Chronic Bowel Diseases

Dr/ Heba Ahmed Hassan

Assistant Professor of Clinical Pharmacology Faculty of Medicine Mutah University

Inflammatory bowel diseases

تقرحي

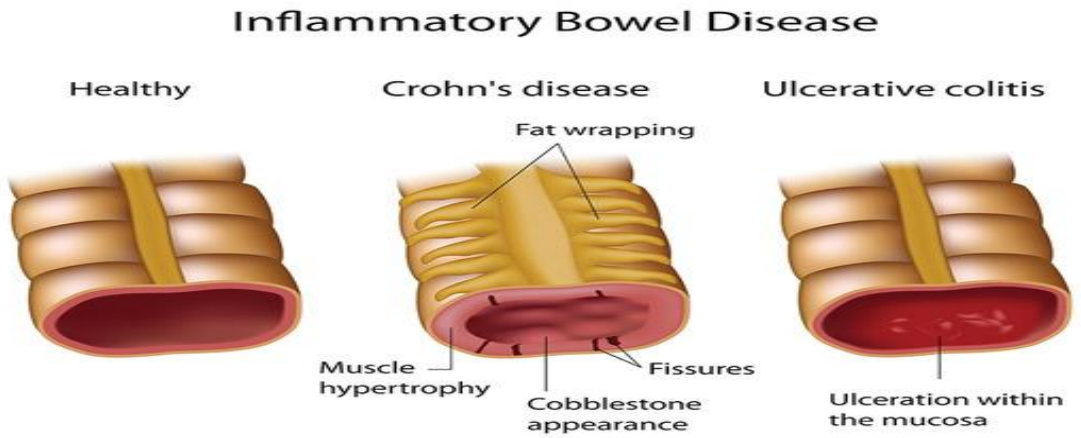
Irritable bowel disease

تهيجي

Chronic inflammatory bowel disease (IBD) includes:
(ulcerative colitis & Crohn's disease).

Drugs used in treatment of IBD include:

- **Corticosteroids:** prednisolone.
- **Immunosuppressive agents:** azathioprine , 6mercaptopurine.
- **Aminosalicylates.**



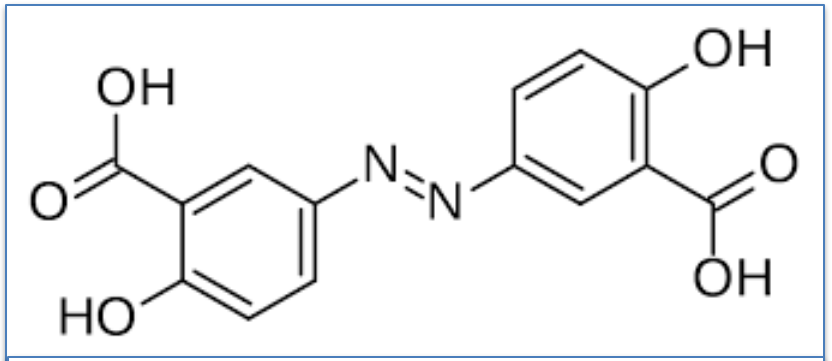
Aminosalicylates

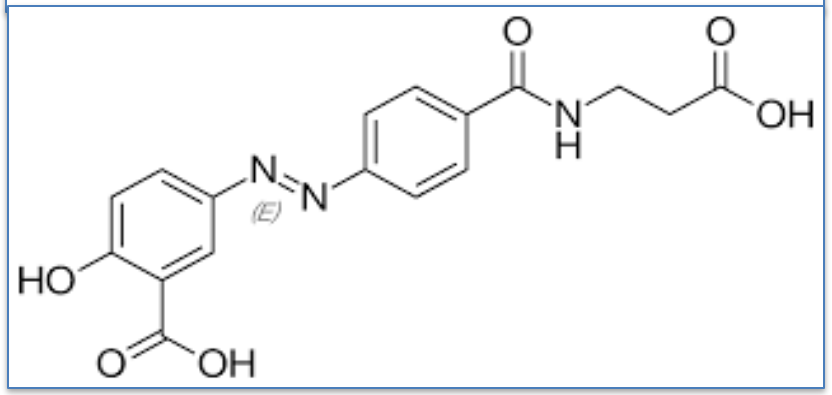
Up to 80% of unformulated, aqueous 5-ASA is absorbed from the small intestine & does not reach the distal small bowel or colon in appreciable quantities.

