Pharmacology
Antidiarrheal Drugs

Diarrhea

Is an increase frequency of bowel evacuation ,with the passage of abnormality soft or watery feces .more than 3-4times daily.

- It is not a disease but a sign of an underlying problem as infection or gastrointestinal disorder or its symptom of numerous conditions.
- Diarrhea may be acute or chronic and mild or severe. Most episodes of acute diarrhea are defensive mechanisms by which the body tries to rid it self of irritants, toxins, and infectious agents.

- **Inflammatory bowel disease (IBD)** : in which inflamed mucous membranes secrete large amounts of fluids into intestinal lumen, a long with mucus , proteins & blood ,characterized by impaired a absorption of electrolyte and water.

- **Irritable bowel syndrome(IBS) :**functional disorder of intestinal motility with no evidence of inflammation or tissue changes.

-IBS plus frequent bowel movements that causes increased diarrhea is often called IBS-D.

-Anti-diarrhea medications like loperamide (Imodium) may help.

Pathophysiology of diarrhea

- Diarrhea is an imbalance in absorption and secretion of water and electrolytes, diarrhea may be associated with specific disease of GIT or with a disease outside GIT .
- ↑ intestinal motility , ↑water secretion , defective water re-absorption cause diarrhea

Causes of diarrhea

1.Drug induced diarrhea(antibiotic ampicillin, clindamycin, Mg sulfate)

- If mild diarrhea, symptoms likely will clear up within a few days after antibiotic treatment ends. In some cases may advise to stop antibiotic therapy until diarrhea subsides.
- *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents ,Pseudomembranous colitis, also called antibiotic-associated colitis or C. difficile colitis, is inflammation of the colon associated with an overgrowth of the bacterium C. diff.

may include:

Watery diarrhea, Abdominal cramps, pain or tenderness, Fever, Pus or mucus stool, Nausea, Dehydration

Symptoms of pseudomembranous colitis can begin as soon as one to two days after start taking an antibiotic, or as long as several months or longer after finish taking the antibiotic.

***Treatment to fight harmful bacteria in C. difficile infection**

If develop C. difficile infection, stop whatever antibiotic currently taking, and might prescribe antibiotics specifically targeted to kill the bacteria causing antibiotic-associated diarrhea.

Causes of diarrhea

2.Infection :viral(Rotavirus), bacterial(Salmonella) , protozoal(Entomoeba Histolytica.. amoebic dysentery)

3.Disease induced diarrhea:(IBS), or with a disease outside GIT e.g respiratory infection)

4.**Hormonal diarrhea** (serotonin , histamine, thyroxin).

5. Overfeeding , underfeeding (starvation), **new unsuitable food**

Treatment of diarrhea

The therapeutic goals of diarrhea treatment are:

1.prevent excessive water, electrolyte and acid-base disturbance.

2.maintain the hydration(prevent dehydration)

3.provide symptomatic relief

4. manage secondary disorders causing diarrhea.

Antidiarrheal drugs:-

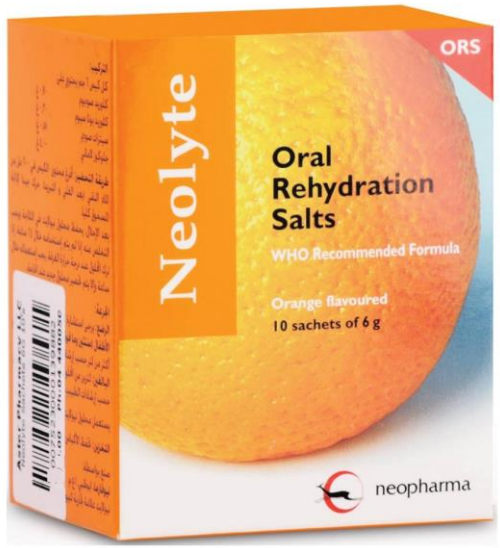
1.Oral Rehydration Solution(ORS):

-ORS for treatment of dehydration, is generally regarded as the first line of treatment for acute diarrhea (infective and non-infective acute diarrhea)

-Can be recommended for patient of any age.
-ORS has no side effect or drug interactions.
-Oral rehydration salts are not intended to relieve symptoms but are designed to replace water and electrolytes lost through diarrhea & vomiting.

