بسم الله الرحمن الرحيم

داروها
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Antiulcer medications

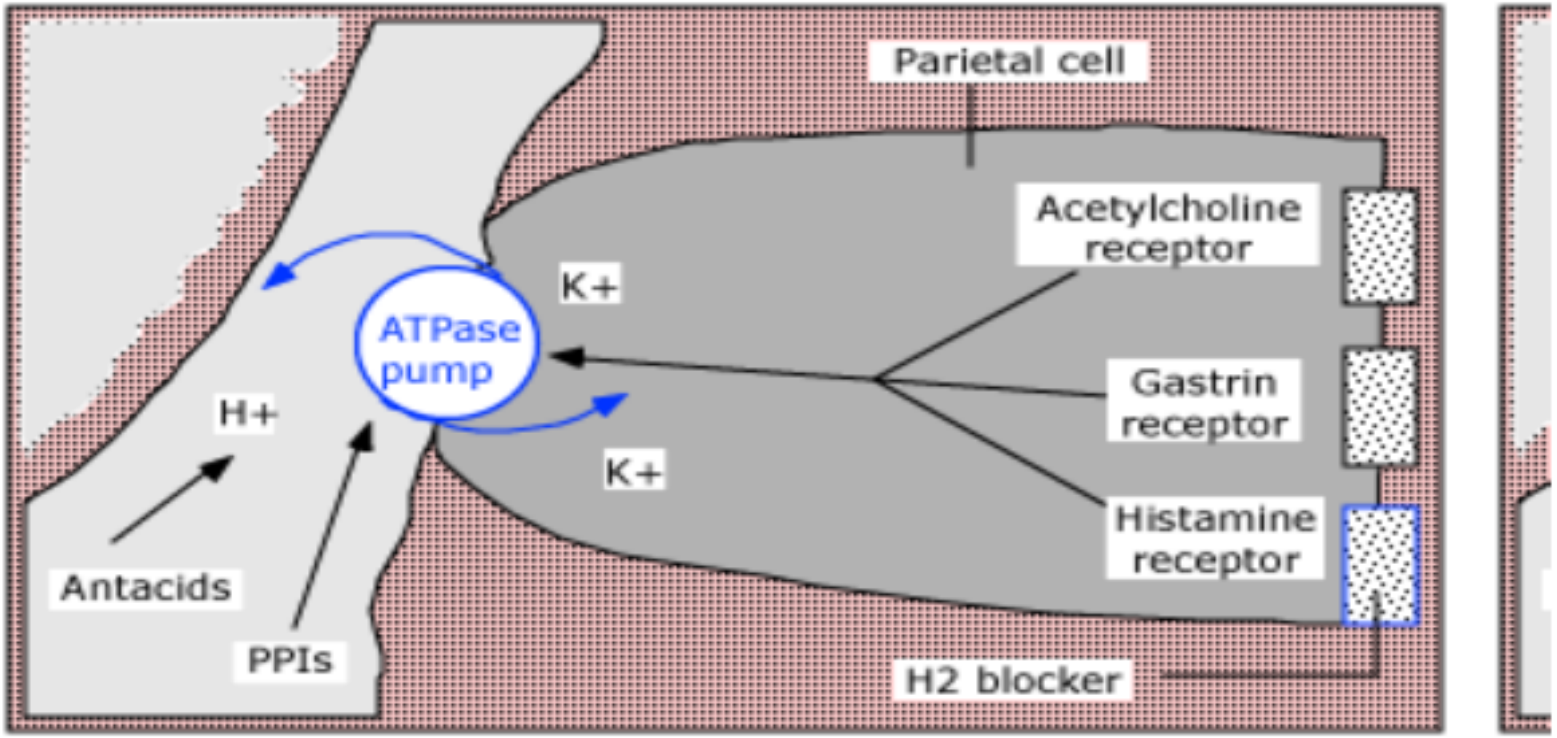
The mainstay of ulcer treatment, apart from curing H. pylori and withdrawing NSAIDs, is the use of antisecretory drugs (H2B and PPI).

