

Pharmacology

“Take me, I am the drug; take me, I am hallucinogenic.”
—Salvador Dali

“I was under medication when I made the decision not to burn the tapes.”
—Richard Nixon

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on autonomic nervous system, central nervous system, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

**High-Yield Clinical
Vignettes**

High-Yield Topics

Pharmacokinetics

Antimicrobial

CNS

Cardiovascular

Cancer Drugs

Toxicology

Miscellaneous

These abstracted case vignettes are designed to demonstrate the thought processes necessary to answer multistep clinical reasoning questions.

- 28-year-old chemist presents with MPTP exposure → what neurotransmitter is depleted? → dopamine. *Pharm. 53*
- Woman taking tetracycline exhibits photosensitivity → what are the clinical manifestations? → rash on sun-exposed regions of the body. *Pharm. 15*
- Young girl with congenital valve disease is given penicillin prophylactically. She develops bacterial endocarditis → what do you give now? → beta-lactamase-resistant penicillin. *Pharm. 44*
- Nondiabetic patient presents with hypoglycemia but low levels of C peptide → what is the diagnosis? → surreptitious insulin injection. *Pharm. 20*
- African-American man who goes to Africa develops anemia after taking prophylactic medicine → what is the enzyme deficiency? → glucose-6-phosphate dehydrogenase.
- 27-year-old female with a history of psychiatric illness now has urinary retention due to a neuroleptic → what do you treat it with? → bethanechol.
- Farmer presents with dyspnea, salivation, miosis, diarrhea, cramping, and blurry vision → what caused this? what is the mechanism of action? → insecticide poisoning; inhibition of acetylcholinesterase.
- 55-year-old man undergoing treatment for BPH has decreased levels of testosterone and DHT as well as gynecomastia and edema → what is the drug? → estrogen (DES).
- Patient with recent kidney transplant is on cyclosporine for immunosuppression. Requires antifungal agent for candidiasis → what drug would result in cyclosporine toxicity? → ketoconazole. *Pharm. 43*
- Man on several medications, including antidepressants and antihypertensives, has mydriasis and becomes constipated → what is the cause of his symptoms? → tricyclic antidepressant. *Pharm. 60*
- Patient presents with renal insufficiency → what alterations in doses of digoxin and digitoxin, respectively? → decreased, same.
- 55-year-old postmenopausal woman is on tamoxifen therapy → what is she at increased risk of acquiring? → endometrial carcinoma.
- Woman on MAO inhibitor has hypertensive crisis after a meal → what did she ingest? → tyramine (wine or cheese). *Pharm. 6*
- After taking clindamycin, patient develops toxic megacolon and diarrhea → what is the mechanism of diarrhea? → *C. difficile* overgrowth.
- Man starts a medication for hyperlipidemia. He then develops a rash, pruritus, and GI upset → what drug was it? → niacin. *Pharm. 8*
- Patient is on carbamazepine → what routine workup should always be done? → LFTs. *Pharm. 49*
- 23-year-old female who is on rifampin for TB prophylaxis and on birth control (estrogen) gets pregnant → why? → rifampin affects estrogen metabolism in the liver. *Pharm. 45*
- Older female goes into OR for emergency surgery; after administration of succinylcholine, she requires respiratory support for over 4 hours. Later it is determined that she is receiving medication for glaucoma → what is she on? → acetylcholinesterase inhibitor.
- Patient develops cough and must discontinue captopril → what is a good replacement drug, and why doesn't it have the same side effects? → losartan, an ATII receptor antagonist, does not ↑ bradykinin as captopril does.

Mechanism, clinical use, and toxicity of:

1. Motion sickness drugs (e.g., scopolamine).
2. Antipsychotics (neuroleptics), low and high potency.
3. Opiates (e.g., analgesic, antidiarrheal, antitussive), receptor types, agonists, mixed agonist-antagonists.
4. Myasthenia gravis drugs.
5. Hormonal treatments of cancer (e.g., leuprolide, flutamide, aminoglutethimide).
6. New oral hypoglycemic agents (acarbose, metformin, troglitazone).
7. Stool softeners (e.g., psyllium, methylcellulose).
8. Angiotensin II receptor blockers (e.g., losartan).
9. Dermatologic agents (e.g., corticosteroids, retinoids, antifungal agents).
10. Other new pharmacologic agents (erythropoietin, RU486).

Know about:

1. Complications of empiric antibiotic use (e.g., resistance, fungal infection, pseudomembranous colitis).
2. Secondary effects of common drugs (e.g., heparin and osteoporosis, thiazides and hyperlipidemia).
3. Fundamental pharmacodynamics (e.g., partial agonists, physiologic antagonists, efficacy).
4. Drug efficacy and potency as demonstrated on dose-response curves.
5. Pharmacogenetics: drugs whose metabolism is affected by inheritance (e.g., isoniazid).
6. Anesthesia: physical properties of gaseous agents (MAC, blood:gas partition coefficient, rate of induction), different IV agents, toxicities (e.g., malignant hyperthermia).
7. Treatment of anemia (e.g., erythropoietin, B₁₂, folate, testosterone, iron supplements).
8. Prevention/treatment of cerebrovascular disease (e.g., aspirin, thrombolytics).
9. Treatment of rheumatoid arthritis.
10. Vaccines: indications, potential side effects.
11. Chemotherapeutic agents: risk of possible secondary cancer.

Pharmacokinetics

- Volume of distribution (V_d) Relates the amount of drug in the body to the plasma concentration. V_d of plasma protein-bound drugs can be altered by liver and kidney disease.
- Clearance (CL) Relates the rate of elimination to the plasma concentration.
- Half-life ($t_{1/2}$) The time required to change the amount of drug in the body by one-half during elimination (or during a constant infusion). A drug infused at a constant rate reaches about 94% of steady state after four $t_{1/2}$.

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}}$$

$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$

# of half-lives	1	2	3	3.3
Concentration	50%	75%	87.5%	90%

Dosage calculations

Loading dose = $C_p \times V_d/F$
 Maintenance dose = $C_p \times CL/F$
 where C_p = target plasma concentration
 and F = bioavailability

In patients with impaired renal or hepatic function, the loading dose remains unchanged, although the maintenance dose is decreased.

Elimination of drugs

- Zero-order elimination Rate of elimination is constant regardless of C (i.e., constant **amount** of drug eliminated per unit time). C_p decreases linearly with time. Examples of drugs: ethanol, phenytoin, and aspirin (at high or toxic concentrations).
- First-order elimination Rate of elimination is proportional to the drug concentration (i.e., constant **fraction** of drug eliminated per unit time). C_p decreases exponentially with time.

Phase I versus phase II metabolism

Phase I (reduction, oxidation, hydrolysis) yields slightly polar, water-soluble metabolites (often still active).
 Phase II (acetylation, glucuronidation, sulfation) yields very polar, inactive metabolites (renally excreted).

Phase I: cyt. P450
 Phase II: conjugation.
 Geriatric patients lose phase I first.

Antimicrobial therapy

Mechanism of action	Drugs
Block cell wall synthesis by inhibition of peptidoglycan cross-linking	Penicillin, ampicillin, ticarcillin, piperacillin, imipenem, aztreonam, cephalosporins
Block peptidoglycan synthesis	Bacitracin, vancomycin
Block protein synthesis at 50S ribosomal subunit	Chloramphenicol, erythromycin/macrolides, lincomycin, clindamycin, streptogramins (quinupristin, dalfopristin)
Block protein synthesis at 30S ribosomal subunit	Aminoglycosides, tetracyclines
Block nucleotide synthesis	Sulfonamides, trimethoprim
Block DNA topoisomerases	Quinolones
Block mRNA synthesis	Rifampin
Disrupt bacterial/fungal cell membranes	Polymyxins
Disrupt fungal cell membranes	Amphotericin B, nystatin, fluconazole/azoles
Unknown	Pentamidine

Penicillin

Mechanism	Penicillin G (IV form), penicillin V (oral): 1. Binds penicillin-binding proteins 2. Blocks transpeptidase cross-linking of cell wall 3. Activates autolytic enzymes
Clinical use	Bactericidal for gram-positive cocci, gram-positive rods, gram-negative cocci, and spirochetes. Not penicillinase resistant.
Toxicity	Hypersensitivity reactions.

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Methicillin, nafcillin, dicloxacillin

Mechanism	Same as penicillin. Narrow spectrum, penicillinase resistant because of bulkier R group.
Clinical use	<i>Staphylococcus aureus</i> .
Toxicity	Hypersensitivity reactions; methicillin: interstitial nephritis.

Ampicillin, amoxicillin

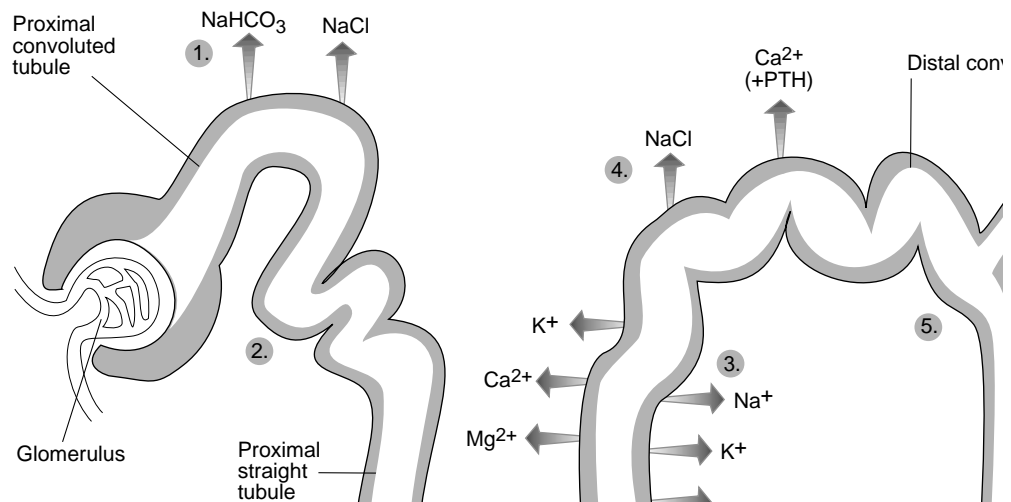
Mechanism	Same as penicillin. Wider spectrum, penicillinase sensitive. Also, combine with clavulanic acid (penicillinase inhibitor) to enhance spectrum. AmOxicillin has greater Oral bioavailability than ampicillin.
Clinical use	Extended-spectrum penicillin: certain gram-positive bacteria and gram-negative rods (<i>Haemophilus influenzae</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> , enterococci). Coverage: ampicillin/amoxicillin HELPS kill enterocci.
Toxicity	Hypersensitivity reactions; ampicillin: rash; pseudomembranous colitis.

Carbenicillin, piperacillin, and ticarcillin

Mechanism	Same as penicillin. Extended spectrum.
Clinical use	<i>Pseudomonas</i> species and gram-negative rods; susceptible to penicillinase; use with clavulanic acid.
Toxicity	Hypersensitivity reactions.

Cephalosporins

Mechanism	β -lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	
Clinical use	First generation: gram-positive cocci, <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> .	1st generation: PECK
	Second generation: gram-positive cocci, <i>Haemophilus influenzae</i> , <i>Enterobacter aerogenes</i> , <i>Neisseria</i> species, <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>Serratia marcescens</i> .	2nd generation: HEN PECKS
	Third generation: serious gram-negative infections resistant to other beta-lactams; meningitis (most penetrate the blood-brain barrier). Examples: ceftazidime for <i>Pseudomonas</i> ; ceftriaxone for gonorrhea.	
Toxicity	Hypersensitivity reactions, increased nephrotoxicity of aminoglycosides, disulfiram-like reaction with ethanol (in cephalosporins with a methylthiotetrazole group, e.g., cefamandole).	



Aztreonam

Mechanism	A monobactam resistant to β -lactamases. Inhibits cell wall synthesis (binds to PBP3). Synergistic with aminoglycosides. No cross-allergenicity with penicillins.
Clinical use	Gram-negative rods: <i>Klebsiella</i> species, <i>Pseudomonas</i> species, <i>Serratia</i> species. No activity against gram-positives or anaerobes.
Toxicity	Usually nontoxic; occasional GI upset.

Imipenem/cilastatin

Mechanism	Imipenem is a wide-spectrum, β -lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dihydropeptidase I) to \downarrow inactivation in renal tubules.	With imipenem, “the kill is lastin with cilastatin.”
Clinical use	Gram-positive cocci, gram-negative rods, and anaerobes. Drug of choice for <i>Enterobacter</i> .	
Toxicity	GI distress, skin rash, and CNS toxicity (at high plasma levels).	

Vancomycin

Mechanism	Inhibits cell wall mucopeptide formation. Bactericidal. Resistance occurs with amino acid change of D-ala D-ala to D-ala D-lac.
Clinical use	Used for serious, gram-positive multidrug-resistant organisms, including <i>Staphylococcus aureus</i> and <i>Clostridium difficile</i> (pseudomembranous colitis).
Toxicity	Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse flushing—“red man syndrome” (can largely prevent by pretreatment with antihistamines and slow infusion rate). Well tolerated in general: does NOT have many problems.