-**Neolyte ,Baby light, Dextrobaby**
- The recommended formulation includes sodium chloride , sodium citrate, potassium chloride, and glucose. , It works as glucose increases the uptake(absorption) of sodium and thus water by the intestines. Soduim and potassium to replace the body losses of these essential ions during diarrhea and vomiting.
- use sterile water to prepare the **ORS**.
- **ORS** must be used within 1 hour of mixing. Any unused **solution** should be discarded unless stored in a refrigerator where it may be kept for up to 24 hours.

Oral Rehydration Solution



2.Anti-Motility Drugs:

1.Diphenoxylate +Atropine :(Lomotil ,Enterostop)

Its indication is for the treatment of diarrhea in adults and children 13 years or older.

- Used for acute diarrhea , diarrhea-predominant-irritable bowel syndrome.
- Not used for infectious diarrhea (viral, bacterial, parasite)

Mechanism of Action

Diphenoxylate is analog meperidine an opioid agonist that acts on the presynaptic opioid receptors (predominantly mu receptors) in the enteric nervous system. By acting on the presynaptic opioid receptors, it blocks the release of acetylcholine and decrease peristalsis .

-It does not have analgesic effects of morphine at standard doses, but at higher doses, it can lead to CNS effects, like euphoria.

Anti-Motility Drugs:

1.Diphenoxylate +Atropine

*Atropine is added, which is a competitive inhibitor of acetylcholine receptors, to prevent patients from misusing diphenoxylate. Atropine produces anticholinergic side effects like nausea/bloating/tachycardia/dryness of mouth/eyes when ingested at higher doses. These adverse effects are unpleasant for the patient and discourage overdosing.

-high doses cause Euphoria &physical addictive properties ,drowsiness, respiratory depression.

Anti-Motility Drugs:

2.loperamide: Vancontil, Imodium,Diara-Stop

Mechanism as diphenoxylate

Loperamide does not cross the blood-brain barrier and has no analgesic properties or potential for addiction

Loperamide is preferred over diphenoxylate/atropine because of its greater efficacy, better tolerance.

Anti-Motility Drugs:

Contraindication

Gastrointestinal obstruction

myasthenia gravis

paralytic ileus

prostatic enlargement

severe ulcerative colitis

toxic megacolon

Infectious enterotoxin-producing bacterial.

Anti-Motility Drugs:

- **Gastrointestinal complications:** can precipitate GI complications, including sepsis and prolonged diarrhea, when administered **Anti-Motility Drugs** in patients with infectious diarrhea. This effect is because of the prolongation of GI transit time and decreased GI motility, which leads to bacterial overgrowth and release of enterotoxins into the bloodstream, creating a septic shock-like picture.

- **Toxic Megacolon:** This drug can precipitate toxic megacolon in patients with acute ulcerative colitis. Due to decreased motility, the physiological secretions might get accumulated in the bowel leading to distension. The colon is already fragile in ulcerative colitis and is prone to rupture.

3.Adsorbents:

Kaolin+pectin (kapect)

Both appear to act as absorbents of bacterial toxins and fluid, thereby decreasing stool liquidity and number.

-Not used with intestinal obstruction or diarrhea with fever.
-They can interfere with absorption of other drugs.

Diastop (contain calcium carbonate and kaolin both are converted to insoluble calicium &aluminium carbonate in intestine and increase viscosity of the intestinal contents helping to stop diarrhea.

4.**Other Drugs**:

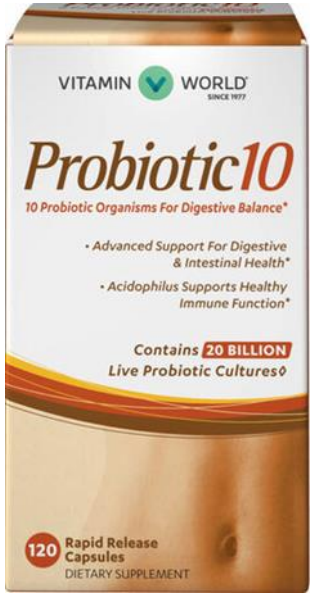
➢**Bismuth subsalicylate(** Pepto-Bismol)

Decrease fluid secretion in the bowel(antisecretory effect)as well as it has coating (protective) action, antibacterial effects.