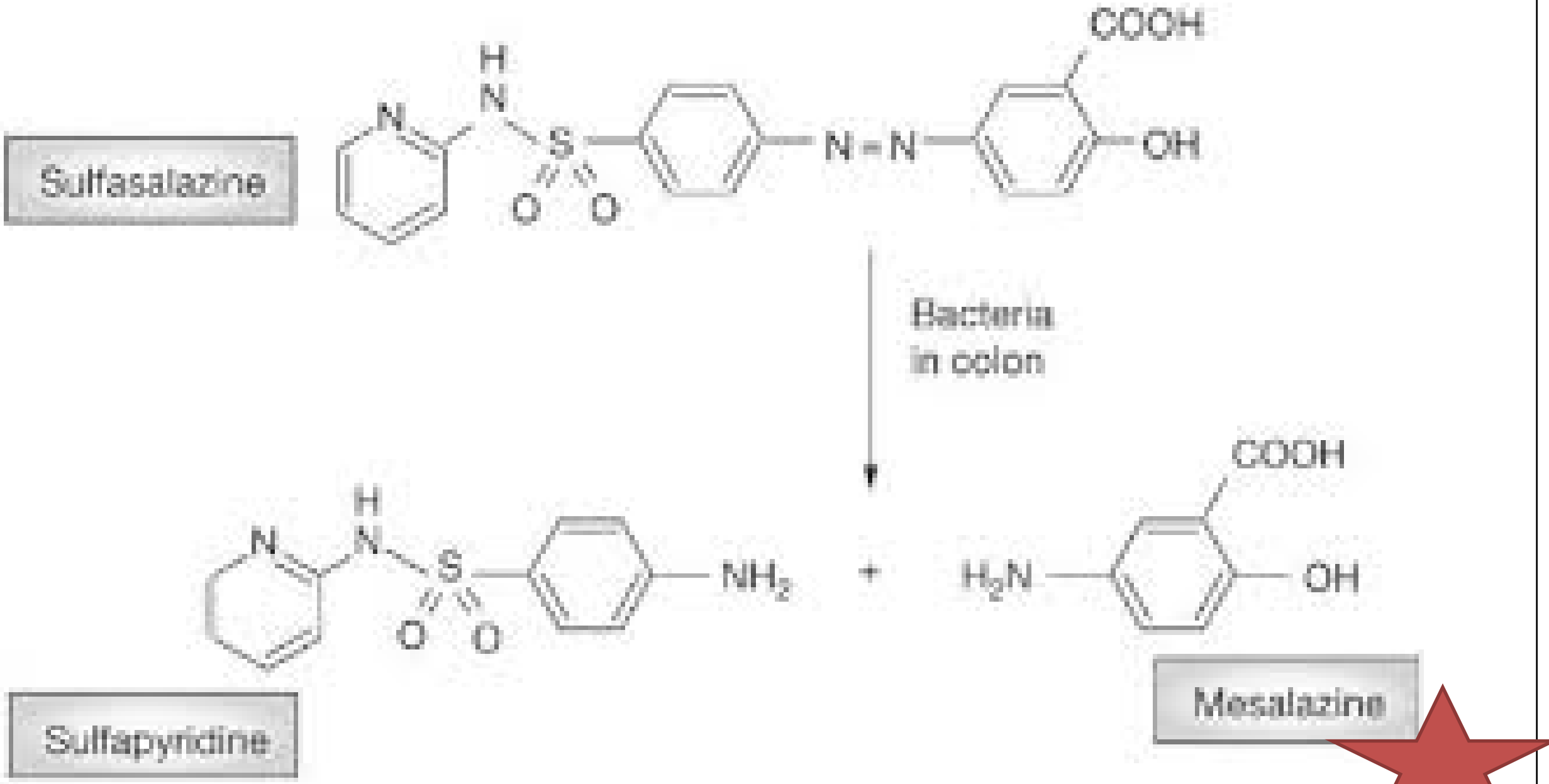
Azo compounds:

- 5-ASA bound by an azo (N=N) bond to an inert compound or to another 5- ASA molecule.
- Azo markedly reduces absorption of the parent drug from the small intestine.
- In terminal ileum & colon, bacteria cleave the azo bond by azo reductase, releasing the active 5-ASA.