- H2RAs inhibit acid
- The proton pump inhibitors
- antacids and sucralfate
- Colloidal bismuth preparations
- Misoprostol
- Potassium-Competitive Acid Inhibitors (PCABs)

H2 RECEPTOR ANTAGONISTS

- H2 receptor antagonists (H2RAs) inhibit acid secretion by blocking histamine H2 receptors on the parietal cell .
  - Cimetidine
  - Famotidine
  - Nizatidine

Actions of antiulcer medications



H2 receptor antagonists (H2RAs) inhibit acid secretion by blocking histamine H2 receptors on the parietal cell. The proton pump inhibitors (PPIs, eg, omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole) effectively block acid secretion by irreversibly binding to and inhibiting the hydrogen- potassium ATPase pump that resides on the luminal surface of the parietal cell membrane. The mechanism involved in antacid healing of peptic ulcers may include neutralizing gastric acid, but probably also includes a number of other factors.

H2 RECEPTOR ANTAGONISTS

- **Less acid suppression** than proton pump inhibitors.

H2 RECEPTOR ANTAGONISTS

- **Absorption and distribution**:
- H2RAs are **well absorbed** after oral dosing
- peak serum concentrations occur within **one to three hours**.
- Absorption is reduced 10 to 20 percent by concomitant antacid administration, **but not by food**.

H2 RECEPTOR ANTAGONISTS

- **Hepatic and renal metabolism**

All drugs are eliminated by a **combination of hepatic and renal metabolism**

The bioavailability of cimetidine , famotidine is reduced 30 to 60 percent by first pass hepatic metabolism

By contrast, nizatidine undergoes very little hepatic metabolism; its bioavailability following oral dosing is 100 percent.

- Similarly, the **bioavailability with intravenous** dosing of all H2RAs approaches **100 percent**.

H2 RECEPTOR ANTAGONISTS

- **Dose adjustments for hepatic failure** The half-life of cimetidine is prolonged with liver failure, but **dose reduction is probably only necessary if renal failure accompanies severe hepatic disease.**

- Cimetidine compete with creatinine for renal tubular secretion, causing a **slight elevation in serum creatinine**.

- Nizatidine and famotidine have the greatest dependence upon renal clearance; their half-life is more prolonged with renal failure.

H2 RECEPTOR ANTAGONISTS

- **Dose adjustments for renal failure** are advised . The dose of all the H2RAs is generally **reduced by 50 percent** in patients with moderate to severe renal failure .
- The quantities of the H2 antagonists removed by peritoneal and hemodialysis are small; replacement doses are not necessary.
- Clearance is decreased in neonates and also in the elderly, suggesting that the **dose should be reduced in individuals over age 75 years**, particularly cimetidine

H2 RECEPTOR ANTAGONISTS

Adverse effects

- Contamination with nitrosodimethylamine (NDMA), a probable human carcinogen, has been found in ranitidine.
- This has led to its withdrawal by the FDA.
- NDMA impurities were found to have been introduced during the manufacturing processes and as the result of product degradation during storage. FDA's testing has not found NDMA in famotidine and cimetidine.

H2 RECEPTOR ANTAGONISTS

- **Gynecomastia and impotence :**

Occur with cimetidine in a dose- and time-dependent fashion and resolve when discontinued. This effect is relatively specific for cimetidine and rarely occurs if treatment is limited to standard doses for eight weeks or less.

H2 RECEPTOR ANTAGONISTS

- **Immune and hematopoietic effects** — H2RAs have been implicated in **idiosyncratic cases of myelosuppression**, thrombocytopenia, neutropenia, anemia, and pancytopenia . **Hemolytic anemia** also has been reported. Concern persists that H2RAs may occasionally **enhance transplant rejection and autoimmune or allergic diseases**.

- **Other uncommon reactions** may be mediated by immune mechanisms. These include polymyositis and interstitial nephritis with cimetidine
- **Absorption of vitamin B12** depends upon gastric acid. As a result, it is not unexpected that long-term H2RA and proton pump inhibitor use has been associated with serum B12 deficiency . The **possibility of B12 deficiency** should be kept in mind in any patient on chronic acid suppression.

H2 RECEPTOR ANTAGONISTS

- **CNS symptoms** — H2RAs have been suspected to cause confusion, restlessness, somnolence, agitation, headaches, and dizziness and, with prolonged therapy, hallucinations, focal twitching, seizures, unresponsiveness, and apnea . Although these symptoms are generally **reversible upon discontinuation** of the drug, cases with more persistent CNS symptoms have been reported .

