Agents that Reduce Introduce Intragastric Acidity

Physiology of Acid Secretion	• Parietal cells have CCK-B receptors, histamine, ACH (muscuranic, M3) receptors for gastrin • ACH/ Gastrin released from antral G cells into blood → bind to parietal cell receptors → increase in cAMP → stimulate protein kinases → stimulate acid secretion by H+/K+ ATP-ase/ proton pump on canalicular surface • Close to parietal cells are gut endocrine cells called enterochromaggin-like cells which have receptors for gastric and Ach which stimulate histamine release • Histamine → adenylyl cyclase activated → increase in cAMP → stimulate protein kinases → stimulate acid secretion by proton pump • Gastrin → acid secretion: an indirect stimulatory effect from ECL cells • Ach → acid secretion: direct parietal cell stimulation
ANTACIDS	
Introduction: anatacids	• Nonprescription • For heartburn and dyspepsia • They are weak bases that work against gastric HCl acid → salt and water • Given 1 hour before after meal: neutralizes acids for up to 2 hours • Efficacy depends on: rate of dissolution, rate of gastric emptying, rate of reaction with acid, water solubility • May affect absorption of other medications by binding to drugs

	or changing pH (THEREFORE DISSOLUTION)
Antacid: sodium bicarbonate	• Reacts rapidly HCl → carbon dioxide and sodium chloride • CO2 → gastric distention and belching • Unreacted alkali is absorbed → potential metabolic alkalosis at high doses or to patients with renal insufficiency • May increase fluid retention with patients of hypertension, renal insufficiency, heart failure
Antacid: Calcium Carbonate	• Less soluble than sodium bicarbonate • Reacts slower → forms carbon dioxide and calcium chloride • May cause belching, metabolic alkalosis
Excessive doses of sodium bicarbonate or calcium carbonate with calcium-containing diary products	• Hypercalcemia • Renal insuffiency • Metabolic alkalosis • Or milk-alkali syndrome: hypercalcemia caused by consumption of calcium and absorbable alkali like calcium carbonate or milk and sodium bicarbonate
Antacids: Magnesium Hydroxide and Aluminum Hydroxide	• Reacts slowly • NO gas formation • Mg salts → diarrhea • Aluminum salts → constipation • Usually given in combination • Contraindicated with renal insufficiency

H2-Receptor Antagonists	
Those rapidly absorbed from the intestine	• Cimetidine • Ranitidine • Famotidine • Nizatidine
Those that undergo first-pass hepatic metabolism, with a bioavailability of 50%	• Cimetidine • Ranitidine • Famotidine • NIZATIDINE HAS LITTLE FIRST-PASS METABOLISM
Duration of Action	• 6-10 hours, twice a day
Meal-Stimulated Acid Secretion	• this acid secretion is stimulated by gastrin, acetylcholine and histamine • these drugs have a modest effect on this
% inhibited of different acids	• nocturnal acid: 90% (depends largely on histamine) • total, 24-hour acid secretion: 60-70% • day-time, meal-stimulated: 60%
CLINICAL USES	
Gastroeseophageal Reflex Disease (GERD)	• prophylactically, before meals • patients with erosive esophagitis: H2 antagonists heal 50% -- PROTEIN PUMP INHIBITORS ARE PREFERRED
Non-Ulcer Dyspepsia	• over the counter agents • for INTERMITTENT dyspepsia
Prevention of Bleeding from Stress-Related Gastritis: IV H2 antagonists	• preferred over IV proton pump inhibitors: better efficacy and lower cost • continuous infusions of h2 antagonists preferred over bolus infusions because more consistent, sustained elevation of intragastric pH
Peptic Ulcer Disease	• replaced by proton pump inhibitors • healing rate more than 80-90% after 6-8 weeks • NOT effective with H. Pylori ○ H. pylori treated with 10-

	14 day course with PPIs and two antibiotics ○ If not eradicated, H2 antagonists can be used daily at bedtime in half of usual ulcer therapeutic dose to prevent ulcer recurrence • NOT effective if NSAID is continued
ADVERSE EFFECTS	• Extremely safe. • Only 3% of patients: diarrhea, headache, fatigue, myalgias, constipation • Cimetidine: inhibits binding of dihydrotestosterone to androgen receptors, inhibits metabolism of estradiol, increases serum prolactin • Long-term use: gynecomastia, or incompetence in men, galactorrhea in women • Crosses placental barrier → breast milk • Rarely cases blood dyscrasias, bradycardia and hypotension • Metnal status changes: confusion, agitation, hallycinations, with IV H2 antagonists
Drug Interactions	• Cimetidine: inhibitrs cytochrome-P450 enzymes → increase half-life of many drugs • Ranitidine binds 4-10 x less • Nizatidine and famotidine: binding is negligible
Proton Pump Inhibitors	
Drug Names	• Omeproazole (oral) • Rapeprazole (oral) • Lanzoprazole (oral and IV) • Pantoprazole (oral and IV) • Esmoprazole (oral and IV)
Introduction	• Among most widely used drugs: efficacy and safety • Formulated as a prodrug, released

