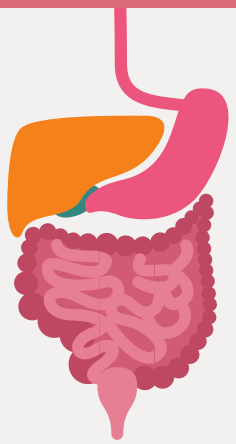
Drugs used in treating constipation and IBS



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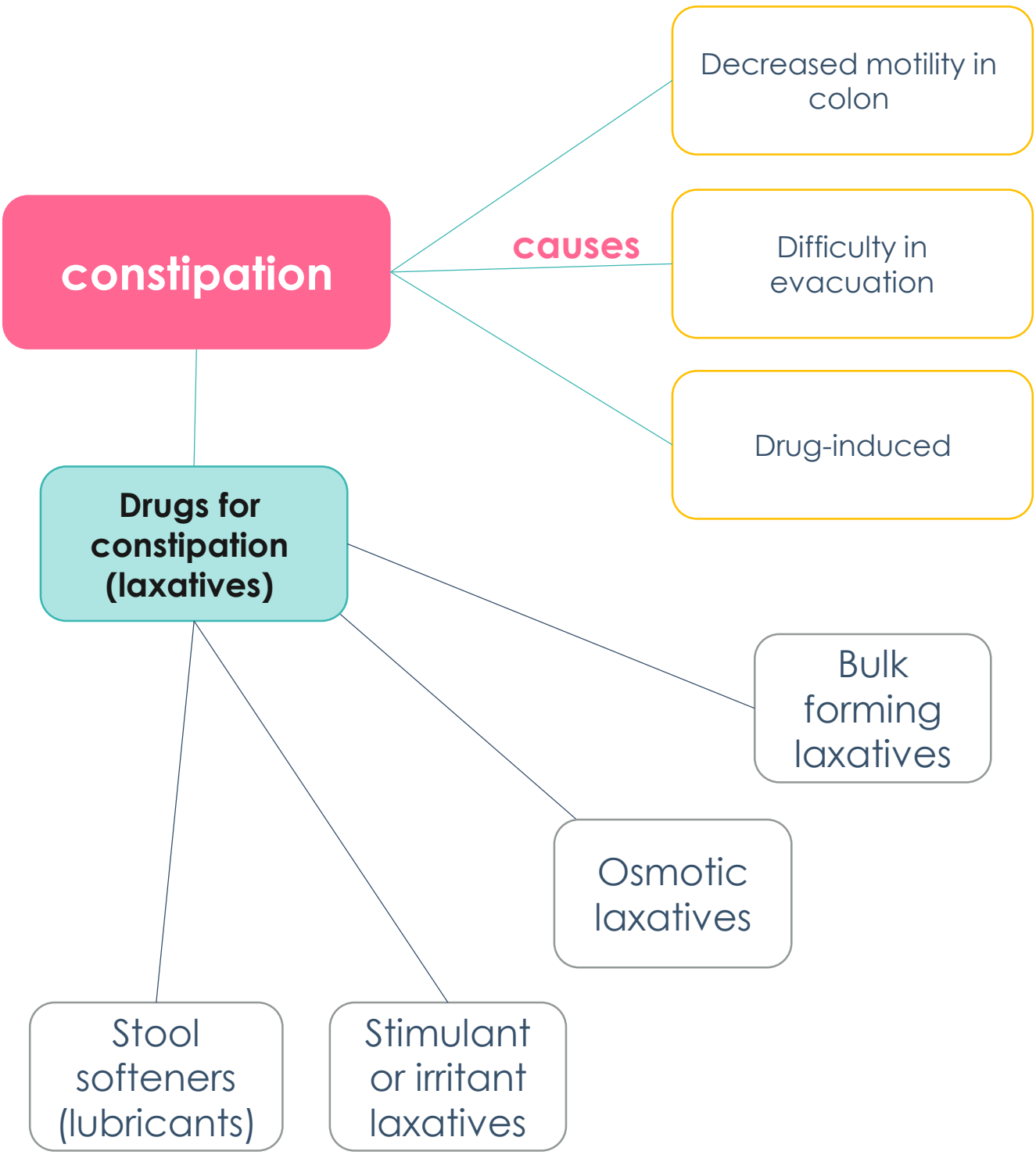
Drugs names | Doctors notes | Important | Extra

« **باذلًا وسعي** في استنقاذها من الهلاك والمرض، والألم والقلق »

Mind Map


constipation
causes
Decreased motility in colon
Difficulty in evacuation
Drug-induced
Drugs for constipation (laxatives)
Bulk forming laxatives
Osmotic laxatives
Stool softeners (lubricants)
Stimulant or irritant laxatives

To Understand Better

What is constipation?

