

Respiratory Diseases

Pseudoephedrine (oral)	<i>Indirect</i> adrenergic agonist. Decongestant, causes nasal vasoconstriction by acting on α_1 receptors.	Taken systemically, causes sympathomimetic AE's (HTN, urinary retention, CNS stimulation).
Oxymetazoline (inhaled)	Nonspecific α agonist Nasal spray	⚠ Rebound rhinorrhea if taken for more than 5 days.
Guafenesin	Expectorant, reduces viscosity & adhesiveness of secretions	Generally well tolerated
Acetylcysteine	Mucolytic. Sulfhydryl group reduces disulfide bonds in mucoproteins, increasing fluidity of mucus.	⚠ Bronchospasm , nausea, hypersensitivity
Codeine & Hydrocodone	Weak opioids: Suppress cough reflex in CNS by agonism at δ receptor	
Dextromethorphan	Agonizes δ receptor & antagonizes NMDA receptor. No true analgesic properties	Ataxia, tremor, seizure
Albuterol, Metaproterenol (inhaled)	Short-acting (inhaled) β_2 agonists. Bronchodilator: Relaxes bronchial SM by \uparrow cAMP, reducing intracellular $[Ca^{2+}]$	Sudden cardiac death (Black box!) ⚠ ⚠ Tachycardia, tremor, hypokalemia, prolonged QT
Terbutaline (IV)	Short-acting β_2 agonists, parenteric.	Same as above
Salmeterol, Formoterol	Long-acting β_2 agonists, given continuously. NOT for relief of acute bronchospasm.	Same as above
Ipratropium (inhaled)	Antimuscarinic (nonselective) to reduce bronchoconstriction. Quaternary amine. Not for acute relief.	Uncommon. Tachycardia, urinary retention, blurry vision, mucosal dryness.
Tiotropium	Selective M1 and M3 antagonist. Long $t_{1/2}$, can be given in once-a-day dosage. Note that M2 receptors are inhibitory and mediate negative feedback. Not for acute relief.	Same as above
Theophylline, Caffeine	Methylxanthines. Inhibit PDE. Smooth muscle relaxation and strengthening of respiratory muscles. Induce mild diuresis due to antagonism at adenosine receptors.	Increase in cAMP causes CNS stimulation, cardiac and skeletal muscle stimulation, relaxation of airway and other smooth muscles. Heartburn, nausea, tremor, seizures. Arrhythmia & hypotension. Theophylline has narrow therapeutic index.
Prednisone (oral), Methylprednisolone (IV), Fluticasone (inhaled), Triamcinolone (inhaled)	Corticosteroids. Chief antiinflammatory medications used to treat respiratory disease, including asthma. Mechanism: 1) Phospholipase-A ₂ suppressed 2) IL1 formation inhibited 3) Granulocytes suppressed	⚠ Thrush, cataract, glaucoma
Cromolyn (inhaled)	Inhibits mast cell degranulation	Generally well tolerated, rare sore throat. OTC eye drops also available

Zileuton	Inhibits 5-LO	Increase in LFT's. Many drug interactions.
Zafirleukast, Monteleukast	LTB4 receptor antagonists.	Sedation, Churg-Strauss (eosinophilic vasculitis) Zafirleukast: inhibits CYP2C9 and 3A4 Monteleukast: fewer drug interactions
Omalizumab	Humanized murine monoclonal Ab targeted against Fc portion of IgE. Inhibits binding of IgE to mast cells. IgE reduced to undetectable levels.	Increased risk of bleeding, due to thrombocytopenia.

Antihistamines

R-α-methylhistamine (H3) 4-methylhistamine (H2) 2-methylhistamine (H1)	Histamine agonists.	Metabolized by two pathways: 1) ring methylation \rightarrow N-methylhistamine (histamine-N-methyl-xferase) \rightarrow converted by MAO to N-methyl imidazole acetic acid 2) oxidative deamination \rightarrow imidazole acetic acid (nonspecific diamine oxidase) Metabolites of histamine not active and are excreted in urine.
Synthesis & Metabolism of Histamine	Formed by decarboxylation of L-histidine Mast cell histamine released by morphine & tubocurarine without degranulation.	
Antihistamines and asthma	Antihistamines have little use in treatment of asthma.	But if asthma pt concurrently has allergic rhinitis, then cetirizine has been shown to \uparrow FEV ₁
Diphenhydramine Chlorpheniramine Brompheniramine Clemastine Dimenhydrinate Pyrilamine Promethazine Hydroxyzine Meclizine Cyproheptadine	First generation H₁-receptor blockers. <i>Dimenhydrinate</i> : prodrug of Diphenhydramine, good antivertigo <i>Promethazine</i> : Good antiemetic, mild D ₂ antagonism <i>Meclizine</i> : Good antivertigo <i>Cyproheptadine</i> : Antiserotonergic <i>Brompheniramine</i> : used for post-nasal drip, colds	<ul style="list-style-type: none"> ▶ Prominent CNS sedation ▶ Antimuscarinic ▶ Dimenhydrinate: porphyria. ▶ Promethazine: EPS, cholestasis, SIDS ▶ Other AE's: fatigue, dizziness, tinnitus, blurred vision, GI distress, weight gain, dry mouth ▶ Overdoses in children \rightarrow convulsions ▶ Drug allergy may develop ▶ Potential for drug-drug interactions
Loratadine, Cetirizine	Second generation H₁-receptor blockers. Less CNS penetration. Cetirizine is metabolite of Hydroxyzine.	Some sedation with higher doses. Very safe.
Terfenadine, Astemizole ☠	Second generation H₁-receptor blockers. Do not cross BBB.	QT elongation, TdP, sudden death, especially with 3A4 inhibitors. Withdrawn ☠
Fexofenadine Desloratadine	Third generation H₁-receptor blockers. Metabolites of 2 nd generation drugs. Clinically identical to other 2 nd generation drugs. Fexofenadine is a metabolite of terfenadine.	Some sedation with higher doses. Very safe.
Doxepin	Antihistamine. Tricyclic antidepressant.	Sedation, antimuscarinic effects, arrhythmia, orthostatic hypotension.

