

Drugs Used in Treating Constipation and IBS

Objectives:

By the end of the lecture , you should know:

- Classify laxatives
- Discuss the pharmacological properties of different classes of laxatives, their pharmacokinetics, uses and side effects
- Define drugs used to treat irritable bowel syndrome

Color index:

Black : Main content
Red : Important
Blue: Males' slides only



Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Constipation

infrequent defecation, often with straining and the passage of hard, uncomfortable stool.

Causes:

1

Decreased motility in colon:

Decrease in water and fiber contents of diet.

2

Difficulty in evacuation:

-Local painful conditions: anal fissures, piles.
- Lack of muscular exercise.

3

Drug-induced:

-Anticholinergic agents
-Antidepressant
-Bismuth, Antacids.
-Opioids, NSAID.
-Iron, Antipsychotics.
-Sympathomimetics
-Ca⁺² channel blockers

Accompanied signs and symptoms

Loss of appetite



Flatulence



Abdominal & rectal pain



Lethargy



Depression

Treatment of Constipation

- Adequate fluid intake.
- High fiber contents in diet.
- Regular exercise.
- Regulation of bowel habit.
- Avoid drugs causing constipation.
- **Use drugs (laxatives or purgatives)¹:**
 - Drugs that hasten the transit of food through the GIT.

Classification of laxatives

1

Bulk forming laxatives

4

Osmotic laxatives

2

Stimulant laxatives

5

Stool softeners (lubricants)

3

Opioid receptor antagonists

6

Serotonin (5-HT₄) agonists

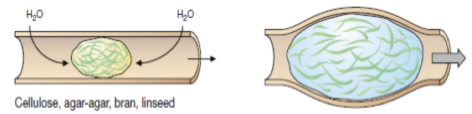
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Intestinal secretagogues (Chloride secretion activators)

1) **Laxatives** are milder in action and deal with evacuation of rectum. With the use of laxatives, there's elimination of soft stool. **Cathartics** are severe in action and deal with evacuation of colon. With their use, liquid form of stool is eliminated. **Purgatives** in between the two.

Bulk forming laxatives

	Dietary fibers	Hydrophilic colloids	Synthetic fibers
Types	<ul style="list-style-type: none"> ● Indigestible parts of vegetables & fruits ● Bran powder 	<ul style="list-style-type: none"> ● Psyllium seed¹ ● Methyl cellulose² ● Carboxymethyl cellulose (CMC) 	<ul style="list-style-type: none"> ● Polycarbophil
MOA	<ul style="list-style-type: none"> ● Dietary fibers and hydrophilic colloids are non absorbable substances → ↑ the bulk of intestinal contents by water retention → ↑ mechanical pressure on the walls of intestine (distend the colon) → stimulation of stretch receptors → ↑ peristalsis → evacuation of soft stool. 		
ADRs	<ul style="list-style-type: none"> ● Delayed³ onset of action (1-3 days). ★ Intestinal obstruction (should be taken with enough water). So not used for patients in which water intake is restricted like heart failure, Kidney failure. ● Bloating, flatulence, distension ● Interfere with other drug absorption e.g. iron, cardiac glycosides. 		



Osmotic Laxatives

- Are water soluble compounds **BUT poorly absorbable compounds** (salts or sugars)
- **MOA:** They remain in the bowel, attract and retain water by **osmosis** thereby increasing the volume of feces → ↑ peristalsis → evacuation of stool.⁴
- Included **3 classes:**

1. Sugars:

- Lactulose
- Sorbitol

2. Salts (Saline laxatives):

- Magnesium sulphate or hydroxide
- Sodium or Potassium phosphate

3. Polyethylene glycol (PEG)

1. Sugars

Drug	lactulose
P.K	<ul style="list-style-type: none"> ● Semi synthetic disaccharide of fructose & galactose. ● Non absorbable. ★ In the colon, metabolized by bacteria to fructose & galactose. ★ These sugars are fermented into lactic acid & acetic acid that function as osmotic laxatives.
Uses	<ul style="list-style-type: none"> ● Prevention of chronic constipation (and opioid induced constipation) ● Hemorrhoids ● Hepatic encephalopathy (Hyperammonemia) ★ Liver cirrhosis <ul style="list-style-type: none"> ● Why is lactulose used in Liver cirrhosis & Hyperammonemia? It increases the H⁺ concentration in the gut, this favors the formation of the non-absorbable NH₄⁺ from NH₃, trapping NH₃ in the colon and reducing its back diffusion into blood.
ADRs	<ul style="list-style-type: none"> ★ Delayed onset action (2-3 Days) ★ Electrolyte disturbance. ● Abdominal cramps & flatulence.
Dose	15 ml for constipation & 30 ml for Liver cirrhosis & portal hypertension.

