Drugs used in treating constipation and IBS

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ILOS

By the end of this lecture, students should be able to:

- 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

What is constipation?

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

May be accompanied by other symptoms:

- Loss of appetite
- Flatulence
- Abdominal & rectal pain
- Lethargy
- Depression

Causes of constipations

- **Decreased motility in colon:**
  - Decrease in water and fiber contents of diet.
- **Difficulty in evacuation:**
  - Local painful conditions: anal fissures, piles
  - Lack of muscular exercise
- **Drug-induced:**
  - Anticholinergics, antidepressants, iron, bismuth, opioids, antacids, NSAIDs, sympathomimetics, antipsychotics, calcium channel blockers.

Treatment of Constipation

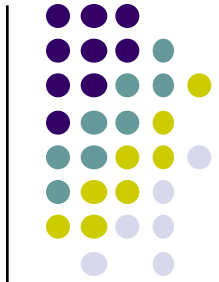
General Measures :

1. Adequate **fluid intake**.
2. **High fiber** contents in diet.
3. Regular exercise
4. Regulation of bowel habit.
5. Avoid drugs causing constipation.
6. Use drugs (laxatives or purgatives)

Medications used in constipations

Drugs that hasten the transit of food through the gastrointestinal tract are called laxatives or purgatives.

Classification of laxatives:



1. Bulk forming laxatives
2. Osmotic laxatives
3. Stimulant laxatives
4. Stool softeners (lubricants)
5. Intestinal secretagogues (Chloride secretion activators)
6. Opioid receptor antagonists
7. Serotonin (5-HT4) agonists

Bulk (fiber) Laxatives

Include:

Dietary fibers:

- Indigestible parts of vegetables & fruits
- Bran powder

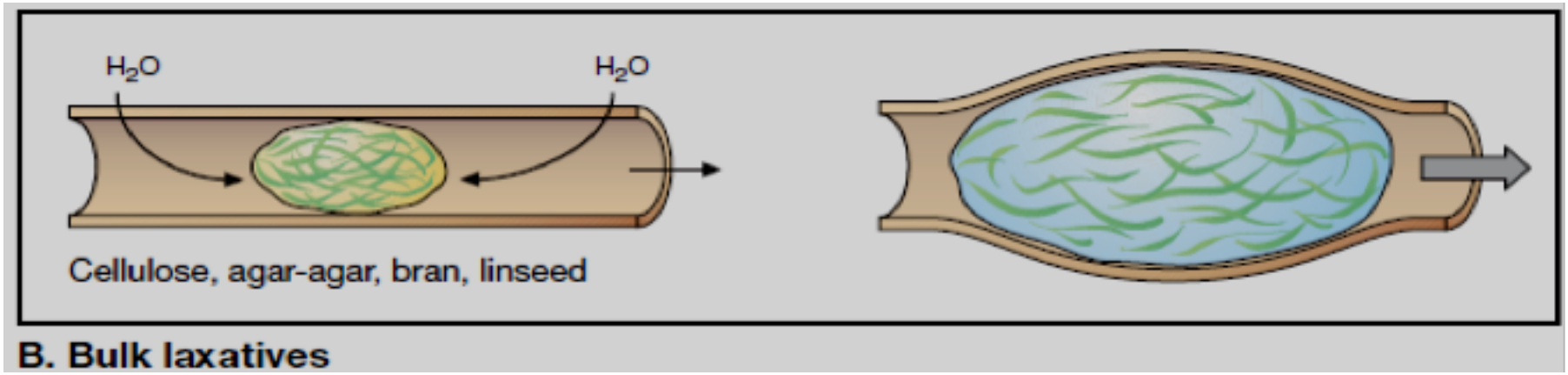
Hydrophilic colloids

- Psyllium seed
- Methyl cellulose
- Carboxymethyl cellulose (CMC)

Synthetic fibers e.g. Polycarbophil

Mechanism of Action

Dietary fibers and hydrophilic colloids are non absorbable substances → Increase the bulk of intestinal contents by water retention → ↑ mechanical pressure on the walls of intestine → stimulation of stretch receptors → → ↑peristalsis → evacuation of soft stool.