➢**Probiotics:** dietary supplement (lactobacillus species) enhancing for the normal flora of GIT.

-Decrease duration of diarrhea caused by antibiotic.

-produce pathogen -inhibiting substances, prevent pathogen adhesion to the GIT tract, inhibit the action of microbial toxins, stimulate immune defense mechanisms.



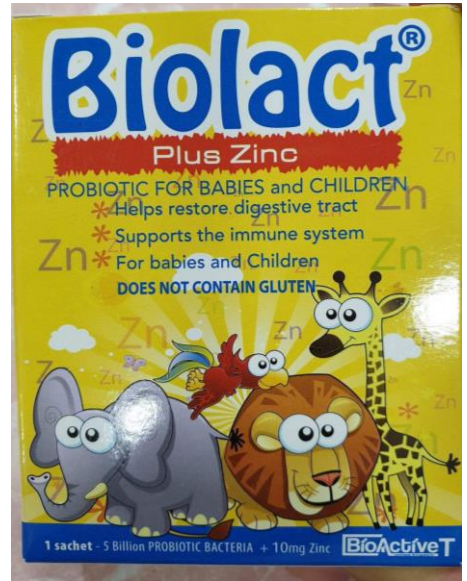
➢**Gelatin Tannate**(Tasectan)

Mechanism:

Acts by forming a film which protects the intestinal mucosa , form a complex with the toxins responsible for the inflammation and promotes their excretion, prevent the adhesion of Salmonella and E.coli on the wall of the small intestine, reducing the frequency and duration of diarrhea episodes.

➢ **Zinc**

Use Zinc in children with diarrhea reduce both the duration and severity of diarrhea



Constipation

- **Constipation**
- It is characterized by the passage of hard, dry stool less frequently than by the person's normal pattern .abdominal pain & distension may occur ,as well as al ow back pain & anorexia.
- Although there is no normal number of stools (which vary from 3/days- 3/weeks) most people report more than 3 bowel movement/week)

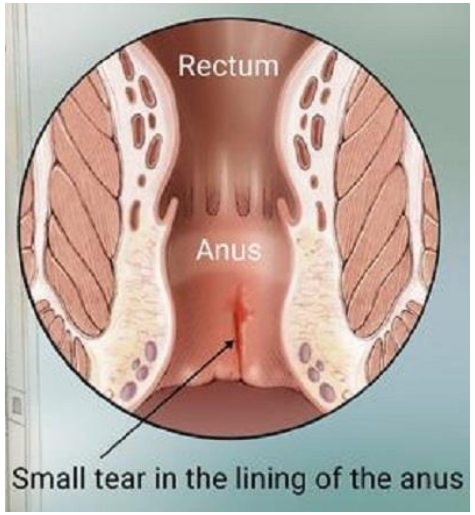
- **Causes of Constipation :**
- 1.Drug induce constipation(opiates, hyoscine, AL salts, phenytoin, chlorpheniramine, ,laxative abuse…..)
- 2.disease induce constipation(diabetes mellitus, hypothyroidism, IBS)
- 3.lifestyle factors low fiber diet , inadequate fluid intake , chronic immobility)
- 4.psychogenic cause: depression
- 5.neurogenic condition (brain trauma, Parkinson dis.)
- 6. advance age due to poor diet ,lack of exercise
- 7. pregnancy especially in the third trimester (due to hormonal change, bowel compression by uterus, iron therapy)

- **Associated symptoms**

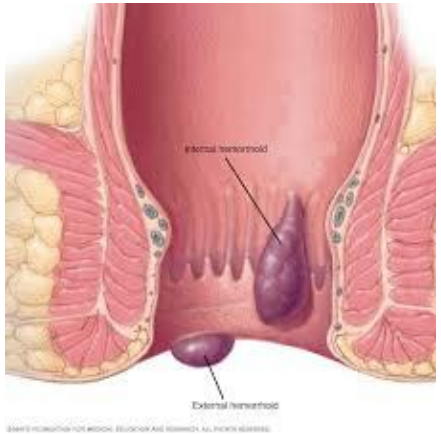
➢ Constipation is often associated abdominal discomfort, bloating and nausea

➢ in some cases constipation can be so severe as to Intestinal obstruction . this become evident by causing colicky abdominal pain ,abdominal distension ,vomiting.

