticulitis

Obstruction

Colitis

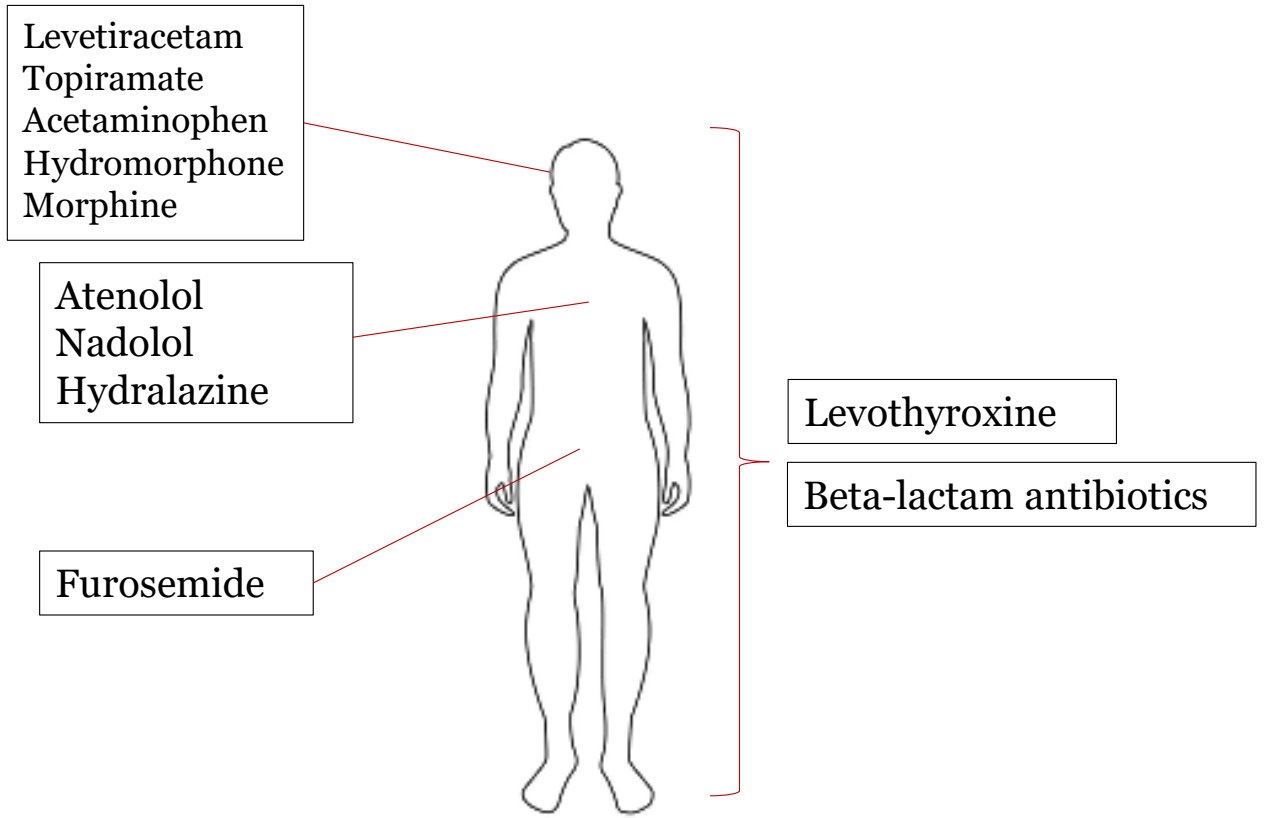


Location	Length	Nutrient
Duodenum	25-30 cm	Calcium, magnesium, iron, zinc
Jejunum	250 cm	Glucose, vitamin C, thiamine, riboflavin, pyridoxine, folic acid
Ileum	350-400 cm	Vitamins A/D/E/K, fat, cholesterol, bile salts, vitamin B12

López-López C, et al. Pharmacology of the gastrointestinal system (pp. 203-218). Springer.