	in intestine • Immediate release suspension contains sodium bicarbonate to protect drug from acid degradation → rapid response
Pharmocokinetics	• Lipophilic weak bases • Ph: 4-5 • Absorption → diffuse across lipid membranes into acidifed compartments (like parietal cells canaliculus) • Prodrug becomes protonated and concentrated: 1000x within parietal cells • Undergoes molecular converstion to active form which binds the H+/K+ ATPase enzyme and inactivates it • Rabeprazole and immediate release omeprazole: faster onsets of action • Given an hour before meal, usually breakfast • Half-lives: short, but effect lasts for 24 hours because of irreversible inhibition • Inhibits both fasting and meal-stimulated acid secretion: 90-98% of 24-hour acid secretion • >18 hours required for synthesis of new H+/K+ ATPase pump molecules • 3-4 days of daily medication required before full-acid inhibiting potential reached
CLINICAL USES	
Gastroesophageal Reflex Disease (GERD)	• most effective agents against GERD, all its forms and complications
Non-Ulcer Dyspepsia	• modest activity • 10-20% more beneficial than placebo
Stress-Related Gastritis	• oral immediate release omeprazole administered by nasogastric tube • for patients without nasoenteric

	tube, IV H2-antagonists are preferred
Gastrinoma and other Hypersecretory Conditions	• high doses of omeprazole
Peptc Ulcer Disease	• heal more than 90% of cases within 4-6 weeks
H. Pylori-associated Ulcers	• eradicates H. Pylori by direct antimicrobial activity and by lowering MIC of antibiotics • Triple Therapy: PPI twice daily + clarithromycin 500 mg twice daily + Amoxcillin 1gm twice daily • OR: metronidazole 500 mg twice Daily + PPI twice daily + clarithromycin 400 mg twice daily
NSAID-associated Ulcers	• Promote ulcer healing despite continued NSAID use, whereas H2-antagonists are ineffective with continued NSAID use
Re-bleeding Peptic Ulcer	• Oral or IV • High pH may enhance coagulation and platelet aggregation
Adverse Effects of PPI's	• Diarrhea • Headache • Abdmonial pain • Not teratogenic in animals, but not used in pregnancy • Reduction of cyanocobalamine absorption • Increased risk of GI and pulmonary infection • Increased serum gastrin levels which causes → hyperplasia of ECL and carcinoid tumors in rats but NOT humans • Increased proliferative rate of colonic mucosa but NO CANCER DEVELOPMENT • Chronic inflammation in gastric body • Atrophic gastritis and intestinal metaplasia ← transformation of epithelium usually of stomach or esophagus to a type that bears

	resemblance to intestine
Drug Interactions	• May affect absorption of drugs ← decreased gastric acidity like digoxin and ketoconazole • Omeprazole: inhibits metabolism Coumadin (warfarin), diazepam, phenytoin • Rabeprazole and pantoprazole: no significant interactions

Mucosal Protective Agents	
Mechanism of Injury/ Protection	• Mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin • Epithelial bicarbonate secretion establishes pH gradient within mucous layer in which pH ranges from 7 at mucosa surface to 1-2 in gastric lumen • Blood flow carries bicarbonate and vital nutrients to surface cells • Areas of injured epithelium are quickly repaired by restitution ← migration of cells from gland neck cells seals small erosions to reestablish intact epithelium • Mucosal prostaglandins stimulates mucous and bicarbonate secretion and mucosal blood flow
Sucralfate: Introduction	• Salt of sucrose complexed to sulfated aluminum hydroxide • In stomach: breaks down tino sucrose sulfate (strongly negatively charged) and an aluminum salt • Negative sucrose sulfate binds to positive proteins in base of ulcers or erosions → physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion • Acts for up to 6 hours • Les than 3% of intact drug and aluminum is absorbed from GIT
Sucralfate: Clinical Uses	• 1 g four times daily on empty stomach: slurry through nasogastric tube • reduces incidence of GI bleeding in critically ill patients in ICU • prevents stress-related bleeding when antacids, H2 antagonists and PPI's can potentially increase risk of nosocomial pneumonia (an

	infection that occurs during hospital stay)
Sucralfate: Adverse Effects	• not absorbed → sucralfate virtually devoid of systemic adverse effects • constipation in 2% of patients due to aluminum salt • small amount of aluminum salt absorbed, therefore should not be used for prolonged periods with renal insufficiency patients
Sucralfate: Drug Interactions	• bind to other medications, impairing their absorption
Prostaglandin Analogs	
Misoprostol: Methyl Analog of PGE1	• half-life: less than 30 minutes • administered 3-4 times/ day • stimulate mucus and bicarbonate secretion, enhances mucosal blood flow • binds to prostaglandin receptors on parietal cells → reducing histamine-stimulated cAMP production → most acid inhibition • stimulates intestinal electrolyte and fluid secretion, intestinal motility and uterine contractions

Clinical Uses of Prostaglandin Analogs	• prevention of NSAID-induced ulcers in high risk patients
	  ○ not widely used for this because of side effects, need for multiple doses/ day
	  ○ PPI may be as effective and better tolerated
	  ○ Cyclooxygenase 2-selective NSAID's are options for such patients

Adverse Effects and Drug Interactions	• Diarrhea and cramping, abdominal pain: in 10-20% of patients • Should not be used during pregnancy • No significant drug interactions

