Gastrointestinal Pharmacology

- Antacids
  - Peptic ulcer therapy
- Antiemetics
- Laxatives
- Antidiarrheal drugs
Acid production:
• 2.5 L per day
• Isotonic HCl solution
• pH < 1
• Produced by parietal cells

Mucus production:
• Produced by mucus-secreting cells
• Also produce bicarbonate, which becomes trapped in the mucus layer => pH gradient across the mucus layer (can become destroyed by alcohol)
Antacids:
Weak bases:

- Aluminum hydroxide
  - Cause constipation
- Magnesium hydroxide
  - Cause diarrhea

=> often combined

Usally taken 5-7 times per day
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Antacids:

- Histamine stimulates acid production by parietal cells
- Mast cells produce a steady basal level of histamine, which increases in response to gastrin or acetylcholine
- Parietal cells express histamine H₂ receptors =>

H₂ receptor blockers:

- Cimetidine (Tagamet®)
  - First H₂-blocker available
  - Inhibits P450 => Drug interaction
- Ranitidine (Zantac®)
  - Does not inhibit P450 => fewer side effects
- Nizatidine (Axid®)
- Famotidine (Pepcid®)
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Antacids:

Proton pump inhibitors:

- Irreversibly inhibit the $\text{H}^+/\text{K}^+$ - ATPase in gastric parietal cells
- Drugs are inactive at neutral pH, but since they are weak bases, are activated in the acidic stomach milieu => restricted activity
- Acid production ablated for 24-48 hours
  
  • Omeprazole (Prilosec®)
  • Lansoprazole (Prevacid®)
  • Esomeprazole (Nexium®)
  • Rabeprazole
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Gastroesophageal reflux disease (GERD):

- Backflow of stomach acid into the esophagus
- Esophagus is not equipped to handle stomach acid => scaring
- Usual symptom is heartburn, an uncomfortable burning sensation behind the breastbone (MI often mistaken for GERD !)
- More severe symptoms: difficulty swallowing, chest pain
- Reflux into the throat can cause sore throat
- Complications include esophageal erosions, esophageal ulcer and narrowing of the esophagus (esophageal stricture)
- In some patients, the normal esophageal lining or epithelium may be replaced with abnormal (Barrett's) epithelium. This condition (Barrett's esophagus) has been linked to cancer of the esophagus.
- Primary treatment option are proton pump inhibitors
Mucosal protective agents:

- **Misoprostol**
  - Prostaglandin E\(_1\) analog (PG stimulate mucus and bicarbonate production)
  - Used when treatment with NSAIDs inhibits endogenous PG synthesis

- **Sucralfate**
  - Complex of aluminum hydroxide and sulfated sucrose
  - Forms complex gels with mucus => mucus stabilized => diffusion of H\(^+\) impaired
  - Not absorbed => essentially free of side effects
  - Must be taken every 6 hours
Peptic Ulcer Disease

Imbalance between defenses and aggressive factors

- **Defensive factors:**
  - Prevent the stomach and duodenum from self-digestion
    - Mucus: continually secreted, protective effect
    - Bicarbonate: secreted from endothelial cells
    - Blood flow: good blood flow maintains mucosal integrity
    - Prostaglandins: stimulate secretion of bicarbonate and mucus, promote blood flow, suppress secretion of gastric acid

- **Aggressive factors:**
  - Helicobacter pylori: gram negative bacteria, can live in stomach and duodenum, may breakdown mucus layer => inflammatory response to presence of the bacteria also produces urease – forms CO$_2$ and ammonia which are toxic to mucosa
  - Gastric Acid: needs to be present for ulcer to form => activates pepsin and injures mucosa
  - Decreased blood flow: causes decrease in mucus production and bicarbonate synthesis, promote gastric acid secretion
  - NSAIDS: inhibit the production of prostaglandins
  - Smoking: nicotine stimulates gastric acid production
Peptic Ulcer Disease

(~25 mill. Americans will have an ulcer in their life)
Most common cause (> 85%): Helicobacter pylorii
(not stress or hot sauce!)

Treatment options:
• Antibiotics
• Antisecretory agents
• Mucosal protectants
• Antisecretory agents that enhance mucosal defenses
• Antacids
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Antibiotic ulcer therapy:

Combinations must be used:

• Bismuth (PeptoBismol®) – disrupts cell wall of H. pylori
• Clarithromycin – inhibits protein synthesis
• Amoxicillin – disrupts cell wall
• Tetracycllin – inhibits protein synthesis
• Metronidazole – used often due to bacterial resistance to amoxicillin and tetracycllin, or due to intolerance by the patient

Standard treatment regimen for peptic ulcer:

Omeprazole + amoxicillin + metronidazole
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**Antiemetic drugs:**

**Vomiting:**
- Infection, pregnancy, motion sickness, adverse drug effects,…
- Triggered by the “vomiting center” or “chemoreceptor trigger zone (CTZ)” in the medulla (CTZ is on the ‘blood side’ of the blood-brain barrier).