Drugs Less Likely Impacted by Malabsorptive States

- Lower log P (Hydrophilic)
- Lack of enterohepatic recirculation
- Minimal intestinal metabolism
- Minimal transportation through efflux pumps

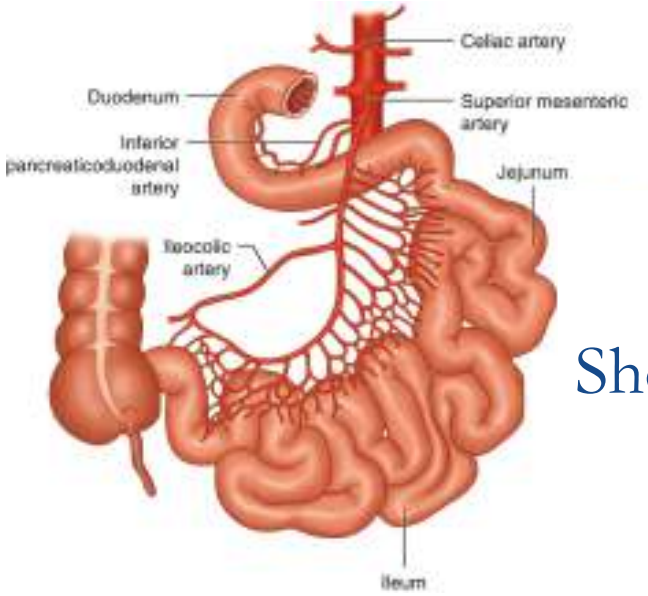


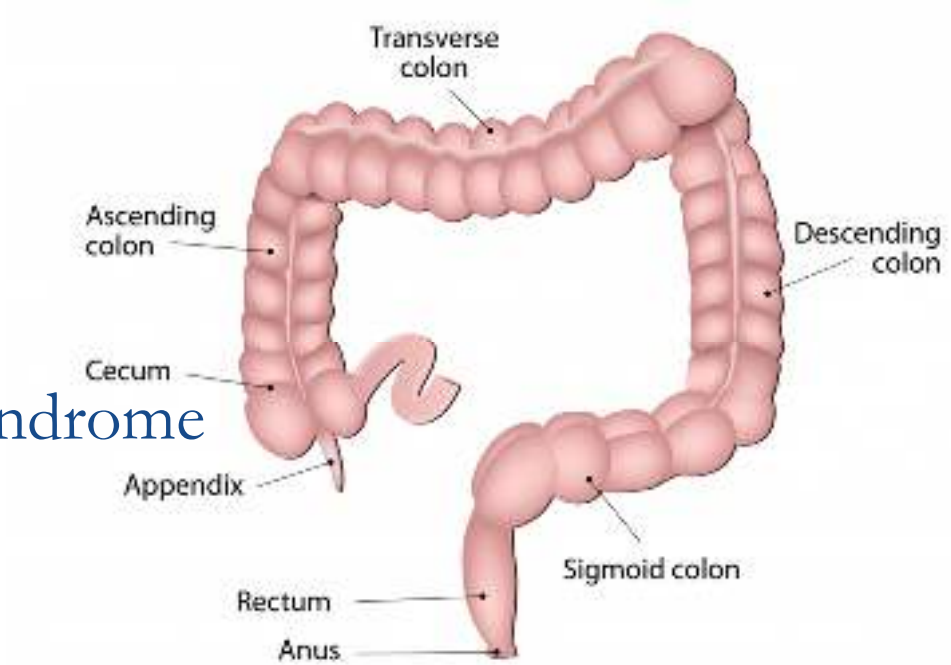
Drug	Alterations	Recommendations
Omeprazole	RYGB: lower exposure	Consider increasing dose
Warfarin	RYGB: decreased absorption	Monitor INR closely
Dabigatran Rivaroxaban Apixaban	SBS ≤ 200 CM: no absorption changes Inter-individual variability	Monitor closely, maintain dosage
Iron	Gastrectomy: decreased solubility with decreased gastric acid secretion	Utilize ferrous sulfate
Digoxin	JIB: no major difference in concentrations	Monitor serum levels
Lithium	RYGB: significant increase in dissolution and absorption	Consider dose decrease and monitor levels
Morphine	RYGB: higher Cmax and AUC	Dose decrease
Tacrolimus	GBS: decreased absorption	Monitor levels, may need higher doses

GBS: gastric bypass surgery, JIB: jejunoileal bypass, SBS: small bowel resection, RYGB: roux-en-Y gastric bypass

Santamaria MM, et al. Eur J Clin Pharmacol (2018): 74:1531-1545.