Protein synthesis inhibitors

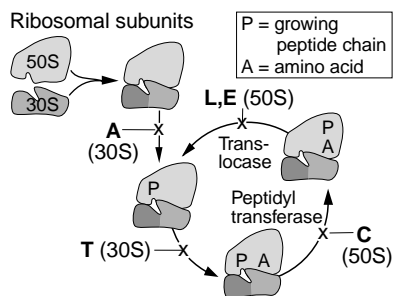
30S inhibitors:

A = Aminoglycosides (streptomycin, gentamicin, tobramycin, amikacin) [bactericidal]
 T = Tetracyclines [bacteriostatic]

“Buy AT 30, CELL at 50”

50S inhibitors:

C = Chloramphenicol [bacteriostatic]
 E = Erythromycin [bacteriostatic]
 L = Lincomycin [bacteriostatic]
 L = clindamycin [bacteriostatic]



Aminoglycosides

Mechanism	Gentamicin, neomycin, amikacin, tobramycin, streptomycin Bactericidal, inhibits formation of initiation complex and causes misreading of mRNA. Requires O_2 for uptake, therefore ineffective against anaerobes.
Clinical use	Severe gram-negative rod infections. Synergistic with β -lactam antibiotics. Neomycin for bowel surgery.
Toxicity	Nephrotoxicity (especially when used with cephalosporins), Ototoxicity (especially when used with loop diuretics). AmiNOglycosides.

Tetracyclines	Tetracycline, doxycycline, demeclocycline, minocycline	
Mechanism	Bacteriostatic, binds to 30S and prevents attachment of aminoacyl-tRNA, limited CNS penetration. Doxycycline fecally eliminated and can be used in patients with renal failure. Must NOT take with milk or antacids because divalent cations inhibit its absorption in the gut.	
Clinical use	<i>Vibrio cholerae</i> , Acne, <i>Chlamydia</i> , <i>Ureaplasma Urealyticum</i> , <i>Mycoplasma pneumoniae</i> , <i>Borrelia burgdorferi</i> (Lyme disease), <i>Rickettsia</i> , tularemia.	VACUUM your Bed Room
Toxicity	GI distress, discolors teeth and inhibits bone growth in children, Fanconi's syndrome, photosensitivity.	

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Macrolides	Erythromycin, azithromycin, clarithromycin	
Mechanism	Inhibits protein synthesis by blocking translocation, binds to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.	
Clinical use	Upper respiratory tract infections, pneumonias, sexually transmitted diseases: gram-positive cocci (streptococcal infections in patients allergic to penicillin), <i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i> , <i>Neisseria</i> .	
Toxicity	GI discomfort (most common cause of noncompliance), acute cholestatic hepatitis, eosinophilia, skin rashes.	

Chloramphenicol

Mechanism	Inhibits 50S peptidyl transferase. Bacteriostatic.
Clinical use	Meningitis (<i>H. influenzae</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i>). Conservative use due to toxicities.
Toxicity	Anemia, aplastic anemia (dose independent), gray baby syndrome (in premature infants lacking liver UDP-glucuronyl transferase).

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Clindamycin

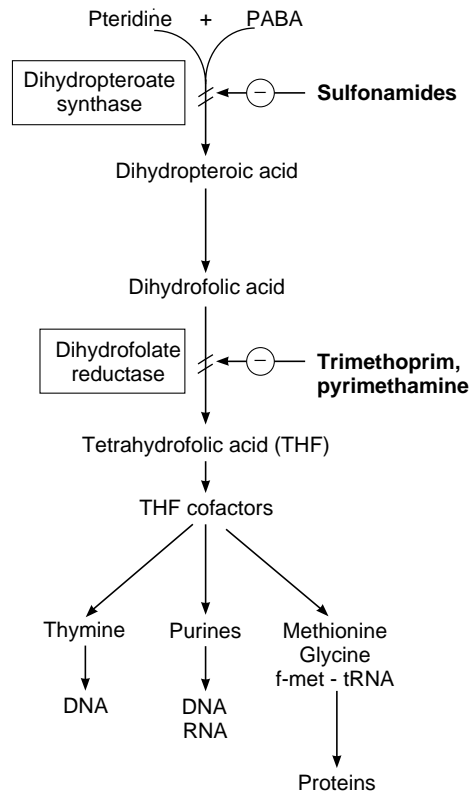
Mechanism	Blocks peptide bond formation at 50S ribosomal subunit.
Clinical use	Treat anaerobic infections (e.g., <i>B. fragilis</i> , <i>C. perfringens</i>).
Toxicity	Pseudomembranous colitis (<i>C. difficile</i> overgrowth), fever, diarrhea.

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Sulfonamides

Mechanism
Clinical use
Toxicity

Sulfamethoxazole (SMZ), sulfisoxazole, triple sulfas, sulfadiazine
PABA antimetabolites inhibit dihydropteroate synthase. Bacteriostatic.
Gram-positive, gram-negative, *Nocardia*, *Chlamydia*. Triple sulfas or SMZ for simple UTI.
Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity, kernicterus in infants, displace other drugs from albumin.



Trimethoprim

Mechanism
Clinical use

Inhibits bacterial dihydrofolate reductase. Bacteriostatic.
Used in combination with sulfonamides (trimethoprim-sulfamethoxazole), causing sequential block of folate synthesis. Combination used for recurrent UTI, *Shigella*, *Salmonella*, *Pneumocystis carinii* pneumonia.
Megaloblastic anemia, leukopenia, granulocytopenia.
(May alleviate with supplemental folic acid.)

Trimethoprim = TMP:
"Treats Marrow Poorly."

Toxicity

Fluoroquinolones

Mechanism
Clinical use
Toxicity

Ciprofloxacin, norfloxacin, ofloxacin, grepafloxacin, enoxacin (fluoroquinolones), nalidixic acid (a quinolone)
Inhibits DNA gyrase (topoisomerase II). Bactericidal.
Gram-negative rods of urinary and GI tracts (including *Pseudomonas*), *Neisseria*, some gram-positive organisms.
GI upset, superinfections, skin rashes, headache, dizziness.
Contraindicated in pregnant women and in children because animal studies show damage to cartilage.
Tendonitis and tendon rupture in adults.

Fluoroquinolones hurt attachments to your bones.

Metronidazole

Mechanism	Forms toxic metabolites in the bacterial cell. Bactericidal.	
Clinical use	Antiprotozoal. <i>Giardia</i> , <i>Entamoeba</i> , <i>Trichomonas</i> , <i>Gardnerella vaginalis</i> , anaerobes (<i>Bacteroides</i> , <i>Clostridium</i>). Used with bismuth and amoxicillin or tetracycline for “triple therapy” against <i>H. pylori</i> .	GET on the Metro!
Toxicity	Disulfiram-like reaction with alcohol, headache.	

Polymyxins

Mechanism	Polymyxin B, polymyxin E Bind to cell membranes of bacteria and disrupt their osmotic properties. Polymyxins are cationic, basic proteins that act like detergents.	
Clinical use	Resistant gram-negative infections.	
Toxicity	Neurotoxicity, acute renal tubular necrosis.	

Isoniazid (INH)

Mechanism	Decreases synthesis of mycolic acids.	INH:
Clinical use	<i>Mycobacterium tuberculosis</i> . The only agent used as solo prophylaxis against TB.	Injures Neurons and Hepatocytes.
Toxicity	Hemolysis if G6PD deficient, neurotoxicity, hepatotoxicity, SLE-like syndrome. Pyridoxine (vit. B ₆) can prevent neurotoxicity.	Different INH half-lives in fast vs. slow acetylators.

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Rifampin

Mechanism	Inhibits DNA-dependent RNA polymerase.	Rifampin's 4 R's:
Clinical use	<i>M. tuberculosis</i> , delays resistance to dapsona when used for leprosy. Always used in combination with other drugs except in the treatment of meningococcal carrier state, and chemoprophylaxis in contacts of children with <i>H. influenzae</i> type B.	RNA polymerase inhibitor Revs up microsomal P450 Red/orange body fluids Rapid resistance if used alone
Toxicity	Minor hepatotoxicity and drug interactions (↑ P ₄₅₀).	

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Anti-TB drugs

Rifampin, Ethambutol, Streptomycin, Pyrazinamide, Isoniazid (INH).	RESPIre INH is used alone for TB prophylaxis.
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Resistance mechanisms for various antibiotics

Drug	Most common mechanism
Penicillins/ cephalosporins	β -lactamase cleavage of β -lactam ring
Aminoglycosides	Modification via acetylation, adenylation, or phosphorylation
Vancomycin	Terminal D-ala of cell wall component replaced with D-lac; \downarrow affinity.
Chloramphenicol	Modification via acetylation
Macrolides	Methylation of rRNA near erythromycin's ribosome-binding site
Tetracycline	\downarrow uptake or \uparrow transport out of cell
Sulfonamides	Altered enzyme (bacterial dihydropteroate synthetase), \downarrow uptake, or \uparrow PABA synthesis

Nonsurgical antimicrobial prophylaxis

Meningococcal infection	Rifampin (drug of choice), minocycline
Gonorrhea	Ceftriaxone
Syphilis	Benzathine penicillin G
History of recurrent UTIs	Trimethoprim-sulfamethoxazole (TMP-SMZ)
PCP	TMP-SMZ (drug of choice), aerosolized pentamidine

Amphotericin B

Mechanism	Binds ergosterol (unique to fungi), forms membrane pores that disrupt homeostasis.	Amphotericin “tears” holes in the fungal membrane by forming pores.
Clinical use	Used for wide spectrum of systemic mycoses. <i>Cryptococcus</i> , <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Aspergillus</i> , <i>Histoplasma</i> , <i>Candida</i> , <i>Mucor</i> (systemic mycoses). Intrathecally for fungal meningitis; does not cross blood–brain barrier.	
Toxicity	Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias (“amphoterrible”).	

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Nystatin

Mechanism	Binds to ergosterol, disrupting fungal membranes.
Clinical use	“Swish and swallow” for oral candidiasis (thrush).

Fluconazole, ketoconazole, clotrimazole, miconazole, itraconazole

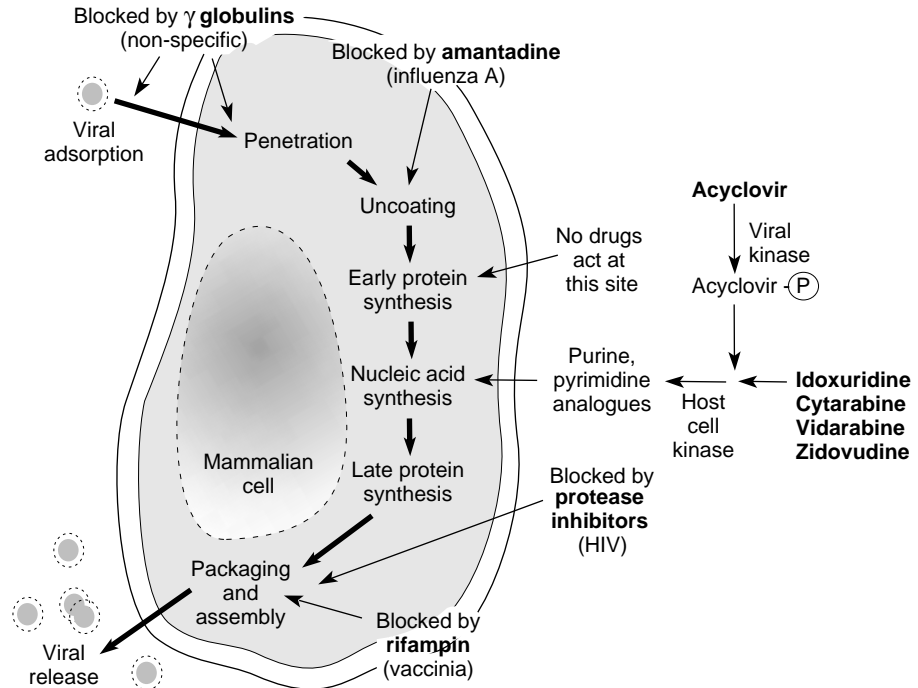
Mechanism	Inhibit fungal steroid (ergosterol) synthesis.
Clinical use	Systemic mycoses. Fluconazole for cryptococcal meningitis in AIDS patients and candidal infections of all types. Ketoconazole for <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>C. albicans</i> ; hypercortisolism.
Toxicity	Hormone synthesis inhibition (gynecomastia), liver dysfunction (inhibits cyt. P450), fever, chills.

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Griseofulvin

Mechanism	Interferes with microtubule function, disrupts mitosis. Deposits in keratin-containing tissues (e.g., nails).
Clinical use	Oral treatment of superficial infections, inhibits growth of dermatophytes (tinea, ringworm).
Toxicity	Teratogenic, carcinogenic, confusion, headaches, ↑ coumadin metabolism.

Antiviral chemotherapy



Amantadine

Mechanism	Blocks viral penetration/uncoating; may buffer pH of endosome. Also causes the release of dopamine from intact nerve terminals.	Amantadine blocks influenza A and rubella and causes problems with the cerebellum.
Clinical use	Prophylaxis for influenza A; Parkinson's disease.	
Toxicity	Ataxia, dizziness, slurred speech.	

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Ribavirin

Mechanism	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase.
Clinical use	RSV.
Toxicity	Hemolytic anemia.

Acyclovir

Mechanism	Preferentially inhibits viral DNA polymerase when phosphorylated by viral thymidine kinase.
Clinical use	HSV, VZV, EBV. Mucocutaneous and genital herpes lesions. Prophylaxis in immunocompromised patients.
Toxicity	Delirium, tremor, nephrotoxicity.

