لجنة عمداء كليات الصيدلة

لجنة توحيد منهاج مادة (Pharmacology I)

Pharmacology I

المرحلة الثالثة

2024

تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتيبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء. نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق ، والله الموفق

Pharmacology

Reference: Lippincott Illustrated Reviews Pharmacology 7th Ed.

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed **pharmacodynamic** processes.
These properties determine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease.

The actions of the body on the drug are called **pharmacokinetic** processes. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, a patient with impaired renal function.

Pharmacokinetics

• **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

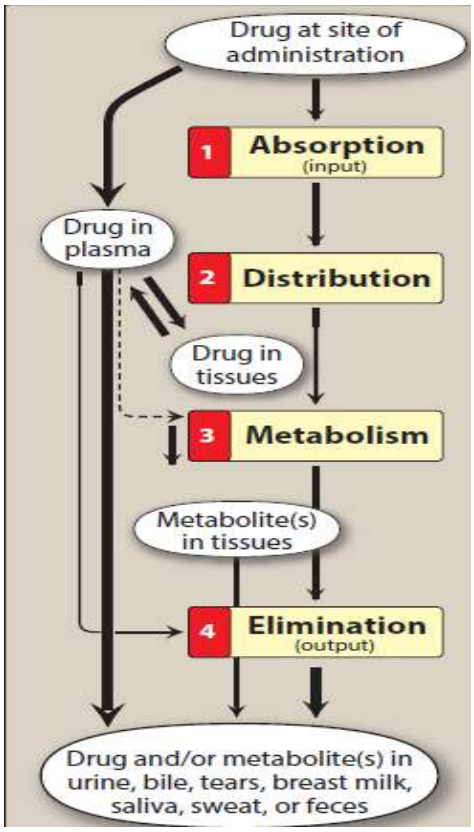
• **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

• **Metabolism:** Third, the drug may be biotransformed by metabolism by the liver or other tissues.

• **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, the dose, the frequency, and the duration of treatment.

Routes of drugs administration:



The route of administration is determined by properties of the drug and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, among others.

A. Enteral:

Enteral administration (administering a drug by mouth) is the safest and most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual), or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

1. Oral: Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal.

However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

a. Enteric-coated preparations: An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs {for example, omeprazole) that are acid labile, and for drugs that are irritating to the stomach, such as aspirin.

b. Extended-release preparations: Extended-release {abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer

duration, as opposed to immediate release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral morphine is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release
tablets are used.

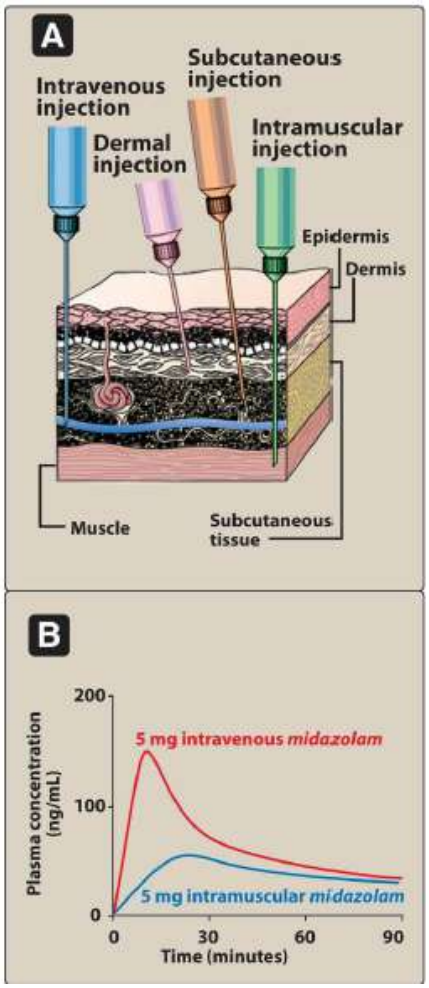
2. Sublingual/buccal: The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism

B. <u>Parenteral</u>:

The parenteral route introduces drugs directly into the body by the injection. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used if a patient is unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action.

In addition, parenteral routes have the highest bioavailability and are not subject to first-pass metabolism or the harsh GI environment. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these routes of administration are irreversible and may cause pain, fear, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous.

1. Intravenous (IV): IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker rocuronium. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.



2. Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly.

Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

3. Subcutaneous (SC): Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur. Drugs commonly administered via the subcutaneous route include *insulin* and *heparin*.

4. Intradermal: The intradermal (I D) route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route

C. <u>Other:</u>

1. Oral inhalation and nasal preparations: Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

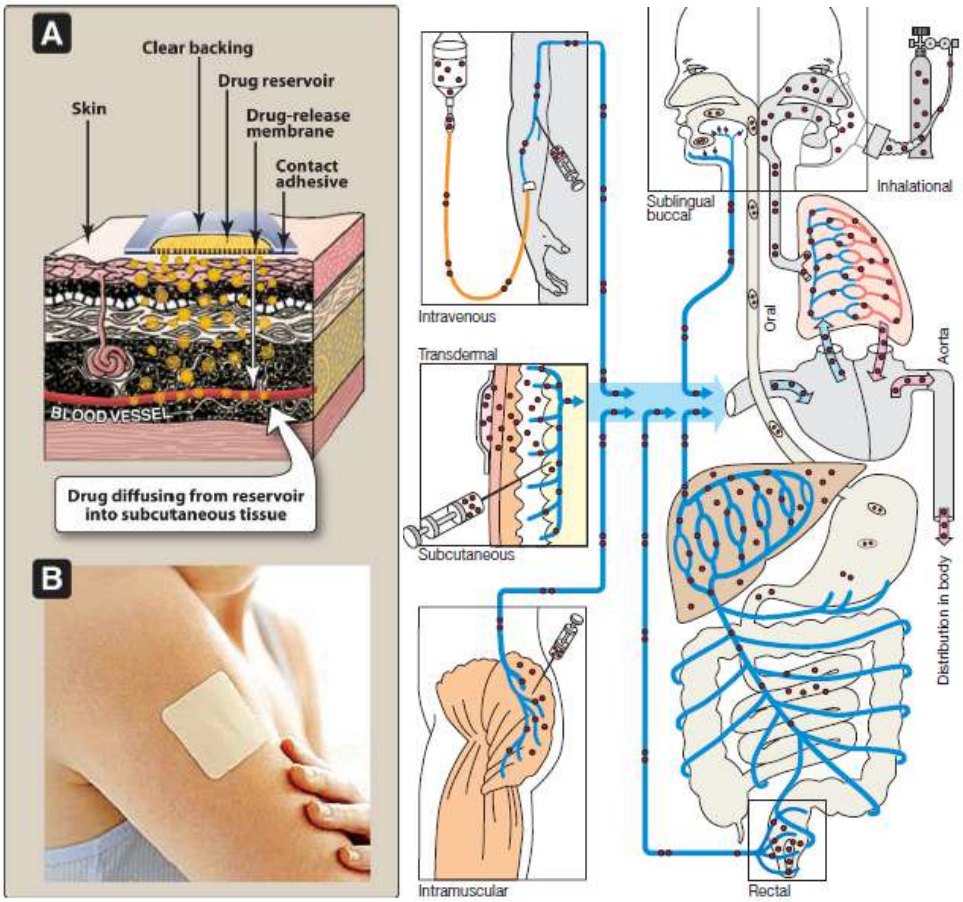
2. Intrathecal/intraventricular: The blood-brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.

3. Topical: Topical application is used when a local effect of the drug is desired.

4. Transdermal: This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.

5. Rectal: Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the Gl environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious.
Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Following figure summarizes characteristics of the common routes of administration, along with example drugs.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueus solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intra-vaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*



Schematic representation of a transdermal patch.

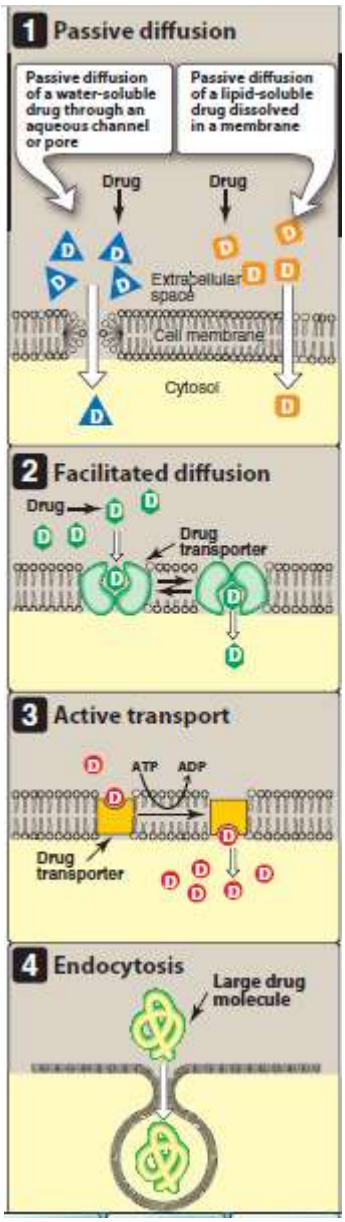
Absorption of drugs:

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

1. Passive diffusion: The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.



2. Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

3. Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other co-transported substances.

4. Endocytosis and exocytosis: This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Vitamin B12 is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.

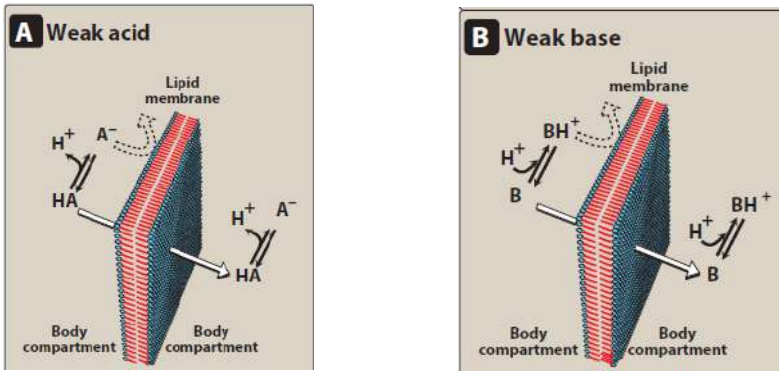
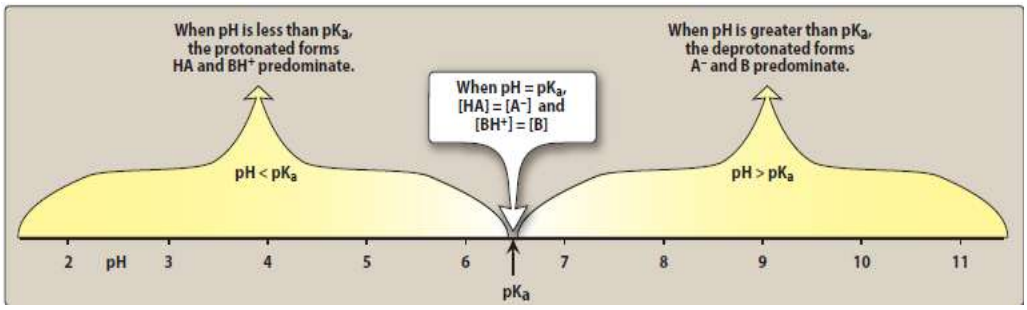


Figure: A. Diffusion of the nonionized form of a weak acid through a lipid membrane. B. Diffusion of the nonionized form of a weak base through a lipid membrane



B. Factors influencing absorption

1. Effect of pH on drug absorption:

Acidic drugs (HA) release a proton (H+), causing a charged anion (A−) to form:

$$HA \leftrightarrows H^+ + A^-$$

Weak bases (BH+) can also release an H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \leftrightarrows B + H^+$$

Most drugs are either weak acids or weak bases. A drug passes through membranes more readily if it is uncharged. Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pKa.

2. Blood flow to the absorption site: The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach.

3. Total surface area available for absorption: With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4. Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

5. Expression of P-glycoprotein:

P-glycoprotein is a trans-membrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.
It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it “pumps” drugs out of the cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

C. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.

1. Determination of bioavailability: Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured.

2. Factors that influence bioavailability: In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

a. First-pass hepatic metabolism: When a drug is absorbed from the Gl tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of nitroglycerin is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual, transdermal, or intravenous route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

b. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids

and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

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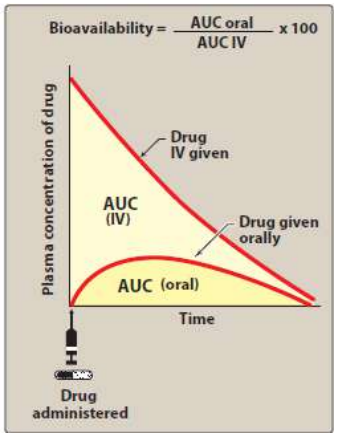
c. Chemical instability: Some drugs, such as penicillin G, are unstable in the pH of gastric contents. Others, such as insulin, are destroyed in the Gl tract by degradative enzymes.

d. Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients {such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Drug distribution:

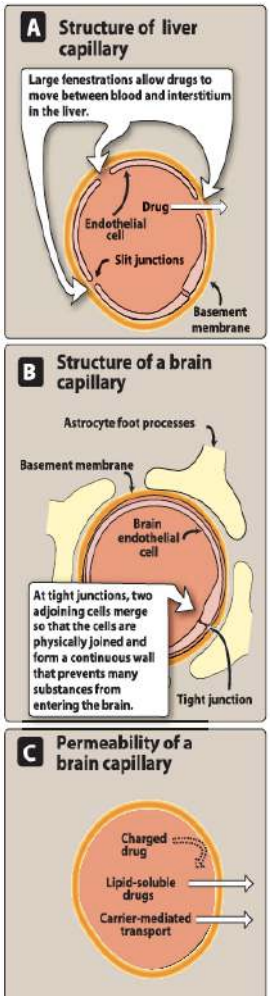


Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

For drugs administered IV, absorption is not a factor, and the initial phase (from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues. The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of propofol. High blood flow, together with high lipophilicity of propofol, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.



B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

In the brain, the capillary structure is continuous, and there are no slit junctions. To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries levodopa into the brain. Lipid soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions. These closely juxtaposed cells form tight junctions that constitute the blood-brain barrier.

C. Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows transfer out of the vascular compartment. Albumin is the major drug binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of cyclophosphamide, can cause hemorrhagic cystitis because it accumulates in the bladder.)

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

The apparent volume of distribution, V_d, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although Vd has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. Distribution into the water compartments in the body: Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

a. Plasma compartment: If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. Heparin shows this type of distribution.

b. Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14L in a 70-kg individual). Aminoglycoside antibiotics show this type of distribution.

c. Total body water: If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. Ethanol exhibits this apparent V_d. [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

2. Determination of V_d: The fact that drug clearance is usually a first order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (Cp) versus time. The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been

achieved if the distribution phase had occurred instantly. This allows calculation of V_d as:

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L, then V_d = 10 mg/1 mg/L = 10 L.

