GI DRUGS

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ANTACIDS

- Indicated (used) for **gastric hyperacidity** - **neutralize gastric acid**
- Adjunctive treatment: peptic ulcers, hiatal hernia, gastritis, GERD, Zollinger-Ellison Syndrome
- Peptic ulcer prevention
- Phosphate binder for patients in renal failure (only aluminum-based agents)
- Most agents not absorbed - excreted via feces

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, alginic 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 regiments
- 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 ANTAGONIST

cimetidine (Tagamet)
ranitidine (Zantac)
famotidine (Pepcid)
nizatidine (Axid)

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 effect 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 bid 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

PROTON PUMP INHIBITORS

omeprazole (Prilosec)
lansoprazole (Prevacid)
rabeprazole (Aciphex)
pantoprazole (Protonix)
esomeprazole (Nexium)

- Some class members are indicated for **H. Pylori treatment**

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 call.

* 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 regiments are available**
    - Both categories have regimens which are effective and backed by research
    - Regiments 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

COMMON ANTICHOLINERGICS

Pirenzepine selective anticholinergic agent

Dicyclomine HCl (Bentyl) caps 10 mg, 20 mg
Bentyl Syrup 10 mg/5ml

Hyoscyamine (Levsin) tabs - 0.125mg
Levsin Elixir 0.125 mg/5 ml
Levsin Drops: 0.125/ml
Levsin/ SL - 0.125 mg
Levbid: hyoscyamine 0.375 mg ext release tabs

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

CONTRAINDICATIONS

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

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**

MECHANISM

- 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.

COMMON OPIOIDS ANTIDIARRHEALS
Codeine
Camphorated opium (Paregoric)
Diphenoxylate and atropine (Lomotil)
Loperamide (Imodium)

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

STARCHES, TALC, CHALKS, ABSORBANTS

Kaopectate: activated attapulgite, pectin - OTC
Donnagel
Activated attapulgite 600 mg/15 ml - mint flavored, ETOH 1.4% OTC
Kapectolin - kaolin, pectin - OTC
Kapectolin PG
Powdered opium, kaolin, pectin, hyoscyamine, atropine, scopolamine CV
Parepectolin: kaolin, paregoric, pectin - CV
Dia-Quel homatropine, paregoric, pectin - CV

BISMUTH

Bismuth subsalicylate (Pepto-Bismol) - OTC
- Antisecretory, antibacterial, antitoxin and anti-inflammatory effects
- Useful for <u>treatment and prevention</u> 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

MISCELLANEOUS ANTIDIARRHEALS

Octreotide (Sandostatin)
Corticosteroids
Clonidine (Catapres)
Zaldaride maleate
Bulk Producing Laxatives

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 (hydrophillic 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 (Citrucel)**
- **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 H20**
    - Adding weight
    - Providing bulk to stool
  - Increased water absorption
    - Feces become soft and bulky
    - Colonic intraluminal pressures decreased

BULK FORMING LAXATIVES

- **Psyllium** (**Metamucil, Perdiem**) natural fiber
- **Methylcellulose** (**Citrucel**) synthetic cellulose
- **Polycarbophil calcium** (**Fiberall, Fiber-Con**) synthetic

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

OSMOTIC LAXATIVES

Lactulose - Cephulac, Cholac, Chronulac, Constilac, Constulose, Dulphalac, Enulose,
Magnesium Citrate - Citroma, Citrate of Magnesium
Magnesium Hydroxide: Milk of Magnesia
Magnesium Sulfate: Epsom salt
Polyethylene Glycol Electrolyte Solution
Co-Lav, Colovage, ColLyte, Go-Evac, GoLYTELY, NuLytely, OCL
Sodium Phosphate and **Sodium Bisphosphate**: Fleet Enema, PhosphoSoda

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

SEQUELAE LAXATIVE ABUSE

- "Cathartic colon"
- Poor propulsive activity
- Major electrolyte imbalance
- Malabsorption
- Melanosis coli:
  Accumulation of dark pigment in colonic mucosa

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

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

STOOL SOFTENERS

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 nutriens

AGENTS **Mineral Oil**: Agoral Plain, Fleet Mineral Oil Enema, Liqui-Doss

EMETIC AND ANTIEMETIC AGENTS

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

ANTIHISTAMINE AGENTS

- **Dimenhydrinate (Dramamine)**
- **Cyclizine , buclizine**
- **Diphenhydramine (Benadryl)**
- **Meclizine HCL (Antivert)**

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

PHENOTHIAZINES

Promethazine (Phenergan)
Prochlorperazine (Compazine)
Chlorpromazine (Thorazine)
Perphenazine (Trilafon)
Thiethylperazine (Torecan)

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 no 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