**Treatment options:**
- $H_1$ antagonists: Meclizine, promethazine, dimenhydramine…
- Muscarinic receptor antagonists: Scopolamine (motion sickness)
- Benzodiazepines: Lorazepam (during chemotherapy)
- $D_2$ antagonists: have also peripheral prokinetic effects $\Rightarrow$ increase motility of the GI tract $\Rightarrow$ increases the rate of gastric emptying. Caution in patients with Parkinson’s disease!
  - **Metoclopramide**
  - **Domperidone**
- Cannabinoids:
  - Marihuana?
  - Synthetic cannabinoids: during chemotherapy
    - **Nabilone**
    - **Dronabinol**
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Laxatives:
- Laxative – production of a soft formed stool over a period of 1 or more days
- Catharsis – prompt, fluid evacuation of the bowel, more intense

Indications for laxative use:
- Pain associated with bowel movements
- To decrease amount of strain under certain conditions
- Evacuate bowel prior to procedures or examinations
- Remove poisons
- To relieve constipation caused by pregnancy or drugs

Contraindications:
- Inflammatory bowel diseases
- Acute surgical abdomen
- Chronic use and abuse
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Laxatives:
- Stimulate peristalsis
- Soften bowel content

Classification:
- Bulk laxatives
  - Non-absorbable carbohydrates
  - Osmotically active laxatives
- Irritant laxatives = purgatives
  - Small bowel irritants
  - Large bowel irritants
- Lubricant laxatives
  - Paraffin
  - Glycerol
Laxatives:

Bulk laxatives:

- Increase in bowel content volume triggers stretch receptors in the intestinal wall
- Causes reflex contraction (peristalsis) that propels the bowel content forward

Carbohydrate-based laxatives

- Insoluble and non-absorbable
- Non-digestable; take several days for effect
- Expand upon taking up water in the bowel
- Must be taken with lots of water

  - Vegetable fibers (e.g. Psyllium, linseed)
  - Bran (husks = milling waste product)

Osmotically active laxatives

- Partially soluble, but not absorbable
- Saline-based (mostly sulfates)
- Effect in 1-3 hrs => used to purge intestine (e.g. surgery, poisoning)

  - MgSO₄ (= Epsom salt)
  - Na₂SO₄ (= Glauber’s salt)
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**Laxatives:**

**Irritant laxatives:**

Cause irritation of the enteric mucose => more water is secreted than absorbed => softer bowel content and increased peristaltic due to increase volume

**Small bowel irritants**

- Ricinoleic acid (Castor oil)
  - Active ingredient of *Ricinus communis*
  - The oil (triglyceride) is inactive
  - Ricinoleic acid released from oil through lipase activity

**Ricin:**

- Lectin from the beans of *R. communis*
- Potent toxin: inhibits protein synthesis
- Potential bioterrorism agent (LD ~100µg)

In 1978, ricin was used to assassinate Georgi Markov, a Bulgarian journalist who spoke out against the Bulgarian government. He was stabbed with the point of an umbrella while waiting at a bus stop near Waterloo Station in London. They found a perforated metallic pellet embedded in his leg that had presumably contained the ricin toxin.
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**Laxatives:**

**Irritant laxatives:**

- Large bowel irritants
- Anthraquinones

Active ingredient of *Senna sp. (Folia and fructus sennae)*, *Rhamnus frangulae* (cortex frangulae) and *Rheum sp. (rhizoma rhei)*: contain inactive glycosides => active anthraquinones released in colon take 6-10 hours to act
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**Laxatives:**

**Irritant laxatives:**

- Large bowel irritants
- Diphenolmethanes
  - Derivatives of phenolphthalein

- **Bisacodyl**
  - Oral administration: effect in 6-8 hrs
  - Rectal administration: effect in 1 hr
  - Often used to prepare for intestinal surgery

- **Sodium picosulfate**
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**Laxative abuse:**

Most common cause of constipation!

- Longer interval needed to refill colon is misinterpreted as constipation => repeated use

- Enteral loss of water and salts causes release of aldosterone => stimulates reabsorption in intestine, but increases renal excretion of $K^+$ => double loss of $K^+$ causes hypokalemia, which in turn reduces peristalsis. This is then often misinterpreted as constipation => repeated use
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Antidiarrheal drugs: treat only symptoms!
- Diarrhea is usually caused by infection (Salmonella, shigella, campylobacter, clostridium, E. coli), toxins, anxiety, drugs…
- In healthy adults mostly discomfort and inconvenience
- In children (particularly mal-nourished) a principal cause of death due to excessive loss of water and minerals.

Antimotility agents:
- Muscarinic receptor antagonists (not useful due to side effects) and opiates:
  - Morphine
  - Codeine
  - Diphenoxylate
  - All have CNS effects - NOT useful for diarrhea treatment
- Loperamide
  - Selective action on the GI tract
  - Does not produce CNS effects
  - First choice antidiarrheal opioid
  - Combined with Dimethicone (Silicon-based gas-absorbent)