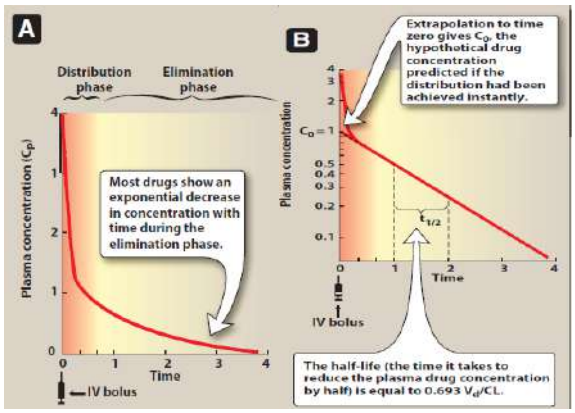


Figure: Drug concentrations in plasma after a single injection of drug at time = 0.
A. Concentration data are plotted on a linear scale. B. Concentration data are plotted on a log scale.

Drug clearance through metabolism:

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary elimination. Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug present is eliminated in a given unit of time.

Most drugs are eliminated according to first-order kinetics, although some, such as *aspirin* in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time.

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble

agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.

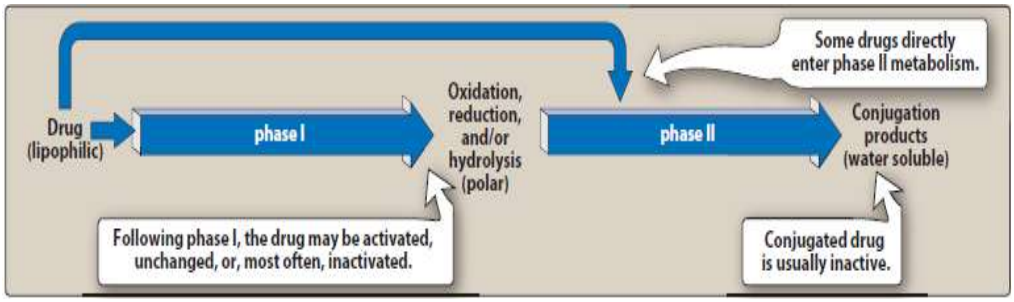


Figure: The biotransformation of drugs

Drug clearance through kidney:

Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes, the most important being elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

Elimination of drugs via the kidneys into urine involves the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1. Glomerular filtration:

Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate. The glomerular filtration rate (GFR) is normally about 125 mL/min but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

2. Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system.

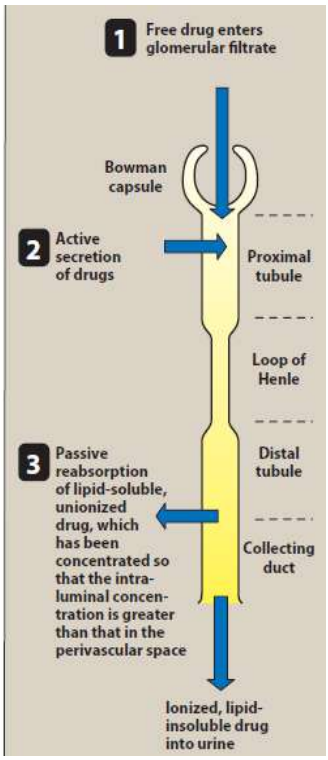


Figure: Drug elimination by the kidney

3. Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called "ion trapping." For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate,* which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

Excretion by other routes:

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, desflurane). Elimination of drugs in breast milk may expose the breast-feeding infant to medications

and/ or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

A. Total body clearance

The total body (systemic) clearance, Cl_{total}, is the sum of all clearances from the drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion. The liver also contributes to drug clearance through metabolism and/or excretion into the bile.

Total clearance is calculated using the following equation:

$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CLother$

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

B. Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

Drug–Receptor Interactions and Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors (that is, specialized target macromolecules) present on the cell surface or within the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction.

Signal Transduction:

Drugs act as signals, and receptors act as signal detectors. A drug is termed an "agonist' if it binds to a site on a receptor protein and activates it to initiate a series of reactions that ultimately result in a specific intracellular response. "Second messenger" or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A. The drug-receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain p-adrenergic receptors that bind and respond to epinephrine or norepinephrine. Cardiac cells also contain muscarinic receptors that bind and respond to acetylcholine.

These two receptor populations dynamically interact to control the heart's vital functions. The magnitude of the cellular response is proportional to the number of drug-receptor complexes. This concept is conceptually similar to the formation of complexes between enzyme and substrate and shares many common features, such as specificity of the receptor for a given agonist. Although much of this chapter centers on the interaction of drugs with specific receptors, it is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

B. Receptor states

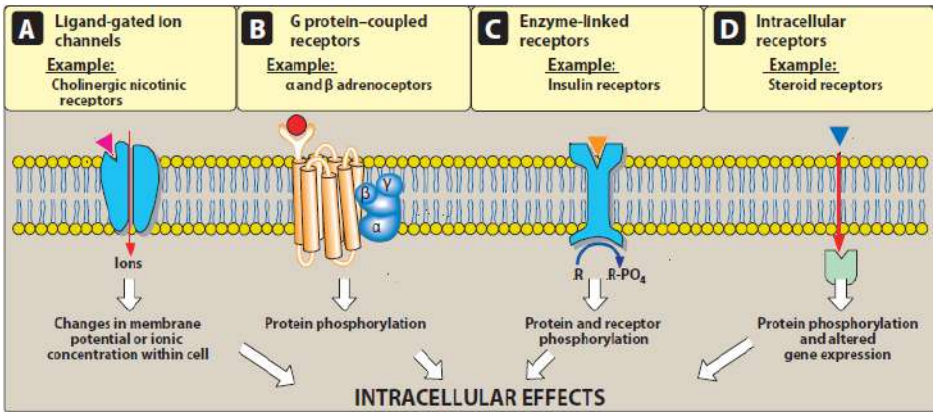
Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state. Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect. Antagonists are drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R. Some drugs (partial agonists) shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist. The magnitude of biological effect is directly related to the fraction of R*. In summary, agonists, antagonists, and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of R*.

C. Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists. However, the richest sources of receptors are membrane bound proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families:

1) ligand-gated ion channels
2) G protein-coupled receptors
3) enzyme-linked receptors.
4) intracellular receptors.

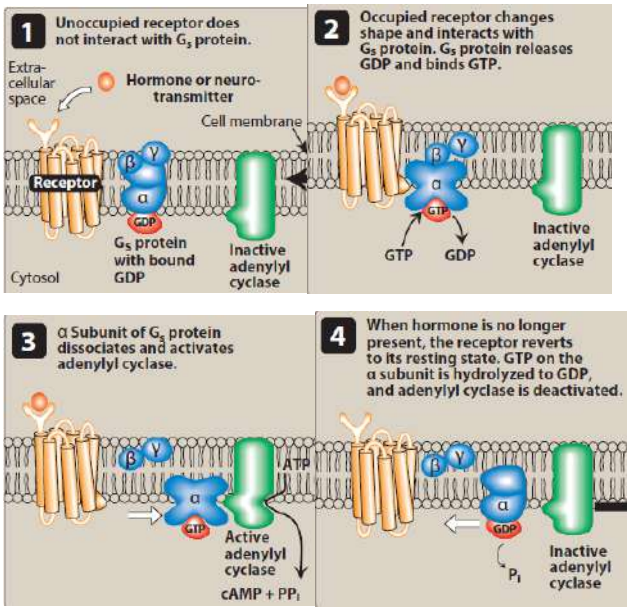
Generally, hydrophilic ligands interact with receptors that are found on the cell surface. In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells.



Transmembrane signaling mechanisms.

1. Transmembrane ligand-gated ion channels:

The extracellular portion of ligand-gated ion channels usually contains the ligand binding site. This site regulates the shape of the pore through which ions can flow across cell membranes. The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron or contraction in skeletal muscle. On the other hand, agonist stimulation of the γ-aminobutyric acid (GABA) receptor increases chloride influx and hyperpolarization of neurons. Voltage-gated ion channels may also possess ligand-binding sites that can regulate channel function. For example, local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.



The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase.

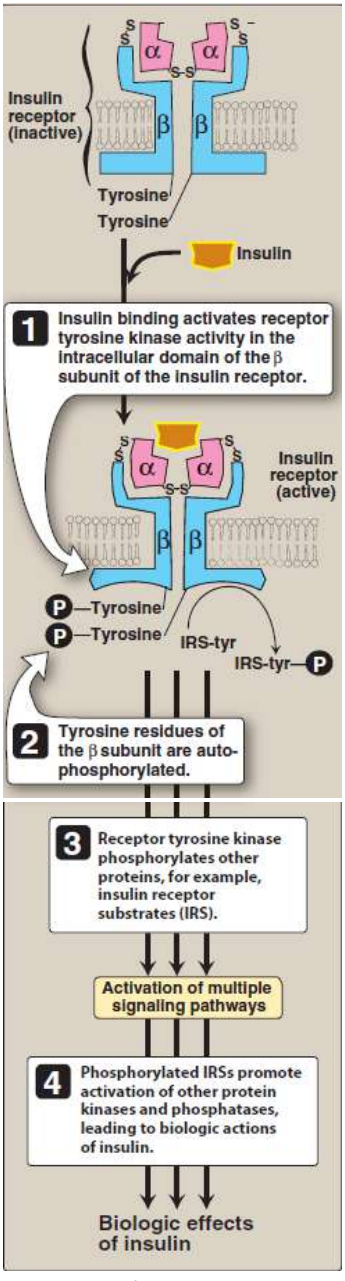
2. Transmembrane G protein–coupled receptors:

The extracellular domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule. There are many kinds of G proteins (for example, Gs, Gi, and Gq), but they all are composed of three protein subunits. The α subunit binds guanosine triphosphate

(GTP), and the β and γ subunits anchor the G protein in the cell membrane. Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex. These two complexes can then interact with other cellular effectors, usually an enzyme, a protein, or an ion channel, that are responsible for further actions within the cell. These responses usually last several seconds to minutes.

Sometimes, the activated effectors produce second messengers that further activate other effectors in the cell, causing a signal cascade effect.

A common effector, activated by Gs and inhibited by Gi, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). Gq activates phospholipase C, generating two other second messengers: inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). DAG and cAMP activate different protein kinases within the cell, leading to a myriad of physiological effects. IP3 regulates intracellular free calcium concentrations, as well as some protein kinases.



Insulin receptor

3. Enzyme-linked receptors:

This family of receptors consists of a protein that may form dimers or multisubunit complexes. When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function (Figure 6). This response lasts on the order of minutes to hours. The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) possess tyrosine kinase activity as part of their structure. The activated receptor phosphorylates tyrosine residues on itself and then other specific proteins. Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone insulin binds to two of its

receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates other peptides or proteins that subsequently activate other important cellular signals. This cascade of activations results in a multiplication of the initial signal, much like that with G protein–coupled receptors.

4. Intracellular receptors:

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor. In order to move across the target cell membrane, the ligand must have sufficient lipid solubility. The primary targets of these ligand–receptor complexes are transcription factors in the cell nucleus.

Binding of the ligand with its receptor generally activates the receptor via dissociation from a variety of binding proteins. The activated ligand–receptor complex then translocates to the nucleus, where it often dimerizes before binding to transcription factors that regulate gene expression. The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins. The time course of activation and response of these receptors is on the order of hours to days. For example, steroid hormones exert their action on target cells via intracellular receptors. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel*, the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim*, and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin*.

D. Characteristics of signal transduction

Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation.

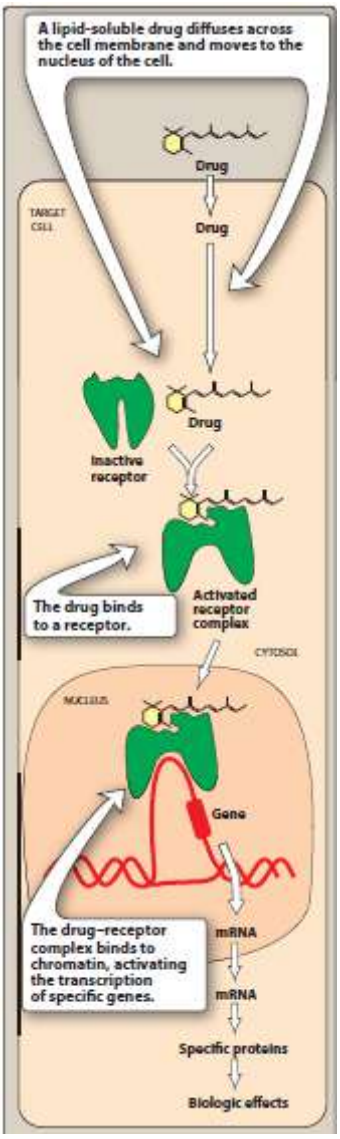
1. Signal amplification: A characteristic of G protein-linked and enzyme-linked receptors is the ability to amplify signal intensity and duration via the signal cascade effect. Additionally, activated G proteins persist for a longer duration than does the original agonist-receptor complex. The binding of albuterol, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal

are mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response. Systems that exhibit this behavior are said to have spare receptors. About 99% of insulin receptors are "spare" providing an immense functional reserve that ensures that adequate amounts of glucose enter the cell. On the other hand, only about 5% to 10% of the total B3-adrenoceptors in the heart are spare. Therefore, little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility.

2. Desensitization and down-regulation of receptors: Repeated or continuous administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation (Figure 2.6), resulting in a diminished response. This phenomenon, called tachyphylaxis, is often due to phosphorylation that renders receptors unresponsive to the agonist. In addition, receptors may be internalized within the cell, making them unavailable for further agonist interaction (down-regulation). Some receptors, particularly ion channels, require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be "refractory." Repeated exposure of a receptor to an antagonist, on the other hand, results in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the number of receptors available. Up-regulation of receptors can make cells more sensitive to agonists and/or more resistant to effects of the antagonist.

Dose-Response Relationship:

Agonist drugs mimic the action of the endogenous ligand for the receptor (for example, isoproterenol mimics norepinephrine on β1 receptors of the heart). The magnitude of the drug effect depends on receptor sensitivity to the drug and the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.