- **Mental status changes** appear to be most **common in elderly** patients in the intensive care unit who have comorbid renal or hepatic dysfunction . Cimetidine has been implicated as the most frequent cause of these CNS symptoms, but similar side effects have also been described with famotidine . CNS toxicity is rare during outpatient therapy.

H2 RECEPTOR ANTAGONISTS

- **Hepatic dysfunction**
- **Transient small increases in serum aminotransferases** can occur with H2RAs, especially with high intravenous doses; these changes resolve during continued therapy.
- None of the H2RAs is directly hepatotoxic; however, rare idiosyncratic or apparent immune hypersensitivity hepatitis, characterized by rash, fever, and/or eosinophilia, can occur
- **Serial monitoring of liver chemistries is not justified** since these events are uncommon and the causality is uncertain. Nevertheless, checking hepatic enzymes approximately five days into high dose intravenous therapy is probably warranted

H2 RECEPTOR ANTAGONISTS

- **Cardiac effects**
- H2 receptors are present in the heart. **Sinus bradycardia, hypotension, atrioventricular block, prolongation of the QT interval**, and sinus and cardiac arrest have occurred with the rapid infusion of an H2RA .
- Possible risk factors for cardiac events include:
  - rapid intravenous infusion
  - high dose
  - conditions that would delay drug clearance (eg, renal or hepatic dysfunction)
  - underlying cardiac disease .

H2 RECEPTOR ANTAGONISTS

- **Renal effects**

- **Mild increases in serum creatinine** have been observed with cimetidine .

- However, clinically significant renal disease appears to be limited to **immune-mediated interstitial nephritis .**Onset ranged from 1 day to 11 months after initiation of therapy.

H2 RECEPTOR ANTAGONISTS

- **Drug interactions** have been described with some of the H2 receptor antagonists, particularly cimetidine .

- **Teratogenicity** — Although data remain limited, there is **no evidence of major teratogenic effects** with H2RAs

SUCRALFATE

- SUCRALFATE: is a sulfated polysaccharide, sucrose octasulfate, complexed with aluminum hydroxide
- It prevents acute chemically-induced mucosal damage and heals chronic ulcers **without altering gastric acid or pepsin secretion** or significantly buffering acid
- Mechanism:
  - stimulates angiogenesis
  - binds to the injured tissue
  - reduce oxidant damage to epithelial cells
  - The binding of this agent to the ulcer base is enhanced at a **pH below 3.5**, leading to the recommendation that the drug be administered **30 to 60 minutes before meals**.

SUCRALFATE

- **Adverse effects**
- Sucralfate has minimal adverse effects other than possible aluminum toxicity
- It can **bind other drugs if taken simultaneously**, and lead to hypophosphatemia..
- **Aluminum toxicity** — Significant absorption of aluminum occurs with several antacid formulations and sucralfate .

Aluminum is readily excreted by normal kidneys. By comparison, **significant aluminum retention occurs in patients with renal failure**, and may result in **neurotoxicity and anemia** following treatment with either antacids or sucralfate

- Simultaneous **consumption of citrate enhances absorption** of aluminum 50-fold in patients with normal renal function.
- To avoid enhanced aluminum absorption, especially in the setting of renal failure, it is advisable to avoid combining antacids and probably sucralfate with foods or other agents that contain citrate.

BISMUTH

- Currently, colloidal bismuth subcitrate (**CBS**) and bismuth subsalicylate (BSS) are used in treatment of H. pylori infection.
- The most dramatic action of these bismuth salts is the suppression of H. pylori
- Bismuth is not effective in H. pylori-negative ulcers, suggesting the healing efficacy of bismuth primarily reflects suppression of the infection.

- Other actions that may promote ulcer healing, including the following:
  - CBS may increase mucosal prostaglandin production, and mucus and bicarbonate secretion
  - Bismuth does not inhibit or neutralize gastric acid.
- In the colon, bismuth salts react with hydrogen sulfide to form bismuth sulfide, which **blackens the stools**

- **Adverse effects** — The primary concern with bismuth compounds is bismuth intoxication
- **Coadministration of H2 receptor antagonists increases bismuth** absorption from CBS.