B. Bulk laxatives

Side Effects

- Delayed onset of action (1-3 days).
- Intestinal obstruction (should be taken with enough water).
- Bloating, flatulence, distension
- Interfere with other drug absorption e.g. iron, cardiac glycosides.

Osmotic Laxatives

- are water soluble **BUT** poorly absorbable compounds (salts or sugars)

- They remain in the bowel, attract and retain water by **osmosis** thereby increasing the volume of feces → ↑ peristalsis → evacuation of stool.

Osmotic Laxatives

Include:

1. **Sugars : e.g. lactulose, sorbitol**
2. **Salts (Saline laxatives)**
   - **Magnesium sulphate or hydroxide**
   - **Sodium or potassium phosphate.**
3. **Polyethylene glycol (PEG)**

Lactulose

- Semisynthetic disaccharide of fructose and galactose.
- Non absorbable.
- In colon, metabolized by bacteria into fructose and galactose.
- These sugars are fermented into lactic acid and acetic acid that function as osmotic laxatives.

Uses

- Prevention of chronic constipation
- Hepatic encephalopathy (Hyperammonemia)
- Hemorrhoids

Lactulose increases the H^+ concentration in the gut, This favors the formation of the non-absorbable NH_4^+ from NH_3, trapping NH_3 in the colon and reducing its back diffusion into blood.

Why lactulose is commonly used in liver cirrhosis?

Mechanism:

Lactulose ⟶ Lactic acid + Acetic Acid

acidification of the colon ⟶ ↓ ammonia absorption (NH_4^+)

Dose:

15 ml for constipation and 30 ml for **portal hypertension & liver cirrhosis.**

Side Effects

1. Delayed onset of action (2-3 days)
2. Abdominal cramps and flatulence.
3. Electrolyte disturbances.

Osmotic laxatives

Saline Laxatives

- Are poorly absorbable salts
- Increase evacuation of watery stool.
- have rapid effect (within 1-3 h).
- Magnesium sulphate (Epson's salt).
- Magnesium hydroxide (milk of magnesia).
- Sodium phosphate or potassium phosphate.
- Isotonic or hypotonic solution should be used.

Uses

Treatment of acute constipation

Side Effects

- Disturbance of fluid and electrolyte balance
- Dehydration
- May have systemic effects.

Contraindications

Sodium salts in congestive heart failure

Magnesium salts are contraindicated in:

- Renal failure (Hypermagnesmia)
- Heart block
- CNS depression
- Neuromuscular block

Side effects

Sodium phosphate

- Hyperphosphatemia & hypernatremia .
- Cardiac arrhythmias
- Acute renal failure → deposition of calcium phosphate "nephrocalcinosis"

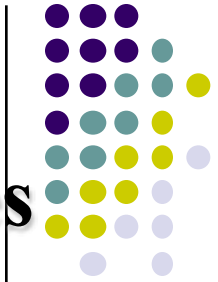
Balanced Polyethylene Glycol (PEG)

- **Isotonic solution of polyethylene glycol & electrolytes** (Na sulfate, NaCl, KCl, Na bicarbonate).
- **Is a colonic lavage solution**
- **Used for whole bowel irrigation prior to colonoscopy or surgery (4L over 2-4 hours).**

Advantages

- **Limited fluid or electrolyte imbalance**
- **less flatulence and cramps**

Stimulant Laxatives



are the most powerful group among laxatives and should be used with care.