A. Graded dose-response relationship

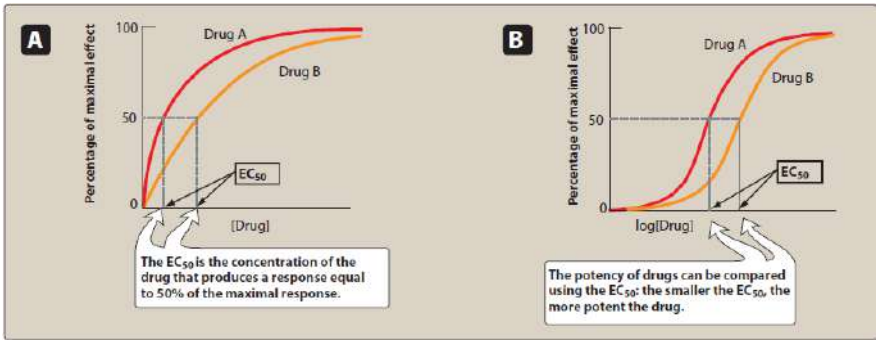
As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose-response curve. Two important drug characteristics, potency and efficacy, can be determined by graded dose response curves.

1. Potency: Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC_{50}) is often used to determine potency.

In below figure, The EC_{50} for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed to obtain 50% effect. Therapeutic preparations of drugs reflect their potency. For example, candesartan and irbesartan are angiotensin receptor blockers used to treat hypertension.

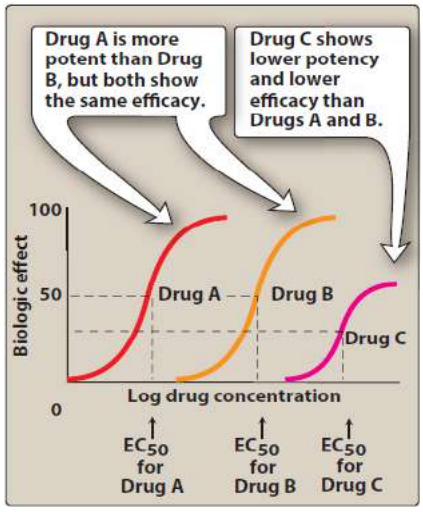
The therapeutic dose range for candesartan is 4 to 32 mg, as compared to 75 to 300 mg for irbesartan. Therefore, candesartan is more potent than irbesartan (it has a lower EC50 value). Since the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude, semilogarithmic plots are

used to graph the complete range of doses. the curves become sigmoidal in shape, which simplifies the interpretation of the dose-response curve.



The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semilogarithmic plot of the same data. EC50 = drug dose causing 50% of maximal response.

2. Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). Maximal efficacy of a drug (E_{max}) assumes that the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug. The maximal response differs between full and partial agonists, even when the drug occupies 100% of the receptors. Similarly, even though an antagonist occupies 100% of the receptor sites, no



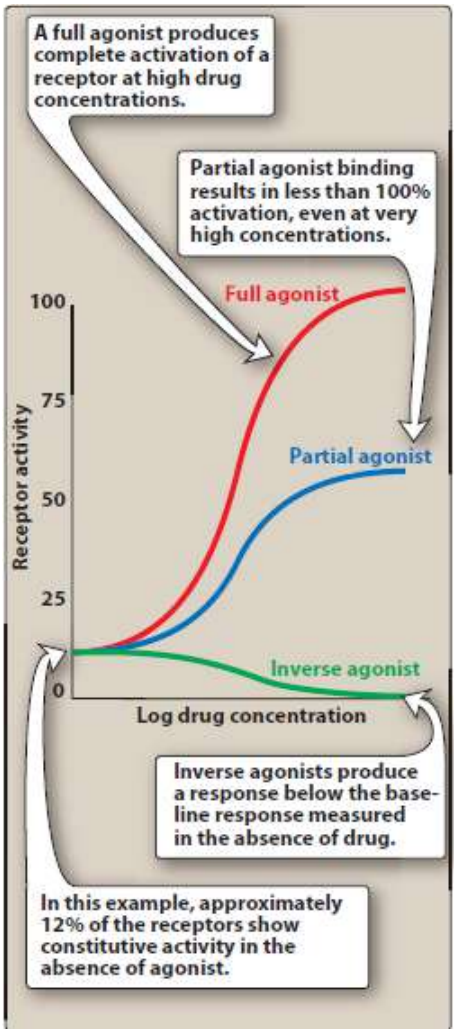
Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent.

Intrinsic Activity:

As mentioned above, an agonist binds to a receptor and produces a biologic response based on the concentration of the agonist and the fraction of activated receptors. The intrinsic activity of a drug determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting Emax values.

A. Full agonists

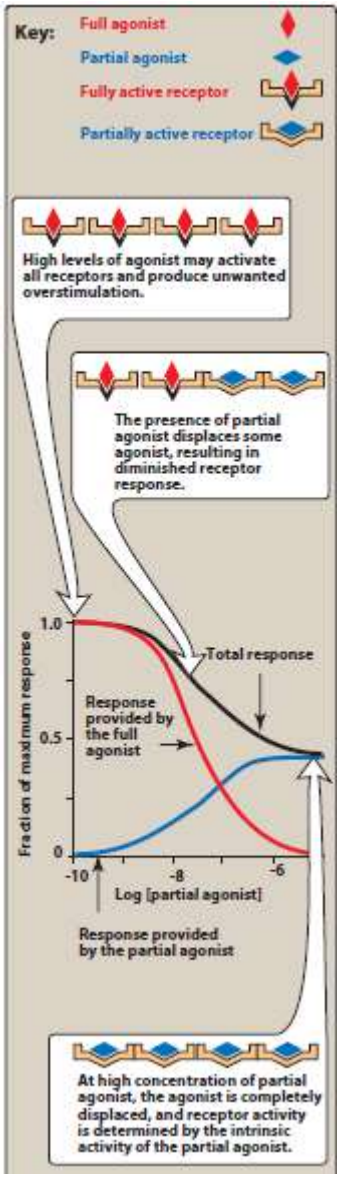
If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist. Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one. All full agonists for a receptor population should produce the same E_{max}. For example, *phenylephrine* is a full agonist at α1-adrenoceptors, because it produces the same E_{max} as does the endogenous ligand, norepinephrine.



Upon binding to α1-adrenoceptors on vascular smooth muscle, *phenylephrine* stabilizes the receptor in its active state. This leads to the mobilization of intracellular Ca^{2+}, causing interaction of actin and myosin filaments and shortening of the muscle cells. The diameter of the arteriole decreases, causing an increase in resistance to blood flow through the vessel and an increase in blood pressure. As this brief description illustrates, an agonist may have many measurable effects, including actions on intracellular molecules, cells, tissues, and intact organisms.

All of these actions are attributable to interaction of the drug with the receptor. For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.

B. Partial agonists



Partial agonists have intrinsic activities greater than zero but less than one. Even if all the receptors are occupied, partial agonists cannot produce the same E_{max} as a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. When a receptor is exposed to both a partial agonist and a full agonist, the partial agonist may act as an antagonist of the full agonist. Consider what would happen to the E_{max} of a receptor saturated with an agonist in the presence of increasing concentrations of a partial agonist. As the number of receptors occupied by the partial agonist increases, the E_{max} would decrease until it reached the E_{max} of the partial agonist. This potential of partial agonists to act as both an agonist and antagonist may be therapeutically utilized. For example, *aripiprazole,* an atypical antipsychotic, is a partial agonist at selected dopamine receptors.

Dopaminergic pathways that are overactive tend to be inhibited by *aripiprazole*, whereas pathways that are underactive are stimulated. This might explain the ability of *aripiprazole* to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects.

C. Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation. However, some receptors show a spontaneous conversion from R to R* in the absence of an agonist (constitutive

activation). Inverse agonists, unlike full agonists, stabilize the inactive R form and cause R* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug. Thus, inverse agonists have an intrinsic activity less than zero, reverse the activity of receptors, and exert the opposite pharmacological effect of agonists.

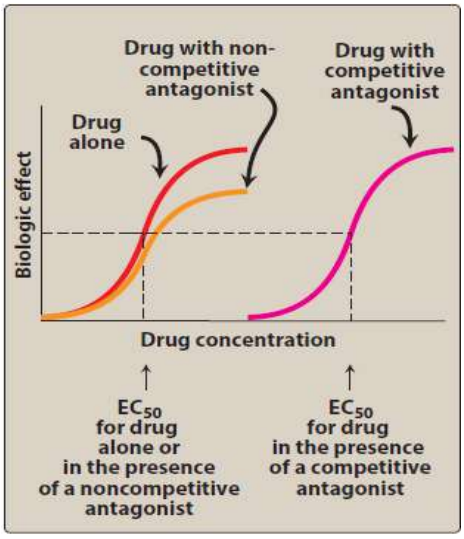
D. Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

1. Competitive antagonists: If the antagonist binds to the same site on the receptor as the agonist in a reversible manner, it is "competitive'' A competitive antagonist interferes with an agonist binding to its receptor and maintains the receptor in its inactive state. For example, the antihypertensive drug terazosin competes with the endogenous ligand norepinephrine at α1-adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure.

However, increasing the concentration of agonist relative to antagonist can overcome this inhibition. Thus, competitive antagonists characteristically shift the agonist dose-response curve to the right (increased EC_{50}) without affecting Emax.

2. Irreversible antagonists: Irreversible antagonists bind covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist. An irreversible antagonist causes a downward shift of the Emax. with no shift of EC_{50} values. In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists. Thus, irreversible antagonists and allosteric antagonists are both



A fundamental difference between competitive and noncompetitive antagonists is that competitive antagonists reduce agonist potency (increase EC_{50}) and noncompetitive antagonists reduce agonist efficacy (decrease Emax).

3. Allosteric antagonists: An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist. This type of antagonist also causes a downward shift of the E_{max} of an agonist, with no change in the EC_{50} value. An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA-controlled chloride channel.
When picrotoxin binds inside the channel, no chloride can pass through the channel, even when GABA fully occupies the receptor.

4. Functional antagonism: An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the functional antagonism by epinephrine to histamine-induced bronchoconstriction. Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at B2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as "physiologic antagonism."

Quantal Dose-Response Curve:

Another important dose-response relationship is that between the dose of the drug and the proportion of a population of patients that responds to it. These responses are known as quantal responses, because, for any individual, either the effect occurs or it does not. Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response as the point at which a response occurs or not. For example, a quantal dose response relationship can be determined in a population for the antihypertensive drug atenolol. A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure. Quantal dose-response curves are useful for determining doses to which most of the population responds. They have

similar shapes as log dose-response curves, and the ED_{50} is the drug dose that causes a therapeutic response in half of the population.

A. Therapeutic index

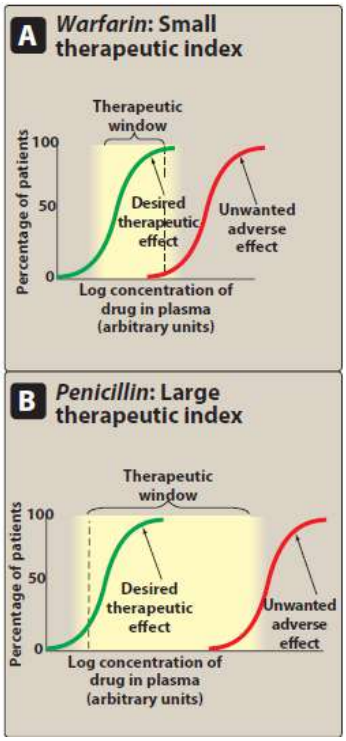
The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

$$TI = TD_{50}/ED_{50}$$

The Tl is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

B. Clinical usefulness of the therapeutic Index

The Tl of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses. Although high Tl values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases. In these cases, the risk of experiencing adverse effects is not as great as the risk of leaving the disease untreated. The responses to warfarin, an oral anticoagulant with a low TI, and penicillin, an antimicrobial drug with a large Tl.



1. Warfarin (example of a drug with a small therapeutic index): As the dose of warfarin is increased, a greater fraction of the patients responds (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually,

all patients respond. However, at higher doses of warfarin, anticoagulation resulting in hemorrhage occurs in a small percent of patients. Agents with a low Tl (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects.

2. Penicillin (example of a drug with a large therapeutic index):

For drugs such as penicillin, it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

The Autonomic Nervous System

The autonomic nervous system (ANS), along with the endocrine system, coordinates the regulation and integration of bodily functions. The endocrine system sends signals to target tissues by varying the levels of blood-borne hormones. In contrast, the nervous system exerts its influence by the rapid transmission of electrical impulses over nerve fibers that terminate at effector cells, which specifically respond to the release of neuromediator substances. Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the ANS are called autonomic drugs. These autonomic agents act either by stimulating portions of the ANS or by blocking the action of the autonomic nerves.

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS (Figure 1). The peripheral nervous system is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.

Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions: the somatic and the ANS (Figure 1). The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. The ANS, conversely, regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, vegetative, or involuntary nervous system.

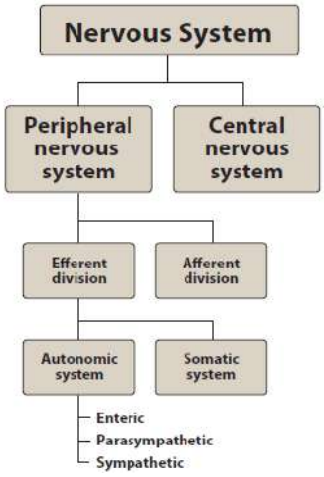


Figure 1: Organization of the nervous system

It is composed of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

Anatomy of the ANS

1. Efferent neurons: The ANS carries nerve impulses from the CNS to the effector organs through two types of efferent neurons: the preganglionic neurons and the postganglionic neuron (Figure 2). The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS. The preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in ganglia (an aggregation of nerve cell bodies located in the peripheral nervous system). The ganglia function as relay stations between the preganglionic neuron and the second nerve cell, the postganglionic neuron. The cell body of the postganglionic neuron originates in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as visceral smooth muscle, cardiac muscle, and the exocrine glands.

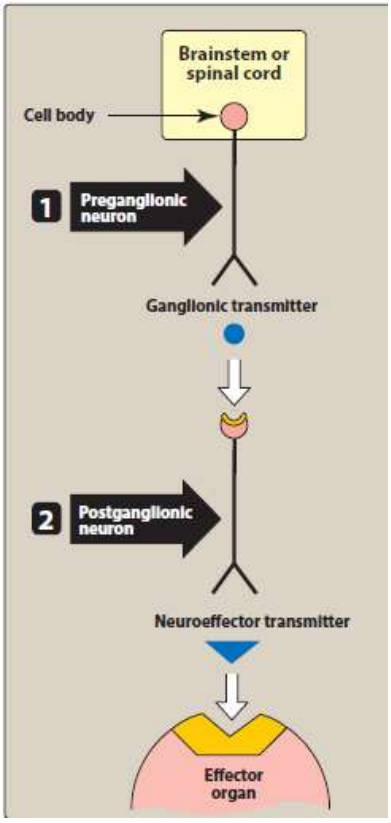


Figure 2: Efferent neurons of the autonomic nervous system.

2. Afferent neurons:

The afferent neurons (fibers) of the ANS are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and in signaling the CNS to influence the efferent branch of the system to respond.