Bismuth should be avoided in patients with renal failure

ANTACIDS

- Antacids usually contain a combination of magnesium trisilicate, aluminum hydroxide, or calcium carbonate.
- Given the effectiveness of PPIs, antacids are not used in the treatment of peptic ulcer disease. The role of antacids is limited to the treatment of heartburn associated with mild intermittent gastroesophageal reflux disease.

ANTACIDS

Antacids can neutralize gastric acid

Acid-independent actions of antacids :

- Aluminum hydroxide binds growth factors and enhances their binding to experimental ulcers, possibly serving to deliver growth factors to injured mucosa.
- Antacids promote angiogenesis in injured mucosa .
- Antacids bind bile acids and also inhibit peptic activity .
- Heavy metals are well known to suppress, but generally not eradicate, H. pylori.

ANTACIDS

Adverse effects

- Magnesium containing antacids cause **diarrhea** and **hypermagnesemia**; the latter only becomes important in patients with renal insufficiency.

- Antacids may also contain considerable **sodium and volume overload** can occur in susceptible patients.

- Ingestion of large amounts of calcium and absorbable alkali, particularly calcium carbonate , can lead to hypercalcemia, alkalosis, and renal impairment, a constellation known as the **milk-alkali syndrome**

- There are also potential adverse effects related to **excessive aluminum absorption**

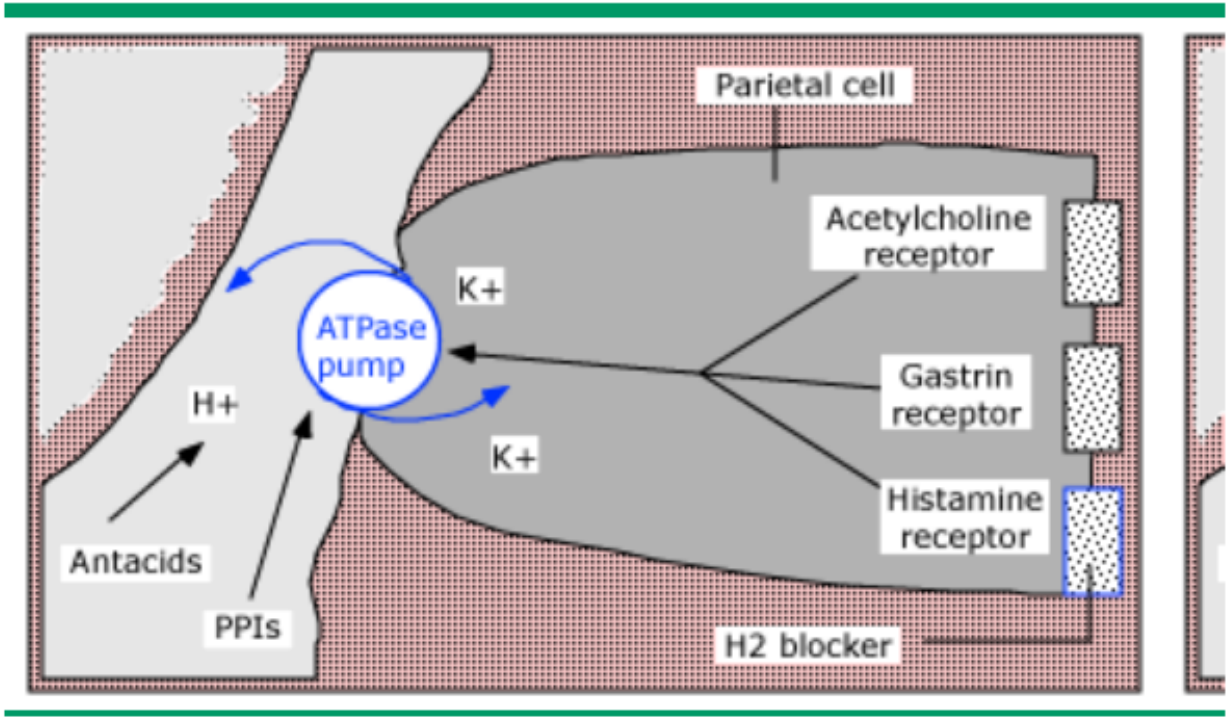
PROTON PUMP INHIBITORS

- The proton pump inhibitors (PPIs) omeprazole , lansoprazole , dexlansoprazole , rabeprazole , pantoprazole , and esomeprazole effectively block acid secretion by **irreversibly binding** to and inhibiting the hydrogen-potassium ATPase pump that resides on the luminal surface of the parietal cell membrane

PROTON PUMP INHIBITORS

- Faster control of peptic ulcer disease symptoms and higher ulcer healing rates.
- More effective in preventing and healing NSAID-induced ulcers.
- PPIs are a component of H. pylori regimens and are used in the treatment of gastrinoma.
- Unlike H2RAs, tolerance does not occur for PPIs.