Drugs

- **Anthraquinone derivatives (senna, cascara, aloes).**
- **Bisacodyl (Diphenyl methane derivatives)**
- **Castor oil**

Stimulant Laxatives

Mechanism of Action:

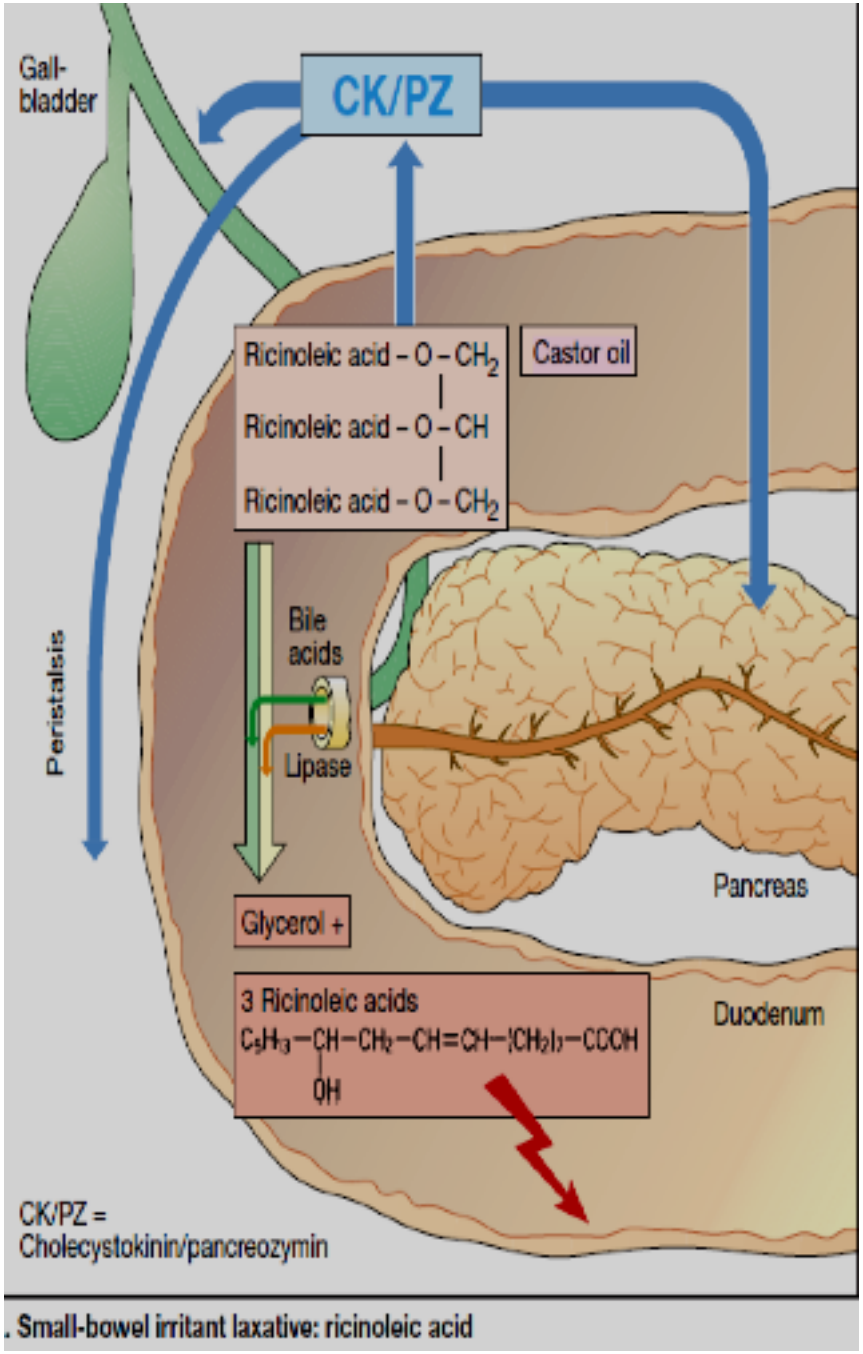
act via direct stimulation of enteric nervous system → increased peristalsis & purgation.

