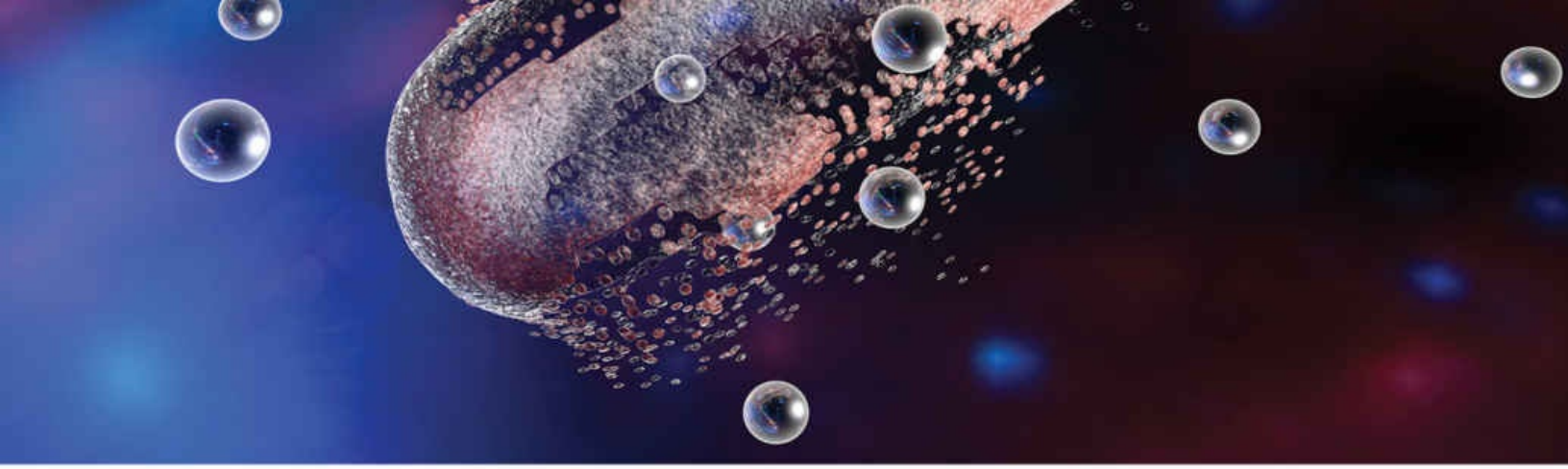

Pharmacology Flashcards

FOURTH EDITION

Everything you need to know about a drug one convenient card! 266 cards for board review and classroom preparation.

Suzanne J. Baron • Christoph I. Lee

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Lange® Pharmacology Flashcards

Fourth Edition

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Notice

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Lange® Pharmacology Flashcards, Fourth Edition

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Contents

Preface

When we began to review the pharmacology material covered in the USMLE Step 1 at the end of our second year at Yale Medical School, we had trouble finding one review source that covered this subject at just the appropriate level. Although we had taken introductory pharmacology during medical school, we found ourselves covering new material as well as reviewing old material from a different angle. Flipping through the highly rated pharmacology review sources, we realized that there was no gold standard review source for this high-yield topic that makes up nearly 20% of USMLE Step 1 questions.

Lange Pharmacology Flashcards are the result of our struggles in studying these topics for Step 1 with the particular slant that the boards demand. These cards offer the most complete, concise, and high-yield information for the major drugs tested on Step 1 and in medical school basic science courses. With this fourth edition, we are confident that the content covered in these cards includes the most current and board relevant information that cannot be found in any other single clinical pharmacology review text. To ensure that these cards are high yield, we commissioned two current Yale Medical School student editors to help write this revised edition.

We are pleased to present this information in a format modeled after *Lange Flashcards: Pathology*, our first publication in this series. Each card provides a structured presentation of a specific drug or drug class, and allows students to easily compare and contrast drugs. The introductory cards in each chapter describe the basic principles of that particular drug class that are board relevant and high yield. Each drug-specific card contains a clinical vignette on one side and important characteristics on the reverse side. These characteristics are organized into sections entitled mechanism of action, clinical uses, and side effects. Unlike other review cards on the market, only the information you need to know for the boards are on these cards. If certain drug-drug interactions or routes of administration are high yield, this information is included. Moreover, the most salient features of each drug are highlighted in bold for ease of rapid review.

We would suggest using these cards as an adjunct to your pharmacology

course in medical school. Being familiar with these cards early on will be very helpful during your Step 1 review. We also encourage you to jot down your own notes in the margins and to make these cards your personal pharmacology review for the boards.

We are confident that the fourth edition of *Lange Pharmacology Flashcards* will be one of the most powerful tools to help prepare you for the boards and will serve as a resource that will bridge your basic science knowledge with the clinical aspects of disease. We wish you the best of luck on Step 1, and welcome your comments on how to improve this study tool in the next edition.

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To our family and friends, we thank you for your continuing support and love that have made this process even more meaningful. Special thanks to John and Jay Lee, Fran and Joe Baron, Paul B. Brennan III, Monique Mogensen, Bettina Lee, and Elena Lee.

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Abbreviations

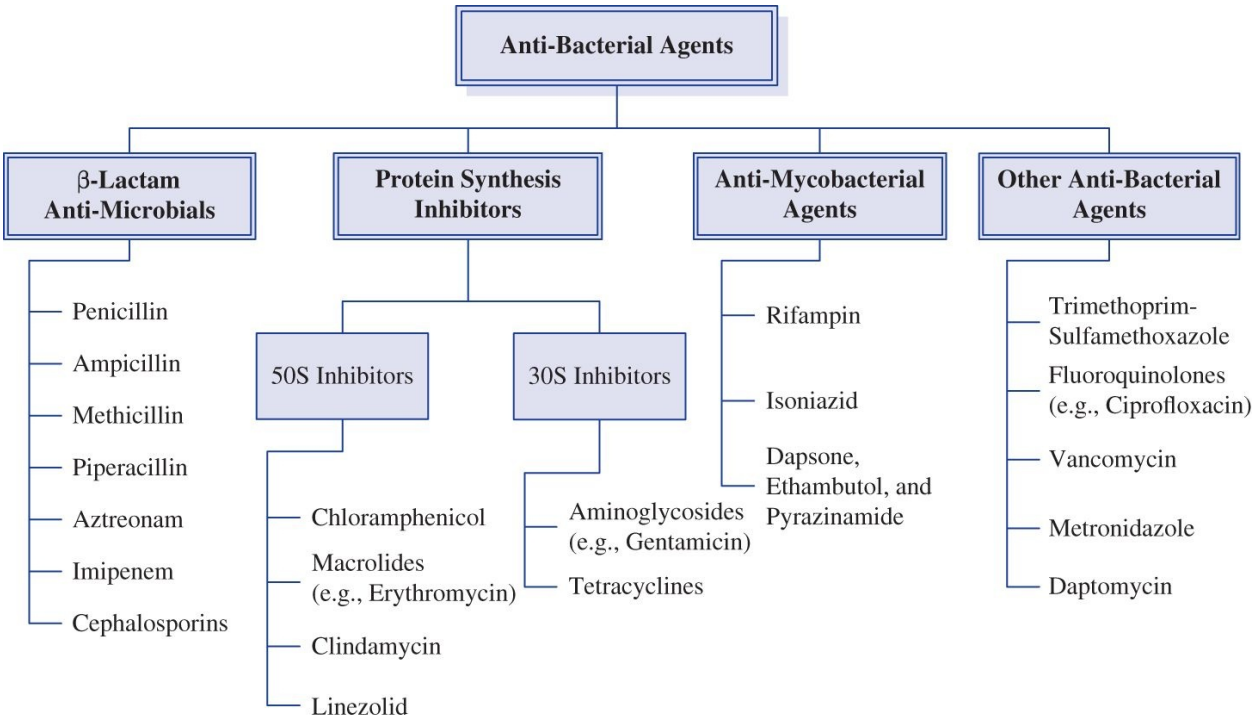
5-ASA: 5-Aminosalicylic acid
5-FU: 5-Fluorouracil
6-MP: 6-Mercaptopurine
AC: adenylyl cyclase
ACE: angiotensin-converting enzyme
ACh: acetylcholine
ACLS: advanced cardiac life support
ADH: anti-diuretic hormone
ALL: acute lymphoblastic leukemia
AML: acute myelogenous leukemia
AP: action potential
ARB: angiotensin receptor blocker
AV: atrioventricular
BAL: British Antilewisite (dimercaprol)
BNP: B-type natriuretic peptide
BUN: blood urea nitrogen
Ca^{2+}: calcium ion
cAMP: cyclic AMP
CHF: congestive heart failure
Cl^{-}: chloride ion
CML: chronic myelogenous leukemia
CMV: cytomegalovirus
CNS: central nervous system
CO: cardiac output
COPD: chronic obstructive pulmonary disease
COX: cyclooxygenase

CSF: cerebrospinal fluid
CV: cardiovascular
DAG: diacylglycerol
DAP: dapsone
DI: diabetes insipidus
DKA: diabetic ketoacidosis
DPP-4: dipeptidyl peptidase-4
DVT: deep vein thrombosis
EBV: Epstein-Barr virus
ECG: electrocardiogram
ED: emergency department
EDTA: ethylenediaminetetraacetic acid
Epi: epinephrine
ERP: effective refractory period
ETH: ethambutol
FH_4: tetrahydrofolic acid
FSH: follicle-stimulating hormone
G6PD: glucose-6-phosphate dehydrogenase
GABA: γ-aminobutyric acid
GERD: gastroesophageal reflux disease
GI: gastrointestinal
GIST: gastrointestinal stromal tumors
GLP-1: glucagon-like peptide-1
GnRH: gonadotropin-releasing hormone
GU: genitourinary
hBNP: human B-type natriuretic peptide
HCO_3^-: bicarbonate ion
HDL: high-density lipoprotein
HGPRT: hypoxanthine-guanine phosphoribosyl transferase
HIT: heparin-induced thrombocytopenia
HSV: herpes simplex virus
HTN: hypertension
IL: interleukin

IMP: inositol monophosphate
IP_3: inositol triphosphate
ITP: idiopathic thrombocytopenic purpura
IV: intravenous
K^+: potassium ion
LDL: low-density lipoprotein
LFT: liver function test
LH: luteinizing hormone
LTB: leukotriene B
LTC: leukotriene C
LTD: leukotriene D
M_3: muscarinic
MAC: minimal alveolar concentration
MAO: monoamine oxidase
MAOI: monoamine oxidase inhibitor
MCP: metacarpophalangeal
MCT: metacarpotarsal
mRNA: messenger ribonucleic acid
MRSA: methicillin-resistant *Staphylococcus aureus*
Na^+: sodium ion
$Na_2HCO_3^-$: sodium bicarbonate
NE: norepinephrine
NMDA: N-methyl D-aspartate
NNRTIs: non-nucleoside reverse transcriptase inhibitors
NO: nitric oxide
NRTI: nucleoside reverse transcriptase inhibitor
NSAID: non-steroidal anti-inflammatory drug
OCD: obsessive compulsive disorder
PABA: para-aminobenzoic acid
PBPs: penicillin-binding proteins
PCP: *Pneumocystis carinii* pneumonia
PFT: pulmonary function test

PGE_2: prostaglandin E_2
PGI_2: prostacyclin
PIP: proximal interphalangeal
PLC: phospholipase C
PPAR: peroxisome proliferators-activated receptors
PPD: purified protein derivative
PSA: prostate-specific antigen
PSVT: paroxysmal supraventricular tachycardia
PT: prothrombin time
PTT: partial thromboplastin time
PYR: pyrazinamide
RA: rheumatoid arthritis
RNA: ribonucleic acid
RPR: rapid plasma regain
rRNA: ribosomal RNA
SA: sinoatrial
SIADH: syndrome of inappropriate ADH secretion
SLE: systemic lupus erythematosus
SSRI: selective serotonin reuptake inhibitor
STD: sexually transmitted disease
SVT: supraventricular tachycardia
$t_{1/2}$: half-life
TFT: thyroid function test
Thio-IMP: 6-thioinosinic acid
TMP-SMX: trimethoprim-sulfamethoxazole
TNF: tumor necrosis factor
tRNA: transfer ribonucleic acid
TSH: thyroid-stimulating hormone
TXA_2: thromboxane A_2
URI: upper respiratory infection
USMLE: United States Medical Licensing Examination
UTI: urinary tract infection

V_d: volume of distribution
VB: vinblastine
VC: vincristine
VDRL: venereal disease research laboratory
VIP: vasoactive intestinal peptide
VLDL: very low-density lipoprotein
VRE: vancomycin-resistant enterococcus
VZV: varicella zoster virus
WBC: white blood cell
WPW: Wolff-Parkinson-White syndrome



CLASSES OF CEPHALOSPORINS AND THEIR ANTI-BACTERIAL ACTIVITY

Generation	Drug Names	Anti-Bacterial Activity
1st	Cefadroxil, **cefazolin**, **cephalexin**, cephalothin, cephapirin, cephradine	**Gram-positive cocci** (pneumococci, streptococci, staphylococci), *Proteus mirabilis*, *Escherichia coli*, and *Klebsiella pneumoniae*
2nd	Cefaclor, cefamandole, cefonicid,	**Gram-positive cocci**, *Proteus, E.*

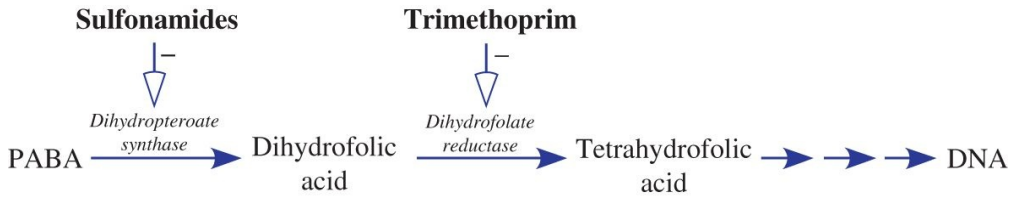
	cefuroxime, cefprozil, loracarbef, ceforanide, **cefoxitin**, cefmetazole, cefotetan	*coli*, *Klebsiella* species, *Enterobacter*, *Serratia*, some **anaerobes**, and ***Haemophilus influenzae***
3rd	Cefoperazone, **cefotaxime**, ceftazidime, ceftizoxime, **ceftriaxone**, cefixime, cefpodoxime proxetil, cefditoren pivoxil, ceftibuten, moxalactam	**Gram-negative bacteria** (*Serratia, Pseudomonas*, *Enterobacter*, *H. influenzae*, *Neisseria*)
4th	**Cefepime**	**Gram-negative bacteria** (*Serratia*, ***Pseudomonas***, *Enterobacter*, *H. influenzae*, *Neisseria*) **Gram-positive bacteria** (*Staphylococcus aureus*, *Streptococcus pneumoniae*)
5th	**Ceftaroline**	**Gram-positive bacteria** (*Streptococcus, S. aureus [MSSA and **MRSA**]*) **Gram-negative bacteria** (*E. coli, Klebsiella, H. Influenzae*)

PROTEIN SYNTHESIS INHIBITORS

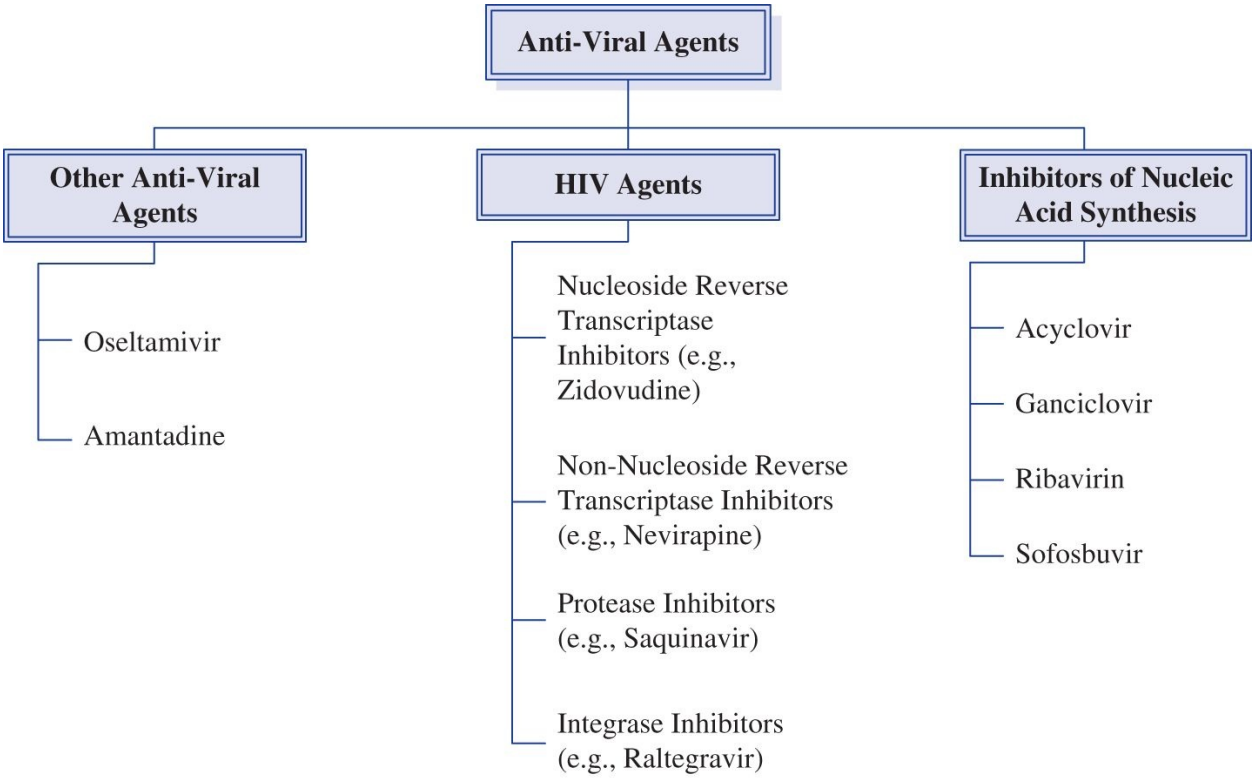
Anti-Bacterial Class	**Type of Inhibitor**	**Mechanism**
Aminoglycosides	30S	Inhibits formation of initiation complex, causing the misreading of mRNA
Tetracyclines	30S	Prevents attachment of aminoacyl-tRNA to acceptor site
Chloramphenicol	50S	Inhibits *peptidyl transferase* (the enzyme responsible for incorporating new amino acid into growing peptide strand)
Macrolides	50S	Blocks aminoacyl-tRNA complex translocation step
Clindamycin	50S	Blocks initiation complex formation and inhibits aminoacyl-tRNA complex translocation step
Linezolid	50S	Blocks formation of initiation complex

The protein synthesis inhibitors act by disrupting the bacterial 70S ribosomal mRNA complex that is responsible for bacterial protein synthesis. Since eukaryotes utilize a different ribosomal complex (80S), these drugs do not interfere with human cellular protein synthesis. The bacterial 70S ribosomal complex is composed of two subunits (30S and 50S), and the protein synthesis inhibitors act at one of these subunits.

SULFONAMIDES AND TRIMETHOPRIM



Sulfonamides are structural analogues of PABA, which is a precursor for dihydrofolic acid. High levels of PABA or a PABA analogue act to competitively inhibit *dihydropteroate synthase*, an enzyme needed for folic acid synthesis. Trimethoprim inhibits bacterial *dihydrofolic acid reductase (DHFR)*, which is the subsequent enzyme needed for folic acid synthesis. Inhibition of folic acid synthesis results in the disruption of DNA synthesis and thus the inhibition of bacterial growth. Notably, trimethoprim is functionally analogous to other drugs (e.g., methotrexate, pyrimethamine) that inhibit the same synthetic reaction in other species. Methotrexate is an anti-neoplastic drug that selectively inhibits human DHFR, and pyrimethamine is an anti-parasitic agent that selectively inhibits DHFR in protozoa.



PRINCIPLES OF ANTI-VIRAL AGENTS

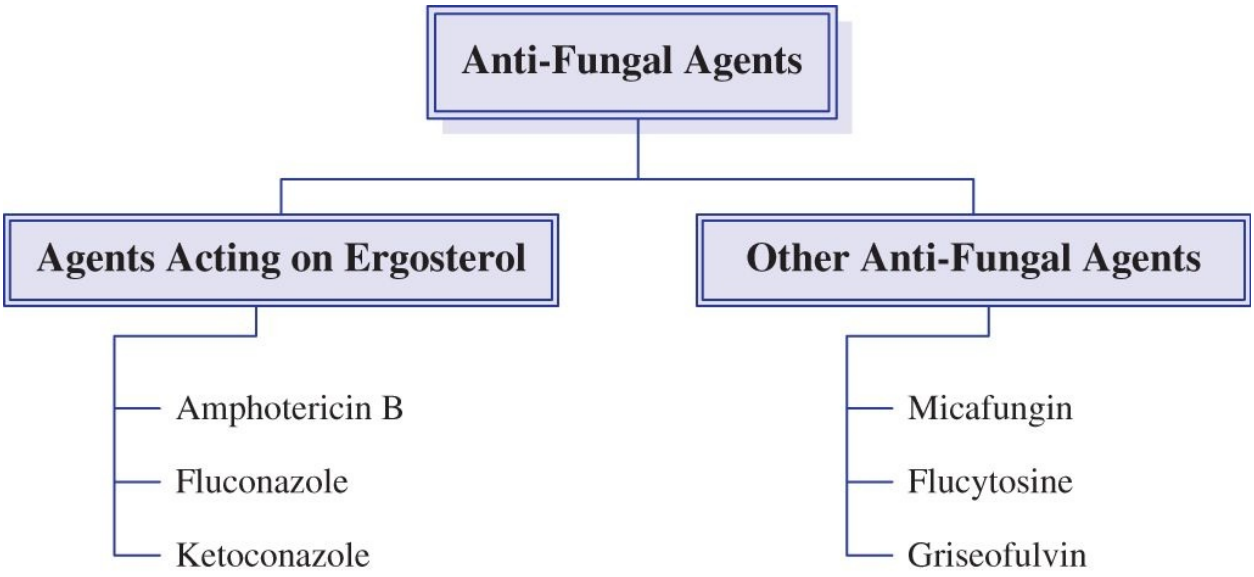
Viruses are intracellular parasites that rely on the synthetic processes of the host cell in order to replicate. In order to act against viruses, anti-viral agents must either block the passages of viruses into or out of the cell or the anti-viral agents must be able to act inside the host cell to inhibit viral replication.

Anti-viral agents can potentially target any of the steps of viral replication, which are the following:

- Entrance into host cells
- Uncoating of viral nucleic acid
- Synthesis of nucleic acid polymerases or nucleic acids (DNA or RNA)
- Synthesis or processing of viral proteins
- Assembly of viral particles
- Release of virus from the cell

SITES OF ACTION OF SELECTED ANTI-VIRAL AGENTS

Anti-Viral Agent Classes	Site of Drug Action
Guanosine analogues	Blocks DNA synthesis
Viral DNA polymerase inhibitors	Blocks DNA synthesis
Reverse transcriptase inhibitors and non-reverse transcriptase inhibitors	Block synthesis of DNA from RNA in CD4+ cell
Protease inhibitors	Block assembly of HIV virions
Integrase inhibitors	Block HIV genome integration into host cell chromosomes
Ribavirin	Blocks synthesis of guanine
Neuraminidase inhibitors	Block release of viral particles from the host cell



PRINCIPLES OF ANTI-FUNGAL AGENTS

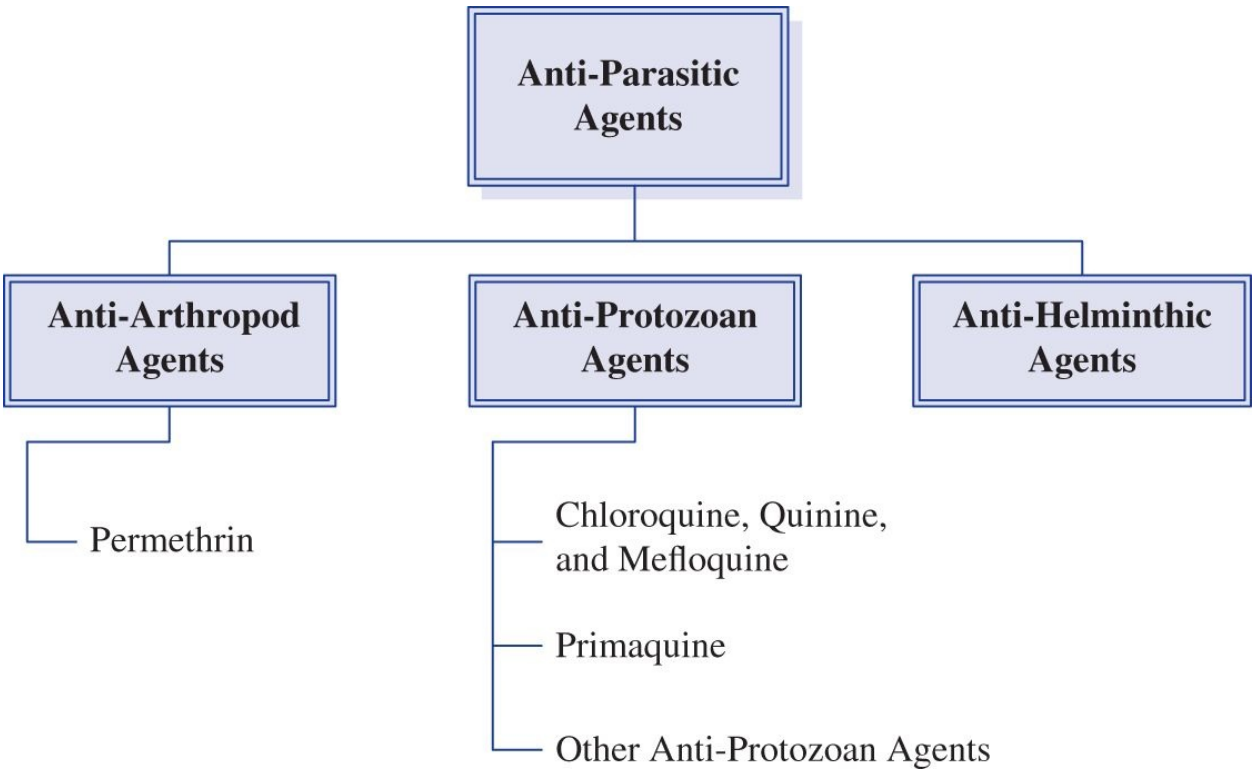
FUNGAL STRUCTURE

Many anti-fungal agents take advantage of the difference in lipid composition between fungal and mammalian cell membranes. While cholesterol is found in

most bacterial and human cell membranes, fungi have a sterol known as **ergosterol** that is only found in fungal cell membranes. Thus, most anti-fungal agents act by selectively targeting ergosterol synthesis and function.

MECHANISMS OF ANTI-FUNGAL AGENTS

Anti-Fungal Agent	**Mechanism of Action**
Amphotericin B, Nystatin	Binds ergosterol and causes the formation of holes in the fungal cell membrane
Flucytosine	Converted to nucleotide analogues by fungal enzymes and then acts to inhibit DNA and RNA synthesis
Azoles (e.g., fluconazole)	Reduce ergosterol synthesis by inhibiting fungal cytochrome P-450 enzymes
Echinocandins (e.g., micafungin)	Disrupts fungal cell wall synthesis



CLINICAL USES OF ANTI-PARASITIC AGENTS

Drug	Clinical Uses
Pentamidine	PCP pneumonia prophylaxis; alternate treatment of *Trypanosoma brucei* and Leishmaniasis
Nifurtimox	Chagas disease (*Trypanosoma cruzi*)
Suramin	*T. brucei* infection before CNS involvement
Melarsoprol	*T. brucei* infection after CNS involvement
Sodium stibogluconate	Leishmaniasis
Ivermectin	Onchocerciasis (river blindness)
Mebendazole/albendazole/thiabendazole	Roundworm (*Ascaris*), whipworm (*Trichuris*), hookworm (*Necator*, *Ancylostoma*), and pinworm (*Enterobius*)
Pyrantel pamoate	Roundworm (*Ascaris*), hookworm (*Necator*, *Ancylostoma*), and pinworm (*Enterobius*)
Praziquantel	Fluke (e.g., schistosomes, *Clonorchis*, *Paragonimus*), agent of choice for cysticercosis
Pyrimethamine	*Toxoplasma*, *Plasmodium falciparum,* and *Plasmodium vivax* malaria, and *Isospora*

A 22-year-old man presents to your clinic complaining of a new lesion on his penis for 1 week. On physical examination, you find a single, painless ulceration with a firm border. Upon further questioning, you discover that he has been having unprotected sexual contact with several individuals over the last several months. Physical examination is also remarkable for enlarged lymph nodes in the groin, axilla, and supraclavicular regions. Suspecting a specific sexually transmitted disease, you send him to the laboratory for RPR and VDRL tests. When he returns from the laboratory, you empirically treat him with a shot of a common antibiotic and you warn him that a rare side effect of this medication is

the development of a hemolytic anemia.

Penicillin

Similar Drugs	Penicillin G (IV); penicillin V (oral).
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. Penicillin **binds PBPs**, **thereby blocking peptidoglycan cross-linking,** which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	Treatment of infections caused by **gram-positive cocci** (streptococci), **gram-negative cocci** (*Neisseria*), and spirochetes (e.g., *Treponema pallidum*).
Side Effects	**Allergic reaction**; drug-induced Coombs positive **hemolytic anemia.**
Other	Penicillin and the other β-lactam drugs (ampicillin, methicillin, piperacillin, aztreonam, imipenem) have a structure that is characterized by a β-lactam ring. If the β-lactam ring is cleaved by bacterial enzymes (e.g., *β-lactamases*), the drug becomes inactive. Certain β-lactam drugs (e.g., penicillin, ampicillin, piperacillin) are more susceptible to bacterial *β-lactamase* cleavage than others.

A 54-year-old man presents to your clinic complaining of a 3-week history of severe sinus congestion. He describes his sinus discharge as green and purulent and he also reports fevers to 100.4°F. He has been trying symptomatic therapy with nasal decongestants for the last 2 weeks with no improvement in his symptoms. You decide to prescribe him an antibiotic to cover the likely pathogens (i.e., *Pneumococcus*, *H. influenzae*, *Moraxella*) that may be causing his symptoms.

Ampicillin

Similar Drugs	Other **aminopenicillins** include Amoxicillin.
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. Ampicillin **binds PBPs, thereby blocking peptidoglycan cross-linking**, which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	Ampicillin has an extended spectrum of coverage as compared to penicillin. It is used to treat infections caused by **gram-negative rods** (*H. influenzae*, *E. coli*, *P. mirabilis*, *Salmonella*), as well as infections caused by gram-positive cocci (*Enterococci*), gram-positive rods (*Listeria monocytogenes*), and gram-negative cocci. Amoxicillin is also indicated for treatment of *H. Pylori* as part of the triple-therapy regimen.
Side Effects	Allergic reaction; **non-allergenic skin rash;** diarrhea.
Other	Ampicillin and the other β-lactam drugs (penicillin, methicillin, piperacillin, aztreonam, imipenem) have a structure that is characterized by a β-lactam ring. If the β-lactam ring is cleaved by bacterial enzymes (e.g., *β-lactamases*), the drug becomes inactive. Certain β-lactam drugs (e.g., penicillin, ampicillin, piperacillin) are more susceptible to bacterial *β-lactamase* cleavage than others.
	Amoxicillin can be given in the oral form and thus is used more often for outpatient treatment.
	Clavulanic acid and sulbactam act to inactivate bacterial *β-lactamases*. They are often added to amoxicillin or ampicillin to broaden the spectrum of coverage against gram-negative organisms.

A 54-year-old IV drug abuser is admitted to the hospital with suspected osteomyelitis in his lumbar spine. Blood cultures are taken in the emergency room and broad-spectrum antibiotics are started. After 2 days, his blood culture

demonstrates growth of pan-sensitive *S. aureus*. In order to prevent overuse of stronger antibiotics that should be reserved for multidrug-resistant cases, you discontinue the current broad regimen of medications and you begin the patient on a more specific IV antibiotic.

Methicillin

Similar Drugs	Nafcillin; oxacillin; dicloxacillin.
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. Methicillin **binds PBPs**, **thereby blocking peptidoglycan cross-linking**, which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	Methicillin is used to treat *Staphylococcus* infections including ***S. aureus***. It is inactive against enterococci, anaerobic bacteria, and gram-negative organisms.
Side Effects	Allergic reaction; **interstitial nephritis** (methicillin); neutropenia (nafcillin); hepatitis (oxacillin).
Other	Methicillin and the other β-lactam drugs (penicillin, ampicillin, piperacillin, aztreonam, imipenem) have a structure that is characterized by a β-lactam ring. If the β-lactam ring is cleaved by bacterial enzymes (e.g., *β-lactamases*), the drug becomes inactive. **Methicillin is *β-lactamase* resistant** due to its bulkier structure, which acts to sterically hinder access of the *β-lactamase* to the β-lactam ring. Methicillin-resistant *S. aureus* species have arisen, most often due to bacterial alteration of target PBPs.

A 43-year-old burn victim is readmitted to the hospital for possible infection at his burn site. He had suffered a third-degree burn 2 months earlier and had just been released from the hospital after a failed skin graft procedure. The patient has a fever of 102°F, a blood pressure of 90/50 mm Hg, and his wound is oozing

purulent discharge. You send a sample of the discharge for culture and you begin broad-spectrum antibiotic therapy. The culture grows out pan-sensitive *Pseudomonas*. You decide to change the patient's antibiotic regimen to a medication that is commonly used to treat this aggressive organism.

Piperacillin

Similar Drugs	Ticarcillin; carbenicillin.
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. Piperacillin **binds PBPs**, **thereby blocking peptidoglycan cross-linking**, which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	Piperacillin is used to treat infections caused by ***Pseudomonas*** and gram-negative rods (e.g., *Klebsiella*).
Side Effects	Allergic reactions.
Other	Piperacillin and the other β-lactam drugs (penicillin, methicillin, ampicillin, aztreonam, imipenem) have a structure that is characterized by a β-lactam ring. If the β-lactam ring is cleaved by bacterial enzymes (e.g., ***β-lactamases***), the drug becomes inactive. Certain β-lactam drugs (e.g., penicillin, ampicillin, piperacillin) are more susceptible to bacterial *β-lactamase* cleavage than others. **Tazobactam** acts to inactivate bacterial *β-lactamases*. It is often added to piperacillin to broaden the spectrum of coverage against gram-negative organisms and ***S. aureus*** infections.

A 45-year-old white woman presents to the emergency room with increased urinary urgency and dysuria. She reports that this has occurred several times over the last year despite antibiotic treatment. Upon review of her medical records, you notice that she has been treated with both first- and second-line

pharmacologic agents for her recurrent urinary tract infections, which have been caused by drug-resistant strains of *Klebsiella* and *Serratia* in the past. Her medical history is also notable for an allergy to penicillins and cephalosporins. On physical examination, she is febrile to 101°F and has a blood pressure of 90/50 mm Hg. You draw urine and blood cultures and you decide to put the patient on a broad-spectrum β-lactam drug that is both effective against gram-negative rod infections and can be used in penicillin-allergic patients.

Aztreonam

Similar Drugs	Belongs to the **monobactam** class of anti-bacterial agents.
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. Aztreonam is a drug with a **monocyclic β-lactam ring** that acts to bind PBPs, thereby **blocking peptidoglycan cross-linking**, which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	Aztreonam is used to treat infections caused by **gram-negative rods (*Klebsiella, Pseudomonas*, *Serratia***). It has no activity against gram-positive bugs or anaerobes.
Side Effects	GI upset; skin rash; elevated LFTs; **not a cross-allergen of penicillin**.
Other	Aztreonam and the other β-lactam drugs (penicillin, methicillin, ampicillin, piperacillin, imipenem) have a structure that is characterized by a β-lactam ring. If the β-lactam ring is cleaved by bacterial enzymes (e.g., *β-lactamases*), the drug becomes inactive. Like methicillin, **aztreonam is relatively resistant to the actions of *β-lactamases***. Aztreonam can be used to treat severe gram-negative infections in **patients allergic to penicillin or in patients who are renally insufficient** and thus cannot tolerate aminoglycosides.

A 72-year-old man presents to the emergency room complaining of right upper

quadrant abdominal pain. On examination, he has significant right upper quadrant tenderness as well as fever up to 102°F and a blood pressure of 88/50 mm Hg. Blood cultures reveal *Klebsiella.* You decide to start the patient on a combination of two medications—one drug to treat the infection and the second drug to keep the first medication potent in the renal tubules.

Imipenem

Similar Drugs	Other **carbapenems** include meropenem, ertapenem, and doripenem.
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. Imipenem **binds PBPs**, **thereby blocking peptidoglycan cross-linking**, which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	Imipenem is a **broad-spectrum antibiotic**, which can be used to treat infections caused by ***Enterobacter***, gram-positive cocci, enterococci, gram-negative rods (especially drug-resistant *Klebsiella*), **anaerobes**, and ***Pseudomonas*** species. Imipenem cannot treat infections caused by VRE or MRSA.
Side Effects	GI upset; allergic reaction (rash); **seizures** at high serum levels, especially in renally insufficient patients.
Other	Imipenem and the other β-lactam drugs (penicillin, methicillin, ampicillin, piperacillin, aztreonam) have a structure that is characterized by a β-lactam ring. If the β-lactam ring is cleaved by bacterial enzymes (e.g., *β-lactamases*), the drug becomes inactive. Like aztreonam, **imipenem is relatively resistant to the actions of *β-lactamases***. **Cilastatin** inhibits ***renal dihydropeptidase I***, which is an enzyme that inactivates imipenem in the renal tubules. Thus, imipenem is usually administered with cilastatin in order to increase imipenem's duration of action.

A 28-year-old Caucasian man presents to the emergency room complaining of

flushing, nausea, vomiting, and headache. He reports that he was feeling fine until he drank a beer 1 hour ago at a local bar. He also tells you that he has been taking an antibiotic for the last 5 days for the treatment of simple cellulitis of the leg. Physical examination is unremarkable and his symptoms have improved while he was waiting in the emergency room. You suspect that he has had a disulfiram-like reaction due to the combination of his antibiotic and his alcohol intake and you instruct the patient not to ingest alcohol until his antibiotic regimen has been completed.

Cephalosporins

Similar Drugs	Please see card 1 for a list of the different cephalosporins.
Mechanism of Action	Formation of bacterial peptidoglycan cell walls are mediated via PBPs. The cephalosporins **bind PBPs**, **thereby blocking peptidoglycan cross-linking**, which leads to the inhibition of bacterial cell wall synthesis.
Clinical Uses	• **1st generation:** Effective against **gram-positive cocci**, *P. mirabilis*, *E. coli*, and *K. pneumoniae*; usually used for surgical prophylaxis or treatment of cellulitis. • **2nd generation:** Effective against **gram-positive cocci**, Proteus, *E. coli*, *Klebsiella*, *Serratia*, some **anaerobes**, and ***H. influenzae***; used to treat sinusitis, otitis, and pneumonia. • **3rd generation:** Effective against **gram-negative bacteria** (*Serratia*, ***Pseudomonas***, *Enterobacter, H. influenzae, Neisseria*); **used to treat serious gram-negative infections**. • **4th generation**: Effective against **gram-negative bacteria** (*Serratia*, *Pseudomonas*, *Enterobacter*, *H. influenzae*, *Neisseria*), **as well as against** some **gram-positive bacteria** (*S. aureus*, *S. pneumoniae*); **used to treat serious gram-negative infections** (e.g., meningitis, *Pseudomonas*, and *Enterobacter* infections). • **5th generation:** Effective against **gram-positive bacteria** (including **MRSA**) as well as **gram-negative bacteria** (though notably *not* pseudomonas).

Side Effects	**Hypersensitivity reaction** (10% of patients with penicillin allergy will have a cephalosporin allergy); **disulfiram-like reaction** with ethanol (cefamandole, cefotetan, and cefoperazone); nephrotoxicity.
Other	The cephalosporins have a structure that is characterized by a β-lactam ring. While other β-lactam drugs (e.g., penicillin) are inactivated by the cleavage of the β-lactam ring by bacterial *β-lactamases*, **the cephalosporins are relatively resistant to *β-lactamases***.

A 74-year-old man with a history of mitral regurgitation presents to the emergency room with a temperature of 102.5°F over the last 3 days. Physical examination is significant for a loud systolic murmur at the apex as well as the presence of splinter hemorrhages on several nail beds. Blood cultures are drawn and he is started on broad-spectrum antibiotics. Given his antibiotic regimen, he will need to be carefully monitored for renal failure.

Gentamicin

Similar Drugs	Other **aminoglycosides** include neomycin, amikacin, tobramycin, and streptomycin.
Mechanism of Action	Gentamicin is a **protein synthesis inhibitor**. It binds the **30S** bacterial ribosomal subunit and acts to **inhibit the formation of the initiation complex**, causes **mRNA misreading** leading to non-functional proteins. It also induces the dissolution of polyribosomes during protein synthesis.
Clinical Uses	The aminoglycosides are used to treat **severe infections with gram-negative rods** (e.g., sepsis, chronic urinary tract infections, endocarditis [when given in conjunction with vancomycin], pneumonia, *Pseudomonas* infections). Neomycin is used for preparation for bowel surgery (kills bowel flora, thereby reducing chances of infection after surgery). Streptomycin is used as a second-line agent to treat tuberculosis

	as well as to treat tularemia.
Side Effects	**Nephrotoxicity** (acute tubular necrosis, especially with cephalosporin use); **neuromuscular blockade**; **ototoxicity** (especially with loop diuretic use); **teratogen**.
Other	Aminoglycosides require oxygen for uptake into the bacterial cell. Thus, they are only active against aerobes.

A 24-year-old graduate female student presents to the clinic complaining of a severe toothache in her left upper palate. She reports feeling slightly feverish and has noticed increased swelling where her wisdom tooth is erupting. Plain films show that there is no wisdom tooth impaction, but that the soft tissue swelling is consistent with a dental abscess. You prescribe her an antibiotic that will be effective against mouth flora (anaerobes and gram-positive organisms) to treat her infection.

Clindamycin

Similar Drugs	
Mechanism of Action	Clindamycin is a **protein synthesis inhibitor**. It binds the **50S** bacterial ribosomal subunit and acts to **inhibit the formation of the initiation complex**. It also inhibits the translocation of the aminoacyl peptide during protein synthesis.
Clinical Uses	Clindamycin is **effective against some anaerobes** (e.g., *Bacteroides fragilis*, *Clostridium perfringens*) as well as **against some gram-positive cocci** (streptococci, staphylococci). It is used to treat severe **anaerobic infections above the diaphragm** (e.g., aspiration pneumonia, lung abscess) and for endocarditis prophylaxis before dental procedures in patients with prosthetic heart valves.
Side Effects	**Pseudomembranous colitis** (*Clostridium difficile* overgrowth), nausea; diarrhea; skin rashes; impaired liver function.

Other	**Chloramphenicol** is a protein synthesis inhibitor that binds the 50S ribosomal subunit and prevents chain elongation by *peptidyl transferase*. It has broad-spectrum coverage for both gram-positive and gram-negative bacteria, and is most commonly used to treat meningitis and Rocky Mountain spotted fever. It is rarely used now due to significant side effects, which include myelosuppression (both a dose-dependent **anemia** and dose-independent **aplastic anemia**) and **gray baby syndrome** (characterized by vomiting, flaccidity, gray skin hue, and shock in newborns, due to lack of *UDP-glucuronyl transferase* in newborn liver).

A 69-year-old male is admitted to the MICU with septic shock. His past medical history is significant for prior staphylococcal skin infections as well as colorectal cancer. He is status-post colectomy 1 week ago. In addition to providing pressor support, you draw blood cultures and start him on broad-spectrum antibiotics. Within 24 hours, the blood cultures return demonstrating vancomycin-resistant enterococcus (VRE). You subsequently adjust his antibiotic regimen to include a bacterial protein synthesis inhibitor commonly used to treat VRE.

Linezolid

Similar Drugs	Linezolid belongs to the **oxazolidinone** class of anti-bacterial agents.
Mechanism of Action	Linezolid is a **protein synthesis inhibitor**. It binds the **50S** bacterial ribosomal subunit and acts to **inhibit the formation of the initiation complex**.
Clinical Uses	Used to treat gram-positive infections, **including MRSA and VRE infections**, as well as infections caused by other gram-positive cocci and *Listeria*.
Side Effects	**Bone-marrow suppression** (especially thrombocytopenia); **peripheral neuropathy;** fungal infections.

Other	The combination drug of **quinupristin and dalfopristin** fall into a category of antibiotics known as the **streptogramins.** Quinupristin and dalfopristin are **protein synthesis inhibitors** that act at the 50S ribosomal unit. As with linezolid, this combination of drugs can be used to treat infections caused by **MRSA** and **VRE**.

A 34-year-old woman with a history of IV drug abuse presents with a 2-week history of fever, weight loss, and chills. Her physical examination is notable for a temperature of 103.1°F, clear lungs, and a new systolic murmur heard best at the left sternal border. You also notice several small red streaks along her fingernails. Initial blood cultures reveal *S. aureus*, confirming your suspicion of endocarditis. While you await the blood culture susceptibilities, you consider your choices of anti-microbial agents to treat her infection, including an agent that is a lipopeptide antibiotic that disrupts bacterial cell membranes and can be effective against methicillin-resistant *S. aureus*.

Daptomycin

Similar Drugs	
Mechanism of Action	Daptomycin is a lipopeptide antibiotic that works primarily by directly **disrupting bacterial cell membranes,** causing cellular depolarization and arrest of protein synthesis.
Clinical Uses	Used to treat severe skin and bloodstream infections caused by **gram-positive cocci** (including **MRSA** and **VRE**).
Side Effects	**Skeletal muscle toxicity**; eosinophilia.
Other	Daptomycin **cannot be used for pneumonia**, as it complexes with and is inactivated by pulmonary surfactant. Other medications used for severe **MRSA** infections include **vancomycin, linezolid, tigecycline** (a tetracycline derivative

with broad gram-positive, gram-negative, and anaerobic coverage), and **ceftaroline** (fifth-generation cephalosporin).

A 24-year-old man presents to your clinic complaining of a 4-day history of a dry cough and a low-grade fever. On physical examination, his temperature is 99.9°F, and you note that there are decreased breath sounds and rales throughout his lung fields. You send the patient for a chest x-ray, the results of which suggest the presence of an atypical pneumonia. You decide to start the patient on a medication that covers the most common infectious agents responsible for such community-acquired atypical pneumonias.

Erythromycin

Similar Drugs	Other **macrolides** include clarithromycin and azithromycin.
Mechanism of Action	Erythromycin is a **protein synthesis inhibitor.** It **binds to the 50S ribosomal subunit** and inhibits the formation of the initiation complex. It also inhibits the translocation of the aminoacyl peptide during protein synthesis.
Clinical Uses	The macrolides are effective against **gram-positive cocci** (streptococci, staphylococci), ***Corynebacteria*** species, **atypical organisms** (*Mycoplasma*, *Legionella*, *Chlamydia* species), *Ureaplasma*, *Listeria* species, *Rickettsia* species, and some gram-negative organisms (*Neisseria* species, *Bordetella pertussis*, *Bartonella henselae*).
	The macrolides are generally used to treat **upper respiratory infections** (e.g., *Mycoplasma*, Legionnaires disease), some STDs (*Neisseria*, ***Chlamydia***, syphilis in patients allergic to penicillin), *Helicobacter pylori* infections, *Corynebacteria* infections (e.g., **diphtheria**), and infections caused by gram-positive cocci in penicillin-allergic patients.
Side Effects	**GI upset** (macrolides have a pro-motility effect on the gut, which can be exploited therapeutically for patients with motility

	disorders); acute cholestatic hepatitis; skin rash; eosinophilia.
Other	Erythromycin **inhibits cytochrome P-450 enzymes**, thereby resulting in increased serum levels of other drugs, such as warfarin, cyclosporine, and theophylline.

A 32-year-old woman presents to your office complaining of a rash. She reports that she was out gardening the day before and woke up this morning with lesions on the back of her neck and forearms. On physical examination, the patient has maculopapular lesions over the sun-exposed areas of her body. Her past medical history is significant for Lyme disease, diagnosed 1 week ago, for which she is currently being treated with antibiotics. You inform the patient that the rash is most likely due to a medication side effect and that she should avoid the sun until her antibiotic treatment is complete.

Tetracycline

Similar Drugs	Doxycycline; minocycline; demeclocycline.
Mechanism of Action	Tetracycline is a **protein synthesis inhibitor**. It binds to the **30S** subunit and **blocks the aminoacyl-tRNA from binding to the ribosome**, thereby inhibiting protein synthesis.
Clinical Uses	Tetracycline and other drugs of this class are broad-spectrum antibiotics that are effective against many gram-positive and gram-negative organisms, including *Vibrio cholerae*, *Chlamydia* species, rickettsiae, mycoplasmas, spirochetes, and some anaerobes. These drugs are used to treat **pneumonia caused by *Mycoplasma* or *Chlamydia***, **Rocky Mountain spotted fever** and other rickettsial infections, **Lyme disease**, cholera, and sexually transmitted ***Chlamydia*** infections. These drugs can also be used in combination with other agents to treat *H. pylori* infections (as part of quadruple therapy), tularemia, and brucellosis.

Side Effects	GI upset; relatively contraindicated in pregnancy (causes **teeth discoloration** and **bone deformity in children)**; **Fanconi syndrome** (aminoaciduria, phosphaturia, acidosis, and glycosuria); **photosensitivity**.
Other	Doxycycline can be used in **renally insufficient** patients since it is fecally eliminated. Drugs in the tetracycline family should not be taken with antacids, milk, or iron-containing substances since **divalent cations present in these substances inhibit absorption of tetracyclines** in small intestine. **Demeclocycline** also acts as a **competitive antagonist at the V2 receptors** and can be **used to treat SIADH**.

A 42-year-old HIV-positive man presents to the emergency room with a fever and cough. He says that he has been compliant with his medication regimen, but he developed a cough 2 weeks ago and now he finds himself feeling short of breath upon exertion. On physical examination, you hear diffuse rhonchi and the chest x-ray shows bilateral infiltrates consistent with *Pneumocystis carinii* pneumonia. You begin antibiotic therapy immediately and inform the patient that he will need to take a prophylactic antibiotic after discharge to ward off future recurrences of this infection.

Trimethoprim-Sulfamethoxazole (TMP-SMX)

Similar Drugs	Other **sulfonamides** include sulfisoxazole, sulfamethizole, sulfadoxine, and sulfadiazine.
Mechanism of Action	**Trimethoprim** is a protein synthesis inhibitor that **inhibits folic acid synthesis by inhibiting *dihydrofolate reductase***. **Sulfamethoxazole** is a structural **analogue of PABA**, which is a dihydrofolic acid precursor. High levels of a PABA analogue acts to **competitively inhibit *dihydropteroate synthase*, an enzyme needed for folic acid synthesis**. Inhibition of folic acid synthesis by both drugs results in **DNA**

	synthesis disruption.
Clinical Uses	TMP-SMX is effective against both gram-positive and gram-negative bacteria, including enteric bacteria (e.g., ***E. coli***; *Enterobacter*, *Klebsiella*, *Salmonella* species), *Chlamydia trachomatis*, ***Nocardia*** species, and ***P. carinii***. It is used to treat **urinary tract infections** (caused by *E. coli*), sinus tract infections, ***P. carinii* pneumonia**, and ocular chlamydial infections.
Side Effects	Allergic reactions (including **Stevens-Johnson syndrome**); **hemolytic anemia**; granulocytopenia (alleviated with folinic acid supplementation); nephrotoxicity; **kernicterus** in newborns.
Other	

A 56-year-old diabetic woman was admitted for diabetic ketoacidosis and a urinary tract infection. The urine culture grew out an *E. coli* species and the patient was put on appropriate antibiotic therapy. A few days after admission, the patient begins to complain about some tenderness in her elbow and knee joints. You immediately become concerned that her new symptoms may be a rare complication of her antibiotic treatment.

Ciprofloxacin

Similar Drugs	Other **fluoroquinolones** include norfloxacin, ofloxacin, sparfloxacin, gemifloxacin, gatifloxacin, moxifloxacin, and levofloxacin.
Mechanism of Action	Ciprofloxacin and the other fluoroquinolones **inhibit bacterial *DNA topoisomerase II***, thereby inducing DNA strand breakage and cell death.
Clinical Uses	Fluoroquinolones are effective against **gram-negative species**, including *Neisseria*, *Haemophilus* species, *Klebsiella*, *E. coli*, and *Enterobacter*, as well as against *Mycoplasma* and *Legionella* species. The **newer fluoroquinolones** (e.g., gatifloxacin, levofloxacin, moxifloxacin) also **have increased activity**

	against some gram-positive organisms (*S. pneumoniae*, some staphylococci species). Fluoroquinolones are used to treat **UTIs**, GI infections, **respiratory tract infections (**e.g., **pneumonias)**, and **gonococcal infections**.
Side Effects	GI upset; skin rash; headache; **tendonitis and tendon rupture** in adults.
Other	Fluoroquinolones are **contraindicated in pregnant women and in children** as they have been shown to damage growing cartilage. **Nitrofurantoin** is an agent that is metabolized to a compound, which then acts to damage bacterial DNA. Clinically, it is used for **recurrent UTIs.** Side effects include GI upset, neuropathy, pulmonary fibrosis, and hemolytic anemia in G6PD-deficient patients.

You are called to evaluate a 32-year-old male patient in the hospital who has been admitted for endocarditis. He is complaining of a red flushing over his entire body. The patient's blood culture had grown out methicillin-resistant *S. aureus* and the intern had started him on the proper antibiotic therapy several hours beforehand. On physical examination, the patient is diffusely flushed from his face down to his legs. You inform the patient that he has had a reaction to the antibiotic and that this reaction can be prevented in the future by slowing the infusion rate of the medication and by administering anti-histamines simultaneously with the medication.

Vancomycin

Similar Drugs	—
Mechanism of Action	Vancomycin binds the D-ala D-ala terminus of bacterial cell wall precursors, thereby **inhibiting *transglycosylase***, which is an enzyme involved in peptidoglycan elongation and cross-linking. The inhibition of *transglycosylase* results in **weakened**

	peptidoglycans in the cell wall, thereby leading to cell wall damage and lysis.
Clinical Uses	Vancomycin is effective against **gram-positive bacteria** (e.g., staphylococci, enterococci, streptococci). It is used to treat serious gram-positive multidrug-resistant infections (e.g., sepsis, endocarditis) including **MRSA infections**. It is also used to treat *C. difficile* pseudomembranous colitis.
Side Effects	**Nephrotoxicity**; "**red man syndrome**" (flushing of the skin; this reaction is not IgE-dependent and can be prevented with simultaneous anti-histamine administration and a slow infusion rate); ototoxicity (seen with early formulations of drug but less common currently).
Other	**Polymyxins** (B and E) are compounds that bind to bacterial cell membranes and increase the permeability of the cell membrane to polar molecules. They are effective against many gram-negative rods; however, because of significant toxicity (e.g., nephrotoxicity, neurotoxicity), they are currently **only used topically to treat infected skin lesions**.

A 21-year-old college senior presents to the student health clinic. She has just returned from a spring break trip to Costa Rica, where she backpacked along the hillsides for several days. She complains of a watery, non-bloody diarrhea that has lasted for 5 days now. On further history, you learn that she had been drinking stream water during her backpacking trip. She denies any strange food consumption. You are confident that the patient has a protozoal infection and you send away for stool cultures to confirm your suspicions. In the meantime, you start the patient on an agent that kills protozoa by forming cytotoxic byproducts and you recommend that the patient abstain from drinking alcoholic beverages while taking this medication.

Metronidazole

Similar Drugs	

Mechanism of Action	Metronidazole is metabolized by bacterial proteins into **reduced reactive compounds** that serve to damage bacterial DNA, proteins, and membranes, thereby **leading to cell death**.
Clinical Uses	Metronidazole is active against **anaerobic bacteria** (e.g., *Clostridium* species, *Bacteroides* species) as well as against **protozoans** including *Giardia*, *Entamoeba*, *Trichomonas*, and *Gardnerella vaginalis*. It is used to **treat giardiasis**, **trichomoniasis**, **and *Entamoeba histolytica* infections**. It is the **agent of choice for anaerobic infections below the diaphragm** (i.e., ***C. difficile* colitis**, diverticulitis). It is also used in combination with a proton-pump-inhibitor, bismuth, and amoxicillin (or tetracycline) as quadruple therapy for **treatment of *H. pylori* infection**.
Side Effects	**Disulfiram-like effect with alcohol**; metallic taste.
Other	Metronidazole is an **inhibitor of the P-450 system** and hence can lead to increased levels of warfarin and phenytoin.

A 34-year-old foreign-born farm worker presents to your clinic complaining of dark orange-red urine over the past several weeks. On further history, you learn that he had a positive PPD 2 months ago. At that time, a chest x-ray indicated a lesion in the right upper lobe, consistent with tuberculosis. He was started on multidrug therapy to eradicate the infection, which he states that he is currently taking. The patient's physical examination is completely within normal limits. You reassure the patient that the urine discoloration is a harmless side effect of his medication, and you order serum and urine studies to ensure that there is no indication of damage to the liver or kidneys.

Rifampin

Similar Drugs	Other **rifamycins** include rifabutin.