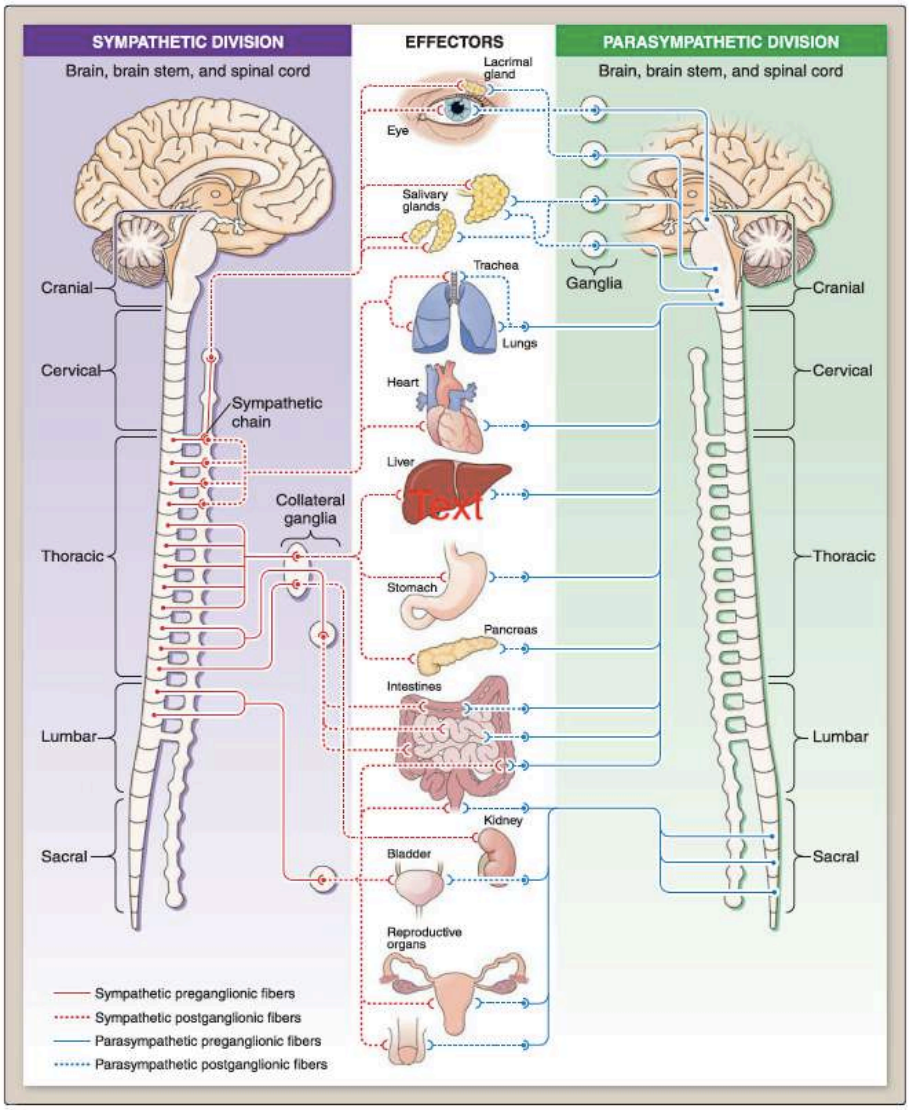
3. Sympathetic neurons:

The efferent ANS is divided into the sympathetic and the parasympathetic nervous systems, as well as the enteric nervous system (Figure 1). Anatomically, the sympathetic and the parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from the thoracic and lumbar regions (T1 to L2) of the spinal cord, and they synapse in two cord-like chains of ganglia that run close to and in parallel on each side

of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones.

Axons of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate. In most cases, the preganglionic nerve endings of the sympathetic nervous system are highly branched, enabling one preganglionic neuron to interact with many postganglionic neurons. This arrangement enables this division to activate numerous effector organs at the same time.

[Note: The adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. The adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, secretes epinephrine (adrenaline), and lesser amounts of norepinephrine, directly into the blood].



4. Parasympathetic neurons:

The parasympathetic preganglionic fibers arise from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus), as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs.

Thus, in contrast to the sympathetic system, the preganglionic fibers are long, and the postganglionic ones are short, with the ganglia close to or within the organ innervated. In most instances, there is a one-to-one connection between the preganglionic and postganglionic neurons, enabling discrete response of this system.

5. Enteric neurons:

The enteric nervous system is the third division of the ANS. It is a collection of nerve fibers that innervate the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the “brain of the gut.” This system functions independently of the CNS and controls the motility, exocrine and endocrine secretions, and microcirculation of the GI tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining the tone of vascular beds), the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise (Figure 3).

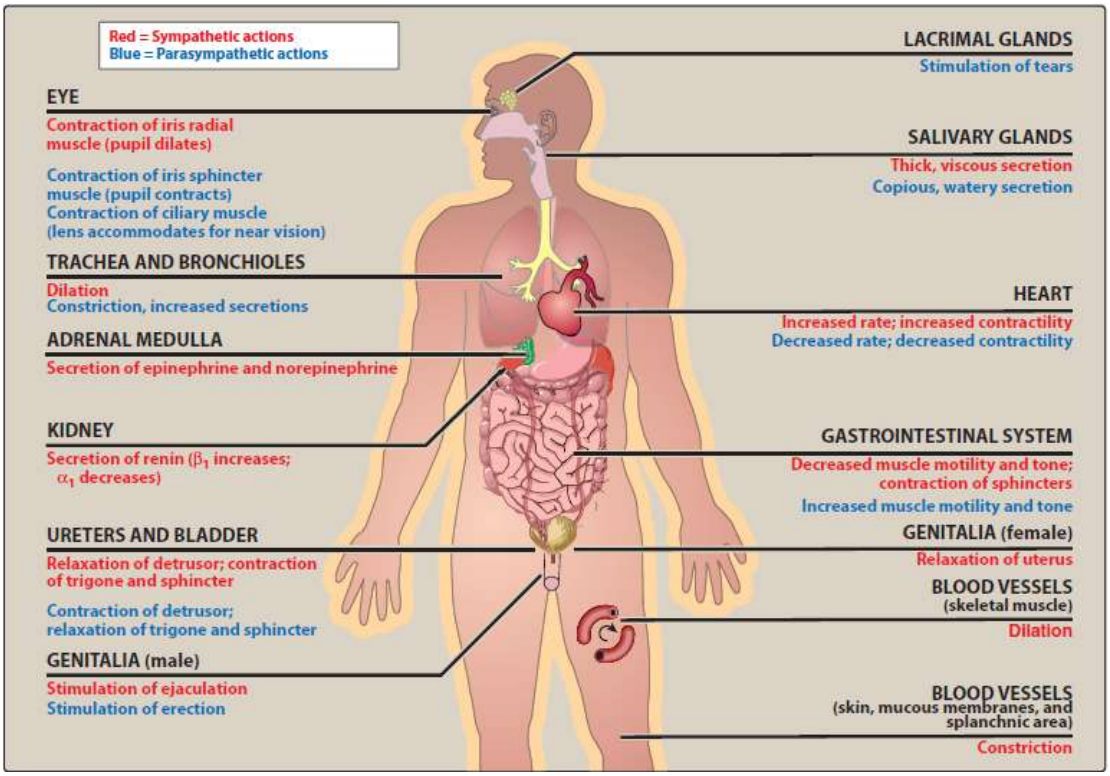


Figure 3: Actions of sympathetic and parasympathetic nervous systems on effector organs.

1. Effects of stimulation of the sympathetic division:

The effect of sympathetic output is to increase heart rate and blood pressure, to mobilize energy stores of the body, and to increase blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs. Sympathetic stimulation results in dilation of the pupils and the bronchioles (Figure 3). It also affects GI motility and the function of the bladder and sexual organs.

2. Fight-or-flight response:

The changes experienced by the body during emergencies are referred to as the "fight or flight" response (Figure 4). These reactions are triggered both by direct sympathetic activation of the effector organs and by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors. The sympathetic nervous system tends to function as a unit and often discharges as a complete system, for example, during severe exercise or in reactions to fear (Figure 4). This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities. Although it

is not essential for survival, it is nevertheless an important system that prepares the body to handle uncertain situations and unexpected stimuli.

Functions of the parasympathetic nervous system

The parasympathetic division is involved with maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and elimination of wastes.

The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in "rest-and-digest" situations. Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation.

Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

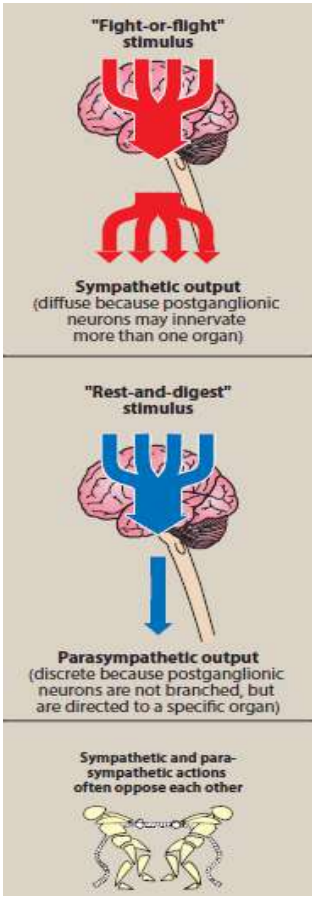


Figure 4: Sympathetic and parasympathetic actions are elicited by different stimuli.

Role of the CNS in the control of autonomic functions

Although the ANS is a motor system, it does require sensory input from peripheral structures to provide information on the current state of the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata, and spinal cord. These centers respond to the stimuli by sending out efferent reflex impulses via the ANS.

Innervation by the ANS

1. Dual innervation:

Most organs in the body are innervated by both divisions of the ANS. Thus, vagal parasympathetic innervation slows the heart rate, and sympathetic innervation increases the heart rate. Despite this dual innervation, one system usually predominates in

controlling the activity of a given organ. For example, in the heart, the vagus nerve is the predominant factor for controlling rate. This type of antagonism is considered to be dynamic and is fine-tuned continually to control homeostatic organ functions.

2. Sympathetic innervation:

Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system.

Somatic nervous system

The efferent somatic nervous system differs from the ANS in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the ANS is involuntary. Responses in the somatic division are generally faster than those in the ANS.

Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division (Figure below). The sympathetic nervous system is widely distributed, innervating practically all effector systems in the body. By contrast, the distribution of the parasympathetic division is more limited. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic fibers. This type of organization permits a diffuse discharge of the sympathetic nervous system. The parasympathetic division is more circumscribed, with mostly one-to-one interactions, and the ganglia are also close to, or within, organs they innervate. This limits the amount of branching that can be done by this division.

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators.

A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body, exerting effects on broadly distributed target cells (figure 5).

B. Local mediators

Most cells in the body secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine and the prostaglandins are examples of local mediators.

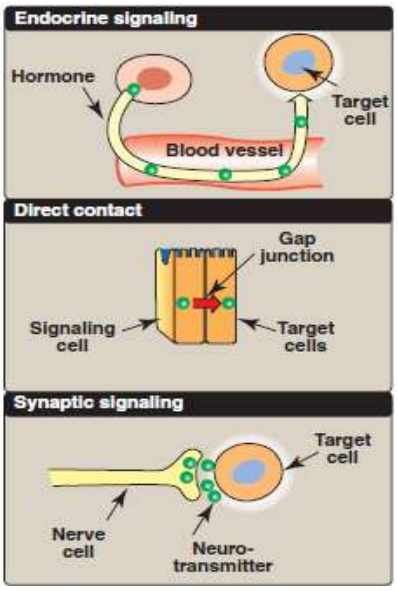


Figure 5: Some commonly used mechanisms for transmission of regulatory signals between cells.

C. Neurotransmitters

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular Ca2+ initiates fusion of the synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell.

1. Membrane receptors: All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers of target cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs.

2. Types of neurotransmitters: Although over 50 signal molecules in the nervous system have been identified, norepinephrine (and the closely related epinephrine),

acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and norepinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS.

a. Acetylcholine: The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic (Figure 6). Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla.

Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system also involves the release of acetylcholine.

In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) is also cholinergic (Figure 6).

b. Norepinephrine and epinephrine: When norepinephrine and epinephrine are the neurotransmitters, the fiber is termed adrenergic (Figure 6). In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs.

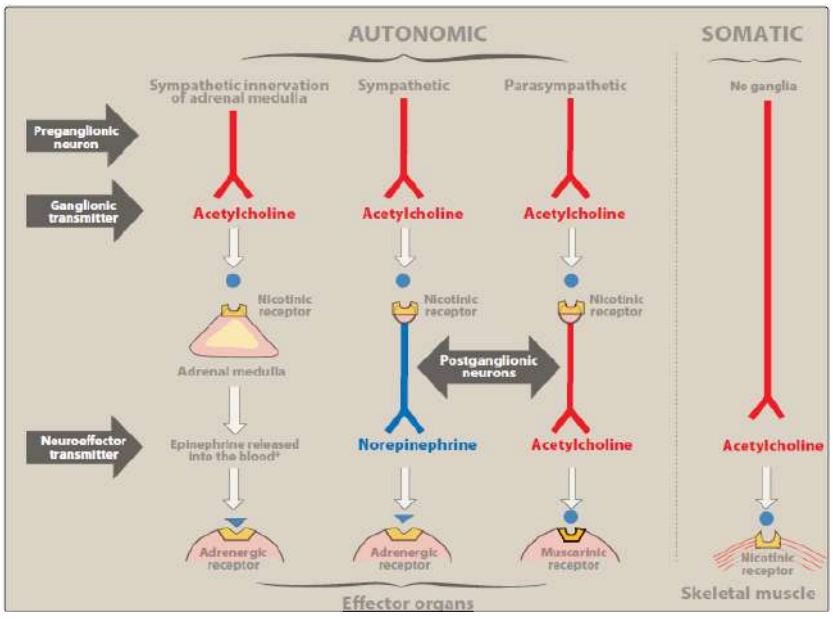


Figure 6: Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems. Cholinergic neurons are shown in red and adrenergic neurons in blue. *[Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that, the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate*

more than one organ system. This allows the sympathetic nervous system to discharge as a unit.]
**Epinephrine 80% and norepinephrine 20% released from adrenal medulla.*

SIGNAL TRANSDUCTION IN THE EFFECTOR CELL

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels. A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer.

Second messenger molecules produced in response to a neurotransmitter binding to a receptor translate the extracellular signal into a response that may be further propagated or amplified within the cell. Each component serves as a link in the communication between extracellular events and chemical changes within the cell.

A. Membrane receptors affecting ion permeability (ionotropic receptors)

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules.

Some receptors, such as the postsynaptic nicotinic receptors in the skeletal muscle cells, are directly linked to membrane ion channels.

Therefore, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability (Figure 3.8A). These types of receptors are known as ionotropic receptors.