Uses

- ✓ In patients who are neurologically impaired
- ✓ Bed- bound patients in long- term care facility

Castor Oil

- Given orally, 5-20 ml on empty stomach in the morning.
- acts in small intestine
- Vegetable oil degraded by lipase → ricinoleic acid + glycerin
- Ricinoleic acid is very irritating to mucosa.
- Onset of action = 2-6 h.
- Could be employed after oral ingestion of a toxin

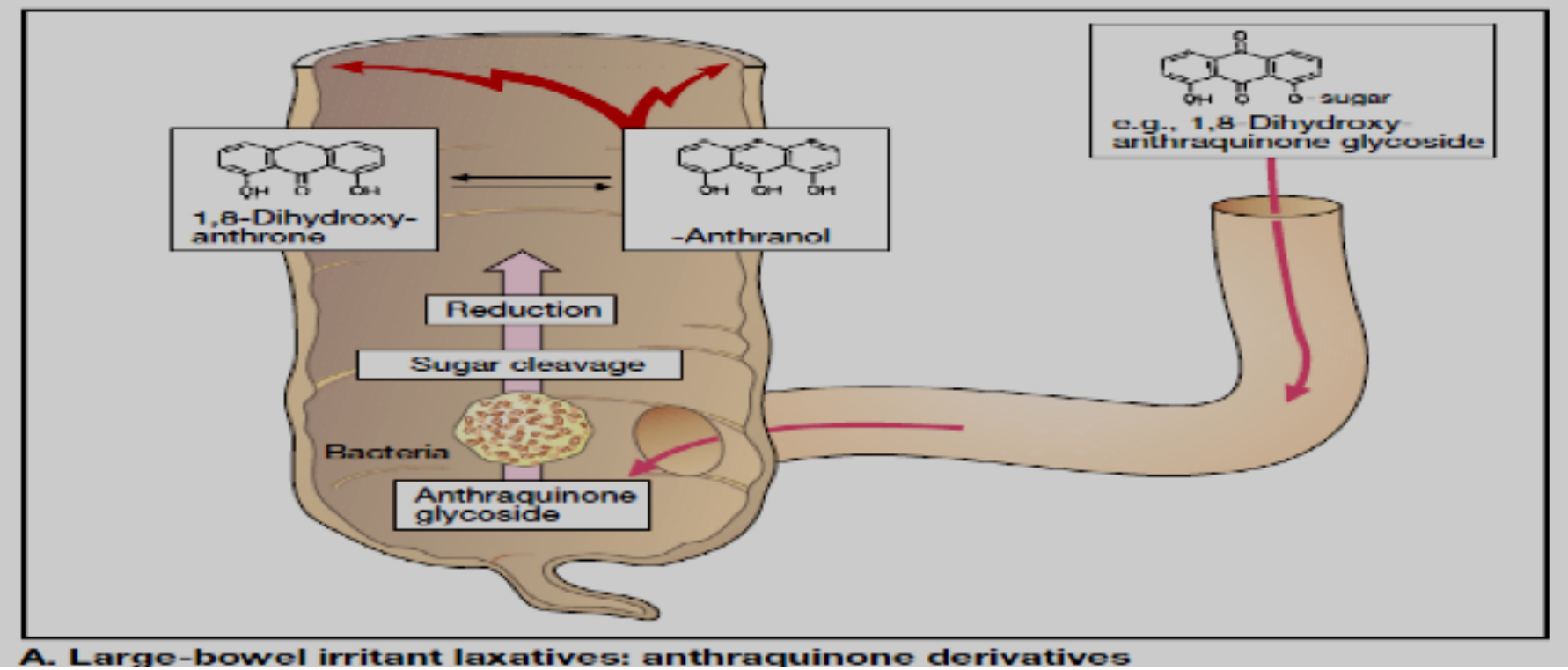


. Small-bowel irritant laxative: ricinoleic acid

Anthraquinone glycosides

e.g. senna, cascara, aloe vera

- **Act in colon, hydrolyzed by bacterial colon into sugar + Anthranol (has direct stimulant action).**