- **Sulfasalazine:** (5-ASA "Active moiety" +Sulfapyridine "side effects").
- **Olsalazine:** (two molecules of 5-ASA).
- **Balsalazide:** (5-ASA + 4-aminobenzol-β- alanine).






Sulfasalazine
COOH
OH
N
H
N
S
O
O
N=N
Bacteria
in colon
Sulfapyridine
NH2
+
H2N
COOH
OH
Mesalazine

Mesalamine compounds

Package of 5-ASA itself in various ways to deliver it to different segments of the small or large bowel.

Pentasa: contains timed-release microgranules that release 5- ASA throughout the small intestine.

Asacol: has 5-ASA coated in pH-sensitive resin that dissolves at pH 7 (the pH of the distal ileum & proximal colon).

Rowasa (enema formulations) &

Canasa (suppositories): To deliver high concentration of 5-ASA to the rectum & sigmoid colon.

Mechanism of action:

- ✓ 5-ASA inhibits inflammatory mediators derived from both the cyclooxygenase &lipooxygenase pathways.
- ✓ Interferes with the production of inflammatory cytokines.
- ✓ Inhibits the activity of nuclear factor-k_B (NF-k_B), an important transcription factor for pro-inflammatory cytokines.
- ✓ Inhibits cellular functions of natural killer cells, mucosal lymphocytes, and macrophages.
- ✓ It may scavenger reactive oxygen metabolites.

Pharmacokinetics:

Mesalamine:

1. 20-30% of 5-ASA is absorbed.
2. 5-ASA undergoes N-acetylation in the liver and gut epithelium.
3. Metabolite is excreted by the kidneys.

Sulfasalazine

- 10% is absorbed.
- After azoreductase, >85% of sulfapyridine is absorbed.
- Sulfapyridine undergoes hepatic metabolism.
- Metabolite is excreted by the kidney.

Balsalazide:

- <1% is absorbed.
- After azoreductase, small amount of systemic absorption occurs.

Therapeutic uses:

1. First-line agents for treatment of mild to moderate active ulcerative colitis
2. Crohn's disease involving the small bowel ***mesalamine*** compounds, which release 5-ASA in the small intestine, have advantage over azo compounds

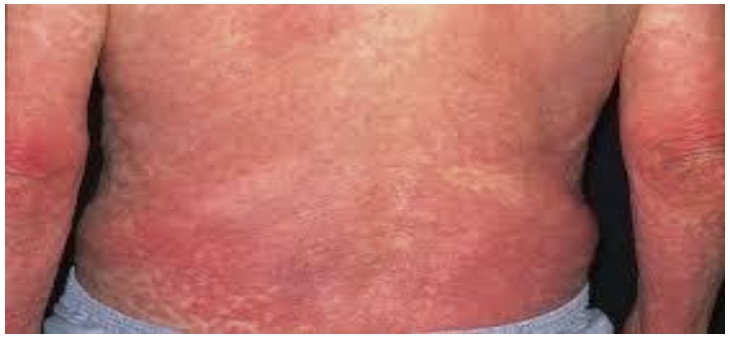
3. Ulcerative colitis or Crohn’s colitis that extends to the proximal colon, both azo & mesalamine compounds are useful.

3. Ulcerative colitis or Crohn’s disease confined to the rectum or distal colon, suppositories or enema are useful.

Adverse effects:

Sulfasalazine (→ sulfapyridine) has high incidence of side effects , >40% cannot tolerate therapeutic doses:

1. GIT upset, headache, arthralgia, bone marrow suppression & malaise
2. Hypersensitivity (fever, exfoliative dermatitis, pancreatitis, pneumonitis, hemolytic anemia, pericarditis, or hepatitis).
3. Reversible oligospermia
4. Impairs folate absorption