B. Membrane receptors coupled to second messengers (metabotropic receptors)

Many receptors are not directly coupled to ion channels. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions that ultimately result in a specific intracellular response. Second messenger molecules, so named because they intervene between the original message (the neurotransmitter or hormone) and the ultimate effect on the cell, are part of the cascade of events that translate neurotransmitter binding into a cellular response, usually through the intervention of a G protein. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.8 B, C).

The receptors coupled to the second messenger system are known as metabotropic receptors. Muscarinic and adrenergic receptors are examples of metabotropic receptors.

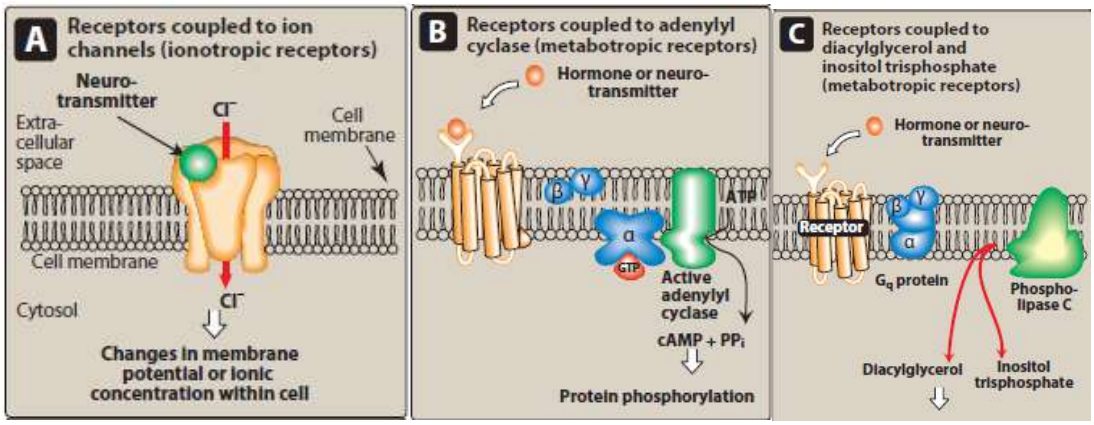


Figure 8: Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

Cholinergic Agonists

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action. The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter (Figure 1). The postganglionic sympathetic division of sweat glands also uses acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and play an important role in the central nervous system (CNS).

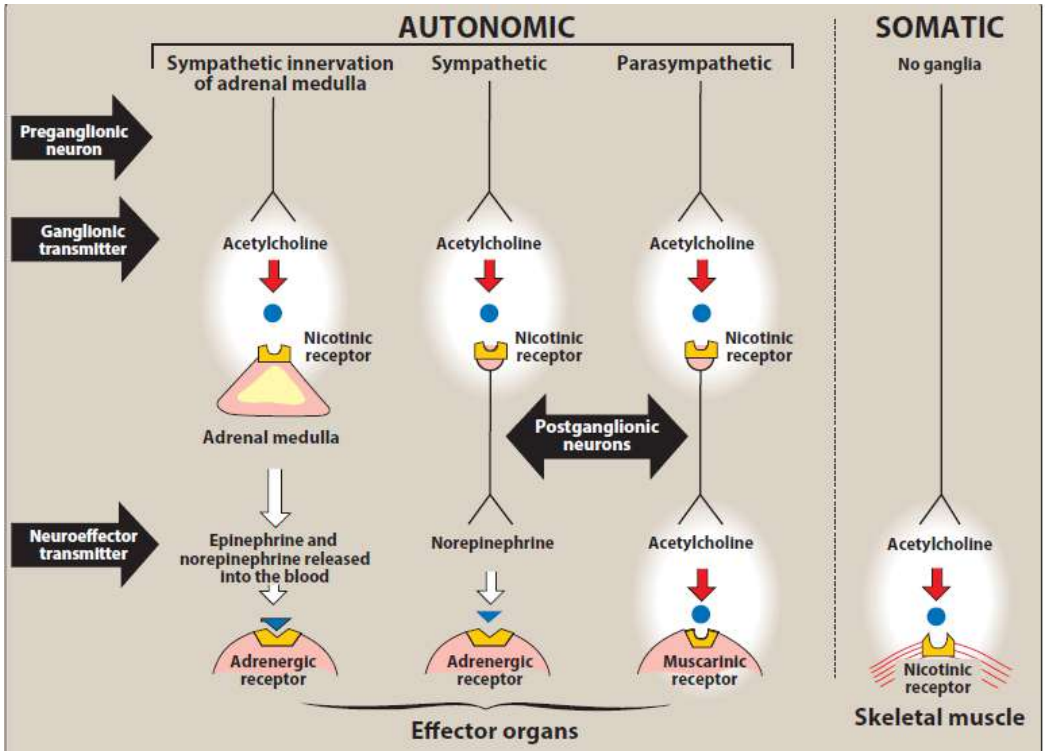


Figure 1: Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis, 2) storage, 3) release, 4) binding of ACh to a receptor, 5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and 6) recycling of choline and acetate (Figure 2).

1. Synthesis of acetylcholine: Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug *hemicholinium.*
[Note: *Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane*.] The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

2. Storage of acetylcholine in vesicles: ACh is packaged and stored into presynaptic vesicles by an active transport process. The mature vesicle contains not only ACh but also adenosine triphosphate (ATP) and proteoglycan. Co- transmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles contain the primary neurotransmitter (here, ACh) as well as a co-transmitter (here, ATP) that increases or decreases the effect of the primary neurotransmitter.

3. Release of acetylcholine: When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

4. Binding to the receptor: ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic (Figure 1). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by second messenger molecules.

5. Degradation of acetylcholine: The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft (Figure 2).

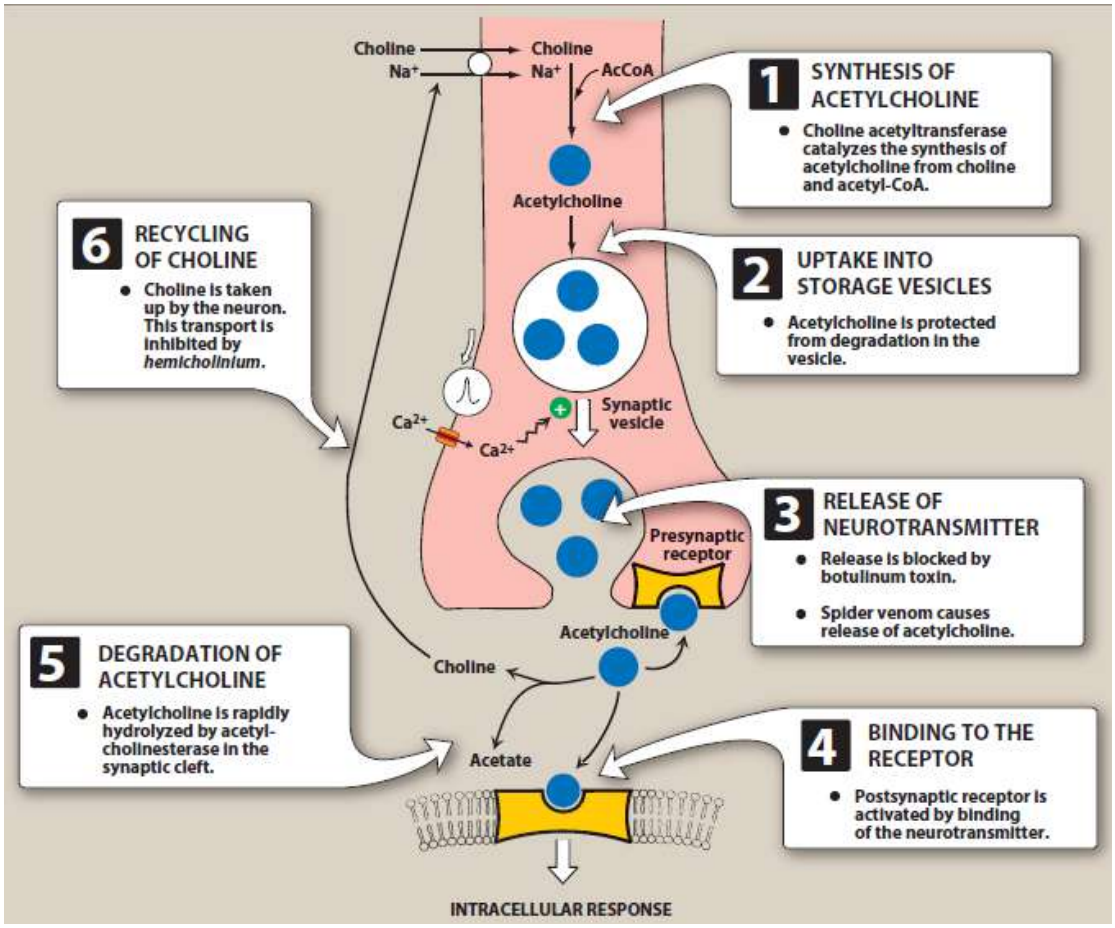


Figure 2: Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

6. Recycling of choline: Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is available to be acetylated into ACh.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of ACh (cholinomimetic agents).

A. Muscarinic receptors

Muscarinic receptors belong to the class of G protein–coupled receptors (metabotropic receptors). These receptors, in addition to binding ACh, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. In contrast, the muscarinic receptors show only a weak affinity for nicotine (Figure 3A). There are five subclasses of muscarinic receptors. However, only M1, M2, and M3 receptors have been functionally characterized.

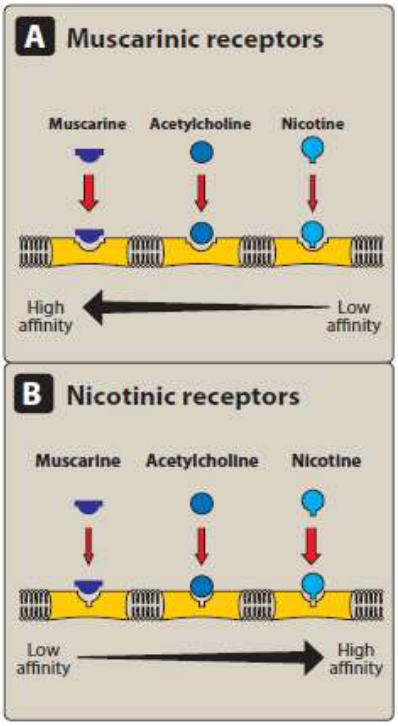


Figure 3: Types of cholinergic receptors

1. Locations of muscarinic receptors: These receptors are found on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands. Although all five subtypes are found on neurons, M1 receptors are also found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle, and M3 receptors on the bladder, exocrine glands, and smooth muscle.

2. Mechanisms of acetylcholine signal transduction: A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when M1 or M3 receptors are activated, the receptor undergoes a conformational change and interacts with a G protein, designated Gq, that in turn activates phospholipase C. This ultimately leads to the production of the second messenger inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 causes an increase in intracellular Ca2+.

Calcium can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction. Diacylglycerol activates protein kinase C, an enzyme that phosphorylates numerous proteins within the cell. In contrast, activation of the M2 subtype on the cardiac muscle stimulates a G protein, designated Gi, that inhibits adenylyl cyclase and increases K+ conductance. The heart responds with a decrease in rate and force of contraction.

3. Muscarinic agonists: *Pilocarpine* is an example of a nonselective muscarinic agonist used in clinical practice to treat xerostomia and glaucoma. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. M1 receptor agonists are being investigated for the treatment of Alzheimer's disease and M3 receptor antagonists for the treatment of chronic obstructive pulmonary disease.

B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine (Figure 3B). The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel. Binding of two ACh molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles. Those at the NMJ are sometimes designated N_M, and the others, N_N. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by mecamylamine, whereas NMJ receptors are specifically blocked by atracurium.

DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic). These agents may be broadly classified into two groups: 1) endogenous choline esters, which include Ach and synthetic esters of choline, such as *carbachol* and *bethanechol*, and 2) naturally occurring alkaloids, such as *nicotine* and *pilocarpine* (Figure 4). All of the direct-acting cholinergic drugs have a longer duration of action than ACh. The more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents.

However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness.

A. Acetylcholine

Acetylcholine is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include the following:

1. Decrease in heart rate and cardiac output: The actions of Ach on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node. [Note: Normal vagal activity regulates the heart by the release of ACh at the SA node.]

2. Decrease in blood pressure: Injection of ACh causes vasodilation and lowering of blood pressure by an indirect mechanism of action. ACh activates M3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine. Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation via phosphodiesterase-3 inhibition. In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities. *Atropine* blocks these muscarinic receptors and prevents ACh from producing vasodilation.

3. Other actions: In the gastrointestinal {GI) tract, acetylcholine increases salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions and causes bronchoconstriction. [Note: Methacholine, a direct-acting cholinergic agonist, is used to assist in the diagnosis of asthma due to its bronchoconstricting properties.] In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination. In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh {1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

B. Bethanechol

Bethanechol is an unsubstituted carbamoyl ester, structurally related to ACh (Figure 4). It is not hydrolyzed by AChE due to the esterification of carbamic acid, although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to the addition of the methyl group) but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration of action.

1. Actions: *Bethanechol* directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects produce urination.

2. Therapeutic applications: In urologic treatment, *bethanechol* is used to stimulate the atonic bladder, particularly in postpartum or postoperative, non-obstructive urinary retention.

3. Adverse effects: *Bethanechol* causes the effects of generalized cholinergic stimulation (Figure 5). These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. *Atropine sulfate* may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

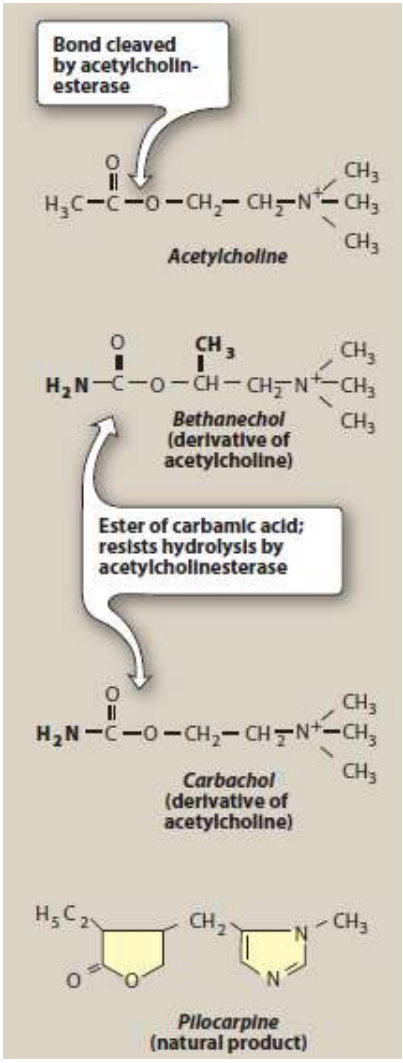


Figure 4: Comparison of the structures of some cholinergic agonists.