Infrequent defecation, often with straining and the passage of hard, uncomfortable stools.
- **May be accompanied by**: Abdominal discomfort and rectal pain, Flatulence, Loss of appetite, 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 by general measures

- Adequate fluid intake.
- High fiber contents in diet.
- Regular exercise
- Regulation of bowel habit.
- Avoid drugs causing constipation.
- Use drugs (laxatives or purgatives).

Medications used in constipations

Drugs that hasten the transit of food through the gastrointestinal tract are called **laxatives** (ملينات) or **purgatives** (محركات) (Or we say the drugs that increase GI motility).

Classification of Laxatives or Purgatives

- **Bulk forming laxatives**
  - **Increase volume** of **non-absorbable** solid residue.
- **Osmotic laxatives**
  - Increase water content in large intestine.
- **Stimulant or irritant laxatives**
  - Act by direct stimulation of nerve endings in colonic mucosa.
- **Stool softeners (lubricants)**
  - Alter the consistency of feces → easier to pass

Drug: Bulk (fiber) Laxatives

Include

Dietary fibers:

- Indigestible parts of vegetables &fruits.
- Bran powder. (مسحوق النخالة) → Powder + water
  → increase the volume (تنفش) (مثل الخميرة لما نحطها مع العجينة تنفش وتكبر)

Hydrophilic colloids: نفس اللي يصير مع الجلي، أساسًا هو بودرة بس لما أضيفه مع الموية بيصير قوامه مثل الجيلاتينين

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

MOA

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.

ADRs

- **Delayed onset of action** (1-3 days) → ما أستخدمه للحالات المستعجلة
- Intestinal obstruction (should be taken with **enough water**) لأنه بودرة، فيحتاج موية عشان يسوي الأكشن حقه ويزيد حجمه.
- Bloating, flatulence, distension.
- **Interfere with other drug absorption** e.g. iron (anti-anaemic drugs), cardiac glycosides.
  → **Decrease their absorption,** especially w\ colloids, bc they have adsorption action (تمسك الأشياء معها وما تخليها تُمتص)

Osmotic Laxatives

- They are **Water soluble** compounds, **poorly absorbed**. أكيد ماراح يصير لها امتصاص كبير لأن الأكشن حقها يصير داخل الأمعاء!
- They remain in the bowl attract water by **osmosis** ➡ increase the volume of feces ➡ increase peristalsis & evacuation

Osmotic Laxatives

Sugars	Lactulose
Salts (saline laxatives)	- Magnesium sulphate or hydroxide. - Sodium or potasium phosphate.
Polyethylene glycol (PEG)	PEG & electrolytes

Osmotic Laxatives

Drug	**Lactulose**
P.K	○ 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** (they cause **acidification** of the colon)
Indications	○ Prevention of chronic constipation ○ Hemorrhoids ○ Hepatic encephalopathy (Hyperammonemia) ○ **Liver cirrhosis** → **Why lactulose is used in Liver cirrhosis & Hyperammonemia?** ❖ **Acidification of the colon** (increases the H^+ concentration) by lactic acid & acetic acid causes increase of H^+ concentration, this will cause NH_3 (ammonia-lipid soluble → absorbed easily) trapping by the formation of NON-absorbable NH_4^+ (ammonium-polar "water soluble" → poorly absorbed) and thus **reducing absorption**. ❖ **Simply**: Lactulose → Lactic acid + Acetic acid → Acidification of the colon → ↓ **ammonia absorption** (NH_4^+).
ADRs	○ **Delayed** on set action (2-3 Days) ○ Abdominal cramps & flatulence. ○ Electrolyte disturbance. } seen with high doses.
dose	○ 15 ml for constipation & 30 ml for Liver crirrhosis. (not imp in our level)

Osmotic Laxatives (cont.)

