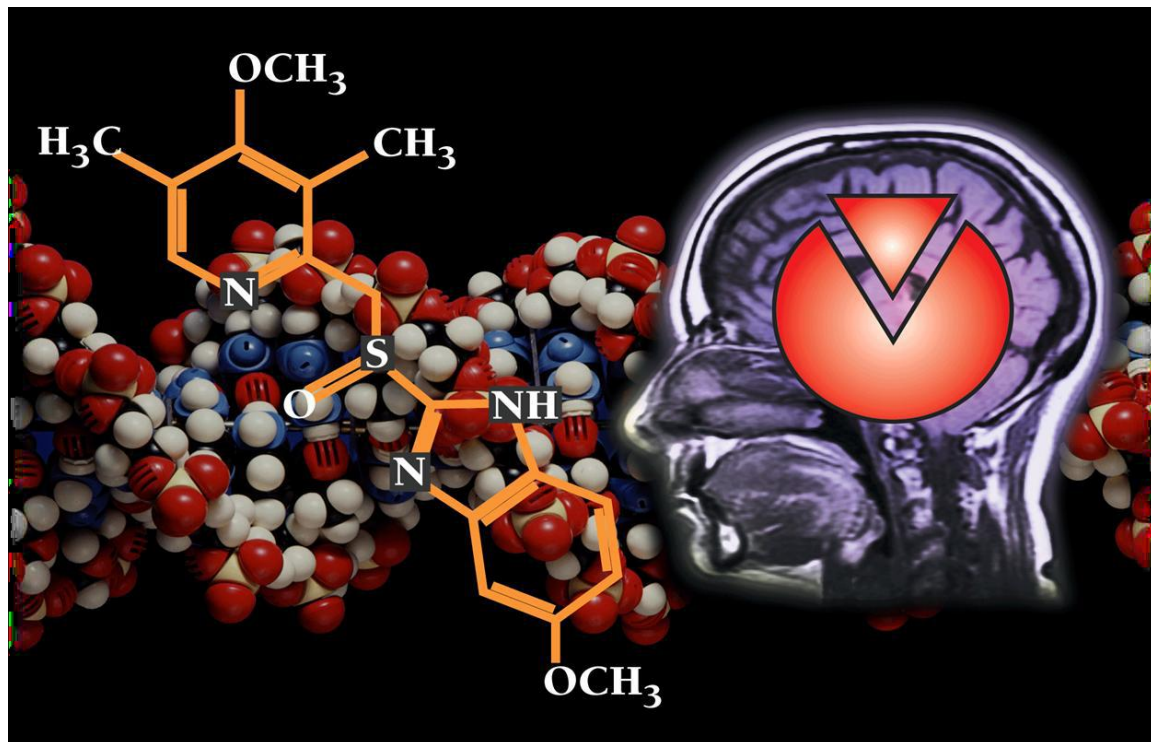


Drugs used in Constipation and IBS



Done By:

Hashem Almahmoud

Mohammed Aldohan

Anfal Alshaya

Aysha J Al-mahbob

Introduction:

Definition of Constipation: Too

infrequent passage of stool that may be due to **decreased motility** in colon or due to **difficulty in evacuation**.

Causes:

- **Diet** : Decrease in **water** intake and **fiber** contents of diet.
 - **Local Painful Conditions**: Anal fissures, piles (Hemorrhoids).
 - **Lack** of muscular exercise.
 - **Drugs** : Muscle relaxants, Anticholinergics, Calcium channel blockers (**they all relax the smooth muscles of the gut, thus leading to decreased motility**) + opioid drugs (narcotic analgesic)
 - **Other** common causes are: Hypokalemia, Hypothyroidism, hypercalcemia, pregnancy etc..
- However**, Doctors (sometimes) may consider a source of chronic constipation.

