GIS 3

PHARMACOLOGY

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Topics to be discussed in this :-
1-Drugs stimulating GI motility
2-Laxatives

1-Drugs stimulating GI motility

They are also called Prokinetic agents.

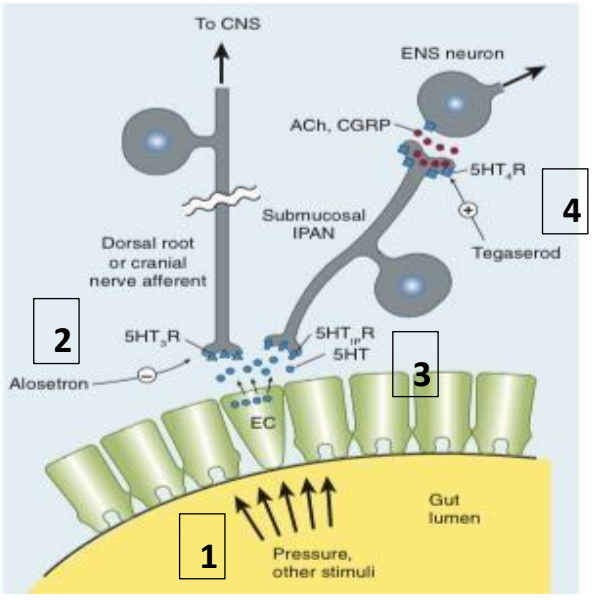
A-Potential uses:

1-Increasing lower esophageal sphincter pressures; useful for GERD.
2-Improving gastric emptying; helpful for gastroparesis and postsurgical gastric emptying delay.
3-Stimulation of the small intestine; useful for postoperative ileus.
4- Enhancing colonic transit; useful in the treatment of constipation.

B-Physiology of the enteric nervous system:-

1-Gut distention stimulates 5-HT (Serotonin (5- Hydroxytryptophan) release from the EC (Enterochromaffin) cells.
2-Stimulation of 5-HT3 receptors on the extrinsic afferent nerves (Sensory part of the vagus nerve), stimulates nausea, vomiting, or abdominal pain.
3- 5-HT also stimulates 5-HT1P receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for peristaltic and secretory reflex activity.
4- Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of ACh & calcitonin gene related peptide (CGRP), promoting reflex activity.

The enteric nervous system can independently regulate GI motility and secretion.



-**The myenteric interneurons control:** peristaltic reflex, promoting release of excitatory mediators proximally and inhibitory mediators distally.

1-**Motilin** may stimulate excitatory neurons or muscle cells directly.
2-**Dopamine** acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal and gastric contractions.

A-Cholinomimetic agents: enhance the activity of GIT

Drug	Mechanism of action	Uses	Side effects
1-Bethanecol	**Stimulates muscarinic M3 receptors on muscle cells and at myenteric plexus synapses.**	**Used for the treatment of GERD and gastroparesis; no longer used because of their side effects and the availability of better performing drugs.**	**_____**
2- Neostigmine	**AchE inhibitor enhances gastric, small intestine, and colonic emptying.**	**IV neostigmine used for the treatment of acute large bowel distention (acute colonic pseudo-obstruction / no true obstruction). Administration of 2mg results in prompt colonic evacuation of flatus and feces.**	**Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia.**

B- Dopamine D2-receptor antagonists:

Drug's name	Mechanism of action	Uses	Side effects
Metoclopramide & Domperidone (D2 Antagonists)	**Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal & gastric contractions.** **These agents block D2 receptors causing:** **1-Increase esophageal peristaltic amplitude.** **2-Increase lower esophageal sphincter pressure.** **3-Enhance gastric emptying.** **4-No effect on small intestine or colonic motility.** **5-Block dopamine D2 receptors in the chemoreceptor trigger zone of the medulla(area postrema), resulting in potent anti-nausea and antiemetic actions. (central action)**	**1-Gastroesophageal Reflux Disease: could be used but Not effective with erosive esophagitis (in this condition we use PPI) because of the superior efficacy and safety of anti-secretory agents in the treatment of heartburn. Prokinetic drugs are mainly used in combination with anti-secretory agents in patients with regurgitation or refractory heartburn.** **2-Impaired Gastric Emptying(Gastroparesis) : to stimulate movement of stomach, widely used in post surgical and diabetic gastroparesis.** **3- Non-ulcer Dyspepsia: evacuation quickly of the stomach, helps to move dyspepsia.** **4-Prevention of Vomiting** **5-Postpartum Lactation Stimulation. Domperidone is used to promote postpartum Lactation; dopamine inhibits the release of the hormone prolactin, these agents antagonize its effect and then stimulate the release of the hormone.**	**Metclopromide** **Crosses BBB; can cause: side effect similar to neuroleptic drugs so it's cause: Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal symptoms (dystonia, akathisia, parkinsonian features) and tardive dyskinesia.** **Domperidone** **Does not cross the BBB, so does not cause CNS effects. Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders.**

C- Laxatives

The overwhelming majority of people do not need laxatives (misused drug), yet they are self-prescribed by a large portion of the population.

