56. H2 Blockers, PPIs – Moorman
57. Palliation of Constipation & Nausea/Vomiting – Kristopaitis
58. Anti-Parasitic Agents - Johnson
KEY CONCEPTS AND LEARNING OBJECTIVES.

1. To understand the clinical uses of H2 receptor antagonists, mechanism of action, elimination and adverse effects.
2. To describe the drug interactions associated with the use of H2 receptor antagonists.
3. To understand when antacids are used and their mechanism of action.
4. To understand the mechanism of action of PPIs
5. To describe the adverse effects and drug interactions with PPIs
6. To understand when histamine antagonists and the PPIs are to be used for treatment
7. To describe the mechanism of action of the mucosal protective agents
8. To describe the drugs used to treat H. pylori infection
Histamine-2 Antagonists and PPIs

I. Overview of Acid Reflux
   A. Acid reflux/GERD occurs when the stomach contents back up into the esophagus or mouth
   B. Patients with GERD experience heartburn, regurgitation, vomiting and pain upon swallowing
   C. Stomach acid can also affect vocal cords
   D. Symptoms of acid reflux/GERD
      1. Heartburn 2-3 times a week
      2. Burning sensation in chest
      3. Acid test in throat
   E. Treatment of acid reflux/GERD
      1. Mild symptoms - dietary changes, non-prescription medications
      2. Antacids and H2 antagonists

II. Antacids – used for short term relief
   A. Neutralizes gastric acid and reduces delivery of acid to duodenum
   B. Adverse effects
      1. Ingestion of large amounts of calcium and alkali can lead to hypercalcemia, alkalosis and renal impairment known as the milk-alkali syndrome
      2. Magnesium containing agents can cause diarrhea

III. H2 Receptor Antagonists
   A. These drugs reduce gastric acid secretion, and are used to treat peptic ulcer disease and gastric acid hypersecretion. These are remarkably safe drugs, and are now available over the counter.

The H2 antagonists are available OTC:
   1. Cimetidine (Tagamet®)
   2. Famotidine (Pepcid®)
   3. Nizatidine (Axid®)
   4. Ranitidine (Zantac®)

All of these have reduce the production of acid by blocking the H2 receptors on the parietal cell. They are used to prevent NSAID-induced ulcers and in the treatment and maintenance of peptic
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Ulcers

B. The H2 antagonists are rapidly and well absorbed after oral administration (bioavailability 50-90%). Peak plasma concentrations are reached in 1-3 hours, and the drugs have a t1/2 of 1-3 hours.

C. Cross the blood-brain and placental barriers

D. Elimination – Hepatic and renal metabolism. Bioavailability is reduced 30-70% by first pass metabolism. Cimetidine exhibits the greatest hepatic metabolism

E. Adverse effects – Rare but can include
   Gynecomastia and impotence occur with cimetidine
   1. Hematopoietic and immune effects-B 12 deficiency and Idiosyncratic myelosuppression
   2. CNS – confusion, agitation
   3. Hepatic effects – metabolized by cytochrome P450 and can cause drug interactions
   4. Cardiac effects-Brachycardia, hypotension-IV cardiac toxicity-Oral
   5. Renal –mild increase in creatinine with cimetidine

Because of the hepatic metabolism and renal excretion, H2 receptor antagonists should be used with care (lower doses) in patients with hepatic and renal impairment.