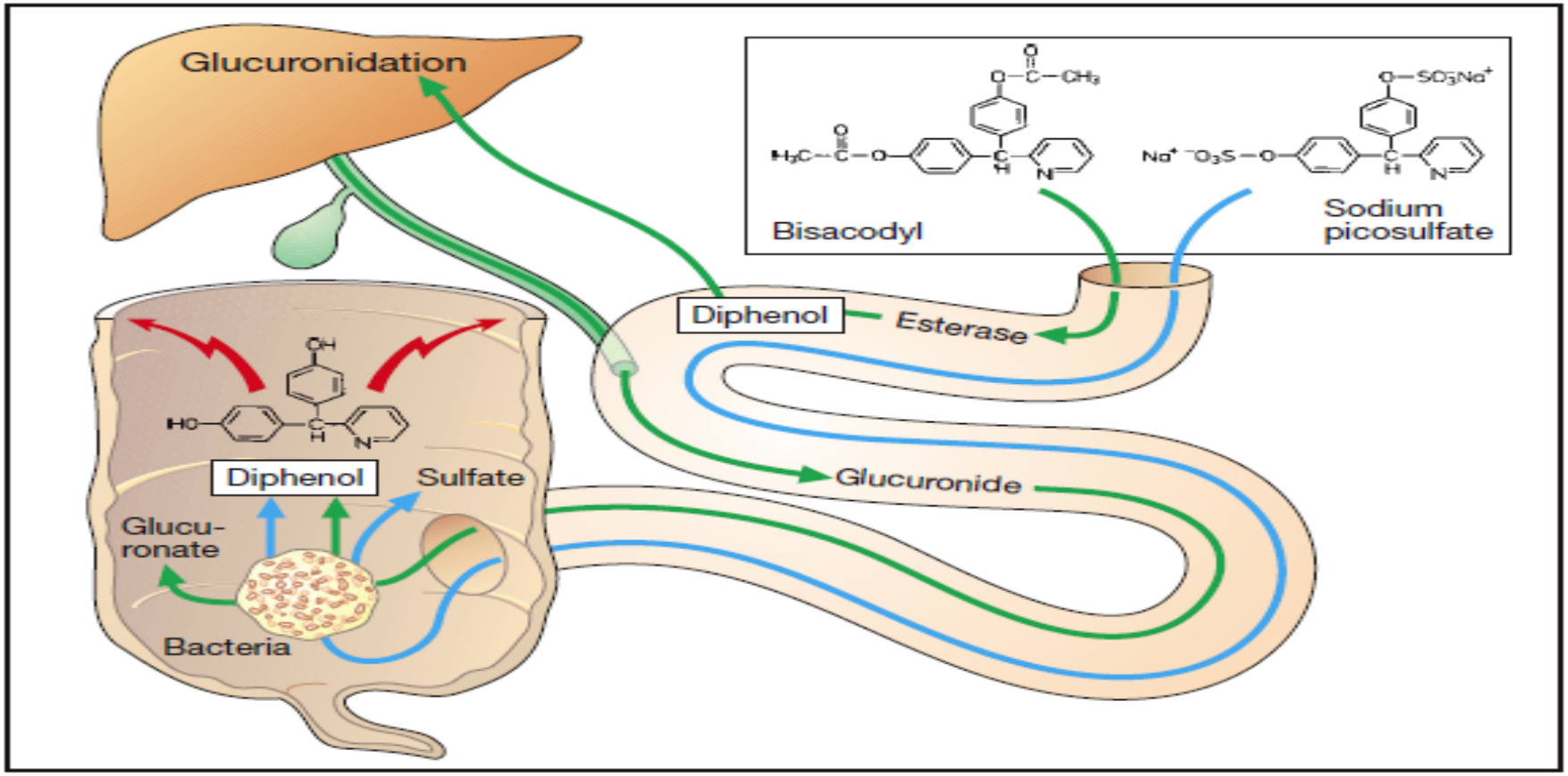
A. Large-bowel irritant laxatives: anthraquinone derivatives