Mechanism of Action	Rifampin **inhibits bacterial *DNA-dependent RNA polymerase***, thereby leading to decreased RNA synthesis in bacterial cells.
Clinical Uses	Rifampin is active against **mycobacteria** as well as against certain gram-negative bacteria (e.g., *Neisseria meningococcus*, *H. influenzae*).
	It is used in combination with other drugs in the treatment of **tuberculosis and leprosy**. It is also used as **prophylaxis for contacts of patients with meningococcal meningitis and *H. influenzae* type B** infection and as part of a combination treatment of prosthetic valve endocarditis and osteomyelitis.
Side Effects	**Harmless orange color to urine** and sweat; rash; thrombocytopenia; nephritis; **hepatitis**.
Other	Rifampin has been shown to **induce the cytochrome P-450 system**, thereby increasing the metabolism and elimination of several other drugs (e.g., warfarin, oral contraceptives, prednisone, ketoconazole, digoxin, glyburide).

A 14-year-old foreign-born Hispanic woman arrives at your pediatric clinic for an annual physical examination. She immigrated to the United States 2 years ago and she lives with her parents, younger brother, and maternal grandmother. Of note, the grandmother was just hospitalized 2 days ago for fevers, chills, and a productive cough with sputum that demonstrated acid-fast bacteria. The patient's parents note that the patient's PPD has been positive in the past due to a BCG vaccination as an infant. She reports no concerning symptoms and her physical examination is unremarkable. Nevertheless, given the grandmother's history, you decide to place the child on a prophylactic pharmacologic regimen to prevent active tuberculosis and you suggest that her brother and parents also consider prophylactic medication as well.

Isoniazid

Similar Drugs

Mechanism of Action	Isoniazid acts to **inhibit the synthesis of mycolic acids**, which are major components of mycobacterial cell walls.
Clinical Uses	Isoniazid is used in combination with other medications in the **treatment of *Mycobacterium tuberculosis***. It is also used as **prophylaxis against active tuberculosis** in patients with a positive PPD.
Side Effects	**Peripheral neuropathy** (*pyridoxine*, or vitamin B_6, is given to prevent peripheral neuropathy in patients taking isoniazid); G6PD-deficient hemolytic anemia; **drug-induced lupus**; **hepatitis**.
Other	Some patients metabolize isoniazid faster than others, due to a genetic difference in the rate of action of a liver enzyme (*N-acetyltransferase*). Thus, serum levels of isoniazid should be monitored initially to ensure therapeutic levels of the drug in patients who are rapid metabolizers.

A 28-year-old foreign-born man comes to your clinic complaining of eye pain over the last week. Besides eye pain, he also reports to you that he has noticed transient spots in the center of his visual fields and that he feels as if he is unable to see as well as he used to. His medical history is significant for active tuberculosis, for which he has been taking several medications for the past 3 weeks. He denies fevers, chills, night sweats, or current productive cough, and he tells you that he has been diligent about his drug regimen. You tell the patient that you believe his symptoms are related to one of the medications that he is taking to treat his tuberculosis and you decide to refer the patient to an ophthalmologist.

Other Anti-Mycobacterial Agents

Similar Drugs	Other medications used to treat mycobacterial infections include **dapsone (DAP)**, **ethambutol (ETH)**, and **pyrazinamide (PYR)**.

Mechanism of Action	**DAP:** PABA antagonist that acts to inhibit folic acid synthesis; behaves similarly to the sulfonamides. **ETH:** Inhibits mycobacterial *arabinosyl transferase*, which is an enzyme involved in the synthesis of the mycobacterial cell wall. **PYR:** Known to lower pH of mycobacteria, but the exact mechanism of action is unknown.
Clinical Uses	**DAP:** Used in combination with rifampin and clofazimine to **treat *M. leprae* infection** (leprosy); also used as prophylaxis against *P. carinii* infection in HIV patients. **ETH and PYR:** Used in combination with other medications to **treat *M. tuberculosis* infection.**
Side Effects	**DAP: G6PD-deficient hemolytic anemia**; GI intolerance; rash. **ETH: Retrobulbar neuritis** resulting in decreased visual acuity and **red-green color blindness**. **PYR:** GI intolerance; fever; **hepatotoxicity**; hyperuricemia (gout).
Other	**Streptomycin** (an aminoglycoside) is also used as second-line treatment of *M. tuberculosis* infection.

A 36-year-old man with HIV presents to the urgent care clinic with epigastric pain that is sharp and radiates toward his back. He states that he is very compliant with his anti-viral medications and was feeling fine 3 days ago. He does not drink alcohol. His laboratory studies demonstrate a markedly elevated lipase. You suspect that his acute pancreatitis is likely secondary to his drug regimen and you order an abdominal ultrasound to confirm your suspicion and to assess for any other cause for his pancreatitis.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Similar Drugs	**NRTIs** include **zidovudine (AZT or ZDV), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), stavudine (d4T), emtricitabine (FTC)**, and **abacavir**.

Mechanism of Action	NRTIs **inhibit HIV *reverse transcriptase***, thereby inhibiting DNA synthesis. NRTIs can also **compete with nucleoside triphosphates** (e.g., dTTP, dATP, dCTP, dGTP) **to be added to the newly synthesized viral DNA strand**. Incorporation of an NRTI into the viral DNA strand leads to a defective viral particle.
Clinical Uses	NRTIs are used in the **treatment of HIV infection**. **Lamivudine** is also used in the treatment of **chronic hepatitis B**.
Side Effects	Neutropenia; **megaloblastic anemia (AZT)**; **pancreatitis (ddI);** peripheral neuropathy (ddC, d4T); hypersensitivity reactions (rash); lactic acidosis (abacavir); GI upset.
Other	The use of AZT during pregnancy and in neonates with HIV+ mothers has been shown to significantly reduce the risk of viral transmission from mother to child. **Nucleotide analogue reverse transcriptase inhibitors** include **tenofovir** and **adefovir**. These drugs also work by inhibiting viral *reverse transcriptase*. They are used to **treat HIV infection** and **hepatitis B infection** (adefovir).

A 36-year-old HIV-positive man presents to the AIDS clinic complaining of having vivid nightmares and delusional thoughts during the day. His current CD4 count is within acceptable range and his viral load is nearly undetectable. He has no other complaints other than the delusions and vivid nightmares, but he is concerned that he may be becoming schizophrenic. Upon reviewing his chart, you see that he was recently switched to a protease-sparing drug regimen and you begin to believe that the medication substituted for the protease inhibitor is the cause of the patient's current symptoms as opposed to a primary psychiatric disorder.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Similar Drugs	**NNRTIs** include **nevirapine**, **efavirenz**, and **delavirdine**.
Mechanism of Action	The **NNRTIs bind specifically to HIV *reverse transcriptase***, thereby blocking DNA synthesis.
Clinical Uses	NNRTIs are used in the **treatment of HIV infection**.
Side Effects	**Nevirapine:** Stevens-Johnson syndrome; fulminant hepatitis; **induction of cytochrome P-450 activity**, which results in the increased metabolism of several drugs, including oral contraceptives, warfarin, metronidazole, ketoconazole, and some protease inhibitors. **Delavirdine:** Elevated LFTs; teratogenic compound. Efavirenz: CNS disturbances including insomnia, dizziness, delusions, and nightmares.
Other	

A 32-year-old HIV-positive man presents to your AIDS clinic for a routine checkup. Although his CD4 count and viral load are within acceptable limits, you find that serum studies have demonstrated markedly elevated cholesterol and triglyceride levels. Upon physical examination, you find that the patient has truncal obesity and a buffalo hump, which he reports has developed only since beginning his drug regimen several months ago. Although the patient feels fine, he is concerned about his appearance and asks what is happening. You report that this altered body fat distribution, as well as his hyperlipidemia, is a common side effect of one of his HIV medications.

Protease Inhibitors

Similar Drugs	Protease inhibitors include **saquinavir**, **ritonavir**, **indinavir**, **nelfinavir**, **lopinavir**, **atazanavir**, **fosamprenavir**, **tipranavir**, **darunavir**, and **amprenavir**.

Mechanism of Action	The protease inhibitors act to **inhibit the HIV protease enzyme**, which is responsible for cleaving precursor proteins into mature proteins that are involved in forming the core of the viral particle. If the protease enzyme is inhibited, the **virus is unable to replicate**.
Clinical Uses	Protease inhibitors are used in the **treatment of HIV infection**.
Side Effects	All protease inhibitors have been associated with **altered distribution of body fat** (often formation of a buffalo hump or increased truncal obesity), insulin resistance, and **hyperlipidemia**. Other side effects include GI discomfort and paresthesias (associated with ritonavir, nelfinavir, and amprenavir), and elevated bilirubin levels and kidney stones (both associated with indinavir).
Other	**Ritonavir** has been shown to **inhibit cytochrome P-450**, thus leading to increased serum levels of certain drugs (e.g., other protease inhibitors, ketoconazole, rifampin, erythromycin, some anti-arrhythmic agents, some benzodiazepines, and some CNS drugs such as clozapine, fluoxetine, and haloperidol). Ritonavir is often used in combination with other anti-retroviral therapy since its effect on cytochrome P-450 can be therapeutically exploited to maximize the half-life of other anti-retroviral agents.

A 28-year-old woman, who was diagnosed with HIV 7 years ago, presents to your infectious disease clinic for follow-up. While she was able to maintain a stable CD4 count and avoid opportunistic infections previously, her lab results today demonstrate both a falling CD4 count as well as an increase in her viral load compared to prior visits. The patient insists that she has been compliant with her medications. After discussing options with the patient, you both agree to try a different class of medication that is sometimes used in conjunction with two nucleoside reverse transcriptase inhibitors as an alternative triple therapy that works by incorporating viral DNA into the host cell genome.

Integrase Inhibitors

Similar Drugs	Integrase inhibitors include **raltegravir, elvitegravir,** and **dolutegravir**.
Mechanism of Action	The integrase inhibitors act to **reversibly inhibit HIV integrase**, which works to incorporate viral DNA (produced via reverse transcription) into the host cell genome. Without the integrase enzyme, HIV is unable to replicate.
Clinical Uses	Integrase inhibitors are primarily used in the **treatment of HIV infection**.
Side Effects	Integrase inhibitors are **generally well-tolerated**. Side effects include rash, diarrhea, and insomnia.
Other	**Entry inhibitors,** including maraviroc and enfuvirtide, work by preventing viral entrance into the host cell. **Maraviroc blocks the binding of the HIV gp120 protein** to the CCR5 co-receptor on the host cell, and **enfuvirtide** inhibits membrane fusion through **blocking the HIV gp41 protein**. Maraviroc carries the risk of **hepatotoxicity.**

A 35-year-old man comes to the urgent care clinic complaining of a painful lesion on his penis. Upon further questioning, the patient admits to having unprotected sexual intercourse with several different partners over the past several months. Physical examination reveals a vesicular lesion on the glans of the penis. You explain to the patient that he has contracted a viral sexually transmitted disease and you prescribe a medication to treat his condition and to suppress future outbreaks of this infection.

Acyclovir

Similar Drugs	Valacyclovir; penciclovir; famciclovir.
Mechanism	Acyclovir is phosphorylated by **viral *thymidine kinase*** into an

of Action	**analogue of dGTP**. After conversion, the drug acts to **inhibit DNA synthesis** through incorporation into the growing viral DNA strand, thereby leading to chain termination.
Clinical Uses	Acyclovir is used to treat **genital herpes**, **herpes meningitis and encephalitis**, acute VZV infection, and oral hairy leukoplakia (associated with EBV infection). Because acyclovir targets DNA replication, it is **inactive against latent herpes virus infections.**
Side Effects	**Nephrotoxicity** (may crystallize in urinary tract), **neurotoxicity** (tremor, delirium).
Other	Valacyclovir has better bioavailability than acyclovir. Resistance to acyclovir can occur if the virus lacks *thymidine kinase*.

A 46-year-old AIDS patient presents to the clinic complaining of progressive decreased visual acuity and loss of peripheral vision. He reports that his symptoms started initially in his left eye, but that the symptoms quickly spread to the right eye as well. Your ophthalmologic examination, combined with serum studies that demonstrate the presence of CMV, suggests that CMV retinitis is a likely diagnosis. You begin administration of an intravenous medication that acts to inhibit viral DNA polymerase after activation by a viral kinase.

Ganciclovir

Similar Drugs	Valganciclovir.
Mechanism of Action	Ganciclovir is an **analogue of guanosine**. After **phosphorylation by a viral kinase** into the nucleotide analogue, ganciclovir acts to preferentially **inhibit CMV *DNA polymerase***, thereby leading to the inhibition of DNA synthesis.
Clinical Uses	Ganciclovir is used to treat **CMV infections**, especially CMV retinitis (often seen in AIDS patients).

Side Effects	**Pancytopenia**; nephrotoxicity; seizures.
Other	**Foscarnet** is a pyrophosphate analogue that acts to **inhibit viral *DNA polymerase*** without requiring activation by a viral kinase. It is used as a second-line treatment of **CMV retinitis and other CMV infections** as well as in the treatment of **acyclovir-resistant HSV and VZV infections**. The major side effect is **nephrotoxicity**. **Cidofovir** is a phosphate nucleotide analogue of cytosine that **inhibits viral *DNA polymerase***. Similar to foscarnet, it also does not require activation with a viral kinase, and thus can be used against **acyclovir-resistant HSV**. It is also indicated for the treatment of **CMV retinitis.** It too carries a risk of **nephrotoxicity.**

A 68-year-old woman with a past medical history of COPD presents to the hospital in January with progressive dyspnea despite a recent increase in her home oxygen administration. She says that she has not received any vaccines in the last year. On physical exam, she has a fever of 102.4°F and her oxygen saturation is 85% on room air. Her breathing is somewhat labored and she is using accessory muscles of respiration. Diffuse crackles are heard during the lung exam. When antibody testing confirms the presence of influenza, you decide to give her an agent that inhibits *neuraminidase* and thereby prevents virus release from infected cells.

Oseltamivir

Similar Drugs	Zanamivir.
Mechanism of Action	Oseltamivir is a prodrug that is activated intracellularly to **inhibit the viral enzyme, *neuraminidase***. *Neuraminidase* acts to cleave the sialic acid moiety on glycosylated hemagglutinin, which subsequently allows budding viral particles to be released

	from the host cell. By inhibiting the action of *neuraminidase*, oseltamivir prevents intercellular viral spread.
Clinical Uses	Oseltamivir can be used for either **prophylaxis or treatment of influenza A and B infections**. It is especially recommended for those patients at risk for severe complications from influenza infections, such as young children, the elderly, patients with COPD, and immunosuppressed patients.
Side Effects	Headache, vomiting.
Other	

A 62-year-old man with no significant past medical history presents to your clinic in December, complaining of malaise, headache, congestion, and weakness that began about 24 hours ago. While interacting with your patient, he tells you that his grandson visited him several days ago, but, unfortunately, his grandson has since come down with the flu. The patient was unable to get a flu vaccine this year due to a vaccination shortage. Physical examination is significant for cervical lymphadenopathy and a fever of 101.7°F. You begin the patient on a course of medication that will reduce the duration of illness and you ask the patient to return to the clinic immediately if he experiences any slurred speech, dizziness, or problems with gait or coordination.

Amantadine

Similar Drugs	Rimantadine.
Mechanism of Action	Amantadine binds to the M2 surface protein proton channel on influenza A viral particles, thereby **blocking the uncoating of the viral RNA** within the host cells and thus inhibiting intracellular viral replication. Amantadine has also been shown to **stimulate the release of dopamine from neurons of the nigra striatum**.

Clinical Uses	Amantadine is used to **reduce the duration of influenza A symptoms** as well as for influenza A prophylaxis in elderly and immunocompromised patients. It is also used in the **treatment of Parkinson's disease**.
Side Effects	**CNS symptoms** (ataxia, slurred speech, dizziness); GI upset.
Other	

A 6-month-old previously healthy infant presents to the emergency room with a 3-day history of rhinitis, non-productive cough, tachypnea, and fever. On physical examination, his respiratory rate is 42 breaths/min and his oxygen saturation is 90% on room air. Further examination reveals subcostal retractions and coarse breath sounds bilaterally with wheezes. When laboratory studies reveal a positive RSV test, you begin treatment with a first-line agent and you admit the infant to the hospital.

Ribavirin

Similar Drugs	
Mechanism of Action	Ribavirin is a **guanosine analogue** that acts to inhibit guanine nucleotide synthesis and to **inhibit viral *RNA polymerase***, thereby resulting in the **inhibition of viral replication**.
Clinical Uses	Ribavirin is used to treat **RSV bronchiolitis** and other RSV infections, influenza A and B infections, and **chronic hepatitis C infection**.
Side Effects	Hemolytic anemia; elevated bilirubin levels; teratogenic compound.
Other	Ribavirin is contraindicated in pregnancy and in patients with renal insufficiency. **Entecavir** is a guanosine nucleoside analogue that acts to

preferentially inhibit hepatitis B *viral polymerase*. It is used to **treat hepatitis B infection**.

A 40-year-old man with a history of chronic hepatitis C arrives for his appointment at the hepatology clinic. He reports that he has been feeling more fatigued than usual. Laboratory studies demonstrate a detectable HCV viral load as well as elevated ALT and AST levels. The patient states that he has been taking his ribavirin as instructed. After confirming the patient's viral genotype, you decide to prescribe a medication that is often given as part of combination therapy with ribavirin for the treatment of chronic HCV, and that can allow patients to avoid medications with more severe side effect profiles.

Sofosbuvir

Similar Drugs	
Mechanism of Action	Sofosbuvir is an **HCV RNA-dependent RNA polymerase inhibitor**, thereby causing chain termination and **inhibition of viral replication**.
Clinical Uses	Sofosbuvir is used to **treat chronic HCV** for genotypes 1, 2, 3, and 4. It is often used in concert with ribavirin with or without pegylated interferon.
Side Effects	Fatigue; headache; insomnia; GI distress.
Other	**Simeprevir** is a **hepatitis C NS3/4A protease inhibitor**, which acts to prevent effective viral replication. It is used often as part of combination therapy with either interferon and ribavirin or sofosbuvir. Side effects include photosensitivity, headache, and fatigue. Simeprevir may also be used in combination with **ledipasvir**, which inhibits the **hepatitis C NS5 protein, thereby further blocking viral replication.** Side effects include headache and fatigue.

A 38-year-old man with advanced AIDS presents to the emergency department with a 6-day history of fever, hemoptysis, pleuritic chest pain, and difficulty breathing. On physical examination, he is in respiratory distress and a lung examination reveals bilateral rales. A CT scan of the chest demonstrates a multifocal pneumonia with a cavitary lesion containing a fungus ball. You immediately begin the patient on an anti-fungal agent, which acts by altering the permeability of the fungal cell membrane, to treat his severe lung infection.

Amphotericin B

Similar Drugs	
Mechanism of Action	Amphotericin B **binds to ergosterol**, a sterol found only in the fungal cell membrane, and **alters permeability of the fungal cell membrane**, eventually leading to cell death.
Clinical Uses	Amphotericin B is a broad-spectrum anti-fungal agent used to treat **systemic mycotic infections** caused by *Cryptococcus, Coccidioides, Aspergillus, Blastomyces, Candida, Histoplasma,* and *Mucor.*
Side Effects	Infusion-related reaction (fever, chills, muscle spasms, headache); **nephrotoxicity (**including renal tubular acidosis and renal insufficiency); **hypotension; anemia; arrhythmias** (potentially related to concurrent electrolyte abnormalities); abnormal LFTs.
Other	Amphotericin B must be given intrathecally when used to treat fungal meningitis since it **does not cross the blood-brain barrier**. Due to the extensive side effect profile of amphotericin B, it is sometimes given in a **liposomal formulations** to reduce side effects. **Nystatin** has a similar mode of action as amphotericin B, altering fungal cell membrane permeability, thereby leading to

cell death. It is more toxic than amphotericin B and thus is not used systemically. It is **used topically to treat oral and cutaneous candidiasis**.

A 32-year-old immigrant from southern Africa presents to the emergency room, complaining of progressive dyspnea and fever. He is currently being treated for tuberculosis. He was previously doing well; however, he admits that he has forgotten to take several doses of his antibiotic regimen. Physical examination reveals a cachectic gentleman with labored breathing and rales heard on auscultation. Imaging demonstrates multifocal lesions in both lobes. He is admitted to the intensive care unit. Bronchoalveolar lavage demonstrates *Aspergillus*. You decide to start treating the patient for invasive aspergillosis with voriconazole as well as an agent that inhibits the formation of a component of the fungal cell wall.

Micafungin

Similar Drugs	Other **echinocandins** include caspofungin and anidulafungin.
Mechanism of Action	Micafungin competitively **inhibits the *beta-1,3-D-glucan synthase* enzyme**. This enzyme is required for production of beta-glucan, an essential component of the fungal cell wall. Depletion of beta-glucan leads to cell lysis through osmotic forces.
Clinical Uses	Used for the treatment of **invasive candidiasis or aspergillosis**.
Side Effects	Hepatotoxicity; infusion-related allergic reactions; GI upset.
Other	Note that micafungin is typically tolerated better than other systemic antifungal agents.

A 52-year-old lymphoma patient has been undergoing several rounds of chemotherapy over the course of the last several weeks. He is admitted to your service due to signs and symptoms consistent with meningitis. Cerebrospinal fluid cultures grow out *Cryptococcus* and you start him on amphotericin B. His condition continues to deteriorate and you are concerned that the intrathecal infusion of amphotericin B may not be enough to counteract the fungal meningitis. You decide to add a second anti-fungal agent that is commonly used in combination with amphotericin B to combat fungal meningitis.

Flucytosine

Similar Drugs	
Mechanism of Action	Within the fungal cell, flucytosine is **converted into nucleotide analogues** (5-FdUMP and FUTP), which then acts to **inhibit *thymidylate synthetase***, thereby **inhibiting fungal DNA and RNA synthesis**. Note that its mechanism of action is **analogous to the chemotherapeutic agent, 5-fluorouracil**, which inhibits the same enzyme.
Clinical Uses	Flucytosine is **used in combination** with other anti-fungal agents (often amphotericin B) for **treatment of systemic mycotic infections and fungal meningitis** caused by *Cryptococcus* and *Candida* species.
Side Effects	Bone marrow suppression; hepatotoxicity.
Other	

A 43-year-old diabetic woman presents to your clinic complaining of a white, itchy vaginal discharge. On physical examination, you observe a cottage cheese-like discharge in the vaginal vault. You believe that the patient's diabetes has predisposed the patient to this infection, and you suggest that the patient obtain an anti-fungal vaginal suppository to cure the infection.

Ketoconazole

Similar Drugs	Miconazole; clotrimazole.
Mechanism of Action	Ketoconazole acts to **inhibit the formation of ergosterol**, an essential component of the fungal cell membrane, **by inhibiting fungal cytochrome P-450 enzymes**. Ketoconazole also inhibits mammalian cytochrome P-450 enzymes, thereby **disrupting gonadal and adrenal steroid synthesis**.
Clinical Uses	Ketoconazole is used as a **broad-spectrum anti-fungal agent** in the treatment of *Blastomycosis, Coccidioides*, *Histoplasmosis, Aspergillus*, *Mucor,* and *Candida* infections. It is also used to treat patients with **Cushing syndrome** and prostate cancer.
Side Effects	Hormone synthesis inhibition (which leads to decreased libido, **gynecomastia**, and menstrual irregularities—this is especially seen in **ketoconazole)**; mild GI upset; abnormal liver enzymes.
Other	Ketoconazole **inhibits cytochrome P-450**, thereby leading to increased serum levels of several drugs (e.g., cyclosporine, warfarin, phenytoin, histamine antagonists). **Miconazole** and **clotrimazole** possess the same mechanism of action as ketoconazole. Since they have high levels of toxicity, they are only used topically to **treat cutaneous fungal infections** (e.g., vulvovaginal candidiasis, tinea pedis, and tinea cruris).

A 43-year-old woman with AIDS presents to the emergency room complaining of fever and chills. Her vital signs upon presentation reveal a temperature of 103°F and a blood pressure of 88/66 mm Hg. Physical examination is significant for the presence of creamy plaques on her tongue and upper palate. You draw blood cultures, which eventually reveal the presence of *Candida albicans*. You immediately begin the proper anti-microbial treatment with a drug that inhibits both fungal and mammalian cytochrome P-450 enzymes, but does not have much effect on gonadal and adrenal steroid synthesis.

Fluconazole

Similar Drugs	Itraconazole; voriconazole.
Mechanism of Action	Fluconazole acts to **inhibit the formation of ergosterol,** an essential component of the fungal cell membrane, by **inhibiting fungal cytochrome P-450 enzymes**. Fluconazole also inhibits mammalian cytochrome P-450 enzymes similar to ketoconazole, but its effects on gonadal and adrenal steroid synthesis are minimal.
Clinical Uses	Fluconazole is used to treat systemic fungal infections (especially **cryptococcal meningitis** and **sepsis from *Candida***). It is also used to treat blastomycosis, coccidiomycosis, and histoplasmosis.
Side Effects	Mild GI upset; abnormal liver enzymes; fevers and chills.
Other	Fluconazole **inhibits cytochrome P-450**, thereby leading to increased serum levels of several drugs (e.g., cyclosporine, warfarin, phenytoin, histamine antagonists).

A 6-year-old girl is brought to the pediatric clinic by her mother, who states that the child has been experiencing hair loss over the last week. The child has no systemic symptoms. On physical examination, you find several ring-shaped lesions with raised papules along its rim and notable alopecia near the lesions. There is no sign of inflammation at the lesions and the child denies pruritus. You believe that the child is suffering from a dermatophytic infection and you begin the patient on oral treatment with a medication that interferes with microtubule function. You also suggest that the mother wash all sheets and clothing and disinfect combs and brushes to prevent reinfection with the offending organism in the future.

Griseofulvin

Similar Drugs	
Mechanism of Action	Griseofulvin **interferes with microtubule function** in fungal cells in keratin-rich tissues (e.g., skin, nails, and hair), thereby inhibiting mitosis and fungal cell replication.
Clinical Uses	Griseofulvin is **an oral anti-fungal agent** used in the treatment of **topical dermatophytic infections** caused by *Epidermophyton*, *Microsporum*, and *Trichophyton*.
Side Effects	Headaches; confusion; GI upset; allergic reaction; hepatitis.
Other	**Terbinafine** acts to inhibit *squalene epoxidase*, a fungal enzyme involved in ergosterol synthesis. It is also used to treat **topical dermatophytic infections** (e.g., onychomycosis).

A 32-year-old male physician is planning to participate in a medical mission to sub-Saharan Africa. In addition to a hepatitis vaccine, he wishes to take prophylactic medications for other serious illnesses that he may encounter. You prescribe a single medication that will serve as chemoprophylaxis for malaria. When asked what side effects he may encounter, you explain that the medication may cause pruritus, GI distress, and blurry vision, and you advise him to contact you or a nearby clinic if any of these side effects occur.

Chloroquine

Similar Drugs	Other anti-malarial drugs include **mefloquine** and **quinine**.
Mechanism of Action	**Chloroquine:** Concentrates in parasite food vacuoles and prevents heme metabolism, thereby causing toxicity and cell death due to the buildup of soluble heme. **Quinine** and **mefloquine:** Mechanisms of action are unknown.
Clinical	**Chloroquine: Treatment of *P. falciparum* malaria;**

Uses	**chemoprophylaxis for malaria**; treatment of erythrocytic form of *P. vivax and Plasmodium ovale*. **Quinine: Treatment** of **drug-resistant *P*. *falciparum* malaria**; also used to treat *Babesia microti* infection. **Mefloquine: Treatment** of **drug-resistant *P*. *falciparum* malaria**; also used for chemoprophylaxis for *P*. *falciparum* malaria.
Side Effects	**Chloroquine:** GI upset; pruritus; visual disturbances; ECG changes. **Quinine: Cinchonism** (tinnitus, headache, dizziness, nausea); Coombs positive hemolytic anemia; fetal toxicity. **Mefloquine:** GI upset; **mental status changes**; cardiac abnormalities.
Other	**Pyrimethamine** inhibits *dihydrofolate reductase*, thereby inhibiting folic acid synthesis and interfering with DNA and RNA synthesis. It is commonly used in the **treatment and prophylaxis of *P*. *falciparum* as well as in the treatment of *Toxoplasma gondii*** (when given in combination with sulfadiazine). Significant side effects include bone marrow suppression.

A 36-year-old man presents with a 10-day history of episodic chills and fever. He states that the fever bouts will occur every 2 to 3 days and last for several hours at a time. His history is significant for malaria, which he contracted during a trip to Southeast Asia 2 months ago. His malaria was believed to be successfully treated with a full course of chloroquine and mefloquine. On physical examination, the patient looks pale with marked hepatomegaly and splenomegaly. You believe that the patient has dormant liver malaria and you prescribe a medication that will eradicate this infection.

Primaquine

Similar

Drugs	
Mechanism of Action	While the mechanism of action of primaquine is not completely understood, researchers have speculated that metabolites of primaquine act as oxidants, which cause parasitic and host cell damage and death.
Clinical Uses	Primaquine is used to **treat the hepatic forms of *P. vivax* and *P. ovale* malaria**.
Side Effects	Hemolytic anemia in G6PD patients; abdominal pain.
Other	Primaquine is contraindicated in pregnancy, since it may cause a hemolytic anemia in the fetus.

A 46-year-old man with AIDS presents to your clinic for a follow-up appointment. His last CD4 count was 150. Although you have advised him that he ought to take antibiotic prophylaxis for *P. carinii* pneumonia, he has refused for the past year, stating that he cannot tolerate any medications used for *P. carinii* pneumonia prophylaxis, including TMP-SMX and dapsone, due to violent allergic reactions to both medications. You suggest that he try an alternative medication to protect him against opportunistic pneumonias that is believed to act by inhibiting parasitic RNA synthesis.

Other Anti-Protozoan Agents

Pentamidine	*Mechanism*: Unknown, although it is believed to inhibit parasitic RNA synthesis. *Clinical use*: **Alternative treatment of *T. brucei* infection** (African trypanosomiasis) and leishmaniasis; alternative treatment and **prophylaxis for *P. carinii* pneumonia**. *Side effects*: Nephrotoxicity; leukopenia; hypotension.
Nifurtimox	*Mechanism*: Breakdown of the drug generates oxygen radicals, which damage the parasite. *Clinical use*: Treatment of ***T. cruzi* infections** (Chagas

	disease). *Side effects*: Neuropathy; seizures.
Suramin	*Mechanism*: It is believed to inhibit parasitic enzymes involved in energy metabolism. *Clinical use*: Treatment of **early *T. brucei* infections** (i.e., before CNS involvement); also used to treat *Onchocerca volvulus* infections. *Side effects*: Neurologic disturbances; renal abnormalities.
Melarsoprol	*Mechanism*: Unknown, although it is believed to inhibit multiple parasitic enzymes. *Clinical use*: Treatment of **late *T. brucei* infections** (i.e., after CNS involvement). *Side effects*: Encephalopathy; hypersensitivity reactions; myocarditis.
Sodium Stibogluconate	*Mechanism*: Unknown, although it is believed to inhibit parasitic glycolysis. *Clinical use*: Treatment of **leishmaniasis**. *Side effects*: Myopathy; cardiotoxicity.

A 19-year-old college student presents to the university health services clinic complaining of an intensely itchy rash over the last 5 days. She states that her two roommates are suffering from similar symptoms. On physical examination, you observe a pimple-like rash that is most prominent between the fingers, on the wrists, and on the waist. You perform a skin scraping to confirm your diagnosis. In the meantime, you prescribe the patient a topical lotion, which acts to block sodium flow in parasitic neuronal cells, and you recommend that she and her roommates wash all bedding, towels, and clothing in their dorm room in hot water.

Permethrin

Similar

Drugs

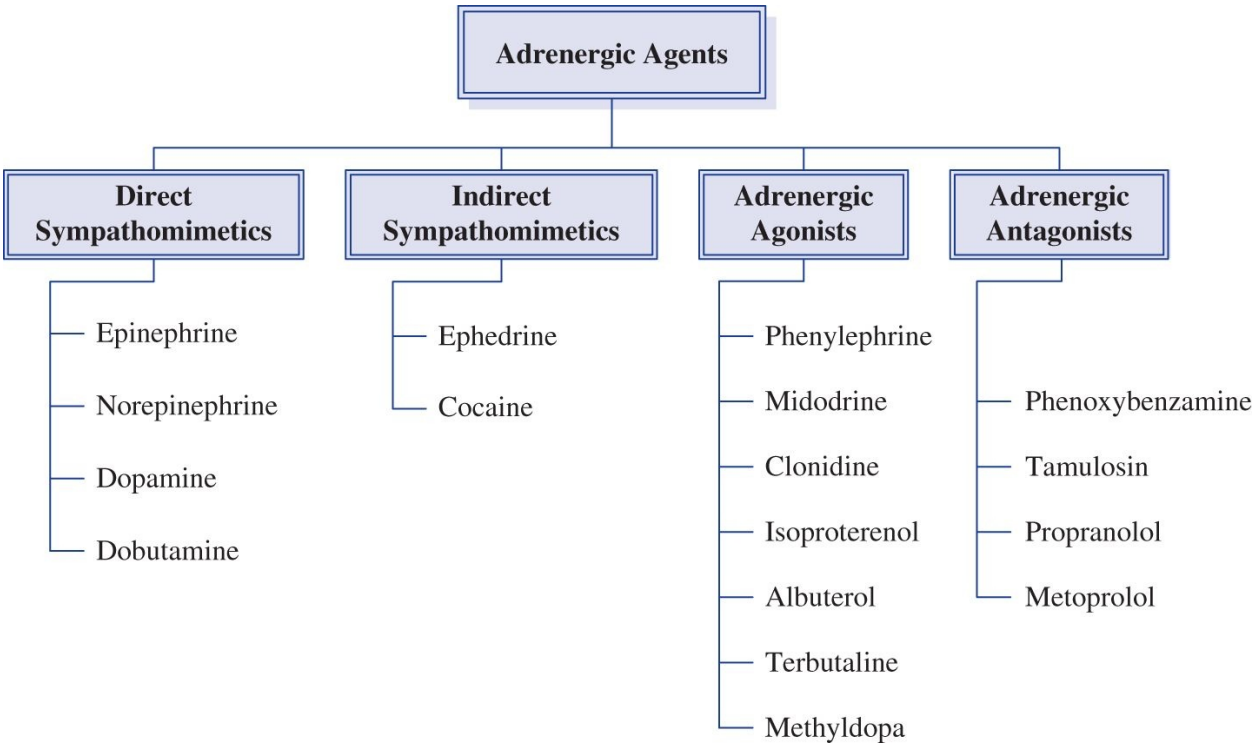
Mechanism of Action	Permethrin acts to **block the movement of sodium ions through neurons** in parasites, ultimately leading to parasitic paralysis and death.
Clinical Uses	Permethrin is used topically for the treatment of **head lice** (*Pediculus; Pthirus*) as well as **scabies** (*Sarcoptes scabiei*).
Side Effects	Pruritus; skin irritation; erythema.
Other	**Malathion** is an *acetylcholinesterase* inhibitor that can be used topically to treat head lice. Because it is an **organophosphate**, it is not administered systemically. Topical **lindane** is used also for the treatment of lice and scabies. It acts by blocking GABA chloride channels on the neuron, thereby leading to neuronal hyperactivity and resulting cell death. Due to the risk of neurologic and hepatic sequelae, as well as a risk of aplastic anemia, lindane is considered a second-line treatment.

While on a medical mission in central Africa, you come across a group of villagers camped by a river, all of whom are suffering from the same ailment. Several young teenagers report larvae appearing near sites where they were bitten by black flies. Some of these children have infections in the areas of their eyes and they tell you that they feel extremely itchy. You note that all of these children exhibit disfiguring skin nodules over the surfaces of their body. Fortunately, you have a large supply of a drug on hand that can cure this nematode infection, and you immediately give the medication to these children in hopes of preventing blindness.

Anti-Helminthic Agents

Ivermectin	*Mechanism*: Activates GABA receptors, thereby leading to worm paralysis and death. *Clinical use*: Treatment of **river blindness**

	(*Onchocerca volvulus*) and strongyloidiasis. *Side effects*: **Mazotti reaction** (fever, rash, hypotension, arthralgias, vertigo).
Mebendazole, albendazole, and thiabendazole	*Mechanism*: Inhibits microtubule synthesis and function. *Clinical use*: **Mebendazole** and **albendazole** are used to **treat whipworm** (*Trichuris*), **hookworm** (*Necator/Ancylostoma*), **roundworm** (*Ascaris*), and **pinworm** (*Enterobius*). **Albendazole** is also used to **treat strongyloidiasis**, **neurocysticercosis**, hydatid disease, and cutaneous larva migrans. **Thiabendazole** is used to **treat strongyloidiasis**, cutaneous larva migrans, and trichinosis. *Side effects*: All cause GI upset and allergic reactions.
Pyrantel pamoate	*Mechanism*: Activates parasitic nicotinic receptors, thereby causing worm paralysis. *Clinical use*: **Treatment of hookworm**, **roundworm**, and **pinworm infections**. *Side effects*: GI upset.
Praziquantel	*Mechanism*: Increases cell Ca^{2+} uptake, thereby causing parasite contraction and paralysis. *Clinical use*: **Treatment of schistosomiasis, neurocysticercosis,** hydatid disease, and infections caused by *Taenia* species, *D. latum*, and *Clonorchis* species. *Side effects*: GI upset; elevated LFTs.
Diethylcarbamazine	*Mechanism*: Exact mechanism is not known, but diethylcarbamazine is believed to inhibit arachidonic acid metabolism, thereby increasing phagocytosis of the microbe. *Clinical use*: Treatment of lymphatic **filariasis** (due to *Wuchereria bancrofti* or *Brugia*) or subcutaneous filariasis (due to *Loa loa* or *Onchocerca volvulus*). *Side effects*: **Mazotti reaction** (fever, rash, hypotension, arthralgias, vertigo).



ADRENERGIC RECEPTORS

Receptor Type	Mechanism of Activation	Location	Action	Preferred Substrate
α_1	PLC activated → increased **IP_3** → and **DAG** → increased intracellular Ca^{2+}	**Vascular smooth muscle**	Promotes **vasoconstriction**	Epi ≥ NE >> Isoproterenol
		Prostrate	Induces contraction	

		Heart	Increase contractility	
		Pupillary dilator muscle	Induces contraction (leads to pupil dilation)	
α_2	AC inhibited → **decreased cAMP**	**Nerve terminals** of adrenergic and cholinergic neurons	**Inhibit release of neurotransmitters**	Epi ≥ NE >> Isoproterenol
		Platelets	Increase aggregation	
β_1	AC activated → **increased cAMP**	**Heart**	**Increase rate and contractility**	Isoproterenol > Epi > NE
β_2	AC activated → **increased cAMP**	**Smooth muscle of respiratory**, **vascular**, **and uterine tissue**	Promotes relaxation, leading to **bronchodilation**, **vasodilation,** and uterine relaxation	Isoproterenol > Epi > NE
		Liver	Increases glycogenolysis	
β_3	AC activated → **increased cAMP**	Adipose tissue	**Enhances lipolysis** and suppresses leptin	Isoproterenol > Epi > NE
		Smooth muscle of gallbladder and urinary bladder	Promotes smooth muscle relaxation, leading to prevention of urination	
D_1	AC activated → **increased cAMP**	Smooth muscle of splanchnic and renal vessels	Vasodilation of renal blood vessels	Dopamine
D_2	AC inhibited → **decreased cAMP**	Nerve terminals of CNS neurons	Regulates neurotransmitter release	Dopamine

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A 24-year-old woman is brought to the emergency room unconscious. According to the emergency medical technician report, she had been eating at a Thai restaurant with a group of friends, when she suddenly began to complain of trouble breathing and then quickly lost consciousness. An ambulance was called and the patient was intubated in the field. Physical examination reveals the presence of hives and poor air movement. You also find a medic alert bracelet on the woman, which states that she is allergic to peanuts. You diagnose her with

anaphylaxis and immediately administer a low dose of a specific medication that will hopefully relieve her bronchospasm.

Epinephrine

Similar Drugs	
Mechanism of Action	Epinephrine acts as an **α-agonist when the drug is given at high doses** and as a **β-agonist when the drug is given at low doses**. When acting as an α_1-agonist, epinephrine causes **vasoconstriction,** thereby leading to increased systolic and diastolic blood pressure. When acting as a β_1-agonist, epinephrine **increases heart rate and contractility**, thereby increasing cardiac output and systolic blood pressure. When acting as a β_2-agonist, epinephrine relaxes vascular and respiratory smooth muscle, thereby producing **bronchodilation** and a mild decrease in diastolic blood pressure.
Clinical Uses	Treatment of **cardiac arrest and severe hypotension**. Treatment of **bronchospasm** in asthma and **anaphylaxis**. Treatment of wide-angle glaucoma when administered as an ophthalmic solution.
Side Effects	Hypertension; cardiac arrhythmias; myocardial infarction; pulmonary edema; headache, anxiety.
Other	Low-dose subcutaneous epinephrine injections can also be given when local anesthetics are administered as epinephrine produces localized vasoconstriction, thus decreasing the ability of the local anesthetic to become absorbed into the systemic circulation and thereby increasing the concentration of the local anesthetic at the desired site.

A 19-year-old man is admitted to the hospital for the treatment of appendicitis.

In the operating room, it is discovered that his appendix has burst. After surgery, he develops a high fever and becomes hypotensive. Blood cultures demonstrate the presence of gram-negative rods and he is diagnosed with septic shock. In an initial attempt to treat his severe hypotension, you administer a pressor drug, which will act to increase his systemic vascular resistance, in addition to broad-spectrum intravenous antibiotics.

Norepinephrine

Similar Drugs	
Mechanism of Action	Norepinephrine is a **potent α_1-, α_2-, and β_1-receptor agonist**. As an α-agonist, norepinephrine causes **vasoconstriction**, thereby leading to increased systolic and diastolic blood pressure. When acting as a β_1-agonist, norepinephrine acts to **increase contractility**. Norepinephrine also increases heart rate through β_1-agonism; however, the simultaneous rise in blood pressure results in a concurrent reflex bradycardia, so no significant change in heart rate is actually observed.
Clinical Uses	Used as a pressor in the emergency **treatment of severe hypotension and shock**.
Side Effects	Angina; myocardial infarction; cardiac arrhythmias; decrease in renal blood flow.
Other	

A 42-year-old man is admitted to the intensive care unit after having suffered a severe motor vehicle accident. He is extremely ill and he has recurrent episodes of hypotension. You, as the intensive care specialist, realize that he needs a medication that can be used to treat his hypotension during his stay in the intensive care unit. You decide to begin him on a continuous infusion of a medication that will act to increase his cardiac output without decreasing blood flow to vital organs, such as his kidneys.

Dopamine

Similar Drugs	
Mechanism of Action	Dopamine acts as an agonist at **α_1-receptors when given in high doses, and as an agonist at β- and D_1-receptors when given at lower doses**. When acting as an α-agonist, dopamine causes **vasoconstriction**, thereby leading to increased systolic and diastolic blood pressure. When given at lower doses, dopamine **increases heart rate and contractility**, thereby increasing cardiac output through stimulation of β_1-receptors. At even lower doses, dopamine also increases renal and splanchnic blood flow through stimulation of D_1-receptors, thereby **promoting renal perfusion**.
Clinical Uses	Used as a pressor in the emergency **treatment of severe hypotension and shock**.
Side Effects	Cardiac arrhythmias; angina; hypertension; nausea.
Other	

A 78-year-old woman presents to the emergency room with difficulty breathing. She has a prior history of congestive heart failure and a depressed ejection fraction. Physical examination reveals a blood pressure of 70/40 mm Hg, diffuse crackles in bilateral lung fields, and a significantly elevated jugular venous pressure. Her skin is cool to the touch. You immediately recognize that this patient is in cardiogenic shock and initiate treatment with diuretics as well as a vasopressor agent that will act to improve the contractility of her heart by acting primarily at the β_1-receptors.

Dobutamine

Similar Drugs	
Mechanism of Action	Dobutamine acts as a direct **agonist at β_1-receptors**. When administered, dobutamine acts to **increase heart rate and contractility**, thereby increasing cardiac output. Dobutamine does have **weak α_1- and β_2-effects**; however, the β-effects predominate resulting in mild vasodilation as opposed to vasoconstriction.
Clinical Uses	Used as a pressor in the **treatment of cardiogenic shock**. Also can be used as a pharmacologic agent during cardiac stress testing.
Side Effects	Cardiac arrhythmias; angina; hypotension; headache.
Other	

A 26-year-old man presents to your clinic complaining of recurrent headaches over the past month. He denies any neurologic symptoms other than mild insomnia and he has no past medical history. Upon taking a social history, you discover that he is a semiprofessional athlete. Physical examination is significant only for a blood pressure of 170/90 mm Hg. You are slightly puzzled until further questioning reveals that the patient has been taking a specific natural supplement to improve his athletic performance. You explain to the patient that his headaches are likely caused by his elevated blood pressure, which is likely due to the supplement that he is taking, and you advise him to discontinue use of the supplement.

Ephedrine

Similar Drugs	

Mechanism of Action	Ephedrine acts by **stimulating the release of norepinephrine** and epinephrine from neurons. It has also been shown to directly stimulate both α- and β-receptors. The overall net effect of ephedrine is to **increase systolic and diastolic blood pressure** (through α_1- and β_1-stimulation), to increase cardiac output (through β_1-stimulation), and to induce **bronchodilation** (through β_2-stimulation). Ephedrine has also been shown to **stimulate the CNS**, causing insomnia, decreased appetite, and improved athletic performance.
Clinical Uses	Ephedrine and its derivative, **pseudoephedrine**, are used as a **nasal decongestant** and in the treatment of stress incontinence in women. Derivatives of ephedrine have also been found in supplements that are marketed for weight-loss and athletic enhancement.
Side Effects	Hypertension; tremor; anxiety; cardiac arrhythmia.
Other	**Amphetamine** is a drug that enters the CNS and **stimulates the release of norepinephrine**, **epinephrine**, **and dopamine from neurons**, thereby leading to a hyper-aroused state. Symptoms of amphetamine use include insomnia and decreased appetite. Amphetamine can be a drug of abuse, and overdoses can lead to psychosis, cardiac arrhythmias, seizures, and death. **Methylphenidate** is a derivative of amphetamine that is used to treat narcolepsy and attention deficit and hyperactivity disorders in children.

A 25-year-old man is brought to the emergency room complaining of severe, substernal chest pain. Upon further history, he admits that he had been using an illegal substance with some of his friends immediately before the onset of chest pain. The patient is hypertensive on examination with a blood pressure of 170/80 mm Hg. An electrocardiogram demonstrates ST-segment elevations in the precordial leads. As you call a cardiologist and begin to treat the patient, you inform the patient that his current cardiac condition is likely directly related to

his ingestion of the illegal drug.

Cocaine

Similar Drugs	
Mechanism of Action	Cocaine **blocks the Na^+/K^+-ATPase that is responsible for the reuptake of norepinephrine**, **serotonin**, **and dopamine** into neural synaptic terminals, thereby acting to potentiate the effects of these neurotransmitters. This results in increased dopamine concentrations in the brain's limbic system, which is responsible for the euphoria associated with cocaine use. The resulting increase in norepinephrine concentrations can lead to vasoconstriction and cause cardiac ischemia. Cocaine has also been shown to **block voltage-gated Na^+ channels**, thereby giving the drug some anesthetic properties.
Clinical Uses	Can be used as a local anesthetic for ear, nose, and throat surgery.
Side Effects	**Hypertension**; paranoia; **drug of abuse**; seizures; **cardiac ischemia** and infarction; **cardiac arrhythmias**.
Other	**Guanethidine** acts to **inhibit norepinephrine release** from sympathetic neurons as well as to cause a gradual depletion of norepinephrine stores in nerve cells. It has been **used to treat hypertension in the past**, but it is rarely used now due to a significant side effect profile (e.g., orthostatic hypotension that may lead to shock).

A 37-year-old woman presents to your ophthalmology office for a routine eye examination. In preparation for her retinal examination, you decide to dilate the patient's pupils with a medicated ophthalmic solution. The patient is curious and she asks you how this ophthalmic solution works. You explain to her that the medication will act to constrict her pupillary dilator muscle, thereby producing

pupillary dilation. You also tell her that this is the same compound that is used to treat nasal congestion as well as severe hypotension and shock.

Phenylephrine

Similar Drugs	
Mechanism of Action	Phenylephrine is an **α_1-agonist**, thereby leading to **systemic vasoconstriction** and pupil dilation. When applied topically to the nasal mucosa or in very low systemic doses, it induces nasal vasoconstriction, thereby leading to a decrease in mucosal secretions.
Clinical Uses	Used to treat **severe hypotension and shock**. Used to **treat nasal congestion**. Used as an ophthalmic solution to **produce mydriasis for retinal examination**.
Side Effects	Cardiac arrhythmias (reflex bradycardia); headache.
Other	**Oxymetazoline** and **terahydrolozine** are also α_1-agonists and are used in nasal decongestant sprays.

A 72-year-old male with diabetes and Parkinson's disease presents to your primary clinic for follow-up. Over the last several months, he has been suffering from persistent orthostatic hypotension. He states that he feels consistently light-headed whenever he rises from sitting to standing despite remaining well-hydrated and using compression stocking. In the clinic today, his blood pressure while seated is 90/50 mm Hg, but drops to 70/40 mm Hg with standing. You explain to him that his orthostatic hypotension is likely related to autonomic dysfunction caused by both his diabetes and his Parkinson's disease and you decide to prescribe him a low dose of a medication to treat his orthostatic hypotension that acts by stimulating the α_1-receptors on the blood vessel wall.

Midodrine

Similar Drugs	
Mechanism of Action	Midodrine is an **α_1-agonist**, thereby leading to **systemic vasoconstriction**. It does not act on the β-receptors of the heart nor does it cross the blood-brain barrier, so its effects on the heart and CNS are minimal.
Clinical Uses	Used to treat **orthostatic hypotension**, which is significantly impairing the patient. It is often used in patients with advanced hepatic disease.
Side Effects	**Supine hypertension**; headache; urinary retention.
Other	

A 59-year-old woman presents to your office for a follow-up visit regarding her hypertension. She was diagnosed with hypertension 1 year ago, which she has been controlling with a regimen of three medications. Her past medical history is also significant for chronic renal insufficiency. You check her blood pressure and you find that it is 186/100 mm Hg, as compared to 136/82 mm Hg, which was the reading at her last office visit only 2 weeks ago. Upon questioning the patient further, she admits that she lost the prescription for one of her hypertensive medications and that she hasn't been taking this medication for the last 2 days. You explain to her that stopping this medication suddenly can result in rebound hypertension and you write her another prescription for this medication.

Clonidine

Similar Drugs	
Mechanism	Clonidine is an **α_2-agonist** that acts primarily at α_2-receptors in

of Action	the vasomotor centers of the medulla. By stimulating these α_2-receptors, the release of norepinephrine and other neurotransmitters is reduced, thereby leading to **decreased central adrenergic activity with a resulting decrease in vasoconstriction and a decrease in cardiac output and heart rate**.
Clinical Uses	Treatment of **hypertension**.
Side Effects	**Rebound hypertension** (if drug is withdrawn quickly); bradycardia; sedation.
Other	Since clonidine does not decrease renal blood flow, it is useful in hypertensive patients who are also suffering from renal disease. **Guanfacine** and **guanabenz** are also **α_2-agonists**, which act in the same mechanism as clonidine. These drugs have similar side effect profiles to clonidine; however, they are much less frequently used.

A 78-year-old woman presents to the emergency room unconscious. The emergency medical technicians report that she was eating at a restaurant with her daughter when she apparently grabbed her chest and promptly passed out. A rhythm strip demonstrates that the patient is in torsades de pointes. You immediately begin the appropriate ACLS protocol in the hopes of saving this woman's life. As you are directing the resuscitation of this patient, a medical student asks whether you will be employing the use of a certain drug that acts as a potent β_1- and β_2-receptor agonist. You explain to the medical student that the drug that she is speaking of is indeed a drug that can be used to treat torsades de pointes in conjunction with magnesium and overdrive pacing.

Isoproterenol

Similar Drugs	

Mechanism of Action	Isoproterenol is a potent **β_1- and β_2-receptor agonist**. It has very little effect on α-receptors. By stimulating β_1-receptors, isoproterenol acts to **increase heart rate and contractility**, thereby increasing cardiac output and slightly increasing systolic pressure. By stimulating β_2-receptors, isoproterenol acts to **produce peripheral vasodilation**, thereby leading to an overall decrease in mean arterial and diastolic pressure, and to produce **bronchodilation**.
Clinical Uses	Used to treat **torsades de pointes** in conjunction with magnesium. Occasionally used in the **treatment of cardiac arrest or complete heart block** or (rarely) to treat severe bronchospasm.
Side Effects	Cardiac tachyarrhythmias; anxiety; pulmonary edema.
Other	**Fenoldopam is a D_1-receptor agonist** that is used to produce splanchnic and renal vasodilation for the **treatment of severe hypertension**.

A 9-year-old girl presents to your pediatric clinic for her routine check-up. Her mother tells you that the child has been generally healthy; however, she does seem to become excessively winded when she plays soccer or any other sports. The patient agrees with her mother, telling you that she never feels like she can play as long as the other children because it becomes hard to breathe. The child denies having any trouble breathing when she is not exercising. Her lung examination is unremarkable. You tell the child and her mother that she may have exercise-induced asthma. You give the child an inhaled medication that will produce bronchodilation via the stimulation of β_2-receptors and you instruct her to use the inhaler prior to soccer practice.

Albuterol

Similar	Pirbuterol; bitolterol.

Drugs

Mechanism of Action	Albuterol is a **β_2-receptor agonist**. When inhaled, it mainly stimulates the β_2-receptors of the respiratory smooth muscle, thereby producing **bronchodilation**. **β_2-Receptor agonism** can also lead to **transcellular shifts of potassium into the cell**.
Clinical Uses	Treatment of **asthma**. Also used to **treat hyperkalemia** when given in high doses.
Side Effects	Tachycardia; tremor; anxiety. Note that side effects are minimal when albuterol is used in the inhaled form.
Other	**Salmeterol** is an analogue of albuterol. It is a **long-acting β_2-agonist** that is used as part of a therapeutic regimen to **prevent asthmatic and COPD attacks**. There has been some concern that use of salmeterol may increase the risk of asthma-related deaths if used alone and hence it is now recommended that salmeterol only be used in addition to another long-acting asthma medication (i.e., inhaled corticosteroids).

A 34-year-old woman, who is 34 weeks pregnant, presents to the labor and delivery department complaining of contractions. She is also exhibiting some wheezing consistent with her history of chronic asthma. After a full physical examination including fetal assessment, you decide to administer a medication that will relax the smooth muscles in both her uterus and her lungs, hopefully helping control both her uterine contractions and respiratory symptoms at the same time. While administering this medication, you admit the patient to a room with telemetry capabilities in order to monitor for tachycardias as well as her blood pressure response.

Terbutaline

Similar Drugs	Ritodrine.
Mechanism of Action	Terbutaline is a direct-acting **β_2-agonist** that relaxes smooth muscle in both the lungs (leading to bronchodilation) and in the uterus (reduces contractions).
Clinical Uses	Used to **delay preterm labor by reducing uterine contractions**, **but should only be used in cases where preterm labor needs to be delayed by 48 hours or less (i.e., if corticosteroids need to be administered to assist in fetal lung maturity)**. Can also be used to treat bronchospasm during status asthmaticus.
Side Effects	Dizziness; **tachycardia**; anxiety; chest pain; **tremor**
Other	**Ritodrine** is another **β_2-agonist** that is also used to **reduce uterine contractions during preterm labor**.

A 77-year-old man presents to your clinic as a new patient. His past medical history is significant only for hypertension and mild chronic renal insufficiency. He currently takes an anti-hypertensive regimen of medications prescribed by his last doctor. As you get to know the gentleman, he confides in you that he is not as steady on his feet as he once was and that he is now very afraid of falling and breaking his hip. After hearing his concerns, you decide to change one of the patient's blood pressure medications, since this medication, which acts by stimulating α_2-receptors, can cause patients to feel dizzy and thus make them more prone to fall.

Methyldopa

Similar Drugs	

Mechanism of Action	Methyldopa is an **α_2-agonist** that acts primarily at α_2-receptors in the vasomotor centers of the medulla. By stimulating these α_2-receptors, the release of norepinephrine and other neurotransmitters is reduced, thereby leading to **decreased central adrenergic activity** with a **resulting decrease in vasoconstriction** and a variable decrease in cardiac output.
Clinical Uses	Treatment of moderate **hypertension**.
Side Effects	Sedation; dizziness; positive Coombs test; **orthostatic hypotension**.
Other	Since methyldopa does not decrease renal blood flow, it is useful in hypertensive patients who are also suffering from renal disease. **Brimonidine** is an **α_2-adrenergic receptor agonist** that is used in the treatment of wide-angle glaucoma. It acts by decreasing production and increasing outflow of aqueous humor secretions. **Mirtazapine** blocks pre-synaptic α_2-adrenergic receptors as well as post-synaptic serotonin receptors. It is used to treat depression and other psychiatric conditions (see Mirtazapine card in Chapter 4).