IV. Proton Pump Inhibitors

A. Mechanism of action

1. Proton Pump Inhibitors (PPI) irreversibly inhibit the gastric parietal cell proton pump H+/K+ ATPase.

2. Activation occurs in 3 phases
   a. PPIs are weak bases concentrated in the acid compartment of the parietal cells
   b. Prodrugs – activated in acid environment – enter the parietal cells from the blood
   c. A sulfhydral group forms a disulfide bond with cysteine residues on the H-K-ATPase pump and inactivates the enzyme

B. Current proton pump inhibitors

1. Omeprazole (Prilosec®)
2. Lansoprazole (Prevacid®)
3. Rabeprazole (Aciphex®)
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4. Pantoprazole (Protonix®)
5. Esomeprazole (Nexium®)
   - A single dose can inhibit 95% of gastric acid secretion
   - H2 antagonist should not be given with PPIs
   - PPIs are the drug of choice for treatment of Zollinger-Ellison syndrome and GERD when there is no response with H2 antagonists

C. Drug Interactions of PPIs

1. PPIs are metabolized by Cytochrome P450 and, therefore, can decrease the metabolism and clearance of benzodiazepines (Diazepam), warfarin, phenytoin, etc.
2. PPIs reduce absorption of ketoconazole but increase absorption of digoxin.

D. Adverse reactions of PPIs

1. Few (<3% of patients) and generally mild
2. Include diarrhea, headache, drowsiness, muscle pain, and constipation.

V. Mucosal Protective Agents

A. Sucralfate (Carafate ®) is aluminum sucrose sulfate.
B. It is thought to polymerize and bind selectively to necrotic tissue, thereby creating a barrier between the gastric contents and the gastric mucosa.
C. Sucralfate is very effective for treating duodenal ulcers, and also suppresses H. Pylori (see below).
D. It is important to note that citric acid, such as that present in grapefruits, promotes absorption of the aluminum in sucralfate. This poses a problem for patients with renal failure who have an impaired ability to eliminate the aluminum.
E. Do not give with cimetidine/ranitidine but can be given 2h prior.
F. Colloidal Bismuth (Pepto-Bismol) also acts like sucralfate to bind necrotic tissue and creates a barrier.
### Histamine Antagonists and PPIs

Debra Hoppensteadt Moorman, Ph.D.

**January 5, 2017**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Mechanism</th>
<th>T½ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Tagamet</td>
<td>H2 antagonist</td>
<td>1-3</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Pepcid</td>
<td>H2 antagonist</td>
<td>1-3</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Aclid</td>
<td>H2 antagonist</td>
<td>1-3</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Zantac</td>
<td>H2 antagonist</td>
<td>1-3</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Prilosec</td>
<td>Proton Pump Inhibitor</td>
<td>24</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Prevacid</td>
<td>Proton Pump Inhibitor</td>
<td>24</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Aciphex</td>
<td>Proton Pump Inhibitor</td>
<td>24</td>
</tr>
<tr>
<td>Carafate</td>
<td>Sulcralfate</td>
<td>Mucosal Protective Agent</td>
<td>6</td>
</tr>
</tbody>
</table>