Anthraquinone glycosides

- Delayed onset of action (8-12 h).
- Bowel movements in 12 h (orally) or 2 h (rectally as suppository).
- Given at night.
- Prolonged use→ brown pigmentation of the colon "Melanosis coli"

Bisacodyl

- Diphenyl methane, given orally
- acts on colon
- Onset of action = orally (6-12 h)/per rectum (1h)



B. Large-bowel irritant laxatives: diphenylmethane derivatives

Common stimulant purgatives

Drugs	Type	Site of Action	Onset of Action
Cascara	Anthraquinone	colon	8-12 hours
Senna	Anthraquinone	colon	8- 12 hours
Aloe vera	Anthraquinone	colon	8-12 hours
Bisacodyl	Diphenylmethane	colon	6-8 hours
Castor Oil	ricinoleic acid	small intestine	2-6 hours

Side Effects of stimulant laxatives

- Abdominal cramps may occur.
- Prolonged use → dependence & destruction of myenteric plexus leading to atonic colon.

Contraindications

- Castor oil # in pregnancy → reflex contraction of uterus → abortion.

Fecal Softeners (Lubricants)/surfactants

- Are non absorbed drugs
- Act by either decreasing surface tension or by softening the feces thus promoting defecation.
- Treat constipation in patients with hard stool or specific conditions and for people who should avoid straining .

Fecal Softeners (Lubricants)/surfactants

Drugs

- Docusate
- Glycerin
- Paraffin oil

Docusate

- 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).
- Used In hospitalized patients→↓constipation & straining.

Paraffin oil

- Is a mineral oil, given orally
- acts as lubricant thus softening the feces and promoting defecation.
- Good for radiology preparation
- not palatable
- impairs absorption of fat soluble vitamins.

Glycerin

- Lubricant
- Given rectally (suppository)

Purgatives	Site of action	Onset time
Bulk purgatives	Small & large intestine	12-72 h Delayed
Saline purgatives	Small & large intestine	1-3 h Rapid
Lactulose	colon	12-72 h Delayed
Mineral oil	colon	6 – 8 hours
Docusate	Small and large intestine	Enema 5-20 minutes Orally 12 – 72 hours
Stimulants	Small intestine Colon	See the previous table

Serotonin 5HT4-receptor agonists

Prucalopride

- Stimulation of 5HT 4 receptors with enterokinetic activities
- Lack CVS side effects
- is used for chronic constipation in women

Chloride secretion activators

e.g. Lubiprostone

- used for chronic constipation & IBS-C
- It stimulates type 2 chloride in the small intestine→↑Cl –fluid rich fluid,→ intestinal motility.

e.g. Linaclotide

- stimulates chloride secretion
- used for chronic constipation & IBS-C
- Most common ADR is diarrhea

Opioid receptor antagonists

e.g. Methylnaltrexone

- μ- receptor antagonist
- don not cross the BBB
- is used in opioid-induced constipation in patients receiving palliative care for advanced illness.

Irritable bowel syndrome (IBS)