Other aminosalicylate formulations

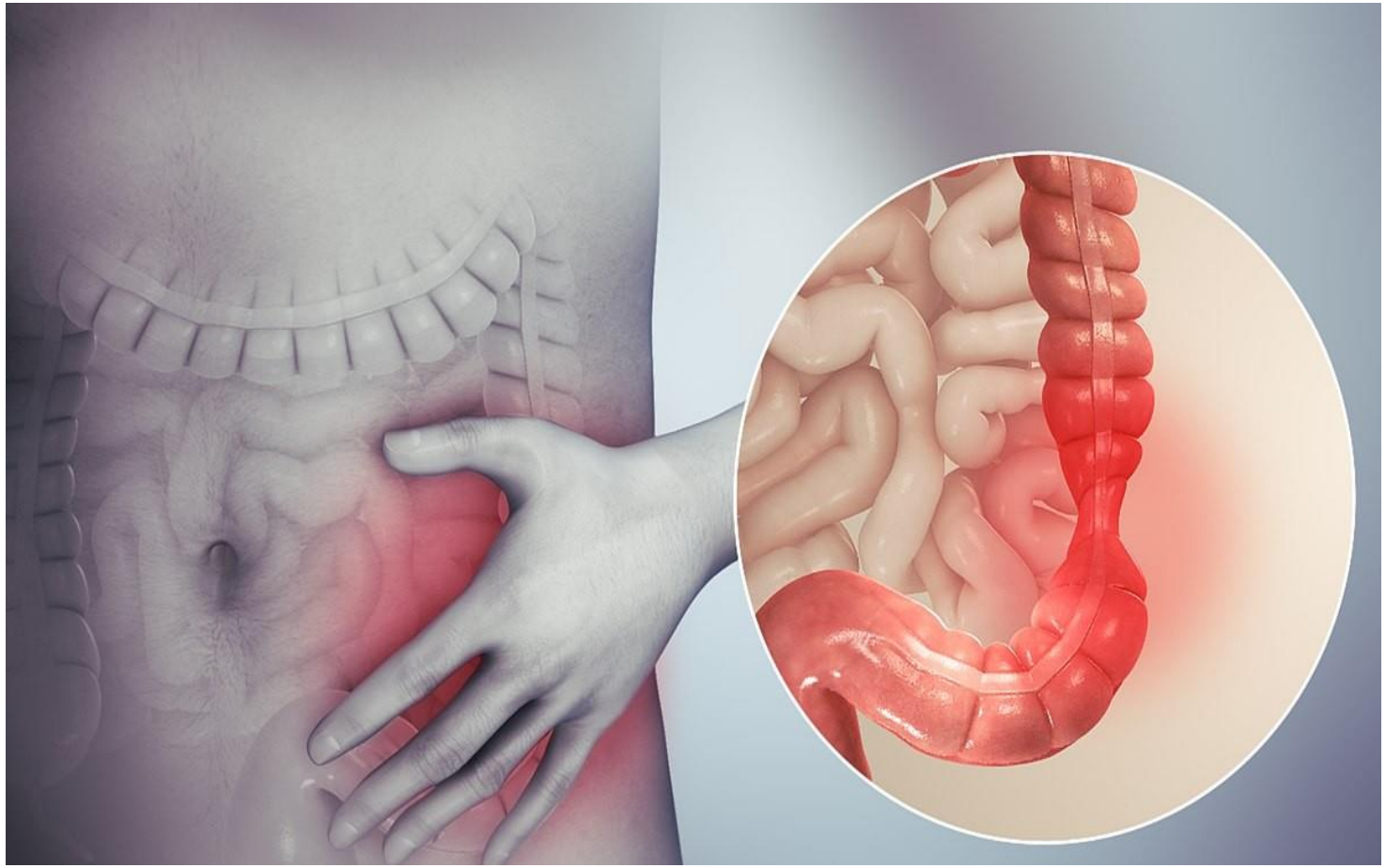
Are well tolerated:

Olsalazine may cause secretory diarrhea (10%).

Hypersensitivity (rare).

Interstitial nephritis (rare, high doses of ***mesalamine***).

Irritable bowel syndrome: IBS



Irritable bowel syndrome:

Idiopathic chronic, relapsing disorder, characterized

by:

Abdominal discomfort (pain, bloating, distention, or cramps).

Alteration of bowel habits (diarrhea, constipation, or both).

Goal of therapy: Relieving abdominal pain and discomfort and improving bowel function.

A-Predominant diarrhea (Diarrhea-predominant IBS):

- Anti-diarrheal agents, **loperamide.**
- **Alosetron** (5-HT_3 antagonist): for women with severe diarrhea- predominant IBS.

Alosetron:

- 5-HT_3 antagonist.
- Binds with higher affinity and dissociates more slowly from 5-HT_3 R than other 5-HT_3 antagonists (long duration).
- **Uses:** Women with sever irritable bowel syndrome with diarrhea.
- **Dose** : 1mg once or twice daily.