Ganciclovir

Mechanism	DHPG (dihydroxy-2-propoxymethyl guanine) Phosphorylation by viral kinase, preferentially inhibits CMV DNA polymerase.
Clinical use	CMV, especially in immunocompromised patients.
Toxicity	Leukopenia, neutropenia, thrombocytopenia, renal toxicity. More toxic to host enzymes than acyclovir.

Foscarnet

Mechanism	Viral DNA polymerase inhibitor that binds to the pyrophosphate binding site of the enzyme. Does not require activation by viral kinase.	Foscarnet = pyroFosphate analog.
Clinical use	CMV retinitis in immunocompromised patients when ganciclovir fails.	
Toxicity	Nephrotoxicity.	

HIV therapy

Protease inhibitors

Mechanism	Saquinavir, Ritonavir, Indinavir, Nelfinavir Inhibits assembly of new virus by blocking protease enzyme
Toxicity	GI intolerance (nausea, diarrhea), hyperglycemia, lipid abnormalities, thrombocytopenia (indinavir).

Reverse transcriptase inhibitors

Nucleosides	Zidovudine (AZT), Didanosine (ddI), Zalcitabine (ddC), Stavudine (d4T), Lamivudine (3TC)
Non-nucleosides	Nevirapine, Delavirdine
Mechanism	Preferentially inhibit reverse transcriptase of HIV, prevent incorporation of viral genome into host DNA
Toxicity	Bone marrow suppression (neutropenia, anemia), peripheral neuropathy, lactic acidosis (nucleosides); rash (non-nucleosides); megaloblastic anemia (AZT).
Clinical use	“Triple therapy” generally entails use of two nucleoside reverse transcriptase inhibitors with a protease inhibitor, though other combinations, such as the substitution of a non-nucleoside for a protease inhibitor, are used. Initiated when patients have low CD4 counts (< 500 cells/mm ³) or high viral load. AZT used during pregnancy to reduce risk of fetal transmission.

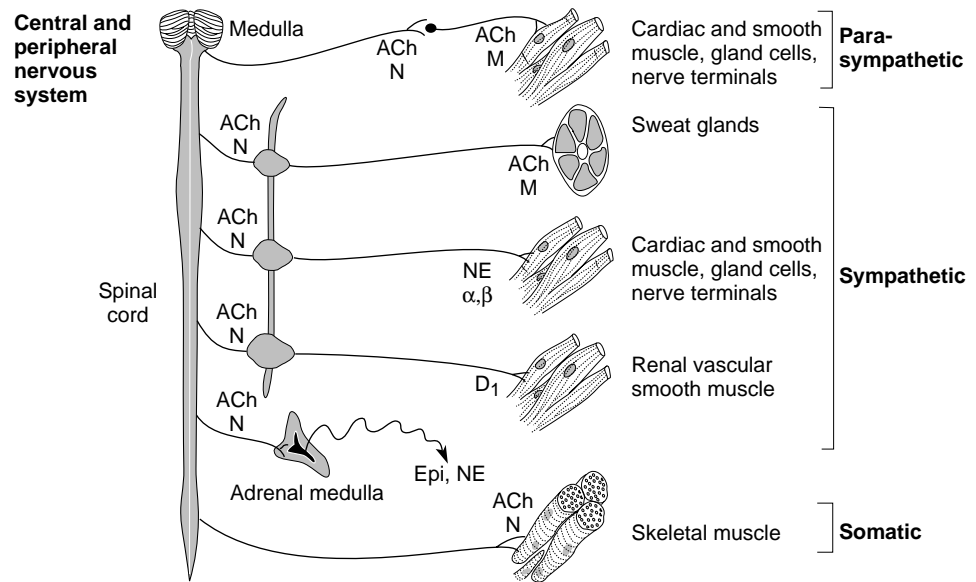
Interferons

Mechanism	Glycoproteins from human leukocytes that block various stages of viral RNA and DNA synthesis.
Clinical use	Chronic hepatitis A and B, Kaposi's sarcoma.
Toxicity	Neutropenia.

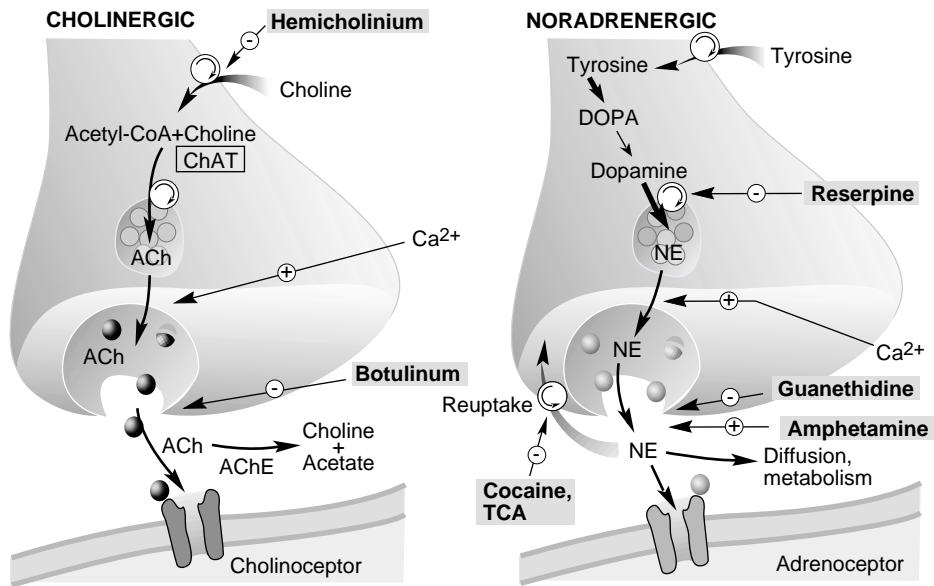
Antiparasitic drugs

Ivermectin	Onchocerciasis (“river blindness” ⇒ r IVER -mectin).
Mebendazole/ thiabendazole	Nematode/roundworm (e.g., pinworm, whipworm) infections.
Pyrantel pamoate	Giant roundworm (<i>Ascaris</i>), hookworm (<i>Necator/Ancylostoma</i>), pinworm (<i>Enterobius</i>).
Praziquantel	Trematode/fluke (e.g., schistosomes, <i>Paragonimus</i> , <i>Clonorchis</i>) and cysticercosis.
Niclosamide	Cestode/tapeworm (e.g., <i>D. latum</i> , <i>Taenia</i> species) infections except cysticercosis.
Pentavalent antimony	Leishmaniasis.
Chloroquine, quinine, mefloquine	Malaria.
Primaquine	Latent hypnozoite (liver) forms of malaria (<i>P. vivax</i> , <i>P. ovale</i>).
Metronidazole	Giardiasis, amoebic dysentery (<i>E. histolytica</i>), bacterial vaginitis (<i>Gardnerella vaginalis</i>).
Pentamidine	<i>Pneumocystis carinii</i> pneumonia prophylaxis.
Nifurtimox	Chagas’ disease (<i>Trypanosoma cruzi</i>).

Central and peripheral nervous system



Autonomic drugs



Circles with rotating arrows represent transporters; ChAT, choline acetyltransferase; ACh, acetylcholine; AChE, acetylcholinesterase; NE, norepinephrine.

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Cholinomimetics

	Clinical applications	Action
Direct agonists		
Bethanechol	Postoperative and neurogenic ileus and urinary retention	Activates bowel and bladder smooth muscle
Carbachol, pilocarpine	Glaucoma	Activates ciliary muscle of eye (open angle), pupillary sphincter (narrow angle)
Indirect agonists (anticholinesterases)		
Neostigmine	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of NMJ blockade (postoperative)	↑ endogenous ACh
Pyridostigmine	Myasthenia gravis	↑ endogenous ACh; ↑ strength
Edrophonium	Diagnosis of myasthenia gravis (extremely short-acting)	↑ endogenous ACh
Physostigmine	Glaucoma (crosses blood-brain barrier → CNS) and atropine overdose	↑ endogenous ACh
Echothiophate	Glaucoma	↑ endogenous ACh

Cholinesterase inhibitor poisoning

Symptoms include: Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Excitation of skeletal muscle and CNS, Lacrimation, Sweating, Salivation (also abdominal cramping).

DUMBBELSS
Parathion and other organophosphates.

Cholinoreceptor blockers

Muscarinic antagonists	Atropine: used to dilate pupil, reduce acid secretion in acid-peptic disease, reduce urgency in mild cystitis, ↓ GI motility, reduce airway secretions. Causes increased body temperature, rapid pulse, dry mouth, flushed skin, disorientation, mydriasis with cycloplegia, and constipation.	Atropine parasympathetic block side effects: Blind as a bat Red as a beet Mad as a hatter Hot as a hare Dry as a bone
Nicotinic antagonists	Hexamethonium: ganglionic blocker.	
Cholinesterase regenerator	Pralidoxime: regenerates active cholinesterase, chemical antagonist, used to treat organophosphate exposure.	Blocks SLUD : Salivation, Lacrimation, Urination, Defecation.

Antimuscarinic drugs

Organ system	Drugs	Application
CNS	Benztropine Scopolamine	Parkinson's disease Motion sickness
Eye	Atropine, homatropine, tropicamide	Produce mydriasis and cycloplegia
Respiratory	Ipratropium	Asthma, COPD

Neuromuscular blocking drugs

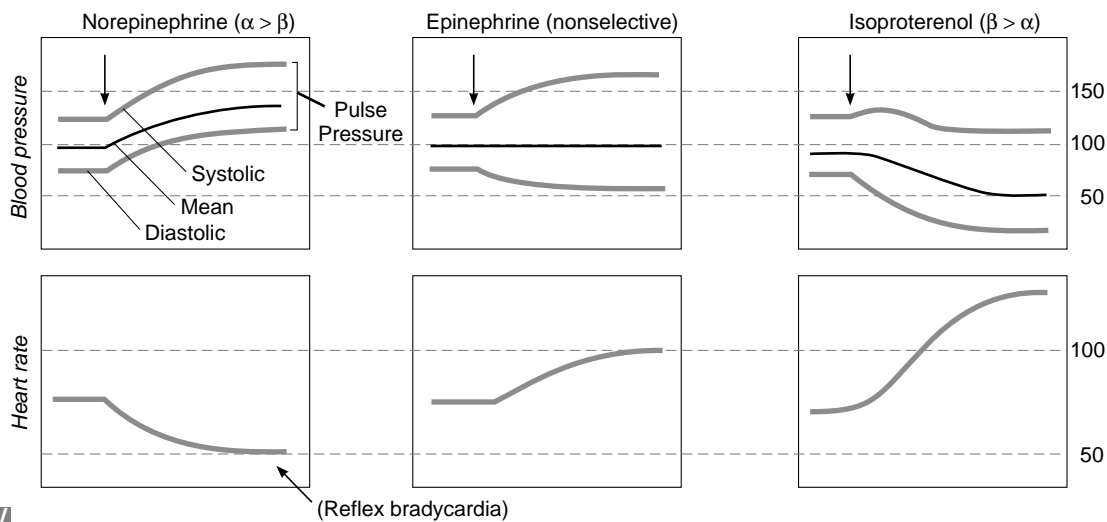
Depolarizing	Used for muscle paralysis in surgery or mechanical ventilation. Succinylcholine Reversal of blockade: Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors. Phase II (repolarized but blocked)—antidote: cholinesterase inhibitors (e.g., neostigmine).
Nondepolarizing	Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium. Reversal of blockade: neostigmine, edrophonium, and other cholinesterase inhibitors.

Dantrolene

Used in the treatment of malignant hyperthermia, which is caused by the concomitant use of halothane and succinylcholine. Also used to treat neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).
Mechanism: prevents the release of Ca²⁺ from the sarcoplasmic reticulum of skeletal muscle.

Sympathomimetics

Drug	Mechanism/selectivity	Applications
Catecholamines		
Epinephrine	Direct general agonist ($\alpha_1, \alpha_2, \beta_1, \beta_2$)	Anaphylaxis, glaucoma (open angle), asthma, hypotension
Norepinephrine	$\alpha_1, \alpha_2, \beta_1$	Hypotension
Isoproterenol	$\beta_1 = \beta_2$	AV block (rare)
Dopamine	$D_1 = D_2 > \beta > \alpha$	Shock (\uparrow renal perfusion), heart failure
Dobutamine	$\beta_1 > \beta_2$	Shock, heart failure
Other		
Amphetamine <small>Pharm. 55, 66</small>	Indirect general agonist, releases stored catecholamines	Narcolepsy, obesity, attention deficit disorder
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal congestion, urinary incontinence, hypotension
Phenylephrine	$\alpha_1 > \alpha_2$	Pupil dilator, vasoconstriction, nasal decongestion
Albuterol, terbutaline	$\beta_2 > \beta_1$	Asthma
Cocaine <small>Pharm. 72</small>	Indirect general agonist, uptake inhibitor	Causes vasoconstriction and local anesthesia



α -Blockers

	Application	Toxicity
Nonselective Phenoxybenzamine (irreversible) and phentolamine (reversible)	Pheochromocytoma	Orthostatic hypotension, reflex tachycardia
α_1 -selective Prazosin, terazosin, doxazosin	Hypertension, urinary retention in BPH	First-dose orthostatic hypotension, dizziness, headache
α_2 -selective Yohimbine	Impotence (effectiveness is controversial)	

β -Blockers

Application	Effect
Hypertension	\downarrow cardiac output, \downarrow renin secretion
Angina pectoris	\downarrow heart rate and contractility, resulting in decreased oxygen consumption
MI	β -blockers decrease mortality
SVT (propranolol, esmolol)	\downarrow AV conduction velocity
Glaucoma (timolol)	\downarrow secretion of aqueous humor
Toxicity	Impotence, exacerbation of asthma, cardiovascular adverse effects (bradycardia, AV block, CHF), CNS adverse effects (sedation, sleep alterations)
Selectivity	Nonselective ($\beta_1 = \beta_2$): propranolol, timolol, pindolol, nadolol, and labetalol (also blocks α_1 receptors) β_1 selective ($\beta_1 > \beta_2$): metoprolol, atenolol, esmolol (short-acting)

UCV Pharm. 1

Glaucoma drugs

	Mechanism	Side effects
a agonists Epinephrine	\uparrow outflow of aqueous humor	Mydriasis, stinging. Do not use in closed-angle glaucoma.
Brimonidine	\downarrow aqueous humor synthesis	No pupillary or vision changes.
b blockers Timolol, betaxolol, carteolol	\downarrow aqueous humor secretion	No pupillary or vision changes.
Cholinomimetics Pilocarpine, carbachol, physostigmine, echothiophate	Ciliary muscle contraction, opening of trabecular meshwork; \uparrow outflow of aqueous humor	Miosis, cyclospasm.
Diuretics Acetazolamide, dorzolamide	\downarrow aqueous humor secretion due to \downarrow HCO_3^- (via inhibition of carbonic anhydrase)	No pupillary or vision changes.
Prostaglandin Latanoprost	\uparrow outflow of aqueous humor	Darkens color of iris (browning).