COLLOIDAL BISMUTH COMPOUNDS	
Drug names	• Bismuth subsalicylate • Bismuth subcitrate
Introduction	• Minimally absorbed from GIT... <1% • Coats ulcers and erosions: protective layer against acid and pepsin • May stimulate prostaglandin, mucus, bicarbonate secretion
Bismuth Subsalicylate	• Reduces stool frequency and liquidity in acute infectious diarrhea ← salicylate inhibition of intestinal prostaglandin and chloride secretion • Direction antimicrobial effect, binds enterotoxins: benefits in preventing and treating traveler's diarrhea • Direct antimicrobial activity against H. Pylori • Widely used for nonspecific treatment of dyspepsia and acute diarrhea and prevention of traveler's diarrhea • Second-line therapy for eradication of H. Pylori infection (PPI + bismuth subsalicylate + tetracycline + metronidazole for 10-14 days) • Adverse effects: blackening of stool and tongue, prolonged use: rarely lead to bismuth toxicity → encephalopathy

Drugs Stimulating GI Motility – prokinetic agents	
Introduction	• They agents that increase lower esophageal sphincter pressures → may be useful for GERD • Drugs that improve gastric emptying: gastroparesis and postsurgical gastric emptying delay • Agents that stimulate small intestine: postoperative ileus, chronic intestinal pseudo-obstruction • Agents that enhance colonic transit: constipation
Physiology of the ENS	• Composed of interconnected networks of ganglion cells and nerve fibers mainly in submucosal plexus and between circular and longitudinal layers of myenteric plexus • Extrinsic sympathetic and para nerves project onto submycosal and myenteric plexuses • ENS can independently regulate GI motility • Extrinsic primary afferent neurons project via dorsal root ganglia or vagus nerve to CNS • Release of serotonin (5-HT) from intestinal mucosa enterochromaffin EC cells stimulates 5-HT3 receptors on extrinsic afferent nerves → nausea, vomiting, abdominal pain • Serotonin also stimulates submucosal 5-HT1P receptors of intrinsic primary afferent nerves (IPANs)
IPANs	• IPANs contain calcitonin gene-related peptide (CGRP) and ACH and project to myenteric plexus interneurons • 5-HT4 receptors on presynaptic terminals of IPANs enhance release of CGRP and ACH

	• mytenteric interneuron control: peristaltic reflex (promoting release of excitatory mediators proximally and inhibitory distally) • motilin may stimulate excitatory neurons or muscle cells directly • dopamine acts as inhibitory neurotransmitter in GI, decreasing intensity of esophageal and gastric ocntractions
Serotonin Release	• by EC cells from G distention stimulates submucosal intrinsic primary afferent neurons through 5-HT1P receptors and extrinsic primary neyrons via 5-HT3 receptors • submucosal IPANs activate ENS neurons responsible for peristaltic and secretory reflex activity • stimulation of 5-HT4 receptors on presynaptic terminals of IPANs→ release of Ach and CGRP, → reflex activity promoted
Cholinomimetic Agents	
Bethanechol	• Stimulates M3 receptors on muscle cells at myenteric plexus synapses • Was used for treatment of GERD and gastroparesis
Neostigmine	• AchE inhibitor can enhance gastric, SI, colonic emptying • IV: used for treatment of acute large bowel distention (acute colonic pseudo-obstruction) • Administration of 2mg → prompt colonic evacuation of flatus and feces • Cholinergic effects include: excessive salivation, nausea, vomiting, diarrhea, bradycardia
Dopamine D2- Receptor Antagonists	
Metoclopramide & Domperidone	• Dopamine inhibits cholinergic

	smooth muscle stimulation • These drugs increase esophageal peristaltic amplitude • Increase lower esophageal sphincter pressure • Have no effect on SI or colonic motility • Block D2 receptors in chemoreceptor trigger zone of medulla (area postrema) → Potent anti-nausea and antiemetic action

Clinical Uses	• GERD
	  ○ Not effective with erosive esophagitis
	  ○ Not superior to antisecretory agents
	  ○ Mainly in combination with antisecretory agents in patients with refractory heartburn
	• Impaired Gastric Emptying (gastroparesis)
	  ○ Widely used in treatment of postsurgical and diabetic gastroparesis
	  ○ Metoclopramide used to promote advancement of nasoenteric feeding tubes form stomach into duodenum
	• Non-ulcer dyspepsia
	• Prevention of vomiting
	• Postpartum lactation stimulation
	  ○ Domperidone

Adverse Effects: Metclopromide	• Crosses BBB → restlessness, drowsiness, insomnia, anxiety, extrapyramidal symptoms (dystonia, akathisia, agitation, parkinsonian features), tardive dyskinesia
Adverse Effects: Domperidone	• Does NOT cross BBB • **Both** drugs can elevate

	serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders

LAXATIVES	
Introduction	• Intermittent constipation: best prevented with a high-fiber diet, adequate fluid intake, regular exercise, responding to nature's call
Bulk-Forming Laxatives	• Indigestible, hydrophilic colloids that absorb water, forming bulk, emollient gel that distends colon and promotes peristalsis • Include natural plant products: psyllium, methylcellulose • Synthetic fibers: polycarbophil • Bacterial digestion of plant fibers within colon → increased bloating and flatus
Stool Surfactant Agents (softeners)	• They soften stool, permitting water and lipids to penetrate • Administered: orally or rectally • Docusate (oral, enema); glycerin (suppository)
Mineral Oil	• Clear, viscous oil that lubricates fecal material, retarding water absorption from stool • Used to prevent, treat fecal impaction • Aspiration can result in severe lipid pneumonitis • Long-term use → impair absorption of fat-soluble vitamins
Osmotic Laxatives • Soluble but non-absorbable compounds → increased stool liquidity due to an increase in fecal fluid	
Osmotic Laxatives: Non-absorbable Sugars or Salts	• Used for treatment of acute constipation or prevention of chronic constipation
Osmotic Laxatives: Magnesium Hydroxide (milk of magnesia)	• Not used for prolonged periods with patients with renal insufficiency due to risk of