➢ the blood in stool associated with constipation , although alarming is not necessarily serious, but does require medical diagnosis ,blood may arise from piles(hemorrhoids) or a small crack in the skin on edge of anus (anal fissure),both caused by low diet fiber →constipation.



anal fissure



hemorrhoids

- **Laxative abuse→ constipation**
- Use of laxative is relevant ,continuous use especially stimulant laxative ,can result in vicious circle where the contents of the gut are expelled , causing a subsequent cessation of bowel actions for 1 or 2 days .
- This then leads to the false conclusion that constipation has recurred and more laxative are taken and so on..
- Chronic over use of stimulant laxatives can result in loss of muscular activity in the bowel wall(an atonic colon) and thus further constipation.

- **Treatment of constipation**

1. Identify underlying causes
2. Treat or remove secondary causes
3. Relieve symptoms
4. Restore normal bowel function

Non pharmacological treatment

- In most cases lifestyle and dietary modifications should be employed prior to use of laxatives .
- ↑dietary fiber can improve normal transit constipation ,
- but drug induced constipation ,dysfunction of colon muscle or nerves that cause constipation are unlikely to respond to increase fiber.
- Fibers present in:
  - Hole wheat , wholegrain and oats
  - Fruit such as berries, pears, melon and oranges, apple
  - Vegetables such as broccoli, carrots and sweetcorn
  - Peas, beans
  - Nuts and seeds

Laxatives

1.Stimulant laxative

2. Bulk forming laxative

3.Osmotic laxative

4.Lubricant

Laxatives promote defecation and are used in the treatment of constipation and for bowel evacuation before investigational procedures such as endoscopy

1.stimulant laxative

Senna, Bisacodyl, Sodium Picosulfate ,Glycerin

Onset of action

Oral→ 6-12 hr

Rectal suppository → 1 hr

Glycerin suppositories:The patient should expect to have bowel movement quickly (within one hour).

Mechanism: stimulant laxative work by increase peristalsis by stimulating enteric nerves, Increasing electrolyte and water secretion by the mucosa .

-Abdominal cramping as side effect with these drugs.

-Prolonged use may result in loss of colonic smooth muscle tone (laxative abuse)

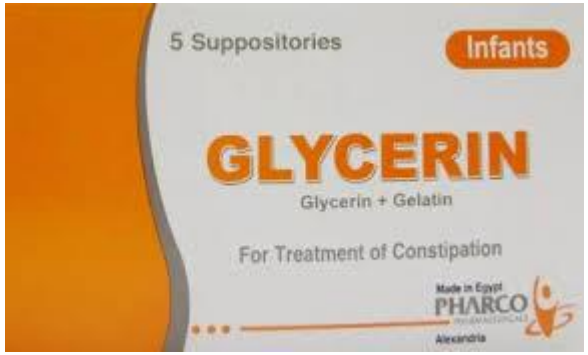
-Should be used for only short period of few days at most, to re-establish bowel habit.

Bisacodyl enteric coated tab., it should be taken within 1 hr. of antacid or milk as this will lead to dissolution of the coating and release of drug into the stomach and cause gastric irritation.

Senna tab

Bisacodyl tab ,supp.

Sodium Picosulfate ,oral drop



Glycerin ,supp.

- **Senna** :its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. After hydrolysis of glycosidic linkage in the intestine ,they directly stimulate the myenteric plexus, result in increase peristalsis and electrolyte and water secretion into the bowel.
- Senna may change color of urine to red-brown colour

- **Caster oil** :brocken down in the small intestine to ricinolic acid which is very irritating to the mucosa and promptly increase peristalsis. Pregnant should avoid it because may stimulate uterine contraction.