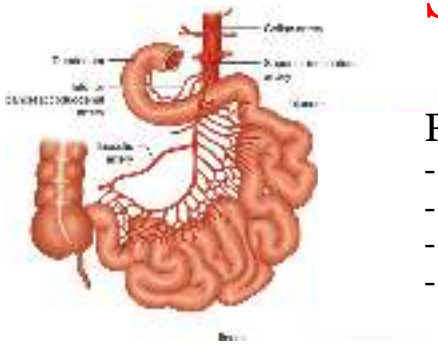
Short Bowel Syndrome





Short Bowel Syndrome

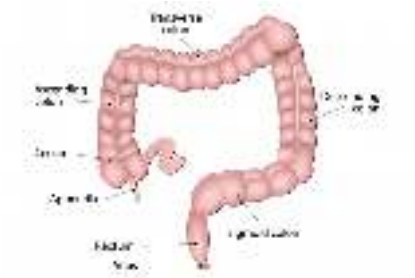
Inability to maintain nutritional, fluid, and electrolyte homeostasis



Small bowel < 200 cm

Duodenum: 25-30 cm
Jejunum: 250 cm
Ileum: 350-400 cm
Total: 600-700 centimeters

Presence of ileal remnant = better prognosis
- Bile salt absorption
- Vitamin B12 absorption
- Water absorption
- Ileocecal valve (slows transit)

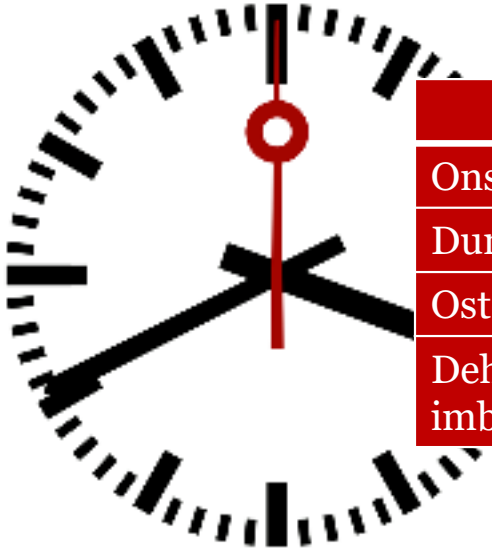


Presence of colon beneficial
- Water absorption
- Electrolyte absorption
- Fatty acid absorption

Clinical Complications

Malabsorption
Dehydration
Gastric acid hypersecretion
Fatty acid deficiency
Small bowel bacterial overgrowth

Phases of Short Bowel Syndrome



Acute Phase
Onset: immediate
Duration: 1-3 months
Ostomy output: >5 L/day
Dehydration, electrolyte imbalances

Sundaram A, et al. J Clin Gastroenterol. 2002 Mar 34(3):207-20.

Short Bowel Syndrome

Antisecretory Agents

- H2RA
- PPI
- Octreotide
- Clonidine

Antimotility Agents

- Loperamide
- Diphenoxylate/atropine
- Codeine
- Tincture of opium

Bile acids binders

- Cholestyramine
- Colesevelam
- Colestipol

Antibiotics

- Rifaximin
- Neomycin
- Tetracycline
- Ciprofloxacin
- Metronidazole
- TMP/SMX
- Amoxicillin-clavulanic acid

Gastric Hypersecretion

Gastric inhibitory peptide

Vasoactive intestinal peptide

Antisecretory Agents

- H2RA
- PPI
- Octreotide
- Clonidine

Decrease volume of secretions
Restore intestinal pH

Loss of feedback mechanisms from resected bowel

Duration: 6-12 months post resection

Gastric hypersecretion

Start immediately after resection: PPI first line

H2Ra second line

Octreotide adjunct, utility limited by tachyphylaxis and reduction of intestinal adaptation

Clonidine adjunct, utility limited by hemodynamic ADR

Johnston RJ, et al. Pract Gastroenterol. 2021;45(10):20-29.

High Ostomy Output

Antimotility Agents

- Loperamide
- Diphenoxylate/atropine
- Codeine
- Tincture of opium

Decrease intestinal motility
Slow gastric transit

Rule out *Clostridioides difficile*

Loperamide or diphenoxylate first line agents

If no improvement: **switch to** diphenoxylate
If partial improvement: **add** diphenoxylate

Add or switch to opioids if max recommended doses fail

Monitor for obstructive symptoms

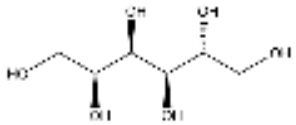
Nausea, vomiting, abdominal pain, distention

Mackowski A, et al. BMJ Case Rep 2015;2015.
Nightingale JMD. Frontline Gastroenterology 2022;13:!401-151.