A 33-year-old man presents to the emergency department complaining of heart palpitations and a severe headache. He tells you that he has had similar episodes of these symptoms in the past. Physical examination reveals a regular pulse of 132 beats/min and a blood pressure of 196/112 mm Hg. While administering appropriate treatment to lower his blood pressure, you begin to wonder if this patient might have an endocrinologic disorder. The patient is admitted to the hospital for further workup of his condition and you later find out that he was diagnosed as having a pheochromocytoma, located in the left adrenal gland. While he awaits surgical resection of his tumor, he is placed on an irreversible α-blocker to control his blood pressure.

Phenoxybenzamine

Similar Drugs	
Mechanism of Action	This drug is an **irreversible α-receptor antagonist,** with slightly more affinity for α_1- than α_2-receptors. By inhibiting α-receptor activation, vasoconstriction is decreased, thereby leading to a decrease in blood pressure.
Clinical Uses	Treatment of **pheochromocytoma** (usually given prior to surgical resection in order to prevent hypertensive crises, or can be used for chronic treatment of non-resectable pheochromocytomas).
Side Effects	Orthostatic hypotension; tachycardia; nasal congestion; inhibition of ejaculation.
Other	**Phentolamine** is a short-acting, **reversible α-receptor antagonist**. It can be used to **diagnose pheochromocytomas** (patients with pheochromocytomas will demonstrate a larger than expected decrease in blood pressure when given phentolamine). The side effect profile is similar to the side effects associated with phenoxybenzamine.

A 69-year-old man presents to your clinic for a routine office visit. He tells you that recently he has had difficulty starting and stopping urination and has also felt an increased urge to urinate. Physical examination is significant for a blood pressure of 166/98 mm Hg and a smooth, symmetrically enlarged prostate, consistent with benign prostatic hypertrophy. You tell the patient that you would like to start him on a medication that will treat both his hypertension and his prostate disorder.

Tamsulosin

Similar Drugs	Prazosin; doxazosin; tamsulosin; alfuzosin.

Mechanism of Action	Tamsulosin is a **selective α_1-antagonist**. By blocking α_1-receptors, prazosin can cause peripheral vascular smooth muscle relaxation, thereby leading to a **decrease in blood pressure**. This class of drugs can also **decrease prostatic and bladder neck contraction**, thereby resulting in the improvement of urinary flow through the prostate and out the urethra.
Clinical Uses	Treatment of **hypertension**. Treatment of **benign prostatic hypertrophy** (terazosin, doxazosin, tamsulosin).
Side Effects	"**First-dose**" **syncope** (first dose of prazosin can lead to severe orthostatic hypotension with resulting syncope); orthostatic hypotension; dizziness; nasal congestion.
Other	

A 46-year-old woman presents to the emergency room complaining of palpitations. Further history reveals that she has also had diarrhea, insomnia, increased irritability, and a weight loss of 10 lb over the last few weeks. Physical examination is significant for a thin, tremulous woman with a heart rate of 122 beats/min and a blood pressure of 150/90 mm Hg. You also note that she has lid lag on examination as well as an enlarged thyroid gland. You diagnose the patient with likely Graves disease and you send off thyroid function tests. In the meantime, you start a non-selective β-blocker to treat her tachycardia.

Propranolol

Similar Drugs	Nadolol; pindolol; timolol.
Mechanism of Action	**Propranolol is a β_1- and β_2-receptor antagonist (e.g., non-selective β blocker)**. By blocking the β_1-receptor, **heart rate and contractility are decreased**, thereby leading to decreased cardiac output and hence a decrease in mean arterial pressure. In

	response to decreased cardiac output, there is a small measure of reflex peripheral vasoconstriction, although the balance in change in blood pressure settles out on the side of **decreased blood pressure**. By blocking the β_2-receptor, respiratory smooth muscle constriction is increased, which results in **bronchoconstriction**.
Clinical Uses	Uses include treatment of cardiovascular disorders **(hypertension**, **angina)**, treatment of **tachycardia associated with hyperthyroidism**, treatment of chronic **migraines** (causes cerebral vasodilation, which likely decreases incidence of migraines), treatment of portal hypertension, treatment of essential tremor, and management of panic disorder (off-label).
Side Effects	**Bronchoconstriction**; arrhythmias; sexual dysfunction; **fasting hypoglycemia** (β_2-receptor blockade leads to decreased glycogenolysis, which may lead to hypoglycemia); hypotension.
Other	**Pindolol** is a weak β-receptor agonist, as well as a β-receptor antagonist that is used to treat patients who have both hypertension and bradycardia. **Timolol is a β_1- and β_2-receptor antagonist** that is used as an ophthalmic solution to decrease aqueous humor secretion by blocking **β-receptors** on the ciliary epithelium. It is used for the treatment of wide-angle glaucoma.

You are seeing a 53-year-old woman with a history of congestive heart failure for an in-patient cardiology consultation. The patient is admitted after an uneventful hip replacement but is having symptoms of pulmonary edema and hypertension likely related to an exacerbation of her known heart failure. She is currently on a standard regimen of ACE inhibitor and diuretics with modest improvement. You decide to add a medication that is both an α_1-receptor blocker as well as β-receptor and a proven adjunct to conventional treatment of congestive heart failure. You ask the nurse to monitor closely for dizziness, hypotension, and bradycardia upon its administration.

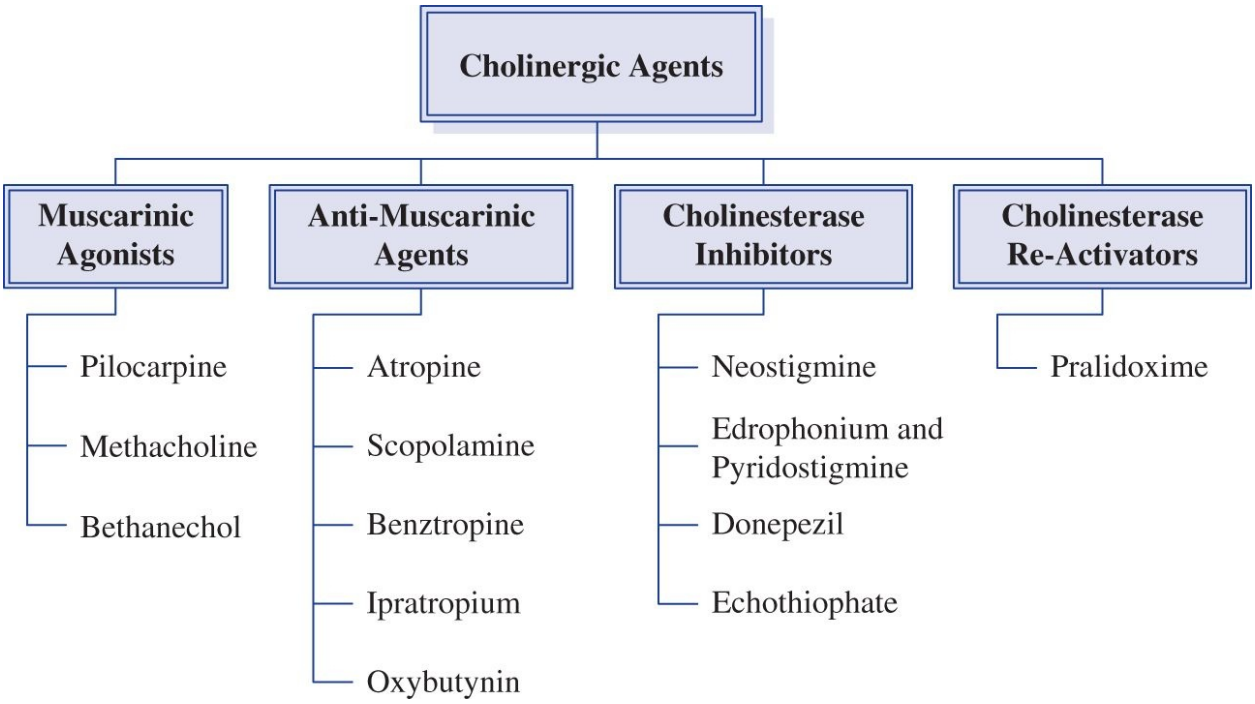
Carvedilol

Similar Drugs	Labetalol.
Mechanism of Action	**Carvedilol** is an **α_1-receptor blocker as well as β-receptor** (β_1 and β_2) **blocker**. By blocking the β_1-receptor, **heart rate and contractility are decreased**, thereby leading to decreased cardiac work. By blocking the β_2-receptor, respiratory smooth muscle constriction is increased, which results in **bronchoconstriction**. By blocking α_1-receptors, it induces vascular smooth muscle relaxation thereby lowering blood pressure.
Clinical Uses	Used to treat **hypertension**. **Carvedilol**, specifically, is also used in the **treatment of chronic congestive heart failure** in addition to ACE inhibitors and diuretics as it has been shown to be cardio-protective and provide a mortality benefit in patients with congestive heart failure and reduced systolic function.
Side Effects	Dizziness; hypotension; bradycardia.
Other	

A 68-year-old woman presents to your clinic for a routine visit. Her past medical history is significant for coronary artery disease, hypertension, and mild emphysema secondary to a 30-year history of heavy smoking. As you are reviewing her medication list with her, she tells you that a TV commercial said that she shouldn't take one of her cardiac medications if she has lung disease. You explain to her that the medication she is taking does not cause bronchospasm as severely as other related drugs because her medication has a more specific site of action. You reassure her that you will monitor her respiratory status closely while she is on this medication.

Metoprolol

Similar Drugs	Atenolol; esmolol; acebutolol; bisoprolol; betaxolol; nebivolol.
Mechanism of Action	Metoprolol is a **selective β_1-receptor antagonist**. By blocking the β_1-receptor, **heart rate and contractility are decreased**, thereby leading to decreased cardiac output. Please note that the selective antagonism is not complete, so some β_2-receptor antagonism is seen with metoprolol.
Clinical Uses	Used in the treatment of **hypertension**, **tachycardias**, and **coronary artery disease**, especially in patients with diabetes. Clinical trials have shown a survival benefit from use of metoprolol succinate in patients with mild to moderate heart failure after myocardial infarction. Used in the treatment of wide-angle glaucoma by reducing aqueous humor production (betaxolol).
Side Effects	Mild bronchoconstriction (avoid in asthmatics if possible); bradycardia; impotence; hypotension.
Other	**Esmolol** is a **short-acting β_1-receptor antagonist** that is used to treat critically ill patients with arrhythmias, hypertension, and myocardial ischemia. **Acebutolol is a β_1-receptor antagonist** that has **weak β-agonist properties** as well. It is used to treat patients who have both hypertension and bradycardia. **Nebivolol** is a **β_1-receptor antagonist** that also acts to **promote nitric oxide release,** resulting in further vasodilation. It is used to treat hypertension.



MUSCARINIC AND NICOTINIC RECEPTORS

Receptor Type	Mechanism of Activation	Location	Action	Substrate
M_1	PLC activated → increased **IP_3** → and **DAG** → increased intracellular Ca^{2+}	CNS (brain and sympathetic ganglia)	**CNS stimulation**	ACh

M_2	AC inhibited → decreased cAMP;also **increase in $K^{é}$ conductance**	Heart	**Decreases heart rate** and contractility	ACh
M_3	PLC activated → increased **IP_3** → and **DAG** increased intracellular Ca^{2+}	Smooth muscle of GI tract	**Increases gut peristalsis** and exocrine secretions	ACh
		Smooth muscle of GU tract	**Increases bladder contraction**, relaxes bladder sphincter	
		Smooth muscle of bronchi	**Increases bronchoconstriction** and respiratory secretions	
		Eye	**Contracts sphincter muscle**, leading to pupil constriction. Contracts ciliary muscle, leading to loss of far vision	
N_M	Activation of **Na^+/K^+ channel**	Neuromuscular junction	Promotes muscle contraction	Nicotine
N_N	Activation of **Na^+/K^+ channel**	Autonomic ganglia and CNS	Vasodilation of renal blood vessels	Nicotine
		Adrenal medulla	Stimulates epinephrine release	

A 68-year-old woman presents to the emergency room complaining of the acute onset of severe left eye pain. She tells you that she is also having decreased vision in her left eye and that she is feeling extremely nauseous. Examination demonstrates a red left eye with a fixed and dilated pupil. You quickly diagnose this patient as having narrow-angle glaucoma and you immediately administer acetazolamide as well as an ophthalmic solution that will contract the sphincter muscle of the iris.

Pilocarpine

Similar Drugs	
Mechanism of Action	Pilocarpine is a direct **muscarinic (M_1-, M_2-, M_3-) receptor agonist**. Since it is applied topically to the eye, pilocarpine **acts mostly at the M_3-receptor**. By stimulating the M_3-receptor, pilocarpine causes **contraction of the sphincter muscle of the iris**, thereby leading to the opening of the canal of Schlemm (treats narrow-angle glaucoma). Pilocarpine also opens the trabecular meshwork of the eye by **contracting the ciliary muscle**, thereby increasing the outflow of aqueous humor (treats wide-angle glaucoma).
Clinical Uses	Treatment of choice for both **narrow- and wide-angle glaucoma**. Has also been shown to stimulate tear production.
Side Effects	Since this medication is used as an ophthalmic solution, side effects are usually minimal; however, excessive salivation and sweating have been reported.
Other	**Carbachol** is both a muscarinic and nicotinic receptor agonist. Via direct M_3-receptor stimulation in the eye, it acts to produce pupillary miosis via contraction of the sphincter muscle of the iris. It is primarily used to treat wide-angle glaucoma or to produce pupillary constriction during ophthalmologic surgery.

A 24-year-old man presents to your clinic, complaining of episodes of wheezing and chronic cough, especially when he is exposed to pollen, cats, and dust. On physical examination today, the patient's lungs sound clear. You suspect that the patient has mild intermittent asthma, but you decide to confirm this diagnosis with a bronchial challenge test. To perform this test, you ask the patient to inhale a small amount of a nebulized drug that will provoke bronchoconstriction. When the patient reacts to a very low-dose of this medication, you feel confident that the patient has reactive airway disease and you prescribe an inhaler for

treatment.

Methacholine

Similar Drugs	
Mechanism of Action	Methacholine is a synthetic derivative of acetylcholine that acts as a **muscarinic (M_1-, M_2-, M_3-) receptor agonist**. Since it is administered in the inhaled form, it acts primarily at the M_3-receptor to produce **smooth muscle contraction of the bronchi**.
Clinical Uses	Primarily used in a **bronchial challenge test** for the diagnosis of **reactive airways disease**.
Side Effects	If given in high doses or given systemically, it can cause bradycardia and hypotension. Its use is contraindicated in patients with recent stroke or heart attack and in patients with known severe asthma or COPD.
Other	

A 29-year-old woman is admitted to the hospital for a caesarian section. The procedure goes well and there are no major intraoperative complications. Three days after surgery, the nursing staff notifies you that the patient has been unable to void on her own and that she has been requiring catheterization in order to empty her bladder. You recognize that the patient's symptoms are likely related to her recent procedure and you decide to administer a medication to treat the patient's bladder atony.

Bethanechol

Similar Drugs	

Mechanism of Action	Bethanechol is a **muscarinic (M_2- and M_3-) agonist**. By stimulating M_3-receptors, this drug causes increased bladder contraction along with relaxation of the bladder sphincter, thereby **promoting urination**. M_3-receptor stimulation can also result in increased gut motility.
Clinical Uses	Used to **treat neurogenic ileus and urinary retention** in the postpartum or postoperative period.
Side Effects	Effects secondary to M_2-receptor stimulation (e.g., bradycardia; hypotension). Effects secondary to M_3-receptor stimulation (e.g., sweating; salivation; **diarrhea**).
Other	Because bethanechol does not cross the blood-brain barrier, it has very little effect on M_1-receptors in the CNS.

A 6-year-old boy is brought to the emergency room by his parents, who tell you that their son has been acting extremely bizarre for the last several hours. The patient's mother informs you that the strange behavior began in the afternoon after she had spent time gardening with the child. While speaking with the parents, the boy continually interrupts to ask for water. Examination of the child reveals a flushed boy with a temperature of 102°F, a heart rate of 148 beats/min, and dilated pupils. After examining the child, you ask the mother whether she grows any plants of the family *Solanaceae*, more commonly known as Nightshade, because these plants contain an alkaloid compound, which is similar to a drug used to treat cardiac emergencies and nerve gas poisoning.

Atropine

Similar Drugs	
Mechanism of Action	Atropine is a **competitive muscarinic (M_1-, M_2-, M_3-) receptor antagonist**. By blocking M_1-receptors, atropine can cause

	sedation and, at high doses, psychosis. By blocking M_2-receptors, this drug can cause **tachycardia** and mild vasodilation at high doses. By blocking M_3-receptors, atropine causes **decreased GI tract motility**, urinary retention, and **cycloplegia** with mydriasis.
Clinical Uses	Used as an **antidote for cholinesterase inhibitor poisoning** (e.g., "nerve gas," insecticide). Used in the **treatment of bradycardia during cardiac emergencies**. Used to treat urinary incontinence and also as an ophthalmic solution to produce mydriasis for retinal examination.
Side Effects	The side effect profile is associated with those symptoms caused by cholinergic blockade, and includes **hyperthermia**, flushing, **decreased salivation**, cycloplegia, psychosis, and **tachycardia**.
Other	Atropine poisoning is treated with cholinesterase inhibitors (e.g., **physostigmine)**. **Tropicamide** is an analogue of atropine that is used in ophthalmic solutions to produce mydriasis for retinal examination.

A 35-year-old woman presents to your clinic for a routine appointment. She tells you that she will be going on a cruise with her husband in the next month and, while she is excited about the trip, she is concerned about developing motion sickness on the ship. You suggest that she try a medication, which is an analogue of atropine that has been shown to improve symptoms of motion sickness. You do warn her that the side effect profile of the medication includes palpitations, sedation, and blurry vision and you suggest that she stop using the medication if she experiences any of these side effects.

Scopolamine

Similar Drugs	

Mechanism of Action	Scopolamine is a plant derivative that acts as an analogue of atropine. It is a **competitive muscarinic (M_1-, M_2-, M_3-) receptor antagonist**. Scopolamine crosses the blood-brain barrier easily and by blocking M_1-receptors, it is thought to interfere with neuronal communication between the vestibular ear and the vomiting center of the brain, thereby **preventing motion sickness**. By blocking M_3-receptors, scopolamine can also cause **decreased GI tract motility**, urinary retention, and **cycloplegia** with mydriasis.
Clinical Uses	Used as a treatment for **motion sickness**. Also used to decrease respiratory secretions and salivation in patients at end of life or with amyotrophic lateral sclerosis.
Side Effects	The side effect profile is associated with those **symptoms caused by cholinergic blockade**, and includes sedation, blurred vision, psychosis, urinary retention, and tachycardias.
Other	**Glycopyrrolate** is a **muscarinic (M_1-, M_2-, M_3-) receptor antagonist** that has slightly increased affinity for M_3- receptors over M_1- or M_2-receptors. It is used to reduce excessive salivation and respiratory secretions, most commonly in the pre-operative setting as well as during end-of-life care. Due to its anti-cholinergic activity, adverse effects are similar to those of other anti-cholinergic medications (tachycardia, hypertension, mydriasis, cardiac arrhythmias, constipation, xerostomia).

A 72-year-old man is referred to your neurology practice with a chief complaint of an unsteady gait, which has developed gradually over the past few months. As you speak with the patient, you notice that he has a “pill-rolling” tremor. Physical examination reveals a shuffling gait, “cogwheel” rigidity in response to passive movement and bradykinesia. You suspect that this patient may be suffering from Parkinson’s disease and you tell him that you would like to start him on a pharmacologic regimen to treat his condition. As you ponder the possible treatments for this patient, you ask the patient whether he suffers from narrow-angle glaucoma as that is a contraindication for one of the drugs that you could prescribe to him.

Benztropine

Similar Drugs	Biperiden; trihexyphenidyl.
Mechanism of Action	This drug acts as a **muscarinic (M_1-, M_2-, M_3-) receptor antagonist**. Since benztropine can cross the blood-brain barrier, it can **act on M_1-receptors present in the corpus striatum**. In the corpus striatum, dopaminergic neurons act to inhibit GABA-ergic outflow, while cholinergic neurons act to stimulate GABA-ergic outflow, and together, the dopaminergic and cholinergic neurons strike a balance in GABA-ergic activity. In Parkinson's disease, dopaminergic neurons are lost, thereby leading to unopposed excitatory cholinergic activity on GABA neurons. By inhibiting M_1-receptors and thereby decreasing cholinergic activity, benztropine acts to restore the dopaminergic-cholinergic balance in the corpus striatum in patients with Parkinson's disease.
Clinical Uses	Used as an **adjuvant treatment in Parkinson's disease**. This drug primarily improves the tremor and rigidity associated with Parkinson's disease, but it has little effect on bradykinesia. Also used to treat **extrapyramidal symptoms** produced by dopamine antagonist agents (e.g., typical anti-psychotics).
Side Effects	Dry mouth; irritability and confusion; constipation; pupillary dilation and blurred vision; urinary retention; hyperthermia; sedation.
Other	Since the production of mydriasis via relaxation of the sphincter muscle of the iris will obstruct the outflow of aqueous humor through the canal of Schlemm, benztropine is **contraindicated in patients with narrow-angle glaucoma**. **Other anti-parkinsonism agents** include dopamine agonists (e.g., bromocriptine, amantadine, levodopa) and MAO type B inhibitors (e.g., selegiline).

A 63-year-old woman presents to your pulmonology office for follow-up of her newly diagnosed chronic obstructive pulmonary disease. When you had seen her initially, you had started her on a therapeutic regimen, which had included the use of a β-adrenergic agonist. She now tells you that she cannot tolerate the side effects of a tremor and a "racing heart," which she experiences every time she uses the β-adrenergic agonist, and she asks you to switch her medication. You agree to try other medications for the management of her lung disease and you write her a prescription for an inhaler that acts at a different set of autonomic receptors to produce bronchodilation in the lung.

Ipratropium

Similar Drugs	Tiotropium.
Mechanism of Action	Ipratropium is a **muscarinic receptor antagonist**. Because it is inhaled, it mostly acts to block the stimulation of **M_3-receptors** in the lung and to relax the smooth muscle around the bronchi, thereby resulting in **bronchodilation**.
Clinical Uses	**Treatment of chronic obstructive pulmonary disease and asthma**, especially in those patients who are unable to take adrenergic agents.
Side Effects	Since this agent is inhaled and thus it only minimally enters the systemic circulation, anti-cholinergic side effects are minimal, although dry mouth and sedation have been reported.
Other	

A 70-year-old woman presents to your office complaining of frequent urination as well as a feeling of incomplete voiding upon urination. She also notes occasional episodes of incontinence. When routine urinalysis demonstrates no signs of urinary tract infection, you suspect that the patient has an overactive bladder. Since the patient does have social anxiety and has complained about

diffuse sweating in the past, you decide to place her on a muscarinic receptor antagonist that will help increase bladder sphincter tone, decrease bladder muscle spasm, and may even help with her hyperactive sweating.

Oxybutynin

Similar Drugs	Tolterodine; solifenacin.
Mechanism of Action	Oxybutynin acts as a **muscarinic (M_1-, M_2-, M_3-) receptor antagonist**, thereby inhibiting cholinergic transmission. By blocking the M_3-receptor, oxybutynin causes increased bladder sphincter tone and decreased bladder contraction, thereby reducing urinary incontinence. It has also been shown to have some effects on the smooth muscle of the bladder through calcium antagonism. In addition to its effects on the bladder, the M_3-receptor blockade can also result in decreased sweating.
Clinical Uses	Used in the treatment of **urinary incontinence** and hyperhidrosis.
Side Effects	The side effect profile consists of **symptoms caused by cholinergic blockade**, including sedation, dry mouth, blurred vision, psychosis, and tachycardias.
Other	**Dicyclomine** and **hyoscyamine** are both **muscarinic receptor antagonists** that are used to treat irritable bowel syndrome. They act by blocking parasympathetic activity on smooth muscle in the GI tract to reduce motility and alleviate intestinal cramping. Hyoscyamine can also be used as an adjunctive treatment for peptic ulcer disease while dicyclomine (which is more of a selective M_1- receptor antagonist) has no effect on gastric acid secretion.

A 42-year-old woman presents to the hospital for an elective cholecystectomy. As her anesthesiologist, you meet with the patient to answer any questions that

she has before she goes into the operating room. She asks you to tell her about some of the medications that you may be administering to her during her operation. You oblige the patient and you begin to explain how it is necessary to paralyze her in order to intubate her and to mechanically ventilate her. She becomes understandably concerned when she hears that you will be paralyzing her and you, realizing that you should have used more tact when speaking with the patient, try to reassure her that you can easily reverse the paralysis at a moment's notice by the administration of a medication that acts to inhibit *acetylcholinesterase* at the neuromuscular junction.

Neostigmine

Similar Drugs	
Mechanism of Action	This drug is an indirect muscarinic agonist because it exerts its effects via **reversible inhibition of *acetylcholinesterase*** in the synaptic junction, which is the enzyme responsible for degrading acetylcholine to acetate and choline. By inhibiting *acetylcholinesterase*, acetylcholine levels remain elevated in the synaptic junction, thereby resulting in **increased stimulation of both nicotinic and muscarinic receptors**.
Clinical Uses	Treatment of **myasthenia gravis**. Used to **stimulate the GI tract and bladder** in cases of postoperative intestinal and bladder atony. Used by anesthesiologists to **overcome non-depolarizing neuromuscular blockade** (e.g., as caused by pancuronium or vecuronium).
Side Effects	Diarrhea; bronchoconstriction; salivation; flushing; nausea; bradycardia. Since neostigmine cannot cross the blood-brain barrier, it does not produce significant effects on the CNS, such as sedation or psychosis.

Other	**Physostigmine** is another **reversible *acetylcholinesterase* inhibitor**. Since it is able to cross the blood-brain barrier, it can be used to **treat atropine poisoning**. It is also used as an ophthalmic solution in the **treatment of glaucoma**, as it can produce miosis and stimulate the outflow of aqueous humor from the eye, thereby decreasing intraocular pressure.

A 28-year-old woman presents to your office because she has been developing double vision in the afternoons and evenings. Physical examination is significant for ptosis of both eyes. When you ask the patient to keep her eyelids elevated for a short period of time, the ptosis worsens, thereby demonstrating marked muscle fatigability. You begin to suspect that the patient may be suffering from myasthenia gravis, so you decide to give the patient a medication that will confirm the diagnosis if her symptoms improve after administration of this medication.

Edrophonium and Pyridostigmine

Similar Drugs

Mechanism of Action	These drugs act **to reversibly inhibit *acetylcholinesterase*** in the synaptic junction, which is the enzyme responsible for degrading acetylcholine to acetate and choline. By inhibiting *acetylcholinesterase*, acetylcholine levels remain elevated in the synaptic junction, thereby resulting in **increased stimulation of both nicotinic and muscarinic receptors**. In patients with myasthenia gravis, the elevated levels of acetylcholine produced by these medications overcome the anti-acetylcholine receptor antibodies, leading to the resumption of stimulation at the neuromuscular junction.
Clinical Uses	**Edrophonium**: This short-acting drug is used to **diagnose myasthenia gravis** (“Tensilon Test”—patient is given drug; if symptoms transiently improve, then the test is positive).

	Pyridostigmine: This long-acting drug is used in the **treatment of myasthenia gravis**.
Side Effects	Side effects of these drugs are related to increased stimulation of muscarinic receptors and include bradycardia, diarrhea, bronchoconstriction, salivation, flushing, and nausea. Overdoses of these drugs can be treated with atropine.
Other	The symptoms of muscle weakness and fatigability are similar in myasthenia gravis patients who are either overmedicated with pyridostigmine or in patients who are undermedicated and thus still experiencing symptoms. Edrophonium is given to these patients to differentiate the etiology of their symptoms. After administration of edrophonium, symptoms should worsen in patients who are overmedicated and improve in those patients who are undermedicated.

An 81-year-old man is brought to your geriatric clinic by his daughter, who is concerned for his safety. She tells you that her father has been very forgetful lately. Recently, he started a small fire in the kitchen because he forgot to turn off the stove after cooking. You perform a mini-mental status examination on the patient, which reveals a short-term memory deficit as well as some word-finding difficulty. You tell the patient and his daughter that you would like to run some laboratory tests in order to more carefully assess the patient's condition. When the tests rule out an organic cause for the patient's declining mental status, you tell the patient and his daughter that the patient may have Alzheimer disease, but that you may be able to slow the disease progression with the use of a specific medication.

Donepezil

Similar Drugs	Galantamine; rivastigmine.
Mechanism of Action	Donepezil acts to **reversibly inhibit *acetylcholinesterase*** in the synaptic junction, which is the enzyme responsible for degrading

	acetylcholine to acetate and choline. By inhibiting *acetylcholinesterase*, acetylcholine levels remain elevated in the synaptic junction, thereby resulting in **increased stimulation of both nicotinic and muscarinic receptors.** Since a loss of cholinergic neuronal activity has been noted in Alzheimer disease, it has been speculated that an increase in the stimulation of cholinergic neurons may be beneficial in treating the disease.
Clinical Uses	**Treatment of Alzheimer disease**.
Side Effects	Nausea; dizziness; insomnia.
Other	This class of drugs has not been shown to improve memory loss associated with Alzheimer disease, but instead has only been shown to slow the progression of the disease by about 6 months.

As part of a medical history project on different medical agents used in combat, you meet with an old war veteran. Given the current age of bioterrorism, he begins to tell you about a compound that was used “in the olden days” against the enemy. He notes that he is not sure how the drug exerted its effects, but he remembered it causing seizures, paralysis, and death in a very short period of time. You remember hearing about this compound in your pharmacology class and you explain to the gentleman that the drug acted by excessively stimulating the autonomic nervous system.

Echothiophate

Similar Drugs	Other **organophosphates** include isoflurophate, parathion, and malathion.
Mechanism of Action	These drugs act to **inhibit *acetylcholinesterase*** in the synaptic junction by covalently binding to the enzyme. By inhibiting *acetylcholinesterase*, acetylcholine levels remain elevated in the synaptic junction, thereby resulting in **increased stimulation of**

	both nicotinic and muscarinic receptors.
Clinical Uses	**Echothiophate and isoflurophate** can be used in ophthalmic ointments to treat wide-angle glaucoma by contracting the ciliary muscle of the eye and therefore improving the outflow of aqueous humor. That said, these agents are seldom used clinically and contact with organophosphates such as these drugs more commonly occurs through their use as **insecticides**. **Parathion and malathion** are **poisons** ("nerve gas") when administered systemically.
Side Effects	When given systemically, these drugs cause widespread muscarinic activation, resulting in **organophosphate poisoning**, which manifests as **seizures**, psychosis, GI upset, salivation, blurry vision, and **bradycardia**. Persistent nicotinic activation results in a neuromuscular blockade that can lead to **flaccid paralysis**.
Other	**Botulinum toxin** is a compound produced by the bacteria *Clostridium botulinum*, which blocks cholinergic activity by preventing the release of acetylcholine from the presynaptic membrane. It is used to treat a number of common medical conditions including cosmetic treatment of wrinkles muscle spasm (especially in the esophagus), chronic migraine, and urinary incontinence due to detrusor instability. **Atropine** and **pralidoxime** can be used to **treat** the muscarinic symptoms (e.g., bradycardia) associated with **organophosphate poisoning**.

A 56-year-old migrant farm worker is brought to the emergency department after working 10 days straight in the fields. He is extremely weak and complains of difficulty breathing. Physical examination reveals a heart rate of 35 beats/min, a blood pressure of 82/50 mm Hg, wheezing throughout both lung fields, and significant weakness on his motor exam in all limbs. You also note that the patient is drooling. After questioning his employer who brought him in, you find that the patient has been working with insecticides in the field. You become concerned that the patient is suffering from organophosphate poisoning and you immediately administer atropine and another drug to counteract the

parasympathetic effects of organophosphate poisoning.

Pralidoxime

Similar Drugs	
Mechanism of Action	Pralidoxime acts to **reverse cholinesterase inhibitor activity,** thereby allowing *acetylcholinesterase* to function normally again and allow for the breakdown of acetylcholine at the neuronal synapse.
Clinical Uses	Used in conjunction with atropine to treat **organophosphate poisoning**. Pralidoxime can also be used to treat overdoses of neostigmine or pyridostigmine (other *acetylcholinesterase* inhibitors).
Side Effects	Flushing; tachycardia; dry mouth; blurry vision; sedation.
Other	

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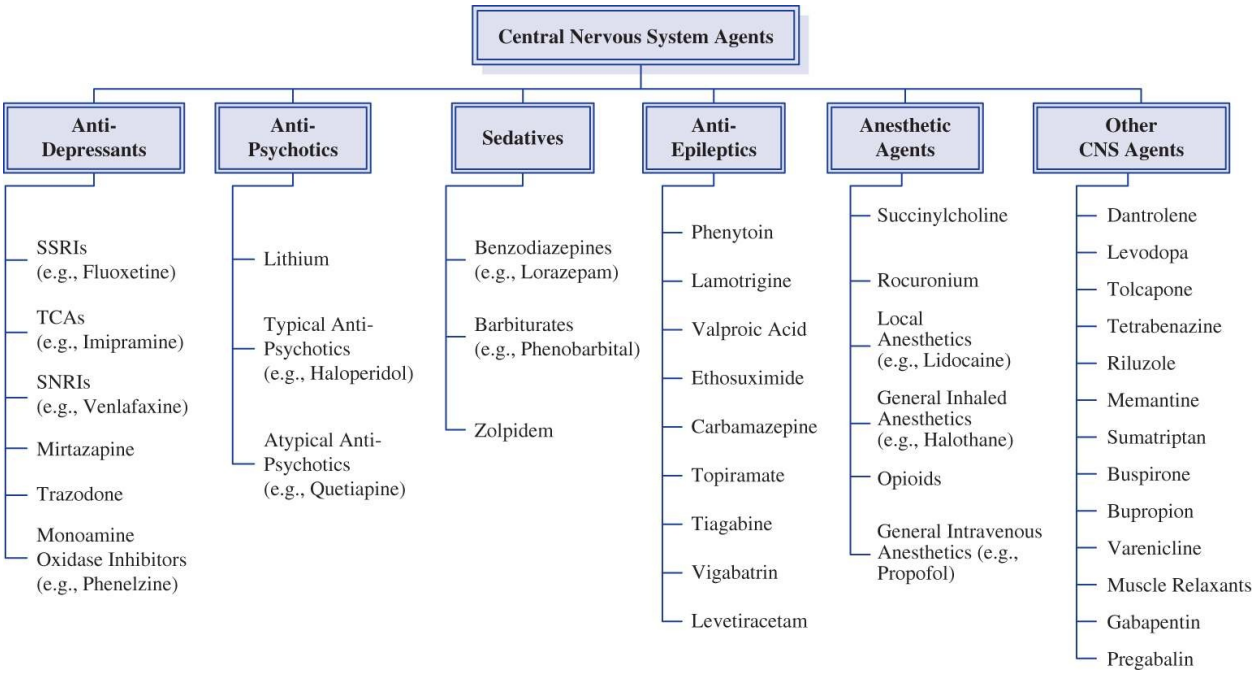


NEUROTRANSMITTERS

NEUROTRANSMITTERS IN THE CENTRAL NERVOUS SYSTEM

Neurotransmitter	Function
Acetylcholine	Attention, memory, and learning
Serotonin	Affects mood and anxiety
NE	Mental arousal and affects mood

Glutamate, GABA	Basis of learning and long-term memory
Dopamine	Controls arousal levels, vital for physical motivation
Enkephalins	Sensation of calm

NEUROTRANSMITTER CHANGES WITH DISEASE

Disease	**Neurotransmitter Changes**
Anxiety disorders	Increased NE; decreased GABA and serotonin
Depression	Decreased NE and serotonin
Parkinson's disease	Decreased dopamine
Schizophrenia	Increased dopamine
Huntington's disease	Decreased GABA and acetylcholine
Alzheimer's disease	Decreased acetylcholine

A 43-year-old businessman presents to your clinic complaining of lethargy. He has been feeling increasingly fatigued over the past several months and he also reports difficulty concentrating at work. He describes his mood as sad almost every day for the past 3 months. When asked about what he enjoys, he states that he does not find enjoyment in hobbies that used to give him a great amount of pleasure. He has lost 10 pounds over the last 2 months, has little appetite, and arises extremely early each morning for no apparent reason. You suspect that the patient is suffering from major depression and you decide to prescribe a medication that will hopefully treat his condition. You warn the patient that he may experience decreased sexual function as a side effect of this new medication.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Similar Drugs

SSRIs include **fluoxetine**, **paroxetine**, **sertraline**, **fluvoxamine**, **escitalopram**, and **citalopram**.

Mechanism of Action	The SSRIs act to **prevent the reuptake of serotonin** from the synaptic cleft, thereby potentiating the effects of serotonin on the postsynaptic receptors.
Clinical Uses	The SSRIs are used to treat major **depression**, anxiety disorders, **obsessive-compulsive disorder**, eating disorders, motor recovery after stroke, and premenstrual dysmorphic disorder.
Side Effects	**Sexual dysfunction** (decreased libido, difficulty with orgasm); drowsiness; **weight gain**. There is some evidence that SSRIs may increase suicidal ideation among adolescents.
Other	The simultaneous use of SSRIs and MAO inhibitors is contraindicated, as a condition known as **serotonin syndrome** may occur. Serotonin syndrome is characterized by changes in mental status, muscle stiffness, autonomic instability, and hyperthermia. Fluoxetine has been shown to **inhibit cytochrome P-450**, thereby enhancing the effects of several drugs metabolized by this enzyme, including the tricyclic anti-depressants, haloperidol, and some anti-arrhythmic medications.

A 14-year-old boy is brought to your clinic by his mother, who tells you that her son has been losing control of his bladder several times during the day over the past couple of weeks. Upon speaking with the boy, he tells you that he has been feeling depressed since he is being bullied at school. After a lengthy workup rules out an organic cause for his enuresis, you decide to treat the boy for depression and you begin him on a psychotropic medication that potentiates the effects of norepinephrine and serotonin at the synaptic cleft.

Tricyclic Anti-Depressants

Similar Drugs	The tricyclic anti-depressants (TCAs) include **desipramine**, **nortriptyline**, **imipramine**, **clomipramine, amitriptyline**, **amoxapine**, and **doxepin**.
Mechanism	The TCAs **block the reuptake of norepinephrine and**

of Action	**serotonin** from the synaptic cleft, thereby potentiating the effects of serotonin and norepinephrine on the postsynaptic receptors. The TCAs have also been shown to inhibit muscarinic, histamine, and α-adrenergic receptors, thereby leading to a host of undesirable side effects.
Clinical Uses	The TCAs are used in the treatment of major **depression**, panic disorder, **enuresis**, fibromyalgia, and **chronic pain syndromes**. Amitriptyline has been used to treat neuropathic pain. Imipramine has been used to treat enuresis. Clomipramine can be used for OCD.
Side Effects	**Sedation** (due to histamine receptor blockade); **postural hypotension** (due to α adrenergic receptor blockade); cardiac arrhythmias (due to sodium channel blockade); **anticholinergic effects** due to muscarinic receptor blockade (leads to **urinary retention**, blurred vision, confusion, constipation, and **dry mouth**).
Other	The simultaneous use of TCAs and MAO inhibitors is contraindicated since interactions between the two classes of drugs can cause seizures. Overdose of a TCA is associated with ECG changes (widening of QRS complex), cardiac arrhythmias, mental status changes, and seizures. Overdose is treated with **sodium bicarbonate** to prevent life-threatening arrhythmias.

A 35-year-old man with a history of major depressive disorder presents to your clinic for a routine follow-up visit. You had initially diagnosed him with an episode of major depression 3 months ago. At that time, you started a selective serotonin reuptake inhibitor to treat his condition. Today, he reports that he continues to feel empty, has difficulty falling asleep, and has been gaining weight. Additionally, he says that he has lost his job because he simply could not muster the energy to drive to work. Because he continues to have no improvement, you discuss options for an alternative regimen. You decide to try a class of medications that is effective in treating depression, but may also cause tachycardia and hypertension secondary to their effects on certain receptors in the central nervous system.

Serotonin-Norepinephrine Receptor Inhibitors (SNRIs)

Similar Drugs	The **SNRIs** include **venlafaxine, desvenlafaxine, duloxetine, milnacipran,** and **levomilnacipram**.
Mechanism of Action	SNRIs **block the reuptake of norepinephrine and serotonin** from the synaptic cleft, thereby potentiating their effects on the postsynaptic receptors.
Clinical Uses	SNRIs have been used to treat **depression** and generalized anxiety disorder. Duloxetine is also used to treat diabetic neuropathy. Venlafaxine may also be used for **panic disorder** and **social anxiety disorder**.
Side Effects	**Hypertension** and **tachycardia** (due to increased sympathetic tone); nausea; sexual dysfunction.
Other	

A 42-year-old woman is referred to your psychiatry practice by her primary care physician. When she enters your office, you immediately notice that she looks emaciated and is wringing her hands nervously. She tells you that she constantly worries about everything in her life as well as about situations in her children's and husband's lives. Upon further questioning, you discover that she sleeps poorly and that she has lost 15 pounds over the last 2 months due to a poor appetite. She also admits to depressed mood. After another session, you make the diagnosis of generalized anxiety disorder and you decide to prescribe a medication that will treat her anxiety and depression as well as stimulate her appetite.

Mirtazapine

Similar Drugs	
Mechanism of Action	Mirtazapine acts as an **α_2, $5HT_2$, and $5HT_3$ receptor**

	antagonist, thereby increasing sympathetic tone and **increasing the release of serotonin and norepinephrine.** It is also an antagonist at H_1 receptors.
Clinical Uses	Mirtazapine is primarily used to treat **depressive disorders** and **generalized anxiety disorder**, especially in **underweight patients.**
Side Effects	**Increased appetite with associated weight gain;** sedation; dry mouth; hypercholesterolemia.
Other	

A 24-year-old male presents to the emergency department complaining of severe pelvic pain. He reports that he has been suffering from insomnia recently, so he took one of his brother's prescription pills to help him sleep earlier in the evening. Unfortunately, he states that he has been experiencing a painful, unremitting erection for the past 5 hours. As you rapidly initiate treatment for his symptoms, you explain that his condition is likely a side effect of the medication he took for sleep, which can also be used as an atypical antidepressant.

Trazodone

Similar Drugs	
Mechanism of Action	Trazodone **inhibits reuptake of serotonin,** and also **blocks 5-HT, α_1, and H_1 receptors**.
Clinical Uses	Trazodone is used to treat **insomnia** and **major depressive disorder**.
Side Effects	**Rare occurrences of priapism**; sexual dysfunction; **sedation**; headache; nausea; **QT prolongation**; hypotension; serotonin syndrome or neuroleptic malignant syndrome when taken in combination with other serotoninergic drugs.

Other	Unlike other anti-depressants, trazodone is not associated with either weight gain or loss.

A 36-year-old woman is seen in your psychiatry clinic for a follow-up appointment. She was recently discharged from a psychiatric hospital, where she was admitted for auditory hallucinations. The admitting physician did not believe her to be suffering from schizophrenia, but instead diagnosed her as having atypical depression with psychotic features. She was started on a new medication to help control her illness. In your office, she asks you about the possible side effects of her new medication. You tell the patient that it is important to avoid certain foods, such as cheese, red wine, and smoked sausage, since ingestion of these foods in conjunction with her new medication could lead to a hypertensive crisis.

Monoamine Oxidase Inhibitors (MAOIs)

Similar Drugs	The MAOIs include **tranylcypromine**, **phenelzine**, **selegiline,** and **isocarboxazid**.
Mechanism of Action	*Monoamine oxidase* is a presynaptic enzyme responsible for metabolizing norepinephrine and serotonin (*monoamine oxidase A*) and dopamine (*monoamine oxidases A and B*). When ***monoamine oxidase* is inhibited by an MAOI**, the **levels of serotonin**, **dopamine**, **and norepinephrine increase** in the presynaptic neuron. These neurotransmitters then leak out of the neuron into the presynaptic space and activate serotonin and norepinephrine receptors.
Clinical Uses	Treatment of **atypical depression**, depression resistant to first- and second-line medications, specific phobias, and panic disorder.
Side Effects	Sedation; hypotension; blurred vision; weight gain.
Other	*Monoamine oxidase* is also responsible for metabolizing

tyramine, which is a sympathomimetic compound contained in wine, cheese, and smoked meats. When taking an MAOI, patients are unable to degrade tyramine, which then builds up in the gut. High levels of tyramine stimulate the release of epinephrine and norepinephrine from nervous tissue, thereby leading to a **hypertensive crisis** (characterized by headache, hypertension, and cardiac arrhythmias). Thus, patients taking MAOIs should avoid tyramine-containing foods.

Selegiline is a medication that selectively **inhibits *monoamine oxidase B***, thereby resulting in increased levels of dopamine in the presynaptic neuron. It is used as an adjunct treatment with levodopa for **Parkinson's disease**.

A 36-year-old woman with a history of bipolar disorder presents to the emergency room complaining of headache, palpitations, and dehydration. She complains of intense and uncontrollable thirst as well as excessive urination. On physical examination, she appears lethargic with dry skin, dry mucous membranes, and a fine hand tremor. Vital signs are significant for tachycardia and a blood pressure of 90/50 mm Hg. Laboratory studies show a high-serum sodium level, high-serum osmolality, and low-urine osmolality. Upon reviewing her medication list, you begin to suspect that the medication being used to treat her bipolar disorder may be causing her symptoms by acting as an anti-diuretic hormone antagonist.

Lithium

Similar Drugs	
Mechanism of Action	The mechanism of action of lithium is not completely understood. Lithium has been shown to **inhibit the phosphoinositol second messenger cascade**, which may interfere with the synthesis, storage, release, and reuptake of serotonin, dopamine, and norepinephrine.
Clinical	Lithium is used as a mood stabilizer for **bipolar disorder**. It has

Uses	also been used in combination with other medications in the treatment of schizoaffective disorder, schizophrenia, refractory depression, and other mood disorders with psychotic features.
Side Effects	Fine hand **tremor**; **hypothyroidism**; ECG changes; edema; **nephrogenic diabetes insipidus** caused by anti-diuretic hormone antagonism (presents with hypernatremia, polyuria, and polydipsia); weight gain; renal failure.
Other	The use of lithium is not advised during pregnancy since it may be teratogenic and may be related to the development of Ebstein anomaly in fetuses. Serum levels of lithium must be monitored closely due to the narrow therapeutic window of the drug and, thus, the increased risk for lithium intoxication.

You are called to see a 74-year-old patient who was initially admitted for pneumonia and is now showing signs of delirium and psychosis. The patient has no relevant psychiatric history recorded in her chart, but she tells you that she can see her deceased husband standing right in front of her. On examination, the patient appears to have fluctuating consciousness, impaired memory, and obvious agitation. You decide to order a series of studies in order to rule out any organic cause for her delirium, but in the meantime, you administer a medication that will block the postsynaptic dopamine receptors in the limbic system and hopefully relieve some of her symptoms.

Typical Anti-Psychotic Agents

Similar Drugs	The typical anti-psychotics include **haloperidol, trifluoperazine, loxapine, perphenazine, pimozide, thiothixene, fluphenazine, chlorpromazine**, and **thioridazine**.
Mechanism of Action	This class of drugs acts by **blocking postsynaptic dopamine D_2 receptors** in the limbic system of the brain, thereby decreasing the response of the postsynaptic neuron to dopamine excitation. These drugs also produce some inhibition at the H_1 histamine

	receptor, cholinergic receptors, and α_1-adrenergic receptors, which leads to a host of undesirable side effects.
Clinical Uses	Used to treat **positive symptoms of schizophrenia** (e.g., delusions, hallucinations), bipolar disorder, and Tourette syndrome. Haloperidol is also used to treat **delirium and agitation**.
Side Effects	**Sedation** (due to histamine receptor blockade); **anti-cholinergic side effects** (e.g., dry mouth, urinary retention, blurry vision); orthostatic hypotension (due to α_1-adrenergic receptor blockade); **extrapyramidal system side effects** including acute dystonia (muscle spasms), akinesia (loss of voluntary movement), akathisia (motor restlessness), and tardive dyskinesia (involuntary oral-facial movements) due to chronic dopaminergic blockade; **galactorrhea** and **amenorrhea** caused by an **hyperprolactinemia**, which is due to inhibition of dopamine release from the pituitary, thereby inhibiting the tubuloinfundibular dopaminergic pathway.
Other	Treatment with typical anti-psychotics may cause some patients to develop **neuroleptic malignant syndrome**, which is characterized by muscle rigidity, a change in mental status, elevated temperature, and autonomic instability. This syndrome can be treated with **dantrolene** (muscle relaxant), dopamine agonists, and cessation of the anti-psychotic agent.

A 27-year-old man is brought to your clinic by his wife. He was recently diagnosed with paranoid schizophrenia, and his wife tells you that he has become increasingly despondent over the last 2 months and is now unable to care for himself. He continues to hear internal voices, which are telling him that the police and the CIA are after him. On physical examination, he appears disheveled. Although he is cooperative, you notice that he has a flat, blunt affect. While he denies suicidal or homicidal ideation, his wife is concerned for his well-being. Currently, he is being treated with a typical anti-psychotic medication. In addition to assessing this patient's need for in-patient evaluation, you also decide to switch him to a medication that will treat both the positive and negative symptoms of schizophrenia, although you inform both him and his

wife that this medication may cause agranulocytosis.

Atypical Anti-Psychotic Agents

Similar Drugs	The atypical anti-psychotics include **clozapine**, **risperidone**, **olanzapine**, **ziprasidone**, **aripiprazole**, **quetiapine, asenapine, ilioperidone, lurasidone,** and **paliperidone**.
Mechanism of Action	This class of drugs has been shown **to block both serotonin ($5HT_2$) and dopamine receptors** in the limbic system of the brain, thereby decreasing the response of the postsynaptic neuron to dopamine and serotonin excitation. These drugs also produce some inhibition at the H_1 histamine receptor, cholinergic receptors, and α-adrenergic receptors, although the activity of the atypical anti-psychotics at these off-target receptors is much less than that of typical anti-psychotics.
Clinical Uses	Used to **treat the positive and negative symptoms of schizophrenia**, bipolar disorder, and other psychotic disorders. Olanzapine, risperidone, and quetiapine can also be used to treat **delirium**.
Side Effects	Drowsiness; **weight gain and other features of metabolic syndrome**; mild hypotension, and parkinsonism symptoms. **Risperidone** is known to cause **hyperprolactinemia,** leading to **sexual dysfunction, menstrual irregularities, gynecomastia, and galactorrhea.** **Ziprasidone** is associated with **QT prolongation.** **Clozapine** can cause mild leukopenia and **agranulocytosis**, and therefore patients using this medication require weekly monitoring of their white blood cell count.
Other	Note that the atypical anti-psychotic medications have **fewer extrapyramidal and anti-cholinergic side effects** than the typical anti-psychotic medications since they have less activity at the H_1 histamine receptor, cholinergic receptors, and α-adrenergic receptors.

A 43-year-old woman is brought into the emergency room by her concerned husband, who reports that he witnessed his wife having convulsions. According to the husband, the patient suffers from severe alcoholism, but she stopped drinking 2 days ago. She has no history of seizures and she does not take any medications. On physical examination, the patient appears agitated, diaphoretic, and confused. She is tachycardic, hypertensive, has bilateral hand tremors, and has a fever of 100.7°F. You immediately start intravenous administration of a medication that will treat the patient for alcohol withdrawal symptoms and you admit her to the hospital for further monitoring and treatment of her condition.

Benzodiazepines

Similar Drugs	The benzodiazepines can be divided into three groups based upon the duration of their action. The short-acting benzodiazepines include **triazolam** and **midazolam**. The intermediate-acting benzodiazepines include **lorazepam**, **temazepam**, **oxazepam**, **alprazolam**, and **chlordiazepoxide**. The long-acting benzodiazepines include **diazepam**, **prazepam**, **clonazepam**, and **flurazepam**.
Mechanism of Action	The benzodiazepines bind to a site, directly adjacent to the $GABA_A$ receptor, and act to enhance the activity of this receptor. **Enhanced $GABA_A$ receptor activation** results in increased flow of chloride ion through adjacent chloride channels, thereby leading to cell membrane hyperpolarization and **decreased activity of the neurons of the limbic**, **thalamic**, **and hypothalamic regions of CNS**.
Clinical Uses	Used to treat **acute anxiety**, **seizures** and **status epilepticus**, muscle spasms, **alcohol withdrawal**, insomnia, and panic disorder. Midazolam and diazepam are also used as **anesthetics**.
Side Effects	**Sedation**; altered mental status; ataxia.
Other	Patients using benzodiazepines can become dependent upon the drug and may **experience withdrawal symptoms** (e.g., altered

mental status, anxiety, tachycardia, vomiting) if the medication is stopped abruptly.

Benzodiazepine overdose is characterized by **cardiac and respiratory depression**. It is treated supportively and with **flumazenil**, which is a competitive antagonist of benzodiazepines at the GABA receptor.

Benzodiazepines should be used with caution in patients who use alcohol, barbiturates, or other CNS depressants as well as in patients who have liver disease, as many benzodiazepines are cleared by the p450 system.

A 46-year-old man is brought to the emergency room after being involved in a serious motor vehicle collision. The trauma team determines that the patient has an isolated head injury and that he will need intubation. As the anesthesiologist on call, you are asked to help with the rapid sequence induction of anesthesia and intubation. As you prepare to intubate the patient, you ask the trauma nurse to administer a medication that indirectly potentiates GABA receptor activity and is commonly used for anesthesia induction.

Barbiturates

Similar Drugs	This class of drugs includes **phenobarbital**, **thiopental**, **secobarbital**, **amobarbital**, and **pentobarbital**.
Mechanism of Action	Barbiturates interfere with electrolyte transport across neural cell membranes, thereby inhibiting neuron activation. They indirectly **potentiate $GABA_A$ receptor activity** in the brain, thereby increasing the flow of chloride ions through adjacent chloride channels, which leads to cell membrane hyperpolarization and **decreased activity of CNS neurons**.
Clinical Uses	Barbiturates are used as a **sedative** in order to treat anxiety and insomnia. Thiopental has also been used for the **induction of anesthesia**. Phenobarbital is used in the **management of seizures** and in the treatment of neonatal hyperbilirubinemia.

Side Effects	Sedation; nausea; teratogen.
Other	Barbiturates **induce cytochrome P-450**, thereby resulting in decreased levels of several drugs such as digitalis, phenytoin, and griseofulvin. Patients using barbiturates can become dependent upon the drug and may **experience withdrawal symptoms** (e.g., nausea, anxiety, seizures, tachycardia) if the medication is stopped abruptly. **Overdose of a barbiturate** is characterized by cardiac and respiratory depression and can be treated with mechanical ventilation, hemodialysis, and alkalinization of the urine with **sodium bicarbonate**. Barbiturates should be avoided in pregnancy, patients with liver disease, patients with porphyria, or in patients who use alcohol, benzodiazepines, or other CNS depressants.

A 48-year-old male patient presents to your primary care clinic, complaining of insomnia. The patient states that he has not been able to sleep since switching to the night shift at his job. His past medical history is notable for substance abuse and you are wary of prescribing medications that have addictive properties. In addition to advising the patient on good sleep hygiene practices, you also prescribe a short-acting sleep aid that acts by potentiating GABA at the same location on the $GABA_A$ receptors that benzodiazepines bind, but is not associated with significant dependence if used for a short period of time.

Zolpidem

Similar Drugs	Zaleplon; eszopiclone.
Mechanism of Action	Zolpidem is a $GABA_A$ receptor agonist that binds to the receptor at the same location that benzodiazepines bind. With increased $GABA_A$ activity, the flow of chloride ions through adjacent

	chloride channels is increased, which leads to cell membrane hyperpolarization and **decreased activity of CNS neurons**.
Clinical Uses	**Short-term treatment of insomnia**.
Side Effects	**Mild anterograde amnesia**; **hallucinations**; ataxia.
Other	Zolpidem is known to disrupt REM sleep patterns less than benzodiazepines.

A 17-year-old girl with a history of grand mal seizures presents to your neurology clinic for a follow-up visit. She reports that she has had one seizure, which lasted 4 minutes, since her appointment 1 month ago. She is currently only on a single medication for seizure control, which acts by blocking sodium channels on the neuronal cell membrane. Upon further questioning, you discover that the patient is sexually active. You strongly encourage the patient to practice birth control as her anti-epileptic medication is associated with severe birth defects, including growth retardation and congenital cardiac and palate malformations.

Phenytoin

Similar Drugs	
Mechanism of Action	Phenytoin acts by **decreasing the flow of sodium and calcium ions** across the cell membrane, thereby resulting in decreased depolarization of the cells of the nervous system.
Clinical Uses	Used to treat simple and complex **partial seizures**, generalized tonic-clonic seizures **(grand mal seizures)**, and **status epilepticus**. Also used to treat trigeminal neuralgia and torsades de pointes.
Side Effects	**Nystagmus**; double vision; gait instability; **gingival hyperplasia**; hirsutism; neuropathy; megaloblastic anemia; rash;

	drug-induced lupus; teratogen (**fetal hydantoin syndrome**, characterized by prenatal growth deficiency and congenital cardiac and palate malformations).
Other	Phenytoin **induces cytochrome P-450**, thereby leading to increased metabolism of several drugs (e.g., oral contraceptives, warfarin, and cyclosporine) that are broken down by this enzymatic system. Phenytoin follows **zero-order kinetics**.