- 1) Natural
- 2) Seminal
- 3) Chronic use
- 4) There's a higher risk for dehydration with osmotic laxatives.

2. Saline laxatives

Drug	<ul style="list-style-type: none"> • Magnesium sulphate/Citrate (Epson's salt) • Magnesium hydroxide (milk of magnesia) 	<ul style="list-style-type: none"> • Sodium phosphate • potassium phosphate.
P.K	<ul style="list-style-type: none"> • Are poorly absorbable salts • Increase evacuation of watery stool. • have rapid effect (within 1-3 h). • Isotonic or hypotonic solution should be used 	
Uses	<ul style="list-style-type: none"> ★ Treatment of acute and chronic constipation (Magnesium hydroxide)¹ ★ Treatment of acute constipation, cleanse of bowel (Magnesium sulphate/Citrate)² • Has antacid effect (Magnesium hydroxide) 	
ADRs	<ul style="list-style-type: none"> • Disturbance of fluid and electrolyte balance • Dehydration • May have systemic effects. • Sodium phosphate: <ul style="list-style-type: none"> ○ May causes Hyperphosphatemia, hypernatremia ,hypokalemia. ○ Cardiac arrhythmias ○ Acute renal failure → deposition of calcium phosphate "nephrocalcinosis" 	
C.I	<ul style="list-style-type: none"> • Magnesium salts: <ul style="list-style-type: none"> ★ Renal failure (Hypermagnesmia)³ ★ Heart block ★ CNS depression ★ Neuromuscular block 	<ul style="list-style-type: none"> • Sodium salts: <ul style="list-style-type: none"> ○ congestive heart failure

3. Balanced Polyethylene Glycol (PEG)

Drug	Polyethylene Glycol (PEG)	
P.K	<ul style="list-style-type: none"> • Isotonic solution of polyethylene glycol & electrolytes (Na sulfate, NaCl, KCl, Na bicarbonate). ★ Is a colonic lavage solution⁴ 	
Uses	<ul style="list-style-type: none"> ★ Used for whole bowel irrigation prior to colonoscopy or surgery (4L over 2-4 hours). • For optimal cleansing 1-2 litres ingested rapidly over 1-2 hours on evening before the procedure & 4-6h before the procedure • Used For chronic constipation PEG mixed with juice 	
Advantage	<ul style="list-style-type: none"> ★ Limited fluid or electrolyte imbalance ★ less flatulence and cramps 	

1) In High and low dose respectively.
 2) For colonoscopy or endoscopy or in barium enema.
 3) In prolonged use.
 4) Complete evacuation of the colon

Stimulant Laxatives

Key:
Yellow highlight= Irritant factor (the active by-product)

	Anthraquinone derivatives	Diphenyl methane derivatives	Castor oil
Drugs	<ul style="list-style-type: none"> Senna Cascara Aloe vera 	<ul style="list-style-type: none"> Bisacodyl 	-
MOA	<ul style="list-style-type: none"> ★ The most powerful group among laxatives and should be used with care. Act via direct stimulation of enteric nervous system → increased peristalsis & purgation. 		
P.K	<ul style="list-style-type: none"> Delayed onset of action (8-12 h). Bowel movements in 12 h (orally) or 2 h (rectally as suppository). Given at night. Act in colon Hydrolyzed by bacterial colon into sugar + Anthranol 	<ul style="list-style-type: none"> Diphenyl methane, given orally Hydrolysed in the gut, absorbed, conjugated to glucuronic acid in the liver acid & secreted with bile. Acts on colon Onset of action = orally (6-12 h)/per rectum (1h) 	<ul style="list-style-type: none"> Given orally, 5-20 ml on empty stomach in the morning. Onset of action = 2-6 h. Acts in small intestine Vegetable oil degraded by lipase → ricinoleic acid + glycerin Ricinoleic acid is very irritating to mucosa.
Specific uses	<ul style="list-style-type: none"> Prolonged use → brown pigmentation of the colon "Melanos coli" 	-	<ul style="list-style-type: none"> Could be employed after oral ingestion of a toxin
Uses	<ul style="list-style-type: none"> In patients who are neurologically impaired in bed-bound patients in long-term care facility 		
ADRs	<ul style="list-style-type: none"> Abdominal cramps may occur. ★ Prolonged use → dependence & destruction of myenteric plexus leading to atonic colon. 		
C.I	-		<ul style="list-style-type: none"> pregnancy → reflex contraction of uterus → abortion.