Caution with Liquid Formulations

Sugar alcohols are potent cathartics and can lead to osmotic diarrhea

- Sorbitol
- Mannitol
- Xylitol
- Maltitol
- Isomalt
- Erythritol
- Lactitol



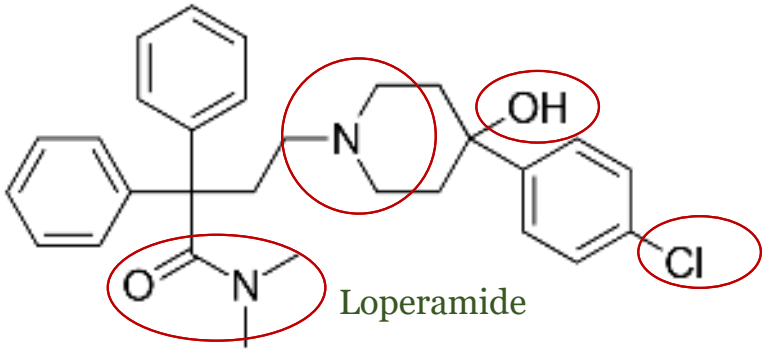
Sugar Alcohol	Medication
Sorbitol	Acetaminophen 160 mg/5 mL Acyclovir 200 mg/5 mL Amantadine 50 mg/5 mL Diphenoxylate and atropine 2.5 mg/0.025 mg/5 mL Furosemide 10 mg/mL Lacosamide 10 mg/mL Metoclopramide 5 mg/5 mL Mycophenolate mofetil 200 mg/mL Valproic acid 250 mg/5 mL

High Ostomy Output

	Loperamide	Diphenoxylate-Atropine
Mechanism	Directly interferes with peristalsis by direction action on the circular/longitudinal muscles of the intestinal wall	Synthetic opiate agonist that inhibits GI motility and slows GI propulsion
Opiate Effects	None Limited ability to cross blood-brain barrier Does not lead to dependence	High doses associated with euphoria and physical dependence
Dosing	2 to 8 mg every 6-12 hours Max: 32 mg/day	5 mg every 6 hours Max: 20 mg/day
Adverse Effects	QTc prolongation*, ventricular tachycardia	Pruritus, xerostomia, toxic megacolon

*Single-dose of 48 mg not shown to prolong QTc in healthy participants

High Ostomy Output



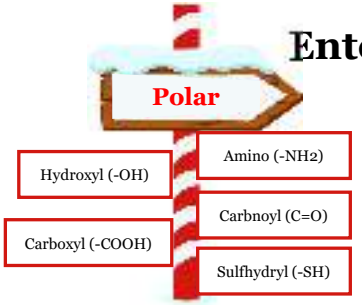
Loperamide

MW: 477

LogP: 5.13

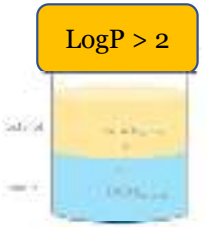
Successful use of high dose loperamide
- 12-24 mg/dose
- 40 mg five times daily
- 100 mg four times daily

Normal Loperamide serum: 0.24 – 1.2 mg/mL



Enterohepatic Circulation Compromised

MW > 300 Da



Mackowski A, et al. BMJ Case Rep 2015;2015.
Nightingale JMD. Frontline Gastroenterology 2022;13:!401-151.

Cholerectic Diarrhea

Ileal resection, intact colon-in-continuity

↓

Bile salts metabolized by bacteria in colon

↓

Lithocholic acid
(caustic, stimulates water secretion)

Image source: Verywell Health: https://www.verywellhealth.com/bile-acid-diarrhea-1945221

Cholerectic Diarrhea

Bile acid binders

- Cholestyramine
- Colesevelam
- Colestipol

Sequester bile acids

Ileal resection, intact colon-in-continuity

↓

Bile salts metabolized by bacteria in colon

↓

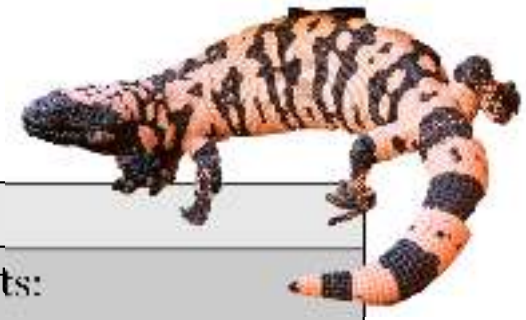
Lithocholic acid (caustic, stimulates water secretion)