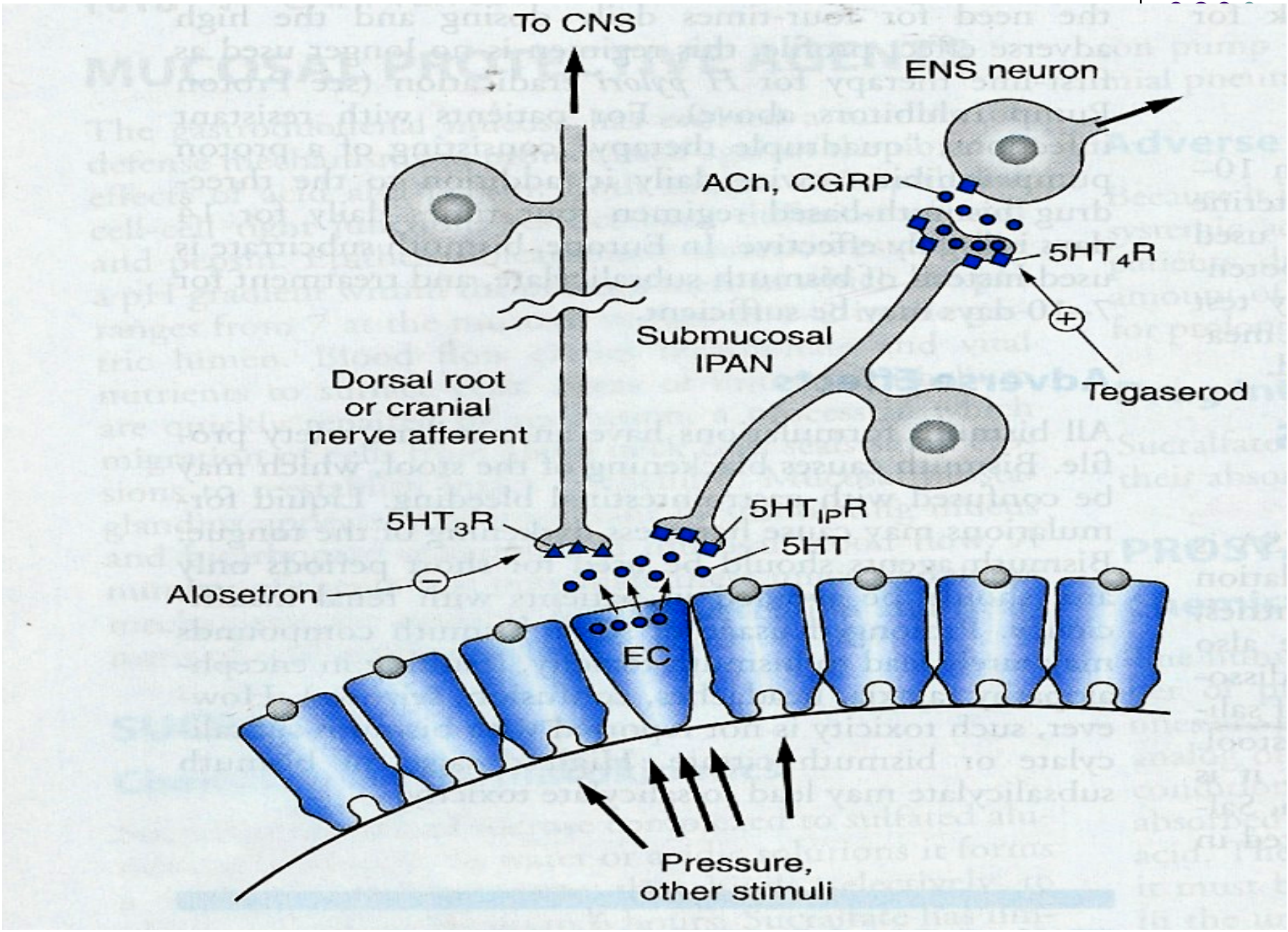
Chronic bowel disorder characterized by abdominal discomfort (bloating, pain, distention, cramps) associated with alteration in bowel habits (diarrhea or constipation or both).

Symptomatic treatment of IBS

- Antispasmodics e.g. mebeverine
- Low doses of tricyclic antidepressants (amitriptyline) act via
  - Anticholinergic action
  - Reduce visceral afferent sensation
- Laxatives in IBS with Constipation.
- Antidiarrheals in IBS with diarrhea (diphenoxylate – loperamide).
- Alosetron (IBS-D)
- Tegaserod (IBS-C)

Alosetron

- Selective $5HT_3$ antagonist
- 5-HT_3 receptors antagonism of the enteric nervous system of the gastrointestinal tract results into:
  - inhibition of colon motility.
  - inhibition of unpleasant visceral afferent pain sensation (nausea, pain, bloating).