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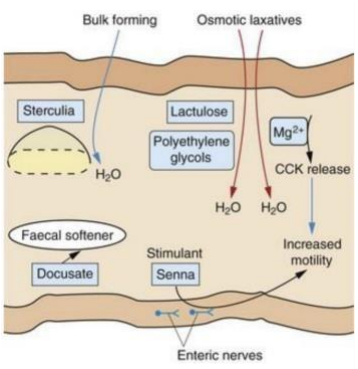


Intermittent constipation is best prevented with:

1-High-fiber diet.

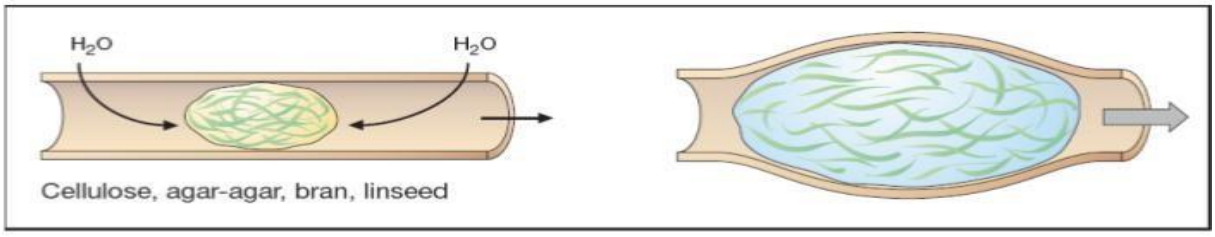
2-Adequate fluid intake.

3-Responding to nature's Call.

4-Regular exercise.

1-Bulk-Forming laxatives

They are the most frequently used because they are harmless, have very little side effects and slowly acting.



Drug's name	Mechanism of action	Side effects	Preparation
Bulk-Forming Laxatives	Indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis. Effective within 1-3 days.	Bacterial digestion of plant fibers within the colon may lead to formation of gas leading to bloating and flatus.	Common preparations include: 1- natural plant products (psyllium, methylcellulose, bran) 2-synthetic fibers (polycarbophil)

2- Stool Surfactant Agents (Softeners)

Surfactant agents: surface active agents help mixing oil and water.

Drug's name	Mechanism of action	uses	Side effects	Preparation
1-Docusate	Detergents or surfactants that act as stool-wetting and stool-softening agents, allowing the mixing of water, lipids, and fecal matter. Alters intestinal permeability and increases net water and electrolyte secretions in the intestine.	Used in symptomatic treatment of constipation & in painful anorectal conditions such as hemorrhoids and anal fissures.		1-Orally: Softening of feces within 1-3 days 2-Rectally: effective within 5 to 20 minutes.
2- Glycerin suppository.	Works by Irritating the lining of the intestine and increasing the amount of fluid, making it easier for stools to pass. Used in infants and children.			

3- Lubricant/Emollient:

-Site of Action: Colon.

-Onset of Action: 6 – 8 hours

-Causing lubrication of the stool, making it slippery so that it slides through the intestine more easily.
-It is not absorbed, but increases the bulk of the intestinal contents as it reduces the water absorption.

Liquid paraffin (It is a Halocarbon from petroleum)

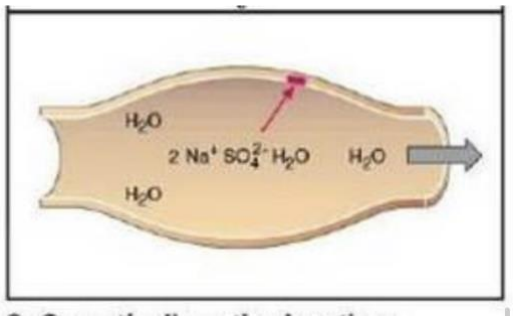
Used to prevent and treat fecal impaction (when the stool becomes too dry and too difficult to pass)

Side effects:

1-Aspiration (enter of it to the lung) can result in severe lipid pneumonitis.
2-Long-term use can impair absorption of fat-soluble vitamins (Not recommended for regular use).
3-Can slip out of anal sphincter, causes embarrassment(uncomfortable).