TABLE 1. Common Causes of Constipation

Drugs <ul style="list-style-type: none">AnalgesicsAntacidsAnticholinergicsAntidepressive agentsAnti-Parkinsonism agentsBarium sulfateBismuthDiureticsIron sulfateOpiates	Neurogenic <ul style="list-style-type: none">Cauda equina tumorCerebrovascular accidentsChagas' diseaseHirschsprung's diseaseMultiple sclerosisParkinson's diseaseShy-Drager syndromeTumors
Large Bowel Diseases <ul style="list-style-type: none">Anal fissureAnal stenosisChronic volvulusDermatomyositisDiverticular diseaseIrritable bowel syndromeRectal prolapseSclerodermaStricturesEndometriosisIschemic colitisLymphogranuloma venereumSurgeryTumor	Metabolic and Endocrine <ul style="list-style-type: none">AmyloidDiabetic neuropathyHypothyroidismHypercalcemiaHypokalemiaPorphyriaPregnancyUremia Diet <ul style="list-style-type: none">Inadequate fiber intakeInadequate fluid intake

Note: If a person establishes regular bowel habits, usually defecating after breakfast when the deodnocolic and gastrocolic reflexes cause mass movements in the large intestine, the development of constipation in later life is less likely

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.

-Drugs (laxatives, purgatives, cathartics): Drugs that hasten the transit of food through the intestine by several methods

Classification of laxatives or purgatives:

1. **Bulk Purgatives:** Increase volume of non- absorbable solid residue.
2. **Osmotic Purgatives:** Increase water content in large intestine.
3. **Stimulant Purgatives:** Increase motility and secretion.
4. **Fecal softeners (lubricants):** Alter the consistency of feces → easier to pass.

1- Bulk purgatives:

Mechanism of Action; Non-absorbed hydrophilic colloids (A substance of **gelatinous consistency**) → Increase the bulk of intestinal contents **by water absorption** → ↑ mechanical pressure on the walls of intestine → stimulation of stretch receptors → ↑ peristalsis.

Note: 1 gm of Carrot absorbs 20 gm of water.

*The bulk purgatives are **not absorbed** and **remain** in the intestinal lumen.*

Plus the water in the intestinal lumen is absorbed (retained)

Both Increase Mechanical pressure on the walls

Increased peristalsis

Members

1. **Dietary fibers:** undigested polysaccharide vegetables, fruits, **grains, bran**, pectin.

2. **Natural plant products & semi synthetic hydrophilic colloids (very important):**

- **Psyllium seed**, methyl cellulose

- Carboxymethyl cellulose (CMC).

3. **Synthetic non absorbed resins:** Calcium polycarbophil.

Note: Bulk purgatives are one of the most commonly used approaches to treat constipation, being the safest with minimal (negligible) side effects.

Side Effects:

1. Delayed onset of action (several **days 1-3**).

2. Intestinal obstruction (**Because of the accumulation of non-absorbable substances, should be taken with enough water**).

3. Malabsorption syndrome, abdominal distention.

4. Interfere with other drug absorption e.g. **iron, calcium, and cardiac glycoside (digoxin)**.
So we should separate the drug in time.

Note: Interference is not that potent.

Clinical Uses:

➤ **Hemorrhoids; Pregnancy;** Colostomy; ileostomy; anal fissure; IBS, UC,

➤ **Chronic diarrheas with diverticular disease.** (A disease characterized by outpocketings of the colonic mucosa and submucosa through weaknesses of muscle layers in the colon wall.)

Note: The cause of diarrhea in diverticular disease is the toxins produced by the bacteria inhabiting the diverticula (pockets) of the colon. **Bulk purgatives (because of the bulk effect)** will **wash out** (clear away) the content of the diverticula (**including the irritants causing this problem**).

2- Osmotic Purgatives

➤ **Water Soluble but non absorbable compounds**

➤ Increase water content in **large intestine**.

Members:

A) Organic (Sugars): lactulose (semisynthetic disaccharide of fructose and galactose).

B) Non-organic (Saline purgatives): **Magnesium salts**, sodium or potassium salts.

A) Organic Osmotic (Lactulose)

➤ Metabolized by colonic bacteria into **fructose and galactose**.