Actions of antiulcer medications



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PROTON PUMP INHIBITORS

- Acidic compartments within the stimulated parietal cell are essential for activation of a PPI .
- Thus, PPIs work poorly in those receiving simultaneous dosing with other antisecretory agents (H2 receptor antagonists, anticholinergic agents, misoprostol , or somatostatin).

- PPIs are most effective when taken **30 to 60 minutes before meals** so that they are in the bloodstream in the few post-prandial hours when parietal cells are stimulated.

PROTON PUMP INHIBITORS

- H-K-ATPase comprises the final pathway by which HCl is secreted into the gastric lumen,Proton pump inhibitors (PPIs) inhibit this enzyme.
- The PPIs are the **most potent inhibitors of gastric acid** secretion available.

- PPIs are effective for **treatment of all acid-related disorders** including:
  - peptic ulcer disease
  - gastroesophageal reflux disease
  - Zollinger-Ellison syndrome.
  - preventing NSAID associated gastroduodenal mucosal injury
  - in eradicating regime for *H. pylori* infection

PROTON PUMP INHIBITORS

- A number of studies have compared the various proton pump inhibitors to one another.

- While some differences have been reported, the **magnitude of differences has been small** and of uncertain clinical importance.

Clinical Review & Education

JAMA | Review

Gastroesophageal Reflux Disease
A Review

John Maret-Ouda, MD, PhD; Sheraz R. Markar, MD, PhD; Jesper Lagergren, MD, PhD

Table 3. Potency Between Different Proton Pump Inhibitors According to Omeprazole Equivalents

Drug at lowest available dosage, mg	Omeprazole equivalent, mg
Pantoprazole, 20	4.5
Lansoprazole, 15	13.5
Omeprazole, 20	20
Esomeprazole, 20	32
Rabeprazole, 20	36

PROTON PUMP INHIBITORS

Adversa effects:

- The main concerns regarding the long-term safety of the PPIs include the effects of **prolonged hypochlorhydria** and **hypergastrinemia**, and the **possible association of PPIs with gastric atrophy**.

- Due to a possible **increased risk of fractures** it is recommended that healthcare professionals who prescribe proton pump inhibitors should consider whether a **lower dose or shorter duration** of therapy would adequately treat the patient's condition.

PROTON PUMP INHIBITORS

- **Vitamin B12 malabsorption**: Long-term therapy with omeprazole has been associated with vitamin B12 malabsorption . Thus, it is reasonable to **assess vitamin B12 levels periodically (eg, annually)** in patients who are on long-term treatment with PPIs.

- **Iron malabsorption** — Gastric acid plays a role in the absorption of nonheme iron, and the use of PPIs has been associated with decreased iron absorption . However, in most cases the decreased absorption **does not appear to be of clinical significance**.

- **Hypergastrinemia** — An initial concern with omeprazole was the induction of hypergastrinemia and gastric carcinoid tumors in rats. While patients treated with omeprazole for up to 11 years have shown no dysplasia or neoplastic changes have been observed .

PROTON PUMP INHIBITORS

- **Atrophic gastritis** — Patients receiving maintenance therapy have a propensity to develop chronic atrophic gastritis(**specially in H.pylori positive patients**). Although the risk of atrophic gastritis in this context remains unclear.

- We do **not routinely test for *H. pylori*** in patients who require long-term therapy with a proton pump inhibitor since the risk of atrophic gastritis is small and, in the uncommon patient who develops it, the clinical consequences are uncertain.