Treatment of Coagulation Disorders

Warfarin (oral)	<p>Blocks vitamin-K-dependent γ-carboxylation of prothrombin (Factor II) and Factors VII, IX, X in liver. "1972"</p> <p>Prevents conversion of vitamin K to its active (reduced hydroquinone) form.</p> <p>Protein bound, long $T_{1/2}$ (~60 hrs).</p> <p>⚡ Takes several days for full antithrombotic effects. Clotting factors degraded at variable rates.</p> <p>S enantiomer: much more potent, 2C9 metabolism.</p> <p>Pharmacogenetics: some pts have ↓ metabolism of Warfarin, must have dosing adjusted.</p> <p>R enantiomer: 1A2 & 3A4 metabolism</p>	<p>Drug interactions:</p> <p>Valproic acids: ↓ plasma protein binding</p> <p>Attenuation of effect: P450 Inducers: chronic EtOH ingestion Barbiturates Rifampin Griseofulvin, Glutethimide</p> <p>Increase of effect: P450 inhibitors Acute EtOH intoxication Cimetidine Chloramphenicol Cotrimoxazole, Disulfiram Metronidazole, Phenylbutazone</p> <p>⚡ Antidote to Warfarin overdose: Vitamin K (phytonadione)</p> <p>AE's: Narrow therapeutic index ⚡ Teratogenic, can interfere with bone mineralization Hemorrhage! ⚡ Monitor: PT</p>
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Heparin HMWH (Unfractionated) LMWH (Enoxaparin, Dalteparin)	<p>Interacts with AT III, exposing binding site of AT III more readily. Only effects soluble clotting factors.</p> <p>Unfractionated is better at inhibiting IIa than Xa.</p> <p>LMWH is better at inhibiting Xa, but poorly inhibits IIa (insufficient saccharide units).</p>	<p>Antidote to Heparin overdose: Protamine sulfate</p> <p>AE's: Hemorrhage! Osteoporosis/Osteopenia ⚡ Thrombocytopenia: Immune & non-immune ⚡ Monitor: PTT</p>
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Heparin vs. Warfarin

	Heparin	Warfarin
Route	IV or SubQ	Oral
Onset	Immediate	1-3 days
Duration of action on cessation of treatment	3-6 hours	3-5 days
Antagonist	Protamine	Vitamin K
Monitoring test	PTT	PT
Site of action	Activated clotting factors in plasma	Clotting factor synthesis in liver
Fate in body	Partially degraded in liver, does not cross placenta	Inactivated in liver, crosses placenta.
Variability in response	little	great, owing to genetic differences in kinetics and effects of other drugs

Fondaparinux Indirect thrombin inhibitor. Inhibits Xa, blocking conversion of prothrombin to thrombin. AT III-mediated selective inhibition of Xa.

Bivalirudin	<p>Direct thrombin inhibitor. Synthetic 20 aa peptide.</p> <p>Targets coagulation cascade AND platelet.</p> <p>Reversible, competitive inhibitor of thrombin. Binds to active site and exo-site of molecule.</p> <p>Inhibits fibrin-bound and circulating thrombin.</p> <p>↓ GpIIb/IIIa receptor density</p> <p>Blocks platelet activation and aggregation</p> <p>Mechanism prevents thrombus formation AND thrombus growth.</p>	<p>✦ Excreted solely by kidney (Adjust dose for renal impairment)</p> <p>Compared to Heparin: Predictable anticoagulant effect, no HIT.</p> <p>Major AE: Bleeding!</p>
Abciximab, Eptifibatide, Ticlopidine	<p>Directly inhibits platelets.</p> <p>Abciximab, Eptifibatide: Blocks GPIIb/IIIa receptor</p> <p>Ticlopidine: ADP receptor antagonist</p>	
Clopidogrel	<p>Irreversibly blocks binding of ADP to ADP R.</p> <p>Inhibits binding of fibrinogen to GPIIb/IIIa receptor & ADP-induced aggregation.</p> <p>✦ Irreversibly modifies platelets.</p> <p>Inhibits ADP-mediated platelet activation via decreased cAMP and PKA activation.</p> <p>Dose adjustment may be necessary for liver impairment (prodrug).</p>	<p>AE's: Pruritis, Purpura, Dyspepsia, Rash, TTP</p> <p>Low risk of bleeding, because only one pathway of platelet aggregation is inhibited.</p> <p>Contraindicated in pts with active pathologic bleeding (peptic ulcer or intracranial hemorrhage)</p> <p>Substrate of 1A2, 3A4</p> <p>Inhibits 2C8/9: potentiates fluvastatin, phenytoin, tamoxifen, tolbutamide, torsemide.</p> <p>Increased risk of bleeding with NSAIDS (ASA, Naproxen, Ibuprofen)</p>
Herbs with anticoagulant properties	<p>Cat's claw, dong quai, primrose, feverfew, garlic, ginger, ginkgo, ginseng, green tea, red clover, horse chestnut</p>	
Aspirin	<p>Inhibits COX, leading to decreased TXA₂ production. Given with Clopidogrel in acute coronary syndrome.</p>	
tPA Alteplase Retepase Urokinase Anistreplase Streptokinase	<p>Thrombolytic. Acts on clot (fibrin). Directly or indirectly activate plasminogen.</p> <p>Alteplase: Recombinant tPA. Fibrin-selective: bound plasminogen > free plasminogen.</p> <p>Streptokinase: inactive until it forms complex with circulating plasminogen. Targets FREE plasminogen.</p> <p>Anistreplase: preformed anisoylated streptokinase-plasminogen complex, Has to undergo deacylation to become active.</p>	<p>AE's:</p> <p>Hemorrhage (especially intracerebral hemorrhage with rt-PA)</p> <p>Hypotension: streptokinase via release of vasodilator bradykinin</p> <p>Allergic rxns: rare, possible with streptokinase due to bacterial origin</p> <p>Antigenic: Streptokinase and anistreplase may be neutralized by streptokinase antibodies.</p>

Coxibs, RA, Gout

Aspirin (ASA)

Acetylates, thereby irreversibly inhibits both COX 1 and COX 2.