Drug	Saline Laxatives	Polyethylene glycol (PEG)
Drugs	○ Magnesium sulphate **(epson salt)** ○ Magnesium hydroxide **(milk of magnesia)** → Antacids, $Mg(OH)_2$ causes diarrhea. ○ Sodium phosphate ○ potassium phosphate	○ Isotonic solution of polyethylene glycol & electrolytes (NaCl, KCl, Na bicarbonate) ○ Is a colonic lavage solution. ○ It is a salt with some modifications.
P.K	○ Poorly absorbed (90% NOT absorbed) ○ **Rapid effect** (1-3 h) acute situations (emergency) ○ **Isotonic** or **hypotonic** solution should be used. If you used hypertonic solution it will cause dehydration by ↑ vomiting. ○ It increases evacuation of watery stool.	
Advantages		○ Limited fluid & electrolyte imbalance. ○ Less flatulence & cramps.
Indications	○ Treatment of **Acute** Constipation.	○ **Used for whole bowel irrigation** (removal of feces) **prior to colonoscopy or surgery.** It should be ingested rapidly (4L over 2-4h) → this is the only use for it!
ADRs	○ Disturbance of fluid & electrolyte ○ May have **systemic** effect (especially Na salts)	
C.I	○ Sodium salts in: • Congestive heart failure. ○ Magnesium salt in: • Renal failure (little % excreted by the kidney) • Heart blockers. • CNS depression. • Neuromuscular blockers (e.g. **Aminoglycosides**)	

Stimulant Laxatives

Stimulant laxatives

- **Bisacodyl**
- **Castor oil**
- **Anthraquinone (Senna)**

- Are the **most powerful groups** among laxative & should be used with care.
- They act via **direct stimulation of ENS** ➡ increase peristalsis & purgation.

ENS: enteric nervous system

Stimulant Laxatives

Drug	Anthraquinone glycoside (Senna, cascara, aloes)	Castor oil زيت الخروع	Bisacodyl
P.K	○ Delayed onset action **(8-12h)** ○ Bowel movements in 12h (orally) or **2h (rectally** as suppository**)** ○ Given at night. ○ Hydrolyzed by bacterial colon into **sugar** + **emodin** (The absorbed **emodin** has direct **stimulant action**) ○ Act on colon ○ Emodin may pass into **milk***. ○ Senna is useful in treating opioid induced constipation.	○ Onset of action (2-6h) ○ Given orally, 5-20 ml on empty stomach in the morning ○ Act in small intestine ○ Vegetable oil degraded by **lipase** gives **ricinoleic acid** + glycerin. ○ **Ricinoleic acid** is very **irritating** to mucosa.	○ Given orally, Onset of action (6-12h) **Per rectum (1h).** ○ Act on colon
ADRs	○ Abdominal cramps ←لأنها تزود حركة الأمعاء ○ **Dependence** & destruction of myenteric plexus leading to **Atonic Colon** in prolonged use (the patient can't go to the bathroom without these drugs!!)		
C.I	**Senna** is contraindicated in **breast feeding*** (lactation)	In **pregnancy** (causes reflex contraction of uterus this will lead to abortion)	

Fecal softeners

general info.	○ **Non-absorbed** drugs ○ Act by either **decreasing surface tension** or by **softening the feces** thus promote defecation. ○ Treat constipation in patient with hard stool or specfice condotion and for people who should **avoid straining**.		
Drug	**Docusate** (sodium dioctyl sulfactants)	**Paraffin oil**	**Glycerin**
Mech. of action	○ **Surfactant** act by decresing surface tension of feces > increase water penetration into it thus softening of feces.	○ Meniral oil, Acts as **lubricant** thus softening the feces snd promote defecation	○ **Lubricant**.
P.K	○ Given orally (1-3 days) or **enema (5-20 min)**	○ Given **orally** (not palatable)	○ given rectally (suppository تحميلة)
Indications	○ often used as **prophylaxis** rather than acute treatment, - especially in hospitalized patients-because of delayed onset when given orally.	○ good for radiology preparation.	○ Good for children.
ADRs		○ Impairs absorption of **fat soluble vitamins** A,D,E,K. ○ **Not palatable** طعمه غير محبذ	

Quick summary of purgatives

Purgatives	Site of action	Onset time
Bulk purgatives	Small & large intestine	12-72 h **(days)** (**Delayed**)
Saline purgatives	Small & large intestine	1-3 h (**Rapid**)
Lactulose	Colon	12-72 h **(days)** (**Delayed**)
Mineral oil	Colon	6-8 h
Docusate	Small & large intestine	**Enema** → 5-20 min **Orally** → 12-72 h
Stimulants		
- Cascara - Senna - Aloe vera **- Their Type: Anthraquinone.**	Colon	8-12 h
Bisacodyl **- Type: Diphenylmethane**		6-8 h
Castor Oil **Type: ricinoleic acid**	Small intestine	2-6 h