A 32-year-old epileptic patient presents to the emergency department, complaining of a severe rash. On physical examination, you note large, warm, red lesions in various stages of blistering all over the patient's body. There are also evidence of lesions on his mucous membranes, including his mouth and lips and conjunctiva. You immediately call for a dermatology consult and begin supportive treatment with intravenous fluids and pain control. The dermatologist confirms your suspected diagnosis of toxic epidermal necrolysis and on further discussion, you discover that the patient had recently started a new anti-epileptic medication, stopped the medication for a while, and then restarted the medication over the last few days. You believe that the patient's dermatological emergency is due to this anti-epileptic drug and you admit him to the hospital.

Lamotrigine

Similar Drugs	
Mechanism of Action	Lamotrigine acts to block **fast voltage-activated sodium channels at the presynaptic neuron**, thereby decreasing the release of glutamate and aspartate at the neuronal synapse.
Clinical Uses	Used in the treatment of **epilepsy** (simple and complex partial seizures and generalized tonic-clonic seizures). Also used to treat mood disorders, such as bipolar disorder and depression.

Side Effects	**Stevens-Johnson syndrome** (malaise and fever prodrome followed by rapid onset of diffuse purpuric macules that involve the mucous membranes); toxic epidermal necrolysis; aseptic meningitis.
Other	

A 26-year-old woman is referred to your neurology clinic for treatment of her seizure disorder. She suffered her first generalized tonic-clonic seizure 2 months ago and has been experiencing seizures about once a week since. Her past medical history is significant for bipolar disorder for which she takes lithium to treat. Upon further questioning, you learn that she started lithium about 2 months ago, but prior to that, she had been taking a different medication to treat her bipolar disorder. You begin to wonder if her prior medication had not only been treating her bipolar disorder, but also had been suppressing her seizures as well.

Valproic Acid

Similar Drugs	
Mechanism of Action	The exact mechanism by which valproic acid acts is unclear. It may **increase GABA concentrations** by inhibiting enzymes that metabolize GABA. Valproic acid has also been shown to have **effects on sodium and potassium conductance across the neuronal cell membrane**, thereby leading to hyperpolarization of the neuron.
Clinical Uses	Valproic acid is used to treat **generalized tonic-clonic seizures**, **myoclonic seizures**, and **absence seizures**. The drug has also been used in the **treatment of mania** associated with bipolar disorder and in the prevention of migraines.
Side Effects	**Hepatotoxicity**; thrombocytopenia; teratogen (**neural tube defects**); GI upset; sedation; weight gain.
Other	

An 11-year-old boy is brought to your pediatric neurology clinic because his mother is concerned about his behavior. The mother tells you that she has noticed that the patient simply stops in his tracks and enters a staring, trance-like state for 15 to 30 seconds. During these episodes, he is unresponsive and unaware of his surroundings. After these episodes, the patient returns to normal and has no memory of the event and no lingering effects. You decide to workup the patient thoroughly for absence seizures, but, in the meantime, you reassure the mother that there is a very effective medication, which acts by reducing calcium current across neuronal cell membranes, that can help manage and treat this patient's symptoms.

Ethosuximide

Similar Drugs	
Mechanism of Action	The mechanism of action of ethosuximide is not completely known, but it is thought to decrease calcium currents across neuronal cells and inhibit GABA metabolism.
Clinical Uses	**Treatment of absence seizures**.
Side Effects	Nausea and diarrhea; rash; pancytopenia; headache; insomnia; Stevens-Johnson syndrome.
Other	

A 33-year-old woman with a history of multiple sclerosis presents to your clinic complaining of shooting pains in her face. She tells you that whenever she brushes her teeth or chews vigorously, she feels a burst of searing pain on her left cheek. You explain to her that her symptoms are consistent with a condition called trigeminal neuralgia and that this condition is often associated with multiple sclerosis. You reassure her that you can prescribe a drug that will treat her symptoms, but you also warn her that this medication may cause low white

blood cell counts and thus she will need to be monitored closely while taking this drug.

Carbamazepine

Similar Drugs	Oxcarbazepine.
Mechanism of Action	Carbamazepine acts by **inhibiting the flow of sodium ions through sodium channels** on neural cell membranes, thereby causing hyperpolarization and decreased activity of the neuron.
Clinical Uses	Carbamazepine is a first-line treatment for simple seizures, complex **partial seizures, trigeminal neuralgia**, and generalized tonic-clonic seizures. It may also be used for other types of neuropathic pain syndromes.
Side Effects	GI upset; double vision; dizziness; **hepatotoxicity**; **agranulocytosis**; **aplastic anemia**.
Other	Carbamazepine has been shown to **induce cytochrome p450**, thereby leading to increased metabolism of certain drugs, including other anti-epileptic medications (e.g., phenytoin).

A 42-year-old woman presents to your clinic, complaining of migraine headaches. She describes her headache episodes as being located to right side of her head with a throbbing quality. She also notes that she is exquisitely sensitive to light and sound when she experiences one of these headaches and that she will sometimes see flashing lights right before the headache begins. She has tried using sumatriptan without relief and is wondering if you can prescribe another medication to treat her migraines. You decide to prescribe a medication for her that is used in the treatment of both migraines and seizure disorders, but you warn her that she may experience difficulties with attention and memory while on this medication.

Topiramate

Similar Drugs	
Mechanism of Action	The exact mechanism of action of topiramate is unknown; however, it is thought to **block the flow of sodium ions through voltage-gated sodium channels** on neural cell membranes, thereby causing hyperpolarization and decreased activity of the neuron. Some studies have also suggested that topiramate may act as an **agonist at $GABA_A$ receptors**.
Clinical Uses	Topiramate is used to treat **epilepsy** as well as **prophylaxis for migraines**. It is also commonly used to treat mood disorders, including as an adjunctive treatment for bipolar disorder.
Side Effects	Cognitive slowing; nausea and diarrhea; paresthesias; nephrolithiasis; sedation.
Other	

A 23-year-old man with a history of complex partial seizures presents to your neurology clinic for a follow-up visit. He reports that his seizures have been occurring more frequently over the last 4 weeks. This increase in seizure frequency occurred after phenytoin was discontinued from his regimen because he was unable to tolerate the drug. He currently is taking only a high dose of carbamazepine for seizure control. You decide to add another anti-epileptic agent, which acts by inhibiting the reuptake of GABA in the synaptic cleft. When he asks you what side effects he can expect from the new medication, you tell him that it may give him some nausea, diarrhea, and drowsiness, but that he will likely not experience any of the serious side effects he suffered while taking phenytoin.

Tiagabine

Similar Drugs	

Mechanism of Action	Tiagabine acts to **inhibit the reuptake of GABA** in the synaptic cleft, thereby potentiating the effect of GABA at the postsynaptic neuron.
Clinical Uses	Tiagabine is used, in combination with other drugs, in the treatment of **partial seizures**.
Side Effects	GI upset; sedation; tremor; ataxia.
Other	

A concerned mother presents to your pediatric neurology clinic with her 1-year-old son, who suffers from Down syndrome. She tells you that her son often suffers from episodes of infantile spasms. You perform a diagnostic electroencephalography test and observe a pathognomonic hypsarrhythmia pattern on the test. You suspect that the boy has West syndrome, a disorder that is seen in up to 5% of Down syndrome patients. You tell the mother that you would like to start her son on a newly approved medication that can effectively treat the infantile spasms, but you warn her that this medication could cause visual field loss.

Vigabatrin

Similar Drugs	
Mechanism of Action	The exact mechanism of vigabatrin is unknown, but it is believed to **irreversibly inhibit *GABA transaminase***, thereby increasing GABA levels in the neuronal synapse.
Clinical Uses	Used for **infantile spasms in children**. Also used as adjunct therapy for adults with **refractory complex partial seizures**.
Side Effects	**Visual field constriction and even visual loss in up to 30% of patients**; somnolence; headache; depression; hyperactivity.

Other

A 47-year-old woman presents to neurology clinic, complaining of several neurological symptoms. The patient reports episodes of inexplicable fear and sadness as well as a concurrent feeling of an altered sense of smell and a sense of spatial distortion. She denies any loss of consciousness during these episodes. After a full neurological examination and workup, you diagnose the patient with simple partial seizures and you prescribe a medication to treat her simple partial seizures. When the patient asks you how the drug works, you explain that the exact mechanism of action of the medication is unknown; however, it likely interrupts nerve conduction across the synapse by binding to synaptic vesicle proteins.

Levetiracetam

Similar Drugs	
Mechanism of Action	The exact mechanism of action of levetiracetam is unknown, but it is hypothesized that it **may bind to synaptic vesicle proteins**, which are located on the surfaces of neuronal vesicles, **thereby interrupting nerve conduction across the neuronal synapse**.
Clinical Uses	Used in the treatment of **partial seizures**, **myoclonic seizures**, **and tonic-clonic seizures**. Levetiracetam has also been used occasionally in the treatment of neuropathic pain.
Side Effects	**Drowsiness**; weakness; forgetfulness; **depression**; hallucinations.
Other	

While moonlighting with an ambulance company, you are called to see a 43-

year-old man, who is in severe respiratory failure secondary to status asthmaticus. He is unable to speak and he is quickly tiring from laborious respiration. With the paramedics at your side, you decide to perform a rapid sequence intubation at the scene before bringing the patient to the hospital. In order to perform proper endotracheal intubation, you will require the use of paralytic agent with rapid onset. You ask the paramedic to administer a depolarizing neuromuscular blocker and you begin to closely monitor the patient for possible bradycardia and other cardiac arrhythmias that may result from the administration of this medication.

Succinylcholine

Similar Drugs	
Mechanism of Action	Succinylcholine is a **depolarizing neuromuscular blocker that competes with acetylcholine to reversibly bind to the nicotinic receptors** at the neuromuscular junction. Initial binding of succinylcholine to these receptors results in a continuous depolarization at the neuromuscular junction with resulting muscle fasciculations. This is known as **phase I blockade**. There is no antidote for a phase I blockade and cholinesterase inhibitors will only potentiate the block. After a short period of time, the ion channel associated with the nicotinic receptor begins to repolarize; however, the receptor is desensitized by the continuous interaction with succinylcholine, and therefore the receptor will no longer transmit an action potential through the neuron even if the receptor is activated. This is known as **phase II blockade**. It can be reversed with a cholinesterase inhibitor such as physostigmine.
Clinical Uses	Succinylcholine is used to produce **muscle paralysis for endotracheal intubation** during surgery or emergency procedures.
Side Effects	Hyperkalemia; hypercalcemia; nausea and vomiting; muscle soreness; rhabdomyolysis; apnea; cardiac arrhythmias;

	bradycardia.
Other	When succinylcholine is administered with halothane, **malignant hyperthermia** can result. Malignant hyperthermia is characterized by muscle rigidity and elevated body temperature, and is treated with **dantrolene**.

An 8-year-old patient with cystic fibrosis is admitted to the hospital for treatment of pneumonia. The attending pulmonologist would like to perform a bronchoscopy in order to obtain biopsies and mucous samples, but he will require the aid of anesthesia to relax the patient. You, as an anesthesiologist, are asked for assistance in providing adequate neuromuscular blockade for this short procedure. You decide to use a non-depolarizing neuromuscular blocker, which is short-acting and easily reversible and thus, it is quite appropriate for use in this situation.

Rocuronium

Similar Drugs	Vecuronium; atracurium; cisatracurium; tubocurarine; mivacurium; rapacuronium; pancuronium.
Mechanism of Action	Rocuronium is a **non-depolarizing neuromuscular blocker that acts to competitively bind nicotinic receptors at the neuromuscular junction**. Rocuronium does not activate the nicotinic receptor, but instead it acts to prevent acetylcholine from binding to and activating these receptors, thereby causing the neuron to remain inactivated with resulting inhibition of muscle contraction.
Clinical Uses	Rocuronium is used as an **adjunct to general anesthesia induction** to reduce skeletal muscle contraction for the facilitation of endotracheal intubation.
Side Effects	**Hypotension**; tachycardia; prolonged respiratory depression.
Other	The effects of rocuronium can be **reversed with the**

administration of a cholinesterase inhibitor (e.g., neostigmine), which acts to increase levels of acetylcholine in the neuromuscular junction and thereby helps to overcome the competitive binding of rocuronium to nicotinic receptors.

A 31-year-old man presents to the emergency room after having been involved in a bar brawl at a local establishment. He has sustained a deep cut to his left forearm. After thoroughly cleaning the wound and confirming that there is no residual debris in the wound, you explain to the patient that he will need stitches. He asks whether he will feel any pain during the procedure, and you reassure him that you will administer a medication to the area of the wound that will dull his sensation to pain by blocking neuronal sodium channels.

Local Anesthetic Agents

Similar Drugs	The local anesthetics can be divided into two groups **(esters and amides)** based on differences in chemical structure. Esters include **procaine**, **cocaine**, **tetracaine**, and **benzocaine**. Amides include **bupivacaine, lidocaine, and mepivicaine**.
Mechanism of Action	The local anesthetics act by **blocking sodium channels** on neuronal cell membranes, thereby decreasing the activation of these neurons. Nerve blockade tends to occur most rapidly in myelinated fibers of small diameter.
Clinical Uses	The local anesthetics are used during **minor surgical procedures** in which sensation needs to be blocked in a localized area of the body, but unconsciousness is not necessary.
Side Effects	**Seizures** and neurotoxicity (associated with systemic uptake of drug); myocardial depression and hypotension (associated with bupivacaine); hypertension and cardiac arrhythmias (associated with cocaine).
Other	**Vasoconstrictors**, **such as epinephrine**, **are often given locally with the local anesthetic**, so that the rate of systemic absorption

of the anesthetic is decreased and a more effective nerve block is obtained since more anesthetic remains in the desired area.

In general, esters tend to have a shorter duration of action than amides (although tetracaine has a reasonably long duration of action).

Within 2 weeks after major abdominal surgery, a 56-year-old man goes into fulminant liver failure and dies. The cause of the liver failure is unknown since he had no signs of liver disease before his surgery. Biopsy during autopsy shows massive centrilobular liver cell necrosis. You hypothesize that the patient may have suffered a rare complication of general anesthesia and that the medication, as opposed to a preexisting liver condition, was responsible for his death.

General Inhaled Anesthetic Agents

Similar Drugs	Examples of general inhaled anesthetics include **halothane**, **isoflurane**, **desflurane**, **sevoflurane**, **enflurane**, and **methoxyflurane**.
Mechanism of Action	The exact mechanism of action of general inhaled anesthetics is not completely understood. Recent research has demonstrated that the general anesthetics directly activate $GABA_A$ receptors throughout the brain, thereby leading to **decreased neuronal activity**.
Clinical Uses	Used for **general anesthetic induction and maintenance** for surgical procedures.
Side Effects	All of the general inhaled anesthetics can cause **myocardial and respiratory depression**, GI upset, and they can increase cerebral blood flow through vasodilation. Specific anesthetics are associated with certain side effects. **Halothane** has been shown to cause **fulminant hepatic necrosis**, hypotension, and **cardiac arrhythmias**. **Methoxyflurane** and **enflurane** have both been shown to be

	nephrotoxic, and enflurane has also been associated with seizures.
Other	When halothane is administered with succinylcholine, **malignant hyperthermia** can result in genetically susceptible patients. Malignant hyperthermia is characterized by muscle rigidity and elevated body temperature, and is treated with **dantrolene**.

A 73-year-old man is brought to the emergency room complaining of palpitations. An electrocardiogram reveals that the patient is in ventricular tachycardia. His blood pressure is marginal at 90/60 mm Hg, so you decide to electrically cardiovert this patient. To prepare the patient for cardioversion, you administer a short-acting intravenous anesthetic agent that acts to prolong activity at the $GABA_A$ receptor, but that also causes only minimal hypotension.

General Intravenous Anesthetic Agents

Similar Drugs	Includes **propofol**, **etomidate**, **ketamine**, **benzodiazepines** (see Benzodiazepine card in Chapter 4), **barbiturates** (see Barbiturates card in Chapter 4), and **opioids** (see Opioids card in Chapter 4).
Mechanism of Action	**Propofol**: mechanism of action is unknown, but may act to prolong activity at the $GABA_A$ receptor, thereby potentiating the effect of GABA at the postsynaptic neuron. **Etomidate**: acts to prolong activity at the $GABA_A$ receptor, thereby potentiating the effect of GABA at the postsynaptic neuron. **Ketamine**: PCP analog that acts as an NMDA receptor antagonist, thereby decreasing neuronal conduction.
Clinical Uses	**Propofol**: used for **induction and maintenance of anesthesia** and conscious sedation. **Etomidate**: used for **induction of anesthesia** and conscious

	sedation. **Ketamine**: **used less often due to side effect profile**; can be used for minor surgical procedures and local anesthetic for neuropathic pain; may be useful in acutely suicidal patients.
Side Effects	**Propofol**: **hypotension**; chemical pancreatitis. **Etomidate**: vomiting; myoclonus; adrenal suppression. **Ketamine**: hallucinations; cardiac and respiratory depressant.
Other	

A 73-year-old man with metastatic prostate cancer is transferred to your hospice for palliative care. Upon transfer from the hospital, he was given a grim prognosis of days to weeks. Upon physical examination, the patient appears to be in severe pain, but he does not exhibit any signs of respiratory distress. In order to control his pain, you provide the patient with a self-controlled pump containing an analgesic that binds to specific receptors in the brain and spinal cord involved in pain transmission.

Opioids

Similar Drugs	This class of drugs includes **morphine**, **codeine**, **oxycodone**, **hydrocodone**, **hydromorphone**, **heroin**, **meperidine**, **fentanyl**, and **dextromethorphan**.
Mechanism of Action	The opioids produce analgesia by **binding to specific opioid receptors** located throughout the nervous system (mostly in the brainstem, spinal cord, peripheral nerves, amygdala, thalamus, and hypothalamus). Activation of these receptors results in the **hyperpolarization and decreased activity of neural cells** through interaction with calcium and potassium ion channels.
Clinical Uses	The opioids are primarily used for **pain control** (morphine, fentanyl, codeine), **cough suppression** (codeine and dextromethorphan act to suppress the cough reflex in the brainstem), **diarrhea** (diphenoxylate, which is an analogue of

	meperidine, acts to decrease smooth muscle motility in the gut), and **acute pulmonary edema and ischemic pain during myocardial infarction** (morphine acts to reduce anxiety and cardiac preload).
Side Effects	**Cardiac and respiratory depression**; **constipation**; **miosis**; nausea; urinary retention.
Other	The development of **tolerance and dependence** is a very serious problem with opioid use. Abrupt withdrawal from opioids can result in severe GI upset, anxiety, and chills. While opioid withdrawal is very uncomfortable, it is unlikely to be fatal. **Naloxone** and **naltrexone** act as opioid receptor antagonists and are used to treat opioid overdoses. **Methadone** is an opioid that is used in maintenance programs for opioid addicts and helps ease withdrawal symptoms without producing the characteristic "high" often associated with opioids.

A 31-year-old woman presents to the hospital in labor. You admit her to the obstetrics ward and allow her labor to progress. Despite treatment with an epidural, the patient continues to be in severe and uncontrollable pain. You decide to administer a synthetic opioid analogue to treat her pain that can also be used to treat severe migraine headaches when given in the intranasal formulation.

Butorphanol

Similar Drugs	Levorphanol.
Mechanism of Action	Butorphanol is a synthetic opioid analogue that exhibits **partial agonist activity at opioid μ receptors and agonist activity at opioid κ receptors**. Activation of these receptors results in the

	hyperpolarization and decreased activity of neural cells through interaction with calcium and potassium ion channels.
Clinical Uses	Used for the treatment of moderate to severe **pain**, especially in the management of migraines (through an intranasal formulation), labor pain, post-operative pain, or as an adjunct to general anesthesia.
Side Effects	Confusion; sedation; dizziness; GI upset.
Other	Long-term use of butorphanol may result in dependence on the drug, and patients may experience symptoms of opioid withdrawal with sudden cessation of the drug. **Pentazocine** also acts as a partial agonist at opioid μ receptors and a full agonist at opioid κ receptors. It is used primarily for relief of **severe pain** as well as an adjunctive surgical analgesic. Patients taking pentazocine are also at risk of withdrawal if they had previously been taking a full agonist.

A 65-year-old woman presents to your clinic, complaining of severe lower back pain that developed after she tried to pick up a heavy box in her attic. Physical examination is suggestive of a herniated disc in the lumbar spine and imaging studies confirm your findings. You begin the patient on a high-dose non-steroidal anti-inflammatory regimen and you suggest that she start physical therapy. After 3 days, the patient calls your office, saying that the pain is unbearable and not controlled on the non-steroidal anti-inflammatory medications. She is very reluctant to try an opiate medication for her pain, so you decide to instead prescribe a medication that acts as a very weak opioid agonist and also has been shown to inhibit the reuptake of norepinephrine and serotonin at the synaptic junction.

Tramadol

Similar Drugs	

Mechanism of Action	The mechanism of action of tramadol is not completely understood, but it is believed to act as a very **weak μ opioid receptor agonist**, thereby resulting in hyperpolarization and decreased activity of neural cells. It is also thought to inhibit the reuptake of norepinephrine and serotonin, thereby increasing the concentration of these neurotransmitters in the synaptic junction.
Clinical Uses	Used to treat moderate to moderately severe chronic **pain**.
Side Effects	GI upset; respiratory depression; **seizures** (tramadol has been reported to decrease seizure threshold); suicidal tendencies; serotonin syndrome.
Other	

A 57-year-old patient presents to the hospital for a planned routine hemicolectomy for the treatment of ulcerative colitis. As the anesthesiologist of the case, you use standard anesthetic agents to sedate the patient including succinylcholine and halothane. About 1 hour into the procedure, you notice that the patient's body temperature has risen to 102°F, his heart rate is 122 beats/min, and he is over-breathing the ventilator at a rate of 40 breaths/min. Examination of the patient's urine from his Foley reveals a very dark fluid that is likely consistent with rhabdomyolysis. You immediately become concerned that this patient is suffering from a rare condition that was likely triggered by the anesthetic agents. You ask the surgeon to stop the procedure and you immediately begin treatment with an intravenous antidote and supportive therapy directed at correcting the patient's hyperthermia and metabolic disarray.

Dantrolene

Similar Drugs	
Mechanism of Action	Dantrolene acts **by inhibiting calcium release from the sarcoplasmic reticulum of myocytes** by binding to the

	ryanodine receptor. This results in the dissociation of the excitation-contraction coupling in the skeletal muscle and, therefore, **muscle relaxation**.
Clinical Uses	Used to treat **malignant hyperthermia** (a condition triggered by exposure to general anesthetic agents (e.g., succinylcholine or halothane) that presents with hyperthermia, tachycardia, acidosis, and muscle breakdown). Also used to treat **neuroleptic malignant syndrome** (a syndrome, which results after treatment with certain anti-psychotic agents or other CNS agents (e.g., haloperidol, levodopa, or metoclopramide), that is characterized by hyperthermia, mental status change, muscle breakdown, and autonomic instability).
Side Effects	**Hepatotoxicity**; CNS effects (speech and visual disturbances, confusion, hallucinations, headache); GI upset.
Other	

A 63-year-old man presents to your clinic complaining of the gradual onset of stiffness in his extremities. He also tells you that he has recently noticed a tremor in his right arm. As you are interviewing the patient, you notice that he has a blank expression on his face. Physical examination is significant for cogwheel rigidity in all extremities, a pill-rolling tremor, and a shuffling gait. While ordering further tests, you decide to start the patient on a medication that will act to increase the levels of dopamine in his brain.

Levodopa

Similar Drugs	
Mechanism of Action	Levodopa is **converted into dopamine in the brain by *DOPA-decarboxylase*** after crossing the blood-brain barrier, thereby leading to increased levels of dopamine in the central nervous

	system.
Clinical Uses	First-line (and most effective) **treatment for parkinsonism**, which is a condition associated with the loss of dopaminergic neurons in the basal ganglia. Levodopa may also be used for the treatment of **restless leg syndrome**.
Side Effects	**Dyskinesia** and sporadic movements; **cardiac arrhythmias** (caused by peripheral conversion of levodopa to dopamine); nausea and vomiting; hallucinations; depression.
Other	Levodopa is administered in combination with **carbidopa**. Carbidopa acts to **inhibit *DOPA-decarboxylase***; however, it is only able to perform this action **in the peripheral circulation**, since carbidopa is unable to cross the blood-brain barrier. By using carbidopa, the side effects of increased dopamine levels in the periphery are limited and the bioavailability of levodopa is increased in the brain. **Bromocriptine** is a **partial dopamine receptor agonist** that is used as an adjunct treatment for **parkinsonism** as well as in the treatment of **hyperprolactinemia**. **Other anti-parkinsonism agents** include other dopamine agonists (e.g., amantadine, pramipexole, and ropinirole), *catechol-O-methyltransferase* inhibitors (e.g., tolcapone), and MAO type B inhibitors (e.g., selegiline).

A 74-year-old woman presents to your clinic for management of her Parkinson's disease. Her daughter, who accompanies her, reports that her mother is experiencing significant side effects from her anti-parkinsonism medications. She reports that she has observed her mother move her arms and legs uncontrollably. You determine that the side effects are likely due to the first-line medication used to treat her condition, and you decide to try to reduce her requirement for that medication by prescribing another medication that works to decrease the breakdown of dopamine.

Tolcapone

Similar Drugs	Entacapone.
Mechanism of Action	Tolcapone selectively and reversibly **inhibits *catechol-O-methyltransferase* (COMT)**, which **catalyzes the degradation of catechol neurotransmitters** such as norepinephrine, epinephrine, and dopamine. By inhibiting the degradation of endogenous dopamine as well as L-dopa, tolcapone increases the available substrate to bind the dopamine receptor.
Clinical Uses	Used to treat **parkinsonism**.
Side Effects	**Hepatotoxicity;** hypotension; drowsiness; headache.
Other	**Other anti-parkinsonism agents** include levodopa, dopamine agonists (e.g., amantadine, pramipexole, and ropinirole), and MAO type B inhibitors (e.g., selegiline).

A 35-year-old woman presents to your clinic complaining of changes in her mood as well as "difficulty with coordination." She reports that family members have told her that her movements are "jerky." She states that sometimes she feels like she cannot control the movements at all. She notes that her father and paternal grandmother both passed away at an early age from "some nerve issue." Physical exam demonstrates involuntary movements of her arms. After running a genetic test, your suspicions are confirmed and you tell the patient that she has a currently incurable genetic disease. However, you emphasize that medications can help manage her symptoms and you prescribe a drug that works by depleting catecholamines.

Tetrabenazine

Similar Drugs	
Mechanism	Tetrabenazine reversibly **inhibits the uptake of catecholamines**

of Action	(norepinephrine, epinephrine, and dopamine) as well as serotonin into synaptic vesicles by **blocking the vesicular monoamine transporter type 2 (VMAT-2)**. This leads to depletion of these neurotransmitters in the synaptic cleft, thereby reducing the pro-kinetic activity of dopamine.
Clinical Uses	Tetrabenazine is primarily used to treat the **choreiform movements seen in Huntington's disease**, though may be used for other choreiform disorders, hemiballismus, tardive dyskinesia, and Tourette syndrome.
Side Effects	**Parkinsonism**; drowsiness; weakness; depression.
Other	**Reserpine** acts to irreversibly inhibit VMAT-2. In comparison to tetrabenazine, reserpine is irreversible and thereby can lead to long-lasting drug-induced parkinsonism. It also has a greater tendency to act upon VMAT-2 outside of the CNS, thereby leading to **hypotension** and **bradycardia**. Reserpine was initially used as an anti-hypertensive agent; however, it is rarely used now for that indication secondary to its side effect profile. It is still occasionally used to treat dyskinesia in patients with Huntington's disease.

A 73-year-old man presents to your clinic with a 3-month history of upper extremity weakness. His wife, who accompanies him to the appointment, also mentions that he has also been behaving differently around the house and is less animated than usual. On physical exam, the patient demonstrates muscular atrophy, fasciculations, and 3/5 strength in both biceps. His light touch, pain, and vibratory sensations are preserved throughout all dermatomes. You suspect that the patient may have a disease affecting both upper and lower motor neurons. After relaying this diagnosis to the patient, you discuss initiating the patient on a medication that may slow disease progression.

Riluzole

Similar

Drugs	
Mechanism of Action	Although the exact mechanism of action is not entirely known, riluzole has been shown to reduce release of glutamate by blocking voltage-gated sodium channels. This is thought to ultimately **reduce neuronal cell death by decreasing glutamine excitotoxicity.**
Clinical Uses	Riluzole is used to **slow disease progression in amyotrophic lateral sclerosis**.
Side Effects	Dizziness; nausea; hypertension.
Other	Amyotrophic lateral sclerosis is a fatal disease and riluzole has **only a mild effect on long-term survival** (likely 2 to 3 months).

An 86-year-old man is brought to your geriatrics clinic by his daughter. He was diagnosed with Alzheimer disease 1 year ago and has been treated with donepezil since. His daughter reports that her father's dementia has continued to worsen. He often forgets who she is and has been found wandering the streets twice in the last 2 weeks. You tell the daughter that her father will likely need full-time care at this point. In the meantime, you also prescribe another medication that acts as an N-methyl-D-aspartate (NMDA) receptor antagonist in the hopes of providing some symptomatic improvement in his dementia.

Memantine

Similar Drugs	
Mechanism of Action	Memantine primarily acts as an **NMDA receptor antagonist**. One of the hypotheses of the etiology of Alzheimer's disease is that the persistent excitation of the NMDA receptors by glutamate leads to a neurotoxic state that results in neuronal damage. By blocking NMDA activation, memantine is thought to **decrease neuronal excitation by glutamate** and therefore

	may lead to symptomatic improvement in Alzheimer patients. There is also some evidence that memantine may also act at a variety of other neurotransmitter receptors (serotonin 5HT-3 receptor, nicotinic acetylcholine receptors, dopamine D_2 receptor), but the contribution of these actions is unknown.
Clinical Uses	Used in the treatment of moderate to severe **Alzheimer's disease**.
Side Effects	**CNS effects** (agitation, dizziness, headache); dystonic reactions.
Other	Memantine has only been shown to provide symptomatic improvement in patients with advanced Alzheimer's disease. There is no data to suggest that memantine can either prevent or slow the progression of Alzheimer's disease. **Donepezil** is also used to treat Alzheimer's disease (see card on Donepezil in Chapter 3).

A 19-year-old college student presents to the university urgent care clinic complaining of a severe headache. She reports that she has a throbbing, pulsatile pain on the right side of her head that started about 3 hours ago and that she is also feeling nauseous. Upon further questioning, you learn that she has suffered from similar headaches on and off for the last year. She also tells you that she experiences blind spots in her left eye just before the headache comes on. In order to treat the attack acutely, you administer a medication that will stimulate presynaptic 5-HT1D receptors in the dura, which you hope will relieve her symptoms.

Sumatriptan

Similar Drugs	Naratriptan; rizatriptan; zolmitriptan.
Mechanism of Action	Sumatriptan acts to **stimulate presynaptic 5-HT_{1D} receptors**, which results in the inhibition of vasodilation and inflammation

	of the dura. The drug has also been shown to activate vascular 5-HT_{1B} receptors, which results in the vasoconstriction of intracranial vessels.
Clinical Uses	Used in the acute treatment of **migraines** and **cluster headaches**.
Side Effects	**Coronary vasospasm** with resulting chest pain; dizziness.
Other	Since sumatriptan can cause coronary vasospasm, this drug is **contraindicated in patients with coronary artery disease or Prinzmetal angina.**

A 35-year-old business professional is seen in your clinic to discuss treatment for his generalized anxiety disorder. He is currently taking benzodiazepines as needed to serve as his anxiolytic. He is concerned about the addictive nature of his current therapy and he is also upset that he cannot use his current medication with social alcohol intake. He would like to change his medication regimen. You prescribe an agent that fits the needs of the patient, but you inform him that it may take 1 to 3 weeks to show efficacy against his generalized anxiety.

Buspirone

Similar Drugs	
Mechanism of Action	Buspirone acts as a **5-HT_{1A} presynaptic receptor partial agonist**. It also has mixed agonist/antagonist activity on postsynaptic dopamine receptors in the brain.
Clinical Uses	Used in the treatment of **generalized anxiety disorder**; may also be used in conjunction with SSRIs in treating depression.
Side Effects	Dizziness; insomnia; nausea.

Other	Buspirone is not effective as an acute treatment for anxiety (unlike benzodiazepines), and may require up to 2 weeks to take effect.

A 21-year-old college student presents to your office complaining of fatigue. He also notes that he no longer enjoys spending time with friends and family and that his grades have suffered this past semester. He denies explicit suicidal ideation, although he does admit that he has recently thought about whether life is worth living. Worried about his performance in school, he has attempted to reduce anxiety by taking up smoking. After telling the patient that his symptoms may be signs of depression, you also voice concern over his smoking habits. You both agree to try a drug that may be effective in reducing his psychiatric symptoms as well as making it easier for him to discontinue his smoking habit.

Bupropion

Similar Drugs	
Mechanism of Action	Bupropion acts to **inhibit reuptake of norepinephrine and dopamine** and also acts as a **nicotinic antagonist**. Preventing norepinephrine and dopamine reuptake increases their activity in the synaptic cleft. As depression is associated with a decrease in dopamine and norepinephrine signaling, increasing the activity of those neurotransmitters may provide benefit for depressed patients. Reduction of nicotinic acetylcholine receptor stimulation results in the **reduction of dopaminergic mesolimbic signaling**, thereby decreased the reward associated with smoking.
Clinical Uses	Used to treat **depression** and attention deficit hyperactivity disorder; also used as a **smoking cessation agent**.
Side Effects	Psychosis; **increased risk of seizures in patients suffering from anorexia or bulimia**; suicidal ideation; hypertension.
Other	Unlike many other anti-depressant agents, bupropion is not

known to induce sexual side effects.

A 32-year-old woman presents to your clinic for a routine physical examination. Overall, she feels well and has no complaints. She has no past medical history other than tobacco use. She states that she has been smoking about 1 pack of cigarettes a day for the last 10 years. You strongly encourage her to quit smoking and she seems willing to try to stop using tobacco. You offer to prescribe her a medication that has been shown to aid in smoking cessation by acting as a partial agonist at nicotinic receptors.

Varenicline

Similar Drugs	
Mechanism of Action	Varenicline acts as a **partial agonist at the $\alpha_4\beta_2$ nicotinic acetylcholine receptors** subtype found in the brain. Blockade of CNS nicotinic acetylcholine receptors is thought to **reduce dopaminergic signaling through the mesolimbic system** (also known as the "reward pathway"), thereby reducing the pleasure associated with smoking.
Clinical Uses	Used to assist patients in **smoking cessation**.
Side Effects	Nausea; seizures; insomnia and vivid dreams; **depression and suicidal ideation**.
Other	

A 44-year-old man presents to your office complaining of lower back pain. The patient works in construction, and he reports that the pain began suddenly after he tried to lift a heavy sandbag at work 5 weeks ago. Since then, he has been managing his symptoms with NSAIDs and acetaminophen. Unfortunately, he has continued to have painful, debilitating back spasms. After discussing several

options, you both agree that opioids are a poor choice and instead decide that physical therapy in addition to an anti-spasmodic agent may provide the most symptomatic benefit.

Muscle Relaxants

Similar Drugs	Commonly used muscle relaxants include **baclofen** and **cyclobenzaprine**.
Mechanism of Action	**Baclofen**: The exact mechanism is unknown, but baclofen may work to reduce reflex muscle activation by hyperpolarization of afferent pathways. **Cyclobenzaprine**: Structurally related to TCAs, cyclobenzaprine acts centrally to depress muscle neuron excitation by an unknown mechanism.
Clinical Uses	Both baclofen and cyclobenzaprine are used to treat **muscle spasms**. Cyclobenzaprine may also be used for temporomandibular joint pain.
Side Effects	**Baclofen**: hypotonia; drowsiness; GI upset. **Cyclobenzaprine**: dry mouth; drowsiness; confusion (primarily related to **anti-cholinergic properties** as a TCA analog).
Other	

A 76-year-old man with a history of recent shingles presents to your clinic complaining of right leg pain for the past month. He describes the pain as a “sharp pins and needles” feeling over his calf exactly where he had suffered from shingles. Physical examination is unremarkable and there is no evidence of deep venous thrombosis, ulceration, or cellulitis. You tell him that you believe his pain is related to his prior episode of shingles and you decide to prescribe him a medication to treat his neuropathic pain.

Gabapentin

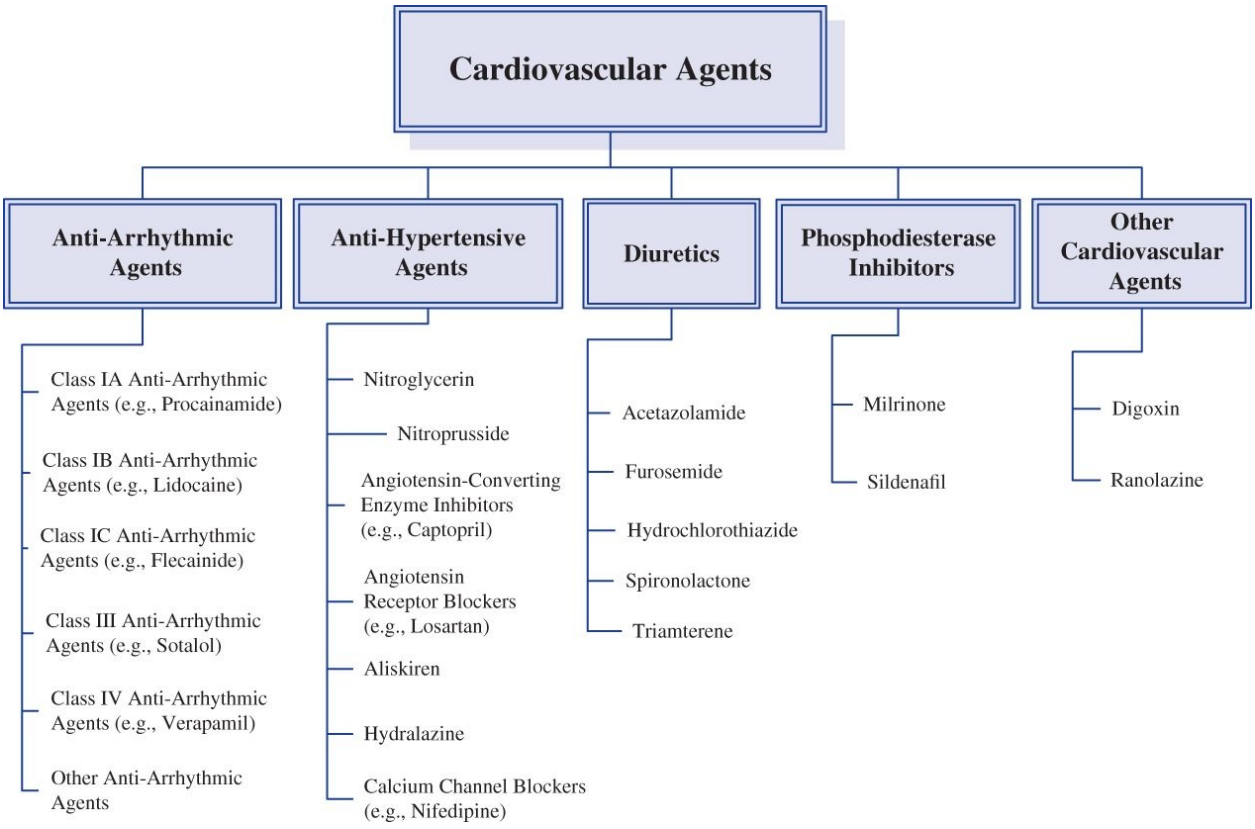
Similar Drugs	
Mechanism of Action	Although gabapentin is a **GABA analogue**, the exact mechanism of this drug is unknown. There is some evidence to suggest that the drug interacts with calcium ion channels in the CNS, which may result in the decrease of glutamate and norepinephrine release.
Clinical Uses	Used to treat **post-herpetic neuralgia**, chronic **neuropathic pain**, and as adjunctive therapy for **partial seizures**.
Side Effects	**Sedation;** peripheral edema; hepatotoxicity.
Other	

A 42-year-old woman presents to your clinic complaining of diffuse body aches for the last 6 months. After a full history and physical examination including assessment of the 18 tender points, you begin to suspect that the patient may be suffering from fibromyalgia. In addition to ordering some routine blood work to rule out inflammatory arthritis, myositis, and metabolic abnormalities, you decide to start the patient on a medication that may improve her symptoms by binding to voltage-gated calcium ion channels in the CNS, thereby decreasing glutamate and norepinephrine release.

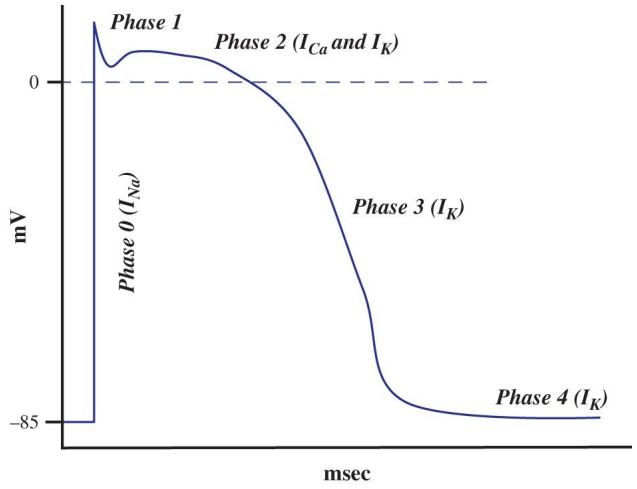
Pregabalin

Similar Drugs	
Mechanism of Action	The exact mechanism of pregabalin is unknown, although it is hypothesized to bind to voltage-gated calcium ion channels in the CNS, thereby decreasing the release of multiple excitatory neurotransmitters, including glutamate and norepinephrine.
Clinical	Used to treat chronic **neuropathic pain**, **fibromyalgia**, and

Uses	post-herpetic neuralgia, and as an adjunct treatment of partial seizures.
Side Effects	**Dizziness**; sedation; ataxia; peripheral edema.
Other	



CARDIAC ACTION POTENTIAL



Phase 0: Rapid Depolarization

– Fast voltage-gated Na^+ channels open leading to rapid inward Na^+ current ($\boldsymbol{I_{Na}}$).

– Membrane potential rises to +25 mV inside the cell.

Phase 1: Initial Repolarization

– Rise in membrane potential leads to inactivation of fast voltage-gated Na^+ channels.

– Membrane potential begins to drop transiently due to movement of K^+ and Cl^- ions ($\boldsymbol{I_{to1}}$, $\boldsymbol{I_{to2}}$).

Phase 2: Plateau

– L-type voltage-gated Ca^{2+} channels open and allow influx of Ca^{2+} into cell ($\boldsymbol{I_{Ca}}$).

– Influx of Ca^{2+} is balanced by efflux of K^+ through slow-delayed rectifier K^+ channels ($\boldsymbol{I_{Ks}}$).

Phase 3: Rapid Repolarization

– L-type voltage-gated Ca^{2+} channels close, while slow-delayed rectifier K^+ channels remain open ($\boldsymbol{I_{Ks}}$), thereby leading to net outward positive current.

– Change in membrane potential also allows more K^+ channels to open (rapid-delayed rectifier K^+ channels ($\boldsymbol{I_{Kr}}$) and inwardly rectifying K^+ current ($\boldsymbol{I_{K1}}$)).

Phase 4: Resting Membrane Potential

– Resting membrane potential is around −85 mV and is dominated by K^+ equilibrium potential as the cell membrane is most permeable to K^+ via "leak" channels ($\boldsymbol{I_{K1}}$).

– Maintenance of electrical gradient is mediated by ion pumps and exchange

mechanisms (e.g., Na^+-K^+ ATPase pump; Na^+-Ca^{2+} exchanger).

A 23-year-old man presents to the emergency room complaining of a prolonged episode of palpitations. He reports that he has had intermittent episodes of palpitations, which he describes as rapid and regular, over the last several months; however, the episodes usually stop on their own. A 12-lead-electrocardiogram reveals a wide complex tachycardia at a rate of 136 beats/min. In looking at an electrocardiogram that was done at a routine primary care appointment, you notice the presence of delta waves. You begin to suspect that this patient may have Wolff-Parkinson-White syndrome. Since his blood pressure is stable, you decide to try an intravenous agent to treat this patient's arrhythmia in the short term, since you worry that long-term use of this medication may lead to a lupus-like syndrome.

Class IA Anti-Arrhythmic Agents

Similar Drugs	The class IA anti-arrhythmic drugs include **quinidine**, **procainamide**, and **disopyramide**.
Mechanism of Action	The class IA anti-arrhythmic agents act by **binding to activated sodium channels and blocking the flow of sodium ions into the sinoatrial node cells and cardiac myocytes**. At the sinoatrial node, this causes an increase in the threshold for action potential and prolongation of phase 4 depolarization. In cardiac myocytes, by blocking activated sodium channels, **phase 0 depolarization of the cardiac action potential is prolonged**, thereby slowing the rate of conduction of the action potential and thus the rate of cardiac muscle contraction. **Phase 3 repolarization is also delayed** by a small interaction of the class IA anti-arrhythmic agent with potassium channels. This interaction results in a longer refractory period for the cardiac myocyte and thus the cardiac myocyte is unable to fire as frequently. (Prolonged phase 3 repolarization is manifested on the ECG as a **prolonged QT interval**.)
Clinical	Used to treat and prevent the recurrence of a variety of

Uses	arrhythmias, including **atrial fibrillation**, **Wolff-Parkinson-White syndrome**, and **ventricular tachycardia**.
Side Effects	All class IA anti-arrhythmic agents may **cause cardiac arrhythmias** (including torsades de pointes due to QT prolongation). **Quinidine**: GI upset; **cinchonism** (vertigo, headache, tinnitus, psychosis). **Procainamide**: **Drug-induced lupus**; psychosis. **Disopyramide**: Urinary retention; double vision; constipation.
Other	All class I anti-arrhythmic agents are **use-dependent**, meaning that they tend to be more active at ion channels that are depolarizing more frequently.

A 73-year-old woman is brought to the emergency department complaining of chest pain. While she is waiting to be seen, she suddenly collapses. You are unable to obtain a pulse and an electrocardiogram reveals that she is in ventricular fibrillation. After a series of electrical shocks and the administration of epinephrine, you restore her heart rhythm to ventricular tachycardia. In addition to evaluating this patient for ischemic causes of her arrhythmia, you decide to administer an anti-arrhythmic agent that is often used in the treatment of ventricular fibrillation and ventricular tachycardia and that is characterized by its ability to decrease the duration of the cardiac action potential.

Class IB Anti-Arrhythmic Agents

Similar Drugs	The class IB anti-arrhythmic drugs include **lidocaine** and **mexiletine**.
Mechanism of Action	The class IB anti-arrhythmic agents act by **binding to both activated and inactivated sodium channels and blocking the flow of sodium ions into the cardiac myocyte**. By blocking inactivated sodium channels and therefore decreasing the ability of those channels to become activated, **phase 3 repolarization of the cardiac action potential as well as the entire duration**

	of the action potential is actually shortened, and the ability for the cardiac myocyte to be stimulated to contract is diminished.
Clinical Uses	The class IB anti-arrhythmic agents are used to treat a variety of ventricular arrhythmias (e.g., **ventricular fibrillation** or **ventricular tachycardia**).
Side Effects	All class IB anti-arrhythmic agents may **cause cardiac arrhythmias**. Other side effects include hypotension, tremor, fatigue, and nausea. Prolonged administration of high doses of lidocaine can lead to neurotoxicity and altered mental status.
Other	Lidocaine is also used as a local anesthetic (see Local Anesthetic Agents card in Chapter 4). Phenytoin is also technically a Class IB anti-arrhythmic; however, it is used to treat epilepsy (see Phenytoin card in Chapter 4). All class I anti-arrhythmic agents are **use-dependent**, meaning that they tend to be more active at ion channels that are depolarizing more frequently.

A 42-year-old man presents to the emergency room complaining of palpitations. On physical examination, he is cool to touch, diaphoretic, and mildly hypotensive with a blood pressure of 90/50 mm Hg. His electrocardiogram demonstrates an irregular supraventricular tachycardia at a rate of 144 beats/min, likely consistent with atrial fibrillation. This is his third presentation to the hospital with supraventricular tachycardia in the 2 months. After you stabilize the patient and control his heart rate, you call for a cardiology consult to assess whether the patient might be a candidate for treatment with an anti-arrhythmic medication. When the cardiologist arrives, he suggests placing the patient on an agent that acts by blocking sodium channels in the cardiac myocyte, but he states that this medication should only be used in patients with structurally normal hearts.

Class IC Anti-Arrhythmic Agents

Similar Drugs	The class IC anti-arrhythmic drugs include **flecainide**, **propafenone,** and **moricizine.**
Mechanism of Action	The class IC anti-arrhythmic agents act by **binding to sodium channels and blocking the flow of sodium ions into the cardiac myocyte**. By blocking sodium channels, **phase 0 depolarization of the cardiac action potential is prolonged**, thereby slowing the rate of conduction of the action potential and thus the rate of cardiac muscle contraction. This class of drugs has no effect on the duration of the action potential.
Clinical Uses	Used to **treat supraventricular arrhythmias**.
Side Effects	**Exacerbation or induction of life-threatening arrhythmias**; **avoid in patients with structurally abnormal hearts** (e.g., depressed left ventricular ejection fraction) **or ischemic heart disease**.
Other	All class I anti-arrhythmic agents are **use-dependent**, meaning that they tend to be more active at ion channels that are depolarizing more frequently.

An 82-year-old man with a known history of both atrial and ventricular arrhythmias presents to your cardiology clinic for a follow-up visit. He denies any palpitations or chest pain currently and his electrocardiogram shows no acute changes, although his QT segment is slightly prolonged. His medication regimen includes a drug that acts by blocking potassium, sodium, and calcium channels in the cardiac myocyte. You explain to him that he appears to be doing well and that his cardiac arrhythmias appear to be controlled, but you caution him that his medication could predispose him to developing pulmonary fibrosis, liver toxicity, or thyroid dysfunction.

Class III Anti-Arrhythmic Agents

Similar Drugs	The class III anti-arrhythmic drugs include **amiodarone, sotalol**, **ibutilide**, **dofetilide**, and **bretylium**.

Mechanism of Action	The class III anti-arrhythmic drugs act by **binding to potassium channels and blocking the flow of potassium ions out of the cardiac myocyte**. By blocking potassium channels, **phase 2 and 3 repolarization is prolonged as is the entire duration of the action potential**, thereby prolonging the refractory period of the myocyte, and thus decreasing the contractile frequency of the cell. Prolonged phase 3 repolarization is manifested on the ECG as a **prolonged QT interval**. **Sotalol also has potent β-blocking activity**.
Clinical Uses	**Dofetilide** and **ibutilide** are used to treat **atrial arrhythmias**. **Bretylium** is used (rarely) in the emergency treatment of some ventricular arrhythmias. **Sotalol** and **amiodarone** have been used for the suppression of both **atrial and ventricular arrhythmias**.
Side Effects	All class III anti-arrhythmic agents may **cause cardiac arrhythmias** (including torsades de pointes). Other side effects include bradycardia and hypotension.
Other	Class III anti-arrhythmic agents exhibit **reverse use-dependency**, meaning that they are more active in prolonging the action potential at slower heart rates, rather than faster heart rates. **Amiodarone** is an anti-arrhythmic agent that has **class I–IV anti-arrhythmic actions**, although it is generally classified as a class III agent. It has been shown to block sodium, potassium, and calcium channels on cardiac myocytes and it has also been shown to have some α- and β-adrenergic blocking effects. It primarily acts to **prolong the action potential duration** as well as the refractory period of the cardiac myocyte. Side effects of amiodarone use include **pulmonary fibrosis**, **hepatotoxicity**, **thyroid dysfunction**, cardiac arrhythmias, and photosensitivity.

A 53-year-old man with a history of coronary artery disease and hypertension presents to the emergency room with palpitations and dyspnea. On physical examination, he is tachycardic, diaphoretic, hypertensive (160/90 mm Hg), and

has an irregular heart beat. His electrocardiogram is consistent with atrial fibrillation at a rate of 152 beats/min. In order to rapidly slow this patient's heart rate down, you institute therapy with an agent that acts by blocking voltage-gated calcium channels.

Class IV Anti-Arrhythmic Agents

Similar Drugs	The class IV anti-arrhythmic agents include **verapamil** and **diltiazem** and are considered **non-dihydropyridine calcium channel blockers**.
Mechanism of Action	This class of drugs works by **blocking voltage-gated calcium channels** of cardiac and smooth muscle, thereby blocking the flow of calcium into the cell. By blocking the calcium channels in the **SA and AV nodal cells**, these drugs act to **slow phase 4 spontaneous depolarization** of these cells, thereby leading to delayed activation and contraction of these cells. (Prolonged phase 4 spontaneous depolarization is manifested on the ECG as a **prolonged PR interval**.) By blocking calcium channels, verapamil and diltiazem also **delay repolarization of the myocyte**, thereby prolonging the refractory period of the myocyte and thus decreasing the contractile frequency of the cell.
Clinical Uses	This class of anti-arrhythmic agents is used to treat **supraventricular tachycardia** (e.g., **atrial fibrillation**).
Side Effects	Hypotension; heart block; constipation.
Other	Since verapamil and diltiazem cause vascular smooth muscle relaxation, they are also used to treat hypertension and angina (see Calcium Channel Blockers card in Chapter 5).

A 29-year-old woman with a history of paroxysmal supraventricular tachycardia since adolescence presents to your clinic complaining of the onset of palpitations 2 hours ago. She denies any syncope, dizziness, dyspnea, or chest pain. An

electrocardiogram demonstrates a supraventricular tachycardia at a rate of 180 beats/min. You try to break the arrhythmia with carotid massage, but you are unsuccessful. You decide to send her to the emergency room, where you expect that she will be given a medication that will attempt to acutely stop her arrhythmia by increasing the potassium efflux out of the cardiac myocytes.

Other Anti-Arrhythmic Agents

Adenosine	*Mechanism*: Increases potassium efflux out of the cells of the sinoatrial and atrioventricular node, thereby hyperpolarizing the cell and decreasing the frequency of cellular activation. *Clinical Use*: Diagnosis and treatment of **supraventricular tachycardias**; also used as a pharmacologic agent in **cardiac stress testing**. *Side Effects*: Flushing; dyspnea; chest pain; hypotension; heart block.
Potassium	*Mechanism*: By increasing the extracellular concentration of potassium, the threshold for a cardiac action potential is raised, therefore making it more difficult for an action potential to be generated. Thus the rate of cardiac myocyte excitation is reduced. *Clinical Use*: **Suppresses ectopic pacemakers**, especially those associated with **digoxin toxicity**. *Side Effects*: Hyperkalemia; cardiac arrhythmias; paralysis; shock.
Magnesium	*Mechanism*: Although the exact mechanism is unclear, magnesium is believed to have effects on the ion flow through sodium, potassium, and calcium channels. *Clinical Use*: **Used to treat torsades de pointes**; also used to treat **digoxin toxicity**. *Side Effects*: Hypermagnesemia; hypotension; delayed deep tendon reflexes; paralysis.
Other	The **class II anti-arrhythmic agents** are the **β-blockers** (refer to **Propranolol**, **Carvedilol**, and **Metoprolol** cards in Chapter

2).

A 56-year-old man presents to your office complaining of mild, intermittent chest pain. He states that over the last 2 months he has been developing shortness of breath and sharp, substernal chest pain after climbing stairs and walking long distances. The pain does not radiate to his arms or throat, is not associated with eating, and resolves within minutes of rest. His past medical history is significant for elevated cholesterol levels. After a thorough cardiac workup including an electrocardiogram and exercise stress test, you decide to start the patient on several cardiac medications, including a medication that will relieve his symptoms by decreasing cardiac preload and by relaxing the coronary vasculature.

Nitroglycerin

Similar Drugs	Isosorbide dinitrate; isosorbide mononitrate; amyl nitrite.
Mechanism of Action	Nitroglycerin is **converted to nitric oxide** intracellularly. Nitric oxide acts to stimulate *guanylate cyclase*, thereby increasing cGMP synthesis. Elevated levels of cGMP leads to dephosphorylation and deactivation of myosin light chain, which thereby **results in smooth muscle relaxation**. Nitroglycerin **preferentially exerts its effects on the smooth muscle of veins**, which results in the pooling of blood in the veins and a **reduction in preload**. Nitroglycerin also **relaxes coronary artery smooth muscle**.
Clinical Uses	Used in the **treatment of angina**, pulmonary edema, hypertension, and **heart failure**.
Side Effects	Transient compensatory tachycardia; **headache (due to dilation of cerebral vessels)**; orthostatic **hypotension**.
Other	Long-term use of nitrates may result in tolerance to the drug, which can be mitigated by incorporating drug-free intervals into the dosing regimen.

A 28-year-old African-American man presents to the emergency room complaining of severe pounding headaches. As you question him further about his symptoms, he also tells you that his vision has become blurry over the past few hours. Physical examination reveals a well-nourished man, who appears slightly disoriented, with a blood pressure of 230/110 mm Hg. You diagnose the patient with hypertensive emergency and you decide to start him on an intravenous medication that will cause direct vasodilation of peripheral veins and arteries in order to reduce his blood pressure.