Salicylic acid (product of acetylation) reversibly inhibits both COX isoforms.

Aspirin produces 5 clinically useful effects:

- 1) **Analgesic** action: Not effective for severe visceral pain. Continued use does not lead to tolerance, dependence, or respiratory depression. Synergizes with opioid analgesics.
- 2) **Antipyretic** action: But toxic doses may increase temperature and cause sweating
- 3) **Antiinflammatory** actions: Reduction in inflammatory symptoms only.
- 4) **Effects on platelets**: Inhibits platelet aggregation (slight ↑ of bleeding time). Can delay, reduce, or prevent vascular events.
- 5) **Miscellaneous**: Chronic use ↓ risk of colon cancer (due to COX inhibition). Reduces risk of alzheimers.

Aspirin and most NSAIDs produce 5 AE's:

- 1) GI irritation (nausea, vomiting, ulceration)
- 2) Inhibition of platelet aggregation and ↑ bleeding time (ALL? OR JUST ASA?)
- 3) Inhibition of uterine motility and prologation of gestation
- 4) Inhibition of PG-mediated renal function with edema and mild hyperkalemia
- 5) Hypersensitivity reactions (urticaria, angioneurotic edema, precipitation of asthmatic attacks) by shunting arachidonic acid metabolism from prostaglandins to leukotrienes.

Reye's syndrome: fulminant hepatitis with cerebral edema. Associated with viral infections and ASA.

Salicylate toxicity: Tinnitus, hyperventilation (respiratory alkalosis), metabolic acidosis, nausea, vomiting, headache, confusion, dizziness. Larger doses produce delirium, hallucinations, convulsions, coma, death from respiratory failure.

Functions of prostaglandins

TXA₂

- ▶ potent vasoconstrictor
- ▶ ↑ platelet aggregation
- ▶ ↓ RBF
- ▶ contract uterus

PGI₂ (**Misoprostol, Alprostadil**)

- ▶ potent vasodilator
- ▶ ↓ platelet aggregation
- ▶ ↑ RBF
- ▶ relax bronchial SM
- ▶ inhibit acid secretion
- ▶ ↑ pain

PGD₂

- ▶ contract bronchial SM
- PGE₂ (**Dinoprostone**)
- ▶ potent vasodilator
 - ▶ relax bronchial SM
 - ▶ contract uterus
 - ▶ inhibit acid
 - ▶ ↑ RBF
 - ▶ relax GI circular muscle
 - ▶ contract GI longitude muscle
 - ▶ ↑ fever
 - ▶ ↑ pain

PGE_{2α} (**Carboprost**)

- ▶ contract bronchial SM
- ▶ contract uterus
- ▶ contract GI longitudinal muscle

Ibuprofen

Naproxen
Fenoprofen
Ketoprofen
Fluriprofen
Oxaprozin

Propionic acid derivatives.
Antiinflammatory, analgesic, antipyretic.
Oral reversible inhibitor of COX 1 and 2.
Used in treatment of RA and osteoarthritis

Weaker GI effects than ASA

Indomethacin
Sulindac

Oral reversible inhibitor of COX 1 and 2.
Used in treatment of acute gouty arthritis, ankylosing spondylitis, osteoarthritis, refractory fever of Hodgekin's disease.
Sulindac: prodrug, less severe AE's

High incidence of AE's: Not well tolerated
Nausea, vomiting, diarrhea
Anorexia
Frequent & severe frontal headache

Etodolac	Relatively COX-2 selective (10x). Generic version available.	Similar to other NSAIDs but fewer GI AE's.
Ketorolac	May also be administered IM in treatment of postoperative pain and topically for allergic conjunctivitis Heteroaryl acetic acid	Severe ☠ GI ulcers with even short-term use
Tolmetin Diclofenac	Tolmetin: Equivalent to aspirin in efficacy and better tolerated Diclofenac: one of the most potent NSAIDs. Given with misoprostol. Heteroaryl acetic acids like ketorolac.	Diclofenac: Lower incidence of GI bleeding
Meclofenamate	Basis for COX-2 inhibitors. No advantages over other NSAIDs. Anthranillic acids	Frequently cause side diarrhea
Piroxicam Meloxicam	Enolic acids. Piroxicam: equivalent of ASA for treatment of RA. Long half-life: once/daily. Meloxicam: similar to piroxicam, but more COX-2 selective.	Piroxicam: higher incidence of PU and GI bleeds than other NSAIDs Meloxicam: slightly less ulcerogenic than other NSAIDs
Nabumetone	Prodrug whose metabolite is COX-2 selective. All 3 activities. Ketone prodrug converted to active acid. Long half-life, once a day dosing. Treatment of arthritis. Alkanone.	Similar to other NSAIDs but fewer GI AE's.
Celecoxib Rofecoxib ☠ Valdecoxib ☠ (Etoricoxib)	COX-2 selective inhibitors. Celecoxib: metabolized by 2C9 and inhibits 2D6 Celecoxib used for treatment of OA, RA, and to reduce # of colonic polyps in FAP Rofecoxib was used for OA, acute pain, and dysmenorrhea.	Increased cardiovascular risks. GI bleeding & ulceration. Adverse renal and hepatic effects Edema, HTN.
Acetaminophen (APAP)	Strong analgesic and antipyretic, but very weak antiinflammatory, because it can inhibit PG formation in CNS but not periphery. Inhibits both COX's. Bioactive metabolite N-acylphenolamine AM404 also acts on the endogenous cannabinoid system: TRPV1 channel (Transient Receptor Potential Vanilloid receptor).	Lacks many of the AE's of NSAIDs. Liver toxicity with overdose or co-administration with alcohol due to formation of highly active metabolite (N-acetyl-benzoquinone) that depletes hepatic glutathione. ☠ Antidote: N-acetylcysteine.
Phenacetin	Metabolized to acetaminophen.	Severe renal toxicity ☠, not really used except for a few proprietary formulations.
Gold Salts	DMARDs. Slow progression of RA. May modify function of macrophages.	