Limited utility in extensive ileal resections > 100 cm

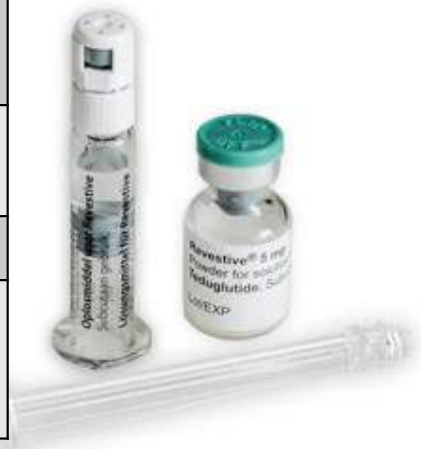
- Worsens steatorrhea, fat-soluble vitamin deficiencies
- Sequestrants indicated when < 100 cm of ileum resected

Teduglutide (Gattex)

Teduglutide (Gattex)

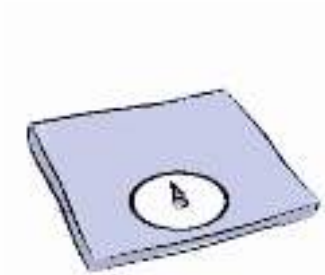


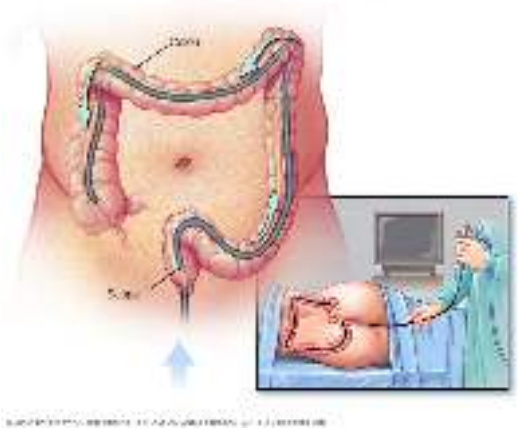
Class	Glucagon-like peptide-2 (GLP-2) analog
Mechanism	Enhances intestinal capacity to absorb nutrients: • Promote intestinal crypt cell proliferation • Inhibit enterocyte apoptosis • Decrease small intestinal motility • Increase mesenteric blood flow
Half-life	2 hours (compared to 7 min for endogenous GLP-2)
Dosing	0.05 mg/kg/day subcutaneous (eGFR < 60: 0.025 mg/kg/day)
Adverse effects	Abdominal pain Headache, nausea, vomiting GI polyps (no carcinogenic effect observed)



Approved in adults and children ≥ 1 year old with SBS and IV nutritional support dependent

Teduglutide Monitoring





1 year after treatment
Q3-5 years while on treatment

48-h Urine Output	IV Supplementation Action
< 1.0 L/day	Increase by ≥ 10% or to previous level
≥ 1.0 L/day but < baseline	If dehydrated or inadequately nourished, increase IVS If not dehydrated, maintain
0% to <10% increase over baseline	Maintain IVS
≥ 10% increase over baseline	Reduce IVS ≥ 10% of stabilized baseline level up to a clinically appropriate amount (max 30%)

Teduglutide Efficacy

85% (n=46/54) had decrease in IV supplementation volume of at least 20% after 6 months of treatment

24% (n = 4/19) had independence of IV supplementation

Time to response: first weeks up to 12 months

Factors for early response:

- Presence of stoma
- Absence of colon in continuity
- Etiology of inflammatory bowel disease

Greif S, et al. Clin Nutr ESPEN. 2022;51:222-230.
Joly F, et al. Clin Nutr. 2020;39(9):2856-2862.