OTC = over the counter medication

Effective = more effective than the H2 antagonists (which are already quite effective!!).
VI. Helicobacter Pylori
   A. Bacteria can enter body and live in your digestive system for years. Can eventually cause ulcers in the lining of the stomach and small intestine
   B. Transmission is person-to-person or fecal contamination of water and food
   C. Pylori is present in only 0.3-0.5 % of the normal healthy population.
   D. Presence of H. Pylori increases the risk of recurrent ulcers
   E. Combination therapy with a PPI plus 2 antibiotics is used to treat this disease for 1 week
   F. If PPI is used with 1 antibiotic patient needs 2 weeks of treatment
<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification</th>
<th>Biochemical mechanism of anti-asthmatic action</th>
<th>Routes of administration</th>
<th>Type of therapeutic use</th>
<th>Contraindications</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (Tagamet®)</td>
<td>Histamine H2 receptor antagonist</td>
<td>Blocks histamine H2 receptors and decreases gastric acid secretion</td>
<td>1. Oral 2. i.v. 3. injection</td>
<td>1. duodenal ulcers 2. gastric ulcers 3. erosive gastroesophageal reflux disease (GERD) 4. Prevention of upper GI bleeding 5. hypersecretory conditions (Zollinger-Ellison Syndrome)</td>
<td>Gyn with and inci ups</td>
<td></td>
</tr>
<tr>
<td>Ranitidine (Zantac®)</td>
<td>Histamine H2 receptor antagonist</td>
<td>Blocks histamine H2 receptors and decreases gastric acid secretion</td>
<td>1. Oral 2. i.v.</td>
<td>Same as Cimetidine</td>
<td></td>
<td>Rare agi conf dept</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>PPI</td>
<td>1. Inhibits H+/K+ pump (proton pump) in the gastric parietal cells</td>
<td>1. Oral</td>
<td>1. Zollinger-Ellison Syndrome 2. GERD 3. short term treatment of duodenal ulcers 4. Rx of H. Pylori in combination with Antibiotics</td>
<td>1. Can increase concentrations of diazepam, warfarin, and phenytoin by decreasing their clearance by the liver. 2. PPIs can reduce absorption of ketoconazole and increase absorption of digoxin.</td>
<td>Diarr skin</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>PPI</td>
<td>1. Inhibits H+/K+ pump (proton pump) in the gastric parietal cells</td>
<td>1. Oral</td>
<td>Same as Omeprazole</td>
<td>Same as for Omeprazole</td>
<td>Hea</td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism of action</td>
<td>Therapeutic use</td>
<td>Adverse effects</td>
<td>Drug interactions</td>
<td>Classification</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>Neutralize the gastric acid and reduces delivery to the duodenum</td>
<td>Used for short term treatment of heartburn and indigestion which can be associated with GERD</td>
<td>Milk-alkali syndrome, diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rantidine (Zantac®)</td>
<td>Reduces acid secretion by blocking the H2 receptor in parietal cells</td>
<td>Treatment of GERD, duodenal ulcers, gastric ulcers</td>
<td>Rare, hematopoietic and immune effects. B12 deficiency, confusion, agitation, cardiac toxicity</td>
<td>Decrease efficacy of PPIs</td>
<td>Histamine2 receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Famotidine (Pepcid®)</td>
<td>Same as above</td>
<td>Treatment of GERD, duodenal ulcers, gastric ulcers</td>
<td>Same as above</td>
<td>Decrease efficacy of PPIs</td>
<td>Histamine2 receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet®)</td>
<td>Same as above</td>
<td>Treatment of GERD, duodenal ulcers, gastric ulcers</td>
<td>Rare, gynecomastia and impotence, mild ↑ in creatinine, additional effects same as above</td>
<td>Decrease efficacy of PPIs</td>
<td>Histamine2 receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Nizatidine (Axid®)</td>
<td>Same as above</td>
<td>Treatment of GERD, duodenal ulcers, gastric ulcers</td>
<td>Rare, hematopoietic and immune effects. B12 deficiency, confusion, agitation, cardiac toxicity</td>
<td>Decrease efficacy of PPIs</td>
<td>Histamine2 receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Omeprazole (Prilosec®)</td>
<td>Prodrug, blocks acid secretion by inhibiting the H-K ATPase pump (proton pump)</td>
<td>Treatment of GERD, duodenal ulcers, gastric ulcers, Zollinger-Ellison Syndrome, H. Pylori infection along with 2 antibiotics</td>
<td>Diarrhea, headache, drowsiness, muscle pain and constipation</td>
<td>Metabolized by CYP450 and can decrease the metabolism and clearance of benzodiazepines, warfarin and phenytoin. PPIs can ↓ absorption of ketoconazole ↑ digoxin</td>
<td>Proton Pump Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole (Prevacid®)</td>
<td>Same as above omeprazole</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Proton Pump Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Rabeprazole (Aciphex®)</td>
<td>Same as above omeprazole</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Proton Pump Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole (Ptrotonix®)</td>
<td>Same as above omeprazole</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Proton Pump Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Esomeprazole (Nexium®)</td>
<td>Same as above omeprazole</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Proton Pump inhibitor</td>
<td></td>
</tr>
<tr>
<td>Sucrulate (Crafate®)</td>
<td>Binds to necrotic tissue to form a barrier</td>
<td>Duodenal ulcers (not NSAID related), H. Pylori</td>
<td>Constipation, dry mouth, nausea, diarrhea</td>
<td>Grapefruit juice promotes absorption of Aluminum in sucrulate. Given 2 hrs. prior to cimetidine.</td>
<td>Mucosal protective agent</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacologic Palliation of Constipation & Nausea/Vomiting