Chloroquine Hydroxychloroquine	DMARDs. Used orally in treatment of <u>refractory</u> RA.	✦ Wide variety of AE's, including irreversible retinal damage.
D-Penicillamine	DMARD. Can slow progression of RA and associated bone destruction.	Serious AE's: Dermatological problems, nephritis, aplastic anemia.
Methotrexate	DMARD for treatment of RA. Immunosuppressant for severe or refractory RA.	Mucosal ulcerations, nausea, cytopenias, hepatic cirrhosis, acute pneumonia-like syndrome
Cyclosporine	DMARD. Inhibits IL-1 & IL-2 receptor production. Inhibits macrophage-T cell interaction and T-cell responsiveness. Slows formation of new bony erosions.	Nephrotoxic, can be enhanced by drug interactions with diltiazem, K-sparing diuretics, and CYP3A4 inhibitors (macrolides, ketoconazole, grapefruit juice). Hypertension, hyperkalemia, hepatotoxic
Infliximab	Chimeric ¼ mouse, ¾ human monoclonal Ab that binds TNF-α (both membrane bound & soluble). Given with methotrexate to inhibit antichimeric Ab formation.	Upper respiratory infections, nausea, headache, cough. ✦ Beware of activation of latent TB! ☠
Etanercept	Recombinant fusion protein containing 2 TNF receptor moieties linked to Fc portion of IgG. Binds 2 TNF-α molecules. SubQ injection. Similar efficacy as methotrexate but quicker.	Primary injection site rxns in 20-40% of pts. Anti-etanercept Ab found, but not significant.
Leflunomide	Orally active immunosuppressive drug whose metabolite inhibits synthesis of rUMP by inhibiting dihydroorotate dehydrogenase (lymphocytes require de novo pyridine synthesis). Inhibits autoimmune T cell proliferation and production of auto-Ab by B cells. Long plasma half life (15 days) due to plasma binding and enterohepatic recirculation of metabolite.	Diarrhea, elevation of liver enzymes Cholestyramine increases drug clearance.
Colchicine	Plant alkaloid used orally for <u>acute attacks of gout in progress</u> . Binds to and depolymerizes tubulin, inhibiting mobility of granulocytes, and preventing expansion of inflammatory process. Effects apparent within 12 hours	Nausea, vomiting, diarrhea Repeated use: myopathy, agranulocytosis, aplastic anemia, alopecia Not used in pregnancy Used cautiously in pts with hepatic, renal, or CV disease
NSAIDs used to treat gout	Indomethacin and other NSAIDs also inhibit phagocytosis of urate crystals (in addition to inhibiting prostaglandin synthesis). All NSAIDs (but NOT aspirin, salicylates, and tolmetin) have largely replaced colchicine to treat acute gout. Aspirin, Salicylates, and Tolmetin NOT USED because they can reduce sodium urate excretion (ASA is uricosuric at doses < 4g/day)	

Allupurinol	Purine analog that inhibits XO, yielding terminal products more soluble than uric acid.	Well tolerated, but produces hypersensitivity rxns (rashes). Interferes with metabolism of 6-MP (antitumor), and azathioprine (immunosuppressant).
Probenecid Sulfinpyrazone	Uricosuric agents. Block renal tubular reuptake of filtered uric acid → enhancement of renal secretion. Probenecid also blocks urinary secretion of penicillin, naproxen, ketoprofen, and indomethacin.	Sulfinpyrazone: severe gastric distress

GI Drugs

Therapy of PUD	<p>1) ↓ gastric acid secretion</p> <p>2) buffer released acid</p>	<p>3) reduce mucosal destruction with cytoprotective agents</p> <p>4) eradicate <i>H. pylori</i> if present</p>
Cimetidine Ranitidine Famotidine Nizatidine	<p>H₂-receptor antagonists.</p> <p>Used to treat gastric and duodenal ulcers, ZE, and GERD. Reduce nocturnal acid “breakthrough” secretion in some patients with reflux (reflux?) esophagitis being treated with PPI.</p>	<p>Rare AE’s: headache, dizziness, myalgia, skin rashes.</p> <p>More serious CNS AE’s with cimetidine, especially in elderly with impaired renal/hepatic function: Confusion, hallucinations, CNS depression, CNS excitation</p> <p>Cimetidine is antiandrogenic: Antagonist at androgen receptor: temporary loss of libido, impotence, gynecomastia.</p> <p>⚡ Cimetidine inhibits 1A2, 2C19, 2D6, 3A4 leading to enhanced responses of warfarin, phenytoin, theophylline, carbamazepine, quinidine, etc.</p>
Omeprazole Lansoprazole Pantoprazole Rabeprazole Esomeprazole	<p>Inhibits H⁺, K⁺-ATPase (proton pump) that secretes H⁺ (in parietal cell).</p> <p>Omeprazole is a prodrug. At pH ~7, it’s an inactive, neutral weak base, widely distributed in tissues. In acid environment, it is protonated and undergoes rearrangement → sulfenic acid reacts with sulfhydryl groups on the proton pump → irreversible inactivation.</p> <p>Unstable in acid (enteric coated).</p> <p>T_{1/2} ~ 2 hrs, but inhibit acid for > 24 hrs.</p> <p>Acid production ↓ ~ 95% → hypergastrinemia.</p> <p>Pantoprazole available in acid-stabilized IV.</p> <p>Esomeprazole is S-isomer of omeprazole.</p> <p>Used for PUD, GERD, ZE. Superior to H₂ antagonists and misoprostol for healing & preventing ulcers caused by NSAIDs.</p>	<p>GI AE’s: Nausea, diarrhea, colic.</p> <p>CNS AE’s: headache, dizziness, somnolence</p> <p>Skin rashes, ↑ LFT’s are rare.</p> <p>2C19 and 3A4 metabolism.</p>
Eradication of <i>H. pylori</i>	<p>Two or three antibiotics (Clarithromycin, Amoxicillin, Tetracycline, Metronidazole) + H₂-blocker or PPI</p> <p>+/- Bismuth subsalicylate</p>	
Aluminum hydroxide	<p>Antacid:</p> $\text{Al(OH)}_3 + 3\text{HCl} \rightleftharpoons \text{AlCl}_3 + 3\text{H}_2\text{O}$	<p>Constipation, Hypophosphatemia, binds some drugs to decrease bioavailability</p>
Calcium carbonate	<p>Antacid:</p> $\text{CaCO}_3 + 2\text{HCl} \rightleftharpoons \text{CaCl}_2 + \text{CO}_2$	<p>Hypercalcemia, nephrolithiasis, milk-alkali syndrome</p> <p>Released CO₂ can cause burps & farts.</p>
Magnesium hydroxide (milk of magnesia)	<p>Antacid:</p> $\text{Mg(OH)}_2 + 2\text{HCl} \rightleftharpoons \text{MgCl}_2 + 2\text{H}_2\text{O}$	<p>Diarrhea, hypermagnesemia if renal insufficiency</p>