Nitroprusside

Similar Drugs	
Mechanism of Action	Nitroprusside is **metabolized into nitric oxide** in the bloodstream. Nitric oxide acts to stimulate *guanylate cyclase*, thereby increasing cGMP synthesis. Elevated levels of cGMP leads to dephosphorylation and deactivation of myosin light chain, which thereby **results in smooth muscle relaxation of peripheral veins** and **arteries**. The result is a **reduction in** peripheral vascular resistance and venous return (i.e., decreased **preload and afterload**).
Clinical Uses	Used in the **acute management of a hypertensive crisis** or in **severe heart failure and cardiogenic shock**.
Side Effects	**Cyanide toxicity**, which manifests as disorientation, psychosis, and seizures (thiocyanate is a metabolite of nitroprusside); orthostatic hypotension; metabolic acidosis; arrhythmias.
Other	Nitroprusside can **only be given intravenously**, since oral administration results in the formation of cyanide via hydrolysis of nitroprusside in the gastrointestinal tract. If cyanide toxicity results after nitroprusside use, the patient can be treated with **thiosulfate**.

A 53-year-old woman with a history of hypertension and diabetes presents to your office complaining of a chronic cough of 2½ months duration. Upon further questioning, she denies any fevers, chills, sweats, or recent respiratory illnesses. She denies cigarette use. Her medications include an oral hypoglycemic agent and an anti-hypertensive agent that she began 3 months ago. Physical examination reveals a blood pressure of 126/82 mm Hg and her lung examination is not significant. You begin to suspect that this patient's cough may be related to her new anti-hypertensive medication and you suggest switching medications.

Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)

Similar Drugs	ACE inhibitors include **lisinopril**, **enalapril**, **captopril**, **benazepril**, **fosinopril**, **moexipril**, **quinapril**, and **ramipril**.
Mechanism of Action	The ACE inhibitors act by **inhibiting the angiotensin-converting enzyme, *peptidyl dipeptidase***, which is responsible for hydrolyzing angiotensin I to angiotensin II and for decreasing the inactivation of bradykinin, a vasodilator. Angiotensin II has the following actions—it is a vasoconstrictor; it increases perfusion pressure in the glomeruli (through vasoconstriction of the efferent arterioles of the kidney); it stimulates aldosterone production (leads to increased salt and water retention by the kidney). By decreasing the levels of angiotensin II and increasing the levels of activated bradykinin, the ACE inhibitors act to decrease peripheral vascular resistance and to decrease the effective circulating volume of fluid in the body.
Clinical Uses	Used in the **treatment of hypertension and congestive heart failure** and to **treat and prevent diabetic nephropathy.** ACE inhibitors have also been shown to **decrease mortality in post-myocardial infarction patients**.
Side Effects	**Cough**; hyperkalemia and renal failure in patients with renal insufficiency; hypotension; teratogen (may cause fetal renal damage if used during pregnancy); **angioedema**.

Other

A 67-year-old man with a history of hypertension and diabetes presents to your clinic for a follow-up appointment. He was recently discharged from the hospital with a diagnosis of new-onset congestive heart failure. He reports that he is feeling relatively well and his physical examination is within normal limits with the exception of a blood pressure of 160/94 mm Hg. Given his suboptimal blood pressure control and his new diagnosis, you decide that a change in his pharmacologic therapy is in order. As you look over his chart, you note that he had developed angioedema when taking an ACE inhibitor, and thus, he is only taking a diuretic for blood pressure control currently. You decide to add a medication that is similar to an ACE inhibitor in that it affects the actions of angiotensin II, but this medication is not associated with the side effect of angioedema as it has no effect on bradykinin metabolism.

Angiotensin Receptor Blockers (ARBs)

Similar Drugs	ARBs include **losartan**, **valsartan**, **candesartan**, **eprosartan**, **irbesartan**, and **telmisartan**.
Mechanism of Action	The ARBs act by **blocking the angiotensin II (AT_1) receptor**, thereby blocking the effects of angiotensin II. Angiotensin II has the following actions—it is a vasoconstrictor; it increases perfusion pressure in the glomeruli (through vasoconstriction of the efferent arterioles of the kidney); it stimulates aldosterone production (leads to increased salt and water retention by the kidney). By blocking the effects of angiotensin II, the ARBs act to decrease peripheral vascular resistance and to decrease the effective circulating volume of fluid in the body.
Clinical Uses	Used in the **treatment of hypertension and congestive heart failure**; also used to **treat and prevent diabetic nephropathy**.
Side Effects	Hyperkalemia and renal failure in patients with renal insufficiency; hypotension; teratogen (may cause fetal renal

damage if used during pregnancy); rash.

Other

Note that, unlike the ACE inhibitors, the ARBs have **no effect on the metabolism of bradykinin**. Accordingly, they are not associated with a cough or the development of angioedema (both of these side effects are believed to be related to elevated levels of bradykinin).

Entresto belongs to a class of drugs known as **ARNIs (Angiotensin Receptor Neprilysin Inhibitors)**. Entresto is composed of a combination of valsartan (an ARB) and sacubitril. **Sacubitril** acts to inhibit the action of *neprilysin*, which is an enzyme responsible for the degradation of atrial and brain natriuretic peptide, and thereby leads to enhanced natriuresis. Entresto has been shown to reduce cardiovascular mortality and heart failure re-hospitalization in patients with chronic heart failure and reduced ejection fraction.

A 43-year-old woman with a history of hypertension and diabetes returns to your office for a follow-up visit. Her blood pressure in the office today is 170/80. Her current anti-hypertensive regimen includes hydrochlorothiazide and losartan. She asks you about a new drug that her sister is on for blood pressure that acts by decreasing angiotensin I levels. You explain to her that this medication is contraindicated in her as it could lead to renal failure given her current treatment with losartan and her history of diabetes.

Aliskiren

Similar Drugs

Mechanism of Action

Aliskiren acts to **directly inhibit renin**, thereby leading to decreased levels of angiotensin I and consequently decreased levels of angiotensin II. Angiotensin II has the following actions—it is a vasoconstrictor; it increases perfusion pressure in the glomeruli (through vasoconstriction of the efferent arterioles of the kidney); it stimulates aldosterone production (leads to

	increased salt and water retention by the kidney). By blocking the effects of angiotensin II, the ARBs act to decrease peripheral vascular resistance and to decrease the effective circulating volume of fluid in the body.
Clinical Uses	Used as a secondary agent for the **treatment of hypertension.**
Side Effects	**Renal failure;** hypotension; hyperkalemia; angioedema
Other	Aliskiren should not be used in combination with an ACE inhibitor or ARB in patients with renal impairment or diabetes.

A 56-year-old obese woman with a past medical history significant for hypertension, diabetes, and chronic renal failure presents to your office complaining of a facial rash and joint pain. On physical examination, you observe that the patient has flushing of her cheeks with a distinct butterfly rash over her face. Her blood pressure is stable at 125/80 mm Hg, but her heart rate is elevated at 110 beats/min. She has diffuse arthralgias. On review of her medication list, you see that she is on multiple drugs to treat her hypertension, including an anti-hypertensive medication that was started just 6 months ago. Laboratory studies are significant for the presence of anti-histone antibodies. You begin to suspect that this patient's symptoms are being caused by this new anti-hypertensive medication and you reassure her that her symptoms should resolve with the discontinuation of this drug.

Hydralazine

Similar Drugs	
Mechanism of Action	Hydralazine has been shown to cause **direct relaxation of arteriolar smooth muscle**, thereby decreasing blood pressure. The mechanism by which hydralazine acts is not completely understood, although some researchers believe that hydralazine

	blocks the release of calcium from the sarcoplasmic reticulum in vascular smooth muscle, thereby leading to the inhibition of vascular smooth muscle contraction.
Clinical Uses	Used in the treatment of **hypertension** as well as in the treatment of **heart failure** (reduces afterload). Hydralazine is considered a first-line treatment for hypertension in pregnancy.
Side Effects	Headache; reflex tachycardia, which may provoke angina in patients with coronary artery disease; GI upset; **drug-induced lupus**; fluid retention (edema); hypotension.
Other	**Minoxidil** is an anti-hypertensive agent that directly **dilates arterial smooth muscle** by opening potassium channels in smooth muscle membranes, thereby hyperpolarizing the myocyte and inhibiting smooth muscle contraction. It is used as an **anti-hypertensive** to treat refractory hypertension. One of the major side effects of minoxidil is hair growth, so it has since been marketed as a product (Rogaine) that **promotes hair growth** when used topically.

A 64-year-old man presents to your office as a new patient. He was referred to your practice after he was recently seen in the emergency room for hypertension. He was sent home from the emergency room on a diuretic to treat his hypertension. His past medical history is also significant for chronic renal insufficiency. In your office, his physical examination is significant for a blood pressure of 160/96 mm Hg with a pulse of 90 beats/min. Given his elevated blood pressure, you decide to start this patient on an anti-hypertensive agent that will not affect his renal insufficiency.

Calcium Channel Blockers

Similar Drugs	The **dihydropyridine** calcium channel blockers include **amlodipine, nifedipine,** and **nicardipine** while the **non-dihydropyridine** calcium channel blockers include the class IV

	anti-arrhythmic agents, **verapamil** and **diltiazem**.
Mechanism of Action	The calcium channel blockers act by **blocking the voltage-gated L-type calcium channels** of cardiac and vascular smooth muscle, thereby inhibiting the flow of calcium into the cells. This leads to decreased muscle contraction with resulting **peripheral vasodilation** and decreased myocardial contractility.
Clinical Uses	This class of drugs is used in the **treatment of hypertension**, Prinzmetal angina, and Raynaud's disease. Verapamil and diltiazem (see Class IV Anti-Arrhythmic Agents card in Chapter 5) are also used to treat **supraventricular tachycardias**.
Side Effects	**Bradycardia** and heart block (verapamil and diltiazem); hypotension; peripheral edema (amlodipine); use in caution in patients with decreased ejection fractions because of negative inotropic effects of calcium channel blockers.
Other	The dihydropyridine calcium channel blockers have a greater effect on vascular smooth muscle as opposed to cardiac tissue, while the non-dihydropyridine calcium channel blockers have a greater effect on cardiac tissue as opposed to vascular smooth muscle. **Nimodipine** is a calcium channel blocker that is used in the treatment of subarachnoid hemorrhage. It has minimal effects on the heart, but acts primarily on the cerebral vasculature to prevent vasospasm.

A 42-year-old avid mountain climber with no significant past medical history presents to your office complaining of weakness, dizziness, headache, and nausea every time he rapidly ascends large mountains. The symptoms are usually mild and they tend to last for a few days. He asks whether there is any prophylactic treatment that he may be able to take beforehand in order to prevent these symptoms from occurring. You decide to prescribe a medication for him that can enhance performance status and diminish symptoms of mountain sickness if he takes it about 24 hours before his next ascent.

Acetazolamide

Similar Drugs	Other *carbonic-anhydrase* inhibitors include **dorzolamide** and **brinzolamide**.
Mechanism of Action	Acetazolamide **inhibits *carbonic anhydrase*** in the cells of the **proximal convoluted tubule** of the nephron. *Carbonic anhydrase* is the enzyme responsible for catalyzing the following reaction: $CO_2 + H_2O \rightarrow H^+ + HCO_3^-$. By inhibiting this enzyme, less bicarbonate is reabsorbed, and more Na^+ is lost in the tubular lumen, thereby leading to an increased renal loss of water and electrolytes. *Carbonic anhydrase* is also present in the eye, where it is involved in the production of aqueous humor.
Clinical Uses	Used to **treat glaucoma** and to **alkalinize the urine** in cases of toxin ingestion (e.g., salicylate, barbiturates); also used in the **treatment and prophylaxis of high-altitude sickness** (it has been shown to decrease CSF production) and as an adjunct treatment for epilepsy; also used for **diuresis in patients with a metabolic alkalosis**.
Side Effects	**Hyperchloremic metabolic acidosis**; **hypokalemia**; sedation; neuropathy; can cause an allergic reaction in patients with pre-existing sulfa allergy.
Other	Acetazolamide causes the increased secretion of Na^+, K^+, Ca^{2+}, and HCO_3^- in the urine.

A 54-year-old man with a history of congestive heart failure and hypertension presents to your office complaining of a swollen, painful big toe on his left foot. He denies any trauma to the toe. Further questioning also reveals that he has been suffering from some minor hearing loss recently. Physical examination of his left foot reveals signs consistent with a gouty attack. You also find that he shows signs of mild dehydration. Believing that all of his symptoms and physical findings may be caused by one of his anti-hypertensive medications, you decide to stop the medication and you treat his gouty attack with colchicine and rehydration.

Furosemide

Similar Drugs	Other **loop diuretics** include **bumetanide** and **torsemide**.
Mechanism of Action	Furosemide is a **sulfonamide** derivative that **inhibits the coupled $Na^+/K^+/2\ Cl^-$ transport system in the thick ascending portion of the loop of Henle** of the nephron. By inhibiting the $Na^+/K^+/2Cl^-$ transport system, there is retention of NaCl, K^+, and water in the tubular lumen, thereby leading to an increased renal loss of water and electrolytes.
Clinical Uses	Furosemide is used to treat **volume overload states associated with heart failure**, **liver failure**, and **renal failure**. It is also used in the treatment of **hypertension** and **hypercalcemia**.
Side Effects	**Hypokalemia**; metabolic alkalosis; **ototoxicity**; hypovolemia; interstitial nephritis; **hyperuricemia** (can lead to gouty attacks caused by increased urate reabsorption secondary to increased proximal Na^+ reabsorption); hypocalcemia; hypomagnesemia; **allergic reaction in patients with a sulfa allergy**.
Other	**Ethacrynic acid** is a **diuretic** that acts in the same manner as furosemide. It is used for diuresis **in patients with sulfa allergies**, who cannot tolerate furosemide, and in patients prone to gouty attacks as it causes less hyperuricemia than furosemide.

A 65-year-old man with no significant past medical history comes to your office for a follow-up visit. He is feeling well, although he reports two visits to the emergency room over the last 3 months for kidney stones. Discharge paperwork from the emergency room reveals that the patient's kidney stones were composed of calcium oxalate. Physical examination is significant for a blood pressure of 160/90 mm Hg, but otherwise is normal. You initiate a workup to evaluate the onset of his nephrolithiasis, but in the meantime, you decide to start him on a medication that will treat his hypertension and may also help with his recurrent nephrolithiasis.

Hydrochlorothiazide

Similar Drugs	The **thiazide diuretics** also include chlorothiazide, metolazone, chlorthalidone, and indapamide.
Mechanism of Action	Hydrochlorothiazide acts by **inhibiting the Na^+/Cl^- cotransporter in the early distal convoluted tubule** of the nephron, thereby increasing the retention of NaCl and water in the tubular lumen and resulting in an increased renal loss of water and salt.
Clinical Uses	Used in the treatment of **hypertension**, heart failure, **nephrogenic diabetes insipidus** (decreases polyuria), and **recurrent kidney Ca^{2+} stones**.
Side Effects	**Hypokalemia**; hyperglycemia; hyperlipidemia; **hyperuricemia**; hypercalcemia; metabolic alkalosis; hypersensitivity reactions.
Other	Hydrochlorothiazide causes the increased secretion of Na^+ and K^+ in the urine and the **decreased secretion of Ca^{2+}** in the urine.

A 47-year-old man with a history of hypertension and heart failure presents to your office complaining of enlarged breasts. He reports that his breasts have grown in size over the last 2 months and that he has become increasingly concerned and embarrassed by this change. Physical examination is significant for the presence of gynecomastia. As you look through his chart, you note that his blood pressure medication was changed about 3 months ago because he was found to have low serum potassium levels on routine laboratory tests. You believe that this new medication may be responsible for this patient's gynecomastia and you decide to change his anti-hypertensive regimen once again.

Spironolactone

Similar Drugs	Other aldosterone receptor antagonists include **eplerenone**.

Mechanism of Action	Spironolactone is a **competitive aldosterone receptor antagonist** that works at the cortical collecting tubule and late distal tubule of the nephron. By blocking the effects of aldosterone, salt and water retention is decreased, thereby leading to increased renal loss of salt and water. Since sodium is usually reabsorbed in exchange for potassium in the collecting tubule, **urinary potassium excretion is decreased** with the use of this drug. Spironolactone also has an anti-androgen effect, by acting as a competitive antagonist at androgen receptors and by decreasing testosterone levels through inhibition of 17-20-*desmolase* (involved in testosterone biosynthesis) and by increasing conversion of testosterone to estradiol.
Clinical Uses	Used to treat **primary hyperaldosteronism**, **volume overload syndromes** associated with **heart failure**, liver failure, and nephrotic syndrome, and **hypertension**. Spironolactone is also used to treat female hirsutism associated with polycystic ovarian syndrome.
Side Effects	**Hyperkalemia**; metabolic acidosis; **gynecomastia** (spironolactone); GI upset.
Other	**Eplerenone** has little anti-androgen effect and hence is not associated with the side effect of gynecomastia often seen with spironolactone.

A 62-year-old woman with a history of hypertension presents to your primary care office for a routine follow-up appointment. She states that she has been feeling ok, although she has noticed being slightly more fatigued and constipated than usual. Her physical examination is unremarkable other than for a blood pressure of 146/88 mm Hg, for which she takes hydrochlorothiazide. Routine blood tests reveal a potassium level of 2.9 mEq/L. You suspect that her hypokalemia is related to her hydrochlorothiazide. In addition to prescribing a low dose of potassium supplements, you decide to add another medication to her regimen that will both treat her hypertension as well as improve her potassium levels.

Triamterene

Similar Drugs	Amiloride.
Mechanism of Action	Triamterene and amiloride act by **blocking the epithelial sodium channels** (ENaC) located in the distal cortical collecting tubule of the nephron, thereby blocking sodium and water reabsorption. This results in a modest diuresis. Since sodium is usually reabsorbed in exchange for potassium in the collecting tubule, by inhibiting sodium reabsorption, **urinary potassium excretion is also decreased** with the use of this drug.
Clinical Uses	Used in combination with other medications to treat **volume overload syndrome** associated with **heart failure**, liver failure, and nephrotic syndrome and **hypertension**. Also used for diuresis in patients who lack endogenous aldosterone (e.g., patients with Addison's disease).
Side Effects	**Hyperkalemia**; metabolic acidosis; GI upset.
Other	

A 51-year-old woman presents to the emergency room, complaining of shortness of breath and dizziness. She has a known history of heart failure with a significantly depressed ejection fraction and is currently awaiting heart transplant. On physical examination, her heart rate is 110 beats/min and her blood pressure is 78/40 mm Hg. She has diffuse crackles in her lung fields and she is cool to the touch. You immediately diagnose her with acute decompensated heart failure. Review of her medical record indicates that she has developed significant ventricular arrhythmias to dobutamine treatment in the past, so you instead opt to start her on a medication that will improve the contractility of the heart by inhibiting *phosphodiesterase isozyme III*.

Milrinone

Similar Drugs	Amrinone (also known as inamrinone).
Mechanism of Action	This class of drugs acts by **inhibiting *phosphodiesterase isozyme 3* (PDE3)**, a form of a *phosphodiesterase* enzyme found in cardiac and smooth muscle. The inhibition of PDE3 results in increased levels of cAMP, which in turn leads to opening of a calcium channel on the surface of the cell. Calcium flows into the cell and leads to **increased contractility and diastolic relaxation**. Activity of PDE3 inhibitors on the peripheral vasculature results in decreased arterial and venous tone.
Clinical Uses	Milrinone is used in the **treatment of acute decompensated heart failure**.
Side Effects	**Nausea** and vomiting; **cardiac arrhythmias**; thrombocytopenia.
Other	**Nesiritide** is synthetic human **B-type natriuretic peptide** (BNP). BNP has been shown to bind to the *guanylate cyclase* receptor on vascular smooth muscle cells, thereby leading to increased levels of cGMP with resulting smooth muscle relaxation and vasodilation. This results in a **reduction in preload and afterload**. It can be used in the treatment of **acute decompensated heart failure** although, since recent studies failed to show a clinical benefit with the drug, it is rarely used. As hypotension is a major side effect, use of nesiritide is contraindicated in patients with systolic BP <100 mm Hg.

A 68-year-old man with a history of hypertension and diabetes presents to your office complaining of erectile dysfunction. He tells you that he has suffered from erectile dysfunction for several years now, but that now he has a new sexual partner and he would like to be treated for his condition. You assure him that you can prescribe a medication that will hopefully treat his erectile dysfunction, but you warn him that he must never take this new medication with nitrates since the consequences could be fatal.

Sildenafil

Similar Drugs	Vardenafil; tadalafil; avanafil.
Mechanism of Action	Sildenafil **selectively inhibits *cGMP-specific phosphodiesterase type 5***, which is found in the corpus cavernosum of the penis as well as in the smooth muscle of the pulmonary vasculature. By inhibiting *cGMP-specific phosphodiesterase type 5*, levels of cGMP are increased, thereby leading to relaxation of the smooth muscle in the penis as well as in the pulmonary vascular bed. This results in increased flow of blood into the corpus cavernosum, leading to erection, as well as vasodilation of the pulmonary vasculature.
Clinical Uses	Used to treat **erectile dysfunction** as well as **pulmonary arterial hypertension**.
Side Effects	Headache; flushing; impaired blue-green vision; dyspepsia; **contraindicated in patients on nitrates** due to risk of life-threatening **hypotension**.
Other	

A 63-year-old obese man comes to your office complaining of blurry vision. His past medical history is significant for hypertension, diabetes, and congestive heart failure. He was recently started on a new medication for the treatment of his heart failure. Upon further questioning, he tells you that, besides being blurry, his vision has a yellow hue to it. An electrocardiogram demonstrates bradycardia, a prolonged PR interval, a shortened QT interval, ST-segment scooping, and T-wave inversion. You begin to suspect that this patient's symptoms and abnormal electrocardiogram are related to his new heart failure medication and you refer him to the emergency department for further treatment.

Digoxin

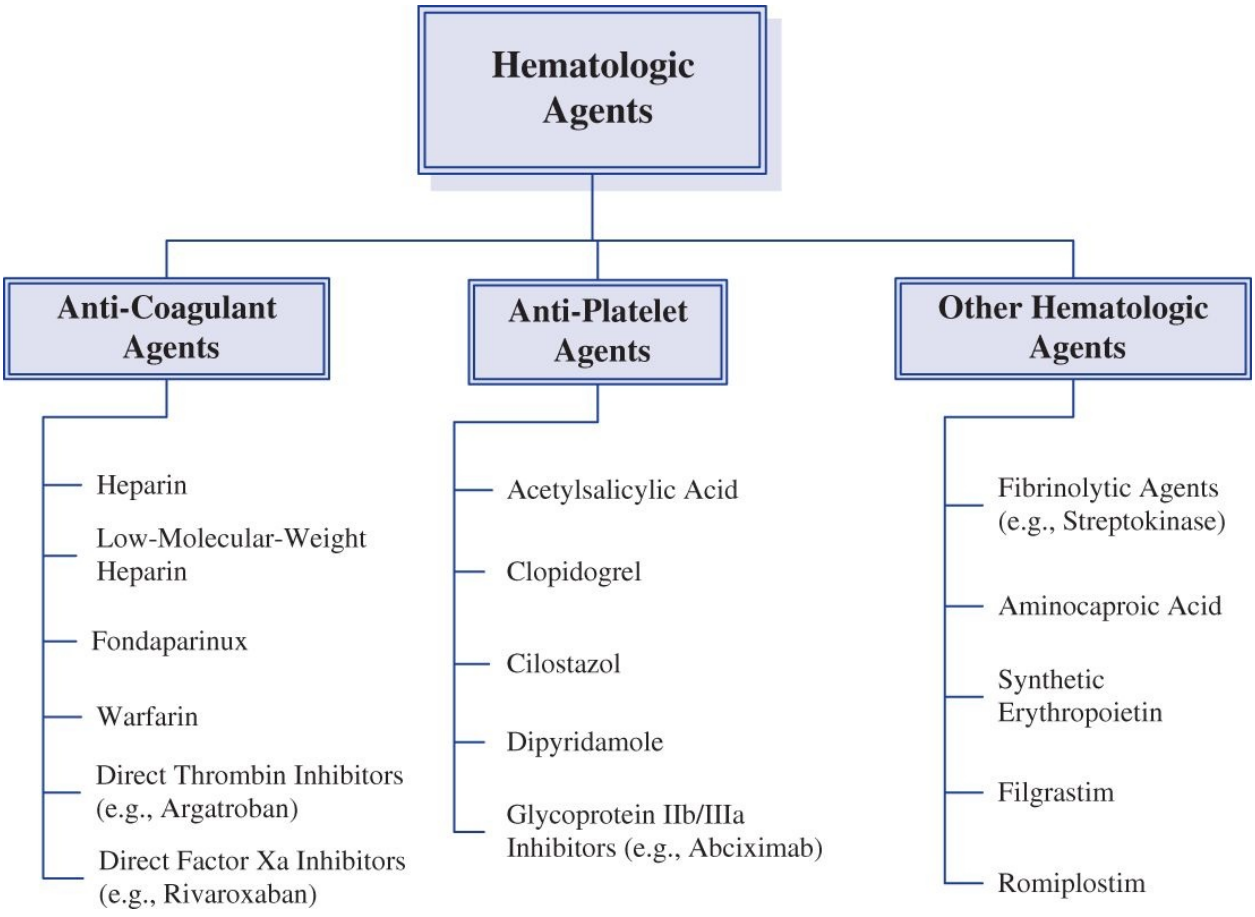
Similar Drugs	Other **cardiac glycosides** include digitoxin and ouabain.
Mechanism of Action	Digoxin acts by **inhibiting the Na^+/K^+ ATPase pump** on the cell membrane of the cardiac myocyte. Inhibition of Na^+/K^+ ATPase results in an increase in intracellular Na^+, which leads to decreased activity of the Na^+/Ca^{2+} exchanger (usually takes Na^+ into the cell in exchange for pumping Ca^{2+} out of the cell). Thus, intracellular Ca^{2+} concentrations are increased, which leads to increased contractility of the cardiac myocyte. Digoxin has also been shown to **increase parasympathetic outflow** at the sinoatrial and atrioventricular node, leading to decreased heart rates and decreased AV node automaticity.
Clinical Uses	Used in the treatment of **heart failure**; also used as an adjunctive treatment for atrial arrhythmias (e.g., atrial fibrillation).
Side Effects	**GI upset**; **blurry**, **yellow vision**; **ECG changes** (prolonged PR interval, decreased QT interval, ST-segment scooping, T-wave inversion); cardiac arrhythmias; heart block.
Other	The **side effects of digoxin are exacerbated by hypokalemia** (K^+ and digoxin compete for binding to Na^+/K^+ ATPase), **renal failure** (decreased excretion of the drug), and the use of certain drugs (e.g., **quinidine, amiodarone,** and **verapamil,** which can displace digoxin from binding sites on albumin, thereby effectively elevating serum levels of digoxin). **Digoxin toxicity can be treated** by stopping digoxin therapy, correcting hypokalemia if present, and administering an antibody to digoxin (**digoxin immune FAB**).

A 60-year-old man with a history of extensive coronary artery disease presents for a follow-up visit after a recent coronary angiogram for the workup of continued anginal chest pain. His angiogram demonstrated diffuse coronary artery disease without a clear revascularization target and the decision was made to optimize his cardiac regimen. He is currently on metoprolol succinate,

isosorbide mononitrate, and lisinopril. His blood pressure and heart rates are well controlled on this regimen; however, he continues to report angina with moderate exertion. In order to improve his symptoms, you decide to start him on a drug that may act by inhibiting the late inward sodium current in the cardiac myocyte, thereby improving myocardial relaxation.

Ranolazine

Similar Drugs	
Mechanism of Action	The exact mechanism of ranolazine is unknown, but it is thought to act by inhibiting the late inward sodium current in cardiac myocytes. This results in reduced calcium influx via the sodium-calcium exchanger and can consequently improve myocardial relaxation, thereby reducing anginal symptoms.
Clinical Uses	Used in the **treatment of chronic angina.**
Side Effects	Dizziness; nausea; constipation; headache.
Other	Ranolazine is known to prolong the QT interval in a dose-dependent manner. In patients with cirrhosis, QT prolongation is particularly pronounced and hence, ranolazine is contraindicated in this population.



BALANCING CLOTTING AND FIBRINOLYSIS IN THE BODY

FORMATION OF THE PLATELET PLUG

- Adhesion

- ▶ von Willebrand factor binds to the subendothelial matrix. When the endothelium is damaged, glycoprotein Ib/IX on the platelet surface binds to vWF thereby causing platelets to adhere to the damaged endothelium.

• Aggregation
- ▶ After a platelet is stimulated, the GPIIb/IIIa complex on the platelet surface binds one end of a molecule of fibrinogen, while the other end of the molecule of fibrinogen binds a GPIIb/IIIa complex on another platelet. This results in the cross-linking of platelets together.

• Secretion
- ▶ Stimulated platelets release multiple factors (e.g., ADP, serotonin, and thromboxane) that promote platelet aggregation and stimulation.

• Procoagulation
- ▶ When activated, platelets produce factor V on their surface, thereby assuring that the coagulating cascade will take place at the site of the platelet plug.

ENDOGENOUS ANTI-THROMBOTIC MECHANISMS

• Inhibition of the coagulation cascade
- ▶ *Anti-thrombin III* inhibits thrombin and factor Xa.
- ▶ *Protein C* is activated by *thrombomodulin.* Activated *protein C* then binds *protein S*, and together, these proteins degrade factors Va and VIIIa.
- ▶ *Tissue factor pathway inhibitor* inhibits factor Xa and VIIa.

• Fibrinolysis
- ▶ *Tissue plasminogen activator* is released from damaged endothelial cells, and converts plasminogen to *plasmin*, which degrades fibrin.

• Circulating factors
- ▶ *Prostacyclin* acts to inhibit platelet activity.
- ▶ *Nitric oxide* inhibits platelet adhesion and aggregation.

A 76-year-old woman presents to the emergency department complaining of the acute onset of severe shortness of breath. Her past medical history is significant for a diagnosis of colon cancer 3 months ago. Further evaluation reveals that she is tachypneic, tachycardic, and has elevated D-dimer levels. You decide to order a high-resolution CT scan of the chest on this patient to confirm your suspicions of her diagnosis, but as you are waiting for the imaging test, you empirically start the patient on anti-coagulation therapy with a drug that acts to accelerate the action of anti-thrombin III to treat her condition.

Heparin

Similar Drugs	
Mechanism of Action	Heparin binds to anti-thrombin III in order to **accelerate the action of anti-thrombin III**, which is responsible for degrading several activated clotting factors, including thrombin and factor Xa.
Clinical Uses	Used for the **acute treatment of DVTs**, **pulmonary embolism**, or other thromboembolic events; also used in the treatment of **acute myocardial infarction**.
Side Effects	**Bleeding** (can be treated with **protamine sulfate**, a compound that inactivates heparin and therefore reverses its anti-coagulant effects); **heparin-induced thrombocytopenia (HIT)** (thought to be caused by cross-reactivity to the complex formed by heparin bound to platelet factor 4 and the resulting formation of platelet-activating antibodies); allergic reactions.
Other	Pharmacokinetic studies indicate that heparin has a **short half-life** and a **rapid onset of action.** The efficacy of heparin treatment is followed by **monitoring the PTT** and dosing is titrated so as to achieve a goal PTT that is about twice the normal control.

A 63-year-old man with a history of known coronary artery disease presents to the emergency room with severe chest pain that began suddenly while he was sitting in his chair at home. He is given aspirin, nitroglycerin, and metoprolol and his chest pain improves. His initial EKG and laboratory studies are normal. However, his symptoms remain concerning for unstable angina so he is admitted to the hospital for further evaluation. As part of his treatment, you suggest starting the patient on a form of heparin that will provide the prophylactic benefits of anticoagulation without the need to regularly measure serum markers.

Low-Molecular-Weight Heparin

Similar Drugs	Enoxaparin; dalteparin.
Mechanism of Action	Low-molecular-weight heparins (LMWH) act in a similar fashion as unfractionated heparin by binding to and accelerating the activity of anti-thrombin III, thereby promoting inhibition of thrombin and factor Xa. The activity of LMWH on thrombin is lower than that of unfractionated heparin due to the shorter pentasaccharide chains in the LMWH molecule.
Clinical Uses	Used for the **acute treatment of DVTs, pulmonary embolism, and myocardial infarction.** Also used for DVT prophylaxis following orthopedic surgery.
Side Effects	**Bleeding** (no reversal agent available); hepatotoxicity; **heparin-induced thrombocytopenia (HIT)**; injection site reactions.
Other	LMWH are more bioavailable and longer-acting than unfractionated heparin and they do not require regular monitoring of PTT.

An 82-year-old man presents to the emergency room complaining of right hip pain after a fall. Past medical history is significant for heparin-induced thrombocytopenia. Physical examination suggests a fracture of the hip and imaging studies confirm this diagnosis. The patient is seen by the orthopedic service and scheduled for surgery. Given that this patient is at risk for developing a deep venous thrombosis following hip surgery, you suspect that this patient will need prophylactic anti-coagulation and recommend the use of a medication that acts by accelerating the selective action of anti-thrombin III in inhibiting factor Xa.

Fondaparinux

Similar Drugs	

Mechanism of Action	Fondaparinux binds to anti-thrombin III in order to **accelerate the selective action of antithrombin III in inhibiting factor Xa**, thereby leading to the inhibiting of the coagulation cascade.
Clinical Uses	Used for the **acute treatment of DVTs or pulmonary embolism**. Also used for DVT prophylaxis following orthopedic surgery.
Side Effects	**Bleeding**; hepatotoxicity; injection site reactions.
Other	Fondaparinux can be safely used as an anti-coagulant in patients who have a history of heparin-induced thrombocytopenia.

A 78-year-old man presents to the emergency room complaining of intermittent palpitations over the last week. He denies any similar prior episodes. His past medical history is significant for hypertension, diabetes, and congestive heart failure. On physical examination, his heart rate is 122 beats/min and is irregularly irregular. An electrocardiogram confirms that this patient is in atrial fibrillation. As you prepare to administer diltiazem in order to lower his heart rate, you tell him that he will likely need chronic anti-coagulation since his condition places him at an increased risk for having a thromboembolic stroke.

Warfarin

Similar Drugs	Dicumarol.
Mechanism of Action	Warfarin **inhibits the vitamin K-dependent γ-carboxylation of factors II**, **VII**, **IX**, **X**, **and proteins C and S** in the liver, thereby resulting in defective molecules.
Clinical Uses	Used for **chronic anti-coagulation** in patients who are at risk for thromboembolic events (e.g., atrial fibrillation; after hip replacement surgery; hypercoagulable state; mechanical heart valve) or who have had a thromboembolic event (e.g., stroke; pulmonary embolism; deep vein thrombosis).

Side Effects	**Bleeding** (may be treated by cessation of warfarin therapy and administration of vitamin K or fresh frozen plasma); skin changes; **teratogen**.
Other	Pharmacokinetic studies indicate that warfarin has a **long half-life** and a **slow onset of action**. The efficacy of warfarin treatment is followed by **monitoring the INR level** regularly and the dose warfarin is titrated accordingly to ensure that the INR level remains within the targeted range. **The metabolism of warfarin is affected by many drugs**. Some drugs inhibit warfarin metabolism, thereby potentiating warfarin's anti-coagulant effects (e.g., cimetidine, metronidazole, TMP-SMX), while other drugs accelerate warfarin metabolism, thereby decreasing warfarin's anti-coagulant effects (e.g., barbiturates, rifampin, cholestyramine).

A 73-year-old woman presents to the emergency room complaining of pleuritic chest pain, dyspnea, and palpitations. Evaluation reveals the presence of a right-sided pulmonary embolism. You start the patient on heparin and you admit her to the hospital for anti-coagulation and supportive treatment. Over the next few days, you notice that the patient has developed a significant thrombocytopenia with her platelet counts dropping from 390,000/μ to 75,000/μ. You become concerned that the patient may be developing heparin-induced thrombocytopenia. You decide to send for an anti-platelet antibody study, but in the meantime, you stop the heparin and begin her on an anti-coagulant medication that acts by directly inhibiting thrombin.

Direct Thrombin Inhibitors

Similar Drugs	Direct thrombin inhibitors include **hirudin**, **bivalirudin**, **lepirudin**, **desirudin**, **argatroban**, **melagatran**, and **dabigatran.**
Mechanism	This class of drugs acts by **directly inhibiting thrombin**,

of Action	thereby interfering with both the intrinsic and extrinsic coagulation cascade.
Clinical Uses	Used for **acute and chronic anti-coagulation** in patients who have indications for anti-coagulation (e.g., DVT; acute coronary syndrome; atrial fibrillation). **Bivalirudin** is commonly used in the treatment of acute coronary syndromes and during **cardiac catheterization**. **Argatroban** is also used to treat **heparin-induced thrombocytopenia**. **Dabigatran** is an oral direct thrombin inhibitor that is being used for chronic anti-coagulation in **atrial fibrillation** in place of warfarin for selected patients.
Side Effects	**Bleeding**; anaphylaxis.
Other	Both the **PT and PTT are increased** with administration of these drugs. These drugs can be used for anti-coagulation in heparin-allergic patients. **Idarucizumab** is a monoclonal antibody to dabigatran that was recently approved by the FDA for the reversal of anticoagulation in patients on dabigatran.

A 45-year-old woman presents to your cardiology clinic for evaluation of her atrial fibrillation. In addition to her atrial fibrillation, the patient also has a history of insulin-dependent diabetes, hypertension, and obstructive sleep apnea. You explain to the patient that her atrial fibrillation places her at significant risk for thromboembolic events and you recommend that she consider treatment with warfarin to prevent such an event. The patient adamantly refuses starting warfarin, saying that she does not want to have the frequent blood tests that are necessary for monitoring patients treated with warfarin. She instead asks you about a new medication, which acts by directly inhibiting factor Xa, that she saw a commercial on television for. You explain to her that this new medication can be used for the prevention of stroke in patients with atrial fibrillation as well as in the prevention of deep vein thrombosis and you write a prescription for the medication for her.

Direct Factor Xa Inhibitors

Similar Drugs	Rivaroxaban; apixaban; betrixaban; edoxaban.
Mechanism of Action	This class of drugs act by **directly inhibiting factor Xa**, thereby interfering with both the intrinsic and extrinsic coagulation cascade.
Clinical Uses	Used for **treatment of and prophylaxis against DVT**. Also used to **prevent thromboembolism in patients with atrial fibrillation**. Studies have suggested that use of rivaroxaban may be beneficial in patients with acute coronary syndrome, but the drug is not currently approved for this indication.
Side Effects	**Bleeding**; allergic reaction.
Other	These drugs can be used for **anti-coagulation in heparin-allergic patients**.

An 11-year-old boy is brought to the hospital by his parents after having been found unconscious in his bed at home. His parents tell you that the boy had been feeling ill for the last 2 or 3 days and that he had been complaining of having “shaking chills” and muscle aches. When they took the patient’s temperature at home, they discovered that he had a fever of 102°F, which they tried to treat with a common over-the-counter medication. Laboratory testing reveals extremely elevated liver enzymes, thereby leading you to believe that the patient may be suffering from Reye syndrome due to the over-the-counter medication.

Acetylsalicylic Acid

Similar Drugs	

Mechanism of Action	Acetylsalicylic acid **irreversibly inhibits *cyclooxygenase 1 and 2***, which are enzymes responsible for converting arachidonic acid to endoperoxides (prostaglandin precursors), thereby **decreasing prostaglandin synthesis** (which generally leads to an anti-inflammatory effect). Without PGE_2, there is decreased sensation to pain (analgesia), a decrease of the set point at the hypothalamic thermoregulatory center (anti-pyretic), and decreased synthesis of protective gastric mucus (leads to gastric ulcers). Without TXA_2, there is decreased platelet aggregation (anti-platelet). Without PGI_2, there is increased gastric acid secretion (leads to gastric ulcers).
Clinical Uses	There are many uses for aspirin, including use as an **anti-pyretic**, an **analgesic**, an **anti-inflammatory agent**, and **an anti-platelet drug** (often used as primary and secondary prevention in patients at risk for cardiovascular or cerebrovascular disease).
Side Effects	**Bleeding** (especially in **GI tract**); increased incidence of gastritis or **gastric ulcers**; allergic reaction; Reye syndrome (sometimes fatal liver failure in children with viral infections); tinnitus.
Other	When aspirin is taken in **toxic amounts**, both **respiratory and metabolic acidosis** can result. Generally, sodium bicarbonate is given to treat an aspirin overdose in order to alkalinize the urine and thus promote salicylate excretion.

A 49-year-old man presents to the emergency room complaining of a severe, crushing, substernal chest pain that began while he was shoveling his driveway 6 hours ago. He tells you that he has experienced this type of pain in the past, especially when he is exerting himself; however, usually the pain will dissipate with rest. An electrocardiogram demonstrates some signs of ischemia, but his cardiac enzymes are normal, thereby ruling out the possibility of a myocardial infarction. You diagnose him with unstable angina pectoris and you admit him to the hospital. The cardiac catheterization reveals significant stenosis of the left anterior descending coronary artery and the patient has a coronary stent placed. After the stent placement, he is placed on a medication that acts to prevent

thrombosis at the stent site by inhibiting the ADP pathway involved in platelet aggregation.

Clopidogrel

Similar Drugs	Prasugrel; ticlopidine.
Mechanism of Action	This drug **irreversibly inhibits the binding of ADP to the platelet $P2Y_{12}$ receptor**, **thereby blocking ADP-mediated platelet aggregation**. By inhibiting the ADP pathway, the interaction of fibrinogen with platelets, and thus the formation of the platelet plug, is halted.
Clinical Uses	Used to **treat acute coronary syndrome along with aspirin** as well as to prevent cerebrovascular ischemic events; also **used in patients undergoing placement of a coronary stent to prevent thrombosis**; also used as an alternative anti-platelet agent in those patients who cannot tolerate aspirin.
Side Effects	GI upset; **bleeding**; neutropenia (associated with ticlopidine) or thrombotic thrombocytopenic purpura (rare; associated with ticlopidine and prasugrel). Prasugrel is contraindicated in patients with active bleeding, prior stroke, or age >75 years.
Other	**In order to become active**, **clopidogrel must be metabolized by** a series of hepatic enzymes within the **cytochrome P450** class (including CYP2C19). Up to 14% of patients have genetic polymorphisms in the CYP2C19 gene, which results in decreased metabolism of clopidogrel to its active metabolite and inadequate platelet inhibition with clopidogrel. While prasugrel is also metabolized to an active form by the cytochrome P450 class (primarily CYP3A4 and CYP2B6), it is less dependent on CYP2C19, posing less risk for inadequate anti-platelet activity due to genetic variability. **Ticagrelor** is a **reversible allosteric inhibitor of the platelet $P2Y_{12}$ receptor** that results in the inhibition of ADP-mediated

platelet aggregation similar to clopidogrel and prasugrel. Side effects include dyspnea, bleeding, and bradycardia.

A 71-year-old man presents to your cardiology office for routine follow-up of his vascular disease. The patient has had two heart attacks in the past as well as a carotid endarterectomy to treat his symptomatic carotid stenosis. He states that he has been feeling relatively well over the last 6 months with no symptoms of chest pain or heart failure. He does mention that he has developed some calf pain in his left leg, which is only present when he is walking up an incline and is relieved with rest. Physical examination is notable for diminished posterior tibial and dorsalis pedis pulses in his left leg. Exercise testing reveals evidence of peripheral arterial disease in the left lower extremity. In addition to recommending a gentle exercise regimen and an aggressive lipid-lowering regimen, you also prescribe a medication, which acts by inhibiting *cyclic AMP phosphodiesterase III* to treat the patient's symptoms of claudication.

Cilostazol

Similar Drugs	
Mechanism of Action	Cilostazol inhibits ***cyclic AMP phosphodiesterase III***, which is an enzyme involved in the breakdown of cyclic AMP. By inhibiting *cyclic AMP phosphodiesterase III*, cyclic AMP levels increase and act to inhibit thromboxane A_2 synthesis and to promote prostacyclin production. By decreasing thromboxane A_2 production and increasing prostacyclin production, platelet aggregation and thrombus formation is inhibited and vasodilation is promoted respectively.
Clinical Uses	Used to treat **claudication** symptoms in patients with peripheral arterial disease.
Side Effects	Headache; palpitations; GI upset. Cilostazol is contraindicated in patients with congestive heart

failure.

Other

A 63-year-old man presents to your office, complaining of chest tightness and shortness of breath while walking. After a full history and physical examination, you are concerned that the patient is experiencing angina symptoms. You would like to evaluate the patient for coronary artery disease using a non-invasive test; however, he is unable to undergo a treadmill stress test since he uses a cane to ambulate due to chronic lower back pain and osteoarthritis of the knees. Instead, you decide to schedule the patient for a pharmacologic stress test and you plan to administer a medication that will simulate the exercise state by causing varying levels of vasodilation in normal and diseased coronary arteries through a cyclic GMP-mediated mechanism.

Dipyridamole

Similar Drugs

Mechanism of Action

This drug has two mechanisms of action. First, dipyridamole **inhibits the uptake of adenosine** into platelets and endothelial cells, thereby leading to an increase in circulating adenosine. Increased levels of adenosine result in increased activation of the platelet A2 receptor, which acts to activate *adenylate cyclase* and hence increase levels of cyclic AMP. Increased levels of cyclic AMP act to inhibit thromboxane A_2 synthesis and to promote prostacyclin production. By decreasing thromboxane A_2 production and increasing prostacyclin production, **platelet aggregation and thrombus formation are inhibited and vasodilation is promoted respectively**. When given at high doses (i.e., during stress testing), dipyridamole has also been shown to ***inhibit cyclic GMP phosphodiesterase***, thereby leading to increased levels of cyclic GMP and further vasodilation.

Clinical Uses	Used to perform **pharmacologic cardiac stress tests**. When administered in conjunction with aspirin, dipyridamole is also used in the **secondary prevention of stroke**.
Side Effects	Hypotension; hepatotoxicity; GI upset.
Other	

A 67-year-old woman presents to your cardiology clinic for a follow-up visit regarding her recent cardiac stress test. You tell the patient that her stress test demonstrated significant ischemia to the lateral wall of the heart during exercise and that these results indicate that she likely has a blockage in her left circumflex coronary artery. You recommend that she have a cardiac catheterization with possible angioplasty or stent placement. She asks that you discuss the procedure in detail with her. As you describe the process of catheterization to her, you also make sure to explain all of the medications that she may receive during the procedure, including telling her about a drug that acts to prevent thrombosis during the procedure by inhibiting platelet aggregation through inhibition at the glycoprotein IIb/IIIa receptor present on platelets.

Glycoprotein IIb/IIIa Inhibitors

Similar Drugs	The glycoprotein IIb/IIIa inhibitors include **abciximab**, **eptifibatide**, and **tirofiban**.
Mechanism of Action	This class of drugs acts by **binding to the GP IIb/IIIa receptor** complex, which is present on the platelet surface, and **inhibiting the binding of fibrinogen and von Willebrand factor to the receptor**. By inhibiting the cross-linking of fibrinogen between GP IIb/IIIa receptors on different platelets, **platelet aggregation is impeded**.
Clinical Uses	**Treatment of acute coronary syndromes**. Adjunctive treatment for prevention of thrombosis during

	percutaneous coronary intervention.
Side Effects	**Bleeding**; thrombocytopenia; diffuse alveolar hemorrhage.
Other	

A 54-year-old man presents to the emergency department complaining of a heavy, substernal chest pain that radiates to his left shoulder and jaw. He tells you that the pain began 2 hours ago. While you are talking to him, you notice that he is breathing heavily and sweating profusely. You immediately order an ECG, which demonstrates ST elevation in leads II, III, and aVF, thereby suggesting that he is suffering from an inferior wall myocardial infarction. There is no cardiac catheterization laboratory within 100 miles of your hospital. In the hopes of minimizing tissue damage caused by his condition, you decide to administer a medication that may dissolve the coronary blockage by promoting the formation of plasmin.

Fibrinolytic Agents

Similar Drugs	Fibrinolytic agents include **streptokinase**, **tenecteplase**, **alteplase**, and **reteplase**.
Mechanism of Action	Although the specific mechanisms of action for the various fibrinolytics are slightly different from each other, the overall mechanism of action is the **promotion of the conversion of plasminogen to plasmin**, which acts to degrade fibrin and thus degrade the thrombus.
Clinical Uses	Fibrinolytic treatment is indicated in cases of **massive pulmonary embolisms**, **stroke**, and **acute myocardial infarction**.
Side Effects	**Bleeding**; allergic reactions. Fibrinolytic agents are contraindicated in patients with active bleeding, recent surgery, and history of hemorrhagic stroke.

Other	In general, the fibrinolytics are most effective if given early after symptom onset (i.e., within a few hours) as older thrombi tend to be more difficult to break down.

A 20-year-old man presents to the emergency room with significant bleeding from the gums. Upon taking a more detailed history, you discover that the patient suffers from hemophilia and that he had his wisdom tooth extracted 1 day ago. Since his dental procedure, he has been continually bleeding from the gums. In order to treat his bleeding, you decide to replace his deficient clotting factors and to administer a drug that would inhibit plasminogen activation.

Aminocaproic Acid

Similar Drugs	Tranexamic acid.
Mechanism of Action	Aminocaproic acid acts to **inhibit plasminogen activation**, thereby resulting in the **inhibition of fibrinolysis**.
Clinical Uses	**Treatment of bleeding** associated with postoperative complications; also used in the treatment of hemophilia.
Side Effects	**Thrombosis**; GI upset; hypotension.
Other	

A 74-year-old man with end-stage renal disease, requiring hemodialysis, presents to your clinic for a follow-up visit. On history, he tells you that he has been feeling more fatigued lately. Physical examination reveals a thin, pale man with a stable heart rate and blood pressure. Laboratory studies demonstrate an anemia with a hematocrit of 26%. Iron studies are consistent with an anemia of chronic inflammation. Furthermore, a workup for gastrointestinal bleeding is negative. You suspect that the patient's anemia is related to his renal failure and you start him on a medication to stimulate the production of red blood cells in his bone

marrow.

Synthetic Erythropoietin

Similar Drugs	Epoetin; darbepoetin.
Mechanism of Action	Synthetic erythropoietin **stimulates the bone marrow to enhance erythroid proliferation and differentiation**, thereby increasing hematocrit.
Clinical Uses	**Treatment of anemia** associated with chronic renal insufficiency, chemotherapy, or critical illness.
Side Effects	**Cardiovascular events and thrombotic complications** in patients with renal failure if used to increase hemoglobin levels over 13 g/dL; teratogen; hypertension.
Other	

A 43-year old woman with metastatic breast cancer, who is receiving chemotherapy, presents to the hospital with a fever of 102°F and general malaise and fatigue. Laboratory studies reveal an absolute neutrophil count of 100/μL. You obtain blood, urine, and sputum cultures and start her on broad-spectrum intravenous antibiotics. When the patient asks you if something can be done to prevent future bouts of neutropenic fever, you assure her that you will plan to start her on a medication that will help to increase her white blood cell count after she recovers from her current illness.

Filgrastim

Similar Drugs	Other **granulocyte-colony stimulating factor (G-CSF) analogues** include sargramostim.
Mechanism	**Filgrastim** is a human recombinant form of G-CSF that acts on

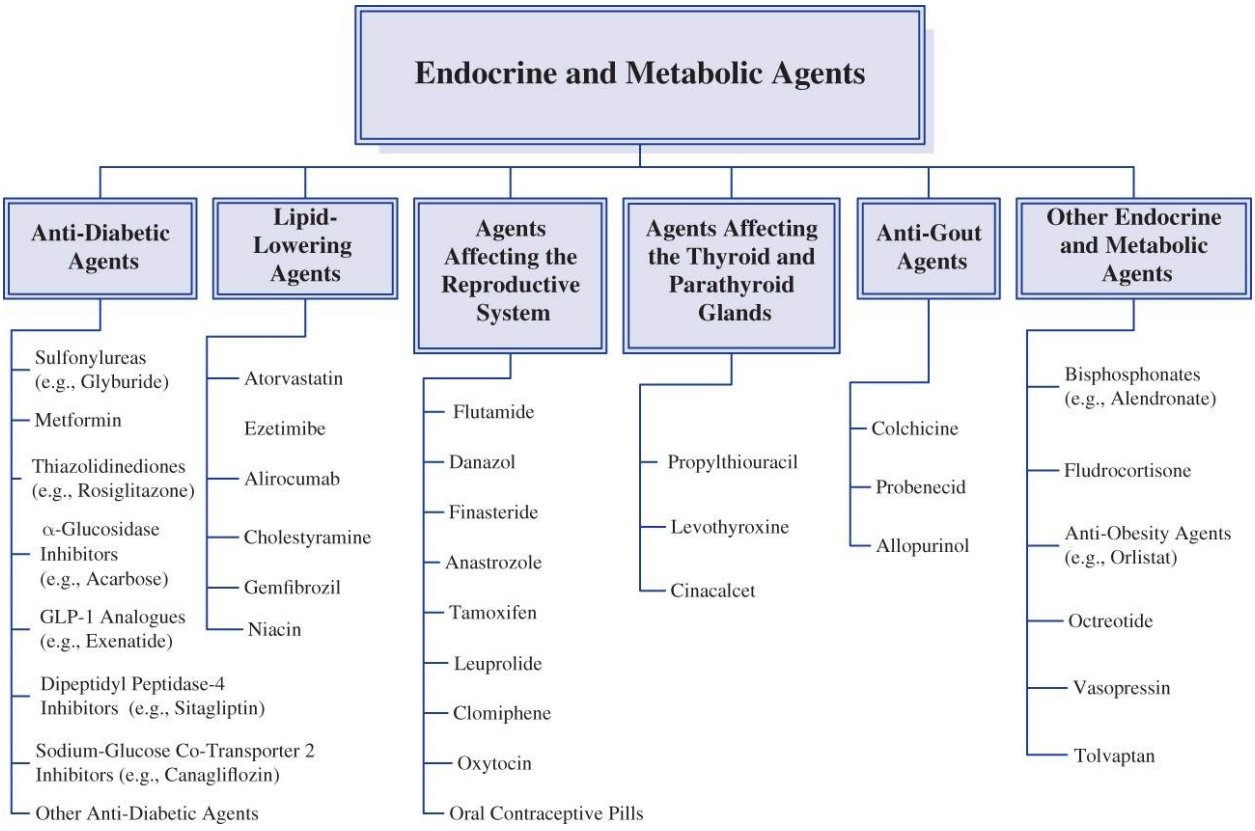
of Action	hematopoetic cells to promote maturation, migration, and activation of neutrophils.
Clinical Uses	**Treatment of neutropenia and neutropenic fever** associated with myelosuppressive states and the use of chemotherapy in the treatment of non-myeloid cancers.
Side Effects	**Bone pain; allergic reactions;** nausea and vomiting; alopecia; diarrhea.
Other	

A 35-year old man with a history of immune thrombocytopenic purpura presents to the emergency department with petechiae, epistaxis, and abdominal pain. He is hospitalized and found to have a gastrointestinal bleed on a tagged red blood cell nuclear medicine study. Notably, his platelet count is 10,000. After he is treated for his GI bleed and is given steroids, his platelet count remains low at 15,000. Your attending recommends starting the patient on a drug that will directly promote an increase in his platelet count in order to improve his condition.

Romiplostim

Similar Drugs	Eltrombopag; oprelvekin.
Mechanism of Action	**Romiplostim** is a thrombopoietin receptor agonist that promotes maturation, migration, and activation of neutrophils, monocytes, and macrophages.
Clinical Uses	Administered in regular injections for the treatment of **chronic immune thrombocytopenic purpura in patients who are at risk for bleeding** and have not responded to other treatments.
Side Effects	Headache; fatigue; myalgias; **thrombocytosis**; bone marrow fibrosis.
Other	Romiplostin should not be used merely to achieve normal

platelet counts.



INSULIN

- **Synthesis**
  - ▶ Proinsulin is broken down into insulin and C-peptide in the pancreatic β-cell.
- **Secretion of insulin**
  - ▶ Glucose binds to a receptor on the pancreatic β-cell and is taken up into the cell.

- In the β-cell, glucose is oxidized and ATP is formed.
- ATP binds a K^+ channel and inhibits the flow of K^+ into the cell, leading to cell depolarization.
- Cell depolarization leads to the release of intracellular Ca^{2+}, which stimulates insulin release into the blood.
- Insulin then travels to the liver, muscle, and adipose tissue, where it binds an insulin receptor in order to exert its effects.

• **Actions of insulin**

- Decreases blood glucose levels by decreasing hepatic gluconeogenesis, inducing glycogen synthesis, and increasing glucose uptake into cells.
- Inhibits lipolysis.
- Stimulates amino acid uptake into cells.
- Decreases serum K^+ levels by increasing K^+ uptake into cells.

• **Synthetic insulin preparations**

- *Lispro insulin/Aspart insulin*: Rapid onset of action (peak 1 hour); very short-acting (3–4 hours).
- *Regular insulin*: Rapid onset of action (peak 2–3 hours); short-acting (5–7 hours).
- *Semilente insulin*: Quick onset of action (peak 6 hours); intermediate-acting (10–12 hours).
- *Lente insulin/NPH insulin*: Intermediate onset of action (peak 10 hours); intermediate-acting (18 hours).
- *Ultralente/Glargine/Detemir insulin*: Slow onset of action (peak 12 hours); long-acting (24 hours).