	hypermagnesemia • Large doses of magnesium citrate and sodium phosphate → purgation → rapid bowel evacuation within 1-3 hours and may cause volume depletion
Osmotic Laxatives: sorbitol, lactulose	• Sugars metabolized by bacteria producing severe flatus and cramps
Osmotic Laxatives: Balanced Polyethlene Glycol	• Inert, non-absorbable, osmoticaly active sugar with sodium sulfate, sodium chloride, sodium bicarbonate, potassium chloride • Safe, no IV fluid or electrolyte shifts • No cramps, or flatus • Used for complete colonic cleansing before endoscopy • For cleansing: ingested rapidly, 4L over 2-4 hours • For chronic constipation: powder is mixed with water/juice
Stimulant Laxatives • Direct stimulation of ENS and colonic electrolyte and fluid secretion	
Stimulant Laxatives: anthraquinone derivatives	• Aloe, senna, cascara • Occur naturally in plants • Poorly absorbed • After hydrolysis in colon – produce bowel movement in 6-12 hours when given orally and 2 hours rectally • Chronic use → brown pigmentation of colon known as melanosis coli • Not carcinogenic
Bisacodyl	• Tablet, suppository • For acute, chronic constipation • Also used in conjunction with PEG solutions for colonic cleansing • Induces bowel movement within 6-10 hours orally and 30-60 minutes rectally • Safe for acute and long-term use

Phenolphthalein	• Removed from market ← concerns of cardiac toxicity
Opioid Receptor Antagonists • Do not cross BBB • Block peripheral mu-opioid receptors without causing central analgesic effects	
Opioid Receptor Antagonists: Methymnaltrexone	• **For opioid-induced constipation in patients with advanced illness not responding to other agents** • **Given SC by injection every 2 days**
Opioid Receptor Antagonists: alvimopan	• **Short-term use for postoperative ileus in hospitalized patients** • **Given orally within 5 hours before surgery, twice after surgery until function of bowel improves** • **No more than 7 days of us because possible cardiac toxicity**

Antidiarrheal Agents

Introduction	• Should not be used in patients with bloody diarrhea, high fever, systemic toxicity because it may worsen underlying condition • Used to control chronic diarrhea caused by IBS or inflammatory bowel disease
Opioid Agents	
Introduction	• Inhibits presynaptic cholinergic nerves in submucosal and myenteric plexuses → increased colonic transit time and fecal water absoption • Also decreases mass colonic movements, CNS effects, potential for addiction limit usefulness of time
Opioid Agents: Loperamide	• Does not cross BBB • No analgesic or addiction potential
Opioid Agents: Diphenoxylate	• Not analgesic in standard doses • Higher doses → CNS effects • Can cause dependence • Commercial preparations contain small amounts of atropine which contribute to antidiarrheal action
Bile Salt-Binding Resins	
The Drugs	• Cholestyramine • Colestipol • Colesevelam
Uses	• Malabsorption of bile salts (Crohn's disease, post-surgical resection) → diarrhea • Drugs that can bind bile salts and decrease diarrhea caused by excess fecal bile acids • Can cause bloating, flatulence, constipation, fecal impaction • Cholestyramine and colestipol reduce absorption of drugs, fat • Colesevelam no effects on other drugs
Octreotide: synthetic octapeptide, actions similar to somatostain	

Somatostatin: 14-AA peptide released in GIT, pancreas, hypothalamus	
Mechanism of Action	• Inhibits release of many hormones • Reduces intestinal fluid and pancreatic secretions • Slows GIT motility and gall bladder contractions • Contracts blood vessels • Inhibits secretion of some anterior pituitary hormones
Clinical Uses of Somatostatin	
Inhibition of Endocrine Tumor Effects	• Carcinoid and VIPoma (neuroendocrine tumors that secret vasoactive intestinal polypeptide) → secretory diarrhea, flushing and wheezing
Diarrhea due to vagotomy or dumping syndrome	• Ingested foods bypass the stomach too rapidly
To Stimulate motility in small bowel bacterial overgrowth	• OR intestinal pseudo-obstruction secondary to scleroderma: a disease affecting skin and other organs and is one of the autoimmune rheumatic diseases
Inhibition of pancreatic secretion	• Used in patients with pancreatic fistula: leakage of pancreatic secretions from damaged ducts
Treatment of pituitary tumors	• Like acromegaly
Other uses	• GI bleeding • AIDS • Short bowel syndrome
Adverse Effects	• Impaired pancreatic secretion → steatorrhea (presence of fat in feces) → fat-soluble vitamin deficiency • Nausea, abdominal pain, flatulence, diarrhea • Formation of sludge/ gallstones because of inhibition of gallbladder contractility and fat absorption • Hyper or hypoglycemia → hormonal imbalance • Hypothyroidism, bradycardia