Sodium bicarbonate	Antacid: $\text{NaHCO}_3 + \text{HCl} \rightleftharpoons \text{NaCl} + \text{H}_2\text{O} + \text{CO}_2$ Not used to treat PUD: brief duration, high sodium content, and risk of alkalosis.	Systemic alkalosis, fluid retention. Released CO_2 can cause burps & farts.
Magaldrate	Antacid: Hydroxy magnesium aluminate complex that is rapidly converted to $\text{Mg}(\text{OH})_2$ and $\text{Al}(\text{OH})_3$ in gastric acid. Poorly absorbed and has sustained antacid activity	
Sucralfate	Cytoprotective agent. Sulfated polysaccharide formed by interacting $\text{Al}(\text{OH})_3$ with the octasulfate of sucrose. In acid, becomes viscous sticky gel that binds to inflamed tissues to protect tissues from acid and pepsin. Should not be taken with Al-containing antacids May inhibit absorption of other drugs	
Bismuth subsalicylate (Pepto-Bismol)	Antisecretory, antiinflammatory, antimicrobial, and has cytoprotective effect. Unknown MOA. Used to treat traveler's diarrhea.	

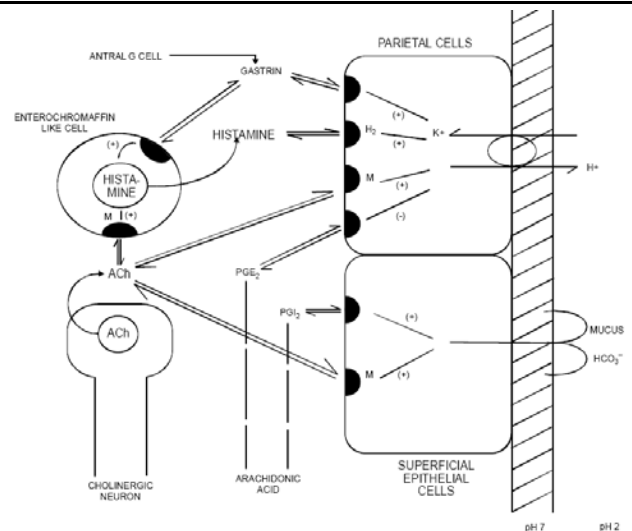
Normal GI Physiology

PGE_2 inhibits acid secretion by parietal cells.

PGI_2 (prostacyclin) increases mucus and bicarbonate production by superficial epithelial cells.

Parietal cells:
 + H_2 secretion:
 Gastrin
 Hist (H_2 receptor)
 Ach (M_3 receptor)
 - H_2 secretion: PGE_2

Surface Epithelial cells:
 + mucus/bicarb secretion: Ach, PGI_2



Misoprostol	PGE_1 analog. High doses can inhibit acid secretion. Used to prevent ulcers in pts taking NSAIDs chronically.	⚠ Contraindicated in pregnancy: can induce uterine contractions and cause abortion. Most frequent AE: diarrhea (30%)
Proprantheline Pirenzepine Dicyclomine Hyoscyamine	Antimuscarinics: inhibit acid secretion by parietal cells Proprantheline: quaternary amine, approved for treatment of ulcers Pirenzepine: selective blocker of gastric M_3 blockers involved in acid secretion. Available in Europe & Canada. Little CNS permeability. AE's: dry mouth, constipation, visual disturbances, nausea, vomiting, diarrhea. Dicyclomine & Hyoscyamine: Older agents, used for symptomatic relief of abdominal pain or IBS discomfort. Available in US. Note that antimuscarinics such as atropine have limited use in PUD because high doses needed to inhibit acid secretion → antimuscarinic AE's (dry mouth, urinary retention, visual disturbances, constipation)	

Metoclopramide	Prokinetic agent. Cholinomimetic and dopamine antagonist. Effective in treating GERD. Antiemetic properties.	
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Bethanechol	Prokinetic agent. Muscarinic agonist.	
Cisapride ☠	Prokinetic agent. 5-HT ₄ agonist. Effective in treating GERD.	Withdrawn (TdP) ☠
Erythromycin	Prokinetic agent. Macrolide with motilin-like activity	
Bran Psyllium preparations Methylcellulose Calcium polycarbophil	Bulk-forming laxatives. Softened stool in 1-3 days.	
Docusates Poloxamers	Surfactant laxatives. Softened stool in 1-3 days.	
Lactulose	Softened stool in 1-3 days.	
Phenolphthalein Bisacodyl Senna Cascara sagrada	Stimulant (irritant) laxatives Soft or semifluid stools in 6-8 hours.	
Sodium phosphates Magnesium sulfate Milk of magnesia Magnesium citrate	Osmotic laxatives. Watery stools in 1-3 hours.	
Castor oil	Irritant laxative. Watery stools in 1-3 hours.	
Loperamide Diphenoxylate	Antidiarrheal agents. Pharmacologically related to opioids (opioids can be used to control diarrhea). Act via opioid receptors to: ↑ tone of rectal sphincter ↓ peristalsis ↓ GI secretory activity Diphenoxylate is co-administered with atropine.	
Bismuth subsalicylate	Antidiarrheal agent. Used for mild-to-moderate diarrhea and “traveler’s diarrhea”	
Ocreotide	Antidiarrheal agent. Somatostatin analog that inhibits severe diarrhea and flushing associated with metastatic carcinoid tumors and VIP-producing tumors.	