Side effects of Alosetron:

Rare but serious G.I.T. toxicity may occur:

- Constipation (↑30%).
- Episodes of ischemic colitis (3 per1000).
- Restricted to women with severe diarrhea-predominant IBS.

B-Predominant constipation (Constipation-predominant IBS):

- Fiber supplements (however ↑gas production may exacerbate bloating and abdominal discomfort).
- Osmotic laxatives, ***milk of magnesia*.**
- ***Tegaserod*** (partial 5-HT_4 agonist).

For short-term treatment of women with constipation- predominant IBS.

C- Chronic abdominal pain:

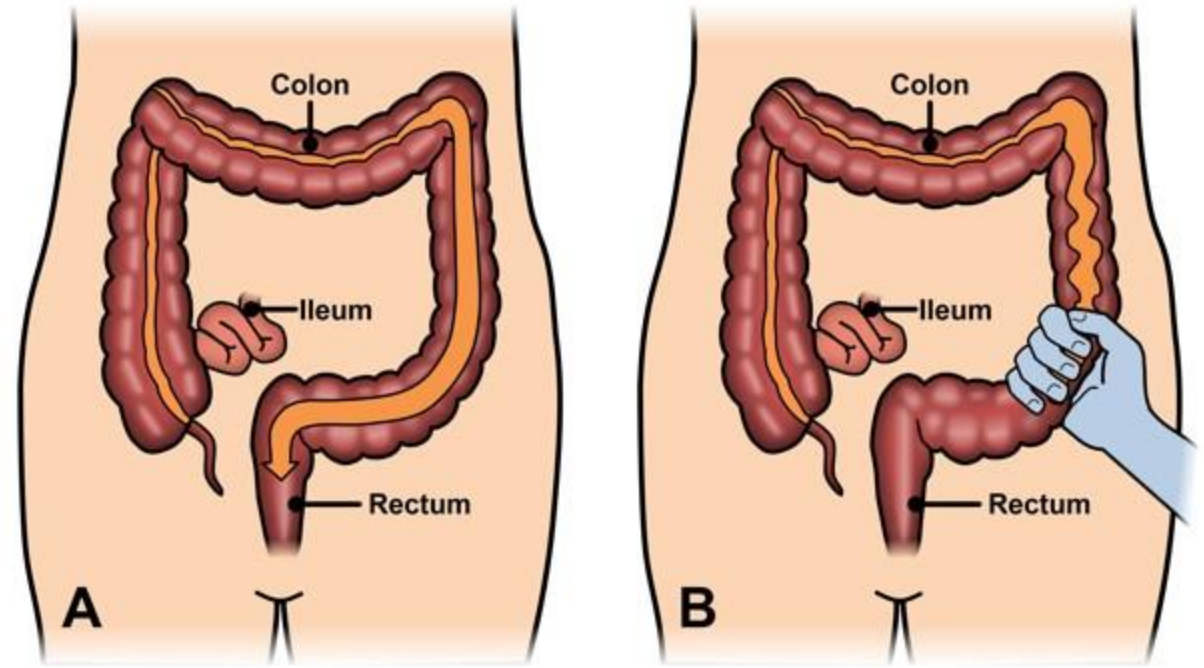
- Low doses of Tricyclic antidepressants **TCAs** (amitriptyline or desipramine, 10-15mg/d).

  At these doses, these agents have no effect on mood but may alter central processing of visceral afferent information.

- Anti-cholinergic effects → reduce stool frequency & liquidity of stool.
- Alter receptors for enteric neurotransmitters such as serotonin, affecting visceral afferent sensation.

4)Spasmolytics (Antispasmodics):

- **Parasympathetic depressants**
- **Direct spasmolytics**



- **Parasympathetic depressants:**
  - Atropine.
  - Atropine substitutes:

Propantheline.

Hyoscine-N-butyl bromide (Buscopan).

Metixene (Spasmocanulase).

Dicyclomin&hyoscyamine (inhibit M receptors in enteric plexus & on smooth muscle).

➢ Direct spasmolytics:

- Volatiles oils.
- Khellin.
- Papaverine.
- Aminophylline.
- Nitrites.
- Mebeverine (Colspasmin).


THANK YOU