Serotonin 5HT₄-receptor agonists

Drug	Prucalopride
MOA	<ul style="list-style-type: none"> Stimulation of 5HT₄ receptors → ↑ release of neurotransmitters ↑ second order enteric neurons. with enterokinetic activities (Enteric neurons stimulates proximal bowel contraction & distal bowel relaxation)
Uses	<ul style="list-style-type: none"> used for chronic constipation in women ¹ ★ Advantage: Lack CVS side effects

1) Because IBS is more common in females, however it can be used for both genders.

Fecal Softeners (Lubricants)/surfactants

Drugs	Docusate	Glycerin	Paraffin oil
MOA	<ul style="list-style-type: none"> Are non absorbed drugs Act by either decreasing surface tension allowing water to interact with the stool or by softening the feces thus promoting defecation. 		
P.K	<ul style="list-style-type: none"> Sodium dioctyl sulfosuccinate One type of surfactants Act by decreasing surface tension of feces allowing water to interact with the stool. is given orally (12-72 hours) or enema (5-20 min). 	<ul style="list-style-type: none"> Lubricant Given rectally (suppository), Hygroscopic (retains water) Thus promote peristalsis Rapid effect (30mins) 	<ul style="list-style-type: none"> Is a mineral oil, given orally Acts as lubricant thus softening the feces and promoting defecation. Not palatable
Specific uses	<ul style="list-style-type: none"> Used In hospitalized patients→↓constipation & straining.¹ 	<ul style="list-style-type: none"> Preferable in children 	<ul style="list-style-type: none"> Good for radiology preparation To prevent fecal impaction in children & debilitating adults
Uses	<ul style="list-style-type: none"> Treat constipation in patients with hard stool or specific conditions and for people who should avoid straining² 		
ADRs	-		<ul style="list-style-type: none"> Impairs absorption of fat soluble vitamins (Vit.A,D,E,K) May leak out from anal sphincter which can be embarrassing

Chloride secretion activators

Drug	Lubiprostone	Linaclotide
MOA	<ul style="list-style-type: none"> It stimulates type 2 chloride in the small intestine→↑Cl⁻ fluid rich fluid,→ intestinal motility→ shortens intestinal emptying 	<ul style="list-style-type: none"> stimulates chloride secretion through activation guanylate cyclase C
Uses	<ul style="list-style-type: none"> Designated category C for pregnancy (Lubiprostone) used for chronic constipation & IBS-C 	
ADRs	<p>After discontinuation, constipation may return to pretreatment</p>	<ul style="list-style-type: none"> Most common ADR is diarrhea

1) In which conditions we don't want straining: Rectal prolapse, aneurysm in brain, heart problems .
 2) Specific conditions e.g. patients with hemorrhoids.
 Avoid straining e.g. post surgery.

Opioid receptor antagonists

Drug	Methylnaltrexone	Alivimopan
MOA	<ul style="list-style-type: none"> • μ- receptor antagonist ¹ 	
P.K	<ul style="list-style-type: none"> • does not cross the BBB 	
Uses	<ul style="list-style-type: none"> ★ is used in opioid-induced constipation in patients receiving palliative care for advanced illness. 	<ul style="list-style-type: none"> ★ used for short term to shorten the period for postoperative ileus

Irritable bowel syndrome (IBS)

Idiopathic Chronic bowel disorder characterized by abdominal discomfort (bloating, pain, distention, cramps) associated with alteration in bowel habits (diarrhea or constipation or both).

Symptomatic treatment of IBS

Antispasmodics e.g. mebeverine

Alosetron (IBS-D)

Tegaserod (IBS-C)

Laxatives in IBS with Constipation.