GU Drugs

Oxytocin	<p>Neurohypophysial hormone related to vasopressin.</p> <p>Stimulates uterine smooth muscle contractions and facilitates parturition. Also contracts myoepithelial cells of lactating mammary gland.</p> <p>IV infusion or nasal spray: Infused to initiate labor (but not to augment normally progressing labor), and inhaled to promote milk letdown.</p> <p>Half life ~ 3 min.</p> <p>Uterus needs to be previously exposed to estrogen in order for oxytocin to have effect.</p>	<ol style="list-style-type: none"> 1) Uterine hyperstimulation → too frequent contractions or uterine tetany. 2) Can have pronounced antidiuretic actions at high doses 3) Vasodilation → hypotension and reflex tachycardia 4) Trauma to mother or fetus from forced passage through incompletely dilated cervix, uterine rupture, and fetal hypoxia from loss of placental O₂ exchange.
NSAIDs	<p>Inhibit COX, promoting the length of gestation. Tocolytic. Interrupt premature labor and prolong the duration of spontaneous labor.</p> <p>The combination of NSAIDS with other classes of tocolytics enhances tocolysis.</p>	<p>Not generally used for premature labor because of their potential impact on fetal development</p>
Dinoprostone	<p>PGE₂: used as vaginal gel or suppository to produce “cervical ripening” (softening, effacement, and dilation of cervix that occurs in preparation for labor and delivery).</p>	<p>Dose-limiting AE’s: vomiting, diarrhea, fever, bronchoconstriction.</p> <p>Hypotension, hypertension, syncope, dizziness, flushing can also occur.</p>
Carboprost	<p>15-methyl PGF_{2α} (synthetic PGF_{2α}): administered via IM injection to produce midtrimester abortion and to ↓ postpartum bleeding.</p>	<p>Local administration of dinoprostone and IM injection of carboprost limit the systemic adverse effects.</p>
Misoprostol	<p>PGE₁ analog used to prevent ulcers in pts taking large doses of NSAIDS chronically.</p> <p>Used off-label to promote cervical ripening and to induce labor.</p>	<p>CONTRAINDICATED in pregnant women.</p> <p>Abnormal uterine contractions, such as hypertonus and hyperstimulation (contractions lasting >90 seconds or >5 contractions in 10 mins)</p>
Mifepristone (RU-486)	<p>Antiprogestin. Used in combination with misoprostol as a oral first trimester abortive agent.</p> <p>Mifepristone blocks uterine progesterin receptors causing decidual breakdown and detachment of the blastocyst.</p> <p>48 hours after mifepristone is given, oral misoprostol is administered to induce uterine contractions to ensure expulsion of blastocyst.</p>	<p>Vomiting, diarrhea, abdominal/pelvic pain.</p> <p>Vaginal bleeding requiring intervention may occur in 5% of patients.</p> <p>Deaths have occurred ☠</p>

Ergot alkaloids	<p>Agonists and/or antagonists at serotonin, dopamine, and α-adrenergic receptors.</p> <p>Can directly produce contractions of pregnant uterus.</p> <p>At low doses: clonic (rhythmic), with contractions and relaxations in succession.</p> <p>At high doses: sustained (tonic) contractions → unacceptable for inducing or facilitating labor.</p>	
Ergonovine Methylergonovine	<p>Ergot alkaloids used for stimulation of uterine contractions.</p> <p>Reduce bleeding of the uterus postpartum and prevent hemorrhage after abortion.</p>	
Ritodrine (IV) Terbutaline Albuterol	<p>β_2 agonists. Tocolytic. Relax the pregnant uterus and used to inhibit uterine contractions in patients with premature labor.</p> <p>Ritodrine is the only agent approved for this use.</p>	<p>Increased maternal and fetal HR, arrhythmias, hypokalemia, maternal pulmonary edema, myocardial ischemia</p>
Magnesium	<p>Tocolytic. IV magnesium sulfate infusion can inhibit uterine contractions in premature labor. May interfere with ability of calcium to provoke contraction.</p> <p>Efforts being made to discourage use of magnesium for tocolysis.</p>	<p>Hypermagnesemia, hypocalcemia, cardiac electrical disturbances</p> <p>Flushing, nausea, vomiting, headaches, Visual disturbances</p> <p>Muscle paralysis</p> <p>Pulmonary edema</p>
Nifedipine	<p>Ca^{2+} channel blockers relax pregnant uterus but not approved by FDA for this use in USA.</p> <p>Nifedipine is at least as effective as ritodrine in halting uterine contractions, associated with fewer maternal side effects and less neonatal morbidity.</p>	<p>Dizziness, lightheadedness, nervousness, flushing, headache, nausea,</p> <p>Muscle cramps or tremors</p> <p>Hypotension</p> <p>Possible ↓ in fetal blood supply.</p>
Atosiban	<p>Oxytocin receptor antagonist. Structural analog of oxytocin, has cross-reactivity to vasopressin receptors.</p> <p>As effective as β_2 agonists and is better tolerated by the mother.</p> <p>Not available in US due to concerns about its actions on fetal health and development</p>	<p>Nausea, headache, fever, insomnia</p>
Pseudoephedrine	<p>oral α_1-agonist used in the treatment of stress incontinence.</p> <p>Increases outflow resistance by contracting smooth muscle of urinary sphincter.</p> <p>(Note that estrogens are effective in women at ↑ sphincter tone, possibly by ↑ sensitivity to NE)</p>	

