COMMON ANTACIDS

Aluminum hydroxide (Amphojel, AlternaGEL)  
Magnesium hydroxide (MOM)  
Aluminum hydroxide and magnesium hydroxide combo (Maalox, Mylanta)  
Calcium carbonate: Tums, Rolaids, Oscal  
Sodium bicarbonate (Alka-seltzer also contains ASA)  
Aluminum OH, trisilicate, aiginic acid, sodium bicarbonate (Gaviscon)

COMMONLY USED AGENTS

Aluminum hydroxide or magnesium hydroxide in liquid or tablet form most widely used

Aluminum hydroxide: Amphojel, AlternaGEL
- Neutralizes HCl w prod of aluminum chloride and water
- Constipation: aluminum binds to bile acids thus preventing their choleretic effect
- Weakness and anorexia due to phosphate depletion

Magnesium hydroxide: MOM
- May produce diarrhea secondary to poor absorption of magnesium ion
- Not for renal patients: can precipitate hypermagnesemia and CNS toxicity
  - Mg++ from drug is absorbed in small intestine; excreted by kidneys
  - Absorbed magnesium cannot be excreted by kidneys in renal failure

Aluminum hydroxide and magnesium hydroxide combo: Maalox, Mylanta
- Prescribed together or in alternating regimens
- Constipating and laxative effects overcome each other

Calcium carbonate: Tums, Rolaids, Oscal
- Potent and unique antacid but may lead to "rebound" gastric acid secretion.
- Mechanism of rebound
  Calcium directly stimulates parietal cells acid secretion
  Calcium stimulates gastrin release (to lesser degree).
- **Milk-alkali syndrome** may result from long term use in combo with milk
  - Hypercalcemia
  - Renal insufficiency
- Generally not recommended for acid suppression due to side effect profile

**Sodium bicarbonate:** Baros granules, Alka-seltzer *

- Potent, rapid acting and inexpensive
- May cause **systemic alkalosis and sodium and fluid retention**
- Side effect profile warrants that this agent should be avoided

* salicylate and antacid (Aspirin 325 mg, sodium bicarbonate 1.916 g, citric acid 1 g; effervescent tabs

**Gaviscon**
Aluminum OH 80 mg, mg trisilicate 20 mg
Contains alginic acid and sodium bicarbonate)

**Gaviscon Liquid**
**Gaviscon Extra Strength**
**MECHANISM**
- Weak antacid
- Alginic acid floats on top of stomach; provides a barrier between stomach acid and esophagus

**DOSING:** 2-4 Tabs qid and hs; follow with water

**INDICATIONS:** sour stomach; heartburn, acid indigestion

**ADVERSE REACTIONS:** constipation or diarrhea

### H2 RECEPTOR ANTAGONISTS

- One of the most frequently prescribed agents
- Indicated for GERD, peptic acid disease and dyspepsia
- Normally physiology:
  - **H2-receptors are occupied by histamines**
  - Histamine is released from gastric mast cells and endochromaffin-like cells
  - Process involves activation of adenylate cyclase and increases cAMP
  - Activation, in turn, stimulates proton pump on luminal surface of parietal cells to secrete H+ ion

**Mechanism for H2 receptor antagonist**
- Selectively and competitively inhibit the binding of histamine to H2 receptor
  - Receptor located on basolateral membrane of acid-secreting parietal cells
  - Reduce intracellular concentration of cAMP
  - Reduce secretion of acid by these cells
- Interference with activation of H2-receptor reduces all phases of gastric acid secretion
  - Stimuli: basal, nocturnal, meal-stimulated
  - Includes those mediated by gastrin, acetylcholine, insulin and caffeine.
H2 receptor antagonism does not affect other gastric function
- Parietal cell secretion of intrinsic factor
- Gastric emptying
- Lower esophageal sphincter pressure
- Post prandial release of bile acids and pancreatic enzymes.

H2 BLOCKING AGENTS

ORIGINAL BLOCKING AGENT - Cimetidine

- Less popular and less frequently used in comparison to newer other class members
- Adverse side effects
  - Numerous of interactions in comparison to other class members *
- Results in increased levels: Theophylline, warfarin, phenytoin, lidocaine or propranolol

* Drugs metabolized by the P450 mixed oxidase enzyme system

Cimetidine

Tagamet - 200 mg, 300 mg, 400 mg, 800 mg - RX
Tagamet Liquid 300 mg/5 mg - RX
Tagamet Injection 300 mg/2ml - RX
Tagamet Premixed: 300 mg/50 ml sodium chloride (for IVSS) - RX