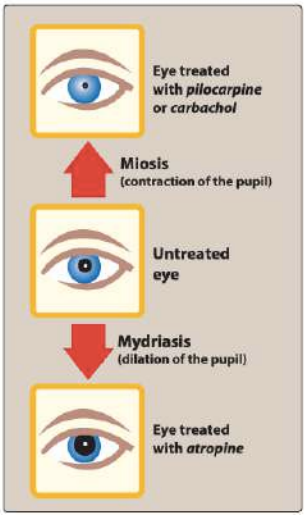
C. Carbachol (carbamylcholine)

Carbachol has both muscarinic and nicotinic actions. Like *bethanechol*, *carbachol* is an ester of carbamic acid (Figure 4) and a poor substrate for AChE. It is biotransformed by other esterases, but at a much slower rate.

1. Actions: *Carbachol* has profound effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of ACh, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction. The vision becomes fixed at some particular distance, making it impossible to focus.

2. Therapeutic uses: Because of its high potency, receptor nonselectivity, and relatively long duration of action, *carbachol* is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.

3. Adverse effects: At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).



D. Pilocarpine

The alkaloid *pilocarpine* is a tertiary amine and is stable to hydrolysis by AChE (Figure 4). Compared with ACh and its derivatives, it is far less potent but is uncharged and can penetrate the CNS at therapeutic doses. *Pilocarpine* exhibits muscarinic activity and is used primarily in ophthalmology.

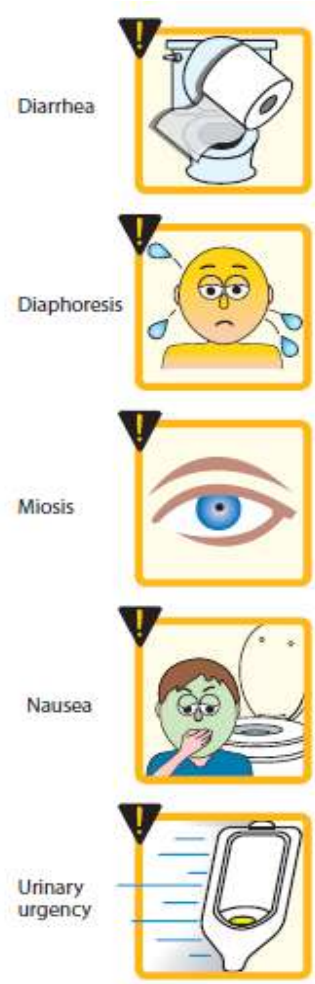


Figure 5: Some adverse effects observed with cholinergic agonists.

1. Actions: Applied topically to the eye, pilocarpine produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. Pilocarpine is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity.

2. Therapeutic use in glaucoma: Pilocarpine is used to treat glaucoma and is the drug of choice for emergency lowering of intraocular pressure of both open-angle and angle-closure glaucoma. Pilocarpine is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure because of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated. [Note: Topical carbonic anhydrase inhibitors, such as dorzolamide and B-adrenergic blockers such as timolol, are effective in treating glaucoma but are not used for emergency lowering of intraocular pressure.] The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine.

The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjogren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and cevimeline, a cholinergic drug that also has the drawback of being nonspecific.

3. Adverse effects: *Pilocarpine* can cause blurred vision, night blindness, and brow ache. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation.

The effects are similar to those produced by consumption of mushrooms of the genus *Inocybe*, which contain muscarine. Parenteral atropine, at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of pilocarpine.

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (REVERSIBLE)

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space (Figure 6). Therefore, these drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain. The reversible AChE inhibitors can be broadly classified as short-acting or intermediate-acting agents.

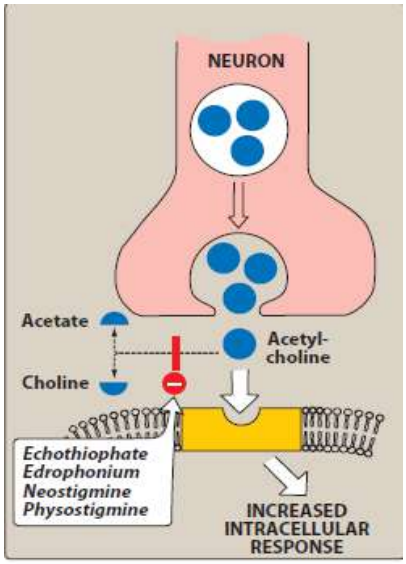


Figure 6: Mechanisms of action of indirect cholinergic agonists

A. Edrophonium

Edrophonium is the prototype short-acting AChE inhibitor. *Edrophonium* binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It is rapidly absorbed and has a short duration of action of 10 to 20 minutes due to rapid renal elimination.

Edrophonium is a quaternary amine, and its actions are limited to the periphery. It is used in the diagnosis of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. This causes their degradation, making fewer receptors available for interaction with Ach.

Intravenous injection of edrophonium leads to a rapid increase in muscle strength in patients with myasthenia gravis. Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote). Edrophonium may also be used to assess

cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing neuromuscular blockers (NMBs) after surgery. Due to the availability of other agents, edrophonium use has become limited.

B. Physostigmine

Physostigmine is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

1. Actions: Physostigmine has a wide range of effects and stimulates not only the muscarinic and nicotinic sites of the ANS, but also the nicotinic receptors of the NMJ. Muscarinic stimulation can cause contraction of Gl smooth muscles, miosis, bradycardia, and hypotension (Figure 7). Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses). Its duration of action is about 30 minutes to 2 hours, and it is considered an intermediate-acting agent. Physostigmine can enter and stimulate the cholinergic sites in the CNS.

2. Therapeutic uses: Physostigmine is used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, and to reverse the effects of NMBs.

3. Adverse effects: High doses of physostigmine may lead to convulsions. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the NMJ causes the accumulation of Ach and, ultimately through continuous depolarization, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

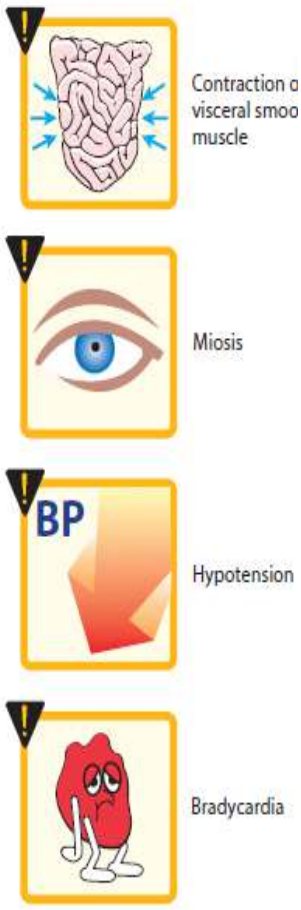


Figure 7: Some actions of physostigmine.

C. Neostigmine

Neostigmine is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to that of *physostigmine.*

1. Actions: Unlike *physostigmine, neostigmine* has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. Its effect on skeletal muscle is greater than that of *physostigmine*, and it can stimulate contractility before it paralyzes. *Neostigmine* has an intermediate duration of action, usually 30 minutes to 2 hours.

2. Therapeutic uses: It is used to stimulate the bladder and GI tract and also as an antidote for competitive neuromuscular-blocking agents. *Neostigmine* is also used to manage symptoms of myasthenia gravis.

3. Adverse effects: Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine. Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present.

D. Pyridostigmine

Pyridostigmine is another cholinesterase inhibitor used in the chronic management of myasthenia gravis. Its duration of action is intermediate (3 to 6 hours) but longer than that of neostigmine. Adverse effects are similar to those of neostigmine.

E. Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease have a deficiency of cholinergic neurons and therefore lower levels of ACh in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. Tacrine, the first agent in this category, has been replaced by others because of its hepatotoxicity.
Despite the ability of donepezil, rivastigmine, and galantamine to delay the progression of Alzheimer disease, none can stop its progression. Gl distress is their primary adverse effect

INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)

A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion* and *malathion*, are used as insecticides.

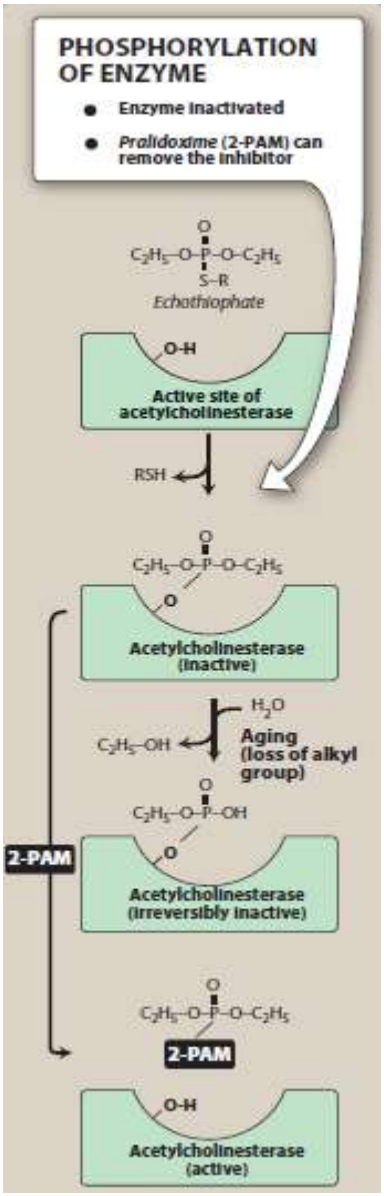


Figure 8: Covalent modification of acetylcholinesterase by *echothiophate*. Also shown is the reactivation of the enzyme with *pralidoxime*.

A. Echothiophate

1. Mechanism of action: *Echothiophate* is an organophosphate that covalently binds via its phosphate group at the active site of AChE (Figure 8). Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as *pralidoxime*, to break the bond between the remaining drug and the enzyme.

2. Actions: Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. *Echothiophate* produces intense miosis and, thus, has found therapeutic use. Intraocular pressure falls from the facilitation of outflow of aqueous humor. Atropine in high dosages can reverse many of the peripheral and some of the central muscarinic effects of echothiophate.

3. Therapeutic uses: A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma. However, echothiophate is rarely used due to its side effect profile, which includes the risk of cataracts.

TOXICOLOGY OF ANTICHOLINESTERASE AGENTS

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides in the United States, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes.

Organophosphate nerve gases such as sarin are used as agents of warfare and chemical terrorism. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be peripheral or can affect the whole body.

Reactivation of acetylcholinesterase

Pralidoxime (2-PAM) can reactivate inhibited AChE. However, it is unable to penetrate into the CNS and therefore is not useful in treating the CNS effects of organophosphates. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects. With the newer nerve agents that produce aging of the enzyme complex within seconds, *pralidoxime* is less effective. *Pralidoxime* is a weak AChE inhibitor and, at higher doses, may cause side effects similar to other AChE inhibitors. In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, *physostigmine*).

Other treatments: Atropine is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. Diazepam is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

Cholinergic antagonist

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists. The most clinically useful of these agents are selective blockers of muscarinic receptors.

They are commonly known as anticholinergic agents (a misnomer, as they antagonize only muscarinic receptors), antimuscarinic agents (more accurate terminology), or parasympatholytics.

A second group of drugs, the ganglionic blockers, shows a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important of the cholinergic antagonists. A third family of compounds, the neuromuscular-blocking agents (mostly nicotinic antagonists), interfere with transmission of efferent impulses to skeletal muscles. These drugs are used as skeletal muscle relaxants in surgical anesthesia and as agents to facilitate intubation in surgical and critical care patients.

ANTIMUSCARINIC AGENTS

Commonly known as anticholinergic drugs, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors, causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. The anticholinergic drugs are beneficial in a variety of clinical situations.

A. Atropine:

Atropine is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh from binding to those sites (Figure 1a). *Atropine* acts both centrally and peripherally. Its general actions last about 4 hours,

except when placed topically in the eye, where the action may last for days. Neuroeffector organs have varying sensitivity to *atropine*. The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva and the heart (Figure 1b).

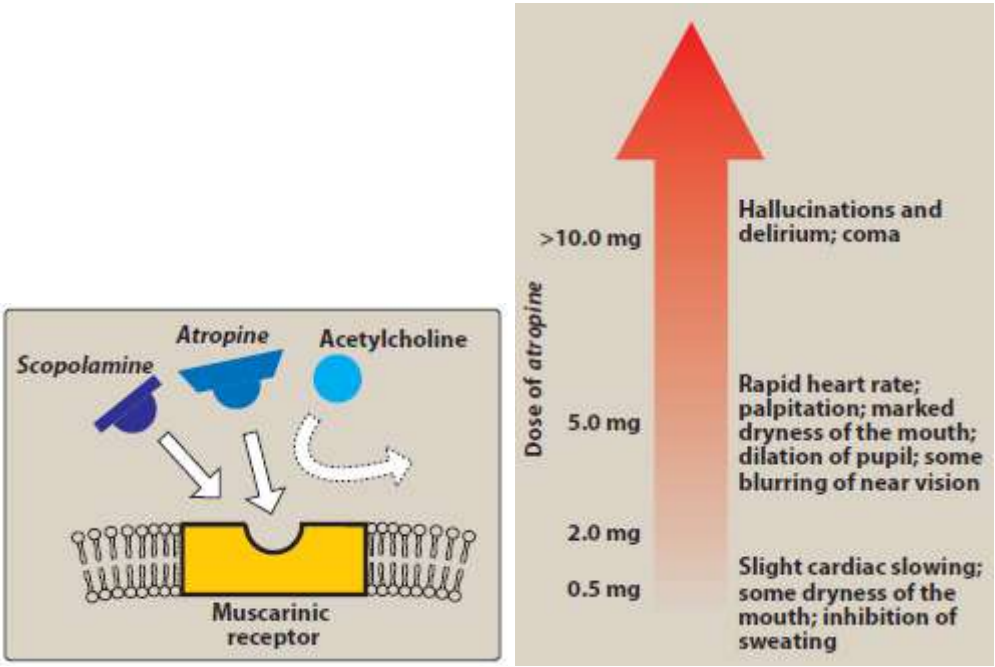


Figure 1: A. Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor. B. Dose-dependent effects of *atropine.*

1. Actions:

a. Eye: *Atropine* blocks muscarinic activity in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.

b. Gastrointestinal (GI): *Atropine* can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* are probably the most potent antispasmodic drugs available. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, *atropine* is not effective for the treatment of peptic ulcer.

Doses of *atropine* that reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with *atropine*.

c. Cardiovascular: *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 1b). At low doses, the predominant effect is a slight

decrease in heart rate. This effect results from blockade of the M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of *atropine* cause a progressive increase in heart rate by blocking the M_2 receptors on the sinoatrial node.

d. Secretions: *Atropine* blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are similarly affected.