Date: January 11, 2017 - 9:30 AM

Reading Assignment: Katzung, Basic and Clinical Pharmacology, 13th Ed
Chapter 62. Drugs used in the treatment of gastrointestinal diseases
   - Drugs used to stimulate gastrointestinal motility
     - Laxatives
     - Antiemetics

LEARNING OBJECTIVES

1. Explain the mechanisms of action, indications, and contraindications of the following classes of drugs used for the relief of constipation and prototype drugs in each class:
   - Bulk laxatives (Psyllium; Fiber)
   - Osmotic laxatives
     - Nonabsorbable sugars (Lactulose; Sorbitol)
     - Saline and magnesium laxatives (Magnesium citrate, magnesium hydroxide)
     - Polyethylene glycol
   - Stimulant laxatives (Senna; Bisacodyl)
   - Detergent laxatives (Docusate)
   - Lubricants (Glycerin suppository, mineral oil enema)
   - Enemas (Warm water; sodium phosphate)

2. Define fecal impaction

3. Explain the mechanisms of action, indications, and contraindications of the following antiemetics and know prototype drug in each class:
   - Dopamine receptor antagonists
     - Metoclopramide
     - Prochlorperazine
   - Prokinetic agent (Metoclopramide)
   - Antihistamines (Promethazine)
   - Serotonin antagonists (Odansetron)
   - Anticholinergics (Scopolamine)

4. Explain the mechanisms of action and indications for the use of
   - Benzodiazepenes (Lorazepam)
   - Corticosteroids (Dexamethasone)
   - In the palliation of nausea and vomiting
Pharmacologic Palliation of Constipation & Nausea/Vomiting

I. A goal of palliative care is to relieve the suffering of patients. Control of pain and other physical symptoms, as well as psychological, social and spiritual problems is paramount.

II. Pharmacologic Palliation of Constipation

A. BULKING AGENTS

Agents

- Dietary fiber (bran)
- Psyllium (Metamucil)

Mechanisms of Action

- Bulk-forming laxatives cause retention of fluid and an increase in fecal mass, resulting in stimulation of peristalsis.
- They usually have an effect within 12 to 24 hours and reach a maximum after several days

Side Effects

Flatulence

Contraindications

In debilitated patients who cannot drink adequate fluid (1.5 – 2 liters/day) could result in fecal impaction, intestinal obstruction

B. OSMOTIC LAXATIVES

These are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

- **Nonabsorbable sugars**
  
  Agents
  
  - Lactulose
  - Sorbitol

Mechanism of Action

Lactulose is a synthetic disaccharide. Bacteria in the colon degrade lactulose into lactic acid, acetic acid and formic acid resulting in an increase in osmotic pressure and acidification of intestinal contents which in turn, softens the stool by promoting stool water content

Side Effects

- Bloating, cramps, flatulence
- Very sweet – may be difficult for patients to tolerate
○ Can worsen dehydration by drawing body water into the bowel lumen

**Saline and magnesium salt laxatives**

**Agents**
- Magnesium citrate
- Magnesium hydroxide (Milk of Magnesia)
- Sodium Phosphate (Fleets Phospho-Soda)

**Mechanism of Action**
- Saline laxatives have an osmotic effect causing increased intraluminal volume that acts as a stimulus for intestinal motility.
- Laxatives that contain magnesium have been shown to release cholecystokinin that causes intraluminal accumulation of fluid and electrolytes and promotes small bowel and possibly even colonic transit.
- Rapid movement of water into distal small bowel and colon leads to high volume of liquid stool.
- High doses produce bowel evacuation in 1-3 hours.