Tagamet HB 200 mg - OTC
Tagamet HB Suspension 200 mg/20 ml - OTC

INDICATIONS

- Active gastric/duodenal ulcer: 800 mg hs x 4-8 wks; maintenance 400 mg hs
- Active benign gastric ulcer: 800 mg hs or 300 mg qid w meals and hs x 6 wks
- Prevention of duodenal ulcer recurrence
- Treatment of gastric acid hypersecretory states: 300 mg qid and hs
  - Gastrinoma
  - Zollinger-Ellison syndrome
- GERD: 800 mg bid or 300 mg qid x 12 weeks
- Stress-related mucosal damage (ulcers, bleeding)

ADVERSE EFFECTS

- Rare, may include diarrhea, nausea, mild/reversible renal insufficiency
- Agitation and confusion especially in elderly
- Antiandrogenic effects with prolonged use:
  - Reversible gynecomastia and impotence with prolonged use
  - Effect is due to inhibition of cytochrome P450 hepatic metabolizing enzyme system which normally degrades circulating estrogens

INTERACTIONS

- Numerous
- Effects drugs metabolized by cytochrome P450 mixed oxidase enzyme system
NEWER H2 RECEPTOR BLOCKING AGENTS - More potent than cimetidine (6-25 times)

- Longer duration of action (up to 5 times)
- Lack inhibitory effects of cimetidine on p450 mixed oxidase enzyme system.
- Safe with adverse effects limited to drug-induced hepatotoxicity and headache
- Now available OTC (dosing is ½ strength of RX)

Ranitidine
Zantac: 150 bid or 300 mg qd (tabs: 150 mg, 300 mg) - RX
Zantac Syrup: 15 mg/ml - RX
Zantac EFFERDOSE: 150 mg effervescent tabs or granules - RX
Zantac Injection: 25 mg/ml: IM or IV - RX
Zantac 75 (ranitidine) 75mg qd or bid OTC

Famotidine
Pepcid 20 or 40 mg qd (tabs: 20 mg, 40 mg) - RX
Pepcid RPD 20 mg or 40 mg disintegrating tabs - RX
Pepcid suspension 40 mg/5 ml - RX
Pepcid AC 10 mg tabs, gelcaps - OTC
Pepcid AC chewable 10 mg - OTC

Nizatidine
Axid 150 mg bid or 300 qd (tabs 150 mg, 300 mg) RX
Axid AR

PROTON PUMP INHIBITORS

- Potent inhibitors of gastric acid secretion.
- Indicated: Peptic ulcer disease (PUD), GERD, Zollinger-Ellison (gastrinoma)
- Heals ulcers (duodenal and gastric) more quickly than conventional H2 receptor antagonists
- Heals ulcers resistant to conventional or large doses of H2 antagonists
- Superior to H2 antagonists in treatment of erosive esophagitis and Zollinger-Ellison syndrome

INDICATIONS

- Short term treatment of active duodenal ulcer
- Heartburn
- Other symptoms of GERD
- Active benign gastric ulcer
- Use with clarithromycin in treatment of duodenal ulcer
- Maintenance of healed erosive esophagitis
- Long term treatment
  - Zollinger-Ellison syndrome
  - Multiple endocrine adenomas
  - Systemic mastocytosis

- Some class members are indicated for H. Pylori treatment

PROTON PUMP INHIBITORS
omeprazole (Prilosec)
lansoprazole (Prevacid)
rabeprazole (Aciphex)
pantoprazole (Protonix)
esomeprazole (Nexium)
MECHANISMS

- Substituted benzimidazole
- Inhibits gastric acid secretion by non-competitive inhibition of H+, K+, ATPase on parietal cell *
  - ATPase which lies within secretory membrane of cell serves as proton pump
  - Exchanges potassium for hydrogen in the final phase of hydrogen ion secretion by parietal cell.

* irreversible inactivation of H+, K+, ATPase

- **Inhibits basal and stimulated gastric output by 50-100%**
- Does NOT effect other gastric functions
  - Gastric emptying
  - Pepsinogen secretion
  - Intrinsic factor production
  - Lower esophageal sphincter pressure.