Barbiturates

	Phenobarbital, pentobarbital, thiopental, secobarbital	
Mechanism	Facilitate GABA _A action by ↑ duration of Cl ⁻ channel opening, thus ↓ neuron firing.	Barbi DURATe (↑ DURATI on).
Clinical use	Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).	Contraindicated in porphyria.
Toxicity	Dependence, additive CNS depression effects with alcohol, respiratory or cardiovascular depression (can lead to death), drug interactions owing to induction of liver microsomal enzymes (cyt. P ₄₅₀).	

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Benzodiazepines

	Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide	
Mechanism	Facilitates GABA _A action by ↑ frequency of Cl ⁻ channel opening. Most have long half-lives and active metabolites.	FRE nzodiazepines (↑ FRE quency) Short acting = TOM thumb = Triazolam, Oxazepam, Midazolam
Clinical use	Anxiety, spasticity, status epilepticus (diazepam), detoxification (especially alcohol withdrawal–delirium tremens).	
Toxicity	Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA receptor).	

Antipsychotics (neuroleptics)

	Thioridazine, haloperidol, fluphenazine, chlorpromazine	
Mechanism	Most antipsychotics block dopamine D₂ receptors (excess dopamine effects connected with schizophrenia).	Evolution of EPS side effects: 4 h acute dystonia 4 d akinesia 4 wk akathisia 4 mo tardive dyskinesia (often irreversible).
Clinical use	Schizophrenia, psychosis.	
Toxicity	Extrapyramidal system side effects, sedation, endocrine side effects, and side effects arising from blocking muscarinic, α, and histamine receptors. Neuroleptic malignant syndrome: rigidity, autonomic instability, hyperpyrexia (treat with dantrolene and dopamine agonists). Pharm. 57, 58 Tardive dyskinesia: stereotypic oral–facial movements probably due to dopamine receptor sensitization; results of long-term antipsychotic use. Pharm. 59	

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Atypical antipsychotics

	Clozapine, olanzapine, risperidone
Mechanism	Block 5HT ₂ and dopamine receptors.
Clinical use	Treatment of schizophrenia; useful for positive and negative symptoms. Olanzapine is also used for OCD, anxiety disorder, and depression.
Toxicity	Fewer extrapyramidal and anticholinergic side effects than other antipsychotics. Clozapine may cause agranulocytosis (requires weekly WBC monitoring).

Lithium

Mechanism	Not established; possibly related to inhibition of phosphoinositol cascade.
Clinical use	Mood stabilizer for bipolar affective disorder, blocks relapse and acute manic events.
Toxicity	Tremor, hypothyroidism, polyuria (ADH antagonist causing nephrogenic DI), teratogenesis. Narrow therapeutic window requiring close monitoring of serum levels.

UCV Pharm. 56

Tricyclic antidepressants

	Imipramine, amitriptyline, desipramine, nortriptyline, clomipramine, doxepin
Mechanism	Block reuptake of norepinephrine and serotonin.
Clinical use	Endogenous depression, bedwetting (imipramine), obsessive-compulsive disorder (clomipramine).
Side effects	Sedation, α -blocking effects, atropine-like (anticholinergic) side effects (tachycardia, urinary retention). Tertiary TCAs (amitriptyline) have more anticholinergic effects than secondary TCAs (nortriptyline). Desipramine is the least sedating.
Toxicity	“ Tri-C ”: convulsions, coma, cardiotoxicity (arrhythmias); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly.

UCV Pharm. 60

SSRIs

	Fluoxetine, sertraline, paroxetine, italoqram.	It normally takes 2–3 wk for antidepressants to have an effect.
Mechanism	Serotonin-specific reuptake inhibitors.	
Clinical use	Endogenous depression.	
Toxicity	Fewer than TCAs. CNS stimulation: anxiety, insomnia, tremor, anorexia, nausea, and vomiting; “Serotonin syndrome” with MAOIs: hyperthermia, muscle rigidity, CV collapse.	

Heterocyclics

	Second- and third-generation antidepressants with varied and mixed mechanisms of action. Used in major depressive disorders.
Trazodone	Primarily inhibits serotonin reuptake. Toxicity: sedation, nausea, priapism, postural hypotension.
Bupropion	Also used for smoking cessation. Mechanism not well known. Toxicity: stimulant effects (tachycardia, agitation), dry mouth, aggravation of psychosis.
Venlafaxine	Also used in generalized anxiety disorder. Inhibits serotonin and dopamine reuptake. Toxicity: stimulant effects (anxiety, agitation, headache, insomnia)
Mirtazapine	Alpha ₂ antagonist (increases release of norepinephrine and serotonin) and potent 5HT ₂ receptor antagonist. Toxicity: sedation, increased serum cholesterol, increased appetite.

Monoamine oxidase (MAO) inhibitors

	Phenelzine, isocarboxazid, tranylcypromine
Mechanism	Nonselective MAO inhibition.
Clinical use	Atypical depressions (i.e., with psychotic or phobic features), anxiety, hypochondriasis.
Toxicity	Hypertensive crisis with tyramine ingestion (in many foods) and meperidine; CNS stimulation. Contraindication with SSRIs or β -agonists.

UCV Pharm. 6

Selegiline (deprenyl)

Mechanism	Selectively inhibits MAO-B, thereby increasing the availability of dopamine.
Clinical use	Adjunctive agent to L-dopa in treatment of Parkinson's disease.
Toxicity	May enhance adverse effects of L-dopa.

L-dopa (levodopa)/carbidopa

Mechanism	Increases level of dopamine in brain. Parkinsonism thought to be due to loss of dopaminergic neurons and excess cholinergic function. Unlike dopamine, L-dopa can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine.
Clinical use	Parkinsonism.
Toxicity	Arrhythmias from peripheral conversion to dopamine. Carbidopa, a peripheral decarboxylase inhibitor, is given with L-dopa in order to increase the bioavailability of L-dopa in the brain and to limit peripheral side effects. Dyskinesias also occur.

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Parkinson's disease drugs

Dopamine agonists	L-dopa/carbidopa, bromocriptine (an ergot alkaloid and partial dopamine agonist), amantadine (enhance dopamine release)	BALSA: Bromocriptine Amantadine
MAO inhibitors	Selegiline (selective MAO type B inhibitor)	Levodopa
Antimuscarinics	Benzotropine (improve tremor and rigidity but have little effect on bradykinesia)	Selegiline Antimuscarinics

Opioid analgesics

Mechanism	Morphine, fentanyl, codeine, heroin, methadone, meperidine, dextromethorphan Act as agonists at opioid receptors (μ - morphine, δ - enkephalin, κ - dynorphin) to modulate synaptic transmission.
Clinical use	Pain, cough suppression (dextromethorphan), diarrhea (loperamide and diphenoxylate), acute pulmonary edema, maintenance programs for addicts (methadone).
Toxicity	Addiction, respiratory depression , constipation, miosis (pinpoint pupils), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone or naltrexone (opioid receptor antagonist).

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Sumatriptan

Mechanism	5-HT _{1D} agonist. Half-life < 2 hours.
Clinical use	Acute migraine, cluster headache attacks.
Toxicity	Chest discomfort, mild tingling (contraindicated in patients with CAD or Prinzmetal's angina).

Ondansetron

Mechanism	5-HT ₃ antagonist. Powerful central-acting antiemetic.	You will not vomit, so you can
Clinical use	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.	go on dancing .
Toxicity	Headache, diarrhea.	

Epilepsy drugs

	PARTIAL		GENERALIZED			TN	Notes
	Simple	Complex	Tonic-clonic	Absence	Status		
Phenytoin	✓	✓	✓		✓		Also a Class IB antiarrhythmic
Carbamazepine	✓	✓	✓			✓	
Lamotrigine	✓	✓	✓				See toxicity below
Gabapentin	✓	✓	✓				Adjunct in refractory seizures. Renal excretion.
Topiramate	✓	✓					Adjunct use
Phenobarbital			✓				Safer in pregnant women Crigler–Najjar II
Valproate				✓			
Ethosuximide				✓			
Benzodiazepines (Diazepam or Lorazepam)					✓		

TN = Trigeminal neuralgia

Epilepsy drug toxicities

Benzodiazepines	Sedation, tolerance, dependence.
Carbamazepine	Diplopia, ataxia, induction of cyt. P450, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity.
Ethosuximide	Gastrointestinal distress, lethargy, headache.
Phenobarbital	Sedation, induction of cyt. P450, tolerance, dependence.
Phenytoin	Nystagmus, diplopia, ataxia, sedation, gingival hyperplasia, hirsutism, anemias, birth defects (teratogenic).
Valproic acid	Gastrointestinal distress, rare but fatal hepatotoxicity, neural tube defects in fetus (spina bifida).
Lamotrigine	Life-threatening rash, Stevens–Johnson syndrome.
Gabapentin	Sedation, movement disorders
Topiramate	Sedation, mental dulling, kidney stones, weight loss

UCV Pharm. 47, 48, 49, 54

Phenytoin

Mechanism	Use-dependent blockade of Na ⁺ channels.
Clinical use	Grand mal seizures.
Toxicity	Nystagmus, ataxia, diplopia, lethargy. Chronic use produces gingival hyperplasia in children, peripheral neuropathy, hirsutism, megaloblastic anemia (↓ vitamin B ₁₂), malignant hyperthermia (rare), teratogenic (fetal hydantoin syndrome).

UCV Pharm. 54

Anesthetics— general principles

Drugs with ↓ solubility in blood = rapid induction and recovery times.

Drugs with ↑ solubility in lipids = ↑ potency = $\frac{1}{\text{MAC}}$.

Examples: N₂O has low blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.

Inhaled anesthetics

Principle

Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, nitrous oxide
The lower the solubility in blood, the quicker the anesthetic induction and the quicker the recovery.

Effects

Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow.

Toxicity

Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), malignant hyperthermia (rare).

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Intravenous anesthetics

Barbiturates

Thiopental: high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by redistribution from brain. ↓ cerebral blood flow.

Benzodiazepines

Midazolam: used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression and amnesia.

Arylcyclohexylamines

Ketamine (PCP analog): dissociative anesthetic. Cardiovascular stimulant. Causes disorientation, hallucination, and bad dreams. Increases cerebral blood flow. Pharm. 51

Narcotic analgesics

Morphine, fentanyl: used with other CNS depressants during general anesthesia.

Other

Propofol: used for rapid anesthesia induction and short procedures. Less postop nausea than thiopental.

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Local anesthetics

Esters: procaine, cocaine, tetracaine

Amides: lidocaine, bupivacaine (amides have 2 i's in name).

Mechanism

Block Na⁺ channels by binding to specific receptors on inner portion of channel.

Tertiary amine local anesthetics penetrate membrane in uncharged form, then bind in charged form.

Principle

1. In infected (acidic) tissue, anesthetics are charged and cannot penetrate membrane effectively. Therefore more anesthetic is needed in these cases.
2. Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination, such that small unmyelinated pain fibers > small myelinated autonomic fibers > large myelinated autonomic fibers. Order of loss: pain (lose first) > temperature > touch > pressure (lose last).
3. Given with vasoconstrictors (usually epinephrine) to enhance local action.