**Side Effects/Contraindications**
- Contraindicated in any form of bowel obstruction
- Can produce dehydration without adequate fluid replacement
- Because the ions can be partially absorbed, laxatives containing magnesium and phosphorous are contraindicated in patients with impaired renal function
- Avoid sodium phosphate-containing formulations in patients with congestive heart failure, liver failure – severe electrolyte abnormalities can occur.
  - Phosphate nephropathy (intratubular deposition of calcium phosphate)
- Rare reports of ischemic colitis with magnesium citrate and sodium phosphate thought secondary to a rapid fluid shift from the intravascular compartment to the gut lumen resulting in transient colonic hypoperfusion and ischemia

**Clinical Indications**
- Magnesium citrate and sodium phosphate indicated for bowel cleansing in preparing patients for surgery or the colon for x-ray or endoscopy
- Magnesium hydroxide is indicated for relief of constipation

**Polyethylene Glycol**

**Trade names**
- Constipation - Miralax, GlycoLax
- Bowel Cleanser - Colyte, Golytely

**Mechanism of Action:**
- Polyethylene glycol is an osmotic agent that causes retention of water in the stool resulting in a softer stool and more frequent bowel movements.
○ It appears to have no effect on active absorption or secretion of glucose or electrolytes
○ No significant intravascular fluid or electrolyte shifts occur

**Side Effects**
Minimal

**Clinical Indications**
○ Large volume (ie 4 liters) ingested rapidly causes rapid evacuation for bowel cleansing before endoscopy
○ Smaller daily doses can be used for constipation.

---

**C. STIMULANT LAXATIVES**

**Agents:**
○ Senna
○ Bisacodyl (Dulcolax)

**Mechanism of Action:**
○ Bisacodyl is a contact laxative that acts on the large intestine to produce strong but brief peristaltic movements. This agent stimulates sensory nerve endings to produce parasympathetic reflexes that results in peristalsis of the colon. Local axon reflexes and segmental reflexes are stimulated, which produces widespread peristalsis of the colon.
○ Senna undergoes conversion to active metabolites in the colon that stimulate the myenteric plexus and induce net fluid secretion.
○ Response in 6-12 up to 24 hours.

**Side Effects**
○ Electrolyte abnormalities depending on volume of stool
○ Senna - Melanosis coli – brown pigmentation of the colon
  ▪ Lipofuscin laden macrophages
  ▪ No clinical sequela

**Clinical Indication**
Relief of constipation

---

**D. DETERGENT LAXATIVES**

**Agent**
Docusate (Colace)
Mechanism of Action
○ Docusate is an anionic surfactant that is believed to increase the penetration of fluid into the stool by emulsifying feces, water, and fat
○ Soft feces = easier passage
○ Minimal effect on peristalsis
○ Initial response in 1-3 days

Clinical Indications
Docusate is used to soften or prevent the formation of hard stools.

E. LUBRICANTS
Agents
○ Glycerin suppository/enema
○ Mineral oil enema

Mechanism of Action
○ Due to its osmotic effect, glycerin softens, lubricates, and facilitates the elimination of inspissated feces. By serving as a bowel irritant it may also stimulate rectal contractions.
○ Mineral oil helps soften (by coating fecal material with mineral oil) and lubricate hard stools, easing their passage without irritating the mucosa.
○ Lubricants may stimulate a response within 30 minutes.

Side effects/contraindications
Mineral oil should never be administered orally to debilitated patients - inhalation/aspiration of the oil can lead to lipoid pneumonitis.