SIGNIFICANT ADVERSE EFFECTS

- None other than elevation of plasma gastrin
- Original black box warning was removed

COMMON SIDE EFFECTS (infrequent)

H/A, abdominal pain, diarrhea, nausea, URI, dizziness, vomiting, rash, constipation, cough, asthenia, back pain

- Research has established that long-term use appears to be safe
  - Original concerns re: risk of gastric carcinoma were unfounded
  - Black box warning for omeprazole was lifted *

* None of the other class members, released subsequently, carried a black-box warning

INTERACTIONS

- Prolong elimination of diazepam, warfarin, phenytoin
- Interactions with drugs metabolized by P-450 enzymes
- May interfere with absorption where gastric pH is determinant of bioavailability
  - Ketoconazole, ampicillin esters, fe salts, digoxin
- Sucralfate delays absorption; separate doses by 30 min
- Theophylline dosing may need adjustment

PRECAUTIONS

- Symptomatic relief does not preclude gastric malignancy
- Pregnancy category: B
TREATMENT REGIMENS FOR H PYLORI

- **H Pylori** (urease producing gram negative rod): major role
  - Long term recurrence rates lower with eradication via antibiotic regimen (esp with bismuth)
    - Treatment of ulcers with H pylori
      - Proton pump inhibitor or H2 agonist
      - Antibiotic therapy (eliminate bacteria)
    - Three (3) classes of drugs have direct effect on H pylori
      - Antibiotics
      - Bismuth salts
      - Proton pump inhibitors
    - Difficult to eradicate: most treatment regimens combine agents from 2 or 3 classes

- **All patients with active peptic ulcer disease should receive 6 weeks of acid suppression**
  - H2 receptor antagonist
  - Proton Pump Inhibitor

THERAPY FOR H. PYLORI

- Infection with *Helicobacter pylori* can cause gastritis and peptic ulcer disease
- Infection usually acquired during childhood
- If eradicated, it rarely recurs during adult life
- Many treatments have been recommended
- Evaluation and efficacy of treatments difficult to compare
  - Differences in study methodology
  - Emergence of antibiotic resistance

- **Both FDA-approved and non-approved regimens are available**
  - Both categories have regimens which are effective and backed by research
  - Regimens involving only generic drugs may not be sufficiently profitable for drug manufacturers to seek FDA approval
  - Therapies containing only proton pump inhibitor and either amoxicillin or clarithromycin are no longer regarded as effective

- Two main antibiotics used are metronidazole and clarithromycin
  - Antibiotic resistance against these two agents is clinically important
  - Both appear to be equally effective

- Cost can be a significant consideration
- No single treatment is considered the final treatment of choice

- **Good clinical evidence of efficacy** (80-90%) for several triple or quadruple antibiotic regimens

- Triple regimens consist of metronidazole, tetracycline or amoxicillin in combo with bismuth
  - Cost effective but many side effects
  - High cure rates with metronidazole-sensitive strains after 7 days but 14 is recommended
  - More recent regimens have variation on original components
    - Replace bismuth with proton-pump inhibitor
    - Reduced treatment period to 7 days
ANTICHOLINERGIC AGENTS

Examples: Atropine, scopolamine, hyoscyamine, glycopyrrolate propantheline bromide

MECHANISM
- Inhibit effects of acetylcholine on postganglionic muscarine cholinergic receptors on parietal cell.
- When used alone, inhibit gastric acid secretion by 15-25%
- When used w H2 receptor antagonists, they greatly enhance effectiveness of latter agents.

CLINICAL APPLICATIONS
- Used as adjunct (not primary) therapy PUD
- Counteract abdominal cramping and pain from temporary GI distress
- Antispasmodics in GI hypermotility
- Biliary dyskinesia
- Antidiarrheals
- Reduce peristaltic contractions:
  - Stomach, small intestines and colon.
  - Tone, amplitude and frequency

ADVERSE EFFECTS
Adverse effects limited usefulness
Used short-term due to side effects
Adverse effects from other organ systems too severe to allow for long-term use

- Delayed gastric emptying
- Dry mouth
- Blurred vision
- Mydriasis
- Urinary retention
- Cardiac arrhythmias

- Atropine contraindicated in GERD
  - Diminishes resting press of lower esophageal sphincter
  - Delays gastric emptying

CONTRAINDICATIONS

- Glaucoma, unstable CV status, GI/urinary obstruction
- Paralytic ileus or intestinal atony; toxic megacolon
- Severe ulcerative colitis; myasthenia gravis, reflux esophagitis

<table>
<thead>
<tr>
<th>COMMON ANTICHOLINERGICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirenzepine selective anticholinergic agent</td>
</tr>
<tr>
<td>Dicyclomine HCl (Bentyl) caps 10 mg, 20 mg</td>
</tr>
<tr>
<td>Hyoscyamine (Levsin) tabs 0.125mg</td>
</tr>
<tr>
<td>Levsin Drops: 0.125/ml</td>
</tr>
<tr>
<td>Levbis: hyoscyamine 0.375 mg ext release tabs</td>
</tr>
</tbody>
</table>