A 59-year-old woman presents to your endocrinology office for follow-up of her type 2 diabetes mellitus. She tells you that she has had difficulty achieving optimal control of her blood sugar. She currently takes metformin. Her hemoglobin A1C level is 7.7%, indicating that her glycemic control over the past 3 months has not been ideal. You decide to add another medication to the metformin that will lower her blood sugar by stimulating increased insulin release from the β-cells of her pancreas.

Sulfonylureas

Similar Drugs	*1st generation:* Chlorpropamide, tolbutamide, tolazamide *2nd generation:* Glyburide, glipizide *3rd generation:* Glimepiride
Mechanism of Action	The sulfonylureas have three mechanisms of action. They (1) **stimulate insulin release** from the pancreas through inhibition of a potassium channel on β-cells, (2) increase insulin action on target tissues by **prolonging binding of insulin to target tissue receptors**, and (3) **reduce serum glucagon levels** through indirect inhibition (increased insulin level inhibits glucagon secretion).
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**.
Side Effects	**Hypoglycemia**; skin rash; allergic reaction; disulfiram reaction with alcohol (chlorpropamide).
Other	Sulfonylureas are **contraindicated in pregnancy**, since they can cross the placenta and cause insulin depletion in the fetal pancreas. Sulfonylureas should be **used with caution in patients with renal or hepatic insufficiency**, since the liver and kidney are responsible for excretion of the drug.

A 48-year-old man presents to his primary care physician's office for an annual check-up. He reports that, over the past few months, he has noticed that he has been thirstier and has been urinating more frequently. His family history is significant for type 2 diabetes in both of his parents. A fasting glucose level is 142 mg/dL. All other laboratory studies are normal. You tell the patient that he has type 2 diabetes and you decide to begin him on a medication that will lower his blood sugar by inhibiting glucose production by the liver.

Metformin

Similar	Metformin belongs to a class of drugs known as the **biguanides**.

Drugs	
Mechanism of Action	Although the exact mechanism of metformin is not known, it is believed to reduce serum glucose levels by **inhibiting hepatic gluconeogenesis**, decreasing absorption of glucose from the GI tract, and **increasing peripheral utilization of glucose** by adipose tissue and skeletal muscle.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**. Also used in the treatment of polycystic ovarian syndrome.
Side Effects	**GI upset**; **lactic acidosis**; impaired absorption of vitamin B_{12}.
Other	Metformin is **contraindicated in patients with renal insufficiency**, since the kidney is responsible for excretion of the drug. Unlike many of the other drugs prescribed to treat diabetes, **metformin does not cause hypoglycemia**. Metformin should be temporarily stopped in patients undergoing radiology studies requiring iodinated contrast, as this may lead to renal dysfunction and subsequently, increased levels of metformin in the body.

A 61-year-old woman presents to your primary care clinic for a follow-up visit. She has recently been diagnosed with mild type 2 diabetes mellitus, and she has been trying to control her blood sugar with diet and exercise. At this clinic visit, random serum glucose is 254. You tell her that she should seriously consider beginning pharmacologic treatment of her diabetes. She becomes concerned and she tells you that her cousin was on a “diabetes drug” and had extensive liver damage several years ago. You reassure her that the “diabetes drug” she is speaking of is not prescribed anymore, and that the other drugs in the class, which exert their effects by binding to PPAR-γ, have not been shown to cause liver failure.

Thiazolidinediones

Similar Drugs	The thiazolidinediones include **rosiglitazone** and **pioglitazone**.
Mechanism of Action	This class of drugs acts by **binding to PPAR-γ**, which results in the upregulation of multiple genes. The end result is a **decrease in insulin resistance**.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**.
Side Effects	**Hypoglycemia**; **edema**; liver damage (mostly associated with troglitazone, which has been withdrawn from the market for this reason); increased risk of congestive heart failure; possible increased risk of cardiovascular events (e.g., heart attacks) with rosiglitazone; possible increased risk of bladder cancer with pioglitazone.
Other	

A 53-year-old man presents to your endocrinology clinic for management of his type 2 diabetes mellitus. He is currently on glyburide, metformin, and pioglitazone, but his HgA1c still remains elevated at 9.7%. He adamantly refuses to begin insulin or any other medication that requires an injection. He asks you if there is another oral medication that he can use to treat his diabetes. You tell him that you could start him on a medication that acts to decrease absorption of postprandial carbohydrates in the gastrointestinal tract, but you warn him that the gastrointestinal side effects of this medication are not minimal.

α-Glucosidase Inhibitors

Similar Drugs	The α-glucosidase inhibitors include **acarbose** and **miglitol**.
Mechanism of Action	These drugs act to **inhibit *α-glucosidase***, an enzyme present in the brush border of the small intestine that is responsible for breaking down oligosaccharides and disaccharides into monosaccharides. By inhibiting this enzyme, **absorption of**

	postprandial carbohydrates is decreased and thus postprandial glucose levels are lowered.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**. Also can be used in combination with insulin for patients with insulin-dependent diabetes.
Side Effects	**GI upset** (flatulence, diarrhea).
Other	

A 55-year-old man presents to your office for follow-up of his type 2 diabetes mellitus. He is currently on metformin and rosiglitazone. Despite his medication regimen and his attempts to control his diet, his most recent HgA1c is still slightly elevated at 7.5%. He is very frustrated with his inability to attain an HgA1c below 7.0% and to lose weight. You inform him that you plan to start him on a drug that not only improves glycemic control by up-regulating insulin secretion by mimicking glucagon-like peptide-1, but also has been associated with weight loss.

GLP-1 Analogues

Similar Drugs	The GLP-1 analogues include **exenatide**, **liraglutide**, **dulaglutide**, and **albiglutide**.
Mechanism of Action	Exenatide and the other drugs in this class act as **agonists at the GLP-1 receptor**. GLP-1 is an incretin hormone that is primarily responsible for promoting insulin secretion in response to glucose. When exenatide binds to the GLP-1 receptors found on pancreatic beta cells, **insulin secretion is up-regulated and glucagon secretion is down-regulated**. Additionally, GLP-1 agonists slow gastric emptying and suppress hunger, leading some patients to experience weight loss.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**.

Side Effects	Nausea and vomiting; **pancreatitis**; hypoglycemia when taken in combination with other anti-diabetic agents (e.g., sulfonylurea or thiazolidinedione).
Other	

A 50-year-old woman with a past medical history of obstructive sleep apnea, hypertension, and type 2 diabetes mellitus presents for a routine follow-up appointment. You have been managing her diabetes for several years—unfortunately, she has been unable to tolerate sulfonylureas or thiazolidinediones in the past and now takes only metformin for her diabetes. Her most recent HgA1c is 8.2%. You suggest that she may benefit from a medication which acts to inhibit the breakdown of incretin hormones including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.

Dipeptidyl Peptidase-4 Inhibitors

Similar Drugs	The dipeptidyl peptidase-4 (DPP-4) inhibitors include **sitagliptin**, **saxagliptin,** and **linagliptin**.
Mechanism of Action	DPP-4 is responsible for degrading glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are incretin hormones that act to increase insulin secretion and decrease glucagon secretion. **By inhibiting DPP-4, GLP-1 and GIP levels are increased,** thereby leading to **increased insulin secretion** and decreased glucagon secretion.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**.
Side Effects	Upper respiratory tract infection; mild hypoglycemia especially when taken with other hypoglycemic medications.
Other	

A 60-year-old woman with a history of type 2 diabetes mellitus presents to your office for routine follow-up. Her HgA1c is elevated at 8.3% despite consistently taking metformin and glipizide as prescribed. She would like to know what other options are available for control of her diabetes besides metformin. You inform her of several new medications, including a medication that acts by promoting glucose excretion in the urine. Although this medication is effective in lowering blood glucose levels, you do inform her that a common and unpleasant side effect of the medication is genitourinary infections.

Sodium-Glucose Co-Transporter 2 Inhibitors

Similar Drugs	The sodium-glucose co-transporter 2 (SGLT-2) inhibitors include **canagliflozin**, **dapagliflozin,** and **empagliflozin**.
Mechanism of Action	SGLT-2 is found in the proximal tubule of the nephron and is responsible for promoting glucose reabsorption. Canagliflozin and the other drugs in this class act by **inhibiting SGLT-2**, thereby leading to **decreased renal glucose reabsorption** and resulting glycosuria as well as lower blood glucose levels.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**.
Side Effects	**Genital yeast infections (due to glycosuria); polyuria;** genital pruritus; thirst.
Other	

An 83-year-old man with a history of type 2 diabetes mellitus presents to the outpatient clinic for optimization of his medications. With his current medication regimen, he has noticed that he has had less of an appetite and, as a result, has lost 15 pounds over the last year. He appears fairly thin and frail. You would like to continue to treat him adequately for diabetes, but consider switching him to an agent that, in addition to reducing blood glucose levels, may promote weight gain as a side effect.

Other Anti-Diabetic Agents

Similar Drugs	**Meglitinides**: repaglinide; nateglinide. **Amylin analogues:** pramlintide.
Mechanism of Action	**Meglitinides**: this class of drugs binds to a potassium channel (different binding site than the sulfonylureas) on the pancreatic β-cell, thereby stimulating the release of insulin from the pancreas. **Amylin analogues:** amylin is a hormone secreted by the pancreatic β-cell along with insulin. In the post-prandial period, amylin downregulates hepatic production of glucose and slows gastric emptying. By mimicking amylin, this class of drugs acts to lower glucose levels via this same mechanism.
Clinical Uses	Treatment of **non-insulin-dependent type 2 diabetes**.
Side Effects	**Meglitinides**: weight gain; **hypoglycemia**. **Amylin analogues:** nausea; vomiting; headache; **hypoglycemia.**
Other	

A 55-year-old man presents to your primary care office for a routine visit. He has not seen a physician in 5 years, but he states that he has been feeling well. You note that he is mildly overweight; however, his physical examination is otherwise unremarkable. Laboratory tests reveal an elevated total cholesterol level of 307 mg/dL with a low-density lipoprotein (LDL) level of 187 mg/dL. His high-density lipoprotein (HDL) and triglycerides levels are within normal limits. You explain to him that his cholesterol is elevated and you recommend that he begin a medication that lowers cholesterol by inhibiting the body's production of cholesterol. You also suggest that he improve his diet and exercise regimen.

Atorvastatin

Similar Drugs	Other ***HMG-CoA reductase* inhibitors** include pravastatin, lovastatin, rosuvastatin, simvastatin, and fluvastatin.
Mechanism of Action	This class of drugs acts by **inhibiting *HMG-CoA reductase***, which is the enzyme that catalyzes the first step in cholesterol biosynthesis in the liver (the conversion of HMG-CoA to mevalonic acid). They also cause an **increase in the concentration of LDL receptors** on hepatocytes, thereby increasing the liver's ability to extract LDL and very-low-density lipoprotein (VLDL) from the serum.
Clinical Uses	Used in treatment of elevated cholesterol levels. This class of drugs acts to **decrease total cholesterol and especially LDL levels**. Levels of triglycerides are also mildly decreased and HDL levels are mildly increased with use of this drug.
Side Effects	**Myopathy** (with or without evidence of muscle breakdown); **abnormal liver function tests**; teratogen.
Other	Since the effects of this class of drugs are mediated in part by an increase of the number of LDL receptors, this drug is not nearly as efficacious in individuals who lack LDL receptors (e.g., patients who are homozygous for familial hypercholesterolemia).

A 58-year-old man presents to your lipid clinic for a second opinion regarding treatment of his hyperlipidemia. He has tried several lipid-lowering medications in the past, including atorvastatin, pravastatin, fluvastatin, and rosuvastatin and has been unable to tolerate these medications secondary to severe myalgias. His primary care doctor also tried him on niacin, but he was unable to tolerate the flushing associated with this medication and he had significant diarrhea with cholestyramine. His most recent cholesterol tests demonstrate an elevated total cholesterol level of 288 mg/dL with an LDL of 192 mg/dL. His HDL and triglycerides levels are within normal limits. You recommend that the patient adhere to a strict low-fat diet and you decide to prescribe a cholesterol-lowering medication that works by decreasing intestinal cholesterol absorption.

Ezetimibe

Similar Drugs	
Mechanism of Action	Ezetimibe **decreases the absorption of cholesterol in the small intestine**. Decreased intestinal cholesterol absorption leads to a decrease in hepatic cholesterol stores. The hepatocyte responds to lower levels of intracellular cholesterol by increasing the concentration of LDL receptors on the cellular surface, thereby resulting in increased uptake of serum LDL into the cell with a **resulting decrease in serum LDL**.
Clinical Uses	Adjunct to diet and/or other medications for the treatment of **hypercholesterolemia (**decreases total cholesterol and LDL levels).
Side Effects	Steatorrhea (diarrhea); **myalgia**; arthralgia; **elevated liver function tests**.
Other	

A 34-year-old man with a history of familial hypertriglyceridemia presents to your clinic for a follow-up visit. Four months ago, his lipid panel was remarkable for an LDL cholesterol of 275. At that time, you had increased his atorvastatin to the maximal dosage. Today, his lipid panel demonstrates a LDL of 200. You inform the patient that there is another medication that can be used to lower his LDL cholesterol in combination with a statin and has been shown to effectively decrease LDL more than with statins alone.

Alirocumab

Similar Drugs	The **PCSK9 inhibitors** include alirocumab and evolocumab.
Mechanism of Action	*Proprotein convertase subtilisin/kexin type 9* (PCSK9) is a serine protease that is responsible for degrading the LDL receptor in

	the liver, thereby decreasing LDL metabolism in the liver and promoting increased LDL concentration in the plasma. This class of drugs acts to **inhibit PCSK9,** thereby resulting in an increased number of LDL receptors in the liver and enhanced LDL clearance from the plasma.
Clinical Uses	Used **in combination with maximally dosed statin therapy to reduce elevated LDL** in patients with familial hypercholesterolemia or atherosclerotic cardiovascular disease.
Side Effects	Injection site reaction; influenza; myalgia.
Other	

A 49-year-old woman presents to your office for a routine visit to follow up her abnormal lipid levels. Six months ago, initial assessment of her cholesterol levels had demonstrated elevated LDL levels, although her HDL and triglyceride levels were within normal limits. At that time, you started her on atorvastatin, but she was unable to tolerate the medication due to myalgias. You then tried a different lipid-lowering medication. Current laboratory studies demonstrate a marked decrease in her LDL levels. You tell her the good news and, although she is pleased with the results, she complains that the medication gives her diarrhea and tastes really terrible.

Cholestyramine

Similar Drugs	Other **bile acid resins** include colestipol and colesevelam.
Mechanism of Action	This class of drugs acts to **inhibit the reabsorption of bile acids in the jejunum and ileum**. Lower levels of bile acids result in the increased conversion of cholesterol to bile acids, thereby leading to lower levels of intracellular cholesterol. The cell responds to lower levels of intracellular cholesterol by increasing the concentration of LDL receptors on the cellular surface, thereby resulting in increased uptake of serum LDL into

	the cell with a resulting decrease in serum LDL.
Clinical Uses	Used in treatment of elevated cholesterol levels. This class of drugs acts to **decrease LDL levels**. There is generally no significant effect on HDL levels. Also used to treat pruritus associated with liver failure and diarrhea after gallbladder removal.
Side Effects	**GI upset**; bad taste of medication; decreased absorption of fat-soluble vitamins (A, D, E and K) and folic acid; impaired absorption of a variety of other drugs (e.g., warfarin, digoxin, tetracycline, thiazide diuretics).
Other	Since the effects of this class of drugs are mediated in part by an increase of the number of LDL receptors, this drug is not nearly as efficacious in individuals who lack LDL receptors (e.g., patients who are homozygous for familial hypercholesterolemia).

A 44-year-old woman presents to the emergency room complaining of severe epigastric pain. She tells you that the pain is associated with nausea and vomiting. Laboratory studies reveal elevated amylase and lipase levels, leading to a diagnosis of acute pancreatitis. She denies any history of alcohol use or gallstone disease, leading you to consider other factors that may have led to her episode of pancreatitis. When a lipid profile reveals a triglyceride level of 1500 mg/dL, you immediately decide to begin her on a triglyceride-lowering agent and you explain to her that her elevated triglyceride level was likely responsible for the development of her pancreatitis.

Gemfibrozil

Similar Drugs	Other **fibrates** include ciprofibrate, bezafibrate, and fenofibrate.
Mechanism of Action	This class of drugs acts to **stimulate *lipoprotein lipase***. *Lipoprotein lipase* is the enzyme responsible for breaking down triglycerides into VLDL and chylomicrons, which are then

	removed from circulation. The fibrates have also been implicated in decreasing hepatic cholesterol biosynthesis.
Clinical Uses	Used in treatment of elevated cholesterol levels. This class of drugs acts to **decrease triglyceride levels**. They also mildly decrease LDL levels and mildly increase HDL levels.
Side Effects	GI upset; increased incidence of gallstone formation; myositis; abnormal liver function tests.
Other	The fibrates circulate in the bloodstream, bound to plasma proteins. They compete with warfarin for binding sites to these plasma proteins. Thus, the effects of warfarin may be increased in patients taking fibrates and warfarin simultaneously.

A 59-year-old woman presents to your clinic for a routine follow-up visit. Her past medical history is notable for hypertension and a family history of premature coronary artery disease. Furthermore, a recent routine blood test demonstrated that she has developed dyslipidemia. Her cholesterol panel showed an elevated total cholesterol level of 252 mg/dL with an LDL of 178 mg/dL and an HDL of 25 mg/dL. You decide to start the patient on atorvastatin to treat her condition in addition to diet and lifestyle modification. Six months later, the patient's lipid panel has improved with a cholesterol level of 199 mg/dL and an LDL of 100 mg/dL, but her HDL has remained low at 28 mg/dL. You tell the patient that you could prescribe her another cholesterol-lowering medication, which is also a water-soluble vitamin that may help raise HDL levels, but you also inform her that recent trials have failed to show a clinical benefit from this medication.

Niacin

Similar Drugs	
Mechanism of Action	Niacin is thought to have many effects on lipid metabolism. It has been shown to **decrease lipolysis in adipose tissue**, thereby decreasing the concentration of precursors for VLDL and LDL

	production. It has also been shown to inhibit triglyceride synthesis in the hepatocyte. Lastly, it may **inhibit apolipoprotein A-1 breakdown** (the apolipoprotein responsible for the transport of HDL in the circulation), thereby increasing HDL levels.
Clinical Uses	Used in treatment of elevated cholesterol levels. This class of drugs acts to **increase HDL levels**. They also mildly decrease LDL levels and triglyceride levels.
Side Effects	**Flushing** (which can be decreased by co-administration with aspirin); eczema or acanthosis nigricans; hyperuricemia (may **exacerbate gout**).
Other	Niacin is vitamin B_3. Recent trials have failed to demonstrate a clinical benefit of niacin in lowering cardiovascular event rates.

A 69-year-old woman presents to your primary care office complaining of a 1-week history of back pain. She states that the pain began after she had been lifting some heavy boxes while cleaning out her husband's study room. She denies any neurologic symptoms. On physical examination, she has no pain with the straight leg maneuver, thereby suggesting that she has not herniated her disk; however, she does have point tenderness around the T12 to L1 region. You send her for imaging studies, which reveal a vertebral compression fracture at L1. A bone scan reveals the presence of significant osteoporosis. You decide to treat her osteoporosis with a medication that acts by decreasing osteoclastic bone reabsorption.

Bisphosphonates

Similar Drugs	Alendronate; etidronate; ibandronate; zoledronate; pamidronate; risedronate.
Mechanism of Action	This class of drugs acts to **decrease osteoclastic bone reabsorption** by inhibiting osteoclastic activity and increasing osteoclastic cellular death.

Clinical Uses	Prevention and treatment of **osteoporosis**. Also used in the treatment of Paget disease of the bone, bone metastasis associated with **hypercalcemia**, and multiple myeloma.
Side Effects	GI upset (especially esophageal erosions); osteonecrosis of the jaw (rare); atrial fibrillation.
Other	**Teriparatide** is a recombinant form of human parathyroid hormone that is used to treat osteoporosis. Increased circulating parathyroid hormone leads to increased calcium reabsorption and osteoblast activity, ultimately resulting in increased bone mass.

A 39-year-old woman presents to the emergency room complaining of a "racing heart." She tells you that she has experienced these sorts of palpitations several times over the past 6 months. Upon further questioning, you discover that she has lost 20 lb over the last 6 months, that she has two or three episodes of diarrhea a day, and that she has been having difficulty sleeping. Her physical examination is remarkable for the presence of exophthalmos and a mildly enlarged thyroid gland. You begin to suspect that this woman would benefit from a medication that inhibits thyroid hormone synthesis.

Propylthiouracil

Similar Drugs	Methimazole.
Mechanism of Action	This drug **inhibits *thyroid peroxidase***, the enzyme involved in iodine organification, by inhibiting the coupling of iodotyrosines. This results in the **inhibition of thyroid hormone synthesis** in the thyroid gland, as well as **inhibiting peripheral conversion of T_4 to T_3**.
Clinical Uses	Treatment of **hyperthyroidism**.

Side Effects	Maculopapular skin rash; arthralgias; agranulocytosis (rare); hepatotoxicity (propylthiouracil); teratogen (methimazole).
Other	

A 48-year-old woman with hypothyroidism presents to your clinic, complaining of insomnia, weight loss, and palpitations over the last 2 months. On further questioning, she also reports a 2-month history of heat intolerance and irritability. You begin to suspect that her symptoms are related to a too-high dose of a prescription medication used to treat her hypothyroidism and you decide to order blood tests to confirm your suspicion. When her TSH level comes back abnormally low and her free T4 level is abnormally high, you instruct her to decrease the dose of her hypothyroid medication and you plan to recheck her thyroid levels in 4 to 6 weeks.

Levothyroxine

Similar Drugs	
Mechanism of Action	Levothyroxine is a **synthetic form of T_4** (thyroid hormone), the hormone normally secreted by follicular cells of thyroid gland.
Clinical Uses	Used in the treatment of **hypothyroidism**. Also used to suppress TSH secretion for the treatment of goiters and as adjunctive therapy for some thyroid cancers.
Side Effects	If titrated to TSH levels within the normal range, there are minimal side effects. Overdose of levothyroxine results in symptoms similar to hyperthyroidism (tachycardia; weight loss; diarrhea; confusion).
Other	

A 50-year-old woman presents to your clinic complaining of palpitations, constipation, and depressed mood that began within the past 2 weeks. You check a parathyroid hormone level and it is elevated. A complete workup reveals a diagnosis of primary hyperparathyroidism due to parathyroid hyperplasia. You assure her that you will prescribe her a drug that can alleviate her symptoms by attacking the problem at its root and lowering levels of parathyroid hormone circulating in her body.

Cinacalcet

Similar Drugs	
Mechanism of Action	Cinacalcet acts by **sensitizing the calcium-sensing receptor of the parathyroid gland to calcium**, thereby resulting in decreased parathyroid hormone and lower calcium levels.
Clinical Uses	Used in the treatment of hypercalcemia due to **primary or secondary hyperparathyroidism**.
Side Effects	Hypocalcemia; GI upset.
Other	

A 68-year-old man with a history of alcoholism and hypertension was admitted after presenting to the ER with severe, unremitting joint pain localized to his knee and first metatarsophalangeal joint on the left. His laboratory results now show very high levels of uric acid in the blood and aspirated fluid from an effusion in his knee shows negatively birefringent crystals. You inform the patient that you would like to start him on an agent that will reduce the activity of inflammatory cells in his affected joints. Continued use of this medication will also be useful for preventing future attacks.

Colchicine

Similar Drugs	
Mechanism of Action	Colchicine acts to **induce microtubular depolymerization** by binding tubulin, thereby leading to decreased activation, migration, and degranulation of neutrophils to the affected site. Colchicine also blocks the formation of leukotriene B_4.
Clinical Uses	Treatment of **acute gouty attack**; also used to treat Behçet's disease, Familial Mediterranean Fever, and scleroderma.
Side Effects	**Diarrhea**; bone marrow suppression.
Other	In addition to colchicine, other medications used to treat acute gouty attacks include prednisone and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., indomethacin or naproxen).

A 70-year-old man with a history of gout presents to the clinic for a follow-up visit after a recent ED visit for severe joint pain. In the ED, he was diagnosed with a gout attack and given anti-inflammatory medications to relieve the pain and swelling in his affected joints. After discharge, he was sent out with a prescription for an agent that would help prevent future attacks. He asks you to explain more about how this medication works and its possible side effects. You explain to him that this medication works by promoting excretion of uric acid in the kidney and that, besides gastrointestinal irritation, there are very few side effects.

Probenecid

Similar Drugs	
Mechanism of Action	Probenecid acts to **decrease reabsorption of uric acid** in the proximal tubule of the kidney by blocking active transport of uric acid.

Clinical Uses	**Prevention of future gouty attacks**; prevention and treatment of hyperuricemia (e.g., tumor lysis syndrome).
Side Effects	GI upset; inhibition of renal excretion of penicillin and NSAIDs.
Other	**Pegloticase** is a recombinant form of *uricase*, which is the enzyme responsible for converting uric acid to allantoin. By increasing levels of *uricase*, there is increased breakdown of uric acid. It is used to **treat chronic gout**. **Rasburicase** is also a recombinant form of *uricase*. It is used to **treat hyperuricemia associated with malignancy**.

A 72-year-old man presents to the urgent care clinic complaining of severe pain in the big toe on his right foot. He denies any trauma to the toe and he states that he has had an episode of symptoms similar to this 1 month ago. His past medical history is significant for non-Hodgkin lymphoma, for which he is currently receiving treatment. On physical examination, you note that the first metatarsal joint of his right foot is swollen and tender to touch. Laboratory studies reveal significantly elevated uric acid levels. You begin treatment with a medication that will decrease the migration of inflammatory cells to the affected joints and you tell him that he may be able to prevent similar attacks in the future by taking a medication that acts by inhibiting xanthine oxidase.

Allopurinol

Similar Drugs	
Mechanism of Action	Allopurinol acts to **inhibit *xanthine oxidase***, an enzyme in the purine degradation pathway that is responsible for converting xanthine to uric acid.
Clinical Uses	**Prevention of further gouty attacks**; prevention and treatment of hyperuricemia (e.g., tumor lysis syndrome).

Side Effects	GI upset; hypersensitivity reactions; decreased metabolism of 6-mercaptopurine and azathioprine.
Other	When therapy with allopurinol is begun, colchicine or an NSAID should be given simultaneously because acute gouty attacks often occur during the first few weeks of allopurinol administration. **Febuxostat** also inhibits *xanthine oxidase*. It is used to treat hyperuricemia in patients with a history of gout.

A 79-year-old woman with a history of COPD presents to your clinic complaining of frequent bouts of dizziness. She now reports that she usually feels light-headed as soon as she gets up in the morning and whenever she stands up quickly. Orthostatic measurements taken in the office show a decrease in systolic blood pressure of 32 mm Hg and an increase in heart rate of 25 bpm when she moves from the supine position to standing. You counsel her on lifestyle modifications that may help her avoid dizzy spells and prescribe her a medication that will better support her blood pressure and prevent future episodes of orthostasis.

Fludrocortisone

Similar Drugs	
Mechanism of Action	Fludrocortisone is a class of **mineralocorticoid** that acts in a similar fashion to aldosterone, **promoting retention of sodium and water** in the body as well as secretion of potassium, without causing as pronounced electrolyte disturbances as aldosterone. Fludrocortisone also exhibits glucocorticoid activity.
Clinical Uses	Treatment of **primary and secondary adrenocortical insufficiency**; also used off-label in the treatment of orthostatic hypotension.
Side	**Immunosuppression** with increased susceptibility to infection;

Effects	**hypertension**; edema; hypokalemia; **adrenocortical insufficiency.**
Other	For other corticosteroids, see Prednisone card in Chapter 10.

A 42-year-old man presents to your weight loss clinic for an initial evaluation. He is morbidly obese with a body mass index of 43. His past medical history is significant for hyperlipidemia, type 2 diabetes mellitus for which he takes insulin, hypertension, and osteoarthritis of bilateral knees. He would like to avoid bariatric surgery and asks you if there are any oral medications available to treat his obesity. You inform him that you can prescribe him a medication that helps with weight loss by inhibiting intestinal fat absorption, but you warn him that a side effect of this medication is fecal incontinence.

Anti-Obesity Agents

Similar Drugs	
Mechanism of Action	**Orlistat**: this drug **inhibits the pancreatic enzyme**, ***lipase***, thereby reducing intestinal fat absorption. **Lorcaserin**: mechanism is poorly understood, but is thought to involve activation of serotonin receptors on neurons in the hypothalamus that control satiety. **Sympatomimetic amines (phentermine, phendimetrazine, diethylpropion):** thought to stimulate appetite reduction via sympathetic stimulation at the level of the hypothalamus. **Bupropion/Naltrexone:** Bupropion and Naltrexone act in concert to increase activity of pro-opiomelanocortin (POMC) neurons, which, in turn, helps regulate the brain's reward system and decrease food cravings.
Clinical Uses	Treatment of **obesity**.

Side Effects	**Orlistat**: steatorrhea and fecal incontinence; decreased absorption of fat-soluble vitamins (A, D, E, and K). **Lorcaserin**: headache; upper respiratory tract infection. **Sympatomimetic amines:** GI disturbances; dry mouth; insomnia. **Bupropion/Naltrexone:** nausea; constipation; headache.
Other	**Fen-Phen** was an anti-obesity drug consisting of phentermine (isomer of methamphetamine, which leads to increased catecholamine release in the brain) and fenfluramine (increased serotonin release at the synaptic cleft). It was withdrawn from the US market due to increased risk of valvular disease and pulmonary hypertension.

A 79-year-old man presents to your clinic complaining of difficulty urinating. On taking a complete history, you learn that he has had trouble in starting and stopping the stream of urine for the last 4 months. He also tells you that he has lost 10 lb in the last 2 months. A digital rectal examination demonstrates easily palpable, prostatic nodules that are firm, enlarged, and irregularly shaped. Laboratory tests demonstrate an elevated PSA level and a biopsy of a prostatic nodule confirms the diagnosis of prostate cancer. You refer the patient to an urologist and you suspect that this patient will likely need treatment with a medication that acts as a competitive antagonist at androgen receptors.

Flutamide

Similar Drugs

Mechanism of Action	This drug acts as a **competitive antagonist at the androgen receptor**, thereby decreasing the growth effects of testosterone on the prostate. By blocking the androgen receptor, flutamide also results in the relief of testosterone's inhibition of gonadotropin secretion. With lower levels of testosterone detected, the body responds by increasing serum LH release. To

	counteract the increased levels of LH, flutamide is always administered with leuprolide (see Leuprolide card in this chapter).
Clinical Uses	Treatment of **prostate cancer**.
Side Effects	GI upset; gynecomastia; abnormal liver function tests.
Other	

A 37-year-old woman presents to your gynecology clinic complaining of chronic breast and pelvic pain and dysmenorrhea. She has also had a long history of infertility; however, she has decided that she will start a family through adoption, and hence is not looking to become pregnant at this time. A thorough workup leads you to conclude that the patient is suffering from endometriosis. In discussing treatment options with the patient, you mention that you could prescribe her a synthetic androgen that can decrease LH and FSH secretion and would likely control her symptoms; however, you inform the patient that she may experience some unwanted side effects from this medication such as acne and hirsutism.

Danazol

Similar Drugs	
Mechanism of Action	Danazol is a synthetic androgen that acts as a **partial agonist at androgen and progesterone receptors**, thereby resulting in the decrease of LH and FSH secretion. With decreased LH and FSH secretion, the growth of endometrial tissue as well as breast tissue decreases. Danazol has also been shown to increase levels of *C1 esterase inhibitor* (the deficient enzyme in hereditary angioedema), thereby increasing levels of C4.

Clinical Uses	Danazol is primarily used to treat **endometriosis**. It has also been used to treat fibrocystic disease of the breast, **hereditary angioedema**, and menorrhagia.
Side Effects	**Androgenic side effects** in women (e.g., masculinization, hirsutism, acne); weight gain; edema; elevation in hepatic enzymes.
Other	

A 69-year-old man presents to your primary care office for his annual visit. He states that he feels healthy overall, except that he has begun to experience an increased frequency of urination. He denies any pain or blood with urination. Upon further questioning, he admits that he also has difficulty starting and stopping the stream of urine. A digital rectal examination reveals a diffusely enlarged prostate gland. Laboratory results demonstrate an increased total PSA with a proportionate increase in the fraction of free PSA, likely consistent with benign prostatic hypertrophy. You reassure the patient that his symptoms are not caused by a malignancy and you start him on a medication that will decrease the production of dihydrotestosterone and thus decrease the size of his prostate, thereby helping his urinary symptoms.

Finasteride

Similar Drugs	
Mechanism of Action	This drug **inhibits *5 α-reductase***, the enzyme responsible for the conversion of testosterone to dihydrotestosterone. In the prostate, dihydrotestosterone acts to stimulate growth of the gland, so by decreasing the levels of dihydrotestosterone, prostate growth is decreased.
Clinical	Treatment of **benign prostatic hyperplasia**, **prostate cancer**, and early male-pattern baldness.

Uses	
Side Effects	Decreased libido; erectile dysfunction.
Other	

A 59-year-old woman presents to your oncology clinic for follow-up of her estrogen-receptor positive breast cancer. In addition to her breast cancer, her past medical history is significant for coronary artery disease. In addition to her cardiac regimen of medications, she has been taking tamoxifen as part of her chemotherapy regimen for the last 6 months. She tells you that her sister told her that tamoxifen can be associated with an increased risk of endometrial cancers, which worries her significantly, and she was wondering if she might be able to take a different steroidal inhibitor to treat her breast cancer. You explain to the patient that there is another medication, which acts to inhibit aromatase that could be used to treat her breast cancer, but this medication has been shown to carry an increased risk of cardiovascular events in patients with preexisting coronary artery disease, thus she is not a candidate for this other medication.

Anastrozole

Similar Drugs	Letrozole; exemestane.
Mechanism of Action	Anastrozole acts to **inhibit *aromatase***, the enzyme that is responsible for converting androgens to estrogens. It thereby results in **decreased estradiol levels**.
Clinical Uses	**Chemotherapeutic agent** used for the treatment of estrogen-receptor positive **breast cancer**. Letrozole has also recently been shown to be useful in treating infertility that is caused by anovulation.
Side Effects	**Osteoporosis**; hyperlipidemia; **increased incidence of cardiovascular events** in patients with preexisting coronary artery disease; hot flashes.

Other

A 65-year-old woman presents to your oncology clinic for evaluation of a newly diagnosed metastatic breast cancer. She is understandably upset regarding her new diagnosis. You review the results of her scans and biopsies and see that her tumor is noted to be estrogen-receptor positive. You explain to her that you will be prescribing a medication that acts as a competitive estrogen-receptor antagonist, but you warn her that while this medication is good at treating breast cancer, it is also associated with an increased incidence of uterine malignancies.

Tamoxifen

Similar Drugs	
Mechanism of Action	Tamoxifen acts as a **competitive estrogen-receptor antagonist**, thereby minimizing the natural growth-promoting effects normally caused by the estrogen-estrogen receptor complex. Because tamoxifen has a lower affinity for the estrogen receptor than estrogen, higher amounts of estrogen (such as those present in premenopausal women) can overcome the competitive inhibition of tamoxifen. Thus, tamoxifen is **most effective in postmenopausal women**.
Clinical Uses	**Chemotherapeutic agent** used for the treatment of estrogen-receptor positive **breast cancer**.
Side Effects	**Increased risk of endometrial cancer**; **increased risk of thromboembolism**; **hot flashes**; GI upset; fluid retention; vaginal bleeding.
Other	**Raloxifene** is an estrogen-receptor modulator that acts as a **mixed estrogen agonist/antagonist**. Clinically, it is used to **treat osteoporosis** and to reduce the risk of invasive breast cancer in postmenopausal women. It **does not increase the patient's risk for endometrial cancer**; however, patients are

still at increased risk for thromboembolism.

An 85-year-old man presents to your oncology clinic for consultation regarding his metastatic prostate carcinoma. He was initially diagnosed with cancer when his primary care physician checked a PSA level after feeling a hard prostatic nodule on digital rectal examination. A subsequent bone scan revealed several areas of bony metastases and a prostate biopsy confirmed the diagnosis. During this initial visit, you explain to him you will be treating him with a regimen of medications that include a drug, which acts as a gonadotropin-releasing hormone agonist.

Leuprolide

Similar Drugs	Other GnRH analogues include nafarelin and goserelin.
Mechanism of Action	This drug is a **GnRH analogue**. When leuprolide binds the GnRH receptors in the pituitary, there is an initial release of LH and FSH; however, continued administration of leuprolide leads to the desensitization and downregulation of the GnRH receptors, thereby eventually resulting in decreased release of LH and FSH. Decreased levels of LH and FSH lead to decreased levels of estrogens and testosterone.
Clinical Uses	Treatment of **metastatic prostate cancer**, **leiomyomas**, and endometriosis when administered in a continuous fashion. **Treatment of infertility** when administered in a pulsatile fashion.
Side Effects	Impotence; hot flashes; GI upset.
Other	

A 39-year-old woman presents to your infertility clinic. She has a history of

polycystic ovarian syndrome, and has tried unsuccessfully to become pregnant with her husband. Previous workup shows no abnormalities in her husband's sperm count. She would like to discuss the possibility of prescription medications that may aid in ovulation. You discuss the possibility of using a medication that acts as a partial agonist at estrogen receptors in the pituitary gland, thereby increasing LH and FSH release and stimulating ovulation. You inform her that possible side effects include hot flashes and abdominal discomfort, and that multiple pregnancies can occur in up to 10% of women.

Clomiphene

Similar Drugs	
Mechanism of Action	Clomiphene acts as a **partial agonist at estrogen receptors in the pituitary gland and as an antagonist at estrogen receptors in the hypothalamus.** By binding to these estrogen receptors, the normal feedback inhibition from estrogen is decreased, thereby resulting in an increase in the release of LH and FSH. The surge of LH and FSH then stimulates ovulation.
Clinical Uses	Used for treatment of **infertility** in patients with ovulatory dysfunction (i.e., polycystic ovarian syndrome).
Side Effects	**Hot flashes**; **abdominal discomfort**; multiple pregnancies (10% of women); visual disturbances.
Other	

You have just delivered a healthy full-term infant for a 28-year-old female patient through vaginal delivery. While the birth was uncomplicated, your patient is now demonstrating signs of significant postpartum hemorrhage. You are concerned that the active hemorrhage is due to uterine atony rather than retained products of conception. Therefore, in order to increase uterine tone and hopefully stop the bleeding, you perform fundal massage while also administering a medication, which is a synthetic analogue of a posterior pituitary hormone.

Oxytocin

Similar Drugs	
Mechanism of Action	Oxytocin is a hormone, produced in the posterior pituitary, which acts to **stimulate uterine contraction** as well as the contraction of the myoepithelial cells in the breast.
Clinical Uses	Oxytocin is used to **induce labor** and to stimulate breast milk "let-down" in the new mother. It is also used to **control postpartum uterine hemorrhage**.
Side Effects	GI upset; cardiac arrhythmias; uterine spasm.
Other	

A 21-year-old woman presents to your office for her annual physical examination. She is feeling well with no complaints. On social history, she tells you that she is sexually active in a monogamous relationship. She is currently using condoms for birth control, but is interested in other forms of birth control. She denies any personal history or family history of blood clots and she does not smoke. You decide to prescribe her a hormonal form of birth control that may also reduce her risk of developing endometrial and ovarian cancer.

Oral Contraceptive Pills

Similar Drugs	
Mechanism of Action	Combined oral contraceptive pills are composed of a **mixture of synthetic estrogens and progestins or just progestins alone**. Synthetic progestin acts to **decrease GnRH release**, which leads to the subsequent **decrease in FSH and LH levels**. Low levels

	of synthetic estrogen act to decrease FSH release and also do not provide enough positive feedback to stimulate LH release. The decrease of FSH levels results in **inhibition of follicular development**, while the decrease of LH levels results in the **absence of ovulation**.
Clinical Uses	Used as a form of **birth control**; also used to treat dysfunctional uterine bleeding, polycystic ovary syndrome, endometriosis, acne vulgaris, and dysmenorrhea.
Side Effects	Breast fullness; nausea and vomiting; increased risk of thromboembolism (especially in women >35 years old who smoke)—progestin-only pills are not associated with an increased risk of thromboembolism.
Other	Combined oral contraceptive use **decreases the risk of ovarian and endometrial cancer**. **Emergency contraception pills** contain high doses of synthetic progestins and can be taken up to 72 hours after unprotected intercourse to inhibit ovulation. **Mifepristone** is a steroid compound that acts as a **competitive receptor antagonist at the progesterone receptor**. At high doses, it acts as an **abortifacient** by causing breakdown of the endometrial lining and cervical dilation. **Ulipristal** is an **antagonist and partial agonist of progesterone receptors,** which is used as emergency contraception. If it is taken immediately after unprotected sex, it can delay ovulation and thereby decrease the likelihood of fertilization.

A 45-year-old man presents to the emergency room complaining of large volumes of bloody vomit. His past medical history is significant for cirrhosis secondary to alcohol abuse. Physical examination is significant for a heart rate of 100 beats/min, a blood pressure of 90/60 mm Hg, and some epigastric pain. You call the gastroenterology service for an endoscopy, which demonstrates the presence of several esophageal varices. You start the patient on synthetic analogue of a naturally occurring pancreatic hormone, which causes vasoconstriction of his esophageal varices.

Octreotide

Similar Drugs	Somatostatin.
Mechanism of Action	Octreotide is a **synthetic analogue of the hormone**, **somatostatin**, which is a pancreatic hormone that acts to inhibit the release of many hormones (including secretin, gastrin, TSH, VIP, and growth hormone), reduce GI motility, and cause vasoconstriction.
Clinical Uses	**Treatment of a variety of endocrine disorders** including treatment of diarrhea associated with VIP-producing tumors, treatment of carcinoid, treatment of acromegaly, and treatment of Zollinger-Ellison syndrome. **Treatment of esophageal varices associated with cirrhosis-induced portal hypertension**.
Side Effects	GI upset; cardiac arrhythmias.
Other	

A 51-year-old woman presents to the emergency room complaining of recurrent headaches. She denies any neurologic symptoms or a history of migraines; however, a thorough review of systems reveals that she has been extremely thirsty lately and that she has been urinating frequently. Her physical examination, including a thorough neurologic examination, is unremarkable. Laboratory tests reveal normal glucose levels, increased serum osmolality, and hypernatremia. You refer her to an endocrinologist in order to determine the etiology of her disorder. In the meantime, you wonder if she might not benefit from treatment with a medication that causes an increase in permeability to water in the collecting ducts of the kidney, thereby resulting in increased renal reabsorption of water.

Vasopressin

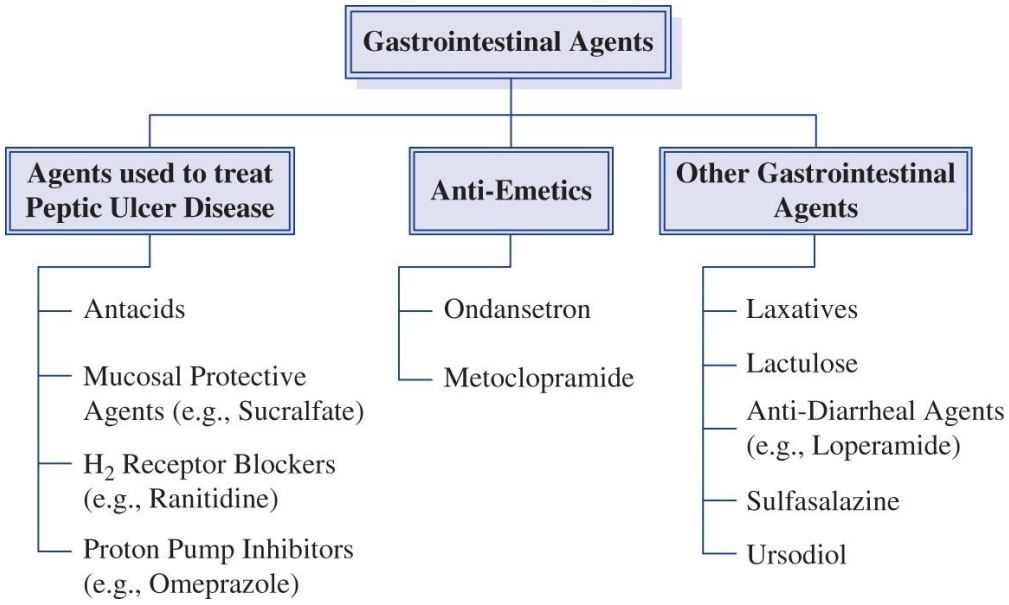
Similar Drugs	Desmopressin.
Mechanism of Action	Vasopressin is a **naturally occurring hormone**, released by the posterior pituitary that can interact with three different types of receptors: (1) V_1 receptors, which are present on vascular smooth muscle, in order to produce **vasoconstriction**; (2) V_2 receptors, which are found on renal tubule cells in the collecting ducts in the kidney; when vasopressin binds to V_2 receptors, it acts to **increase the permeability to water in the collecting ducts**, thereby increasing water reabsorption; (3) V_2-like receptors in order to **increase factor VIII activity**.
Clinical Uses	Treatment of **central diabetes insipidus**. Treatment of **septic shock and cardiac arrest**. Desmopressin acetate is also given to patients with mild hemophilia A or von Willebrand disease before minor surgical procedures to decrease the risk of uncontrollable bleeding.
Side Effects	**Hyponatremia**; hypersensitivity reactions; vasoconstriction (only associated with vasopressin and not desmopressin).
Other	

A 45-year-old man with a history of alcoholic cirrhosis is admitted to the floor due to painful ascites and hyponatremia. After he undergoes paracentesis and the fluid analysis comes back negative for infection, you speak with the patient about your plan to treat his hyponatremia. You tell him that you would like to give him a medication that will help raise his serum sodium level by promoting increased water losses in the intentionally kidneys.

Tolvaptan

Similar Drugs	Conivaptan.

Mechanism of Action	Tolvaptan is a **selective antagonist of vasopressin V_2 receptors,** while conivaptan acts at both **V_1 and V_2 receptors.** They act to increase serum sodium by preventing vasopressin-induced reabsorption of water in the kidneys.
Clinical Uses	Treatment of **euvolemic and hypervolemic hyponatremia**.
Side Effects	Nausea; dry mouth.
Other	**Demeclocycline** is a tetracycline that also acts as a vasopressin antagonist. For more information on demeclocycline, see "Tetracyclines" card in Chapter 1.



GASTRIC ACID SECRETION

- **Mechanism of gastric acid secretion**
  - Gastric parietal cells contain *carbonic anhydrase*, which is an enzyme that transforms CO_2 and H_2O into H^+ and HCO_3^-.
  - HCO_3^- is transported out of the parietal cell into the bloodstream via a Cl^-/HCO_3^- exchange.
  - H^+ is pumped out of the parietal cell via an **H^+/K^+ ATPase**, and Cl^- follows H^+ out of the parietal cell into the stomach lumen.
- **Regulation of gastric acid secretion**
  - *Stimulation of acid secretion*

- **Gastrin** stimulates H^+ secretion by interacting with an uncharacterized receptor on the parietal cell.
- **Histamine** activates H_2 receptors on the parietal cell, leading to an increase in cyclic AMP levels, which acts to stimulate acid secretion.
- The **vagus nerve** stimulates acid secretion through two pathways—through activation of an M_3 receptor on the parietal cell and through the activation of an M_3 receptor on the G cell of the stomach, which is responsible for secreting gastrin.

- *Inhibition of acid secretion*
  - **Chyme** directly inhibits acid secretion.
  - **Low pH** in the stomach inhibits gastrin secretion, thereby leading to a decrease in acid secretion.

A 34-year-old woman presents to your primary care clinic complaining of heartburn. She tells you that the pain begins after spicy meals and is generally worse when she lies down to go to sleep. She denies dysphagia, weight loss, low-grade fevers, or blood in the stool. Physical examination is unremarkable. You tell her that she likely has gastroesophageal reflux disease and you explain to her that there are several pharmacologic treatment options, including an over-the-counter class of drugs that act as weak bases to reduce the acidity in the stomach.

Antacids

Similar Drugs	Aluminum hydroxide; magnesium hydroxide; calcium carbonate; sodium bicarbonate.
Mechanism of Action	**Antacids are weak bases** that form a salt and water upon reaction with gastric hydrochloric acid. The net result is to increase the pH and thereby **reduce the acidity of the gastric contents.** Furthermore, since pepsin is inactivated at pH levels >4, antacids may also act to decrease the peptic activity of protein breakdown. Also, it has been postulated that antacids may increase the mucosal barrier of the gastric lining by stimulating prostaglandin synthesis.

Clinical Uses	Treatment of **gastroesophageal reflux disease**; also used to **promote the healing of duodenal ulcers.**
Side Effects	**Aluminum hydroxide**: Constipation. **Magnesium hydroxide**: Diarrhea. **Calcium carbonate**: Hypercalcemia; milk-alkali syndrome. **Sodium bicarbonate**: Flatulence; metabolic alkalosis.
Other	

A 40-year-old woman presents to your clinic with a complaint of black-colored stools and epigastric pain. You refer her for endoscopy, which reveals evidence of peptic ulcer disease. Biopsy results do not reveal the presence of *Helicobacter pylori* infection. In addition to starting her on a proton pump inhibitor, you decide to prescribe a medication, which acts to enhance the mucosal barrier in the stomach through the promotion of prostaglandin synthesis.

Mucosal Protective Agents

Similar Drugs	
Mechanism of Action	**Sucralfate**: believed to **enhance the mucosal barrier** either through the stimulation of prostaglandin synthesis or by acting as a physical barrier itself and thereby protecting the delicate mucosal lining from the acidic stomach contents. **Bismuth subsalicylate**: believed to inhibit intestinal motility through inhibition of prostaglandin synthesis, to bind intestinal toxins produced by *Escherichia coli*, and to stimulate fluid absorption from the bowel lumen.
Clinical Uses	These drugs are used in the treatment of **peptic ulcer disease** and to **promote the healing of duodenal ulcers. Bismuth subsalicylate**, specifically, is also used as an **anti-diarrheal agent** as well as part of quadruple therapy to **treat *H. pylori***.

Side Effects	**Sucralfate**: constipation. **Bismuth subsalicylate**: dark-colored tongue and stool; hinders tetracycline absorption.
Other	Since sucralfate requires an acidic environment for activation, it should not be taken with antacids, H_2 blockers, or proton pump inhibitors. Furthermore, because sucralfate binds non-specifically to positively charged molecules in the lumen, it can interfere with the absorption of other drugs if they are taken simultaneously. As a result, other drugs must be taken at least 2 hours before sucralfate administration.

A 62-year-old man presents to your primary care office for a follow-up visit regarding his multiple medical problems, including gout and atrial fibrillation, for which he is anti-coagulated with warfarin. He tells you that he has been feeling generally well, although he has been suffering from some heartburn over the past couple of months. On physical examination, you notice the appearance of some mild gynecomastia. Furthermore, laboratory testing reveals that his PT is much higher than would be expected given his current dose of warfarin. On further questioning, he admits that he has been taking a drug that his wife was prescribed for her gastroesophageal reflux disease many years ago. You advise him to stop taking his wife's medication immediately, as it is likely causing both his gynecomastia as well as his elevated PT levels.

H_2 Receptor Blockers

Similar Drugs	The H_2 receptor blockers include **ranitidine**, **cimetidine**, **famotidine**, and **nizatidine**.
Mechanism of Action	This class of drugs acts by **reversibly blocking the binding of histamine to the H_2 receptor** that is present on the parietal cells of the gastric mucosa. By inhibiting stimulation of the H_2 receptor, cyclic AMP levels are decreased, which then leads to the **decreased activity of the H^+/K^+ proton pump**. The end

	result is that gastric acid secretion is decreased.
Clinical Uses	Treatment of **gastroesophageal reflux disease**, **peptic ulcer disease**, and other diseases associated with gastric ulcers.
Side Effects	Headache; **Cimetidine**, in particular, has been shown to have anti-androgenic effects, leading to gynecomastia, and is also a known **CYP450 inhibitor** (and, therefore, can cause decreased hepatic metabolism of certain drugs, such as warfarin, anti-epileptics, and oral contraceptives).
Other	

A 59-year-old man presents to the clinic complaining of upper abdominal pain after meals. Upon further questioning, he tells you that he has lost 15 lb over the last 2 months because of a decreased appetite connected with the pain associated with his meals. He denies any frank blood in his stools, but he has noticed that his stool has been darker recently. His social history is significant for heavy alcohol and tobacco use over the past 35 years. You refer him to a gastroenterologist for an endoscopic evaluation of his stomach as you suspect that he may have gastric ulcers. For symptomatic relief, in the meantime, you place him on a drug that will directly suppress gastric acid secretion by inhibiting the H^+/K^+ ATPase pump in the gastric lining.

Proton Pump Inhibitors

Similar Drugs	The proton pump inhibitors include **omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole,** and **dexlansoprazole**.
Mechanism of Action	This class of drugs binds directly to and **irreversibly inhibits the H^+/K^+ ATPase pump**, which is present on the parietal cells of the gastric mucosa, thereby **suppressing gastric acid secretion**.
Clinical Uses	Treatment of **peptic ulcer disease**, **gastroesophageal reflux disease**, Zollinger-Ellison syndrome, and esophagitis. Also used

	as part of regimen to **treat *H. pylori* infection**.
Side Effects	Headache; rash; possible increased risk for fractures in the elderly; long-term use may cause atrophic gastritis as well as deficiencies of vitamins that require acid for absorption (e.g., calcium, iron, magnesium, vitamin B_{12}).
Other	Animal studies have shown an increased incidence of gastric carcinoid tumors with prolonged administration of omeprazole; however, there have been no reports of this in humans.

A 68-year-old woman with ovarian cancer is admitted to the hospital for a course of chemotherapy. After she has received her first treatment, she begins to complain of severe nausea and she vomits twice. To treat her nausea and vomiting, she was initially given an anti-emetic medication; however, you are notified that her blood pressure dropped to 90/50 mm Hg soon after administration of this medication. You decide to switch her anti-emetic medication to a drug that acts by blocking 5-HT3 receptors.

Ondansetron

Similar Drugs	
Mechanism of Action	Ondansetron acts to **block 5-HT_3 receptors**. 5-HT_3 receptors are present in the chemoreceptor trigger zone in the brainstem, which is part of the vomiting reflex pathway, and in the gastrointestinal tract. When the 5-HT_3 receptors are activated in the GI tract by the release of serotonin from damaged enterochromaffin cells, a signal is sent via the vagus nerve to the brainstem to activate the vomiting reflex pathway. By blocking 5-HT_3 receptors, ondansetron **inhibits activation of the vomiting reflex pathway**.
Clinical	Treatment of **nausea and vomiting.**

Uses	
Side Effects	Headache; constipation.
Other	**H_1 receptor antagonists** (e.g., diphenhydramine, dimenhydrinate, promethazine, and doxylamine) are also used to treat nausea and vomiting. H_1 receptors are present throughout the body, including in the GI tract. By blocking these receptors in the GI tract, GI tract motility is decreased, and symptoms of nausea and vomiting are lessened. Side effects of this class of drugs include blurry vision and dry mouth. Other drugs used to treat nausea and vomiting associated with chemotherapy include haloperidol, benzodiazepines, corticosteroids, and marijuana derivatives.

You are seeing a 53-year-old insulin-dependent diabetic patient, who is 3 days post-cholecystectomy on your surgical service. His bowel exam is normal with no signs of bowel obstruction and his surgical site is healing well. Nevertheless, he has had significant nausea and vomiting since his surgery and he complains of some mild abdominal bloating. You suspect that he may be experiencing some mild gastroparesis, likely related to both his postsurgical state as well as his diabetes. You decide to administer a medication that acts at the D_2 dopamine receptors in the chemoreceptor trigger area and will both stimulate his gastric motility as well as treat his nausea and vomiting.

Metoclopramide

Similar Drugs	
Mechanism of Action	Metoclopramide acts as an **antagonist at the D_2 dopamine receptors** in the chemoreceptor trigger zone of the medulla by raising the threshold of chemoreceptor activity required and,

	thereby, blocking activation of the vomiting reflex pathway. Metoclopramide has also been shown to **stimulate gastric and small intestinal motility**. Although the exact mechanism of action of this effect is unclear, this drug does have cholinomimetic activity which can lead to increased activation of the myenteric plexus of the enteric nervous system.
Clinical Uses	Used to treat **diabetic gastroparesis**. Also used as a potent **anti-emetic agent**.
Side Effects	**Sedation**; hypotension; diarrhea; **extrapyramidal symptoms**, including tardive dyskinesia; peripheral edema; depression; neuroleptic malignant syndrome
Other	**Prochlorperazine** is another **anti-emetic agent**, which acts by blocking the D_2 dopamine receptor in the chemoreceptor trigger zone, thereby blocking activation of the vomiting reflex pathway. There is also evidence that prochlorperazine may have some antagonistic activity at anti-cholinergic receptors as well as α_1 adrenergic receptors. Similar to metoclopramide, side effects include hypotension and extrapyramidal symptoms, including tardive dyskinesia.