Clinical use

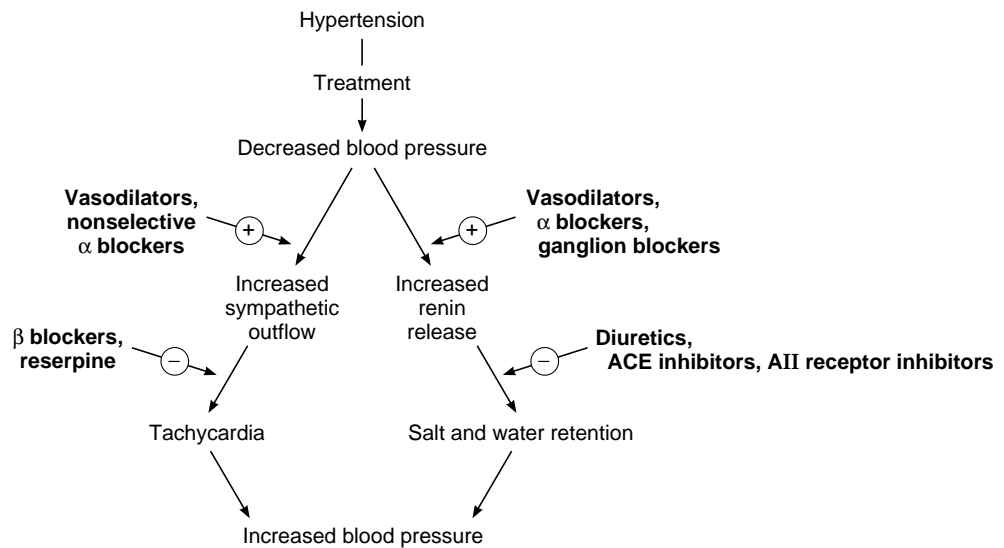
Minor surgical procedures, spinal anesthesia.

Toxicity

CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension and arrhythmias (cocaine).

Antihypertensive drugs

Drug	Adverse effects
Diuretics	
Hydrochlorothiazide	Hypokalemia, slight hyperlipidemia, hyperuricemia, lassitude
Loop diuretics	Potassium wasting, metabolic acidosis, hypotension
Sympathoplegics	
Clonidine	Dry mouth, sedation, severe rebound hypertension
Methyldopa	Sedation, positive Coombs' test <i>Pharm. 7</i>
Ganglionic blockers	Severe orthostatic hypotension, blurred vision, constipation, sexual dysfunction
Reserpine	Sedation, depression, nasal stuffiness, diarrhea
Guanethidine	Orthostatic and exercise hypotension, sexual dysfunction, diarrhea
Prazosin	First-dose orthostatic hypotension, dizziness, headache
β blockers	Impotence, asthma, CV effects (bradycardia, CHF, AV block), CNS effects (sedation, sleep alterations)
Vasodilators	
Hydralazine	Nausea, headache, lupus-like syndrome, tachycardia, angina, salt retention
Minoxidil	Hypertrichosis, pericardial effusion, tachycardia, angina, salt retention
Nifedipine, verapamil	Dizziness, flushing, constipation (verapamil), nausea
Nitroprusside	Cyanide toxicity (releases CN)
ACE inhibitors	
Captopril	Fetal renal toxicity, hyperkalemia Cough, Angioedema, Proteinuria, Taste changes, hypOtension, Pregnancy problems (fetal renal damage), Rash, Increased renin, Lower AII.
AII receptor inhibitors	
Losartan	Fetal renal toxicity, Hyperkalemia



Hydralazine

Mechanism	↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.
Clinical use	Severe hypertension, CHF.
Toxicity	Compensatory tachycardia, fluid retention. Lupus-like syndrome.

Calcium channel blockers

	Nifedipine, verapamil, diltiazem
Mechanism	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle and thereby reduce muscle contractility. Vascular smooth muscle: nifedipine > diltiazem > verapamil. Heart: verapamil > diltiazem > nifedipine.
Clinical use	Hypertension, angina, arrhythmias.
Toxicity	Cardiac depression, peripheral edema, flushing, dizziness, and constipation.

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ACE inhibitors

Mechanism	Captopril, enalapril, lisinopril Inhibit angiotensin-converting enzyme, reducing levels of angiotensin II and preventing inactivation of bradykinin, a potent vasodilator. Renin release is ↑ due to loss of feedback inhibition.	Losartan is an angiotensin II receptor antagonist. It is not an ACE inhibitor and does not cause cough.
Clinical use	Hypertension, congestive heart failure, diabetic renal disease.	
Toxicity	Cough, Angioedema, Proteinuria, Taste changes, hypotension, Pregnancy problems, fetal renal damage, Rash, Increased renin, Lower AII.	CAPTOPRIL

Acetazolamide

Mechanism	Carbonic anhydrase inhibitor. Causes self-limited NaHCO ₃ diuresis and reduction in total-body HCO ₃ ⁻ stores. Acts at the proximal convoluted tubule.	
Clinical use	Glaucoma, urinary alkalinization, metabolic alkalosis, altitude sickness.	
Toxicity	Hyperchloremic metabolic acidosis, neuropathy, NH ₃ toxicity, sulfa allergy.	ACIDazolamide causes acidosis.

Furosemide

Mechanism	Sulfonamide loop diuretic. Inhibits cotransport system (Na ⁺ , K ⁺ , 2 Cl ⁻) of thick ascending limb of loop of Henle. Abolishes hypertonicity of medulla, preventing concentration of urine. Increases Ca ²⁺ excretion.	Loops Lose calcium.
Clinical use	Edematous states (CHF, cirrhosis, nephrotic syndrome, pulmonary edema), HTN, hypercalcemia.	
Toxicity	Ototoxicity, Hypokalemia, Dehydration, Allergy (sulfa), Nephritis (interstitial), Gout.	Toxicity: OH DANG!

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Ethacrynic acid

Mechanism	Phenoxyacetic acid derivative (NOT a sulfonamide). Essentially same action as furosemide.
Clinical use	Diuresis in patients allergic to sulfa drugs.
Toxicity	Similar to furosemide except no hyperuricemia, no sulfa allergies.

Hydrochlorothiazide

Mechanism	Thiazide diuretic. Inhibits NaCl reabsorption in early distal tubule, reducing diluting capacity of the nephron. Decreases Ca ²⁺ excretion.
Clinical use	Hypertension, congestive heart failure, calcium stone formation, nephrogenic diabetes insipidus.
Toxicity	Hypokalemic metabolic alkalosis, hyponatremia, hyperGlycemia, hyperLipidemia, hyperUricemia, and hyperCalcemia. "HyperGLUC." Sulfa allergy.

K⁺-sparing diuretics

	Spironolactone, Triamterene, Amiloride	The K ⁺ STAs.
Mechanism	Spironolactone is a competitive aldosterone receptor antagonist in the cortical collecting tubule. Triamterene and amiloride act at same part of the tubule by blocking Na ⁺ channels in the CCT.	
Clinical use	Hyperaldosteronism, K ⁺ depletion, CHF	
Toxicity	Hyperkalemia, endocrine effects (gynecomastia, anti-androgen effects).	

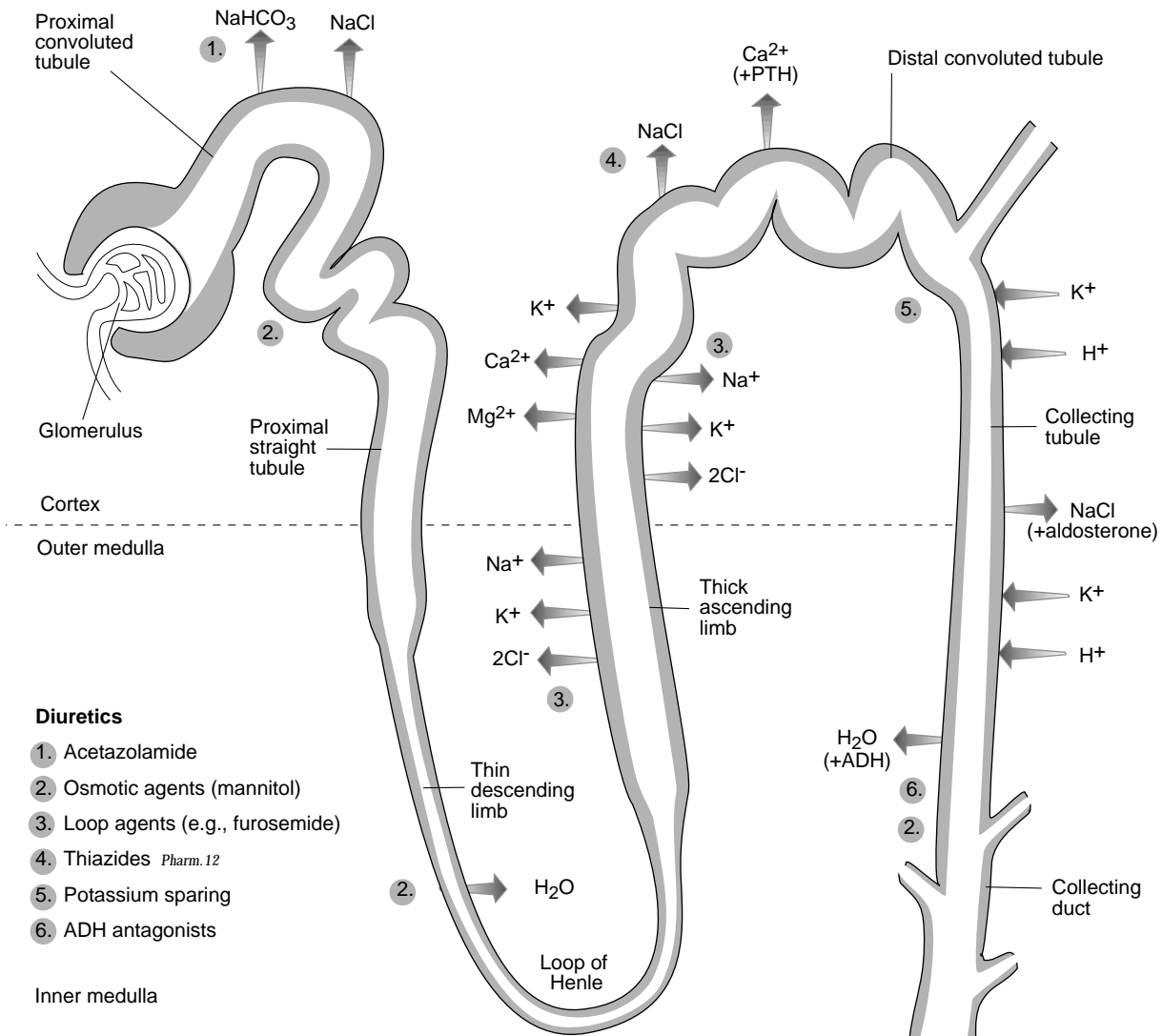
Mannitol

Mechanism	Osmotic diuretic, ↑ tubular fluid osmolarity, producing ↑ urine flow.
Clinical use	ARE, shock, drug overdose, ↓ intracranial/ intraocular pressure.
Toxicity	Pulmonary edema, dehydration. Contraindicated in anuria, CHF.

Diuretics: electrolyte changes

Urine NaCl	↑ (all diuretics: carbonic anhydrase inhibitors, loop diuretics, thiazides, K ⁺ -sparing diuretics)
Urine K ⁺	↑ (all except K ⁺ -sparing diuretics)
Blood pH	↓ (acidosis): carbonic anhydrase inhibitors, K ⁺ -sparing diuretics ↑ (alkalosis): loop diuretics, thiazides
Urine Ca ⁺	↑ loop diuretics, ↓ thiazides, ↑ spironolactone, ↓ amiloride

Diuretics: site of action



Anti-anginal therapy

Goal: Reduction of myocardial O₂ consumption (MVO₂) by decreasing one or more of the determinants of MVO₂: end diastolic volume, blood pressure, heart rate, contractility, ejection time.

Component	Nitrates	β blockers	Nitrates + β blockers
End diastolic volume	↓	↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	↓
Ejection time	↓	↑	Little/no effect
MVO ₂	↓	↓	↓↓

Calcium channel blockers:

- Nifedipine is similar to Nitrates in effect
- Verapamil is similar to β blockers in effect

UCV Pharm.10

Nitroglycerin, isosorbide dinitrate

Mechanism	Vasodilate by releasing nitric oxide in smooth muscle, causing increase in cGMP and smooth muscle relaxation. Dilate veins >> arteries.
Clinical use	Angina, pulmonary edema. Also used as an aphrodisiac and erection-enhancer.
Toxicity	Tachycardia, hypotension, headache, "Monday disease" in industrial exposure development of tolerance for the vasodilating action, during the work week and loss of tolerance over the weekend, resulting in tachycardia, dizziness, and headache.

Cardiac glycosides

	Digoxin: 75% bioavailability, 20–40% protein bound, T _{1/2} = 40 hr, urinary excretion Digitoxin: > 95% bioavailability, 70% protein bound, T _{1/2} = 168 hrs, biliary excretion (enterohepatic recycling; no need to ↓ dose of digi-toxin in renal failure)
Mechanism	Inhibit the Na ⁺ -K ⁺ -ATPase of cell membrane, causing ↑ intracellular Na ⁺ . Na ⁺ -Ca ²⁺ antiport does not function as efficiently, causing ↑ intracellular Ca ²⁺ ; leads to positive inotropy. May cause ↑ PR, ↓ QT, scooping of ST segment, T-wave inversion on EKG.
Clinical use	CHF, atrial fibrillation.
Toxicity	Nausea, vomiting, diarrhea. Blurry yellow vision (think Van Gogh). Arrhythmia. Toxicities of digoxin are increased by renal failure (↓ excretion), hypokalemia (potentiates drug's effects), and quinidine (↓ digoxin clearance; displaces digoxin from tissue binding sites).
Antidote	Slowly normalize K ⁺ , lidocaine, cardiac pacer, anti-dig Fab fragments.

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Antiarrhythmics—Na⁺ channel blockers (class I)

Local anesthetics. Slow or block (↓) conduction (especially in depolarized cells).
 ↓ slope of phase 4 depolarization and increase threshold for firing in abnormal pacemaker cells. Are state dependent (i.e., selectively depress tissue that is frequently depolarized, e.g., fast tachycardia).