COMBINATION PRODUCTS

Librax - chlordiazepoxide (Librium) Hcl 5 mg 
- clidinium bromide 2.5mg) caps

Donnatal: scored tabs - 1-2 tabs tid to qid 
- Phenobarbital 16.2 mg 
- Hyoscyamine sulfate 0.1037 mg 
- Atropine sulfate 0.0194 mg 
- Scopolamine HBr 0.0085 mg

Donnatal Elixir per 5 ml 
Donnatal Extentabs - sust release tabs

Robinul (Glycopyrrolate) 1 mg dye-free tabs 
Robinul Forte: 2 mg dye free tabs

© 2002 Lois E. Brenneman, MSN, CS, ANP, FNP 
all rights reserved  – www.npceu.com
CYTOPROTECTIVE AGENTS

Agents which act without inhibiting gastric acid secretion
- Enhance mucosal defense vs acid erosion (mucus, bicarbonate secretion).
- Healing (epithelial cell renewal and microcirculatory changes)

Mechanism (s)
- Prostaglandin-dependent mechanisms
- Independent mechanisms

### CLASS OF CYTOPROTECTIVE AGENTS

- Sucralfate (Carafate)
- Exogenous prostaglandin analogs
  - misoprostol (Cytotec)
- Bismuth compounds
  - bismuth subsalicylate (Pepto Bismol)
  - colloidal bismuth subcitrate

### PROSTAGLANDINS

- E class (PGE1 and PGE2) have cytoprotective and gastric acid antisecretory properties.

- Mechanisms (enhance mucosal defenses vs acid erosion)
  - Stimulation of gastric acid mucus secretion
  - Stimulation of gastric and duodenal bicarbonate secretion
  - Preservation of gastric mucosal blood flow
  - Preservation of gastric mucosal barrier to back diffusion of H+
  - Stimulation of mucosal cellular renewal

Sucralfate (Carafate) 1 g scored tab
Carafate Suspension 1 g/10 ml

- Complex polyaluminum hydroxide of sucrose sulfate
- Dissociates in acid environment
- Forms viscous adhesive gel over erosions or ulcer beds for up to 12 hours
- Adherence impedes diffusion of H+ to ulcer base, reducing further damage.
- Exerts a trophic effect on normal mucosa
- Increases binding and salivary epidermal growth factor to ulcerated mucosa
- Effective as antacids and H2 receptor antagonist in treatment/prevention of peptic ulcer
MECANISM
- Binds bile acids and pepsin thus reducing injurious effects
- Increases mucosal defenses
  - Enhanced endogenous tissue prostaglandin production
    - Increased binding to endogenous sulfhydryl compounds
- Not absorbed
- Does not alter volume or pH of gastric secretions
  - Maintains the gastric acid antimicrobial barrier
  - Prevents bacterial colonization of stomach *
* bacterial colonization can occur with h antacids or H2 receptor antagonists

INDICATIONS
- Labeled uses
  - Active duodenal ulcer
  - Maintenance of healed ulcer (tab only)
- Widely used off-label applications
  - Treat drug-induced gastritis
  - Stress-related mucosal damage
  - Bile reflux gastritis; GERD

DOSING
  Active: 1 g qid on empty stomach x 4-8 weeks
  Maintenance: 1 g bid

ADVERSE EFFECTS: Constipation and GI disturbances

INTERACTIONS
- Avoid antacids within 30 minutes of dosing
- May reduce absorption of other drugs
  - Tetracyclines, phenytoin, cimetidine, digoxin, theophylline
  - Ciprofloxacin, norfloxacin, ketoconazole, ranitidine
- Dose concomitant drugs 2 hours after sucralfate
- Additive aluminum load with aluminum-containing antacids
- Monitor warfarin

Misoprostol (Cytotec): synthetic PGE1 methyl ester analog
- Gastric cytoprotective activity at low doses
- Gastric antisecretory activity at high doses
- Few systemic actions

INDICATIONS: Prevention of ASA and NSAID-induced gastric ulcers in high-risk patients.