➤ These sugars are fermented into **lactic acid and acetic acid** that function as osmotic laxatives.

Side Effects

1. Delayed onset of action (2-3 days)

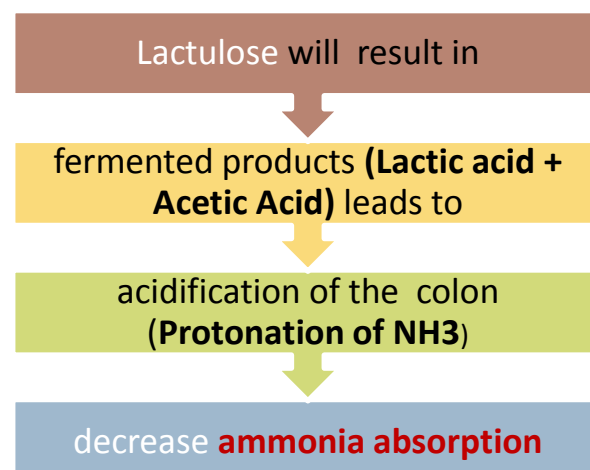
2. Abdominal cramps and flatulence.

3. Electrolyte disturbance. (Because of the water drainage)

Why Lactulose is commonly used in liver cirrhosis?

➤ **Dose:** 15 ml for constipation and 30 ml for liver cirrhosis.

Note: In liver cirrhosis, **NH₃ (Ammonia)** metabolism in the liver is defected. It can accumulate in larger amounts, travel to the brain and cause **encephalopathy**. Therefore patients cannot have any food that will give **NH₃** as an end product in its digestion. However we can solve this problem by administering **lactulose**, as it will **protonate** the **NH₃** (in the intestine) turning it into **NH₄⁺ (Ammonium)**. **NH₄⁺** Cannot be **absorbed by intestine**.



B) Saline Purgatives (e.g: Magnesium)

- Magnesium sulphate (Epson's salt).
- Magnesium oxide (milk of magnesia).
- Sodium phosphate.
- Rapid effect (within 1-3h).

Mechanism of Action: Are poorly absorbed salts. They remain in the bowel and retain water by osmosis thereby increasing the volume of feces → ↑ distension → ↑ peristalsis → evacuation of watery stool.

Uses

1. **Treatment of acute constipation** because it has rapid action.
2. Prevention of chronic constipation

Side Effects:

1. Intravascular volume depletion.
2. Electrolyte fluctuations: severe in children

Can you mention other uses of magnesium sulphate?

Treatment of **eclampsia** which is a condition in which one or more convulsions occur in a pregnant woman suffering from high blood pressure, often followed by coma. (In this case it is administered intravenously)

Contraindications:

1. Elderly patients
2. **Renal insufficiency.** (Because they already have elevated Mg levels –usually with chronic usage)
3. Sodium salts in CHF.
4. Magnesium salts renal failure, heart block, CNS depression, neuromuscular block.

Balanced polyethylene glycol (PEG*)

- Balanced **isotonic solution** of **osmotically** active sugar, NaCl, KCl, Na bicarbonate
 - No intravascular fluids or electrolyte shifts
 - No flatus or cramps
 - Lavage solution
 - **Used for complete cleansing prior to gastrointestinal endoscopic procedures** (4L over 2-4 hours).
 - Also, **small doses used for treatment or prevention** of chronic constipation.
- } Advantages

3 - Stimulant Purgatives (cathartics) “Drugs that should be avoided”

-Mechanism of Action: act via direct stimulation of enteric nervous system → peristalsis & purgation.

-Members

- a. Bisacodyl.
- b. Anthraquinone derivatives.
- c. Castor oil.

A) Bisacodyl

- Acts on large intestine (weak).
- Onset time 6-10 h, taken at night. **Why?** Simply so that the person can evacuate the bowel in the morning before leaving to work or school

B) Anthraquinone derivatives

Senna, Cascara, Aloes

- In colon, glycosides are hydrolyzed by bacteria into **emodin + sugar**
- The absorbed **emodin** has direct stimulant action on **myenteric plexus** → ↑ smooth muscle contraction → defecation.
- Bowel movements in 12 h (orally) or 2 h (rectally).
- Given at night.
- Causes brown pigmentation of the colon (**melanosis coli**).

