Drugs used in treating constipation and IBS

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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 and 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:**
  - Anticholinergic agents
  - Opioids
  - Iron
  - Antipsychotics

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)

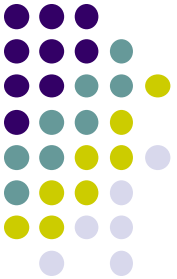
Medications used in constipations

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)

Classification of laxatives or purgatives



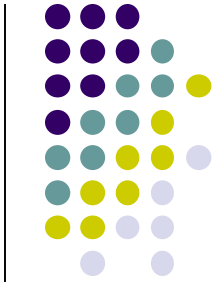
I) Bulk forming laxatives:

Increase volume of non-absorbable solid residue.

II) Osmotic laxatives:

Increase water content in large intestine.

Classification of laxatives or purgatives



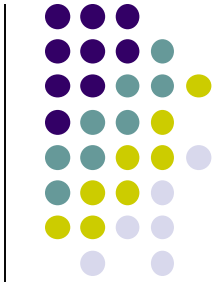
III) Stimulant or irritant laxatives:

Act by direct stimulation of nerve endings in colonic mucosa.

IV) Stool softeners (lubricants):

Alter the consistency of feces → easier to pass

Bulk (fiber) Laxatives



Include:

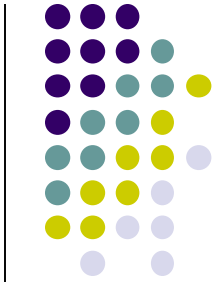
Dietary fibers:

- **Indigestible parts of vegetables & fruits**
- **Bran powder**

Hydrophilic colloids

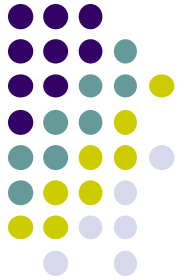
- **Psyllium seed**
- **Methyl cellulose**
- **Carboxymethyl cellulose (CMC)**

Mechanism of Action



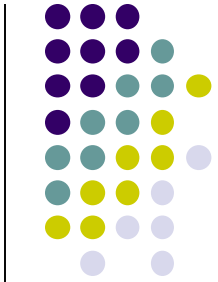
Dietary fibers and hydrophilic colloids are non absorbable substances → Increase the bulk of intestinal contents by water retention → ↑ mechanical pressure on the walls of intestine → stimulation of stretch receptors → → ↑peristalsis → evacuation of soft stool.

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.**

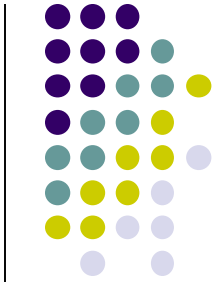
Osmotic Laxatives



- **are water soluble compounds**
- **Poorly absorbable compounds (<u>salts or sugars</u>)**

- **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**
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

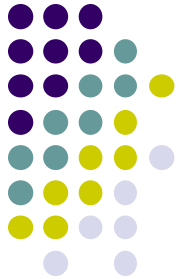
absorption (NH_4^+)

Dose:

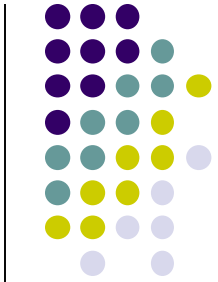
15 ml for constipation and 30 ml for liver cirrhosis

Side Effects

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



Saline Laxatives



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

Uses

Treatment of acute constipation

Side Effects

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

Contraindications

Sodium salts in congestive heart failure

Magnesium salts are contraindicated in:

- Renal failure
- Heart block
- CNS depression
- Neuromuscular block

Balanced Polyethylene Glycol (PEG)

- Isotonic solution of polyethylene glycol & electrolytes (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.

Mechanism of Action:

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

Drugs

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

Bisacodyl

Is given orally, acts on colon

Onset of action = orally (6-12 h)/ per rectum (1 h)

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.**

Anthraquinone glycosides

e.g. senna, cascara, aloe vera

- **Act in colon**
- **Hydrolyzed by bacterial colon into sugar + emodin (The absorbed emodin has direct stimulant action).**
- **Emodin may pass into milk.**
- **Delayed onset of action (8-12 h).**
- **Bowel movements in 12 h (orally) or 2 h (rectally as suppository).**
- **Given at night.**

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

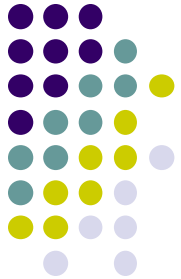
Side Effects

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

Contraindications

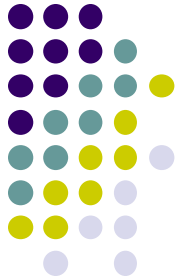
- Senna is contraindicated in breast feeding.
- Castor oil # in pregnancy → reflex contraction of uterus → abortion.