CLINICAL APPLICATIONS
- Indicated use to prevent NSAID-induced gastric ulcers
- Effective in treatment of gastric and duodenal ulcers
- Intrapartum cervical ripening (off label)
- Abortifacient (off-label) - use not supported by the manufacturer
* Used off-label for cervical ripening to induce labor. Company has issued a statement indicating that it does not advocate use as an abortifacient and that it cannot provide data for use, off-label intrapartum use.
ADVERSE EFFECTS

- **Diarrhea**
- Abdominal and uterine cramping (will induce abortion)
- Extra-gastric adverse effects uncommon

CONTRAINDICATIONS

- **Black box warning for use in pregnancy** (causes abortion) *
- Use with caution in women of childbearing age

Colloidal bismuth

- Can heal peptic ulcers without neutralizing or inhibiting gastric acid secretion
- Bismuth compounds form a bismuth-protein coagulant in acid environment of stomach
- Bismuth-protein coagulant protects the ulcer from acid-peptic digestion
- **Bismuth compounds eradicate H pylori** in combo with antibiotics
  - Metronidazole (Flagyl)
  - Tetracycline
  - Amoxicillin

Bismuth subsalicylate (Pepto Bismol)

- Widely used for symptomatic treatment of indigestion and diarrhea
- Decreases gastric motility, intestinal motility
- Reduces intestinal spasm

Colloidal bismuth subcitrate: treatment/prevention recurrences of gastric/duodenal ulcers

Ranitidine bismuth citrate (Tritec) eradication of H pylori in combo with clarithromycin

- Days 1-14: ranitidine bismuth citrate 400 mg bid plus clarithromycin 500 mg tid
- Days 15-28: ranitidine bismuth citrate
- Can result in false positive for urine protein as tested with Multistix
ANTIDIARRHEAL AGENTS

OPIOIDS

Widely used as antidiarrheals: reduce urgency, frequency and stool volume.
Mechanism:
   - Reducing propulsive activity of gut
     - Reduced stool frequency
     - Allows enhanced contact time: luminal contents and intestinal mucosa
     - Allows for greater absorption of fluid thus reduced stool volume.
   - Stimulate active chloride absorption
   - Antisecretory effect on several intestinal secretagogues.

<table>
<thead>
<tr>
<th>COMMON OPIOIDS ANTIDIARRHEALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Camphorated opium (Paregoric)</td>
</tr>
<tr>
<td>Diphenoxylate and atropine (Lomotil)</td>
</tr>
<tr>
<td>Loperamide (Imodium)</td>
</tr>
</tbody>
</table>

**Codeine** and synthetic opioids - 30-60 mg PO bid-qid
   - Avoid in children: more sensitive to respiratory depression
   - Avoid in patients with ulcerative colitis: toxic megacolon or colonic perforation
   - Avoid use with infections
     - May prolong illness in salmonella and shigella infections
     - Antibiotic associated diarrhea
     - Possibly other invasive bacteria

**Opium Tincture, Camphorated (Paregoric, Pantopon) CIII**
5 ml: morphine equivalent 2 mg, anise oil, benzoic acid in 45% ETOH
Do not confuse with opium tincture, deodorized containing 25X morphine
Adults: 5-10 ml p each loose BM to qid; children 0.25-0.5 ml/kg to qid
Neonatal withdrawal syndrome: 4-6 drops q 3-6 hrs - taper over weeks

**Diphenoxylate and atropine** * - CV - 5 mg qid; children 0.3-0.4 mg/K/d in divided dose
   - Lomotil - tabs: diphenoxylate HCl 2.5 mg; atropine sulfate 0.025 mg
   - Lomotil Liquid - per 5 ml: diphenoxylate HCl 2.5 ml; atropine sulfate 0.025 mg

   Crosses blood brain-barrier but no morphine-like activity in therapeutic doses
   - Larger doses (25-fold higher) produce opioid effects
   - Salts are insoluble in water hence does not have IVDA potential
   - Atropine (anticholinergic) added to prevent abuse with using high doses

**Loperamide** * OTC - 4 mg then 2 p each loose BM to 16 mg/d
   - Imodium A-D 1 mg/5 ml
   - Imodium 2 mg caps
   - Imodium Advanced (loperamide 2 mg, simethicone 125 mg)

   - Equally effective vs codeine
   - Does not cross blood-brain barrier hence no potential for abuse
STARCHES, TALC, CHALKS AND ABSORBENT COMPOUNDS

Not recommended for routine use in acute diarrhea

Mechanism: **act as nonspecific adsorbents of water creating firmer stool**
- May adsorb microorganisms/toxins, alter intestinal flora or coat/protect intestine but no concrete evidence of such activity
- No evidence that they decrease intestinal fluid loss (the most serious sequelae of diarrhea)

Commonly used compounds:
- **Kaolin** (hydrated aluminum silicon clay)
- **Pectin** (purified CHO gel)
- **Activated attapulgite** (magnesium aluminum silicate)
- **Bismuth salts**: subgallate, subsalicylate
- **Cholestyramine** - anion exchange resin