Clinical Indications
Usually reserved for treatment of fecal impaction

F. LARGE VOLUME ENEMAS
Agents
Sodium phosphate enema (Fleet’s enema)
Tap water

Mechanism of Action
Soften stool by increasing water content
Distend distal colon inducing peristalsis

Clinical Indications
Usually reserved for treatment of fecal impaction
III. Pharmacologic Palliation of Nausea and Vomiting

A. Pathophysiology of nausea and vomiting

Psychological stimuli → Cerebral Cortex
Intracranial pressure
Motion sickness → Vestibular apparatus (cholinergic, histaminic Receptors)
Vestibular disease
Drugs → Chemoreceptor Trigger Zone (dopaminergic, 5HT3 Receptors, NK1)
Uremia
Ketosis
Irradiation
Gastric irritation
Intestinal distention → Gastrointestinal tract (vagal nerve)
Gag reflex (cholinergic, histaminic, 5HT3, dopamine receptors)

Chemoreceptor trigger zone is located in the area postrema outside the blood brain barrier.
Vomiting Center is located in the lateral reticular formation of the medulla and coordinates the motor mechanisms of vomiting.

B. Antiemetic Drugs

Dopamine receptor antagonists
Phenothiazines - Prochlorperazine (Compazine)
Butyrophenones - Haloperidol (Haldol)
Benzamides – Metoclopramide (Reglan)

Serotonin (5HT3) antagonists
Ondansetron (Zofran)
Granisetron (Kytril)
Dolasetron
Polansetron
Antihistamines
Promethazine (Phergan)
Diphenhydramine

Anticholinergics
Scopolamine

Corticosteroids
Dexamethasone

Benzodiazepenes
Lorazepam
Alprazolam

Cannabinoids
Dronabinol (Marinol)
Nabilone

Neurokinin (NK1) receptor antagonist
Aprepitant

B. Select Antiemetics

Agent - Prochlorperazine (Compazine)

Mechanisms of Action
○ Prochlorperazine acts centrally by inhibiting the dopamine receptors in the medullary chemoreceptor trigger zone

Adverse Effects
Extrapyramidal effects, dystonic reactions

Clinical Indications
○ Opioid related nausea and vomiting
○ Moderately effective for nausea caused by various GI disorders (ie gastroenteritis)

Agent - Metoclopramide (Reglan)

Mechanism of Action
○ Antiemetic properties are due to central and peripheral dopamine receptor inhibition
○ Prokinetic - Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of metoclopramide. Metoclopramide increases esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but has no effect on small intestine or colonic motility

**Adverse Effects**
○ Extrapyramidal effects, such as dystonia, akathisia, parkinsonism, may develop due to central dopamine receptor blockade.
○ Tardive dyskinesia – black box warning – risk increases with total cumulative dose. Avoid use for greater than 12 weeks
○ Acute dystonic reactions, such as trismus, torticollis, facial spasms, can be treated with an anticholinergic agent (benztropine or diphenhydramine).
○ Cautious use in patients with Parkinson’s Disease

**Clinical Indications**
○ Chemotherapy induced nausea and vomiting
○ Vomiting due to dysmotility of the upper GI tract - gastric stasis and diabetic gastroparesis

**Agent** - Ondansetron (Zofran); Granisetron (Kytril)

**Mechanism of Action**
○ Ondansetron is a competitive, highly selective antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT 3) receptors. 5-HT 3 receptors are present peripherally on vagal nerve terminals and centrally in the area postrema of the brain. Cytotoxic drugs and radiation appear to damage gastrointestinal mucosa, causing the release of serotonin from the enterochromaffin cells of the gastrointestinal tract. Stimulation of 5-HT 3 receptors causes transmission of sensory signals to the vomiting center via vagal afferent fibers to induce vomiting. By binding to 5-HT 3 receptors, ondansetron blocks vomiting mediated by serotonin release.