PROTON PUMP INHIBITORS

- **Increase the risk of *Clostridium difficile*** (C. *difficile*)-associated diarrhea.
- **Hypomagnesemia** due to reduced intestinal absorption has been described with PPI use.
  - It is recommended that serum **magnesium levels be obtained prior to starting a PPI** when patients are expected to be on the medication for long periods of time, or in patients who take PPIs in conjunction with other medications associated with hypomagnesemia (eg, digoxin or diuretics).
  - The FDA also suggests that providers consider obtaining magnesium levels periodically in such patients while they are on a PPI

- **Drug interactions**

- Clinically important drug interactions with PPIs are rare. However, some data suggest decreased activation of clopidogrel when used in conjunction with omeprazole on the basis of a shared hepatic metabolic pathway.

- Although the relevance of these in vitro data remains highly controversial, the **FDA advised against co-prescribing these medications**.

PROTON PUMP INHIBITORS

- In patients treated with PPIs for a period of **six months** or longer, a **dose taper** should be considered prior to discontinuation.
- Patients with GERD or dyspepsia should also be considered for a **taper after being asymptomatic for a minimum of three months**.

- For patients on a moderate- to high-dose PPI (eg, omeprazole 40 mg daily or twice daily), we **reduce the dose by 50 percent every week** until the patient is on the lowest dose of the medication. Once on the lowest dose for one week, the patient is instructed to stop the medication.

PROTON PUMP INHIBITORS

- In one large cohort, exposure to PPIs during the first trimester of pregnancy was **not associated with a significantly increased risk of major birth defects**.

POTASSIUM-COMPETITIVE ACID INHIBITORS (PCABs)

- Competing for potassium on the luminal side of the parietal cell, and cause rapid and reversible inhibition of pumps and therefore acid secretion.
- They have a rapid onset of action and achieve a full effect with the first dose. The effect is also seen with

POTASSIUM-COMPETITIVE ACID INHIBITORS (PCABs)

- In randomized controlled trials, the efficacy with regard to ulcer healing and prevention of NSAID-induced ulcers has been similar to proton pump inhibitor therapy with a comparable safety profile

PCABs

- The PCAB Vonoprazan has been approved for the prevention of NSAID-induced ulcers and treatment of peptic ulcer disease in Japan.
- Another PCAB, Revaprazan, has been approved in Korea.
- PCABs are not widely available outside of Asia, and data on safety and comparative efficacy with antisecretory agents are limited.

IBS treatment

Antispasmodic agents

- Antispasmodic agents are the **most frequently used** pharmacologic agents in the treatment of IBS.
- Certain antispasmodic drugs (hyoscine) may provide short-term relief but long-term efficacy has not been demonstrated
- **Peppermint oil** may also act as a smooth muscle relaxant

Antispasmodic agents

- The antispasmodic agents include:
  - those that directly affect intestinal smooth muscle relaxation (eg, mebeverine and pinaverine)
  - those that act via their anticholinergic or antimuscarinic properties (eg, dicyclomine and hyoscyamine) .

- The selective inhibition of gastrointestinal smooth muscle reduces stimulated colonic motor activity and may be beneficial in patients with **postprandial abdominal pain**, **gas**, **bloating**, and **fecal urgency** .

Antidepressants

- Antidepressants have **analgesic properties** independent of their mood improving effects and may therefore be beneficial in patients with neuropathic pain

- **TCAs**, via their **anticholinergic properties**, also slow intestinal transit time , which may provide benefit in diarrhea-predominant IBS

- Improvement in neuropathic pain with TCAs occurs at lower doses than required for treatment of depression.

- As a result, if an antidepressant is chosen for the treatment of IBS, **low doses** should be administered initially and titrated to pain control or tolerance.

- Because of the delayed onset of action, **three to four weeks of therapy** should be attempted before considering treatment insufficient and increasing the dose.

- Examples of antidepressant medications used in patients with IBS include amitriptyline , imipramine , nortriptyline , and desipramine .

- TCAs should be used cautiously in patients with constipation.

- Amitriptyline, nortriptyline, and imipramine can be started at a dose of 10 to 25 mg at bedtime and increased every three to four weeks based upon clinical response and tolerance.

- If the patient is intolerant of one TCA, another may be tried.

- Paroxetine (10 to 20 mg daily), fluoxetine (20 to 40 mg daily), sertraline (50 to 100 mg daily), or other antidepressant medications can be considered if depression is a cofactor .

- There is **less published experience with other antidepressants** such as SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs), although they are used clinically.