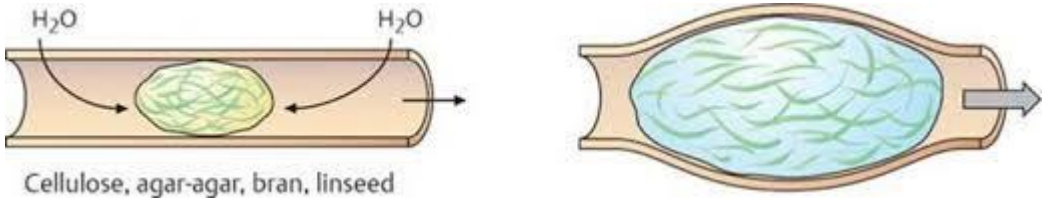
2.Bulk forming laxative

Methylcellulose ,and certain plant extracts as **sterculia, bran, Ispaghula**

Are polysaccharide polymers that not digested in the upper part of GIT

They form a bulky hydrated mass in the gut lumen (that absorb water and swelling in the gut)promoting peristalsis and improving fecal consistency.

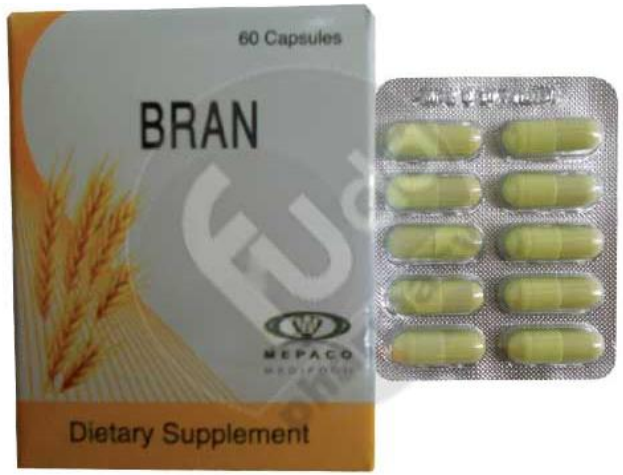
-Onset of action 1-3 days



-In the form of granules or powder , the preparation should be mixed with afull glass of liquid (fruit juice or water).

-Intestinal obstruction may result from inadequate fluid intake in patients taking bulk laxatives, particularly those whose gut not functioning properly as a result of abuse of stimulant laxatives.

Ispaghula



bran

3.Lubricant: the drug acts by softening the feces and coats the intestine with an oily film.

Liquid paraffin and glycerin suppositories are lubricant and act by facilitating the passage of hard stools.

4.Osmotic laxative

Osmotic laxatives draw water from the rest of the body into your bowel to soften stool and make it easier to pass.

Lactulose, Macrogol also known as polyethylene glycol, Magnesium salts

- onset 1-2 days

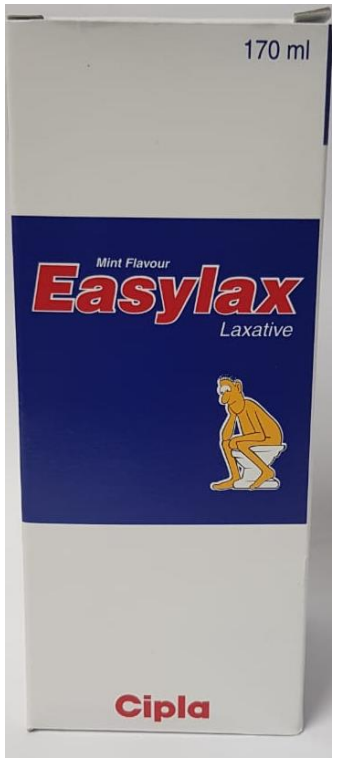
Lactulose, Macrogol work by maintaining the volume of fluid in the bowel & may take 1-2 days to work

Magnesium salts Hold water in the intestine by osmosis ,this distend bowel , increase intestinal activity and produce defecation.

- **polyethylene glycol** used as colonic lavage to prepare the gut for radiologic or endoscopic procedure.

-**lactulose** semisynthetic disaccharide sugar act as osmotic laxative. increase osmotic pressure ,fluid accumulation ,colon distention , soft stool and defecation.

Stool softener : **docusate sodium** emollient laxatives and as stool softeners.



Liquid paraffin

Macrogol

Lactulose

Combination stimulant and bulk laxative

- **Ispaghula husk**
- **senna**

THANK YOU