Considerations for Teduglutide Initiation

GATTEX REMS (Risk Evaluation and Mitigation Strategy)

Prior authorizations every 3-12 months

~$300,000/patient annually

Patients > 76 kg will need 2 kits per month

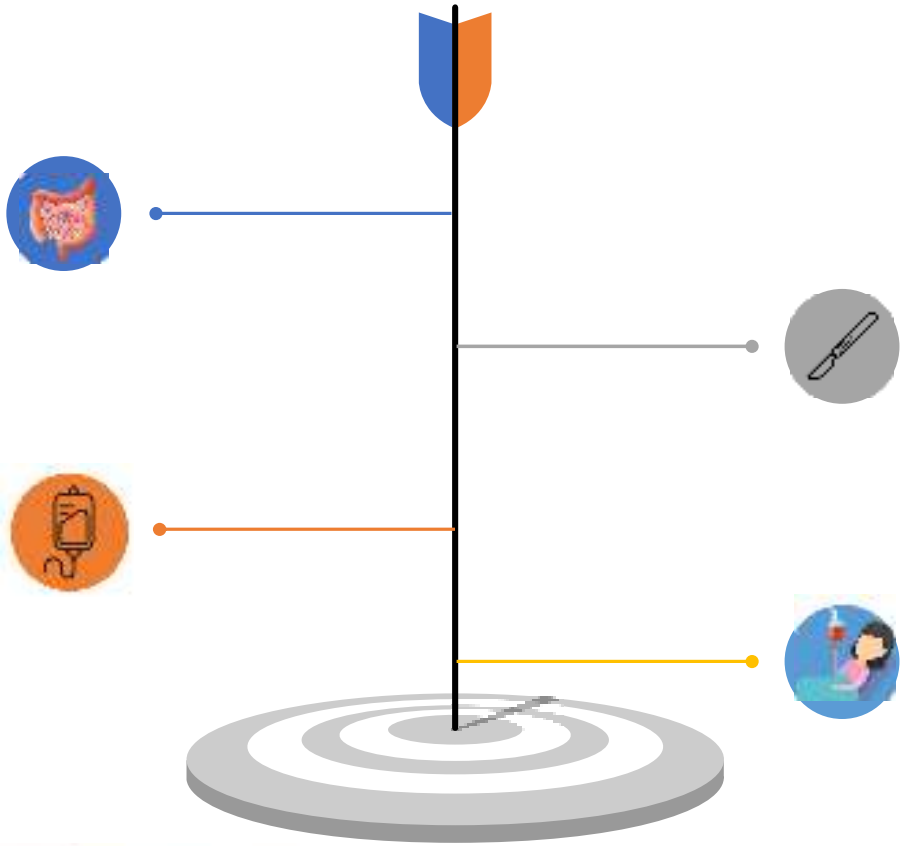
Conclusion

Anatomy

The gastrointestinal tract plays a crucial role in drug absorption and metabolism

Pharmacotherapy

Limited published data on PK variability according to surgical procedure



Pathophysiology

Alterations in GI physiology can significantly impact pharmacokinetics

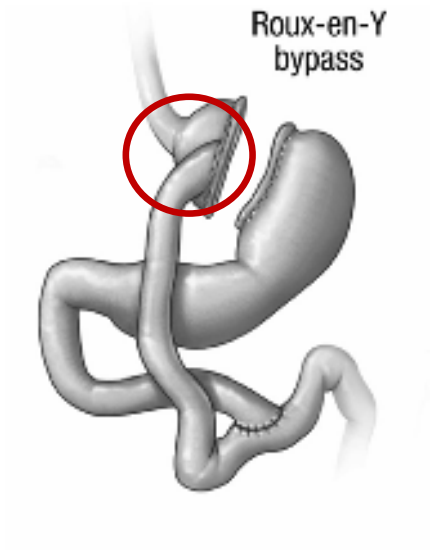
Pharmacotherapy

Various pharmacologic modalities are available to manage short bowel syndrome

Patient Case

Patient Case

50 male admitted to the surgical ICU for septic shock after suture repair of a gastrojejunostomy leak from a recent Roux-en-Y gastric bypass



Weight: 120 kg
CrCl: > 120 ml/min

PMH: hypertension, diabetes

Medications

Acetaminophen 650 mg every 6 hours as needed

Fluconazole 400 mg IV every 24 hours

Norepinephrine @ 12 mcg/h

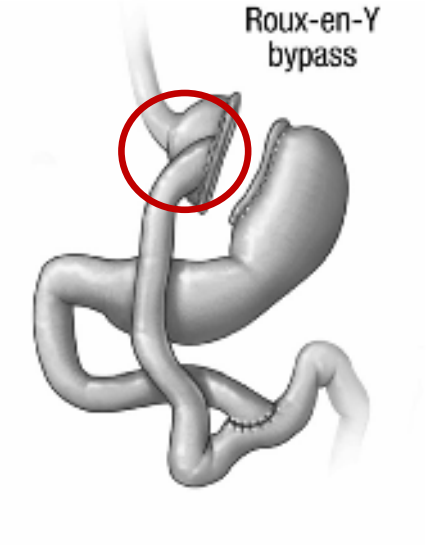
Oxycodone 5 mg every 6 hours as needed

Pantoprazole 40 mg IV every 24 hours

Piperacillin/tazobactam 4.5 g every 6 hours

Vasopressin @ 0.04 units/min

Patient Case



Which of the following statements is NOT true regarding drug absorption after Roux-en-Y bypass?