Irritable bowel syndrome (IBS)

Chronic bowel disorder charachterized by:
1- **Abdominal discomfort** (bloating, pain, distension, cramps)
2- **Alteration in bowel habits** (diarrhea or constipation or both)

Symptomatic treatment

- Low dose of tricyclic antidepressant e.g. amitriptyline or SSRIs→ TCAs acts via:
  - ↓ GI motility because of **anticholinergic action**.
  - **↓ visceral afferent sensation.**

- Antispasmatic e.g. Mebeverine (↓ GI motility → smooth muscle relaxant)		- Alosetron (IBS-D)
- Luxative in IBS-cons.	Anti-diarrheal in IBS-D → (diphenoxylate – loperamide)	Tegaserod (IBS-C)

Treatment of IBS (cont.)

Alosetron

MOA

- **Selective 5HT$_3$ antagonist**
- Block 5-HT$_3$ receptors of the **enteric nervous system** of the GIT results into:
  - **Inhibition of colon motility** → means there is time for the water to be absorbed → thus hardening of stool.
  - **Inhibition of unpleasant visceral afferent pain sensation** (nausea, pain, bloating).

Uses

- Used in **severe IBS with diarrhea** in women (not approved for men) who have not had success with any other treatment.
- Used as a late stage when other medications not worked.

ADRs

- **Sever Constipation** and **ischemic colitis** (blood flow to GIT is restricted) may occur.
- → People taking alosetron must sign a consent form before starting to take the medicine.

Tegaserod

MOA

- **5HT$_4$ agonist**.
- Stimulation of 5HT$_4$ of enteric nervous system of GIT → increases peristalsis

Uses

- Short term treatment of **IBS with constipation** in women <55 years old with **no history of heart problems.**
- May still be used in limited **emergency situations**.

ADRs

- **CVS side effects**

MOA of 5-HT agonist \ antagonist

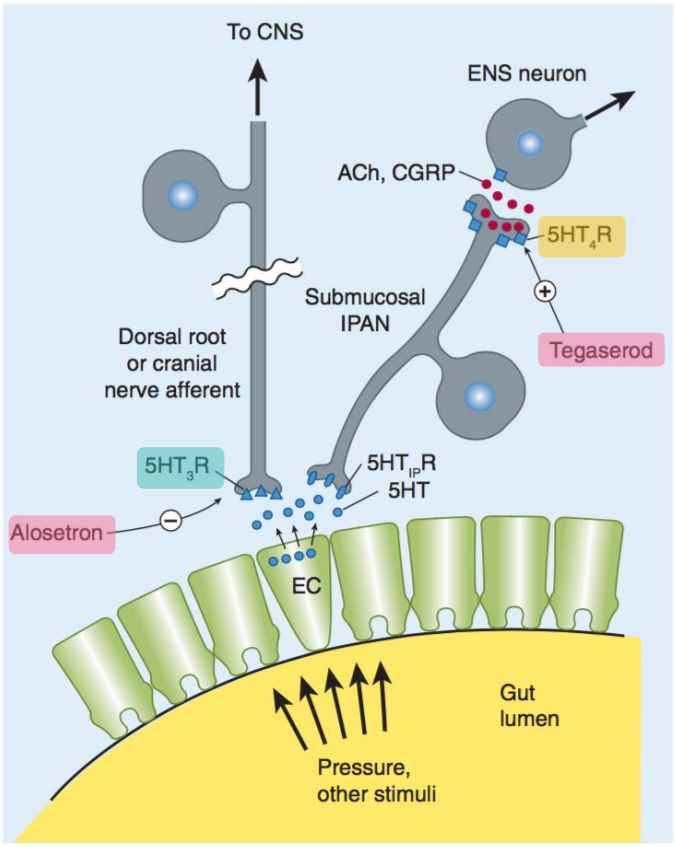


FIGURE 62–4 Release of serotonin (5-HT) by enterochromaffin (EC) cells from gut distention stimulates submucosal intrinsic primary afferent neurons (IPANs) via 5-HT_{1P} receptors and extrinsic primary afferent neurons via 5-HT_3 receptors (5-HT_{1P}R, 5-HT_3R). Submucosal IPANs activate the enteric neurons responsible for peristaltic and secretory reflex activity. Stimulation of 5-HT_4 receptors (5-HT_4R) on presynaptic terminals of IPANs enhances release of acetylcholine (ACh) and calcitonin gene-related peptide (CGRP), promoting reflex activity. CNS, central nervous system; ENS, enteric nervous system. (Redrawn from Gershon MD: Serotonin and its implication for the management of irritable bowel syndrome. Rev Gastroenterol Dis 2003;3[Suppl 2]:S25.)