<table>
<thead>
<tr>
<th>STARCHES, TALC, CHALKS, ABSORBANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kaopectate</strong> : activated attapulgite, pectin - OTC</td>
</tr>
<tr>
<td><strong>Donnagel</strong></td>
</tr>
<tr>
<td>Activated attapulgite 600 mg/15 ml - mint flavored, ETOH</td>
</tr>
<tr>
<td>1.4% OTC</td>
</tr>
<tr>
<td><strong>Kapectolin</strong> - kaolin, pectin - OTC</td>
</tr>
<tr>
<td><strong>Kapectolin PG</strong></td>
</tr>
<tr>
<td>Powdered opium, kaolin, pectin, hyoscyamine, atropine, scopolamine - CV</td>
</tr>
<tr>
<td><strong>Parepectolin</strong>: kaolin, paregoric, pectin - CV</td>
</tr>
<tr>
<td><strong>Dia-Quel</strong> homatropine, paregoric, pectin - CV</td>
</tr>
</tbody>
</table>

BISMUTH

**Bismuth subsalicylate (Pepto-Bismol)** - OTC
- Antisecretory, antibacterial, antitoxin and anti-inflammatory effects
- Useful for treatment and prevention of bacterial or viral diarrhea
- May be useful prophylactically for travelers diarrhea
  - Can prevent up to 65% of cases of diarrhea in high risk areas
  - Reduces stools by 50% with travelers diarrhea
  - Large doses may be needed: 30 ml q ½ h to 8 doses

Mechanism unclear
- May work via salicylate component
- May interfere with adhesion of bacteria to intestinal mucosa

Adverse effects: tinnitus, black stools, black tongue

Interactions: may interfere with other drugs esp doxycycline (taken to prevent malaria)

Prophylactic use should be limited to 3 weeks

Concerns exist re: cumulative effects of absorption of small amounts of bismuth
OTHER ANTIDIARRHEAL AGENTS

Octreotide (Sandostatin) somatostatin analog
- Long acting octreotide for severe refractory diarrhea
- Clinical uses
  - Metastatic carcinoid syndrome
  - Vasoactive peptide tumors
  - Diarrhea from HIV disease
- Dosing: 100-600 mug SC or IV in 2-4 divided doses

Adrenergic Receptor Agonists
- Decrease diarrhea via B-adrenergic receptors
- Stimulate intestinal electrolyte absorption
  Clonidine (Catapres) - alpha adrenergic agonist - useful in diabetics
  - Large volume diarrhea
  - Diarrhea occurs due to degeneration of intestinal autonomic nervous system

Corticosteroids: reduce inflammation in gut
- Stimulate water and electrolyte absorption
- Inhibits prostaglandin and leukotriene synthesis
- Useful in refractory chronic diarrhea
  - Pancreatic cholera
  - Indicated for inflammatory bowel disease

Zaldaride maleate: new antisecretory agent - Not yet available in US
- Mechanism: inhibits intestinal calmodulin
- Travelers diarrhea: decreases duration of diarrhea from average of 43 hours to 20 hours

Bulk Producing Laxatives (hydrophilic colloids)

Mechanism:
- Substances have the ability to absorb excess fecal fluid and they swell in intestinal tract
- Fluid absorption helps aids in production of formed stools
- Suitability for most forms of diarrhea remain speculative

Agents
- Carboxymethylcellulose (Citruce)
- Polycarbophil (Fiberall, Fiber-Con, others)
- Psyllium seed (Metamucil, others)
ANTI-CONSTIPATION AGENTS

BULK FORMING AGENTS: contain one of three classes of fiber components

- Widely used: constipation, diverticular disease, IBS, hemorrhoids
- Good efficacy and safety - no systemic side effects

  - Mechanism: Fiber
    - Normalizes colonic transit time via absorption H2O
      - Adding weight
      - Providing bulk to stool
      - Increased water absorption
      - Feces become soft and bulky
      - Colonic intraluminal pressures decreased

LAXATIVES

Osmotic agents:
- Poorly absorbed compounds - pull water into stool via osmotic pressure
- Sulfates, phosphates and magnesium salts
- Retained water in bowel lumen results in softening and movement of stool

<table>
<thead>
<tr>
<th>OSMOTIC LAXATIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose - Cephulac, Cholac, Chronulac, Constilac, Constulose, Dulphalac, Enulose,</td>
</tr>
<tr>
<td>Magnesium Citrate - Citroma, Citrate of Magnesium</td>
</tr>
<tr>
<td>Magnesium Hydroxide: Milk of Magnesia</td>
</tr>
<tr>
<td>Magnesium Sulfate: Epsom salt</td>
</tr>
<tr>
<td>Polyethylene Glycol Electrolyte Solution</td>
</tr>
<tr>
<td>Co-Lav, Colovage, CoLyte, Go-Evac, GoLYTELY, NuLytely, OCL</td>
</tr>
<tr>
<td>Sodium Phosphate and Sodium Bisphosphate: Fleet Enema, PhosphoSoda</td>
</tr>
</tbody>
</table>