Drugs Used for Irritable Bowel Syndrome	
About IBS	• Idiopathic, chronic, relapsing disorder • Characterized by: abdominal pain, bloating, distention, cramps; alteration in bowel habits (diarrhea, constipation, or both) • Treatments for IBS are directed at relieving abdominal pain and improving bowel function
Antispasmodics (Anticholinergics): Dicyclomine and Hyoscyamine	• Inhibit muscuranic cholinergic receptors in enteric plexus and on smooth muscle • Efficacy for relief of abdominal symptoms not yet proven • Low doses → minimal autonomic effects • Higher doses → anticholinergic effects: dry mouth, visual disturbances, urinary retention, constipation • INFREQUENTLY USED
Serotonin 5-HT3 Receptor Antagonists	
Introduction	• Inhibition of afferent GIT 5-HT3 receptors → reduces nausea, bloating, pain • Blockage of central 5-HT3 → reduces central responses to visceral afferent stimulation • Blocking those on the terminal of enteric cholinergic neurons --? Inhibits colonic motility, especially left colon → increasing total colonic transit time
Alosetron	• Highly potent • Selective antagonist of the 5HT3 receptor • Rapidly absorbed • Plasma half-life of 1.5 hours, longer duration of action • Restricted to women with severe diarrhea-predominant IBS not

	responding to conventional therapies • Can cause ischemic colitis, severe constipation → surgery, hospitalization • Efficacy in men not established
Serotonin 5-TH4 Receptor Agonists	
Introduction	• Stimulation of 5-HT4 receptors on presynaptic terminal of submucosal intrinsic primary afferent nerves → release of neurotransmitters → peristaltic reflex
Tegaserod	• Approved for short-term treatment of women with IBS who had predominant constipation • Removed form market → increased number of cardiovascular deaths
Prucalopride	• High-affinity 5HT4 agonist • No cardiovascular toxicity • Used for chronic constipation in women
Chloride Channel Activator	
Lubiprostone	• PG Analog • Stimulates type 2 chloride channel CIC-2 in SI → increases liquid secretion in intestine → stimulates intestinal motility and bowel movement within 24 hours of taking one dose • Used in treatment of chronic constipation • Approved for women with IBS with predominant constipation • Efficacy for men unproven • Should be avoided in child-bearing age • May cause nausea in 30% due to delayed gastric emptying

Antiemetic Drugs	
Causes of Nausea and Vomiting	• Adverse effects of meds • Systemic disorders, infections • Pregnancy • Vestibular dysfunction • CNS infection • Hypertension • Peritonitis • Hepatobiliary disorders • Radiation, chemo • GIT obstruction, dysmotility, infections
Pathophysiology	• Brainstem: vomiting center • Interactions with CN 8 and 10 and neural networks in nucleus tractus solitaries that control respiration, salivation, vasomotor centers • Vomiting center contains high concentration of muscranic M1 receptors, neurokinin 1 receptors, serotonin 5-HT3 receptors
Sources of Afferent Input 1. Chemoreceptor trigger zone CTZ, area postrema 2. Vestibular system 3. Vagal 4. CNS	1. CTZ: outside BBB, but accessible to emotogenic stimuli in blood or CSF a. Rich in D2 receptors, opioid receptors, serotonin 5-HT3 and NK1 receptors 2. Vestibular: important in motion sickess via CN 8 a. Rich in M1, H1 3. Vagal and spinal afferent nerves from GIT: rich in 5-HT3 receptors a. Irritation of GI mucosa by chemo, radiation therapy, distention, acute infectious gastroenteritis → release of mucosal 5-HT → activation of receptors --? Vagal afferent input to the vomiting center and CTZ 4. CNS: role in vomiting due to psychiatric disorders, stress, anticipatory vomiting prior to

	cancer chemo a. Combinations of antiemetic agents with different MoA are used
Serotonin 5-HT3 Antagonists (--Setrons)	
Drugs & Routes	• Ondansetron (oral or IV) • Granisteron (half-life of 4-9 hours) • Dolasetron • Palnosetron (half-life 40 hours)
Mechanism of Action	• Block central 5-HT3 and peripheral (mainly) receptors on extrinsic intestinal vagal and spinal afferent nerves • Prevent esmesis due to vagal stimulation and chemo • Other emetic stimuli such as motion sickness are poorly controlled
Uses of Serotonin 5-HT3 Antagonists	• Prevention of acute chemo-induced nausea and emesis and popoperative nausea, vomiting • Efficacy enhanced by combination with DEXAMETHASONE and NK1-RECEPTOR antagonist • Prevention and treatment of nausea, vomiting in patients with radiation therapy
Adverse Effects of Serotoning 5-HT3 Antagonists	• Headache • Dizziness • Constipation • Small prolongation of QT interval
Neurokinin 1 Receptor Antagonists • They have antiemtic properties through central blockade in area postrema	
Aprepitant	• Used in combination with 5-HT3 antagonists and corticosteroids for prevention of acute and delayed nausea and vomiting from chemo • Adverse effects: fatigue, dizziness, diarrhea
Antipsychotic Drugs (--zine and dol)	
The Drugs	1. Prochlorperazine