Class IA

Quinidine, Amiodarone, Procainamide, Disopyramide.
 ↑ AP duration, ↑ effective refractory period (ERP), ↑ QT interval. Affect both atrial and ventricular arrhythmias. *Pharm. 11*

“Queen Amy Proclaims
 Diso’s pyramid.”

Toxicity: quinidine (cinchonism: headache, tinnitus; thrombocytopenia; torsade de pointes due to increased QT interval); procainamide (reversible SLE-like syndrome).

Class IB

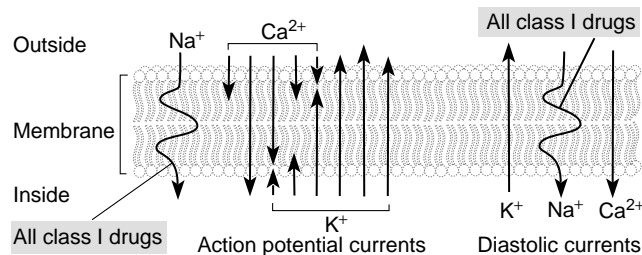
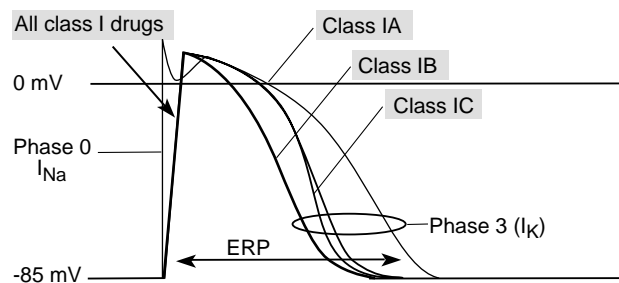
Lidocaine, mexiletine, tocainide. *Pharm. 5*
 ↓ AP duration. Affect ischemic or depolarized Purkinje and ventricular tissue. Useful in acute ventricular arrhythmias (especially post-MI) and in digitalis-induced arrhythmias.

Toxicity: Local anesthetic. CNS stimulation/ depression, cardiovascular depression.

Class IC

Flecainide, encainide, propafenone.
 No effect on AP duration. Useful in V-tachs that progress to VF, and in intractable SVT. Are usually used only as last resort in refractory tachyarrhythmias because of toxicities.

Toxicity: proarrhythmic.



Antiarrhythmics— β blockers (class II)

Propranolol, esmolol, metoprolol, atenolol, timolol.

\downarrow cAMP, \downarrow Ca^{2+} currents. Suppress abnormal pacemakers by \downarrow slope of phase 4. AV node particularly sensitive: \uparrow PR interval. Esmolol very short-acting.

Toxicity: impotence, exacerbation of asthma, CV effects (bradycardia, AV block, CHF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia.

UCV Pharm. 1

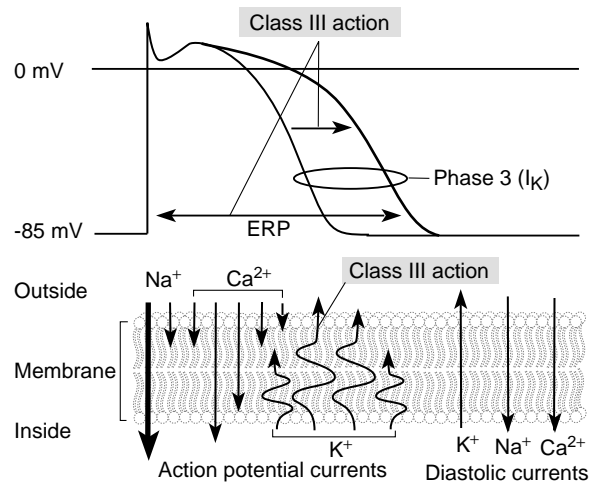
Antiarrhythmics— K^+ channel blockers (class III)

Sotalol, ibutilide, bretylium, amiodarone. Pharm. 62

\uparrow AP duration, \uparrow ERP. Used when other antiarrhythmics fail.

Toxicity: sotalol—torsade de pointes, excessive β block; ibutilide—torsade; bretylium—new arrhythmias, hypotension; amiodarone—**pulmonary fibrosis**, corneal deposits, **hepatotoxicity**, skin deposits resulting in photodermatitis, neurologic effects, constipation, CV effects (bradycardia, heart block, CHF), **hypo/hyperthyroidism**.

Remember to check PFTs, LFTs, and TFTs when using amiodarone.



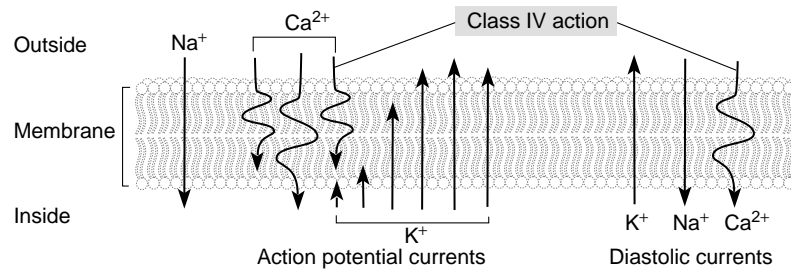
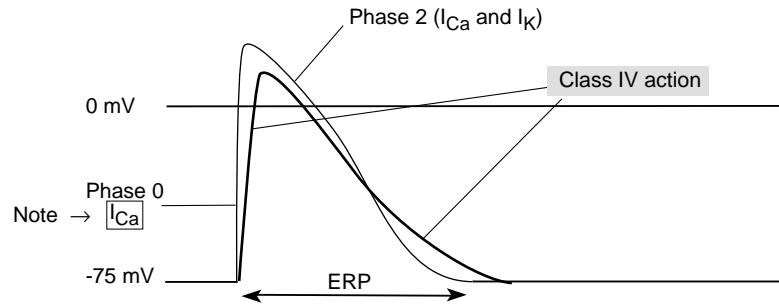
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Antiarrhythmics—Ca²⁺ channel blockers (class IV)

Verapamil, diltiazem, bepridil.

Primarily affects pacemaker cells. ↓ conduction velocity, ↑ ERP, ↑ PR interval. Used in prevention of nodal arrhythmias (e.g., SVT).

Toxicity: constipation, flushing, edema, CV effects (CHF, AV block, sinus node depression); torsade de pointes (bepridil).



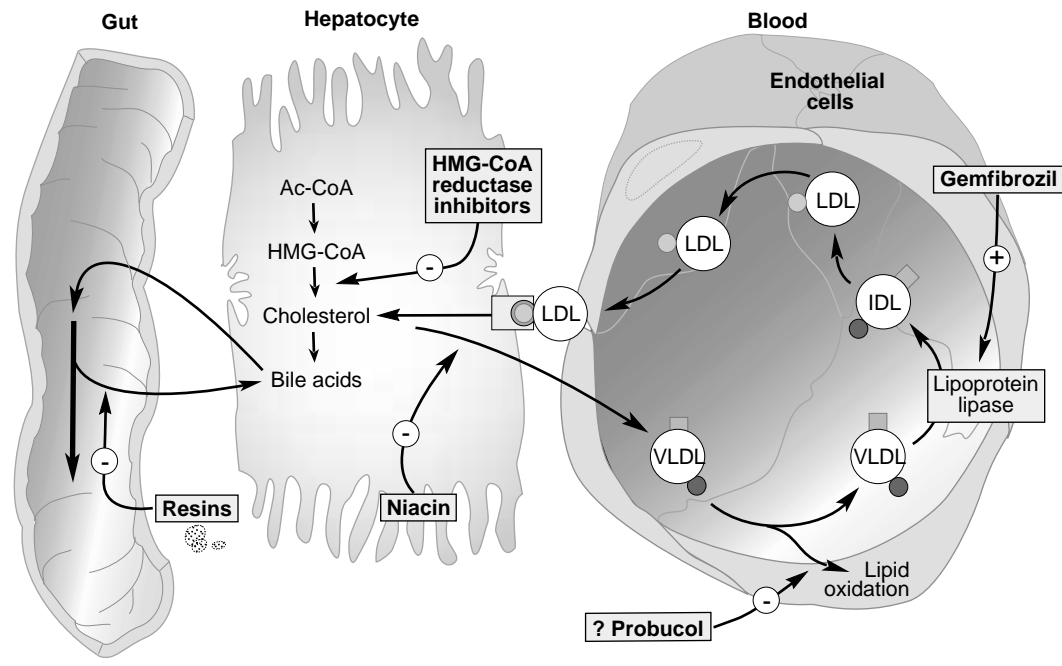
UCV Pharm.13

Antiarrhythmics—miscellaneous

Adenosine	Drug of choice in diagnosing/abolishing AV nodal arrhythmias.
K ⁺	Depresses ectopic pacemakers, especially in digoxin toxicity.
Mg ⁺	Effective in torsade de pointes and digoxin toxicity.

Lipid-lowering agents

Drug	Effect on LDL "bad cholesterol"	Effect on HDL "good cholesterol"	Effect on triglycerides	Side effects/problems
Bile acid resins (cholestyramine, colestipol)	↓↓	No effect	Slight ↑	Patients hate it—tastes bad and causes GI discomfort
HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin, atorvastatin)	↓↓↓	↑	↓	Expensive Reversible ↑ LFTs Myositis
Niacin <i>Pharm. 8</i>	↓↓	↑↑	↓	Red, flushed face which is ↓ by aspirin or long-term use
Lipoprotein lipase stimulators (gemfibrozil, clofibrate)	↓	↑	↓↓↓	Myositis, ↑ LFTs
Probucol	↓	↓	No effect	↓ HDL



UCV

Cancer drugs—site of action

Nucleotide Synthesis



DNA



mRNA



Protein

1. Methotrexate— ↓ thymidine + purine synthesis
2. 5-FU— ↓ thymidine + purine synthesis
3. 6-MP
4. Alkylating agents + cisplatin—DNA cross-linkage
5. Dactinomycin + doxorubicin—intercalate DNA strands
6. Bleomycin
7. Etoposide—strand breakage
8. Steroids
9. Tamoxifen
10. Vinca alkaloids—inhibit microtubule formation
11. Paclitaxel

Methotrexate

Mechanism	S-phase-specific antimetabolite. Folic acid analog that inhibits dihydrofolate reductase, resulting in decreased dTMP and therefore decreased DNA and protein synthesis.
Clinical use	Leukemias, lymphomas, choriocarcinoma, sarcomas. Abortion, ectopic pregnancy, rheumatoid arthritis, psoriasis.
Toxicity	Myelosuppression, which is reversible with leucovorin (folinic acid) “rescue.”

UCV Pharm.35

5-fluorouracil (5-FU)

Mechanism	S-phase-specific antimetabolite. Pyrimidine analog bioactivated to 5FdUMP, which covalently complexes folic acid. This complex inhibits thymidylate synthase, resulting in decreased dTMP and same effects as methotrexate.
Clinical use	Colon cancer and other solid tumors, basal cell carcinoma (topical). Synergy with methotrexate.
Toxicity	Myelosuppression, which is NOT reversible with leucovorin; photosensitivity.

6-Mercaptopurine (6MP)

Mechanism	Inhibits HGPRT, thus blocking purine synthesis.
Clinical use	Leukemias, lymphomas (not CLL or Hodgkin’s)
Toxicity	Bone marrow, GI, liver. Metabolized by xanthine oxidase, thus ↑ toxicity with allopurinol.

Busulfan

Mechanism	Alkylates DNA.
Clinical use	CML
Toxicity	Pulmonary fibrosis, hyperpigmentation.

Cyclophosphamide

Mechanism	Alkylating agent; covalently x-links (interstrand) DNA at guanine N-7. Requires bioactivation by liver.
Clinical use	Non-Hodgkin's lymphoma, breast and ovarian carcinomas. Also an immunosuppressant.
Toxicity	Myelosuppression, hemorrhagic cystitis.

UCV Pharm.74

Nitrosureas

	Carmustine, lomustine, semustine, streptozocin
Mechanism	Alkylates DNA. Requires bioactivation. Crosses blood-brain barrier → CNS.
Clinical use	Brain tumors (including glioblastoma multiforme).
Toxicity	CNS toxicity (dizziness, ataxia).

Cisplatin

Mechanism	Acts like an alkylating agent. X-links via hydrolysis of Cl ⁻ groups and reaction with platinum.
Clinical use	Testicular, bladder, ovary, and lung carcinomas.
Toxicity	Nephrotoxicity and acoustic nerve damage.

UCV Pharm.32

Doxorubicin (adriamycin)

Mechanism	Noncovalently intercalates in DNA creating breaks to decrease replication and transcription and generate free radicals.
Clinical use	Part of the ABVD combo regimen for Hodgkin's and for myelomas, sarcomas, and solid tumors (breast, ovary, lung).
Toxicity	Cardiotoxicity; also myelosuppression and marked alopecia. Toxic extravasation.

UCV Pharm.34

Bleomycin

Mechanism	Intercalates DNA strands, induces free radical formation, causing strand breaks.
Clinical use	Testicular cancer, lymphomas.
Toxicity	Pulmonary fibrosis, skin changes, minimal myelosuppression.

Etoposide

Mechanism	G ₂ -phase-specific inhibits topoisomerase II so that double-strand breaks remain in DNA following replication, with subsequent DNA degradation.
Clinical use	Oat cell carcinoma of the lung and prostate, testicular carcinoma.
Toxicity	Myelosuppression, GI irritation, alopecia.