C) Castor Oil

- Fixed oil degraded by **lipase** in upper small intestine → **ricinoleic acid + glycerin**
- **Ricinoleic acid** irritates mucosa.
- **Acts on small intestine** (strong).
- 5-20 ml on empty stomach in the morning.
- O.T. = 4 h.

Side Effects of Stimulant Laxative

1-Abdominal cramps may occur.

2-Prolonged use → dependence & destruction of **myenteric plexus** and **atonic colon**.

Contraindications

1. **Senna** in lactation
 2. **Castor oil** in pregnancy → reflex contraction of uterus → abortion.
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4 - Fecal Softeners (Lubricants)

- Are non absorbed drugs that soften the feces ,thus promoting defecation.
- May be given orally or rectally(faster).

Members:

1. Surfactants

- decrease surface tension of feces
 - e.g. Docusate (sodium dioctyl sulfosuccinate).
 - is given orally or enema.
 - Is commonly prescribed in hospitalized patients to minimize straining.
3. **Glycerin (Suppository)**. (Usually given twice after surgery to avoid any damage to the Surgery) and it's preferable with children

3. Mineral oil (Liquid Paraffin) (good for radiology preparation) given in enema in that case.

Side effects of liquid paraffin

1. Not palatable (bad taste)
2. Impairs absorption of fat soluble vitamins.
3. Increase activity of oral anticoagulant.

Irritable Bowel Syndrome

It is a functional bowel disorder associated by characteristic cluster of symptoms in the absence of detectable structural abnormalities. However, it is a condition of diverse pathophysiology associated with abnormalities in GIT motility (either diarrhea or constipation). Prevalence is around 15% of population. Recent work concentrated to the important role that serotonin plays in such syndrome. Therefore, many of drugs that used for Rx of IBS may act by **serotonergic mechanisms** (see Table).

1) 5-HT₃ receptor antagonists (Alosetron and Cilanestron) are used for diarrhea associated IBS.

➤ **Dose:** 1 mg BID

➤ **Side Effects:** Constipation; Ischemic Colitis

2) 5-HT₄ partial agonist (Tegaserod): This is used for constipation-predominant IBS in women and also recommended for treatment of chronic constipation.

MOA: Stimulation **Of 5-HT₄** receptor enhances the release **of ACH**. **The latter (ACH) increases peristalsis.**

Dose: 6 mg BID for 8 weeks.

Side Effects: Diarrhea; Headache

Limitation: does not have significant effect on symptoms of abdominal pain and discomfort.

	Alosetron	Tegaserod
MOA	5-HT₃ receptor antagonists	5-HT₄ partial agonist
USES	Woman with IBS and sever diarrhea	Woman with IBS and constipation
Side effects	Constipation; Ischemic Colitis	Diarrhea; Headache

As Used in the Management of Irritable Bowel Syndrome

Medications	Dosage	AFP Level of Evidence	Comment
Loperamide (Imodium)	2 to 4 mg up to four times a day	Level A	Use as needed or prophylactically in times of anticipated stress
Cholestyramine (Questran)	4 g one to six times a day	Level C	Second-line agent
Alosetron	1 mg per day titrated to two times a day if tolerated	Level A	Restricted use in female patients only
Fiber	Start low and titrate up to 20 to 30 g a day	Level A	May worsen bloating
Osmotic laxative	Magnesium citrate, lactulose, or polyethylene glycol dosed as appropriate	Level C	
Antispasmodics and anticholinergics (e.g., dicyclomine [Bentyl], hyoscyamine [Levsin])	Dicyclomine, 10 to 20 mg, two to four times a day	Level B	Used as needed only
Tricyclic antidepressant (e.g., amitriptyline [Elavil])	Start amitriptyline, 10 to 25 mg at bedtime or twice	Level A	Needs to be given daily, not as needed, therefore generally reserved

- **Loperamide** is used in case of **diarrhea**.
- **Fibers, osmotic laxatives** in case of **constipation**.