4- Osmotic laxatives

Soluble but non-absorbable compounds that result in increased stool liquidity due to an increase in fecal fluid.



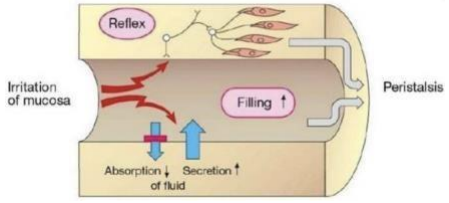
Drug's name	Notes
1- Non-absorbable sugars or salts: A- Magnesium hydroxide (milk of magnesia)	Not used for prolonged periods in renal insufficiency due to the risk of hypermagnesemia.

B- Magnesium citrate and sodium phosphate	**Large doses of magnesium citrate & sodium phosphate cause purgation (rapid bowel evacuation within1-3 h). This might cause volume depletion.** **These agents are taken to produce this effect, with large amount of water (because we have loss of water and electrolytes in this process and the patient goes to the bathroom every 5-10 mins) until we have full evacuation of the GI contents.**
C- Lactulose	**Disaccharide; not absorbed causing retention of water through osmosis leading to softer, easier to pass stool.** **In the colon, it is fermented by the gut flora, producing osmotic metabolites that cause severe flatus and cramps (and due to that they are not popular)** **Drug of choice in hepatic encephalopathy to trap NH3; Lactulose is converted into lactic acid, which decreases the luminal pH. So, NH3 is trapped and prevented from absorption.**

2- Balanced polyethylene glycol	-Safe solution: no intravascular fluid or electrolyte shifts. -Does not cause cramps or flatus. -It is a laxative solution that increases the amount of water in the intestinal tract to stimulate bowel movements. -PEG (Polyethylene Glycol) is an inert, non-absorbable, cosmetically active sugar. -It also contains Sodium sulfate, bicarbonate and potassium chloride to replace electrolytes that are passed from the body in the stool. -Used to clean the bowel before colonoscopy; a barium x-ray or other intestinal procedures. For colonic cleansing, it is ingested rapidly(only problem) (4L over 2-4 h). -For chronic constipation, PEG powder is mixed with water or juice.

5- Stimulant laxatives

Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion



Drug's name	Notes
1- Anthraquinone Derivatives: Aloe, Senna, and Cascara.	-Occur naturally in plants. -Poorly absorbed & after hydrolysis in the colon, produce a bowel movement in 6–12 h when given orally and within 2 h when given rectally. So when taken orally, they are preferred to be taken at the night or in the morning. -Chronic use leads to a brown pigmentation of the colon known as "melanosis coli".

2- Bisacodyl	**-Tablet and suppository for treatment of acute and chronic constipation.** **-Induces bowel movement within 6–10h orally and 30–60 minutes rectally.** **-Safe for acute and long-term use.**
3- Phenolphthalein	**-Removed from the market owing to concerns about possible cardiac toxicity.** ***Note:** **It was used because of its good taste and it has been added to food stuff and chocolate.**
4- Castor Oil	**-Hydrolyzed in the upper intestine into ricinoleic acid which is a local irritant.** **-Was used as purgative to clean the colon before procedures.** ***note:** **We have to know three terms:** **-Laxatives, Purgatives and cathartics are all used for evacuation of GI contents but the difference between them is that:** **1- Laxatives have mild effects** **2- Purgatives and cathartics have stronger effects.**

6-Opioid receptor antagonists:

Do not cross the BBB. Block peripheral (μ) mu – opioid receptors without central analgesic effects, but they act on the GI to prevent constipation.

*** Used in critically ill patients or in patients that have to take opioids; these opioids produce constipation.**

Drug's name	Notes
1- Methylnaltrexone	**-Used for opioid-induced constipation in patients with advanced illness not responding to other agents.** **-S.C. (Subcutaneous) injection every 2 days.**
2- Alvimopan	**-Short-term use for postoperative ileus(when no movement in the intestine) in hospitalized patients.** **-Given orally 5 hours before surgery and twice daily after surgery until bowel function has recovered, but for no more than 7 days because of possible cardiovascular toxicity.**