Oxybutynin Flavoxate Tolterodine	<p>Antimuscarinics used in the treatment of urge incontinence. Relax the bladder by blocking its cholinergic innervation.</p> <p>“Antispasmodic” action which relaxes the detrusor through unknown mechanism.</p> <p>Oxybutynin available as sustained released preparation (reduction in systemic antimuscarinic AE’s) and transdermal patch.</p> <p>Tolterodine has bladder selectivity but no evidence for specific M-receptor subtypes. Available in immediate release and long-acting formulations.</p>	Antimuscarinic AE’s (dry mouth, blurred vision, dizziness, fatigue, constipation, etc)
Treatment of overflow incontinence	Not amenable to drug treatment.	
Doxazosin Terazosin Tamsulosin	<p>Selective α_1 antagonists that block sympathetic innervation of the bladder sphincter → reduced outflow resistance.</p>	<p>Orthostatic hypotension, dizziness, fatigue.</p> <p>Orthostatic hypotension less likely with Tamsulosin</p>
Finasteride Dutasteride	<p>5α-reductase inhibitors.</p> <p>Finasteride promotes hair growth.</p> <p>Dutasteride only approved for treatment of BPH.</p> <p>Both only approved for males and metabolized by 3A4</p>	<p>Impotence, ↓ libido, ↓ volume of ejaculate</p> <p>Women should not touch pills! Absorbed through the skin, and contraindicated in pregnancy due to risk to male fetal development.</p>
Yohimbine	May have activity as an aphrodisiac, but evidence for effectiveness is very weak.	
Alprostadil	PGE ₁ : Direct penile injection or urethral suppository for treatment of impotence. I think I’ll pass.	
Phentolamine Papaverine Alprostadil	<p>Phentolamine: Nonspecific α blocker</p> <p>Papaverine: Nonspecific muscle relaxant</p> <p>Not approved by FDA for this purpose, but Phentolamine is injected with Papaverine and alprostadil in a combination called “trimix.”</p>	AE’s of trimix: pain at injection site, painful erections, priapism.
Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)	<p>Oral inhibitors of cGMP-specific phosphodiesterase type 5 (PDE5). Used to treat ED.</p> <p>Tadalafil and vardenafil are more selective for PDE5 than sildenafil. Tadalafil has a 36 hour duration of action vs. 4 hours for the others.</p>	<p>Headache, flushing, dyspepsia</p> <p>Sildenafil: abnormal vision.</p> <p>⚠ Contraindicated in patients using organic nitrates or most alpha antagonists because hypotensive effects may be potentiated.</p>

Kidney Drugs

Acetazolamide
Methazolamide
Dichlorphenamide

Carbonic-Anhydrase (CA) inhibitors.

CA is a zinc metalloenzyme, with membrane bound (Type IV) and cytoplasmic (Type II) forms.

Bicarb is normally reabsorbed (with the help of CA) in the proximal tubule.

CA inhibitors cause:

- ▶ alkaline urine (pH ~8) due to
 ↓ bicarb reabsorption, causing
 ↑↑ HCO₃⁻ excretion to ~ 1/3 filtered
- ▶ ↓ H⁺ and NH₄⁺ excretion in CT
- ▶ ↑ K⁺ excretion, ↑ Na⁺ excretion

Ceiling effect due to ↓↓ HCO₃⁻ in filtrate.

CA inhibitors are not very good diuretics since patients become refractory in a few days.

Uses of CA inhibitors:

- 1) **Glaucoma: ↓ aq humor formation**
- 2) ↓ intraocular pressure
- 3) ↓ seizures
- 4) Tumor lysis syndrome:
 ↑ uric acid excretion
- 5) ↓ mountain sickness
 prophylaxis > treatment
 lessens respiratory alkalosis

- ▶ Somnolence
- ▶ Paresthesias
- ▶ Hyperchloremic metabolic acidosis
- ▶ ↑ Amine reabsorption (↓ ammonium trapping) →
 Worsens hepatic encephalopathy.
 ↳ **CONTRAINDICATED** in cirrhotic patients
- ▶ Sulfonamide allergies
- ▶ Renal calcium stone formation
 (↑ urine pH → ↓ calcium phosphate solubility)
- ▶ Potassium loss
- ▶ Don't use in aspirin poisoning because systemic acidosis may ↑ CNS penetration

Mannitol (IV)
Urea (IV)
Isosorbide (oral)
Glycerine (oral)

Osmotic diuretics. Primary effect in parts of tubule that are permeable to water (proximal tubule & loop of henle).

Osmotic diuretics cause:

- ▶ ↑ ECF by drawing out intracellular water
 ↑ excretion of all ions
- ▶ ↑ RBF
- ▶ ↓ NaCl concentration in medulla
 ↓ urine concentrating ability

Use of osmotics:

- 1) Prophylaxis of ARF, ATN prior to ischemia or nephrotoxin.
- 2) ↓ cerebral edema (Mannitol)
- 3) ↓ IOP (emergency ↓ in IOP)
- 4) Mannitol: free-radical scavenger

- ▶ ↑ ECF (transient) → acute pulmonary edema or acute heart failure
- ▶ ↑ or ↓ in plasma ion concentrations (unpredictable):
 Electrolyte imbalance may occur.
- ▶ Contraindicated in anuria

Furosemide
Torsemide
Bumetanide
Ethacrynic acid

Loop diuretics. "High-ceiling" diuretics that dissipate the countercurrent multiplier.

Inhibit $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symporter in TAL:

- ▶ $\uparrow\uparrow$ NaCl excretion
 - ↓ medullary tonicity
 - ↓ renal concentrating ability
- ▶ \uparrow K^+ and H^+ excretion (due to \uparrow delivery of Na^+ to DT)
- ▶ \uparrow Ca^{++} and Mg^{++} excretion (due to changes in tubular electrochemical potential)

Kidneys can't concentrate (countercurrent multiplier effected) or dilute (Na^+ reabsorption in final diluting segment affected) urine

Urine is $\sim \frac{1}{2} P_{\text{osm}}$

"-ide" diuretics have sulfonamide group.
Ethacrynic acid has methylene group (less potential for allergies)

Furosemide:

Also inhibits CA
Causes venous dilation: immediate improvement in pulmonary edema symptoms.