a) Gastric pH increases
b) Ionization of basic drugs is decreased, absorption increases
c) Ionization of acidic drugs is increased, absorption decreases
d) Small intestine absorption is minimally affected

Patient Case

True or False: The majority of drug absorption takes place in the jejunum and ileum.

a) True
b) False

Patient Case

Your patient develops an occlusion of the superior mesenteric artery leading to ischemia and is taken to the operating room for extensive small bowel resection with < 100 cm small bowel remaining. Which of the following agents is recommended first line for gastric hypersecretion?

a) Octreotide
b) Sucralfate
c) Pantoprazole
d) Clonidine

Patient Case

The patient's ostomy output has been consistently > 2.5 liters/day. After starting loperamide 4 mg every 6 hours, output has decreased to 2 liters/day. Which of the following is the most appropriate recommendation to decrease the ileostomy output?

a) Continue loperamide, add tincture of opium
b) Discontinue loperamide, start diphenoxylate-atropine
c) Continue loperamide, start diphenoxylate-atropine
d) Discontinue loperamide, start diphenoxylate-atropine and codeine

Patient Case

All of the following drug properties would potentially have an effect on absorption caused by altered GI anatomy except for:

a) Low log P
b) Enterohepatic recirculation
c) Intestinal metabolism
d) Substrate of efflux transporter

Gut Instincts: Navigating Pharmacotherapy after Gastrointestinal Procedures

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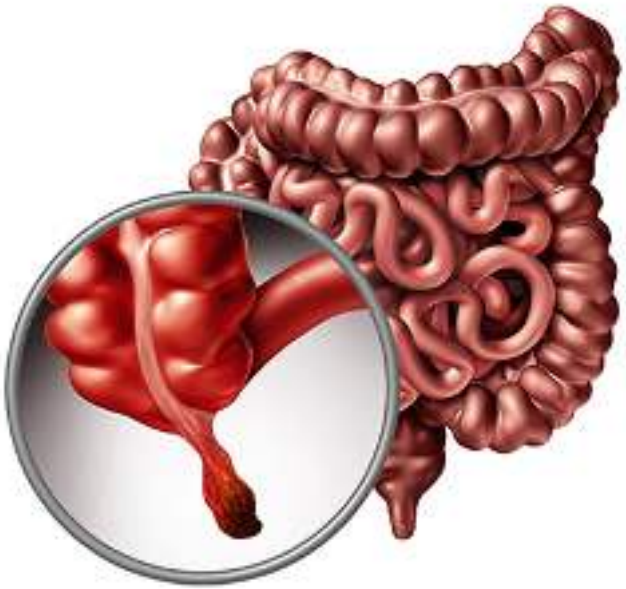
Clinical Pharmacy Specialist – Trauma, Surgical, Burn ICU

WMC Health
Westchester Medical Center Health Network

Appendix



Common Enteral Access

Tube Type	Purpose	Size (Fr)	Notes
Nasogastric (NG)	Gastric drainage, decompression, or short-term feeding	12–16	Common for adults
		6–10	Pediatric & neonates or for more comfortable feeding in adults
Post-Pyloric	Feeding into the small intestine (e.g. jejunum)	8–12	Smaller sizes preferred to minimize irritation and migration
PEG (Gastrostomy)	Long-term feeding into the stomach	12–24	Typical range for adults
PEJ (Jejunostomy)	Long-term feeding into the jejunum	8–12	Standard for jejunal feeding
Sump Drainage Tubes	Gastric decompression and drainage	12–18	Double-lumen tubes (e.g., Salem Sump) allow for air venting and suction simultaneously.