Antidiarrheal agents

- Overall, the trials suggested that **loperamide** was more effective than placebo for treatment of diarrhea, but not for treatment of global IBS symptoms or abdominal pain.
- Administration on an **as needed basis** is preferred to a regular scheduled dosing in patients with diarrhea.
- Patients who consistently develop diarrhea after meals may benefit from **taking a dose before meals**.

Benzodiazepines

- Anxiolytic agents are of **limited usefulness in IBS** because of the risk of drug interactions, habituation, and rebound withdrawal.

- Furthermore, benzodiazepines may **lower pain thresholds** by stimulating gamma aminobutyric acid (GABA) receptors, thereby decreasing brain serotonin.

- They may, however, be useful for **short-term (less than two weeks')** reduction of acute situational anxiety that may be contributing to symptoms

5-hydroxytryptamine (serotonin) 3 receptor antagonists

- 5-hydroxytryptamine-3 receptor antagonists (such as alosetron , cilansetron, ondansetron and granisetron) modulate visceral afferent activity from the gastrointestinal tract and may improve abdominal pain

- A meta-analysis that included 14 randomized controlled trials in IBS (involving alosetron or cilansetron,) found a benefit in **global improvement in IBS and relief of abdominal pain** and discomfort

Antibiotics

- Some patients with IBS have shown improvement when treated with antibiotics . Most of the improvement has been in symptoms of **bloating**, **abdominal pain**, or **altered bowel habits**.

- Rifaximin , a nonabsorbable antibiotic, led to symptomatic improvement in global IBS symptoms and bloating

- The mechanisms leading to the benefit are unclear but may be due to **suppression of gas producing bacteria** in the colon

- However, in patients with moderate to severe IBS (particularly those with bloating) who have failed to respond to all other therapies, including a low carbohydrate diet and elimination of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs), it is reasonable to **consider two-week trial of rifaximin**

- The mechanisms leading to the benefit are unclear but may be due to **suppression of gas producing bacteria** in the colon.

Constipation

- As initial management in the treatment of idiopathic constipation, we suggest dietary fiber and bulk forming laxatives such as psyllium or methylcellulose , together with adequate fluids .

- For patients who do not tolerate bulk forming laxatives or respond poorly to fiber, we suggest an osmotic laxative next if tolerated .

- Other options include stool softeners, stimulant laxatives (bisacodyl , senna , and sodium picosulfate), and secretory agents (lubiprostone , linaclotide).

- **Bulk forming laxatives** :

- Bulk forming laxatives include psyllium seed

- They are natural or synthetic polysaccharides or cellulose derivatives that primarily exert their laxative effect by **absorbing water and increasing fecal mass**.

- These laxatives are effective in increasing the frequency and softening the consistency of stool with a **minimum of adverse effects**.

Osmotic agents :

1-Polyethylene glycol (PEG), poorly absorbed or nonabsorbable sugars, increase stool frequency.

- PEG :A reasonable approach is to **start with 17 g** of powder dissolved in 8 oz(236cc) of water once daily and titrate up or down (to a maximum of 34 g daily) to effect.
- If patients do not respond, one can decrease PEG to 17 g daily and **add a stimulant laxative** every other to every third day as needed.

- **2-Synthetic disaccharide – Lactulose** is a synthetic disaccharide. It is not metabolized by intestinal enzymes; thus, water and electrolytes remain within the intestinal lumen due to the osmotic effect of the undigested sugar.
- Lactulose requires some time (24 to 48 hours) to achieve its effect. Sorbitol is an equally effective and a less expensive alternative.
- Both lactulose and sorbitol may cause abdominal bloating and flatulence.
- PEG, however, is superior to lactulose

- **3– Saline laxatives** such as milk of magnesia and magnesium citrate are poorly absorbed agents that act as hyperosmolar solutions. Hypermagnesemia, seen primarily in patients with renal failure, is the major complication.

Stimulant laxatives

- Stimulant laxatives such as bisacodyl , senna primarily exert their effects via alteration of electrolyte transport by the intestinal mucosa.
- They also **increase intestinal motor activity**.
- Continuous daily ingestion of these agents may be associated with **hypokalemia**, **protein-losing enteropathy**, and **salt overload**. Thus, these drugs should be used with caution if taken chronically.