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 .**

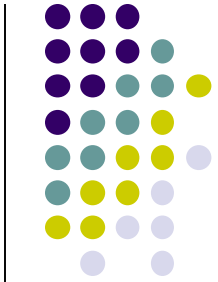
Fecal Softeners (Lubricants)/surfactants



Drugs

- Docusate
- Glycerin
- Paraffin oil

Docusate



- Sodium dioctyl sulfosuccinate
- One type of surfactants
- Act by decreasing surface tension of feces
- is given orally (12-72 hours) or enema (5-20 min).

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

Irritable bowel syndrome (IBS)

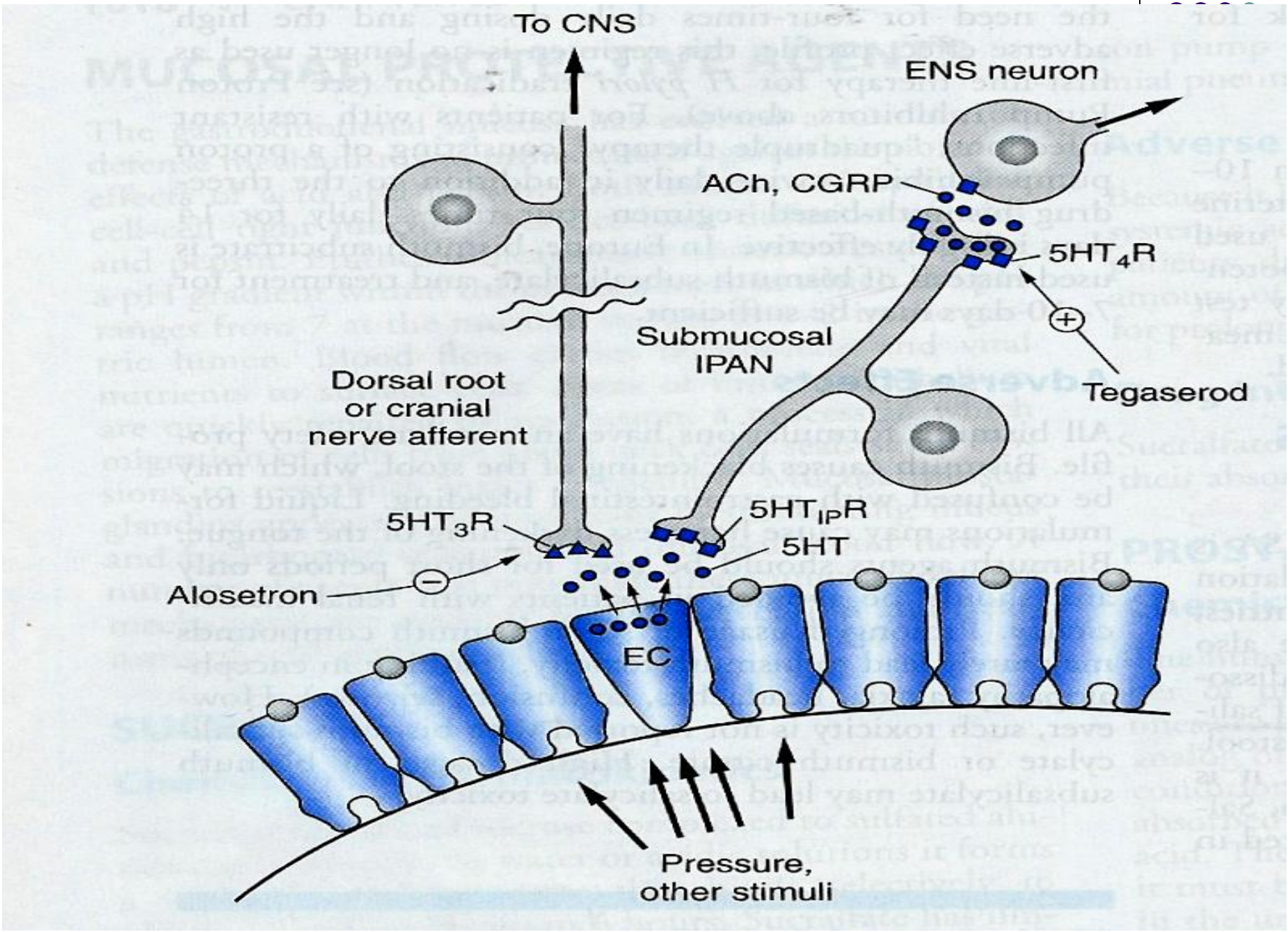
Chronic bowel disorder characterized by abdominal discomfort (bloating, pain, distention, cramps) associated with alteration in bowel habits (diarrhea or constipation or both).

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
- $5\text{-}HT_3$ 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**