To CNS
ENS neuron
ACh, CGRP
5HT4R
Submucosal
IPAN
Tegaserod
Dorsal root
or cranial
nerve afferent
5HT3R
5HTIPR
5HT
Alosetron
EC
Pressure,
other stimuli

Uses of Alosetron

Used in IBS with severe diarrhea in women who have not had success with any other treatment.

Adverse effects

Constipation and ischemic colitis may occur.

People taking alosetron must sign a consent form before starting to take the medicine.

Tegaserod

- $5HT_4$ agonist.
- Stimulation of $5HT_4$ of enteric nervous system of GIT $\rightarrow$ increases peristalsis.
- Short term treatment of IBS-associated with constipation in women <55 years old with no history of heart problems.
- Tegaserod has CVS side effects
- may still be used in limited emergency situations..

Summary

Bulking agents	**Oral, 48–72 hours**	**Acute & chronic constipation**
stool softeners	**oral, 24–72 hours; rectal, 5 --20 minutes**	**prevention of straining after rectal surgery and in acute perianal disease**
Osmotic laxatives (lactulose)	**oral, 24–72 hours**	**- chronic constipation -hepatic encephalopathy - opioid constipation**
Saline laxatives	**oral, 0.5–3 hours; rectal, 30 minutes**	**short term treatment of moderate-to-severe constipation; acute constipation; bowel preparation for colonoscopy**

Table 1. Medications for the Treatment of Constipation

Agent	*Typical dosage**	*Time of onset*	*Adverse effects*
Bulking agents			
Methylcellulose powder	19 g per day	12 to 72 hours	None compared with placebo[17]
Polycarbophil (Fibercon) tablets	1,250 mg, one to four times per day	12 to 72 hours	None recorded[18]
Psyllium (Metamucil) powder	1 tsp or 1 packet one to three times per day	12 to 24 hours	Bloating, abdominal distension in 4% to 18%[16,17]
Osmotic laxatives			
Lactulose solution	15 to 30 mL per day	24 to 48 hours	Bloating and cramping; nausea in up to 20%[19]
Magnesium citrate solution	150 to 300 mL, single dose or short-term daily dose	30 minutes to 6 hours	Increase in magnesium, causing lethargy, hypotension, respiratory depression[20]
Magnesium hydroxide suspension	30 to 60 mL per day	30 minutes to 6 hours	Increase in magnesium, causing lethargy, hypotension, respiratory depression[20]
Polyethylene glycol (Miralax) powder	17 g per day	24 to 48 hours	Minimal adverse effects of cramping and gas[18]
Sorbitol solution	2 to 3 tbsp, single dose or short-term daily dose	24 to 48 hours	Bloating, cramping, and nausea[19]
Stool softeners			
Docusate sodium (Colace) capsules	100 mg twice per day	24 to 48 hours	None reported[16]
Stimulant laxatives			
Bisacodyl (Dulcolax) tablets	5 to 15 mg per day	6 to 10 hours	Diarrhea and abdominal pain in 56% in week 1 and 5% in week 4[21]
Senna tablets	15 mg per day	6 to 12 hours	Abdominal pain in up to 12%[16]
Chloride channel activators			
Lubiprostone (Amitiza)† capsules	24 mcg twice per day	Within 24 hours	Nausea in 18%[22]
Peripherally acting mu-opioid antagonists			
Methylnaltrexone (Relistor)‡ solution	Weight-based subcutaneous injection, once or twice per day	30 to 60 minutes	Diarrhea in 8% Abdominal pain in 13%[23]
Other			
Linaclotide (Linzess)† capsules	145 mcg per day	—	Diarrhea in 16%, which led to treatment cessation in 4%[24]

**—All formulations are oral, unless specified.*

†—Estimated retail price for one month's treatment is $300, based on information obtained at http://www.goodrx.com (accessed May 15, 2015).

‡—Estimated retail price for one month's treatment is $1,200, based on information obtained at http://www.goodrx.com (accessed June 10, 2015).

Information from references 16 through 24.