Therapeutic uses:

a. Ophthalmic: Topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. Shorter-acting antimuscarinics (*cyclopentolate* and *tropicamide*) have largely replaced *atropine* due to prolonged mydriasis observed with *atropine* (7 to 14 days vs. 6 to 24 hours with other agents).

b. Antispasmodic: *Atropine* is used as an antispasmodic agent to relax the GI tract.
c. Cardiovascular: The drug is used to treat bradycardia of varying etiologies.

d. Antisecretory: *Atropine* is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

e. Antidote for cholinergic agonists: *Atropine* is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as *physostigmine*, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of *atropine* may be required over a long period of time to counteract the poisons. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

3. Pharmacokinetics: *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

4. Adverse effects: Depending on the dose, *atropine* may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity. Atropine may also induce troublesome urinary retention. The drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature.

B. Scopolamine

Scopolamine, another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamine* has greater action on the CNS (unlike *atropine,* CNS effects are observed at therapeutic doses) and a longer duration of action as compared to *atropine*.

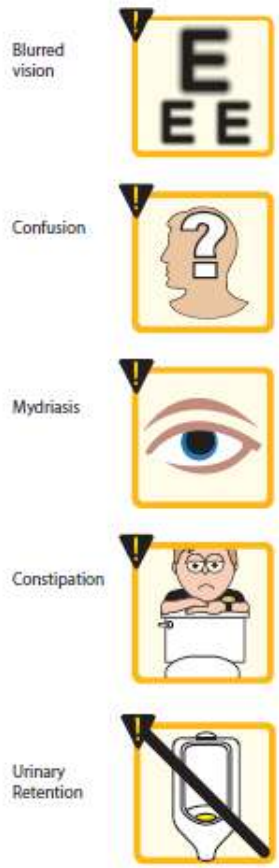


Figure 2: Adverse effects commonly observed with muscarinic antagonists.

1. Actions: *Scopolamine* is one of the most effective anti–motion sickness drugs available. It also has the unusual effect of blocking short-term memory. In contrast to *atropine, scopolamine* produces sedation, but at higher doses, it can produce excitement. *Scopolamine* may produce euphoria and is susceptible to abuse.

2. Therapeutic uses: The therapeutic use of *scopolamine* is limited to prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days.

3. Pharmacokinetics and adverse effects: These aspects are similar to those of atropine, with the exception of longer half-life.

C. Aclidinium, glycopyrrolate, Ipratropium and tiotropium

lpratropium and tiotropium are quaternary derivatives of atropine, and glycopyrrolate and aclidinium are synthetic quaternary compounds. lpratropium is classified as a short-acting muscarinic antagonist (SAMA), while glycopyrrolate, tiotropium, and aclidinium are classified as long-acting muscarinic antagonists (LAMAs) based on the duration of action. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

lpratropium and tiotropium are also used in the acute management of bronchospasm in asthma and chronic management of asthma, respectively. All of these agents are delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

D. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*. *Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

E. Benztropine and trihexyphenidyl

Benztropine and *trihexyphenidyl* are useful as adjuncts with other antiparkinsonian agents to treat Parkinson's disease and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

F. Oxybutynin and other antimuscarinic agents for overactive bladder:

Oxybutynin, *darifenacin*, *fesoterodine*, *solifenacin*, *tolterodine*, and *trospium* are synthetic *atropine*-like drugs with antimuscarinic actions.

1. Actions

By competitively blocking muscarinic (M3) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Antimuscarinic actions at M3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. *Darifenacin* and *solifenacin* are

relatively more selective M3 muscarinic receptor antagonists; however, the other drugs are mainly nonselective muscarinic antagonists, and binding to other muscarinic receptor subtypes may contribute to adverse effects.

2. Therapeutic uses

These agents are used for management of overactive bladder and urinary incontinence. *Oxybutynin* is also used in patients with neurogenic bladder.

3. Pharmacokinetics

All of the agents are available in oral dosage forms. Most agents have a long half-life, which allows once-daily administration. [Note: Immediate-release *oxybutynin* and *tolterodine* must be dosed two or more times daily; however, extended-release formulations of these agents allow for once-daily dosing.] *Oxybutynin* is also available in a transdermal patch and topical gel formulation. These drugs are hepatically metabolized by the cytochrome P450 system (primarily CYP 3A4 and 2D6), with the exception of *trospium*, which is thought to undergo ester hydrolysis.

4. Adverse effects

Side effects include dry mouth, constipation, and blurred vision, which limit tolerability of these agents. Extended-release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated. *Trospium* is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia

GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. The responses of the nondepolarizing blockers are complex and mostly unpredictable. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

Nicotine

A component of cigarette smoke, *nicotine*, is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, *nicotine* depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitters, due to effects on both sympathetic and parasympathetic ganglia. The overall response of a physiologic system is a summation of the stimulatory and inhibitory effects of *nicotine*. These include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.

NEUROMUSCULAR-BLOCKING AGENTS

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle. They possess some chemical similarities to ACh and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ. Neuromuscular blockers (NMBs) are clinically useful to facilitate rapid intubation when needed due to respiratory failure (rapid sequence intubation). During surgery, they are used to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses. This increases the safety of anesthesia by allowing patients to recover quickly and completely. NMBs should not substitute for inadequate anesthesia. NMBs are also used in the intensive care unit (ICU) as adjuvant therapy to facilitate intubation and mechanical ventilation in critically ill patients.

A. Nondepolarizing (competitive) blockers

The first known NMB was curare, which Amazon hunters used to paralyze prey. The development of tubocurarine followed, but it has been replaced by agents with fewer adverse effects, such as cisatracurium, mivacurium, pancuronium, rocuronium, and vecuronium.

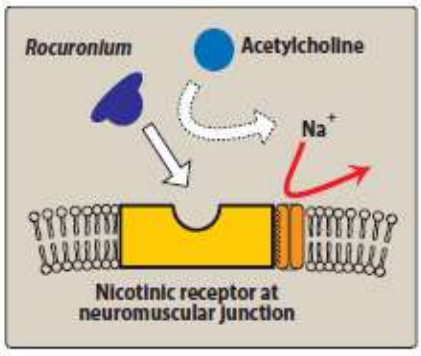


Figure 3: Mechanism of action of competitive neuromuscular-blocking drugs.

1. Mechanism of action:

a. At low doses: Nondepolarizing agents competitively block ACh at the nicotinic receptors (Figure 3). That is, they compete with ACh at the receptor without stimulating it, thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Their competitive action can be overcome by administration of cholinesterase inhibitors, such as *neostigmine* and *edrophonium*, which increase the concentration of ACh in the neuromuscular junction. Anesthesiologists employ this strategy to shorten the duration of the neuromuscular blockade. In addition, at low doses the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade.

b. At high doses: Nondepolarizing agents can block the ion channels of the motor endplate. This leads to further weakening of neuromuscular transmission, thereby reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers. With complete blockade, the muscle does not respond to direct electrical stimulation.

2. Actions: Muscles have differing sensitivity to blockade by competitive agents. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles. Next, the intercostal muscles are affected and, lastly, the diaphragm. The muscles recover in the reverse manner. [Note: Sugammadex is a selective relaxant binding agent that terminates the action of both rocuronium and vecuronium and can be used to speed recovery

3. Pharmacokinetics: All NMBs are injected intravenously or occasionally intramuscularly. These agents possess two or more quaternary amines in their bulky ring structure that prevent absorption from the gut. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Drug action is terminated in a variety of ways. Pancuronium is excreted unchanged in urine. Cisatracurium undergoes organ-independent metabolism (via Hofmann elimination) to laudanosine, which is further metabolized and renally excreted. The amino steroid drugs vecuronium and rocuronium are deacetylated in the liver and excreted unchanged in bile. Mivacurium is eliminated by plasma cholinesterase. The choice of agent depends on the desired onset and duration of muscle relaxation and the route of elimination.

Drug interactions:

a. Cholinesterase inhibitors: Drugs such as *neostigmine*, *physostigmine, pyridostigmine,* and *edrophonium* can overcome the action of nondepolarizing neuromuscular blockers.

However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh concentrations at the endplate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

b. Halogenated hydrocarbon anesthetics: Drugs such as *desflurane* act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of neuromuscular blockers.

c. Aminoglycoside antibiotics: Drugs such as *gentamicin* and *tobramycin* inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with *pancuronium* and other competitive blockers, enhancing the blockade.

d. Calcium channel blockers: These agents may increase the neuromuscular blockade of competitive blockers.

B. Depolarizing agents

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can thus more persistently depolarize the muscle fibers. *Succinylcholine* is the only depolarizing muscle relaxant in use today.

1. Mechanism of action: *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarize the junction (Figure 4). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing constant stimulation of the receptor.

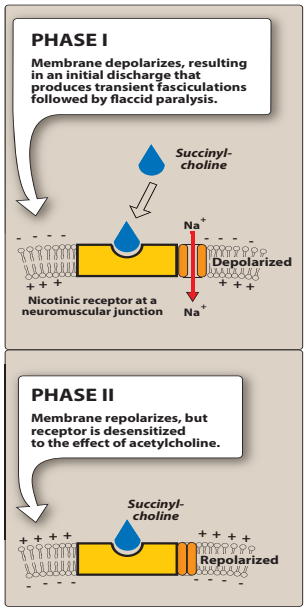


Figure 4: Mechanism of action of depolarizing neuromuscular-blocking drugs.

The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.

2. Actions: As with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces brief muscle fasciculations that cause muscle soreness. This may be prevented by administering a small dose of nondepolarizing neuromuscular blocker prior to *succinylcholine*. Normally, the duration of action of *succinylcholine* is extremely short, due to rapid hydrolysis by plasma pseudocholinesterase. However, *succinylcholine* that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).

3. Therapeutic uses: Because of its rapid onset of action, *succinylcholine* is useful when rapid endotracheal intubation is required during the induction of anesthesia. It is also used during electroconvulsive shock treatment.

4. Pharmacokinetics: *Succinylcholine* is injected intravenously. Its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudocholinesterase. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect. Drug effects rapidly disappear upon discontinuation.

5. Adverse effects:

a. Hyperthermia: S*uccinylcholine* can potentially induce malignant hyperthermia in susceptible patients.

b. Apnea: Administration of *succinylcholine* to a patient who is deficient in plasma cholinesterase or who has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm. The rapid release of potassium may also contribute to prolonged apnea in patients with electrolyte imbalances who receive this drug. In patients with electrolyte imbalances who are also receiving *digoxin* or diuretics (such as heart failure patients) *succinylcholine* should be used cautiously or not at all.

c. Hyperkalemia: *Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost or in patients with renal failure.

Adrenergic Agonists

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Adrenergic drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block the activation of adrenergic receptors are termed sympatholytics. Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists).

Catecholamines are compounds containing a catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side chain. Pharmacologically, the most important ones are:

• **Noradrenaline** (**norepinephrine**), a transmitter released by sympathetic nerve terminals

• **Adrenaline** (**epinephrine**), a hormone secreted by the adrenal medulla.

• **Dopamine**, the metabolic precursor of noradrenaline and adrenaline, also a transmitter/neuromodulator in the central nervous system.

• **Isoprenaline** (**isoproterenol**), a synthetic derivative of noradrenaline, not present in the body.

Adrenergic Neuron:

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ.

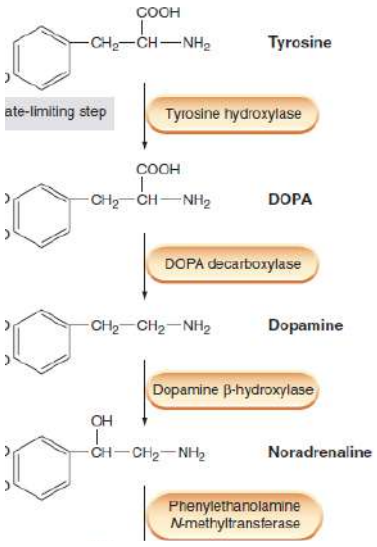


Figure 1: *Structures of the major catecholamines*

A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons, except that norepinephrine is the neurotransmitter instead of acetylcholine.

Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 2).

1. **Synthesis of norepinephrine:** Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme aromatic I-amino acid decarboxylase to form dopamine in the presynaptic neuron (figure 1).
2. **Storage of norepinephrine in vesicles:** Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by *reserpine*. Dopamine is next hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase.
3. **Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse. Drugs such as *guanethidine* block this release.

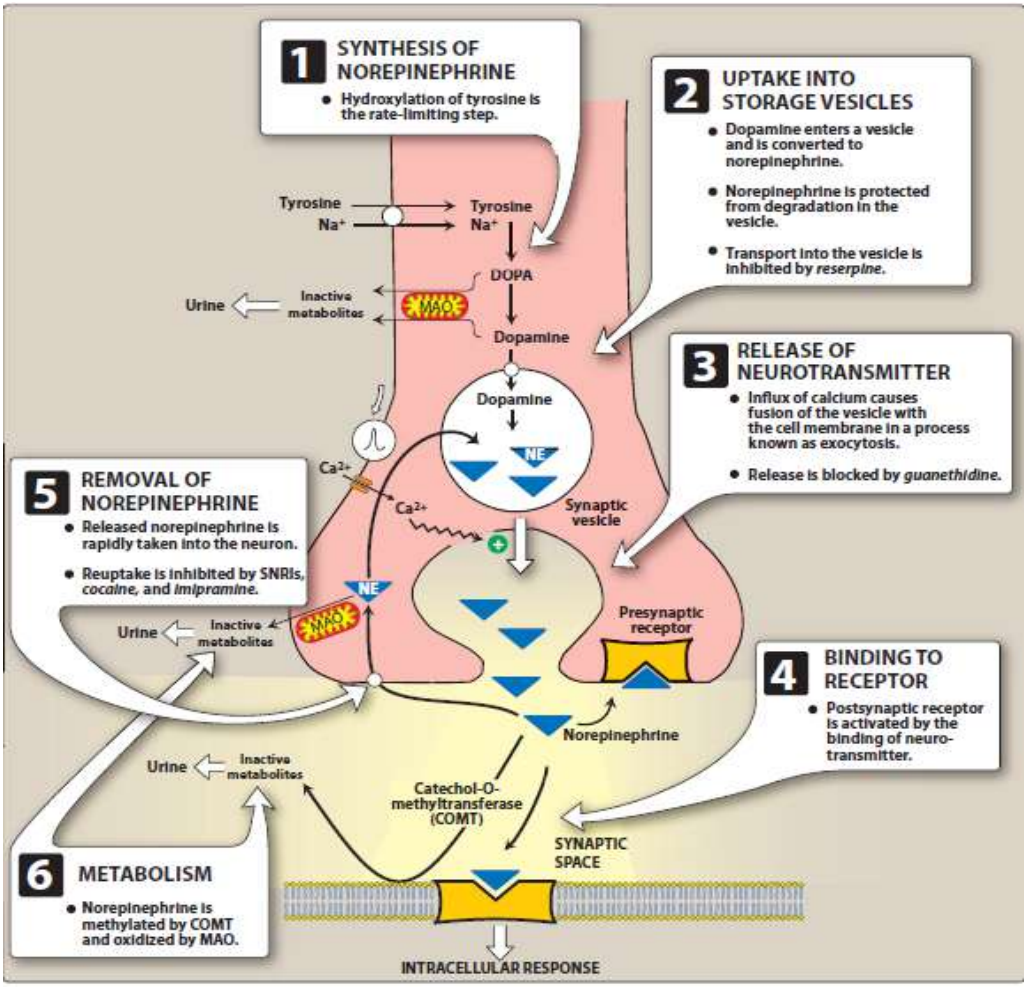


Figure 2: *Synthesis and release of norepinephrine from the adrenergic neuron. MAO = monoamine oxidase, SNRI = serotonin norepinephrine reuptake inhibitor.*

4. **Binding to receptors:** Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly α_2 subtype) that modulate the release of the neurotransmitter.