TCAs are very useful in managing irritable bowel syndrome because in this condition the psychopathology aspect plays an important role in the pathophysiology of the disease.

A, B, and C represent the quality of the trials that were performed in testing the approach of treatment. Or we can say, those letters represent the level of benefit, "A" being the most beneficial.

For more info go to <http://www.aafp.org/online/en/home/publications/journals/afp/afplevels.html>

SUMMARY:

- ✓ **Bulk Purgatives** like **grains, bran, and Psyllium seed**: Increase volume of non-absorbable solid residue we should take them **with water**.
- ✓ They are used in Hemorrhoids; Pregnancy, **Chronic diarrheas with diverticular disease**.
- ✓ They have **delayed onset of action**, and may cause Intestinal obstruction (**should be taken with enough water**).
- ✓ **Osmotic Purgatives**: are **Water Soluble** but **non absorbable** compounds that Increase water content in large intestine.
- ✓ **lactulose** is used in liver cirrhosis
- ✓ **Magnesium salts** are poorly absorbed salt that function as an **osmotic purgatives**. They are used in **acute cases of constipation**, contraindicated in **renal failure, and its main side effects are: Intravascular volume depletion, electrolyte fluctuations: severe in children**
- ✓ **Balanced polyethylene glycol** (PEG): is a balanced **isotonic solution** of **osmotically** active sugar, NaCl, KCl, Na bicarbonate, which is used **for complete cleansing prior to gastrointestinal endoscopic procedures** (High doses), treatment or prevention of chronic diarrhea
- ✓ **Stimulant Purgatives**: **act** via direct stimulation of enteric nervous system → peristalsis & purgation.
- ✓ **Bisacodyl** has a weak effect on the large intestine.
- ✓ **Antraquinone derivatives** are hydrolyzed by bacteria into **emodin** (stimulate myenteric plexus) + **sugar**. It causes brown pigmentation of the colon
- ✓ **Castor Oil** is a Fixed oil degraded by **lipase** in upper small intestine → **ricinoleic acid + glycerin**. Ricinoleic acid irritates the mucosa. (**acts on strongly on the small intestine**)
- ✓ **Senna** is contraindicated in lactation. **Castor oil** in pregnancy → reflex contraction of uterus → abortion.
- ✓ **Fecal softeners (lubricants)**: Are non absorbed drugs that soften the feces, thus promoting defecation.
- ✓ **Surfactants**: like **Docusate** (sodium dioctyl sulfosuccinate): decrease surface tension of feces, and is commonly prescribed in hospitalized patients to minimize straining.
- ✓ **Glycerin (Suppository)**. (Usually given twice after surgery to avoid any damage to the Surgery)
- ✓ **Mineral oil (Liquid Paraffin)** (good for radiology preparation) given in enema in that case.
- ✓ **Side effects of liquid paraffin**: Not palatable (bad taste), impairs absorption of **fat soluble vitamins** (A,D,E,K), and Increase activity of oral anticoagulant.
- ✓ **2) 5-HT4 partial agonist (Tegaserod)**: used for constipation-predominant IBS in women and also recommended for treatment of chronic constipation.
- ✓ **1) 5-HT3 receptor antagonists (Alosetron and Cilanestron)** are used for diarrhea associated IBS.
- ✓ **TCAs** are very useful in managing irritable bowel syndrome because in this condition the psychopathology aspect plays an important role in the pathophysiology of the disease.

Treatment of IBD

- ✓ Antispasmodics e.g. **mebeverine** (**atropine like action**)
- ✓ Low doses of tricyclic antidepressants (**amitriptyline**): has an Anticholinergic action and reduces visceral afferent sensation
- ✓ Alosetron (diarrhea)
- ✓ Tegaserod (constipation)