Stimulant (contact) agents

Mechanism:
- Stimulating intestinal fluid secretion
- Increasing propulsive motor activity
Varying potency: mild to strong purgatives

Most frequently used (and abused) agents
- OTC
- Inexpensive
- BM within 6-12 h thus quick relief constipation

Can "cause cathartic" - poor propulsive activity
Phenolphthalein (old formulation Ex-Lax, Feen-a-Mint) removed from market
  Can destroy intramural nerve plexus in colon

<table>
<thead>
<tr>
<th>SEQUELAE LAXATIVE ABUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Cathartic colon&quot;</td>
</tr>
<tr>
<td>Poor propulsive activity</td>
</tr>
<tr>
<td>Major electrolyte imbalance</td>
</tr>
<tr>
<td>Malabsorption</td>
</tr>
<tr>
<td>Melanosis coli:</td>
</tr>
<tr>
<td>Accumulation of dark pigment in colonic mucosa</td>
</tr>
</tbody>
</table>

© 2002, Lois E. Brenneman, MSN, CS, ANP, FNP
all rights reserved − www.npceu.com
STIMULANT LAXATIVES

- **Bisacodyl**: (PO, suppository, enema) Bisco-Lax, Dulcagen, Dulcolax, Fleet Bisacodyl
- **Bisacodyl Tannex**: Clysodrast (enema)
- **Cascara Sagrada**: Cascara Sagrada, Cascara Aromatic
- **Castor Oil**: Emulsoil, Fleet Castor Oil, Purge
- **Phenolphthalein**: off market - Ex-Lax, Feen-a-Mint
- **Senna Concentrate**: Gentlax, Castoria, Fletcher’s Castoria, Senokot, Senna-Gen, Senolax
- **Sennosides A & B - Calcium Salts**: Ex-Lax Gentle Nature

Hyperosmolar agents

- Produces dehydration of exposed mucosal tissue leading to irritation and evacuation
- Laxative effect occurs within 15-30 minutes
- One suppository or 4 mL liquid inserted high into rectum

- **Glycerin**: Fleet BabyLax, Sani-Supp, Glycerol

STOOL SOFTENERS

- Anionic surfactants considered wetting agents
  - Increases the wetting efficiency of intestinal water
  - Facilitating the mixing of aqueous and fatty substances to soften fecal mass
  - Stimulates fluid secretion
  - Does not exert laxative effect but used as adjunctive treatment in constipation
  - Useful in patients with hard dry stools or in patients who should avoid straining

- **Docusate Calcium**: (Sulfolax, Surfak)
- **Docusate Sodium**: (Colace, Dioeze)
  - With casanthranol (Peri-Colace)
  - With senna concentrate (Senokot S)
  - With sodium carboxymethylcellulose (Disoplex)
  - **Docusate Potassium**: Dialose, Diocto-K

LUBRICANTS

Useful to maintain soft stools to avoid straining; coats stool to prevent colonic absorption
- Not as effective or safe as stool softeners
- May interfere with absorption of fat soluble vitamins and nutrients

- **Mineral Oil**: Agoral Plain, Fleet Mineral Oil Enema, Liqui-Doss
PHYSIOLOGY OF VOMITING

Mechanism of vomiting
- Both smooth and striated muscles
- Glands leading to expulsion of stomach contents through mouth

Triggers of vomiting
- GI tract
- Labyrinth of inner ear, limbic area and cerebral cortex

Chemoreceptive trigger zone is most important source for vomiting
- Floor of fourth ventricle
- Location
  - Medulla oblongata
  - Near other centers for control of autonomic function outside blood-brain barrier
- Contains abundance of dopamine receptors
- Chemoreceptive trigger zone must be stimulated for vomiting to occur

EMETIC AGENTS: Ipecac, apomorphine, salt water and eggs

Indicated when need to artificially stimulate vomiting e.g. poisoning

Ipecac Syrup - contains emetine and cephaline
- Direct action on chemoreceptive trigger zone
- Indirect action: irritation of stomach
- Vomiting occurs within 30 min
- Better results if few glasses H20
- Unabsorbed it may have fatal cardiotoxic effects (myocarditis)
- Do not give to unconscious patient due to risk of non-absorption