Pharmacokinetics:

- ▶ high protein binding, not well filtered
- ▶ actively secreted in proximal tubule
- ▶ oral bioavailability:
 - Furosemide: 60%
 - Ethacrynic acid: 100%
- ▶ disposition:
 - $\approx 2/3$ excreted unchanged
 - $\approx 1/3$ metabolized

Uses of loop diuretics:

- 1) Acute pulmonary edema
 - 2) Hypertension
 - 3) CHF
 - 4) Edema of Nephrotic syndrome
 - 5) Edema of Cirrhosis (usually K^+ sparing diuretic tried first)
 - 6) \uparrow excretion of (some) toxins
 - 7) SIADH
 - *8) evading drug monitoring
 - *9) very rapid weight loss
- * = not officially endorsed by UMMS ethics committee

- ▶ Fluid and electrolyte imbalances:
 - hypokalemia** (eat bananas and a \downarrow Na^+ diet)
 - hyponatremia**, (hypochloremia, hypocalcemia, hypomagnesemia)
 - hypovolemia, metabolic alkalosis**
- ▶ \uparrow Ca^{2+} excretion in osteoporotic women
- ▶ Ototoxicity due to altered endolymph
 - hearing loss, vertigo, usually reversible
 - Ethacrynic acid MORE ototoxic, only used if allergic to Furosemide.
- ▶ Hyperuricemia (occasionally can get gout)
- ▶ Hyperglycemia (can exacerbate poor glycemic control)
- ▶ Hypersensitivity cross-reactivity with other sulfonamides (not Ethacrynic Acid)

Hydrochlorothiazide
Chlorothiazide
Chlorthalidone
Metalazone

Thiazide diuretics:

Inhibit Na⁺/Cl⁻ symporter in DCT.
Sulfonamide derivatives.
Weakly inhibit CA

Not as effective in increasing NaCl excretion as loop diuretics because much of the NaCl has already been absorbed before the DCT.

Metalazone used in combination with loop diuretics for maximal diuretic effect.

Pharmacokinetics:

- ▶ actively secreted in proximal tubule
- ▶ wide range in durations of action
HCTZ half-life ≈ 2.5 hr

Thiazides cause:

- ▶ ↑ NaCl excretion
- ▶ ↑ K⁺ and H⁺ excretion
(due to ↑ delivery of Na⁺ to DT, same as loop diuretics)
- ▶ ↓ Ca⁺⁺ excretion with chronic use
(in contrast to loop diuretics)

Impair ability to excrete dilute urine, but ability to form concentrated urine is NOT affected.

Uses of thiazides:

- 1) Edema of heart, kidney, liver failure
- 2) Hypertension
- 3) Nephrogenic DI

- ▶ Volume and electrolyte imbalances similar to those caused by loop diuretics (except hypercalcemia instead of hypocalcemia)
 - ▶ hypokalemia
 - ▶ hypochloremia
 - ▶ metabolic alkalosis
- ▶ Hyperuricemia and hyperglycemia (may unmask DM)
- ▶ Sulfonamide allergies: hypersensitivity cross-reactions with other sulfonamides
- ▶ Erectile dysfunction

Spirolactone
Eplerone

K⁺-sparing diuretics.

Aldosterone analog (antagonist):

binds to mineralcorticoid receptor in late DT and CT, blocking aldo's Na⁺-reabsorption in exchange for K⁺ and H⁺

Eplerone: A new spironolactone analog with greater selectivity for aldosterone receptors. No hormone-related AE's.

Causes:

- ▶ ↑ Na⁺ excretion
- ▶ ↑ K⁺ and H⁺ **retention**

Uses:

- 1) Balance K⁺ loss of loop diuretics or thiazides
- 2) hyperaldosteronism
- 3) ↓ mortality in CHF
- 4) ↑ aldosterone due to CHF/cirrhosis

▶ Electrolyte imbalance:

hyperkalemia

⚠ (especially with ACE-I or ARB's)
metabolic acidosis

▶ hormone-related AE's (Spirolactone)

estrogen effect:

gynecomastia
impotence

androgen effect (mostly in females)

hirsutism
deepening of voice
BPH

▶ May cause malignancies (Spirolactone)

Triamterene
Amiloride

K⁺-sparing diuretics.

Block Na⁺ channels in late DT and CT that contribute to Na⁺ reabsorption.

Amiloride is more potent and has a longer half-life than triamterene

Causes:

- ▶ ↑ Na⁺ excretion (a little)
- ▶ ↓ K⁺, H⁺, Ca⁺⁺, Mg⁺⁺ excretion
Na⁺ absorption coupled to excretion of those ions.

Used to balance K⁺ loss of loop diuretics or thiazides: **Used most commonly with other diuretics**

▶ **Hyperkalemia** most important

Increased risk of hyperkalemia in renal disease or when any K⁺-sparing diuretics are used with NSAID's, ACE-I's, ARB's

‡ Watch out for dietary salt substitutes that contain potassium.

Desmopressin

Long-acting analog of ADH (agonist).

May be taken nasally or via long-acting injection.

V₁ receptors → vasoconstriction

V₂ receptors → in kidney, concentrate urine

Causes:

- ▶ ↑ water permeability in collecting duct
- ▶ potent vasoconstrictor

Used to treat DI

(DI is an underproduction of ADH where a huge volume of dilute urine is made)

Nephrogenic DI can be caused by lithium, demeclocycline, and other drugs.

Treatment of SIADH

SIADH: ↑ ADH → inappropriately concentrated urine

SIADH often follows head injury, and usually resolves spontaneously

Treated with diuretics (loop) and demeclocycline

Can also be caused by drugs (cyclophosphamide, cisplatin, phenothiazines, etc)

Probenecid

Inhibits organic acid transporter

Inhibits tubular **secretion** of many acids (penicillin)

Inhibits tubular **reabsorption** of uric acid → ↑ uric acid excretion, useful in gout