An 82-year-old woman presents to your primary care clinic complaining of constipation. While taking a thorough history, you discover that she had been experiencing some right shoulder pain, for which she has been taking her late husband's leftover OxyContin for the last 2 months. You advise her that it is not a good idea to take other people's medications and you instruct her to discontinue using the OxyContin. In addition to working up the cause of her right shoulder pain, you prescribe her a new pain regimen as well as two medications that will treat her constipation by softening her stool and by increasing gut motility by mucosal stimulation.

Laxatives

Similar	**Irritants or stimulants**: Castor oil, senna, bisacodyl.

Drugs	**Bulking laxatives**: Lactulose, sorbitol, polyethylene glycol, magnesium salts. **Stool softeners**: Docusate, mineral oil.
Mechanism of Action	**Irritants or stimulants**: In general, these compounds act to increase intestinal peristalsis through mucosal irritation or stimulation, thereby leading to increased gut motility. **Bulking laxatives**: In general, these compounds draw water into the intestine via osmosis, thereby distending the bowel, which results in increased intestinal motility. **Stool softeners**: These compounds become emulsified with the stool, thereby softening the stool.
Clinical Uses	Treatment of **constipation**; also used for bowel preparation for colonoscopic procedures.
Side Effects	Abdominal cramps; diarrhea.
Other	**Lactulose** is also used in the treatment of hepatic encephalopathy. Bacteria in the intestine acts to degrade lactulose into lactic acid and acetic acid, which are two compounds that promote nitrogen excretion and hence improves the encephalopathy associated with hyperammonemia.

A 54-year-old man with a history of alcoholic cirrhosis presents to the Emergency Department with altered mental status. He is jaundiced and quite lethargic, requiring aggressive and repeated verbal stimulation to rouse. When questioned, he is oriented only to person, not place or time. On physical exam, you note that his hands flap noticeably when he extends his arms and dorsiflexes his hands. Among other labs, you order an ammonia level and start the patient on a drug that will help to lower serum levels of ammonia in the hopes of treating his encephalopathy.

Lactulose

Similar Drugs	
Mechanism of Action	Bacteria in the intestines degrade lactulose into lactic acid and acetic acid, which are two compounds that acidify the gut pH and **promote nitrogen excretion**, thereby improving the encephalopathy associated with hyperammonemia. Lactulose is also an **osmotic laxative** which acts by drawing water into the intestinal lumen.
Clinical Uses	**Treatment of hepatic encephalopathy**; also used as a laxative.
Side Effects	Abdominal cramps; diarrhea.
Other	**Rifaximin** is a non-absorbable derivative of rifampin that inhibits bacterial *RNA polymerase*, thereby resulting in the reduction of ammonia-producing bacteria in the gut. It has been shown to be effective in **reducing the risk of recurrence of hepatic encephalopathy**. Rifaximin is also used to treat diarrhea associated with **irritable bowel syndrome** and foreign travel. Side effects include peripheral edema, fatigue, and nausea.

A 23-year-old man presents to your clinic with a list of vaccines and prescription medications, which he will require for his summer international travel. He asks if there is anything else he should take with him in terms of medications. After reviewing his list, you see that he has not listed any drugs that could be used to treat simple traveler's diarrhea. You suggest that he take a medication with him which works by binding to opioid receptors in the intestine and thereby decreasing gut peristalsis; however, you instruct him to seek medical attention if he develops a high fever or notices blood in his stool.

Anti-Diarrheal Agents

Similar Drugs	Anti-diarrheal agents include **diphenoxylate** and **loperamide**.
Mechanism of Action	Diphenoxylate and loperamide act by **binding to opioid receptors in the intestine**, which leads to the inhibition of acetylcholine release and thereby results in decreased gut peristalsis.
Clinical Uses	Used for the symptomatic treatment of **diarrhea**.
Side Effects	Constipation; abdominal pain and bloating.
Other	**Bismuth subsalicylate** is also used as an anti-diarrheal agent (see Mucosal Protective Agents card in Chapter 8).

A 28-year-old man presents to the gastroenterologist's office complaining of abdominal pain and alternating bouts of diarrhea and constipation. Your physical examination is significant for a temperature of 100º F and several oral aphthous ulcers. You decide to order an upper gastrointestinal series with a small bowel follow-through, the results of which are suggestive of mild Crohn's disease. Since the patient is adverse to the idea of taking steroids, you decide to begin the patient on a medication that is structurally related to aspirin.

Sulfasalazine

Similar Drugs	Other **5-ASA derivatives** include olsalazine and mesalamine.
Mechanism of Action	In the colon, bacteria metabolize sulfasalazine into its two constituents, **sulfapyridine** and **5-ASA**. **5-ASA acts as an anti-inflammatory** by inhibiting prostaglandin and leukotriene production through the inhibition of COX. 5-ASA may also scavenge for oxygen radicals, thereby preventing further mucosal damage.

Clinical Uses	Treatment of **inflammatory bowel disease**; also used in the treatment of rheumatoid arthritis and juvenile arthritis.
Side Effects	GI upset; skin rash; headache; bone marrow suppression; infertility.
Other	Because this drug is metabolized to sulfapyridine, which can impair folic acid absorption, this drug should be administered with folic acid supplementation.

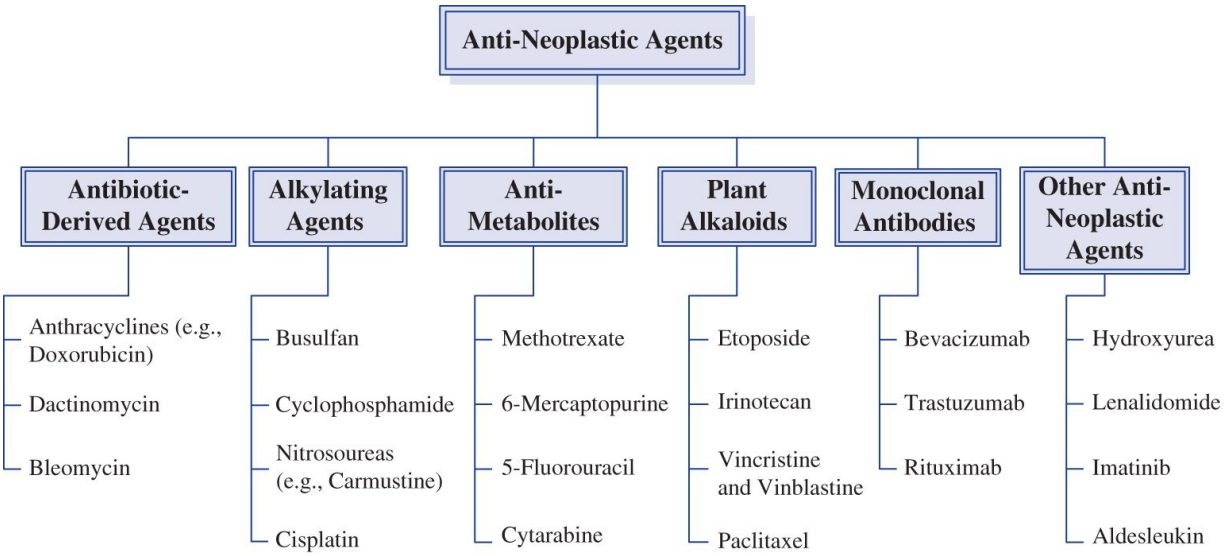
A 76-year-old woman presents to your primary care clinic complaining of right upper quadrant abdominal pain after meals. Upon further questioning, you discover that the pain tends to occur after she eats fast food or after she drinks alcohol. On physical examination, you note that she is obese and has mild tenderness in the right upper quadrant of her abdomen. An ultrasound of her gallbladder demonstrates the presence of several gallstones. Laboratory studies reveal elevated cholesterol levels. You tell the patient that you believe that she is suffering from cholesterol gallstones. She has a complicated past medical history and is not a good surgical candidate for a cholecystectomy. You decide to place her on a lipid-lowering regimen as well as on a drug that is specifically aimed at dissolving cholesterol gallstones.

Ursodiol

Similar Drugs	Chenodiol.
Mechanism of Action	Ursodiol decreases the incidence of cholesterol gallstones in three ways: (1) It inhibits *HMG-CoA reductase*, thereby **decreasing cholesterol synthesis**; (2) It **decreases intestinal reabsorption of cholesterol**; and (3) It **inhibits the secretion of cholesterol into bile**.
Clinical Uses	Treatment of **primary biliary cirrhosis**; also used to **treat cholesterol gallstones** in patients who desire an alternative to cholecystectomy.

Side Effects	GI upset.

Other



CLASSIFICATION OF ANTI-NEOPLASTIC AGENTS BY SITE OF ACTION

Site of Action	Agent		
Interferes with nucleotide synthesis or degradation	• 6-Mercaptopurine • 5-Fluorouracil	• Pentostatin	• Methotrexate
Interferes with conversion of ribonucleotides to deoxyribonucleotides	• Hydroxyurea		
Interferes with DNA synthesis	• Cytarabine • Anthracyclines	• Procarbazine • 5-Fluorouracil	

Damages DNA	• Anthracyclines • Mechlorethamine • Bleomycin • Nitrosoureas • Ifosfamide	• Busulfan • Cisplatin • Cyclophosphamide • Etoposide • Irinotecan	
Interferes with RNA synthesis	• Dactinomycin		
Interferes with cell signaling	• Imatinib		
Monoclonal antibody against cancer cells	• Trastuzumab • Rituximab	• Bevacizumab	
Interferes with mitosis	• Vincristine	• Paclitaxel	• Vinblastine
Interferes with hormonal action (*see* *Chapter 7*)	• Tamoxifen • Flutamide • Anastrozole	• Leuprolide • Raloxifene	

A 14-year-old boy presents to your office for initiation of chemotherapy to treat his acute lymphoblastic leukemia. You explain to the boy and his mother that you will be using several different chemotherapy agents to treat his disease. One of the agents you will be administering acts by blocking DNA and RNA synthesis; however, this drug also causes the production of oxygen free radicals, which can damage cardiac tissue when given at high doses. You assure the patient that you will be carefully monitoring levels of this drug so as to avoid cardiac toxicity if possible.

Anthracyclines

Similar Drugs	The class of anthracyclines includes **doxorubicin**, **daunorubicin**, and **idarubicin**.
Mechanism of Action	The anthracyclines **block DNA and RNA synthesis** both through **direct steric inhibition** as well as by **inhibiting *topoisomerase II***. They also cause **production of oxygen free**

	radicals, which lead to membrane damage.
Clinical Uses	**Doxorubicin**: **chemotherapeutic agent** in treating a variety of **solid tumors** (breast, ovary, bladder, endometrium, stomach, lung) as well as in treating a variety of **hematologic malignancies** (acute leukemia, lymphoma, multiple myeloma) and in treating AIDS-related Kaposi sarcoma. **Daunorubicin**: **chemotherapeutic agent** in treating **acute leukemia** (AML, ALL, CML) and neuroblastoma. **Idarubicin**: **chemotherapeutic agent** in treating acute myeloid leukemia.
Side Effects	**Cardiac toxicity**; bone marrow suppression; GI distress; alopecia.
Other	The cardiotoxic effects of the anthracyclines are caused, in part, by production of oxygen free radicals within myocardial cells and subsequent damage of the myocyte. This adverse effect is cumulative, dose-dependent, and can be largely avoided by keeping doses below a certain life-time dose and by administering **dexrazoxane**, a compound that acts to decrease free radical formation.

A 2-year-old boy is brought to your oncology clinic after having been recently diagnosed with Wilms tumor. Physical examination is significant for a palpable left flank mass. You explain to the child's mother that the best course of treatment will include surgical excision of the tumor and chemotherapy. You recommend the use of at least two drugs, one of which acts by interfering with RNA synthesis through the inhibition of *DNA-dependent RNA polymerase*. Since this drug can also cause bone marrow suppression, the child's blood cell counts, especially his platelets and leukocytes, will have to be monitored closely.

Dactinomycin

Similar Drugs	Plicamycin.

Mechanism of Action	Dactinomycin intercalates between cytosine-guanine base pairs of DNA, thereby acting to **inhibit *DNA-dependent RNA polymerase***, and thereby impairing both DNA and RNA synthesis.
Clinical Uses	**Chemotherapeutic agent** for several **solid tumors** including Wilms tumor, Ewing sarcoma, and metastatic testicular cancer. Also used in conjunction with methotrexate to treat gestational choriocarcinoma.
Side Effects	**Bone marrow suppression**; GI upset; skin abnormalities at sites that have previously received radiation ("radiation recall").
Other	**Plicamycin** has a similar mechanism of action as dactinomycin, but is primarily used for the treatment of some testicular cancers and Paget's disease of bone.

A 69-year-old man presents to your clinic complaining of shortness of breath that has become progressively worse over the past month. He tells you that he was diagnosed with testicular cancer 4 months ago, for which he is currently receiving chemotherapy. Physical examination is significant for an oxygen saturation of 89% on room air and decreased air movement on lung examination. When imaging studies reveal pulmonary fibrosis, you begin to suspect that this patient's symptoms are likely related to his chemotherapeutic regimen.

Bleomycin

Similar Drugs	
Mechanism of Action	Bleomycin binds to DNA and **triggers the formation of oxygen free radicals**. The oxygen radicals then act to damage the DNA, leading to strand breaks and inhibition of DNA synthesis.
Clinical Uses	**Chemotherapeutic agent** for the treatment of **testicular tumors**, squamous cell carcinomas (head and neck, skin, penis, cervix), and Hodgkin's lymphoma.

Side Effects	**Pulmonary fibrosis**; allergic reactions (fever, anaphylaxis); mucositis; skin changes. Note that **myelosuppression is rare** with bleomycin.
Other	Bleomycin is **cell cycle-specific**, thereby leading to the accumulation of cells in the G_2 phase of the cell cycle.

A 51-year-old man presents to your oncology clinic for evaluation of his CML. He will be undergoing bone marrow transplantation in the coming weeks, and he will need to have his marrow ablated prior to his transplantation. You inform him that his bone marrow will be ablated with a combination of medications, including an alkylating agent that acts to damage DNA via the cross-linking of DNA strands. You explain to him that this medication has many side effects, including adrenal insufficiency, seizures, and pulmonary fibrosis. The patient realizes that there may be serious side effects, but is more than willing to undergo the treatment to prepare for potentially life-saving bone marrow transplantation.

Busulfan

Similar Drugs	
Mechanism of Action	Busulfan acts as an **alkylating agent** that acts to damage DNA via the cross-linking of DNA strands.
Clinical Uses	Treatment of **CML**. Also used in combination with other drugs to ablate bone marrow before bone marrow transplantation.
Side Effects	**Pulmonary fibrosis**; **bone marrow suppression**; adrenal insufficiency with associated hyperpigmentation; seizures.
Other	

A 72-year-old woman presents to the emergency room complaining of the onset of pain and bleeding with urination over the past 24 hours. She denies any fever, flank pain, or history of kidney stones. Her past medical history is significant for breast cancer, for which she is currently receiving chemotherapy. Urinalysis is significant for copious amounts of blood and red blood cells. You admit the patient to the hospital for a urology workup and you begin to wonder if her symptoms might be related to her chemotherapeutic regimen.

Cyclophosphamide

Similar Drugs	Ifosfamide.
Mechanism of Action	Cyclophosphamide is metabolized to a hydroxylated intermediate compound by the cytochrome P-450 system in the liver. This hydroxylated intermediate then acts as an **alkylating agent** and **cross-links DNA**, thereby decreasing DNA and RNA synthesis. The drug has also been implicated in the **suppression of B- and T-cell function**.
Clinical Uses	**Chemotherapeutic agent** used in the treatment of a variety of **solid and hematologic malignancies** (e.g., breast, ovarian, non-Hodgkin lymphoma). **Immunosuppressive agent** used to treat rheumatoid arthritis, SLE, Wegener granulomatosis, and nephrotic syndrome.
Side Effects	**Hemorrhagic cystitis** (caused by accumulation of the metabolite, acrolein, in the urine; incidence can be greatly reduced by giving the patient copious fluids as well as MESNA [sodium 2-mercaptoethane sulfonate]); **bone marrow suppression**; GI upset; alopecia; infertility.
Other	**Mechlorethamine** is another **alkylating agent** that is used as part of the **MOPP protocol** in the treatment of **Hodgkin's lymphoma**. **Procarbazine** is another **alkylating agent** that is also used as part of the **MOPP** protocol in the treatment of **Hodgkin's**

disease as well as some brain tumors. A metabolite of procarbazine inhibits *monoamine oxidase*, and thus patients taking this drug should not ingest foods containing tyramine (wine, smoked meat, cheese) due to risk of norepinephrine buildup causing a hypertensive crisis.

A 42-year-old man presents to your neurology clinic complaining of severe headaches that have been present almost every day for the past month. The pain is usually lateralized to the right side and is often present upon waking. Over the past few days, he has also experienced several episodes of projectile vomiting. Physical examination is significant for the presence of papilledema on funduscopic examination. You become concerned and send the patient for an MRI of the brain. The imaging study reveals a mass in the right temporal lobe. Characteristics of the mass on imaging are consistent with a likely malignancy. You refer the patient to a neurosurgeon as well as to an oncologist. You believe that he will need chemotherapy and radiation to treat his condition and you suspect that his chemotherapy regimen will likely include a class of drugs that can cross the blood-brain barrier and then cross-link DNA strands to inhibit DNA synthesis.

Nitrosoureas

Similar Drugs	The nitrosoureas include **carmustine**, **lomustine**, **semustine**, and **streptozocin**.
Mechanism of Action	Drugs in this class are **alkylating agents**, which act to **cross-link DNA strands**, and thereby result in the inhibition of DNA and RNA synthesis.
Clinical Uses	**Chemotherapeutic agents** used in the treatment of **brain tumors** (e.g., glioblastoma multiforme), multiple myeloma, and lymphomas. Streptozocin is also used in the treatment of insulinomas.
Side Effects	**CNS toxicity;** bone marrow suppression; nephrotoxicity; pulmonary fibrosis.

Other	The nitrosoureas are one of the few chemotherapeutic agents that are highly lipid-soluble and **cross the blood-brain barrier**, and thus are useful in treating CNS malignancies.

A 76-year-old man presents to your clinic complaining of a ringing in both of his ears that has been present over the past month. He also tells you that he seems to be having more trouble hearing during this period as well. His past medical history is significant for bladder cancer, for which he is currently being treated with chemotherapy. Physical examination is remarkable for gross sensorineural hearing loss bilaterally. You suspect that his hearing loss is related to one of his medications and you decide to call his oncologist to see if there is an alternative chemotherapeutic agent that can be used to treat his malignancy, but will not cause acoustic nerve damage.

Cisplatin

Similar Drugs	Carboplatin.
Mechanism of Action	Cisplatin acts as an **alkylating agent**, thereby inhibiting DNA and RNA synthesis by binding DNA strands and leading to the formation of cross-links between strands.
Clinical Uses	**Chemotherapeutic agent** used in the treatment of many **genitourinary tumors** (testicular, ovarian, bladder), other solid tumors (small cell lung cancer, stomach, esophageal) and lymphomas.
Side Effects	**Nephrotoxicity**; **ototoxicity**; neurotoxicity; bone marrow suppression.
Other	Cisplatin-induced nephrotoxicity is dose-dependent and can be mitigated with the use of **amifostine**, which acts as a scavenger of free radicals in tissues treated with cisplatin, as well as aggressive IV fluids to induce diuresis. **Mitomycin** is another alkylating agent that damages DNA via

cross-linking of DNA strands. It is mostly used in combination with other agents to treat certain solid malignancies (e.g., breast, gastric, esophageal, pancreas, bladder).

A 42-year-old woman presents to your rheumatology clinic for follow-up of her rheumatoid arthritis. She is currently being treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids, but she states that her symptoms are still severe. Physical examination demonstrates swelling of the proximal interphalangeal and metacarpophalangeal joints of both hands, ulnar deviation of the fingers, and subcutaneous nodules over both of her elbows. You decide to start the patient on a medication that acts to inhibit *dihydrofolate reductase* and will thereby decrease her body's supply of activated folic acid.

Methotrexate

Similar Drugs	
Mechanism of Action	Methotrexate **inhibits *dihydrofolate reductase***, the enzyme that transforms folic acid to the active form, FH_4. FH_4 is a necessary precursor for the formation of thymidylate. Without FH_4, thymidylate supplies are diminished, thereby resulting in decreased DNA synthesis. Methotrexate is an **S-phase specific** chemotherapeutic agent.
Clinical Uses	**Chemotherapeutic agent** used to treat a variety of malignancies (e.g., ALL, lymphomas, breast cancer, head and neck cancer, osteosarcoma, choriocarcinoma). **Immunosuppressant** used to treat many autoimmune disorders (e.g., **RA**, Crohn's disease, scleroderma, psoriasis). **Abortifacient** when administered with a prostaglandin (used to treat missed abortions or small ectopic pregnancies).
Side Effects	**Bone marrow suppression**; nephrotoxicity (may crystallize in renal tubules); hepatotoxicity (steatosis); **teratogen**; **pulmonary toxicity**; mucositis; seizures; GI upset; alopecia.

Other	**Leucovorin (folinic acid)** is often given in conjunction with methotrexate in order to **minimize bone marrow suppression**, which occurs because of the lack of folate coenzymes. In the cell, leucovorin is converted to N^5N^{10}-methylene-FH_4, which is a downstream product of the reaction catalyzed by *dihydrofolate reductase*. Therefore, leucovorin **acts to bypass the inhibited enzyme** and provides an adequate supply of activated folate. Methotrexate has the same molecular target as the antibiotic, trimethoprim, and the anti-parasitic drug, pyrithiamine, but the drugs work to target different isoforms of *dihydrofolate reductase.*

A 10-year-old girl presents to your oncology clinic for follow-up of her acute lymphoblastic leukemia, for which she is currently receiving chemotherapy. She was recently discharged from the hospital 2 days prior to her appointment at your clinic. Her mother tells you that the patient developed an episode of acute gout while in the hospital, after which she was placed on allopurinol to prevent future gouty attacks. You immediately decide to alter the doses of the patient's chemotherapeutic regimen, as allopurinol indirectly inhibits the metabolism of one of the drugs in the patient's chemotherapeutic regimen and can thus result in increased serum levels of this drug.

6-Mercaptopurine

Similar Drugs

Mechanism of Action	6-MP is converted into thio-IMP by *HGPRT*, an enzyme involved in the salvage pathway. Thio-IMP acts as a purine analogue, which **inhibits purine synthesis** through feedback inhibition of several enzymes involved in de novo purine synthesis. Thio-IMP is also converted to thio-GTP, which is incorporated into DNA and RNA, leading to strand instability.
Clinical	**Chemotherapeutic agent** used primarily in treatment of

Uses	leukemias (especially **acute lymphoblastic leukemia**) as well as non-Hodgkin lymphoma. **Immunosuppressant** used to treat inflammatory bowel disease and psoriasis and prevent allograft rejection.
Side Effects	**Bone marrow suppression**; GI upset; increased susceptibility to infection.
Other	**6-MP is metabolized by *xanthine oxidase***, an enzyme involved in purine degradation. Allopurinol, a drug used to treat hyperuricemia and gout, is a potent inhibitor of *xanthine oxidase*. When allopurinol and 6-MP are given simultaneously, levels of serum 6-MP become increased because of decreased metabolism of 6-MP by *xanthine oxidase*. **Azathioprine** is a structural analogue of 6-MP and is converted to 6-MP within the cell. It is primarily used as an **immunosuppressant** in autoimmune diseases such as SLE, inflammatory bowel disease, RA, ITP, multiple sclerosis, and allograft rejection. Side effects are similar to those caused by 6-MP, and include **bone marrow toxicity** as well as GI upset. Both azathioprine and 6-MP are **S-phase specific chemotherapeutic agents**.

A 58-year-old man presents to your office for a follow-up visit. He was recently diagnosed with colon cancer and underwent colonic resection. He is currently receiving chemotherapy as an adjuvant treatment. At this visit, he tells you that he has noticed increased sensitivity of his eyes to light as well as painful ulcers on his lips and in his mouth. After examining his eyes and oral pharynx, you tell him that you suspect that his photosensitivity and mucosal ulcers are likely a side effect of one of the chemotherapeutic drugs being used to treat his colon cancer.

5-Fluorouracil

Similar

Drugs	
Mechanism of Action	5-FU is converted into 5-FdUMP, which then acts to **inhibit *thymidylate synthase***, the enzyme responsible for synthesizing thymine nucleotides. Inhibition of *thymidylate synthase* leads to a **disruption of nucleotide synthesis** because of a lack of thymidine. 5-FU can also be incorporated into RNA, leading to dysfunctional RNA processing.
Clinical Uses	**Chemotherapeutic agent** used to treat a variety of **adenocarcinomas** (gastric, pancreatic, **colon**, breast, ovarian) and for basal cell carcinoma.
Side Effects	**Bone marrow suppression**; photosensitivity; anorexia; oral ulcerations.
Other	5-FU is a **cell cycle-specific** drug, acting during the S phase of the cell cycle.

A 36-year-old woman presents to your oncology clinic for follow-up of her acute myelogenous leukemia. She has been receiving several chemotherapeutic agents for the treatment of her disease. Her most recent treatment involved a cell cycle-specific drug that acts by competitively inhibiting *DNA polymerase*. She tells you that lately she has been feeling extremely tired and that she had a nosebleed last week that took a long time to stop bleeding. On physical examination, you note that she is a pale, thin woman with a 3/6 systolic flow murmur at the left upper sternal border and a diffuse petechial rash over her limbs. Concerned, you send her to the emergency room for blood tests, which you suspect will reveal pancytopenia that is most likely caused by her recent chemotherapy treatment.

Cytarabine

Similar Drugs	
Mechanism of Action	In the cell, cytarabine is converted to araCTP, which acts to **competitively inhibit *DNA polymerase*** and thus impair DNA

	synthesis. araCTP can also be incorporated into DNA, leading to the termination of DNA strand elongation during DNA synthesis. Cytarabine is a **cell cycle-specific agent**, acting during the **S phase** of the cell cycle.
Clinical Uses	**Chemotherapeutic agent** for the treatment of **AML** as well as lymphomas.
Side Effects	**Bone marrow suppression with resulting pancytopenia**; alopecia; GI upset; ataxia.
Other	**Cladrabine** acts by interfering with DNA synthesis as well. After becoming activated through phosphorylation, cladrabine incorporates into growing DNA strands and leads to **DNA strand breakage**. Because the activated form of the drug also inhibits *ribonucleotide reductase*, it also induces a depletion of adenosine triphosphate (ATP). Cladrabine is a **cell cycle-non-specific agent**, and thus can induce cell death in resting as well as proliferating cancer cells. It is used primarily for treatment of **hairy cell leukemia.** Side effects include **bone marrow suppression**, neurotoxicity, and nephrotoxicity.

A 65-year-old woman presents to your oncology clinic for a follow-up visit. She had been diagnosed with small cell carcinoma of the lung 2 months earlier and she was started on a chemotherapy regimen at that time. Upon questioning, she tells you that she has started to lose her hair and that she has been feeling increasingly nauseous. You explain to her that these symptoms are likely related to one of her cell cycle-specific chemotherapy drugs, which acts by inhibiting *DNA topoisomerase II*. You then ask her about any gastrointestinal symptoms and you order serum studies to assess for myelosuppression.

Etoposide

Similar Drugs	Teniposide.
Mechanism	Etoposide acts by **inhibiting *topoisomerase II***, which leads to

of Action	DNA strand breakage.
Clinical Uses	**Chemotherapeutic agent** used in the treatment of solid tumors (**testicular**, prostate, glioblastoma multiforme, **small cell lung carcinoma**) as well as hematologic malignancies (lymphoma, leukemia).
Side Effects	**Bone marrow suppression**; alopecia; GI upset.
Other	Etoposide is a **cell cycle-specific** drug, acting during the late **S-G_2** phase of the cell cycle.

A 67-year-old man presents to your clinic complaining of a 20-pound weight loss, night sweats, and worsening malaise. He states that he has multiple family members who have been diagnosed with cancer, but he is not sure which type they have. He also says that he has not had any cancer screening, including colonoscopies, because of "insurance issues." A stool occult blood test is positive, and a subsequent colonoscopy shows cancerous growths in the sigmoid colon. A follow-up PET scan shows metastatic spread of his cancer. After delivering the diagnosis to the patient and his family, you begin to discuss initial treatment options. You note that one medication used to treat metastatic colon cancer works by inhibiting the enzyme *topoisomerase I*.

Irinotecan

Similar Drugs	Topotecan.
Mechanism of Action	Irinotecan acts by **inhibiting *topoisomerase I***, which leads to excessive DNA supercoiling and eventual DNA strand breakage and cell death.
Clinical Uses	**Chemotherapeutic agent** used in the treatment of recurrent or metastatic solid tumors (notably **metastatic colon cancer** for irinotecan and **metastatic ovarian** or **cervical cancer** for topotecan). Other cancers treated with these agents include

	pancreatic, esophageal, and small-cell lung cancer.
Side Effects	**Bone marrow suppression**; GI upset.
Other	Irinotecan and topotecan are **cell cycle-specific** drugs, active during the **S phase** of the cell cycle.

A 21-year-old man presents to the emergency room complaining of unsteady gait, which he began to notice over the past week. Upon further questioning, you learn that he was recently diagnosed with Hodgkin lymphoma and is currently receiving chemotherapy for his disease. Physical examination is significant for hyporeflexia in his lower extremities and right foot-drop. Laboratory studies are unremarkable and, notably, his platelets, white blood cell counts, and red blood cell counts are normal. As you prepare to admit the patient to the neurology service, you wonder if his neurologic deficits are related to his chemotherapeutic regimen.

Vincristine and Vinblastine

Similar Drugs	
Mechanism of Action	**Vincristine** (VC) and **Vinblastine** (VB) **bind to tubulin**, a microtubular protein, thereby leading to the **depolymerization of the mitotic spindle**. Thus, cells are unable to progress past metaphase during mitosis or meiosis, leading to decreased cellular proliferation.
Clinical Uses	**VC**: **Chemotherapeutic agent** used in the treatment of **ALL**, **lymphomas** (part of the MOPP protocol used to treat **Hodgkin's disease**), Wilms' tumor, and Ewing's sarcoma. **VB**: **Chemotherapeutic agent** used to treat **testicular cancer**, breast cancer, non-small cell lung cancer, and various **lymphomas**.
Side	**VC**: **Peripheral neuropathy**; GI upset; alopecia;

Effects	**myelosuppression is rare** and usually mild when it does occur. **VB**: **Bone marrow suppression**; GI upset; alopecia.
Other	VC and VB are **cell cycle-specific drugs**, acting during the **M** phase of the cell cycle.

A 43-year-old woman with metastatic breast cancer returns to your oncology clinic. She has undergone combination chemotherapy for her metastatic disease without a positive response. She is quite distraught and asks if her chemotherapy can be changed. You inform her that there is a new therapy for treatment of breast cancer in case combination chemotherapy fails. You decide to switch her regimen to include this other medication, which acts by interfering with the ability of the mitotic spindle to break down and thus halting mitosis.

Paclitaxel

Similar Drugs	Docetaxel.
Mechanism of Action	Paclitaxel **binds to tubulin**, a microtubular protein. The paclitaxel-tubulin complex acts to **promote stabilization and polymerization of the mitotic spindle**, which leads to the halt of mitosis during metaphase (anaphase cannot occur).
Clinical Uses	**Chemotherapeutic agent** used in the **treatment of ovarian and breast cancer**, small cell cancer of the lung, advanced Kaposi sarcoma, and head and neck cancers. Paclitaxel has been used in the past to **coat coronary artery stents** so as to prevent restenosis of the artery at the site of the stent.
Side Effects	Hypersensitivity reactions (rash); **bone marrow suppression**; neurotoxicity.
Other	

A 56-year-old gentleman with a past medical history significant for hypertension and tobacco use presents to your office complaining of hematuria. On physical exam, you palpate a flank mass on the left. Ultrasound confirms an irregular, non-cystic, vascular lesion in his left kidney. Follow-up biopsy confirms your suspicion that the patient has a malignant growth in his kidney. You suspect that the patient's chemotherapy regimen will include an agent to inhibit angiogenesis.

Bevacizumab

Similar Drugs	
Mechanism of Action	Bevacizumab is a **monoclonal antibody** specific for **vascular endothelial growth factor** (VEGF). By blocking the activity of VEGF, bevacizumab **prevents angiogenesis**, thereby reducing vascular supply to tumors and retarding their growth.
Clinical Uses	**Chemotherapeutic agent** used in the treatment of solid tumors (ovarian, colorectal, cervical, renal cell carcinoma). It is also used to treat dysregulated angiogenesis in wet age-related **macular degeneration**.
Side Effects	**Arterial thromboembolism**; hypertension; hemorrhage.
Other	**Cetuximab** is a **monoclonal antibody** against **epidermal growth factor receptor** (EGFR). Inhibiting EGFR **prevents cell growth** and induces apoptosis. It is used to treat **solid cancers** including head and neck cancer, non-small cell lung cancer, and colorectal cancer. Side effects include an **acne-like rash**. Similar to bevacizumab, **ranibizumab** is a monoclonal antibody with activity against VEGF. It is used for the treatment of macular degeneration.

A 50-year-old woman returns to your oncology clinic for a follow-up visit. She

is currently on a multidrug regimen for metastatic breast cancer. She appears to be responding well after the addition of a chemotherapeutic agent aimed at the *HER-2/neu* receptors within her cancer cells. While she is in the office, you schedule her for an imaging study to evaluate her heart. She asks why this test needs to be done and you remind her that, although the new medication is highly effective against her type of breast cancer, it can also cause cardiac dysfunction in up to 10% of patients.

Trastuzumab

Similar Drugs	
Mechanism of Action	Trastuzumab acts as a **monoclonal antibody** against the ***HER-2/neu* (*erb-B2*) receptor**. The *HER-2/neu* receptor is involved in growth-promoting pathways of the cell; 20% to 30% of breast cancers will overexpress *HER-2/neu*, thereby contributing to uncontrolled cellular growth. Trastuzumab directly blocks *HER-2/neu* signaling and also induces antibody-dependent cell-mediated cytotoxicity.
Clinical Uses	**Chemotherapeutic agent** used to treat **breast cancer** and gastric cancer that overexpress *HER-2* receptor.
Side Effects	**Cardiac toxicity**; neutropenia; GI upset.
Other	

A 55-year-old man with non-Hodgkin lymphoma presents to your oncology clinic for a follow-up appointment. The patient started treatment with chemotherapy and immunotherapy for his lymphoma about 3 months ago; however, you have not seen the type of tumor regression that you would like. You inform the patient that you would like to add another drug to his regimen, which acts by binding to the CD20 antigen on B cells and inducing cell lysis. You warn him, though, that there is a risk of a serious infusion reaction with administration of this medication, which you will try to prevent by pre-

medicating him with an anti-histamine and acetaminophen 20 to 30 minutes prior to him receiving the drug.

Rituximab

Similar Drugs	
Mechanism of Action	Rituximab is a **monoclonal antibody**, **which is aimed against antigen CD20**, which is found on the surface of B-cells. Upon binding to the B cell, the rituximab/CD20 complex induces B-cell lysis.
Clinical Uses	Used to treat **non-Hodgkin lymphoma** and **chronic lymphocytic leukemia**. Also used in the treatment of certain autoimmune disorders (e.g., **rheumatoid arthritis**, Wegener granulomatosis, microscopic polyangiitis).
Side Effects	**Infusion reaction** (can include hypotension, respiratory failure, and cardiac arrest; avoid by premedicating patients with an anti-histamine and acetaminophen prior to infusion); tumor lysis syndrome causing **acute renal failure**; increased susceptibility to infection; pulmonary toxicity; neutropenia; progressive multifocal leukoencephalopathy related to activation of JC virus.
Other	**Alemtuzumab** is a **monoclonal antibody** targeting **CD52**, which is found on a variety of lymphoid and myeloid cells, including **mature B and T cells**. Alemtuzumab induces antibody-dependent cellular cytotoxicity of these cells. It is used primarily to treat **CLL**, T-cell lymphoma, and multiple sclerosis. Side effects include bone marrow suppression and infusion reactions.

A 49-year-old man presents to your oncology office for follow-up of his chronic myelogenous leukemia, for which he is currently receiving chemotherapy. You

ask him whether he is experiencing any nausea, vomiting, or diarrhea, all of which are common side effects of his medications. You also tell him that his blood counts are at the low end of normal, which is expected since his chemotherapeutic regimen can also cause bone marrow suppression. He was biochemistry major in college, so he is interested in knowing how the drugs that he is taking work. You explain to him that one of his medications acts by inhibiting *ribonucleotide reductase*, an enzyme involved in making deoxyribonucleotides, the building blocks for DNA.

Hydroxyurea

Similar Drugs	
Mechanism of Action	Hydroxyurea **inhibits *ribonucleotide reductase***, the enzyme responsible for reducing ribonucleotides to deoxyribonucleotides. Inhibition of this enzyme results in **decreased DNA synthesis**. Hydroxyurea has also been shown to increase levels of fetal hemoglobin (Hb F), although the exact mechanism for this effect is unknown.
Clinical Uses	**Chemotherapeutic agent** used to treat myeloproliferative disorders (e.g., **CML**, polycythemia vera) as well as **melanoma**. Hydroxyurea has also been used in the treatment of **sickle cell disease** to promote production of Hb F over hemoglobin S.
Side Effects	**Bone marrow suppression**; GI upset.
Other	Hydroxyurea is a **cell cycle-specific agent**, acting during the **S phase** of the cell cycle. **Pentostatin** is a chemotherapeutic agent primarily used to **treat hairy cell leukemia**. Pentostatin acts by inhibiting *adenosine deaminase*, an enzyme involved in purine nucleotide degradation, thus inducing **bone marrow suppression**.

A 72-year-old man presents to your clinic complaining of fatigue and back pain. He has no significant past medical history and states that he has felt quite well until the last few months, when he has had to stop running in the morning because he is "just too tired." He also notes that recently he seems to have "gotten sick more often than usual." Concerned that the patient might have a plasma cell disorder, you order several hematologic tests, including a blood smear and serum protein electrophoresis. Both tests show a monoclonal neoplastic proliferation of plasma cells. After discussing treatment options with the patient, you both decide to start the patient on a medication that kills cancer cells both directly as well as by stimulating the immune system.

Lenalidomide

Similar Drugs	Thalidomide.
Mechanism of Action	Lenalidomide and thalidomide act to promote cancer cell death through multiple mechanisms, including **stimulation of cell-mediated immunity**, **inhibition of angiogenesis**, and **directly inducing cancer cell death**. It is also thought to have some anti-inflammatory effect, such as decreasing TNF-α.
Clinical Uses	**Lenalidomide**: **Chemotherapeutic agent** used primarily in the treatment of **multiple myeloma**, select lymphomas, and **myelodysplastic disease**. **Thalidomide**: **Multiple myeloma**, erythema nodosum leprae.
Side Effects	**Lenalidomide**: **Bone marrow suppression**; teratogen; venous thromboembolism. **Thalidomide**: **Teratogen** (associated with phocomelia, which is the shortening or absence of limbs); venous thromboembolism; neuropathy.
Other	

A 64-year-old man with chronic myelogenous leukemia is being seen in your

oncology clinic. He has been treated with α-interferon and cytarabine with no improvement. He asks you if there are any other options to treat his disease. You tell him that you would like to try a different agent that acts by inhibiting a tyrosine kinase on a mutated gene product, *bcr-abl*, which has been shown to be associated with his disease.

Imatinib

Similar Drugs	
Mechanism of Action	Imatinib acts as a **competitive inhibitor of *tyrosine kinase* enzymes** in *abl*, *c-kit*, and *PDGF-R*, all genes involved in cellular growth. By inhibiting the *tyrosine kinase* enzymes, the activation of these genes is severely decreased, and cellular growth is slowed.
Clinical Uses	**Chemotherapeutic agent** used to treat **CML**, **GISTs**, and brain tumors.
Side Effects	Fluid retention (edema); nausea; rash; heart failure.
Other	CML is commonly associated with translocations between chromosomes 9 and 22, yielding what is known as the **Philadelphia chromosome**. The translocation produces a fusion protein, *bcr-abl*, which is constitutively active. By inhibiting the tyrosine kinase of the *abl* portion of this mutated gene product with agents such as imatinib, the cellular growth of CML is decreased. **Erlotinib** is a **tyrosine kinase inhibitor** active against EGFR. By blocking EGFR signal transduction, cellular growth is arrested. It is primarily used in **non-small cell lung cancer** and **pancreatic cancer**. Side effects include rash and GI distress.

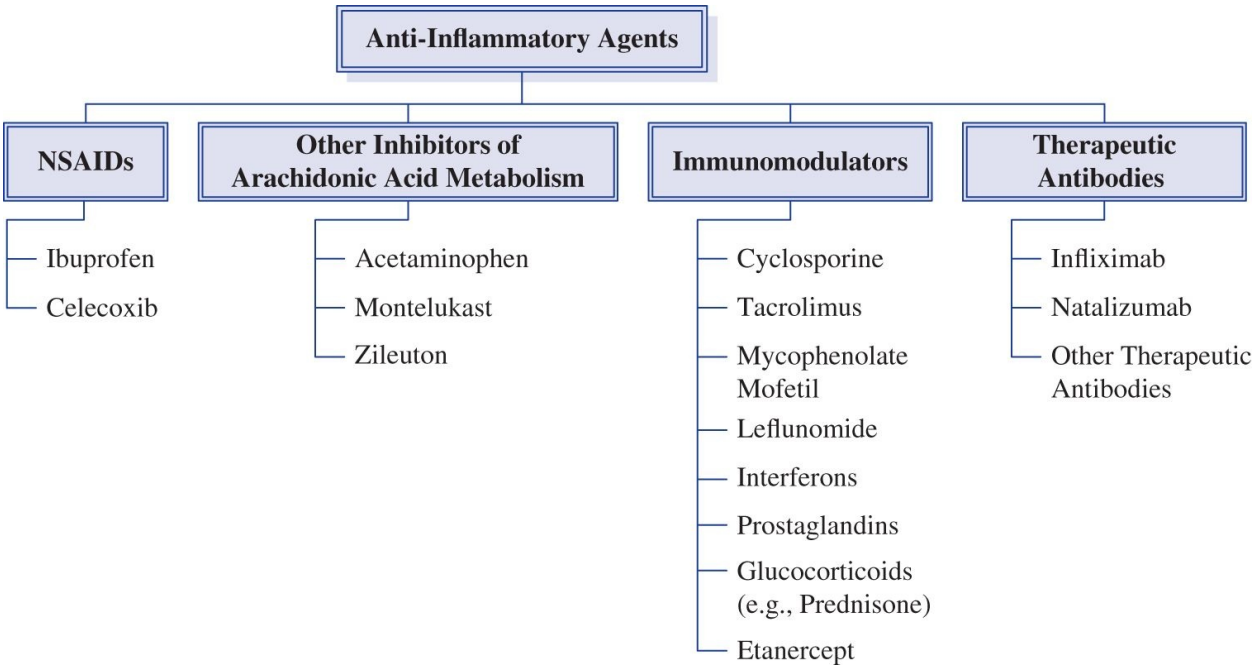
A 62-year-old gentleman presents for his scheduled chemotherapy infusion. He was diagnosed with renal cell carcinoma 3 months ago. Unfortunately, his initial

treatment regimen has not slowed tumor growth, and recent imaging has confirmed stage IV (metastatic) disease. Due to the rapid progression of his disease, you have decided to give this patient an immunomodulatory therapy that mimics a naturally occurring T cell-activating molecule. Because this treatment can induce shock, however, you plan to carefully monitor his hemodynamics during and after infusion.

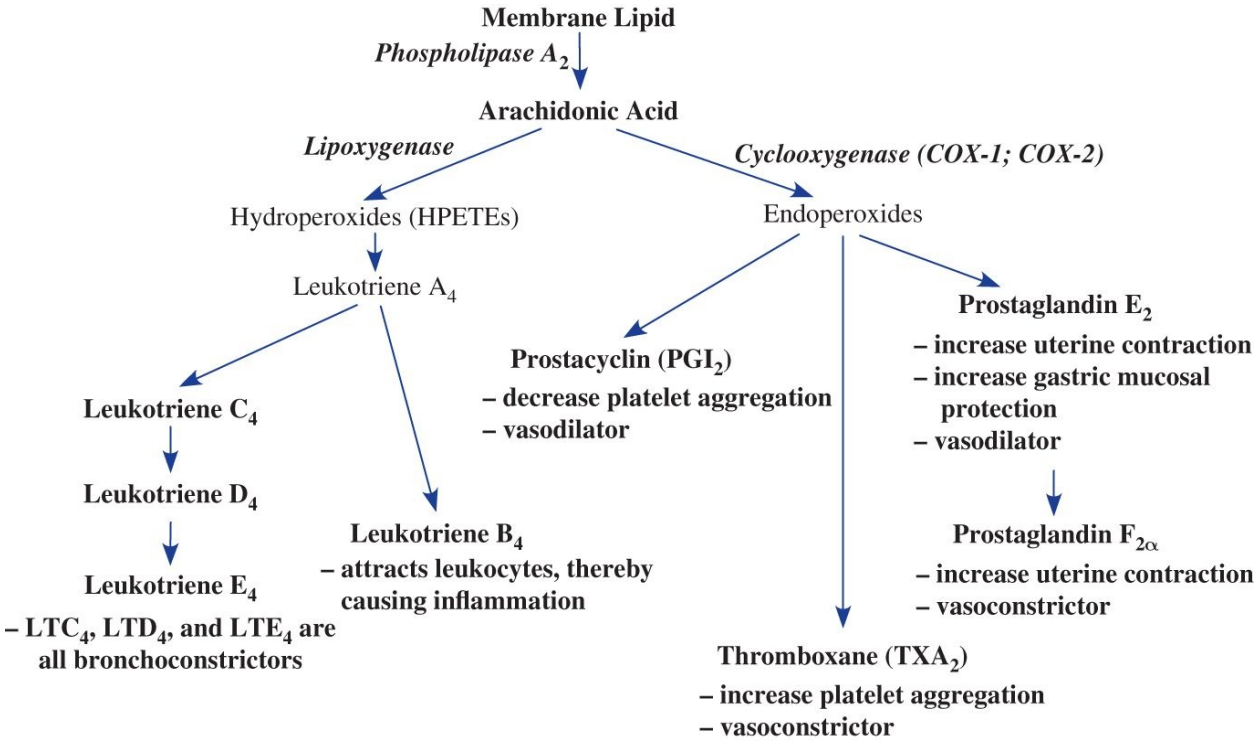
Aldesleukin

Similar Drugs	
Mechanism of Action	Aldesleukin is a recombinant form of **interleukin-2** (IL-2), which induces **proliferation and activation of T cells**, including tumor-infiltrating lymphocytes, which can directly kill cancer cells. Aldesleukin also has some activating effects on B cells and natural killer cells.
Clinical Uses	Used to treat **metastatic melanoma** and **renal cell carcinoma**.
Side Effects	**Capillary leak syndrome** (IL-2 acts as a pro-inflammatory agent and thereby induces permeability of vasculature leading to hypotension); tachycardia; GI distress.
Other	**Vemurafenib** is an **inhibitor of the enzyme *B-raf* with the V600E mutation**. *B-raf* is a key mediator of cellular growth, and the V600E mutation induces unregulated cellular proliferation. Vemurafenib does not have any effect on wild-type B-raf, but inhibits kinase activity of the V600E variant, which is commonly found in **malignant melanoma**, as well as some non-small cell lung cancers. Common side effects include skin lesions, photosensitivity, and arthralgias.

10



PROSTAGLANDIN AND LEUKOTRIENE SYNTHESIS AND ACTIONS



A 71-year-old woman presents to your clinic complaining of pain in her right knee. Upon further questioning, she tells you that she has noticed that the pain is usually worse during the evening after a full day of activity. Physical examination reveals a swollen, tender right knee with a minimal joint effusion. You also notice bony nodules on her distal and proximal interphalangeal joints. You tell the patient that you suspect that she has osteoarthritis and you recommend an over-the-counter medication that will help relieve her symptoms by reversibly inhibiting *cyclooxygenase 1* and *2*.

Ibuprofen

Similar Drugs	Other **non-selective NSAIDs** include meloxicam, piroxicam, ketorolac, naproxen, indomethacin, diclofenac, sulindac, and oxaprozin.
Mechanism of Action	Ibuprofen is a **reversible inhibitor of *cyclooxygenase-1 (COX-1)* and *COX-2***. Inhibition of *COX-1* and *COX-2* reduces the conversion of arachidonic acid to prostaglandin precursors,

	thereby resulting in **decreased prostaglandin synthesis** (which generally leads to an anti-inflammatory effect). Without PGE_2, there is decreased sensation to pain (analgesia), a decreased set-point at the hypothalamic thermoregulatory center (anti-pyretic), and decreased synthesis of protective gastric mucus. Without PGI_2, there is increased gastric acid secretion (leads to gastric ulcers).
Clinical Uses	There are many uses for ibuprofen including use as an **anti-pyretic**, an **analgesic**, and an **anti-inflammatory** (including the treatment of **rheumatoid arthritis** and **osteoarthritis**). Indomethacin is also used in the treatment of **gout**, as a labor suppressant that acts by decreasing uterine contractions, and as an agent to **close a patent ductus arteriosus**.
Side Effects	**GI bleeding**; allergic reactions; **interstitial nephritis**; tinnitus; hepatitis.
Other	Ibuprofen **does not have a significant anti-platelet effect**. Because ibuprofen reversibly inhibits *COX-1* and *COX-2*, platelets can eventually replenish thromboxane A_2 (TXA_2) levels. When *COX-1* and *COX-2* are irreversibly inhibited (as with aspirin), aspirin-treated platelets are unable to synthesize TXA_2 for the lifespan of the platelet (8 to 10 days), thereby leading to decreased platelet aggregation. Because prostaglandins vasodilate the afferent arteriole, NSAIDs decrease blood flow to the kidneys and may **induce renal ischemia**.

A 43-year-old woman presents to your rheumatology clinic for consultation regarding her newly diagnosed rheumatoid arthritis. The patient explains to you that her biggest concern is that she has had gastric ulcers in the past and she heard that some of the medications used to treat rheumatoid arthritis can aggravate the lining of the stomach. You explain to the patient that there are many treatment options for rheumatoid arthritis, some of which can modify the progression of her disease, while others are appropriate for symptom relief. As you begin to write out prescriptions for her, you explain that one of the drugs

that you are recommending for her will act as an anti-inflammatory with a lower risk of developing gastric ulcers as compared to ibuprofen. You do warn her though that use of this drug may also increase her risk for stroke.

Celecoxib

Similar Drugs	
Mechanism of Action	Celecoxib **irreversibly inhibits *COX-2***, thereby resulting in **decreased prostaglandin synthesis** (which generally leads to an anti-inflammatory effect). *COX-1* is generally regarded as being present in most tissues (e.g., the stomach), whereas *COX-2* is thought to be upregulated at sites of inflammation (e.g., endothelium and inflammatory cells). Thus, by selectively inhibiting *COX-2*, the negative side effects of other NSAIDs, such as gastric ulcers, may be minimized since those effects are thought to be mediated through *COX-1* inhibition.
Clinical Uses	Used in the treatment of **rheumatoid arthritis**, **osteoarthritis**, and acute pain, especially in patients with gastric ulcers or renal disease. Also used to reduce colonic polyps in patients with familial adenomatous polyposis.
Side Effects	**GI upset**; **interstitial nephritis**; allergic reaction if also allergic to sulfa; **increased risk of thrombosis**, including **stroke** and **myocardial infarction**.
Other	**Rofecoxib** is another irreversible inhibitor of *COX-2* and was used to treat arthritis and chronic pain. It was withdrawn from the market in 2004 because of **increased incidence of heart attack and stroke**, which was observed to be associated with use of the drug. **Acetylsalicylic acid** acts to **irreversibly inhibit *COX-1 and 2***. It is used as an anti-platelet agent, an anti-pyretic drug, an analgesic, and an anti-inflammatory agent (see Acetylsalicylic Acid card in Chapter 6).

A 25-year-old woman calls your clinic with a question regarding treatment of her headaches. She tells you that she has been suffering from occasional headaches that usually are worse at the end of a stressful day. She also notes that she often feels shoulder tightness and she mentions that she is under a lot of stress at work. After more questioning, you feel comfortable enough to diagnose her with likely tension headaches. You tell her that she can treat her headaches with the use of a common over-the-counter medication that acts to inhibit *cyclooxygenase* in the nervous system and you instruct her to set up a follow-up appointment at your office if her symptoms worsen.

Acetaminophen

Similar Drugs	
Mechanism of Action	Despite its ubiquity, the mechanism of acetominophen (tylenol) is not completely understood. Acetaminophen acts to **preferentially inhibit *COX-2* in the CNS**, thereby leading to decreased prostaglandin synthesis in the CNS. It is largely inactivated peripherally, thus it has **minimal anti-inflammatory effects**. Without PGE_2 in the CNS, there is decreased sensation to pain (analgesia) and a decrease of the set-point at the hypothalamic thermoregulatory center (anti-pyretic). Acetaminophen is also believed to **act at cannabinoid receptors**, perhaps contributing to some of its analgesic properties.
Clinical Uses	There are many uses for acetaminophen including use as an **anti-pyretic** and an **analgesic**. Acetaminophen is a good anti-pyretic and analgesic alternative in patients who cannot tolerate aspirin or other NSAIDs, or in children with viral infections who should not take aspirin because of the risk of Reye syndrome.
Side Effects	Dizziness; **fatal hepatotoxicity with overdose**.

Other	Acetaminophen overdose occurs when the dose exceeds the capacity of the liver to safely metabolize acetaminophen through glucoronidation or sulfation. In this situation, acetaminophen is converted to a highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which causes hepatocellular necrosis. ***N*-Acetylcysteine** is used as an **antidote for acetaminophen overdose**. It contains sulfhydryl groups, which bind to and inactivate NAPQI.

A 6-year-old girl is seen in your pediatrics office for follow-up of her asthma. The patient's mother tells you that her daughter generally uses her albuterol "rescue" inhaler five or six times a day and that she often wakes up in the middle of the night coughing. Physical examination reveals mild expiratory wheezes. You decide that the patient requires more aggressive treatment of her asthma and you begin to explain the different pharmacologic options to the patient and her mother. When the patient's mother mentions that the child has multiple allergies, you decide that the girl might benefit from the addition of a leukotriene receptor antagonist to her treatment regimen.

Montelukast

Similar Drugs	Zafirlukast.
Mechanism of Action	Montelukast is a **reversible inhibitor of the cysteinyl leukotriene-1 receptor**. By blocking the binding of leukotrienes C_4, D_4, and E_4 to the receptor, the actions of leukotrienes C_4, D_4, and E_4 (bronchoconstriction and increased mucus secretion) are blocked.
Clinical Uses	**Preventative treatment of asthma**, including aspirin-induced asthma. Not useful in acute asthma attacks.
Side Effects	GI distress; headache; eosinophilic vasculitis.

Other	**Zafirlukast** inhibits hepatic cytochrome P-450, thereby leading to the potentiation of drugs that are metabolized by this system (e.g., warfarin).

A 9-year-old boy presents to an urgent-care clinic complaining of shortness of breath, which began after the child was playing with the neighbor's cat. While obtaining a history from the boy's parent, you notice that the boy is using his accessory muscles of respiration. Physical examination demonstrates expiratory wheezes across all lung fields. As you begin to administer an inhaled β_2-adrenergic agonist for relief of the patient's symptoms, his mother asks whether she can give her son a medication that she takes for asthma if his symptoms return in the future. When she pulls out her medication, you see that it inhibits *5-lipooxygenase*. You explain to her that her medication acts to prevent asthmatic exacerbations, but that it is not useful in treating acute asthmatic attacks.

Zileuton

Similar Drugs	
Mechanism of Action	Zileuton acts to **inhibit *5-lipooxygenase***, which is the enzyme responsible for converting arachidonic acid to leukotriene A_4. By decreasing leukotriene A_4 levels, **levels of leukotriene B_4** (a downstream product of leukotriene A_4 modification) **are also decreased**. Leukotriene B_4 acts to attract neutrophils and eosinophils which can contribute to airway inflammation as well as smooth muscle reactivity and mucous secretion. By decreasing leukotriene B_4 levels, airway inflammation is decreased.
Clinical Uses	**Preventative treatment of asthma**.
Side Effects	Abnormal liver function tests; headache; eosinophilic vasculitis.

Other	**Cromolyn** is an inhaled anti-inflammatory agent that acts by **inhibiting the release of histamine and other inflammatory compounds from mast cells**. It is used for the **prevention of asthma exacerbations** that are associated with allergens or exercise. It can also be used to treat allergic rhinitis or conjunctivitis.

A 43-year-old woman presents to your office for follow-up after having undergone a kidney transplant 3 weeks prior. After her transplant, she was started on an immunosuppressive drug. She tells you that, overall, she has been feeling well over the past few weeks. Her physical examination is significant only for an elevated blood pressure of 150/90 mm Hg. Laboratory studies reveal mildly elevated liver function tests. You decide to check a blood level of the immunosuppressant drug, as you suspect that her abnormal liver tests and blood pressure may be related to drug toxicity and that these measures will likely improve with lowering of the dosage of this specific immunosuppressive medication.