Prednisone

Mechanism	May trigger apoptosis. May even work on non-dividing cells.
Clinical use	Most commonly used glucocorticoid in cancer chemotherapy. Used in CLL, Hodgkin's lymphomas (the "P" in the MOPP regimen). Also an immunosuppressant used in autoimmune diseases.
Toxicity	Cushing-like symptoms; immunosuppression, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia.

UCV Pharm. 19

Tamoxifen/raloxifene

Mechanism	Estrogen receptor mixed agonist/antagonist that blocks the binding of estrogen to ER+ cells.
Clinical use	Breast cancer.
Toxicity	May increase the risk of endometrial carcinoma via partial agonist effects; "hot flashes."

Vincristine and vinblastine

Mechanism	M-phase-specific alkaloid that binds to tubulin and blocks polymerization of microtubules so that mitotic spindle can't form.
Clinical use	Part of MOPP (O ncovin [vincristine]) combo regimen for lymphoma, Wilms' tumor, choriocarcinoma.
Toxicity	Vincristine—neurotoxicity (areflexia, peripheral neuritis), paralytic ileus. Vin B lastine B lasts B one marrow (suppression).

Paclitaxel

Mechanism	M-phase-specific agent obtained from yew tree that binds to tubulin and hyperstabilizes polymerized microtubules so that mitotic spindle can't break down (anaphase cannot occur).
Clinical use	Ovarian and breast carcinomas.
Toxicity	Myelosuppression and hypersensitivity.

Specific antidotes

Toxin	Antidote/treatment
1. Acetaminophen	1. N-acetylcysteine
2. Salicylates	2. Alkalinize urine, dialysis
3. Anticholinesterases, organophosphates	3. Atropine, pralidoxime
4. Antimuscarinic, anticholinergic agents	4. Physostigmine salicylate
5. β blockers	5. Glucagon
6. Digitalis	6. Stop dig, normalize K^+ , lidocaine, anti-dig Fab fragments
7. Iron	7. Deferoxamine
8. Lead	8. CaEDTA, dimercaprol, succimer, penicillamine
9. Arsenic, mercury, gold	9. Dimercaprol (BAL), succimer
10. Copper, arsenic, gold	10. Penicillamine
11. Cyanide	11. Nitrite, hydroxocobalamin
12. Methemoglobin	12. Methylene blue
13. Carbon monoxide	13. 100% O_2 , hyperbaric O_2
14. Methanol, ethylene glycol (antifreeze)	14. Ethanol, dialysis, fomepizole
15. Opioids	15. Naloxone/naltrexone
16. Benzodiazepines	16. Flumazenil
17. Tricyclic antidepressants	17. $NaHCO_3$ (nonspecific)
18. Heparin	18. Protamine
19. Warfarin	19. Vitamin K, fresh frozen plasma
20. t-PA, streptokinase	20. Aminocaproic acid

UCV Pharm. 63, 64, 67, 70, 73, 78, 82, 84, 86, 87

Lead poisoning

Lead Lines on gingivae and on epiphyses of long bones on x-ray.
 Encephalopathy and Erythrocyte basophilic stippling.
 Abdominal colic and sideroblastic Anemia.
 Drops: wrist and foot drop. Dimercaprol and EDTA as first line of treatment.

LEAD

High risk in houses with chipped paint.

UCV Pharm. 84

Urine pH and drug elimination

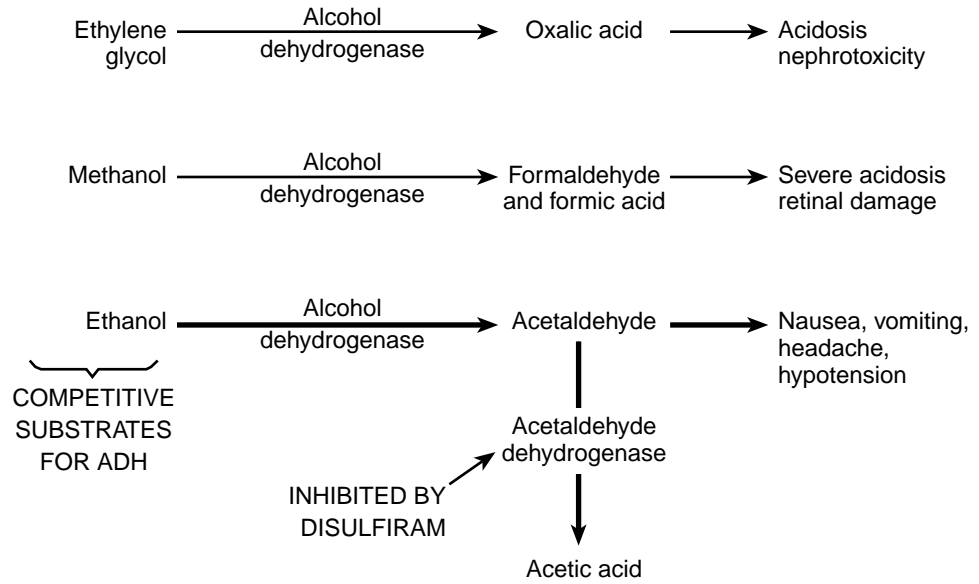
Weak acids (phenobarbital, methotrexate, aspirin) \Rightarrow alkalinize urine with bicarbonate to increase clearance.
 Weak bases (amphetamines) \Rightarrow acidify urine to increase clearance (give NH_4Cl).

Drug reactions

Drug reaction	Causal agent
1. Pulmonary fibrosis	1. Bleomycin, amiodarone, busulfan <i>Pharm.31</i>
2. Hepatitis	2. Isoniazid (INH)
3. Focal to massive hepatic necrosis	3. Halothane, valproic acid, acetaminophen, <i>Amanita phalloides</i>
4. Anaphylaxis	4. Penicillin
5. SLE-like syndrome <i>Pharm.77</i>	5. Hydralazine, procainamide, INH, phenytoin
6. Hemolysis in G6PD-deficient patients	6. Sulfonamides, INH, aspirin, ibuprofen, primaquine, nitrofurantoin, pyrimethamine, chloramphenicol
7. Thrombotic complications	7. Oral contraceptives (e.g., estrogens and progestins)
8. Adrenocortical insufficiency	8. Glucocorticoids (HPA suppression)
9. Photosensitivity reactions	9. Tetracyclines, amiodarone, sulfonamides
10. Induce (↑) P450 system	10. Barbiturates, phenytoin, carbamazepine, rifampin, griseofulvin, quinidine
11. Inhibit (↓) P450 system	11. Cimetidine, ketoconazole, erythromycin, INH, sulfonamides
12. Tubulointerstitial nephritis <i>Pharm.98</i>	12. Sulfonamides
13. Hot flashes	13. Tamoxifen
14. Cutaneous flushing	14. Niacin, Ca ²⁺ channel blockers, adenosine, vancomycin
15. Cardiac toxicity	15. Doxorubicin (Adriamycin)
16. Agranulocytosis	16. Clozapine, carbamazepine, colchicine
17. Stevens-Johnson syndrome	17. Ethosuximide, sulfonamides <i>Pharm.14</i>
18. Cinchonism	18. Quinidine, quinine
19. Tendonitis, tendon rupture	19. Fluoroquinolones <i>Pharm.42</i>
20. Disulfiram-like reaction	20. Metronidazole, certain cephalosporins, procarbazine, sulfonyleureas
21. Ototoxicity and nephrotoxicity	21. Aminoglycosides, loop diuretics, cisplatin
22. Drug-induced Parkinson's	22. Haloperidol, chlorpromazine, reserpine, MPTP.

PHARMACOLOGY—TOXICOLOGY (continued)

Alcohol toxicity



UCV Pharm. 50, 78

Coma treatment

ER treatment	<p>Airway (protect)</p> <p>Breathing (assist)</p> <p>Circulation (assist)</p> <p>Dextrose (and thiamine, naloxone IV)</p>	ABCD (in that order).
Rule out	<p>Infections (lumbar puncture)</p> <p>Trauma (bleeding, consider CT scan)</p> <p>Seizure</p> <p>Carbon monoxide (give O₂)</p> <p>Overdose (pills)/Opioids (give naloxone)</p> <p>Metabolic (hypo/hyperthermia, hypo/hyperglycemia, thiamine deficiency)</p> <p>Alcohol (check serum osmolality)</p>	IT'S COMA!

PHARMACOLOGY—MISCELLANEOUS

Sildenafil (Viagra)

Mechanism	<p>Inhibits cGMP phosphodiesterase, causing ↑ cGMP, smooth muscle relaxation in the corpus cavernosum, ↑ blood flow, and penile erection.</p>	Sildenafil fills the penis.
Clinical use	Erectile dysfunction.	
Toxicity	<p>Headache, flushing, dyspepsia, blue-green color vision.</p> <p>Risk of life-threatening hypotension in patients taking nitrates.</p>	

H₂ blockers

Mechanism	Cimetidine, ranitidine, famotidine, nizatidine Reversible block of histamine H ₂ receptors.
Clinical use	Peptic ulcer, gastritis, esophageal reflux, Zollinger–Ellison syndrome.
Toxicity	Cimetidine is a potent inhibitor of P450; it also has an antiandrogenic effect and decreases renal excretion of creatinine. Other H ₂ blockers are relatively free of these effects.

UCV Pharm.23

Omeprazole, lansoprazole

Mechanism	Irreversibly inhibits H ⁺ /K ⁺ ATPase in stomach parietal cells.
Clinical use	Peptic ulcer, gastritis, esophageal reflux, Zollinger–Ellison syndrome.

Sucralfate

Mechanism	Aluminum sucrose sulfate polymerizes in the acid environment of the stomach and selectively binds necrotic peptic ulcer tissue. Acts as a barrier to acid, pepsin, and bile. Sucralfate cannot work in the presence of antacids or H ₂ blockers (requires acidic environment to polymerize).
Clinical use	Peptic ulcer disease.

Misoprostol

Mechanism	A PGE ₁ analog. Increases production and secretion of gastric mucous barrier.
Clinical use	Prevention of NSAID-induced peptic ulcers, maintains a PDA.
Toxicity	Diarrhea. Contraindicated in women of childbearing potential (abortifacient).

Antacid overuse

Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.	
Overuse can also cause the following problems:	
1. Aluminum hydroxide: constipation and hypophosphatemia	Alu MINIMUM amount of feces
2. Magnesium hydroxide: diarrhea	Mg = Must go to the bathroom
3. Calcium carbonate: hypercalcemia, rebound acid ↑.	
All can cause hypokalemia.	

Heparin

Mechanism	Catalyzes the activation of antithrombin III. Short half-life. Check the aPTT.
Clinical use	Immediate anticoagulation for PE, stroke, angina, MI, DVT. Used during pregnancy (does not cross placenta). Follow PTT.
Toxicity	Bleeding, thrombocytopenia, drug–drug interactions. Use protamine sulfate for rapid reversal of heparinization (positively charged molecule that acts by binding negatively charged heparin).
Note	Newer low-molecular-weight heparins (enoxaparin) have better bioavailability and 2 to 4 times longer half-life. Can be administered subcutaneously and without laboratory monitoring.

UCV Pharm.3

Warfarin (Coumadin)

Mechanism	Interferes with normal synthesis and γ -carboxylation of vitamin K-dependent clotting factors II, VII, IX, and X, Protein C and S via vitamin K antagonism. Long half-life.	WEPT: Warfarin affects the Extrinsic pathway and prolongs the PT.
Clinical use	Chronic anticoagulation. Not used in pregnant women (because warfarin, unlike heparin, can cross the placenta). Follow PT values.	
Toxicity	Bleeding, teratogenic, drug–drug interactions.	