	2. Promethazine 3. Droperidol (extremely sedating) a. Extremely sedating b. May prolong QT interval c. Extrapyramidal effects, hypotention
Mechanism of Action	• Antiemetics due to inhibition of dopamine and muscuranic receptors • Sedative due to antihistamine activities
Benzodiazepines -- pams	
Drugs, Mechanism of Action	• Reduce anticipatory vomiting caused by anxiety • Lorazepam • Diazepam
H1 Antihistamines and Anticholinergic Drugs	
Introduction	• Particularly useful in motion sickess
Adverse Effects	• Confusion, dry mouth, sedation, dizziness, cycloplegia, urinary retention
Diphenhydramine, Dimenhydrinate	• Significant anticholinergic activity
mECLIZINE	• MINIMAL ANTICHOLINERGIC PROPERTIES • LESS SEDATING • FOR PREVENTION OF MOTION SICKNESS • TREATMENT OF VERTIGO DUE TO LABYRINTH DYSFUNCTION
Hyoscine (scopolamine)	• Very high anticholinergic effects • Better tolerated as a transdermal patch
Cannabinoids	
Dronabinol & Nabilone	• Delta-9- tetrahydrocannabinol from marijuana • Psychoactive agents • Used as appetite stimulates • for chemo-induced vomiting • mechanisms not understood
Adverse effects	• euphoria • dysphoria • sedation • hallucinations • dry mouth • increased appetite

	• tachychardia, conjunctival injection (redness of white scelera of eye) • orthostatic hypotension

Drugs Used to Treat Inflammatory Bowel Disease	
About IBD	• compromises Ulcerative colitis and Corhn's disease • unknown etiology, pathogenesis • therefore drugs used belong to different classes of nonspecific mechanisms of anti-inflammatory reaction • drugs chosen on basis of severity, responsiveness, drug toxicity
Aminosalicylates: 5-Aminosalicylic acid (5-ASA)	• Work topically, not systemically in areas of diseased GI mucosa • 80% of formulated 5-ASA absorbed from SI and does not reach distal small bowel or colon in appreciable quantities • number of formulations deliver 5-ASA to various distal segments of small bowel or colon
Azo Compounds: Sulfasalazine, Balsalazide, Olsalazine	• 5-ASA bound by an azo (N=N) to an inert compound or to another 5-ASA • structure markedly reduces absorption of parent drug from SI • in terminal ileum and colon: resident bacteria cleave azo bond by means of azoreductase enzyme, releasing 5-ASA • high concentrations of 5-ASA therefore made available in ileum or colon
Mesalamine Compounds: Pentasa, Asacol, Rowasa, Canasa	• Pentasa: timed-release microgranules that release 5-ASA throughout SI • Asacol: 5-ASA coated in pH-sensitive resin that dissolves at pH of distal ileum and proximal colon • Enema: rowasa • Suppositories: Canasa
Mechanism of Action of 5-ASA	• Not certain • It modulates inflammatory mediators derived from both COX

	and LOX pathways • Other potential mechanisms include: interference with production of cytokines; inhibition of nuclear factory-B (NF-B) transcription factor for proinflammatory cytokines • Inhibition of cellular functions of natural killer cells, mucosal lymphocytes, macrophages • Scavenge reactive oxygen metabolites
Clinical Uses	• FIRST-LINE gents for treatment of mild-moderate: ulcerative colitis • Efficiency in Crohn's Disease: unproven. But still used as FIRST-LINE therapy for mild-moderate disease involving COLON, DISTAL ILEUM
Adverse Effects	• Systemic absorption, especially in low acetylators → nausea, headache, ARTHALGIA, myalgia, bone marrow suppression, malaise • Allergic reactions, oligospermia, folate deficiency
Glucocorticoids	• Inhibition of inflammatory cytokine production, chemokine production • Reduces expression of inflammatory cell adhesion molecules • Inhibits gene transcription of nitric oxide synthase, phospholipase A2, COX-2, NF-B
Glucocorticoids: Clinical Uses	• Moderate to severe IBD • Not useful for maintenance
Glucocorticoids: the Drugs	• Prednsilone (Oral, IV) • Hydrocortisone: rectally, preferred for rectal and sigmoid involvement • Budesonide: controlled-release oral formulation, releases drug in distal ileum and colon—for ileal

	and proximal colon involvement
Antimetabolites: Azathioprim, 6-Mercaotopurine	• Purine analongs • Produce thioguanine nucleotides in active form • Immunosuppressants • Inhibit pyrine nucleotide metabolism and DNA synthesis and repair → inhibition of cell division and proliferation, promote T-lymphocyte apoptosis
Antimetabolites: Clinical Uses	• Onset delayed for 17 weeks • Used in induction and maintenance of remission of iBD • Allow dose reduction or elimination of steroids
Antimetabolites: adverse effects	• Nausea, vomiting, allergic reactions (fever, rash, PANCREATITIS, diarrhea, HEPATITIS) • HEPATIC TOXICITY • Allopurinol increases levels of drugs
Antimetabolites: Methotrexate	• Used in cancer chemotherapy, RA, psoriasis • MOA: inhibits dihydrofolate reductase enzyme which is important in synthesis of thymidine and purines • High doses: inhibits cellular proliferation • Low doses: used in IBD --> reduces inflammatory actions of IL-1; stimulates adenosine release, apoptosis and death of activated T-lymphocytes • Uses: INDUCTION, maintenance of remissions of CROHN'S disease • Adverse effects: high doses --? Bone marrow depression, megaloblastic anemia, alopecia, mucositis • Renal insufficiency may increase risk of hepatic accumulation and toxicity • Side effects counteracted by