Cyclosporine

Similar Drugs	
Mechanism of Action	Cyclosporine binds to cyclophilin in the T cell. The cyclosporine-cyclophilin complex then acts to **inhibit calcineurin**, which normally increases the expression of transcription factors that activate the transcription of IL-2. **IL-2 production is decreased**, and this results in the **reduced proliferation, differentiation, and activation of T cells**, thereby decreasing production of other cytokines.
Clinical Uses	**Immunosuppressant in transplant patients**; treatment of **graft-versus-host disease**; treatment of many autoimmune diseases (e.g., **rheumatoid arthritis**, psoriasis, inflammatory bowel disease).
Side	**Nephrotoxicity**; **hepatotoxicity**; **gingival hyperplasia**;

Effects	**hirsutism**; increased susceptibility to infection; increased incidence of lymphomas; hyperglycemia; hypertension; hyperkalemia. Note that most side effects of cyclosporine are dose-dependent and can be decreased by administering lower doses of the drug.
Other	Cyclosporine is metabolized by **cytochrome P-450 (CYP3A4)**.

A 52-year-old man presents to your hepatology clinic. He has end-stage liver failure secondary to alcoholic cirrhosis. He has been sober for the last 3 years and is now being considered for liver transplant. He asks you about medications that he would have to take if he were to undergo a liver transplant. You begin to explain to him about possible immunosuppressive regimens, including a drug that acts by binding to FKBP-12 and thereby decreasing IL-2 production through calcineurin inhibition.

Tacrolimus

Similar Drugs

Mechanism of Action	**Tacrolimus** is a drug that binds to an intracellular protein, FKBP-12. The tacrolimus-FKBP complex acts to **inhibit calcineurin**, thereby resulting in the decreased production of IL-2. **IL-2 production is decreased** and this results in the **decreased proliferation, differentiation, and activation of T cells**, thereby leading to the decreased production of other cytokines.
Clinical Uses	**Immunosuppressant in transplant patients**. May also be used in the treatment of Crohn's disease.
Side Effects	**Increased risk for infection**; increased risk for lymphoma or skin malignancy; **hyperglycemia**; **nephrotoxicity**; **neurotoxicity**; hypertension.

Other	Tacrolimus is metabolized by **cytochrome P-450 (CYP3A4)**. **Sirolimus** is another medication used as an **immunosuppressant in kidney transplant patients**. Similar to tacrolimus, it also binds to FKBP-12; however, instead of inhibiting calcineurin, the sirolimus-FKBP complex **inhibits *mTOR***, a regulatory enzyme involved in cytokine-driven T-cell proliferation. By inhibiting *mTOR*, T-cell production and activation and subsequent cytokine creation is decreased. Side effects include increased susceptibility to infection, increased risk of lymphoma, hypertriglyceridemia, and hyperglycemia. Of note, unlike some other immunosuppressants, it is **not nephrotoxic**.

A 52-year-old woman presents to your rheumatology clinic for follow-up of her systemic lupus erythematosus. The course of her illness has been complicated by the development of lupus nephritis for which she has been on a few different immunosuppressive drugs. Laboratory studies today confirm continued hematuria and proteinuria with worsening renal function tests. You tell her that you have spoken with her nephrologist and that you would like to start her on another immunosuppressant medication to treat her condition. She asks how this medication works and you explain that it decreases lymphocyte proliferation by inhibiting *inosine monophosphate dehydrogenase*, which is an enzyme involved in purine synthesis.

Mycophenolate Mofetil

Similar Drugs

Mechanism of Action	Mycophenolate mofetil is metabolized to mycophenolic acid in the liver. It **acts to inhibit *inosine monophosphate dehydrogenase***, an enzyme involved in GMP synthesis in the *de novo* pathway of purine synthesis. Without GMP, DNA synthesis within B and T cells is decreased, and hence cellular proliferation of B and T cells is also decreased.

Clinical Uses	**Immunosuppressant in transplant patients**; also used to treat **autoimmune disorders** (e.g., psoriasis; systemic lupus erythematosus).
Side Effects	Allergic reactions; hypertension; **increased susceptibility to infection (especially CMV)**; pancytopenia; GI upset.
Other	

A 39-year-old woman presents to your clinic for a follow-up visit. She was seen in your office several months ago, at which time you diagnosed her with rheumatoid arthritis and started her on methotrexate to prevent long-term progression of disease. Today, the patient says that she has not tolerated the methotrexate well with increasing dizziness, and would like to try something different to manage the progression of her disease. After discussing options with the patient, you mutually agree upon an agent that reduces T-cell proliferation by inhibiting synthesis of pyrimidines. You warn her that she may experience some diarrhea as a common side effect.

Leflunomide

Similar Drugs	
Mechanism of Action	Leflunomide reversibly **inhibits the enzyme *dihydroorotate dehydrogenase***, which catalyzes the conversion of carbamoyl phosphate to orotic acid as **part of the pyrimidine synthesis pathway**. Inhibiting the production of pyrimidines has the most effect on rapidly dividing cells, including T cells, which are in part responsible for the pathology seen in autoimmune disease.
Clinical Uses	**Rheumatoid arthritis**; psoriatic arthritis; immunosuppression in transplant patients.
Side Effects	Diarrhea; hypertension; transaminitis.

Other	Leflunomide also has activity against several viruses, including CMV, and is occasionally used to **treat infection in transplant patients**. It is thought that leflunomide inhibits virion formation, and thus blocks viral propagation.

A 34-year-old man presents to your clinic for follow-up of his hepatitis C, which was diagnosed 6 months ago. Since his diagnosis, he has continued to have intermittent right upper quadrant abdominal pain, and he has noticed yellowing of the whites of his eyes. Physical examination reveals tender hepatomegaly as well as scleral icterus. Serum studies demonstrate elevated levels of liver enzymes as well as the continued presence of hepatitis C viral RNA. You inform the patient that he has chronic hepatitis C and you tell him that one of his treatment options includes a medication that is also used to treat multiple sclerosis and certain types of cancer.

Interferons

Similar Drugs	**Interferon-α** (produced by leukocytes). **Interferon-β** (produced by fibroblasts). **Interferon-γ** (produced by CD4+ T cells).
Mechanism of Action	Interferons are **usually produced in response to a viral infection**. They have multiple actions designed to **boost the immune system** in response to viral infection, including increased expression of MHC molecules, increased activation of natural killer cells and CD8+ T cells, increased *ribonuclease* activity (acts to degrade viral mRNA), and inhibition of elongation factor 2 (part of protein synthesis machinery).
Clinical Uses	**Interferon-α**: Treatment of certain types of **cancer** (e.g., Kaposi sarcoma, melanoma, hairy cell leukemia); treatment of **chronic hepatitis B and C**. **Interferon-β**: Treatment of **multiple sclerosis** (reduces exacerbations). **Interferon-γ**: Treatment of **chronic granulomatous disease**.

Side Effects	Fatigue; bone marrow suppression; flu-like symptoms after each administration of the medication; hepatotoxicity.
Other	

A 28-year-old woman presents to your gynecology clinic complaining of vaginal bleeding. She is 15 weeks pregnant. She tells you that the bleeding started the day before, but she denies the passage of any tissue. You perform a pelvic examination, which shows a closed and long cervix. An ultrasound shows no evidence of a fetal heartbeat. You gently tell the woman that she has suffered a missed abortion and that the fetal remains will need to be removed from her body. She is averse to the idea of a surgical procedure, so you begin pharmacologic treatment with methotrexate and a synthetic prostaglandin analogue.

Prostaglandins (Part 1)

Similar Drugs	Alprostadil, misoprostol, latanoprost, dinoprostone, carboprost.
Mechanism of Action	**Alprostadil (A):** Synthetic analogue of **PGE_1**; acts as a vasodilator and a smooth muscle relaxant. **Misoprostol (M):** Synthetic analogue of **PGE_1**; increases uterine contractions, inhibits gastric acid secretion, and increases mucosal protection in the stomach. **Latanoprost (L):** Synthetic analogue of **$PGF_{2\alpha}$**; increases aqueous humor drainage. **Dinoprostone (D):** Synthetic analogue of **PGE_2**; increases uterine contractions. **Carboprost (C):** Synthetic analogue of **$PGF_{2\alpha}$**; increases uterine contractions.
Clinical Uses	**A:** Treatment of **erectile dysfunction**; maintain **patent ductus arteriosus** in fetus.

	M: Prevention of NSAID-induced **gastric ulcers**; **abortifacient** when given with methotrexate. **L:** Treatment of **chronic glaucoma**. **D & C: Abortifacient**; ripening of cervix for induction of labor.
Side Effects	**A:** Penile pain; priapism; hypotension; bradycardia. **M:** Diarrhea; abortifacient in patients using drug as treatment for gastric ulcer. **L:** Blurry vision; foreign body sensation in the eye. **D:** GI upset. **C:** Anaphylaxis; pulmonary hypertension.
Other	

A 32-year-old woman presents to your pulmonary clinic for follow-up of her idiopathic pulmonary arterial hypertension. She has been treated with sildenafil as well as diuretics and oxygen therapy for the past year. Unfortunately, her symptoms have continued to worsen and she states that she is short of breath even when walking from the waiting area to the exam room of your office. You decide that the patient will need to be treated with a prostacyclin analogue and you begin to discuss the various options available to her.

Prostaglandins (Part 2)

Similar Drugs	Treprostinil, epoprostenol, iloprost.
Mechanism of Action	**Treprostinil**, **epoprostenol**, and **iloprost** are all synthetic analogues of **PGI_2** (i.e., prostacyclin). PGI_2 acts to **inhibit platelet aggregation** (by binding to platelet surfaces and increasing cyclic AMP levels, thereby antagonizing thromboxane A_2) and to **produce vasodilation** (by binding to endothelial cells and increasing cyclic AMP levels, which leads to a protein cascade that results in smooth muscle relaxation).

Clinical Uses	Treprostinil, epoprostenol, and iloprost are used for the treatment of **pulmonary arterial hypertension**.
Side Effects	**Treprostinil**: Infusion site pain in patients receiving IV form; headache; hypotension. **Epoprostenol**: Flushing; headache; GI upset; hypotension; jaw pain. **Iloprost**: Headache; GI upset; hypotension; congestive heart failure; cardiac arrhythmias.
Other	

A 31-year-old woman presents to the ED with unilateral vision loss and right arm weakness. A neurological exam confirms that the patient has loss of vision in her left eye as well as 2/5 strength for arm flexion on the right. When you ask the patient to stand with her eyes closed, she quickly loses her balance and falls to the right. Concerned for demyelinating disease, you obtain a brain MRI which shows several hyperintense plaques in the periventricular area. You discuss the findings with the patient, and tell her that, in addition to potentially needing long-term medication to prevent disease progression, she will need acute treatment to decrease the inflammation in her central nervous system.

Glucocorticoids

Similar Drugs	Other synthetic corticosteroids include **prednisone**, **hydrocortisone**, **cortisone**, **prednisolone**, **methylprednisolone**, **betamethasone**, and **dexamethasone**.
Mechanism of Action	This class of drugs **mimics the actions of endogenous glucocorticoids**. Such actions include vasoconstriction, induction of **apoptosis of lymphocytes**, the stimulation of hepatic gluconeogenesis and protein catabolism, the **inhibition of prostaglandin and leukotriene formation** through inhibition of *phospholipase* A_2, and the stimulation of gastric acid and pepsin production.

Clinical Uses	Glucocorticoids are used in the treatment of **adrenocortical insufficiency**, **allergic reactions**, **collagen-vascular disorders** (e.g., SLE, RA, polymyositis), **inflammatory bowel disease**, ITP, arthritis, **multiple sclerosis**, **asthma**, nephrotic syndrome, and **spinal cord compression**. Other uses include the diagnosis of Cushing syndrome, stimulation of fetal lung maturity, **treatment of leukemia and lymphoma** (part of several chemotherapeutic regimens), and **immunosuppression in organ transplants**.
Side Effects	**Symptoms of Cushing syndrome (osteoporosis**; hypertension; psychosis and **irritability**; increased susceptibility to infection; **hyperglycemia**; **fat redistribution** ("buffalo hump"—fat pad at back of neck; development of central obesity; "moon facies"—characteristic edematous facial appearance); thinning of skin with development of striae; **impaired wound healing**; peptic ulcer disease; peripheral muscle wasting; edema).
Other	**Beclomethasone** is an inhaled glucocorticoid that is used to treat chronic asthma. Because the drug is inhaled and not administered systemically, side effects are minimal. Although steroids are known to be anti-inflammatory, they may paradoxically cause an **increase in WBC count** by decreasing leukocyte margination.

A 49-year-old woman presents to your rheumatology clinic for follow-up of her rheumatoid arthritis. She tells you that her symptoms are worsening, despite her treatment with ibuprofen and steroids. Physical examination reveals a worsening of the swelling of the MCP and PIP joints of her hands. You tell her that she might benefit from the addition of another medication to her therapeutic regimen and you recommend a drug that acts to reduce inflammation by inhibiting the binding of TNF-α and TNF-β to their receptors.

Etanercept

Similar

Drugs

Mechanism of Action	Etanercept is a **solubilized version of the TNF-α receptor.** It acts to compete with membrane-bound receptor for ligand, thereby **inhibiting the binding of TNF-α and TNF-β molecules to their receptors**, resulting in the decreased TNF-α activity. TNF-α is a cytokine produced by macrophages and T cells, which stimulates the release of other inflammatory cytokines (such as IL-1, IL-6, and IL-8). Thus, a decrease in TNF-α activity produces an anti-inflammatory effect.
Clinical Uses	Treatment of **autoimmune diseases** (e.g., **rheumatoid arthritis**, psoriatic arthritis, ankylosing spondylitis).
Side Effects	Injection site reactions; upper respiratory infections; exacerbations of multiple sclerosis; may have increased risk of developing malignancy with use of drug.
Other	**Gold salts** may also be used in the treatment of **rheumatoid arthritis**. Although the exact mechanism is unknown, gold salts are believed to exert their anti-inflammatory effect by inhibiting macrophage activity and decreasing lysosomal enzyme activity. They are rarely used due to their relatively poor efficacy and side effects, which include nephrotoxicity.

A 36-year-old man with Crohn's disease arrives at your gastroenterology clinic for a follow-up visit. He has a history of strictures and has had two small bowel resections. He returns today complaining of a skin opening with stool material coming out of it. This is not the first enterocutaneous fistula that the patient has experienced. He would rather not have surgery and is currently afebrile and has no signs of obstruction. He has been off immunosuppressive agents for 1 year. You decide to treat the patient with both corticosteroids as well as a drug that is a chimeric antibody that inhibits the binding of TNF-α to its receptor and has been shown in clinical trials to be useful in treating Crohn's disease.

Infliximab

Similar Drugs	
Mechanism of Action	Infliximab is a **chimeric antibody** that binds to TNF-α and **inhibits binding of TNF-α with its receptor**. TNF-α is a cytokine, produced by macrophages and T cells, which stimulates the release of other inflammatory cytokines (such as IL-1, IL-6, and IL-8). Thus, a decrease in TNF-α activity produces an anti-inflammatory effect.
Clinical Uses	Used to treat **autoimmune diseases** (e.g., **rheumatoid arthritis**, **inflammatory bowel disease**, psoriasis, ankylosing spondylitis).
Side Effects	Increased susceptibility to infection; **possible reactivation of latent TB**; infusion reaction; abnormal LFTs; may have increased risk of developing malignancy with use of this drug.
Other	**Adalimumab** is a **monoclonal antibody** that binds to TNF-α and **inhibits binding of TNF-α with its receptor**. It is also used to **treat autoimmune diseases** such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. Side effects are similar to infliximab.

A 27-year-old woman presents to your clinic. Several days ago, she was seen by your colleague in the local emergency department for a relapse of her multiple sclerosis. Although she is starting to feel better after having been treated for the acute exacerbation, she is frustrated by how the disease has begun to take over her life. She tells you that she wants to be more proactive in preventing relapses in the future. After comforting the patient, you name several options for preventing relapses of multiple sclerosis. After a discussion, you both agree upon an agent that prevents leukocyte migration into tissue by inhibiting their adhesion to endothelium.

Natalizumab

Similar Drugs	

Mechanism of Action	Natalizumab is an **antibody that targets α_4-integrin**, which is expressed on vascular endothelial cells. Inflammatory cells are thought to gain access to tissue in part by binding to these proteins on the endothelial surface. By blocking the interaction of α_4-integrin with *VCAM-1* on leukocytes, natalizumab **prevents leukocyte adhesion** and therefore inhibits inflammation.
Clinical Uses	Used to prevent relapses in **multiple sclerosis** and **Crohn's disease**.
Side Effects	**Reactivation of JC virus causing progressive multifocal leukoencepholopathy**; increased susceptibility to other infections; infusion reactions.
Other	**Eculizumab** is a monoclonal antibody specific for **complement protein C5**, which is part of the membrane attack complex in the complement pathway. It is used to **inhibit complement-medicated lysis of RBCs** in **paroxysmal nocturnal hemoglobinuria** or **atypical hemolytic uremic syndrome**. Side effects include hypertension, GI distress, and rash.

A mother brings her 6-month-old son to your clinic for a routine appointment. Her son was born prematurely at 30 weeks and required oxygen supplementation within the first month of his life. The child is doing reasonably well now without evidence of respiratory compromise. However, you are concerned that a respiratory infection could be deadly for this child given his past medical history. You tell his mother that you would like to administer a monoclonal antibody, which acts against the F protein of a common respiratory virus, in the hope of preventing infection for her son.

Other Therapeutic Antibodies

Denosumab	*Mechanism*: Blocks the maturation of osteoclast progenitors by **inactivating RANK ligand**, which acts to bind RANK on osteoclast precursors and induce maturation.

	Clinical Use: **Osteoporosis**; bone disease in malignancy. *Side Effects:* Arthralgias; myalgias; increased risk of infection.
Omalizumab	*Mechanism:* Antibody targeting IgE. IgE binds to mast cells and basophils and induces the release of several pro-inflammatory molecules that mediate the allergic response. By **preventing IgE activity**, allergic response is decreased. *Clinical Use:* **Treatment of asthma**; also used in chronic idiopathic urticaria. *Side Effects:* Anaphylaxis; small increase in risk of stroke and heart disease.
Palivizumab	*Mechanism:* Antibody targeting the F protein on respiratory syncytial virus (RSV), the agent responsible for bronchiolitis. Palivizumab inhibits viral fusion with human cells and thereby **blocks viral propagation**. *Clinical Use:* **Treatment of RSV.** *Side Effects:* GI upset; rash.
Daclizumab and Basiliximab	*Mechanism*: Antibodies targeting CD25, also known as the α chain of the high-affinity IL-2 receptor. **Blocking the activity of CD25** inhibits T-cell activation. *Clinical Use*: Daclizumab is primarily used to **treat multiple sclerosis**; basiliximab is used to **prevent rejection of renal grafts**. *Side Effects*: Increased risk of infection; rash; hepatotoxicity.

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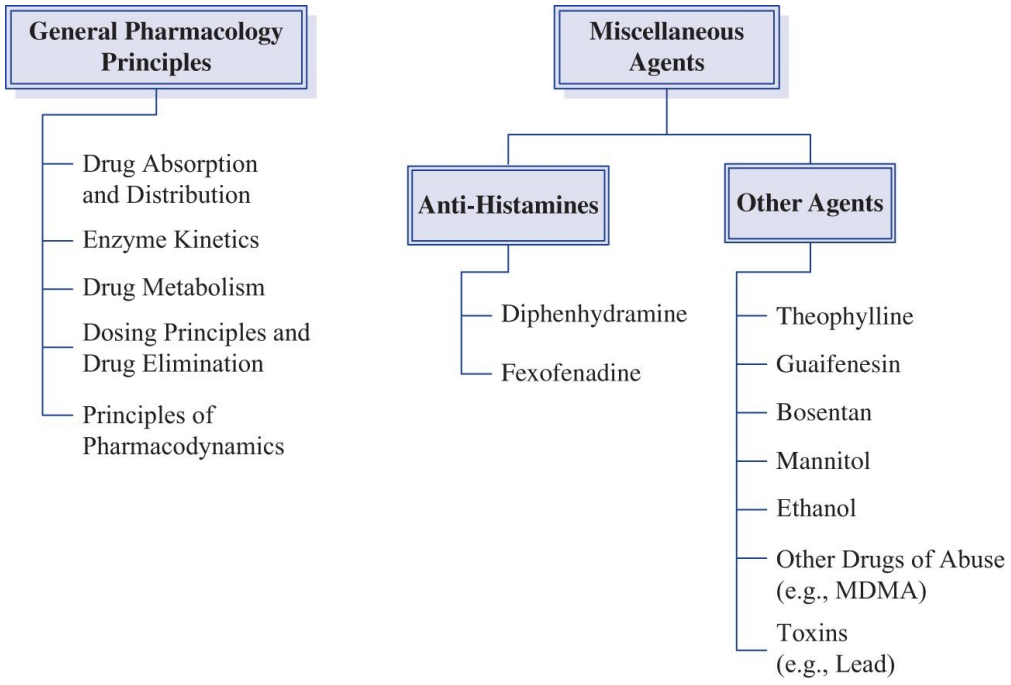


PRINCIPLES OF DRUG ABSORPTION AND DISTRIBUTION

BIOAVAILABILITY

The bioavailability of a drug refers to the amount of a drug that reaches the systemic circulation. Bioavailability is affected by the amount of initial hepatic metabolism of the drug after absorption from the GI tract to the portal circulation, by the ability of the drug to be absorbed in the cell, and by the stability of the drug in the GI tract.

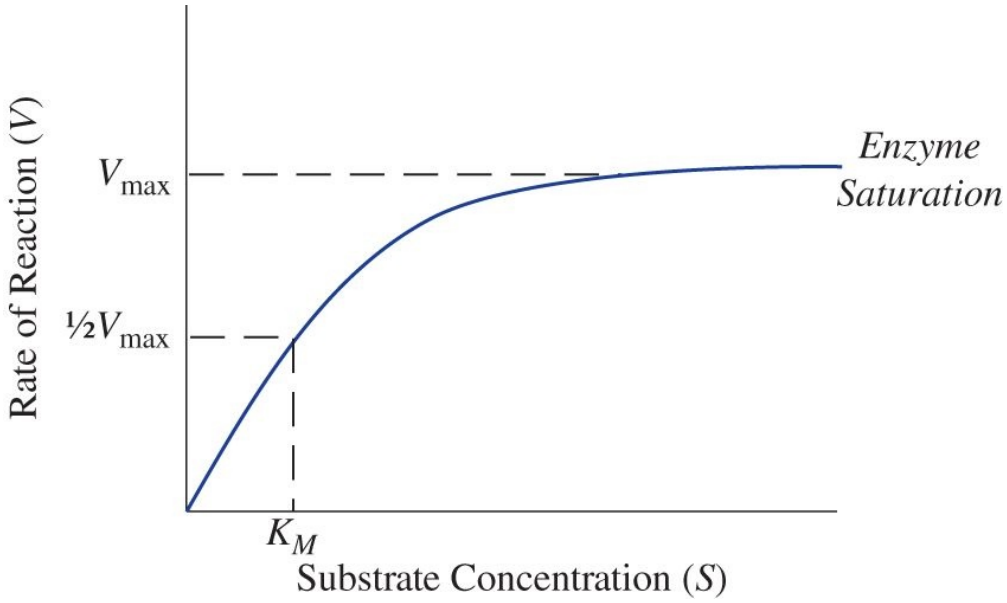
VOLUME OF DISTRIBUTION

The volume of distribution (V_d) refers to the apparent volume into which the drug is able to distribute. Possible compartments for the drug to distribute into include the intravascular space, the extracellular space, and the intracellular space. V_d can be calculated as the amount of drug in the body (D) divided by the plasma concentration of the drug (C).

$$V_d = D/C$$

ENZYMATIC REACTIONS—MICHAELIS-MENTEN KINETICS

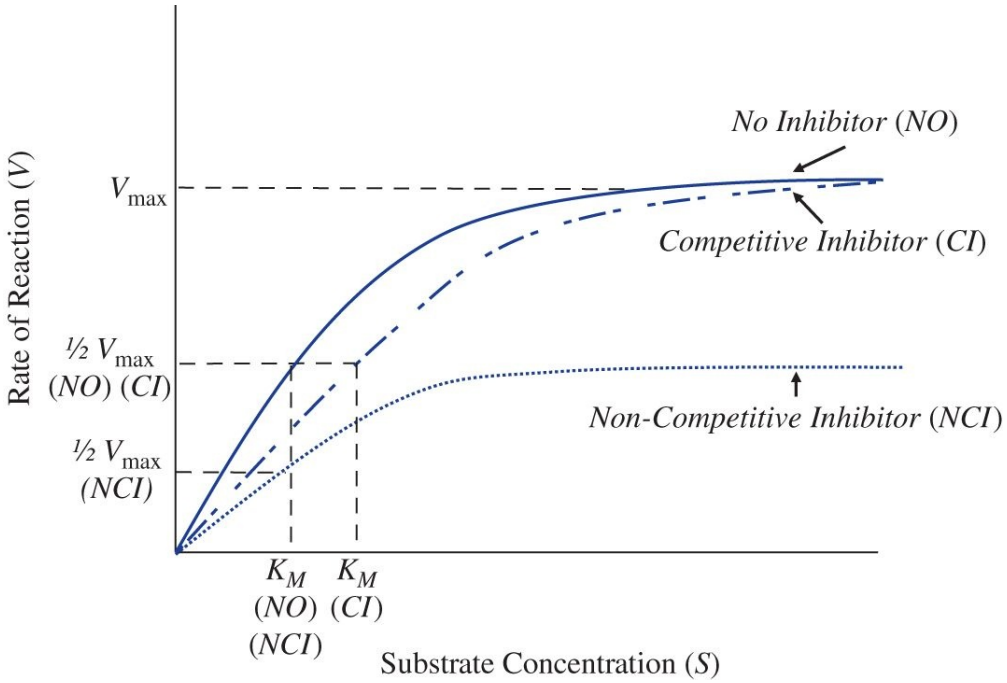
MICHAELIS-MENTEN SATURATION CURVE



The Michaelis-Menten equation describes enzymatic reactions by relating reaction rate (V) to substrate concentration (S). V_{max} represents the maximum rate achieved by the reaction at a substrate concentration in which all enzymatic binding sites are saturated. K_M reflects the substrate concentration at which the reaction rate is half of V_{max} and is inversely related to the substrate's affinity for the enzymatic binding site. A small K_M indicates high affinity of the substrate for

the enzyme, meaning that V_{max} will be achieved at a lower S than those reactions with a high K_M.

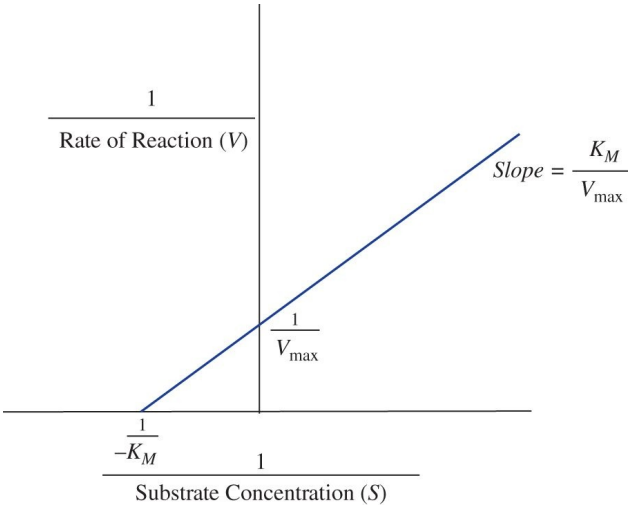
EFFECTS OF ENZYME INHIBITION



Enzyme inhibitors lead to a change in the enzymatic reaction as demonstrated by the Michaelis-Menten saturation curves above. Non-competitive inhibitors lead to an overall decrease in the ability of the enzyme to react with the substrate. As such, V_{max} is decreased. K_M is unaffected though, since the substrate's affinity for the enzyme is unchanged. Reversible competitive inhibitors do not affect V_{max}, however K_M is increased as it takes more substrate to overcome the competitive inhibitor at the enzymatic binding site to thereby achieve ½ V_{max}.

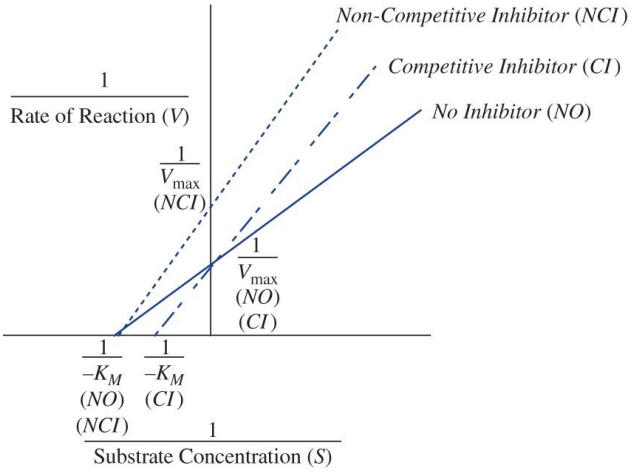
ENZYMATIC REACTIONS—LINEWEAVER-BURK KINETICS

LINEWEAVER-BURK PLOT



The Lineweaver-Burk equation also describes enzymatic reactions by relating the inverses of reaction rate (***V***) to substrate concentration (***S***), thereby allowing for a more intuitive way to determine $\boldsymbol{V_{max}}$ and $\boldsymbol{K_M}$. As shown above, $1/[\boldsymbol{V_{max}}]$ is reflected as the Y-intercept , while $-1/[K_M]$ is reflected as the X-intercept. As $\boldsymbol{V_{max}}$ increases, the value of the Y-intercept will decrease. As $\boldsymbol{K_M}$ increases, the value of the X-intercept will decrease, thereby reflecting lower affinity of the substrate for the enzyme.

EFFECTS OF ENZYME INHIBITION



The effects of enzyme inhibitors can also be reflected on the Lineweaver-Burk Plot. Non-competitive inhibitors lead to a decrease in $\boldsymbol{V_{max}}$, thereby leading to a greater value of the Y-intercept. $\boldsymbol{K_M}$ is unaffected though, and so the X-intercept is unchanged. Reversible competitive inhibitors do not affect $\boldsymbol{V_{max}}$ and so the Y-

intercept is unchanged. Since reversible competitive inhibition leads to an increase in K_M though, the X-intercept is decreased.

DOSING PRINCIPLES

LOADING DOSE

The loading dose for a drug is defined as the single amount of drug that is needed to achieve the desired plasma concentration (C_{target}) of the drug quickly. It can be calculated using the equation below.

$$\textbf{Loading Dose} = C_{target} \times V_d \textbf{ /bioavailability}$$

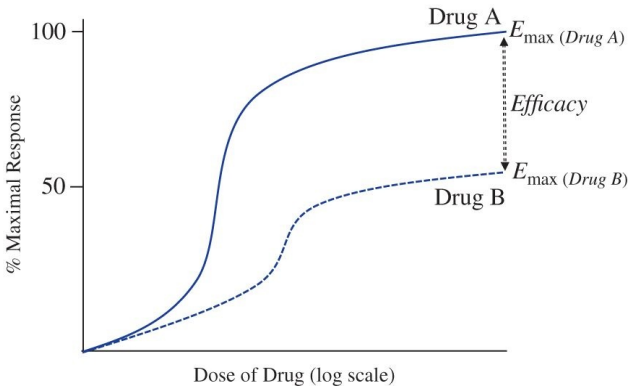
MAINTENANCE DOSE

The maintenance dose for a drug is defined as the amount of drug that must be given over time in order to maintain the desired plasma concentration of the drug. It is affected by the rate of clearance (**CL**) of the drug. Since patients with liver disease or renal disease will have reduced rates of drug clearance, maintenance doses in these patients often need to be decreased. The maintenance dose can be calculated using the equation below.

$$\textbf{Maintenance Dose} = C_{target} \times \textbf{CL/bioavailability}$$

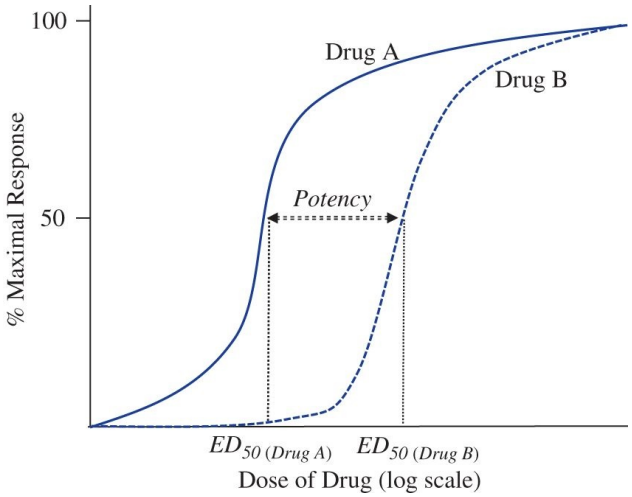
DRUG EFFICACY AND POTENCY

EFFICACY



Efficacy refers to the maximal response that can be achieved by a drug ($\boldsymbol{E_{max}}$). As $\boldsymbol{E_{max}}$ rises, the efficacy of a drug rises as well. Efficacy is unrelated to potency (e.g., an efficacious drug can have high or low potency).

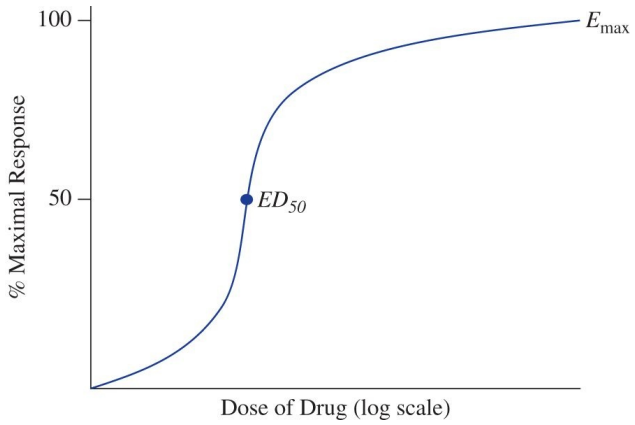
POTENCY



Potency refers to the amount of a drug needed to elicit a desired response. Drugs of high potency require a small amount of the drug to achieve the desired response. The dose of the drug required to achieve 50% of the maximal response is termed $\boldsymbol{ED_{50}}$. Potency is unrelated to efficacy (e.g., a potent drug can have high or low efficacy).

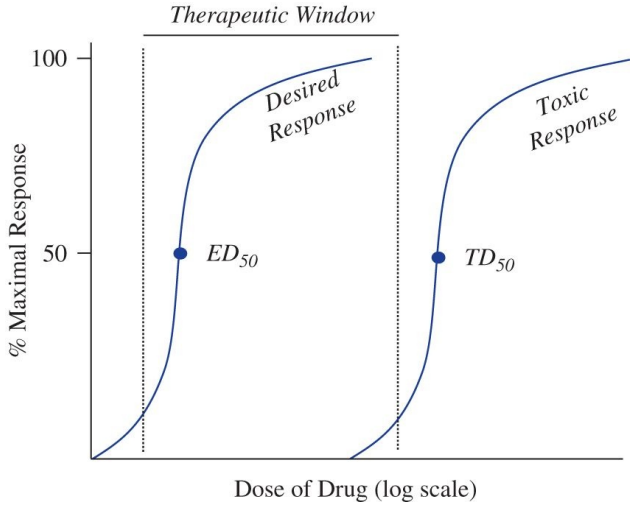
PRINCIPLES OF PHARMACODYNAMICS

GRADED DOSE-RESPONSE CURVE



A graded dose-response curve is obtained by charting the change in effect of the drug as the administered drug dose increases. Both the potency and efficacy of a drug can be reflected in this graph in terms of $\boldsymbol{ED_{50}}$ and $\boldsymbol{E_{max}}$ respectively.

DETERMINING THE THERAPEUTIC INDEX



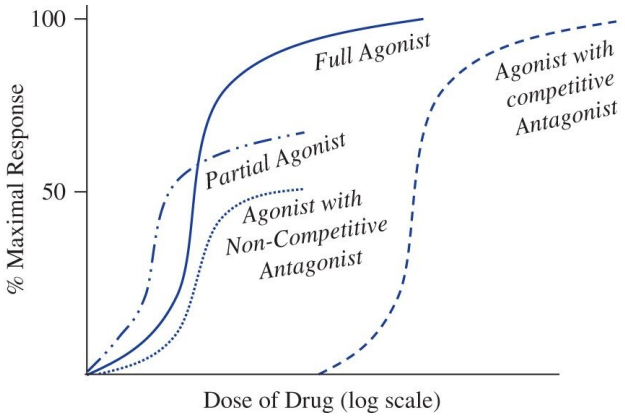
The **therapeutic index** of a drug is used as a measure of a drug's safety. The therapeutic index compares the median dose of drug necessary to achieve a desired effect ($\boldsymbol{ED_{50}}$) with the median dose of a drug necessary to produce toxicity ($\boldsymbol{TD_{50}}$). It can be quantified using the following equation.

$$\textbf{Therapeutic Index} = \boldsymbol{TD_{50}/ED_{50}}$$

The **therapeutic window** refers to the doses of drugs that can be given, which will produce the desired effect without producing unwanted toxic side

effects.

EFFECTS OF DRUG AGONISTS AND ANTAGONISTS ON THE GRADED DOSE-RESPONSE CURVE



Depending on the interaction of the drug with its receptor site, a drug can shift the position of the graded dose-response curve and thus can affect the value of $\boldsymbol{ED_{50}}$ and $\boldsymbol{E_{max}}$.

Competitive antagonist: When a drug acts as a competitive antagonist, it will shift the graded dose-response curve of an agonist to the right, thereby increasing the amount of the agonist that is needed to achieve a desired effect. This is reflected quantitatively as an **increase in the value of $\boldsymbol{ED_{50}}$**. There is **no effect on $\boldsymbol{E_{max}}$,** as the agonist is still able to achieve the maximum effect.

Irreversible antagonist: When a drug acts as an irreversible antagonist, it will depress the graded dose-response curve of an agonist, thereby effectively blocking the ability of the agonist to achieve the maximum effect. This is reflected quantitatively as a **decrease in the value of $\boldsymbol{E_{max}}$**. There is **no effect on $\boldsymbol{ED_{50}}$**.

Partial agonist: When a drug acts as a partial agonist, it will not be able to produce the same maximum effect as a full agonist. This is reflected quantitatively as a **decrease in the value of $\boldsymbol{E_{max}}$**. The $\boldsymbol{ED_{50}}$ of a partial agonist may be greater than, equal to, or lesser than the $\boldsymbol{ED_{50}}$ of a full agonist depending on the potency of the drug. In the example shown here, the partial agonist has a

lower potency, and thus a higher $\boldsymbol{ED_{50}}$ than the full agonist.

KINETICS OF DRUG METABOLISM

ZERO-ORDER KINETICS

- Drugs that obey zero-order kinetics are **eliminated at a constant rate over time**, such that the plasma concentration of the drug will decrease in a linear manner over time.
- A fixed **amount** of the drug is eliminated over time.
- The rate of elimination is not affected by the serum concentration of the drug, but is instead fixed.
- **Aspirin**, **phenytoin**, and **alcohol** are examples of drugs that display zero-order kinetics.

FIRST-ORDER KINETICS

- Drugs that obey first-order elimination are **eliminated at a rate that is proportional to the serum concentration of the drug**, such that the plasma concentration of the drug will decrease exponentially over time.
- A fixed **fraction** of the drug is eliminated over time.
- The rate of elimination decreases as the serum concentration of the drug decreases.
- Most drugs obey first-order elimination.

DRUG METABOLISM

PHASE I AND PHASE II METABOLISM

In order for drugs to be properly eliminated by the kidney, they must be metabolized from a lipophilic molecule into a polar molecule. Generally, the liver produces a polar metabolite of the drug using two sets of reactions (Phase I

and II).

Phase I metabolism involves using the **cytochrome P-450 system** to alter the drug in such a way so that it will be more amenable to combining with polar molecules. These reactions usually involve oxidation, reduction, or hydrolysis of the drug. Some Phase I reactions do not involve the use of the cytochrome P-450 system.

Phase II metabolism involves the **addition of a polar moiety** (usually sulfate, acetate, or glucuronate) to the drug, thereby making the drug water soluble and able to be excreted by the kidney.

CYTOCHROME P-450

Cytochrome P-450 system is a family of heme-containing enzymes, which are found in the liver and intestinal tract and are involved in phase I metabolism. There are multiple isoforms of cytochrome P-450 and some drugs can induce or inhibit specific isoforms of the enzyme or just generally affect many of the isoforms. Below is a table of the major drugs that inhibit and induce the P-450 system, as well as drugs that are major substrates of the enzyme.

Inducers	Inhibitors	Substrates
Phenobarbital Rifampin Carbamazepine Phenytoin	Cimetidine Isoniazid Fluoxetine Erythromycin Ketoconazole Ritonavir Isoniazid Grapefruit juice	Warfarin Phenytoin Tricyclic anti-depressants Theophylline Carbamazepine Cyclosporine β-Blockers Calcium channel blockers Haloperidol Benzodiazepines Oral contraceptives

PRINCIPLES OF DRUG ELIMINATION

CLEARANCE

The clearance (**CL**) of a drug describes the rate at which a specific drug is cleared from the system. Clearance of a drug is affected by the plasma concentration of the drug as well as by the rate constant for elimination of the specific drug (k_e). The clearance can be calculated using the following equation.

$$\mathbf{CL} = V_d \times k_e$$

HALF-LIFE

The half-life ($t_{1/2}$) of a drug refers to the amount of time required for the amount of the drug in the body to decrease to half of its value after the administration of the drug has been stopped. The half-life of a drug also describes the amount of time required for the plasma concentration of the drug to increase by 50% during constant infusion of the drug. Note that about 95% of a drug is eliminated from the body after four half-lives, and that 95% of the steady-state concentration will be attained after four half-lives during a constant infusion. The half-life can be calculated using the following equation.

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

URINE pH AND DRUG ELIMINATION

URINE pH

The majority of drugs are filtered by the glomerulus. The pH of the urine (e.g., acidic vs. alkalinized) can affect the excretion of drugs that exist in a charged form.

DRUGS ACTING AS WEAK ACIDS

When a drug that has weakly acidic properties is protonated, it becomes neutralized and more lipid soluble. Lipid-soluble molecules are reabsorbed at a greater rate through passive diffusion in the nephron. Hence, alkalinized urine will lead to deprotonation of a weakly acidic drug and cause increased excretion from the kidney. Common examples of weakly acidic drugs include salicylic acid, methotrexate, and phenobarbital. Overdoses of these medications can be

treated with bicarbonate to alkalinize the urine.

DRUGS ACTING AS WEAK BASES

When a drug that has weakly basic properties is protonated, it becomes charged and less lipid soluble, thereby leading to increased excretion from the kidney. Acidifying the urine can therefore lead to increased excretion from the kidney for these agents. Common examples of weakly basic drugs include amphetamine and tricyclic anti-depressants. Overdoses of these medications can be treated with ammonium chloride to acidify the urine.

A 36-year-old patient with a history of childhood asthma and allergic rhinitis presents to your clinic in preparation for an upcoming cruise. He is currently not taking any medications for his allergies. On physical examination, you observe turbinate congestion and inflammation of the nasal passage bilaterally. He has no evidence of conjunctivitis or lymphadenopathy. He reports that he is rather susceptible to motion sickness and he asks if there are any over-the-counter products that would benefit him. You suggest that he could try a medication that contains a pharmacologic agent that may treat both his allergic rhinitis as well as any motion sickness symptoms, but you warn him that the medication will likely make him very drowsy, and hence he may want to consider alternative treatments for his allergies.

Diphenhydramine

Similar Drugs	Other **first-generation H_1 histamine receptor blockers** include **promethazine**, **meclizine**, **hydroxyzine**, and **doxylamine**.
Mechanism of Action	Diphenhydramine acts by **blocking H_1 histamine receptor sites**, thereby blocking the effects of histamine on H_1-receptors on the uterus, large blood vessels, sensory nerves, GI tract, skin, and bronchial muscle. Normally, activation of the H_1-receptors produces smooth muscle contraction, pruritus, and increased capillary permeability. By blocking these receptors, diphenhydramine is able to produce bronchodilation, decreased pruritus, decreased peripheral vascular resistance, decreased GI

	tract motility, and decreased rash formation. Diphenhydramine also has some antagonistic effects on cholinergic and α-adrenergic receptors, thereby accounting for the side effect profile of this drug.
Clinical Uses	Used in the prevention and treatment of allergic rhinitis, **urticaria**, and other forms of **allergic reactions**; also used to treat **motion sickness** and used as a sleep aid. **Promethazine** is used primarily as an **anti-emetic** (see Ondansetron card in Chapter 8). **Meclizine** is used to treat vertigo and motion sickness.
Side Effects	**Sedation**; **anti-cholinergic effects** (dry mouth, blurry vision); tremors.
Other	

A 19-year-old woman presents to your clinic complaining of a runny nose and hives. She tells you that she has been suffering from intermittent hives and "hay fever" during the spring and autumn for the last several years. Physical examination reveals nasal congestion, but is otherwise not significant. You decide to send this patient to an allergist for allergen testing, but in the meantime, you prescribe a medication that will treat her symptoms by blocking H_1 histamine receptors, but will not cause significant sedation since it does not cross the blood-brain barrier very readily.

Fexofenadine

Similar Drugs	Other **second-generation H_1 histamine receptor blockers** include **loratadine** and **cetirizine**.
Mechanism of Action	Fexofenadine acts by **blocking H_1 histamine receptor sites**, thereby blocking the effects of histamine on H_1-receptors on the uterus, large blood vessels, sensory nerves, GI tract, skin, and bronchial muscle. Normally, activation of the H_1-receptors produces smooth muscle contraction, pruritus, and increased

	capillary permeability, so by blocking these receptors, fexofenadine is able to produce bronchodilation, decreased pruritus, decreased peripheral vascular resistance, decreased GI tract motility, and decreased rash formation.
Clinical Uses	Used to treat **allergic rhinitis** and other symptoms of seasonal allergies.
Side Effects	Mild sedation; GI upset.
Other	Because fexofenadine does not cross the blood-brain barrier as readily as the first-generation H_1 histamine receptor blockers, it causes less sedation than diphenhydramine.

A 23-year-old woman presents to your pulmonary clinic for follow-up of her severe asthma. She has required hospitalization for her asthma three times in the last 6 months. She is on a maximal medical regimen, including long-acting beta-agonists, systemic steroids, and a leukotriene receptor inhibitor. You would like to wean her off of systemic steroids, since long-term treatment with steroids can have significant side effects. You decide to try another medication to treat her symptoms that is very effective in the treatment of both acute and chronic asthma, but that is not used as frequently as other asthma medications since it has a high incidence of cardiac arrhythmias and seizures with overmedication.

Theophylline

Similar Drugs	
Mechanism of Action	Although the exact mechanism is unknown, theophylline has been shown to **inhibit *phosphodiesterase***, which is the enzyme responsible for the breakdown of cAMP, thereby leading to increased levels of cAMP. Since cAMP has been shown to lead to bronchial smooth muscle relaxation, theophylline administration can result in **bronchodilation**.

Clinical Uses	Theophylline is used in the **treatment of acute and chronic asthma**.
Side Effects	GI upset; anxiety; **cardiac arrhythmias**; seizures.
Other	The use of theophylline is limited by a **narrow therapeutic index**, such that many patients suffering from chronic overmedication may develop seizures and serious cardiac arrhythmias. Theophylline is **metabolized by cytochrome P-450**, so simultaneous administration with the cytochrome P-450 inducers (e.g., rifampin or phenobarbital) may result in decreased serum levels of theophylline.

A 36-year-old woman presents to your office, complaining of a cough, runny nose, and general body aches. After examining the patient, you determine that she likely has a viral upper respiratory tract infection. You recommend symptomatic treatment, including fluids, rest, decongestants, and an over-the-counter medication that will help stimulate her respiratory tract secretion flow and assist in the clearing of phlegm.

Guaifenesin

Similar Drugs	
Mechanism of Action	While the mechanism of action is not completely understood, guaifenesin is thought to irritate vagal receptors in the gastrum. This, in turn, activates a series of parasympathetic reflexes, which result in the **secretion of a less viscous mucous** from the bronchial endothelium. Thinner phlegm acts to **stimulate respiratory tract secretion flow**, allowing cilia in the bronchial tree to carry loosened secretions upward toward the mouth.
Clinical	**Expectorant** used to help with the clearing of phlegm in the

Uses	setting of acute respiratory infections.
Side Effects	Side effects are minimal. GI upset may occur.
Other	***N*-acetylcysteine** is a compound that exhibits both **mucolytic** and antioxidant properties. Via its own sulfhydryl moiety, it disrupts disulfide bonds in mucus so that mucus can be more easily dissolved and cleared. *N*-acetylcysteine is also used as an **antidote for Tylenol toxicity** and for acute liver injury in general. **Dextromethorphan** is an **opioid agonist** used for cough suppression. It acts by desensitizing receptors responsible for transmission of the coughing impulse in the medulla.

A 37-year-old woman with a history of pulmonary arterial hypertension presents to your pulmonary clinic. She continues to report worsening shortness of breath despite treatment with sildenafil, iloprost, and diuretics. She is reluctant to start a continuous infusion medication such as treprostinil. You decide to start the patient on a new medication that acts by blocking endothelin receptors in the pulmonary bed. You inform her that you will need to monitor her liver function test and red blood cell counts closely while she is on this medication and you tell her that she will also have to refrain from becoming pregnant due to the teratogenicity of this drug.

Bosentan

Similar Drugs	Ambrisentan; darusentan; sitaxsentan.
Mechanism of Action	Bosentan acts to **competitively inhibit the binding of endothelin-1 to endothelin receptors.** Endothelin is a neurohormone that binds to receptors (ET_A and ET_B) in the vascular smooth muscle and causes vasoconstriction. By blocking endothelin receptor activation, pulmonary vasodilation results.

Clinical Uses	Used in the treatment of **pulmonary arterial hypertension**.
Side Effects	**Hepatotoxicity**; anemia; **teratogen**; edema.
Other	

A 34-year-old man presents to the emergency room after having been involved in a massive motor vehicle accident. The patient is unconscious and physical examination reveals bilateral papilledema, bilaterally dilated pupils, bradycardia, and an irregular respiratory rate. You immediately become concerned about a serious head injury, which is now causing increased intracranial pressure. After calling for the neurosurgeon, you attempt to decrease this patient's intracranial pressure by hyperventilating the patient and by trying to reduce the patient's effective circulatory volume with a medication that acts as an osmotic diuretic.

Mannitol

Similar Drugs	Other osmotic diuretics include **urea**, **glycerin**, and **isosorbide**.
Mechanism of Action	Mannitol is an **osmotic diuretic** that acts at the **proximal tubule and descending limb of loop of Henle** of the nephron to increase tubular osmolarity, thereby drawing water into the tubular lumen. The net effect of mannitol is to increase urine outflow and decrease the effective circulating volume in the body.
Clinical Uses	Mannitol is used for **decreasing intracranial or intraocular pressure** by volume depletion. It can also be used to treat acute renal failure and to prevent the development of acute renal failure following toxin exposure, trauma, or shock.
Side Effects	Pulmonary edema; GI upset; headache; dehydration.

Other	The use of mannitol is **contraindicated in patients with congestive heart failure** as it can lead to pulmonary edema by initially causing an expansion of the effective circulating volume before renal elimination. Isosorbide and glycerin are used only for ophthalmologic procedures.

A 32-year-old man is brought to the emergency room in an unconscious state by his wife. His wife tells you that she believes that the patient may have tried to commit suicide by drinking from an unidentified bottle that was under the kitchen sink. Serum studies show a severe metabolic acidosis and elevated levels of ethylene glycol as well as signs of liver and kidney damage. You begin to prepare the patient for emergent hemodialysis in order to remove the toxic metabolites of ethylene glycol, but in the meantime, you decide to administer a pharmacologic agent that will act to competitively inhibit the metabolism of ethylene glycol.

Ethanol

Similar Drugs	
Mechanism of Action	Ethanol acts by enhancing the flow of chloride ions through GABA-associated channels, thereby **potentiating the inhibitory effects of GABA** in the brain.
Clinical Uses	Used in the **treatment of ethylene glycol and methanol overdose**. (The metabolites of methanol and ethylene glycol are toxic. Since methanol, ethylene glycol, and ethanol are metabolized by similar enzymes, ethanol acts as a competitive substrate for these enzymes, thereby decreasing the metabolism of ethylene glycol and methanol and thus decreasing the formation of toxic metabolites.)
Side Effects	Orthostatic hypotension; **CNS depression** (dizziness; sedation; impaired judgment); **GI inflammation** (gastritis, pancreatitis,

hepatitis); teratogen (fetal alcohol syndrome).

Other

Disulfiram is used in the **treatment of alcohol cessation**. Ethanol is metabolized in liver by two oxidation reactions that utilize NAD^+ as the limiting reagent. It is converted into acetaldehyde by *alcohol dehydrogenase*. Acetaldehyde is then converted into acetate by *acetaldehyde dehydrogenase*. Disulfiram **inhibits *acetaldehyde dehydrogenase***, leading to the accumulation of acetaldehyde. Acetaldehyde accumulation leads to nausea and vomiting, thus providing negative feedback for drinking alcohol while taking disulfiram.

Ethanol is also a **drug of abuse**. Long-term alcohol use can lead to alcoholic liver disease with eventual cirrhosis, portal hypertension, renal failure, and encephalopathy.

A 22-year-old man is brought to the emergency department by EMS after being found wandering the streets and exhibiting erratic behavior. Upon presentation, he is agitated and inattentive and occasionally attempting to punch members of the medical team. After he is put in four-point restraints and given some chemical sedation, you conduct a brief physical exam. Notably, during his HEENT exam, you note that his eyes demonstrate vertical nystagmus. You now have a strong sense that this patient has ingested an illicit drug and advise the medical team to monitor the patient closely and send labs to evaluate for a variety of potential complications.

Other Drugs of Abuse

Marijuana

Mechanism: Binds cannabinoid receptors in brain leading to modulation of several neurotransmitters.

Clinical Signs: Paranoia; hallucinations; euphoria; increased appetite.

Treatment: Supportive care (benzodiazepines for agitation).

Caffeine

Mechanism: Acts as an antagonist to adenosine, resulting in peripheral vasodilation and CNS stimulation.

	Clinical Signs: Anxiety; diuresis; palpitations; GI upset; muscle twitching. *Treatment*: Supportive care (treat any arrhythmias and electrolyte imbalances).
PCP	*Mechanism*: Acts as an antagonist at glutamate NMDA receptors, and as a sympathomimetic by inhibiting reuptake of norepinephrine and dopamine. *Clinical Signs*: Violent behavior; vertical nystagmus; psychosis; hypertension; seizures. *Treatment*: Supportive care (management of seizures; haloperidol for psychosis).
MDMA	*Mechanism*: Amphetamine derivative that promotes the release of catecholamines and serotonin from presynaptic vesicles. *Clinical Signs*: Hallucinations; euphoria; hyperactivity; hypertension; tachycardia; hyperthermia. *Treatment*: Supportive care (management of hypertension and tachycardia; cooling for hyperthermia; benzodiazepines for agitation).
LSD	*Mechanism*: Acts as both an agonist and antagonist at serotonin receptors. *Clinical Signs*: Paranoia; hallucinations; psychosis. *Treatment*: Supportive care (treat agitation with benzodiazepines).
Nicotine	*Mechanism*: Acts on neuronal acetylcholine receptors to modulate the regulation of several neurotransmitters, resulting in anxiety reduction and increased energy. Nicotine also promotes the release of cortisol and endorphins. *Clinical Signs*: Relaxation; appetite reduction. *Treatment*: Treatments for smoking cessation include behavioral counseling, nicotine replacement, bupropion, and varenicline.

An 8-year-old boy is brought to the pediatric clinic by his mother, who reports that he has become progressively tired over the last 6 months. On physical

examination, the patient appears pale with lines appearing on his gingival tissue. He reports having abdominal pain on almost a daily basis although your abdominal examination is unrevealing. Serum studies demonstrate an anemia. A peripheral blood smear is significant for erythrocytic basophilic stippling. On further questioning, you discover that the boy and his family have recently moved into an older building with chipped paint. You are concerned about a possible toxic exposure and you decide to order a blood level to confirm your suspicion. As you wait for the results of the blood test, you begin to suspect that the patient may benefit from a course of calcium EDTA treatment.

Other Toxins

Iron	*Mechanism*: Forms reactive oxygen species. *Clinical Signs*: Abdominal pain; bloody diarrhea; unconsciousness. *Antidote*: Deferoxamine.
Lead	*Mechanism*: Interferes with heme synthesis; alters cell membrane structure. *Clinical Signs*: Abdominal pain; neuropathy; anemia; basophilic stippling of erythrocytes. *Antidote*: Calcium EDTA; dimercaprol; penicillamine.
Arsenic	*Mechanism*: Inhibits several enzymatic processes, especially those involved in oxidative phosphorylation. *Clinical Signs*: Garlic odor on breath; bloody diarrhea; hair loss; neuropathy. *Antidote*: Dimercaprol; penicillamine.
Cyanide	*Mechanism*: Blocks a cytochrome complex in the electron transport chain. *Clinical Signs*: Headache; GI upset; seizures; coma. *Antidote*: Sodium thiosulfate; nitrites.
Carbon Monoxide	*Mechanism*: Binds to hemoglobin, thereby reducing oxygen binding and delivery to tissues.

Clinical Signs: Headache; GI upset; seizures; coma.
Antidote: 100% oxygen.

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