**Side Effects**
Most common side effect is headache
Small but statistically significant prolongation of the QT interval

**Clinical Indications**
○ Chemotherapy induced nausea and vomiting and its prophylaxis
○ Radiation induced nausea and vomiting and its prophylaxis
Agent - Promethazine (Phenergan)

Mechanism of Action
Antiemetic effects come from its H(1) receptor blocking properties.

Adverse Effects
Sedation

Clinical Indications
Promethazine is effective in the active and prophylactic treatment of motion sickness

Agent Scopolamine

Mechanism of Action
Pure anticholinergic agent

Adverse Effects
- Dry mouth (xerostomia)
- Acute narrow angle glaucoma (contraindicated in patients with known glaucoma)
- Urinary retention
- Confusion

Clinical Indications
- Treatment of motion sickness
- In patients who are hours to days from death and who can no longer swallow their own secretions, it is used to decrease production of saliva

Agent Dronabinol (Marinol)

Mechanism of Action
Synthetic delta-9-tetrahydrocannabinol
Cannabinoid 1 (CB1) central receptor agonist

Adverse Effects
- Euphoria
- Dysphoria
- Paranoid delusions
- Cognitive clouding
- Somnolence, sedation
Clinical Indications

- Breakthrough chemotherapy induced nausea/vomiting
  - AIDS-related anorexia and wasting

- Hypotension
### Antimalarial Drugs Used for Treatment or Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Method of action</th>
<th>Stage of life cycle inhibited</th>
<th>Use</th>
<th>Unique or major adverse reactions</th>
<th>Use in Children</th>
<th>Use in Pregnancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>Inhibit heme</td>
<td>RBC Schizont</td>
<td>Treatment and chemoprophylaxis</td>
<td>Pruritis (Africans)</td>
<td>Safe</td>
<td>Safe</td>
<td>Resistance is major limitation</td>
</tr>
<tr>
<td></td>
<td>polymerase; incr free heme</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine, Quinidine</td>
<td>Inhibit heme (toxic)</td>
<td>RBC Schizont</td>
<td>Treatment of</td>
<td>Cinchonism* Hypoglycemia Blackwater fever</td>
<td>OK</td>
<td>Quinine - OK, if needed</td>
<td>Cinchonism: tinnitus, headache, nausea, dizziness, flushing and visual disturbances</td>
</tr>
<tr>
<td></td>
<td>polymerase; incr free heme (P. vivax &amp; ovale)</td>
<td>(gametocytes of</td>
<td>P. falciparum</td>
<td></td>
<td></td>
<td>Quinidine - OK, but contractions in 3rd trimester</td>
<td>Only iv quinidine available in US; DOC for severe malaria; cardiac monitoring recommended; used with a 2nd agent</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Inhibit heme</td>
<td>RBC Schizont</td>
<td>Treatment and chemoprophylaxis</td>
<td>Neuropsychiatric toxicities (less common with prophylaxis)</td>
<td>Safe</td>
<td>OK</td>
<td>DOC for chemoprophylaxis in most regions; Not recommended for treatment of severe malaria</td>
</tr>
<tr>
<td></td>
<td>polymerase; incr free heme (toxic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primaquine</td>
<td>Inhibit heme</td>
<td>Hypnozoite, Gametocyte</td>
<td>Radical cure for</td>
<td>Hemolysis in G6PD-deficiency</td>
<td>OK</td>
<td>UNSAFE</td>
<td>Testing for G6PD-deficiency recommended; Terminal prophylaxis is rarely necessary</td>
</tr>
<tr>
<td></td>
<td>polymerase; incr free heme (toxic)</td>
<td></td>
<td>P. vivax &amp; ovale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proguanil</td>
<td>Inhibit plasmodial DHFR</td>
<td>RBC Schizont, Hepatic Schizont of P. falcip</td>
<td>With chloroquine or atovaquone for chemoprophylaxis</td>
<td></td>
<td>OK</td>
<td></td>
<td>(never given alone, see atovaquone)</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Inhibit parasite mitochondrial electron transport</td>
<td>RBC Schizont, Hepatic Schizont of P. falcip</td>
<td>With proguanil (Malarone) for chemoprophylaxis</td>
<td>GI side affects, contraindicated in severe renal impairment Photosensitivity, Esophagitis</td>
<td>NO, if &lt; 5kg</td>
<td>NO, unless benefit outweighs risk (Category C)</td>
<td>Give with food or milky drink</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Inhibit protein synthesis in parasite organelles</td>
<td>RBC Schizont</td>
<td>Adjuvant treatment of P. falciparum and chemoprophylaxis</td>
<td></td>
<td>NO</td>
<td>NO</td>
<td>Used for chemo-prophylaxis in areas with high mefloquine resistance (e.g., areas within Southeast Asia)</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>Binds Iron in malaria pigment producing free radicals</td>
<td>RBC Schizont, Gametocyte</td>
<td>Treatment</td>
<td>Potential neurotoxicity (ototoxicity) unresolved</td>
<td>Probably OK, Not approved in US</td>
<td>Probably OK, Not approved in US</td>
<td>Used for treatment (Asia/Africa) in combination with other antimalarial agents</td>
</tr>
</tbody>
</table>