Apomorphine
- Morphine derivative with little analgesic activity
- Administer SQ; acts directly on chemoreceptor trigger zone within minutes
- Excessive doses: respiratory depression
ANTIEMETIC AGENTS

**Antihistamines - H-1 receptor agonists**
- Depress hyperstimulation of labyrinth of inner ear
- Most effective in treating nausea and vomiting of motion sickness
- Also treats Meniere’s disease, labyrinthitis

- Side effects:
  - All elicit varying degrees of drowsiness
  - May have significant anticholinergic effects
  - Dry mouth, blurred vision, fatigue, etc.
  - Must give 1 hr before as it is slower to absorb

**Anticholinergic**

**Scopolamine - (Hyoscine, Transderm Scop, Scopace)** anticholinergic
- Transderm Scop: 72h patch
  - Circular flat disk that adheres to skin behind ear
  - Provides for continuous steady rate of drug release over 3d (5 ug/h)
  - Minimal side effects
- Depress vestibular apparatus and inhibit cholinergic activation of vomiting center
- Very effective in preventing motion sickness
- High incidence of side effects limits oral usefulness
- Antagonism of cholinergic receptors in vestibular nuclei and reticular formation

**Phenothiazines:** dopamine and H1 receptor antagonists

**Mechanism**
- Inhibit dopaminergic transmission at chemoreceptor trigger zone
- Reduces gastric irritation due to
  - Inhibition of H1
  - Possibly cholinergic receptors

**Clinical uses**
- Drug-induced emesis
- Nausea/vomiting: surgery, anesthesia, radiation, carcinoma, severe infection
- Little use in motion sickness because no effect on vestibular apparatus

**Adverse effects** limit to short-term use
- Sedation, orthostatic hypotension, cholestatic hepatitis
- Extrapyramidal problems

Most drugs also used as **antipsychotic agents** (except thiethylperazine)

**Metoclopramide (Reglan):** anti-dopaminergic (see Prokinetic Agents)
- Antagonism of dopamine receptors in CTZ and periphery
- Enhancing propulsive gastroduodenal motility
- Clinical indications
  - Radiation therapy
  - Drug and chemotherapy-induced nausea/vomiting
Dronabinol (Marinol) CII
- Tetrahydrocannabinol (THC) - *psychoactive ingredient in marijuana* (Cannabis sativa)
- Effective in reducing nausea and vomiting associated with chemotherapy
- Can cause profound CNS effects
  - Extreme mood changes (euphoria, anxiety, depression, panic, paranoia)
  - Altered states of reality
  - Impaired memory, distorted perception, hallucinations
- Other side effects: tachycardia, orthostatic hypotension, fainting
- Has been used to stimulate appetite in HIV disease
- Strongly habituating

Ondansetron (Zofran)
- Selective 5HT 3 receptor antagonist
- Serotonin 5HT3 receptors occur on both central and peripheral GI receptors
- Particularly effective in *chemotherapy-induced nausea and vomiting*
  - Chemotherapy-induced nausea and vomiting may be due to release of serotonin (5-HT) from enterochromaffin cells in small intestine
  - Resultant stimulation of vagal afferents (via 5HT3 receptors) may instigate vomiting reflex
- Also effective for *post-operative nausea and vomiting*
- No effect on gastric emptying
- Accordingly limited role as prokinetic agent in gastroparesis
- Side effects: headache, diarrhea, dizziness, muscular pain, drowsiness
- Significant adverse reactions
  - Constipation, rash, fever, abdominal pain, weakness, shivering, malaise, urinary retention.
  - Rare: bronchospasm, tachycardia, angina, hypokalemia, EKG changes, grand mal seizures

Granisetron (Kytril)
- Selective serotonin (5 HT3) receptor antagonist (see ondansetron)
- Little or no effect on other on other serotonin receptors
- Newer agent similar to ondansetron
- Used in *chemotherapy-induced nausea and vomiting*
- No head to head studies with ondansetron
- Adverse effects
  - Headache, diarrhea, somnolence, asthenia
  - Elevated liver enzymes in 2-4%

Trimethobenzamide (Tigan)
- Mechanism not established
- May directly depress chemoreceptor trigger zone or vomiting center
- Does not appear to block direct activation of vomiting center
- Weak antihistamine activity
- Contraindicated in children: may contribute to Reye’s Syndrome with viral illness
- Extra-pyramidal symptoms can occur
- Adverse reactions
  - Hypersensitivity and Parkinson-like symptoms
  - Hypotension with parenteral route in surgical patients
  - Allergic-like skin reactions; d/c drug at first sign of sensitization