	FOLATE SUPPLEMENTS
Anti-Tumor Necrosis Factor Therapy: --MABS	
Pathophysiology	• If epithelial barrier impaired: bacterial antigens can gain access to antigen-presenting cells (APC) like dendritic cells in lamina propria • These cells present antigens to CD4+ lymphocytes and also secrete cytokines like IL-12, 18 -> inducing differentiation of TH1 cells in Crohn's disease or IL-4, TH2 in ulcerative colitis • TH1 produce cytokines, IFN, TNF → activate macrophages • Macrophages positively regulate TH1 cells by secreting additional cytokines, IFN, TNF • Recruitment of variety of leukocytes mediated by activation of resident immune cells including neutrophils • Cell adhesion molecules like integrins are important in infiltration of leukocytes
Anti-Integrin Therapy	• Aimed at blocking leukocyte recruitment, effective in inflammation • Site-specific intervention involve intestinal bacteria and therapy directed at TNF, IL-12 • TNF-alpha is one of principal cytokines mediating TH1 immune response characteristic of Crohn's Disease
Anti-TNF: Infliximab	• Chimeric immunoglobylin (75% human, 25% mouse) that binds to neutralized TNF • Binds membrane-bound TNF and may cause lysis of these cells by antibody-dependent or cell-mediated cytotoxicity • Half-life: 8-10 days, persistent antibodies for 8-12 weeks • USES: acute, chronic moderate-

	severe Crohn's
	• Given in repeated doses at 0, 2 6 weeks for induction by IV
	• Response adequate: infusions repeated every 8 weeks
	• Response might be lost due to resistance
	• Effective for refractory ulcerative colitis
	• Side effects:
	  ○ Acute: fever, chills, urticarial, anaphylaxis
	  ○ Subacute: serm-like sickness, lupus-like syndrome rarely
	• Antibodies to drug reduces effectively
	• Therapy associated with increased incidence of respiratory infections, reactivation of TB
	• Contraindicated in patients with severe congestive heart failure
	• Concern about increased incidence of non-Hodgkin's lymphoma

Anti-TNF: adalimumab	• Humanized recombinant IgG1 monoclonal antibody against TNF • Effective in inducing remission in mild-moderate and severe Crohn's disease • Route: SC
Anti-TNF: certolizumab	• Pegylated (polyethelene glycol) • Humanized fragment antigen binding, Fab that binds to TNF • Route: SC • As effective as infliximab and adalimumab for crohn's disease • With both adalimumab and certilizumab, immunogenicity appears to be less of a problem than that associated with infliximab
Anti-TNF: natalizumab	• Humanized IgG4 monoclonal AB against cell adhesion molecule

	alpha 4-integrin subunit • Prevents binding of several integrins on circulating inflammatory cells to vascular adhesion molecules • Used for patients with moderate-severe Crohn's disease who have failed with other therapies • Given IV for 4 weeks • Patients should not be given other immune suppressants to prevent risk of progressive multifocal leukoencephalopathy (rare, fatal viral disease) • Adverse effects: acute infusion reactions, small risk of opportunistic infections

Pancreatic Enzyme Supplements: Mixture of amylase, lipase, proteases for pancreatic enzyme insufficiency	
Pancrelipase	• Two forms: non-enteric coated (given with acid suppression therapy) and enteric-coated • Administered with each meal and snack • Excessive doses → diarrhea, abdominal pain • High purine content of pancrease extracts may lead to hyperuricosuria and renal stones

AMEBIASIS

The Infection	• An infection with entamoeba histolytica
The conditions	• Asymptomatic intestinal infection • Mild-severe colitis • Severe intestinal infection (dysentery) • Ameboma: tumor-like mass caused by granulomatous reaction in itnestines in amebiasis ← large local lesion of bowel • Liver abscess, extraintestinal infection • CHOICE OF DRUG DEPENDS ON: CLINICAL PRESENTATION
Asymptomatic Intestinal Infection	• Treated with LUMINAL AMEBICIDE • Treatment with luminal amebides are also required for treatment of other forms of amebiasis • Standard luminal amebicides: 1. Diloxanide furate 2. Lodoquinol 3. paramomycin
Amebic Colitis	• metronidazole + luminal amebicide (also for dysentery) • tetracyclines + erythromycin: alternative drugs for moderate colitis, not effective against extraintestinal disease • dehydroemetine/ emetine: avoided because of toxicity
Metronidazole & Tinidazole	• Metronidazole; Drug of choice for treatment of EXTRALUMINAL AMEBIASIS ○ Kills trophozoites but not cysts of E. histolytica ○ Effectively eradicates intestinal and extraintestinal tissue infections • Tinidazole: similar activity but better toxicity profile
Metronidazole & Tinidazole:	• Oral

Pharmacokinetics and MOA	• Half-life: 7.5 hours (M) and 12-14 hours for (T) • Readily absorbed • Nitro group of metronidazole chemically reduced in anaerobic bacteria and sensitive protozoans • Reactive reduction products responsible for antimicrobial activity • Mechanism of tinidazole assumed to be the same