UCV Pharm.37

Heparin vs. warfarin

	Heparin	Warfarin
Structure	Large anionic polymer, acidic	Small lipid-soluble molecule
Route of administration	Parenteral (IV, SC)	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
Mechanism of action	Activates antithrombin III	Impairs the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X (vitamin K antagonist)
Duration of action	Acute (hours)	Chronic (weeks or months)
Inhibits coagulation <i>in vitro</i>	Yes	No
Treatment of acute overdose	Protamine sulfate	IV vitamin K and fresh frozen plasma
Monitoring	aPTT (intrinsic pathway)	PT (extrinsic pathway)

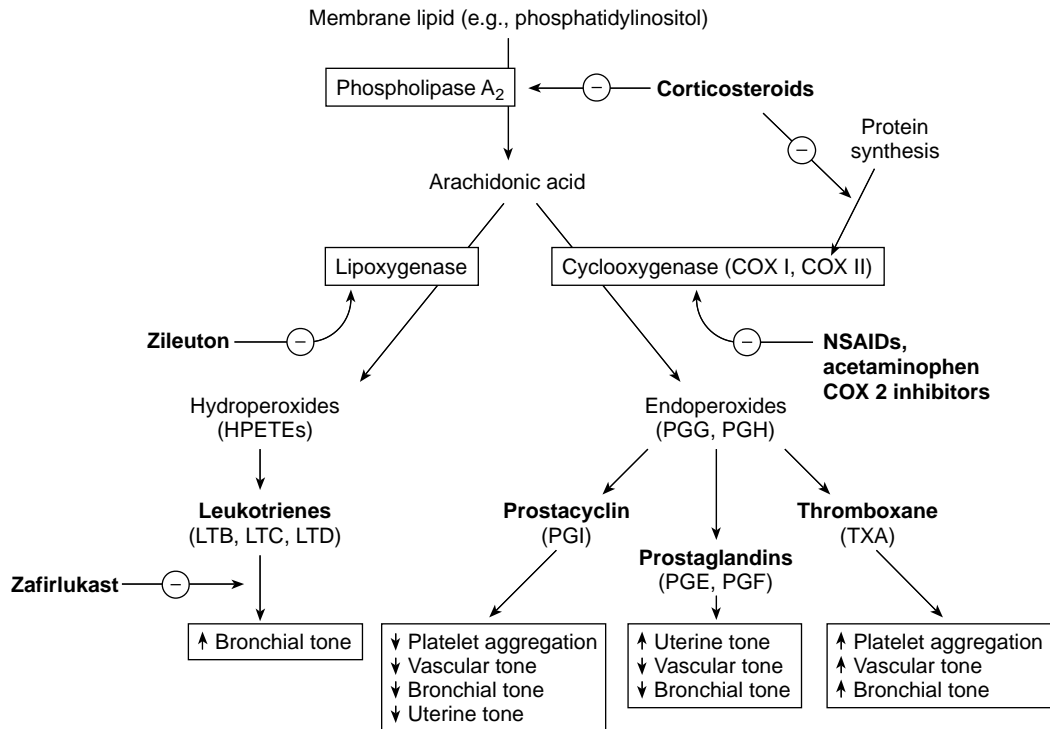
Thrombolytics

Mechanism	Streptokinase, urokinase, tPA (alteplase), APSAC (anistreplase) Directly or indirectly aid conversion of plasminogen to plasmin which cleaves thrombin and fibrin clots. It is claimed that tPA specifically converts fibrin-bound plasminogen to plasmin.
Clinical use	Early myocardial infarction.
Toxicity	Bleeding.

Ticlopidine

Mechanism	Inhibits platelet aggregation by irreversibly inhibiting the ADP pathway involved in the binding of fibrinogen.
Clinical use	Decreases the incidence or recurrence of thrombotic stroke.
Toxicity	Neutropenia; reserved for those who cannot tolerate aspirin.

Arachidonic acid products



Aspirin

Mechanism	Acetylates and irreversibly inhibits cyclooxygenase (both COX I and COX II) to prevent conversion of arachidonic acid to prostaglandins.
Clinical use	Antipyretic, analgesic, anti-inflammatory, antiplatelet drug.
Toxicity	Gastric ulceration, bleeding, hyperventilation, Reye's syndrome, tinnitus (CN VIII).

UCV Pharm.95, 96

Other NSAIDs

Mechanism	Ibuprofen, naproxen, indomethacin Reversibly inhibit cyclooxygenase (both COX I and COX II). Block prostaglandin synthesis.
Clinical use	Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a patent ductus arteriosus.
Toxicity	Renal damage, aplastic anemia, GI distress.

UCV Pharm.95, 96

COX 2 inhibitors (celecoxib, rofecoxib)

Mechanism	Selectively inhibits cyclooxygenase (COX) isoform 2, which is found in inflammatory cells and mediates inflammation and pain; spares COX 1, which helps maintain the gastric mucosa. Thus, should not have the corrosive effects of other NSAIDs on the gastrointestinal lining.
Clinical use	Rheumatoid and osteoarthritis.
Toxicity	Similar to other NSAIDs; may have less toxicity to GI mucosa (i.e., lower incidence of ulcers, bleeding).

Acetaminophen

Mechanism	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
Clinical use	Antipyretic, analgesic, but lacking anti-inflammatory properties.
Toxicity	Overdose produces hepatic necrosis; acetaminophen metabolite depletes glutathione and forms toxic tissue adducts in liver.

UCV Pharm. 63

Glucocorticoids

Mechanism	Hydrocortisone, prednisone, triamcinolone, dexamethasone, beclomethasone Decrease the production of leukotrienes and prostaglandins by inhibiting phospholipase A ₂ and expression of COX II.
Clinical use	Addison's disease, inflammation, immune suppression, asthma.
Toxicity	Iatrogenic Cushing's syndrome: buffalo hump, moon facies, truncal obesity, muscle wasting, thin skin, easy bruisability, osteoporosis, adrenocortical atrophy, peptic ulcers.

UCV Pharm. 19

Asthma drugs

Nonspecific β agonists	Isoproterenol: relaxes bronchial smooth muscle (β_2). Adverse effect is tachycardia (β_1).
β_2 agonists	Albuterol: relaxes bronchial smooth muscle (β_2). Use during acute exacerbation. Adverse effects are tremor and arrhythmia.
Methylxanthines	Theophylline: mechanism unclear—may cause bronchodilation by inhibiting phosphodiesterase, enzyme involved in degrading cAMP (controversial).
Muscarinic antagonists	Ipratropium: competitive block of muscarinic receptors preventing bronchoconstriction.
Cromolyn	Prevents release of mediators from mast cells. Effective only for the prophylaxis of asthma. Not effective during an active asthmatic attack. Toxicity is very rare.
Corticosteroids	Beclomethasone, prednisone: Prevent production of leukotrienes from arachidonic acid by blocking phospholipase A ₂ . Are drugs of choice in a patient with status asthmaticus (in combination with albuterol).
Antileukotrienes	Zileuton: blocks synthesis by lipoxygenase. Zafirlukast: blocks leukotriene receptors.

Exposure to antigen (dust, pollen, etc.)

Avoidance

Antigen and IgE on mast cells

Cromolyn Steroids

Mediators (leukotrienes, histamine, etc.)

Steroids

β agonist
Theophylline
Muscarinic antagonists

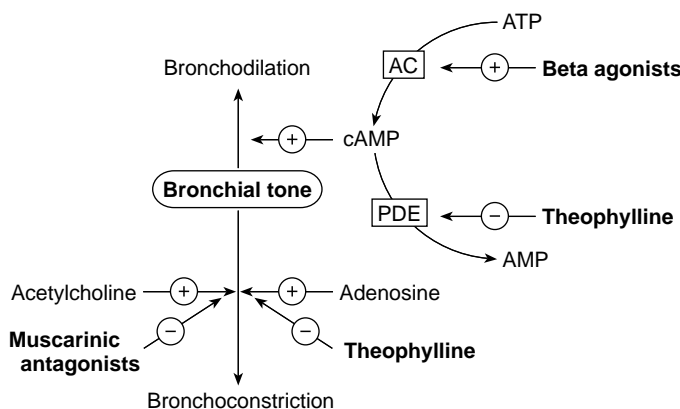
Late response: inflammation

Early response: bronchoconstriction

Bronchial hyperreactivity

Symptoms

Treatment strategies in asthma



UCV Pharm. 61

Gout drugs

Colchicine	Acute gout. Depolymerizes microtubules, impairing leukocyte chemotaxis and degranulation. GI side effects, especially if given orally.
Probenecid	Chronic gout. Inhibits reabsorption of uric acid (also inhibits secretion of penicillin).
Allopurinol	Chronic gout. Inhibits xanthine oxidase, decreasing conversion of xanthine to uric acid.

Diabetes drugs

Insulin	Binds insulin receptor which has tyrosine kinase activity. In liver, increases storage of glucose as glycogen. In muscle, stimulates glycogen and protein synthesis, and K ⁺ up take. In adipose, facilitates triglyceride storage. Clinical use includes life-threatening hyperkalemia and stress-induced hyperglycemia. Toxicities are hypoglycemia and hypersensitivity reaction.
Sulfonylureas	Tolbutamide, chlorpropamide, glyburide, glipizide. Oral hypoglycemic agents used to stimulate release of endogenous insulin in NIDDM (Type II). Close K ⁺ channels in β cell membrane \rightarrow cell depolarizes \rightarrow insulin release triggered. Inactive in IDDM (Type I) because requires some residual islet function. Toxicities includes hypoglycemia (more common with 2nd generation drugs: glyburide, glipizide) and disulfiram-like effects (not seen with 2nd generation drugs: glyburide, glipizide).
Metformin	Mechanism unknown; decreases serum glucose levels. Used as an oral hypoglycemic. Can be used in patients without islet function. Most grave adverse effect is lactic acidosis.
“Glitazones”	Pioglitazone, rosiglitazone, troglitazone. Increase target cell response to insulin. Used as monotherapy in Type II diabetes, or in combination with above agents. Toxicity: weight gain.
α -glucosidase inhibitors	Acarbose, miglitol. Inhibit intestinal brush border α -glucosidases; delayed hydrolysis of sugars and absorption of glucose lead to \downarrow postprandial hyperglycemia. Used as monotherapy in Type II diabetes, or in combination with above agents. Toxicity: GI disturbances.

UCV Pharm.20

Leuprolide

Mechanism	GnRH analog with agonist properties when used in pulsatile fashion and antagonist properties when used in continuous fashion.	When used in continuous fashion, it causes a transient initial burst of LH and FSH.
Clinical use	Infertility (pulsatile), prostate cancer (continuous: use with flutamide), uterine fibroids.	
Toxicity	Antiandrogen, nausea, vomiting.	

Propylthiouracil

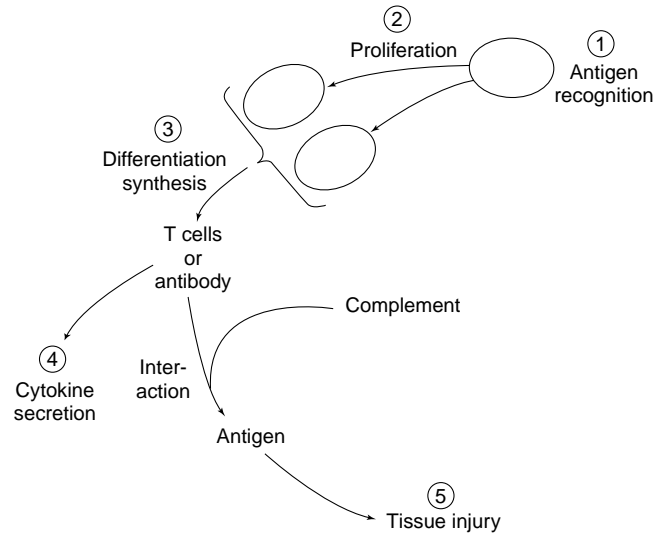
Mechanism	Inhibits organification and coupling of thyroid hormone synthesis. Also decreases peripheral conversion of T ₄ to T ₃ .
Clinical use	Hyperthyroidism.
Toxicity	Skin rash, agranulocytosis (rare), aplastic anemia.

Antiandrogens

Finasteride	A 5 α -reductase inhibitor (\downarrow conversion of testosterone to dihydrotestosterone). Useful in BPH.
Flutamide	A nonsteroidal competitive inhibitor of androgens at the testosterone receptor. Used in prostate carcinoma.
Ketoconazole, spironolactone	Inhibit steroid synthesis, used in the treatment of polycystic ovarian syndrome to prevent hirsutism.

Immunosuppressive agents: sites of action

Agent	Site
Prednisone	2, 5
Cyclosporine	2, 3
Azathioprine	2
Methotrexate	2
Dactinomycin	2, 3
Cyclophosphamide	2
Antilymphocytic globulin and monoclonal anti-T-cell antibodies	1, 2, 3
Rh ₃ (D) immune globulin	1
Tacrolimus	4



Cyclosporine

Mechanism	Binds to cyclophilins (peptidyl proline <i>cis-trans</i> isomerase), blocking the differentiation and activation of T cells mainly by inhibiting the production of IL-2 and its receptor.
Clinical use	Suppresses organ rejection after transplantation; selected autoimmune disorders.
Toxicity	Predisposes patients to viral infections and lymphoma; nephrotoxic (preventable with mannitol diuresis).

UCV Pharm. 75

Azathioprine

Mechanism	Antimetabolite derivative of 6-mercaptopurine that interferes with the metabolism and synthesis of nucleic acid. Toxic to proliferating lymphocytes after antigenic stimulus.
Clinical use	Kidney transplantation, autoimmune disorders (including glomerulonephritis and hemolytic anemia).

Tacrolimus (FK506)

Mechanism	Similar to cyclosporine; binds to FK-binding protein, inhibiting secretion of IL-2 and other cytokines.
Clinical use	Potent immunosuppressive used in organ transplant recipients.
Toxicity	Significant: nephrotoxicity, peripheral neuropathy, hypertension, pleural effusion, hyperglycemia.

Drug name

Ending	Category	Example
-ane	Inhalational general anesthetic	Halothane
-azepam	Benzodiazepine	Diazepam
-azine	Phenothiazine (neuroleptic, antiemetic)	Chlorpromazine
-azole	Antifungal	Ketoconazole
-barbital	Barbiturate	Phenobarbital
-caine	Local anesthetic	Lidocaine
-cillin	Penicillin	Methicillin
-cycline	Antibiotic, protein synthesis inhibitor	Tetracycline
-ipramine	Tricyclic antidepressant	Imipramine
-navir	Protease inhibitor	Saquinavir
-olol	Beta antagonist	Propranolol
-operidol	Butyrophenone (neuroleptic)	Haloperidol
-oxin	Cardiac glycoside (inotropic agent)	Digoxin
-phylline	Methylxanthine	Theophylline
-pril	ACE inhibitor	Captopril
-terol	β_2 agonist	Albuterol
-tidine	H ₂ antagonist	Cimetidine
-triptyline	Tricyclic antidepressant	Amitriptyline
-tropin	Pituitary hormone	Somatotropin
-zosin	α_1 antagonist	Prazosin