*Cinchonism: tinnitus, headache, nausea, dizziness, flushing and visual disturbances*
### Antihelmintic drugs used for treatment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease for which agent is the Drug of Choice</th>
<th>Dose</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole</td>
<td>Cysticercosis</td>
<td>15 mg/kg/d (Max 800 mg) in 2 divided doses x 21 d</td>
<td>Absorption increased 5-fold with fatty meals, No interaction with corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Hydatid disease</td>
<td>400 mg BID x 3 mos</td>
<td>Check CBC, LFTs Q 2 weeks</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>(Pinworm)</td>
<td>100 mg x 1, repeat in 2-4 wks</td>
<td>Absorption increased with fatty meals; chew before swallowing</td>
</tr>
<tr>
<td></td>
<td>(Ascaris, Trichuria, Hookworm)</td>
<td>100 mg BID x 3 d</td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Strongyloidiasis</td>
<td>200 mcg/kg daily x 2</td>
<td>check stool by concentration method x 3 monthly to ensure eradication</td>
</tr>
<tr>
<td></td>
<td>Onchocerciasis</td>
<td>150 mcg/kg x 1, repeat Q 3 mo x 4, then yearly x 10</td>
<td>Mazzotti reaction* occurs due to microfilariae death</td>
</tr>
<tr>
<td>Pyrantel pamoate</td>
<td>(Pinworm, Ascaris)</td>
<td>11 mg/kg x 1, repeat 2-4 wks</td>
<td>Treat all family members</td>
</tr>
<tr>
<td>Praziquantel</td>
<td>Schistosomiasis**</td>
<td>20 mg/kg Q 4-6 h x 3 doses</td>
<td>Swallow without chewing</td>
</tr>
<tr>
<td></td>
<td>(Cysticercosis)</td>
<td>50 - 60 mg/kg/d in 3 divided doses x 14 d</td>
<td>Bioavailability decreased ~ 50% with phenytoin and corticosteroids</td>
</tr>
<tr>
<td>Diethyl carbamazine citrate</td>
<td>Filariasis, Loiasis, Tropical eosinophilia</td>
<td>2 mg/kg TID for 3 weeks, titrate up from Q daily to TID over first 3 d</td>
<td>Reactions to dying microfilariae are common, sometimes serious (BLINDNESS may occur in Onchocerciasis)</td>
</tr>
</tbody>
</table>

*Mazzotti reaction: fever, headache, dizziness, somnolence, weakness, rash, increased pruritis, diarrhea, joint & muscle pains, hypotension, tachycardia, ** Oxamiquine is DOC for S. mansoni