Metronidazole & Tinidazole: Clinical Uses	• Drug of choice in treatment of ALL tissue infections with E. histolytica
	• Neither drug is effective against luminal parasites, therefore must be used for luminal amebicide
	• Used for giardiasis: metronidazole is the drug of choice
	  ○ Efficacy after single treatment is about 90%
	  ○ Tinidazole is equally effective
	• Trichomoniasis: metronidazole is drug of choice (single dose of 2 g is effective)

Metronidazole & Tinidazole: Adverse Effects	• Common:
	  ○ Nausea, headache, DRY MOUTH
	  ○ METALLIC TASTE
	• Infrequent:
	  ○ Vomiting, diarrhea, INSOMNIA, weakness, DIZZINESS, THRUSH, dysuria, DAR URINE, paresthesias, neutropenia, vertigo
	• Rare:
	  ○ Pancreatitis
	  ○ Severe CNS toxicity (ataxia, encephalopathy, seizures)
	• Tinidazole better tolerated
	• Metronidazole: best avoided in

	pregnant, nursing women. But no congenital abnormalities have been proven
Iodoquinol: a luminal ambecide, but NOT against trophozoites in intestinal wall or extraintestinal tissue	• 90% excreted in feces • infrequent adverse effects: diarrhea, ANOREXIA, nausea, vomiting, abdominal pain, headache, rash, pruritis • taken with MEALS to limit GI toxicity • used with caution with optic neuropathy, renal/thyroid disease, nonamebic hepatic disease • discontinued if produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticarial, pruritis, fever)
Diloxanide Furoate: drug of choice for luminal infections, not active against tissue trophozoites	• in gut: splits into dilaxanide and furoic acid • 90% of dilaxanide rapidly absorbed • unabsorbed diloxanide: active antiamebic • MAO: unknown • Used with a tissue amebicide, usually metronidazole: serious intestinal and extraintestinal infections • Adverse effects: flatulence is common, nausea and abdominal cramps, rash rare • Drug NOT recommended in pregnancy
Paromomycin Sulfate: an aminoglycoside antibiotic	• Not absorbed from GI tract • Used ONLY as luminal amebicide • No effect against extraintestinal amebic infections • Adverse effects: occasional abdominal distress, diarrhea • Parenteral paromomycin now used to treat visceral leishmaniasis
Emetine and Dehydroemetine	• Emetine: alkaloid derived from ipecac

	• Dehydroemetine: synthetic analog • Effective against trophozoites of E. histolytica • Use limited to severe amebiasis when metronidazole cannot be used • Used for minimum period needed to relieve symptoms (3-5 days) • Should be administered SC, proffered… or IM • Adverse effects: pain, tenderness, sterile abscesses at injection site; diarrhea, nausea muscle weakness, discomfort • Serious toxicities: cardiac arrhythmias, heart failure, hypotension

Antihelminthic Drugs	
Albendazole:	• Broad-spectrum • Oral • DRUG OF CHOICE FOR: HYDATID disease (tapeworm cysts in viral organs like liver and lungs) • DRUG OF CHOICE FOR: CYSTICERCOSIS (tissue infection with larval stage of pork tapeworm) • Usually given with corticosteroids to decrease inflammation caused by dying organism • Erratically absorbed • Undergoes first-pass metabolism in liver • Active metabolite: albendazole sulfoxide • Acts by inhibiting microtubule synthesis • Against: pinworm, hookworm, ascariasis, trichuriasis, strongyloidiasis
Albendazole: Clinical Uses	• Administered on an empty stomach when used against intraluminal parasites but with

	FATTY meal when used against parasites
Albendazole: adverse reactions	• When used for 1-3 days: nearly free of side effects • Mild transient epigastric distress, diarrhea, LASSITUDE, INSOMNIA • Long-term use: for hydatid disease, well tolerated but can cause abdominal pain, alopecia, increases in liver enzyme and pancytopenia (low level of all blood cells produced by bona marrow)
Bithionol: alternative treatment for fascioliasis (sheep liver fluke) and pulmonary paragoniasis (lung fluke)	• Adverse reactions: 40% of patients experience diarrhea, cramps, anorexia • Skin rashes may occur after a week or more of use (reaction to antigens released from dying worms)
Diethylcarbamazine Citrate: drug of choice for FILARIASIS, LOIASIS (LOA LOA), TROPICAL EOSINOPHILIA (MONOSONELLA STREPTOCECA)	• Mechanism: immobilizes microfilariae and alters surface structure displacing them from tissues and making then more susceptible to destruction by host • Mode of action against adult worm is unknown
Diethylcarbamazine Citrate: Adverse Effects	• Generally mild, transient: headache, anorexia, etc. • Adverse effects also occur as a result of release of proteins from dying microfilariae or adult worms • Reactions include fever, malaise, popular rash, GI symptoms, cough, chest pain, muscle/ joint pain • Leukocytosis common (WBC count above normal range in blood) • Eosinophilia (abnormally high amounts of eosinophils) • Proteinuria • Caution when using in patients with hypertension or renal

	disease
Doxycycline	• Macrofilaricidal activity against w. bancrofti • Better activity than any other drug against adult worms • Active also against onchocerciasis (river blindness) by onchocerca volvulus, roundworm • Acts indirectly by killing wolbachia: an intracellular bacterial symbiont of filarial parasites • May be used for filariasis, both for treatment of active disease and in mass chemotherapy campaigns