Different Release Mechanisms

Release Mechanism	Description
Sustained Release (SR)	Release drugs at a predetermined rate for constant drug concentrations • Reduced dosing frequency • Absorbed throughout the GI tract • First order kinetics
Delayed Release (DR)	Release drug at a specific time dependent on pH-triggered mechanism • Typically bypasses stomach • Decreases gastric irritation
Controlled Release (CR)	Release drug at a controlled rate (constant vs. variable) • Precisely regulates release rate • Useful for narrow therapeutic index drugs • Zero order kinetics
Extended Release (ER)	Release drug over an extended period of time • Reduce peak-trough fluctuations • Reduced dosing frequency

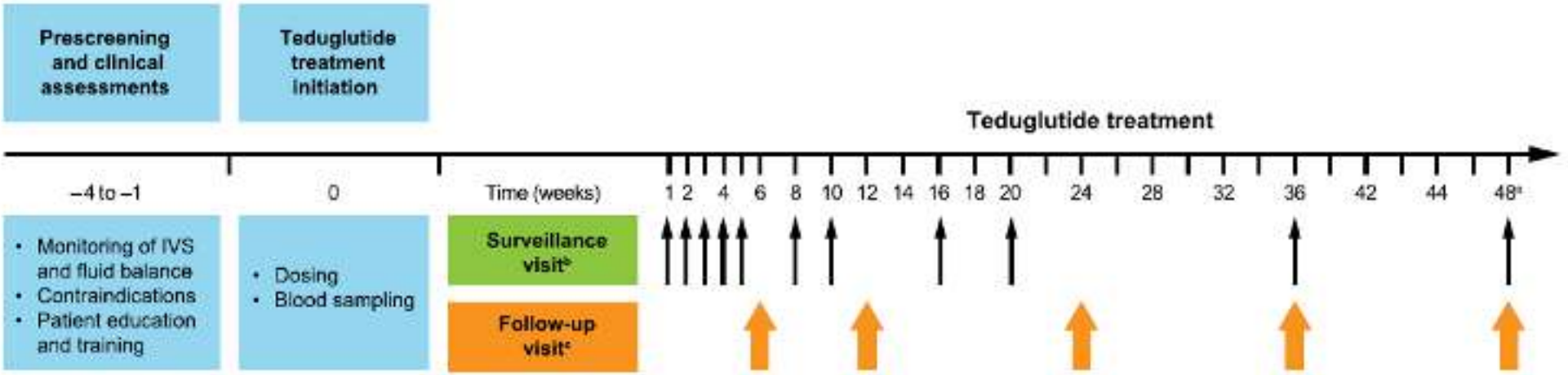


FIGURE 2 Monitoring regimen for teduglutide treatment. [a]After 48 weeks patients are monitored biannually for as long as teduglutide treatment is ongoing. [b]Surveillance visit with specialist nurse: monitoring of adverse events and fluid balance; the black arrows indicate blood sampling. [c]Follow-up visit with physician, specialist nurse, and dietitian: assessment of teduglutide effectiveness and side effects, monitoring of adverse events and IVS, adjustments to IVS (if required), blood sampling, and assessment of nutrition and hydration status (broad orange arrows). IVS, intravenous supplementation.

High Ostomy Output

	Diphenoxylate-Atropine	Tincture of Opium	Codeine	Loperamide
LogP	5.7	Morphine: 0.8	1.1	5.13
MW (Da)	452	~300	299	477
Polar Groups?	Yes	Yes	Yes	Yes

Drugs More Likely Impacted by Malabsorptive States

Drug	Log P	Enterohepatic Circulation	Intestinal Metabolism	Efflux
Olanzapine	3.5	Minimal	CYP1A2, UGT1A4	P-gp
Risperidone	2.7	Minimal	CYP2D6	P-gp
Alprazolam	2.8	None	CYP3A4	P-gp
Clonazepam	3.6	None	CYP3A4	P-gp
Oxycodone	0.7	Minimal	CYP3A4	P-gp
Amiodarone	7.6	Minimal	CYP3A4	P-gp
Amlodipine	3.2	Minimal	CYP3A4	None
Diltiazem	3.9	Minimal	CYP3A4	None
Apixaban	1.9	Minimal	CYP3A4	P-gp
Rivaroxaban	1.5	Minimal	CYP3A4	P-gp

C. Difficile Enteritis

- Can occur after radical surgery
- Median time from colectomy to onset of enteritis ~ 129 days in 22.7% cases
- 56 cases reported between 1980 to 2010

Kim JH, et al. Anaerobe. 2011 Apr;17(2):52-5.
Bott J, et al. Open Forum Infect Dis 2015;2 (suppl1):1022.

C. Difficile Proctitis

- Incidence limited to case reports
- Inconclusive evidence regarding optimal treatment
- Vancomycin enema vs. mini-fecal microbiota transplantation