Extra explanation

✓ **For Tegaserod:**

Stimulation of 5-HT_4 receptors on the presynaptic terminal of submucosal intrinsic primary afferent nerves enhances the release of their neurotransmitters, including **calcitonin gene-related peptide**, which stimulate second-order enteric neurons to **promote the peristaltic reflex.** These enteric neurons **stimulate proximal bowel contraction** (via acetylcholine and substance P) and **distal bowel relaxation** (via nitric oxide and vasoactive intestinal peptide).

✓ **For Alosetron:**

5-HT3 receptors in the gastrointestinal tract activate visceral affer- ent pain sensation via extrinsic sensory neurons from the gut to the spinal cord and central nervous system. Inhibition of afferent gastrointestinal 5-HT3 receptors may reduce unpleasant visceral afferent sensation, including nausea, bloating, and pain. Blockade of central 5-HT3 receptors also reduces the central response to visceral afferent stimulation. In addition, 5-HT3-receptor blockade on the terminals of enteric cholinergic neurons inhibits colonic motility, especially in the left colon, increasing total colonic transit time.

Summary-1

Treatment of constipation

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

Laxatives drugs

Drug	Bulk forming laxatives	Osmotic laxatives		
MOA	Increase volume of non-absorbable solid residue.	Increase water content in large intestine.		
includes	• **Hydrophilic colloids** - Psyllium seed - Methyl cellulose. - Carboxymethyl cellulose (CMC) • **Dietary fibers:** - Indigestible parts of vegetables & fruits - Bran powder.	Sugars: e.g. **lactulose**	Salts (**saline**)	**Polyethylene glycol**
P.K		are water soluble compounds Poorly absorbable compounds (salts or sugars)		
Indications	acute & chronic constipation	- Prevention of chronic constipation - Hepatic encephalopathy (Hyperammonemia) - Hemorrhoids	Treatment of acute constipation.	Is a colonic lavage solution Used for whole bowel irrigation prior to colonoscopy or surgery
ADRs	- Delayed onset of action (1-3 days). - Intestinal obstruction (should be taken with enough water). - Bloating, flatulence, distension	Delayed onset of action (2-3 days) Abdominal cramps and flatulence. Electrolyte disturbances.	Disturbance of fluid and electrolyte balance May have systemic effects.	Advantages: Limited fluid or electrolyte imbalance less flatulence and cramps
C.I	Interfere with other drug absorption e.g. iron, cardiac glycosides.		Renal failure Heart block CNS depression Neuromuscular block.	

Summary-2

Laxatives drugs (cont.)

Drug	Stimulant or irritant laxatives			Stool softeners (lubricants)		
MOA	Act by direct stimulation of nerve endings in colonic mucosa.			Alter the consistency of feces → easier to pass Act by either decreasing surface tension or by softening the feces thus promoting defecation.		
includs	**Bisacodyl**	**Castor Oil**	**Anthraquinone glycosides** e.g. senna, cascara, aloe vera	**Docusate**	**Paraffin oil**	**Glycerin**
P.K	Is given orally, acts on colon	Given orally 5-20 ml on empty stomach in the morning. acts in small intestine	Act in colon	Sodium dioctyl sulfosuccinate One type of surfactants Act by decreasing surface tension of feces	Is a mineral oil, is given orally acts as lubricant thus softening the feces and promoting defecation. Good for radiology preparation	Lubricant Given rectally (suppository)
Indications				Treat constipation in patients with hard stool or specific conditions and for people who should avoid straining. prevention of straining after rectal surgery and in acute perianal disease		
ADRs	Abdominal cramps may occur. Prolonged use → dependence & destruction of myenteric plexus leading to atonic colon.				impairs absorption of fat soluble vitamins.	
C.I	Senna is contraindicated in breast feeding. Castor oil → in pregnancy → reflex contraction of uterus → abortion.					