Antidiarrheals in IBS with diarrhea (diphenoxylate, loperamide)

Antispasmodics (anticholinergics)
Dicyclomine & hyoscine: Inhibits muscarinic cholinergic receptors in enteric plexus & smooth muscle

Low doses of TCA (amitriptyline) act via: Anticholinergic action, reduce visceral afferent sensation

Drug	Alosetron
MOA	<ul style="list-style-type: none"> • Selective 5HT₃ antagonist (it bind with high affinity & dissociate slowly from the receptor) • 5-HT₃ receptors antagonism of the enteric nervous system of the gastrointestinal tract results into: <ul style="list-style-type: none"> ○ inhibition of colon motility. ○ inhibition of unpleasant visceral afferent pain sensation (nausea, pain, bloating).
P.K	<ul style="list-style-type: none"> • Rapidly absorbed from GIT, 50-60% bioavailability, half life= 1.5 h • Undergo extensive CYT P450 metabolism
Uses	<ul style="list-style-type: none"> ★ Use restricted in IBS with severe diarrhea in women who have not had success with any other treatment.
ADRs	<ul style="list-style-type: none"> ★ Severe Constipation and ischemic colitis may occur (People taking alosetron must sign a consent form before starting to take the medicine)

Drug	Tegaserod
MOA	<ul style="list-style-type: none"> • 5HT₄ agonist • Stimulation of 5HT₄ of enteric nervous system of GIT → increases peristalsis.
Uses	<ul style="list-style-type: none"> • Short term treatment of IBS-associated with constipation in women <55 years old with no history of heart problems. • may still be used in limited emergency situations.
ADRs	<ul style="list-style-type: none"> • Tegaserod has CVS side effects

1) It acts **peripherally** by blocking μ -opioid receptor to reverse some of the side effects of opioid drugs such as constipation without affecting pain relief or precipitating withdrawals.

Case from doctors slide:

A 70-year-old woman who was previously very active but whose mobility has recently been limited by osteoarthritis on the knees & hips sees her general practitioner because of a recent change in bowel habit from once daily to once every three days. Her current medication includes regular co-codamol (paracetamol + codeine) for her osteoarthritis, oxybutynine for urinary frequency, aluminium hydroxide prn for dyspepsia, and bendrofluazide and verapamil for hypertension. Following bowel evacuation by a phosphate enema, proctoscopy & colonoscopy are reported as normal.

1-What general approach(non-pharmacological) should be employed to this patient?

- Adequate fluid intake.
- High fiber contents in diet.
- Regular exercise.

2-What are the possible contributing causes of her constipation?

- Immobility
- Old age
- Gender(female)

3-Which of these patient's medications may contribute to her constipation?

Drugs that can cause constipation

Aluminium hydroxide
Amiodarone
Anticholinergics (older antihistamines)
Diltiazem
Disopyramide
Diuretics
Iron preparations
Opioids
Tricyclic antidepressants
Verapamil

4-What pharmacologic would be appropriate to this patient?

First we want quick relief so for example Stimulant Laxatives, then we use drugs for prevention like Lactulose

MCQ

1- 55 years old patient with known angina, recently he develop constipation. Which of the following is suitable for his condition?

A- Castor oil B- Prucalopride C- Docusate

2- Patients must sign a consent form before administering which drug?

A- Mebeverine B- Alosetron C- Tegaserod

3- Which of the following drugs often used for radiology preparation ?

A- Glycerin B- Anthraquinone C- Paraffin oil

4- 23 years old man with history of iron deficiency anemia and take supplements for it, visited the clinic complaining of constipation. Which of the following must be avoided?

A- Bulk forming laxatives B- Osmotic laxatives C- Stimulant laxatives

5- Alcoholic patient who has liver cirrhosis and he may develop hepatic encephalopathy, to prevent that, which one of the following could be used ?

A- Lactulose B- Bisacodyl C- Macrogol

SAQ

1-3. A 32 years old female patient who diagnosed with severe irritable bowel syndrome associated with diarrhea.

Q1-What is the best drug to be used in this case ?

Q2-What is the M.O.A of that drug ?

Q3-Mention 2 ADR of that drug.

Q4- A 45 years old male patient is undergoing colonoscopy, Which drug should the doctor give him the night before?

Q5- A 49 years old patient with Diabetes Mellitus has a peripheral neuropathy, he came to the clinic complaining of constipation. Which class of drugs can be helpful in his case

MCQ

Q1	B
Q2	B
Q3	C
Q4	A
Q5	A

SAQ

Q1	Alosetron
Q2	Selective 5-HT ₃ antagonist
Q3	Constipation - ischemic colitis
Q4	Polyethylene glycol (PEG)
Q5	Stimulant Laxatives

Answers:



Share with us your
ideas!

***Good Luck ,
Future Doctors!***

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