Summary-3

Drug	Alosetron	Tegaserod
MOA	Selective 5HT3 antagonist 5-HT3 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).	5HT4 agonist. Stimulation of 5HT4 of enteric nervous system of GIT → increases peristalsis.
Indications	Used in IBS with severe diarrhea in women who have not had success with any other treatment.	Short term treatment of IBS-associated with constipation in women <55 years old with no history of heart problems.
ADRs	Constipation and ischemic colitis may occur	CVS side effects
C.I		Cardiac problems

Extra summary

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
LAXATIVES				
• Magnesium hydroxide, other nonabsorbable salts and sugars	Osmotic agents increase water content of stool	Usually causes evacuation within 4–6 h, sooner in large doses	Simple constipation; bowel prep for endoscopy (especially PEG solutions)	Magnesium may be absorbed and cause toxicity in renal impairment
• *Bulk-forming laxatives: Methylcellulose, psyllium, etc: increase volume of colon, stimulate evacuation*				
• *Stimulants: senna, cascara; stimulate activity; may cause cramping*				
• *Stool surfactants: Docusate, mineral oil; lubricate stool, ease passage*				
• *Chloride channel activator: Lubiprostone, prostanoic acid derivative, stimulates chloride secretion into intestine, increasing fluid content*				
• *Opioid receptor antagonists: Alvimopan, methylnaltrexone; block intestinal μ-opioid receptors but do not enter CNS, so analgesia is maintained*				
• *5-HT_4 agonists: Tegaserod; activates enteric 5-HT_4 receptors and increases intestinal motility*				
DRUGS FOR IRRITABLE BOWEL SYNDROME (IBS)				
• Alosetron	5-HT_3 antagonist of high potency and duration of binding	Reduces smooth muscle activity in gut	Approved for severe diarrhea-predominant IBS in women	Rare but serious constipation • ischemic colitis • infarction
• *Anticholinergics: Nonselective action on gut activity, usually associated with typical antimuscarinic toxicity*				
• *Chloride channel activator: Lubiprostone (see above); useful in constipation-predominant IBS in women*				

MCQs

1- A patient is undergoing colonoscopy, which of the following drugs should the doctor give him the night before?
A- PEG
B- Senna
C- Castor oil
D- Lactulose

2- Which of these drugs act on small intestine?
A- Senna
B- Bisacodyl
C- Castor oil
D- Saline laxatives

3- Which of the following is used to treat liver cirrhosis?
A- Saline laxatives
B- Lactulose
C- Senna
D- Sodium salts

4- Which of the following drugs used for treatment of constipation by increasing the bulk of intestinal content:
A- Castor oil
B- Saline laxative
C- Methyl cellulose
D- Glycerin

5- Which of the following drugs may cause iron deficiency?
A- Bulk forming laxatives
B- Osmotic laxatives
C- Stimulant laxatives
D- Stool softeners

6- Which of the following drugs acts as a lubractant:
A- Paraffin oil
B- Docusate
C- Tegaserod
D- Amitriptyline

7- A patient presented with abdominal pain and frequent unsatisfactory bowel movement. For the last one year he has been using a purgative twice weekly to open his bowel. On colonoscopy the colon was found to be atonic with bluish pigmentation of the mucosa. Which is the most likely purgative that the patient has been using:
A- Liquid paraffin
B- Ispaghula
C- Senna
D- Lactulose

8- The following laxative lowers blood ammonia level in hepatic encephalopathy
A- Bisacodyl
B- Lactulose
C- Liquid paraffin
D- Magnesium sulfate

9- Used as a laxative, liquid paraffin has the following drawbacks except:
A- It causes gripping
B- It is unpleasant to swallow
C- It interferes with absorption of fat soluble vitamins
D- It may produce foreignbody granulomas

10- Select the purgative that should not be taken at bed time:
A- Ispaghula
B- Bisacodyl
C- Senna
D- Magnesium sulfate

11- The most suitable laxative for a patient of irritable bowel syndrome with spastic constipation is:
A- Dietary fibre
B- Bisacodyl
C- Liquid paraffin
D- Senna

Answers: 1-A 2-C 3-B 4-C 5-A 6-A 7-C 8-B 9-A 10-D 11-A

Thank you for checking our team!

Pharmacology 435

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Sources:

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3. Basic & Clinical Pharmacology by Katzung, chapter 62,12th edition.
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