5. **Removal of norepinephrine:** Norepinephrine may

1) Diffuse out of the synaptic space and enter the systemic circulation. 2) Be metabolized to inactive metabolites by catechol-*O*-methyltransferase (COMT) in the synaptic space.

3) Undergo reuptake back into the neuron. The reuptake by the neuronal membrane involves a sodium-chloride (Na^+/Cl^-)-dependent norepinephrine transporter (NET) that can be inhibited by tricyclic antidepressants (TCAs), such as *imipramine*, by serotonin–norepinephrine reuptake inhibitors such as *duloxetine*, or by *cocaine* (Figure 2). Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

6. **Potential fates of recaptured norepinephrine:** Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β, are classified on the basis of their responses to the adrenergic agonists *epinephrine*, *norepinephrine*, and *isoproterenol*.

Each of these main receptor types has a number of specific receptor subtypes that have been identified. Alterations in the primary structure of the receptors influence their affinity for various agents.

1. α-Adrenoceptors: The α-adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and *norepinephrine* (Figure 3). For α receptors, the rank order of potency and affinity is *epinephrine* ≥ *norepinephrine* >> *isoproterenol*. The α-adrenoceptors are subdivided into two subgroups, α_1 and α_2, based on their affinities for α agonists and blocking drugs. For example, the α_1 receptors have a higher affinity for *phenylephrine* than α_2 receptors. Conversely, the drug *clonidine* selectively binds to α_2 receptors and has less effect on α_1 receptors.

a. **α1 Receptors:** These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α_1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 3).

Receptor	Agonist	Antagonist	G Protein	Effects
α_1 type	Phenylephrine	Prazosin	G_q	↑ IP3, DAG common to all
α_{1A}		Tamsulosin		
α_{1B}				
α_{1D}				
α_2 type	Clonidine	Yohimbine	G_i	↓ cAMP common to all
α_{2A}	Oxymetazoline			
α_{2B}		Prazosin		
α_{2C}		Prazosin		
β type	Isoproterenol	Propranolol	G_s	↑ cAMP common to all
β_1	Dobutamine	Betaxolol		
β_2	Albuterol	Butoxamine		
β_3	Mirabegron			

b. α_2 Receptors: These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine. When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α_2 receptors on the presynaptic membrane (Figure 2). Stimulation of α_2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. [Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as inhibitory autoreceptors.] α_2 receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release.

This is another mechanism to modulate autonomic activity in a given area. In contrast to α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.

c. Further subdivisions: The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example, *tamsulosin* is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets α_{1A} subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α_{1B} subtype found in the blood vessels.

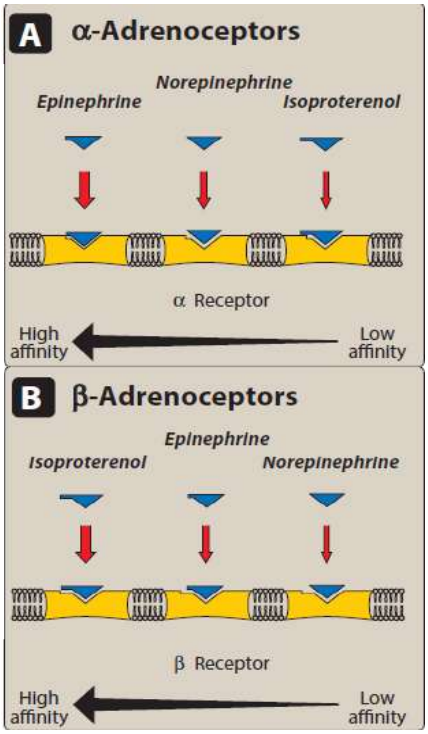


Figure 3: Types of adrenergic receptor

2. β-Adrenoceptors: Responses of β receptors differ from those of α receptors and are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and *norepinephrine* (Figure 3). For β receptors, the rank order of potency is *isoproterenol* > *epinephrine* > *norepinephrine*. The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists.

β_1 receptors have approximately equal affinities for *epinephrine* and *norepinephrine*, whereas β_2 receptors have a higher affinity for *epinephrine* than for *norepinephrine*. Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the effects of circulating epinephrine released by the

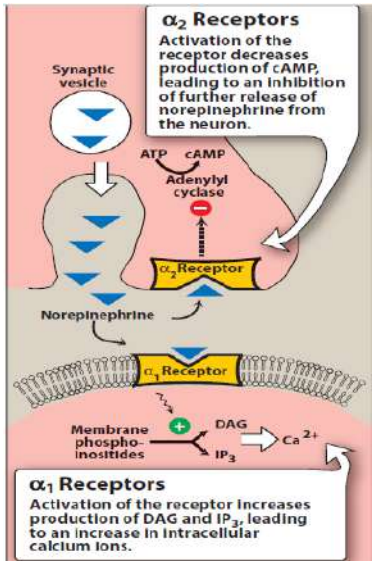


Figure 4: Second messengers mediate the effects of α receptors.

adrenal medulla. β_3 receptors are involved in lipolysis and also have effects on the detrusor muscle of the bladder. Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.

3. Distribution of receptors: Adrenergically innervated organs and tissues usually have a predominant type of receptor. For example, tissues such as the vasculature of skeletal muscle have both α_1 and β_2 receptors, but the β_2 receptors predominate. Other tissues may have one type of receptor almost exclusively. For example, the heart contains predominantly β_1 receptors.

4. Characteristic responses mediated by adrenoceptors: It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor. Figure below summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of α1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure.

Stimulation of β_1 receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation of β_2 receptors produces vasodilation (in skeletal muscle vascular beds) and smooth muscle relaxation. β_3 Receptors are involved in lipolysis (along with β_1), and also have effects on the detrusor muscle of the bladder.

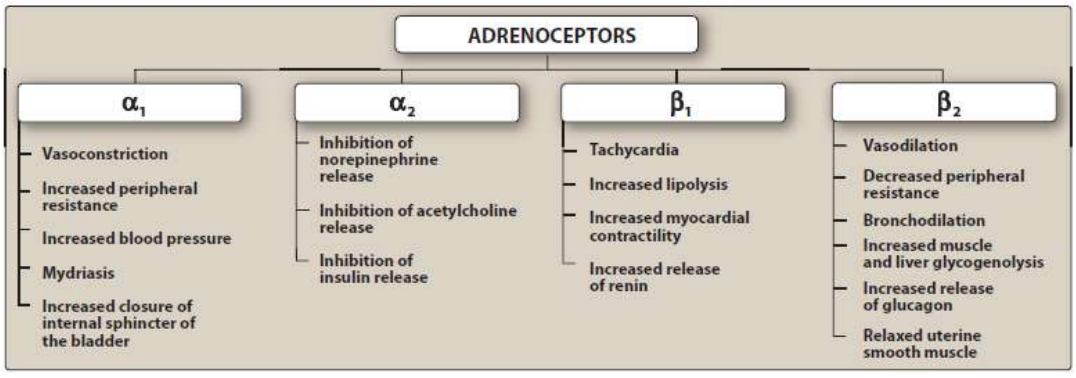


Figure 5: Major effects mediated by α- and β-adrenoceptors

5. Desensitization of receptors: Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three

mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

Characteristics of Adrenergic Agonist:

Most of the adrenergic drugs are derivatives of β-phenylethylamine (Figure 1). Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are 1) the number and location of OH substitutions on the benzene ring and 2) the nature of the substituent on the amino nitrogen.

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as *epinephrine*, *norepinephrine*, *isoproterenol*, and *dopamine*) are called catecholamines. These compounds share the following properties:

1. High potency: Catecholamines (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors.

2. Rapid inactivation: Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, as well as by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.

3. Poor penetration into the CNS: Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

B. Non-catecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include *phenylephrine*, *ephedrine*, and *amphetamine* (Figure 1). These agents are poor substrates for MAO (an important route of metabolism) and, thus, show a prolonged duration of action. Increased lipid solubility of many of the non-catecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Mechanism of action of adrenergic agonists:

1. Direct-acting agonists: These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla (Figure 2). Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, and *phenylephrine*.

2. Indirect-acting agonists: These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (Figure 2).

The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include *cocaine* and *amphetamines*, respectively.

3. Mixed-action agonists: *Ephedrine* and its stereoisomer, *pseudoephedrine*, both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron (Figure 2).

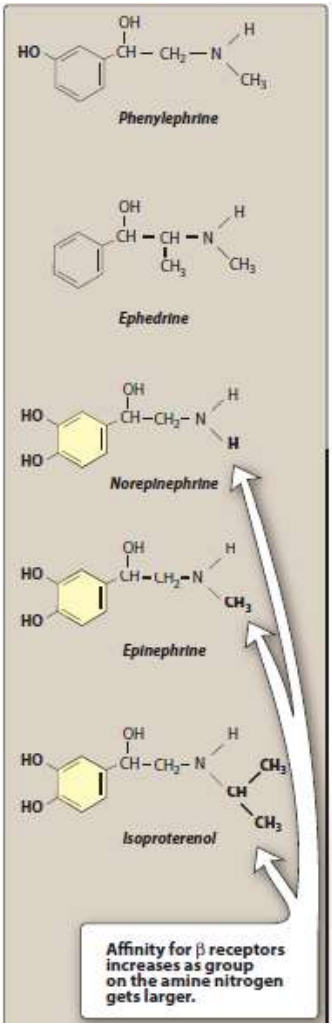


Figure 1: *Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.*

Direct-acting agonists:

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

A. Epinephrine

Epinephrine is one of the four catecholamines (*epinephrine*, *norepinephrine*, *dopamine*, and *dobutamine*) commonly used in therapy. The first three are naturally occurring neurotransmitters, and the latter is a synthetic compound. In the adrenal medulla, *norepinephrine* is methylated to yield *epinephrine*, which is stored in chromaffin cells along with *norepinephrine*. On stimulation, the adrenal medulla releases about 80% *epinephrine* and 20% *norepinephrine* directly into the circulation.

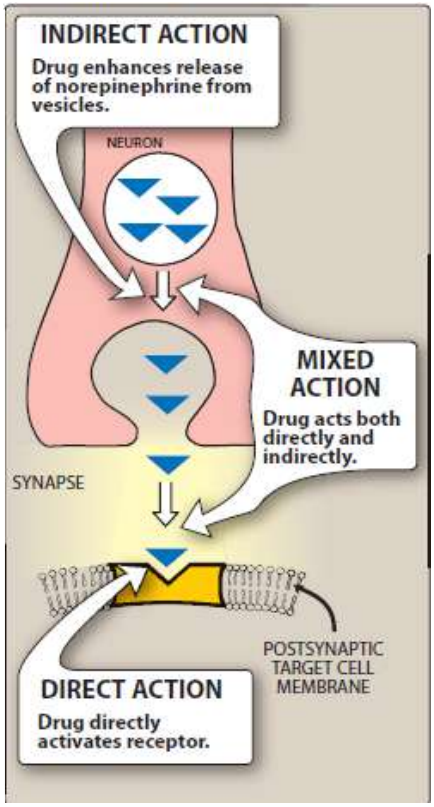


Figure 2: Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

1. Actions:

a. Cardiovascular: The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotrope: β1 action) and increases its rate of contraction (positive chronotrope: β1 action). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. *Epinephrine* activates β1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor.

Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β2 effects). Renal blood flow is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β2 receptor–mediated vasodilation in the skeletal muscle vascular bed (Figure 3).

b. Respiratory: *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). It also inhibits the release of allergy mediators such as histamines from mast cells.

c. Hyperglycemia: *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect).

d. Lipolysis: *Epinephrine* initiates lipolysis through agonist activity on the β receptors of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.

2. Therapeutic uses:

a. Bronchospasm: *Epinephrine* is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function.

Thus, in treatment of acute asthma and anaphylactic shock, *epinephrine* is the drug of choice and can be life saving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves. However, selective β2 agonists, such as *albuterol*, are favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effects.

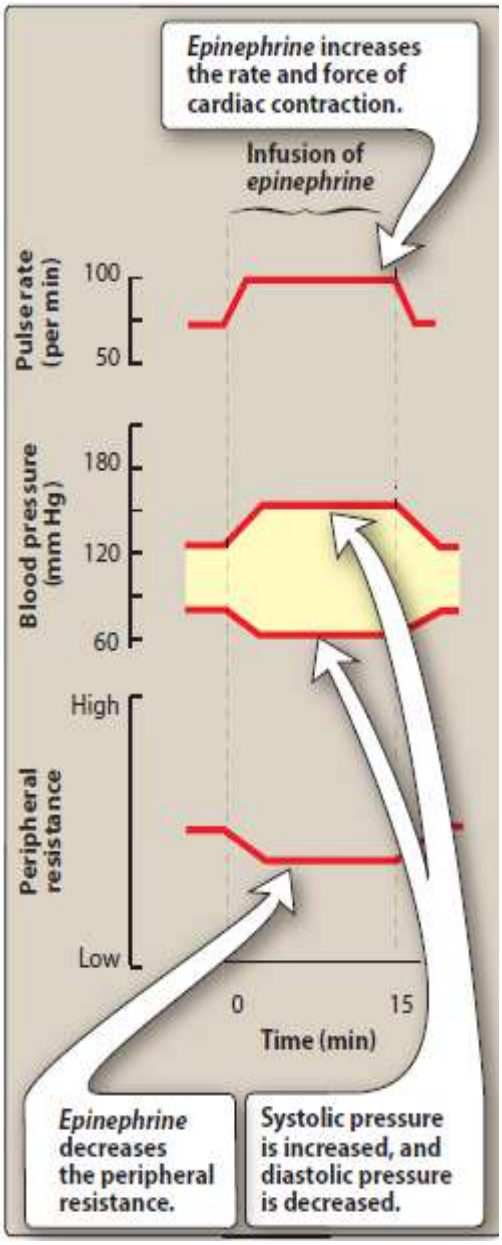


Figure 3: Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

b. Anaphylactic shock: *Epinephrine* is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens.

c. Cardiac arrest: *Epinephrine* may be used to restore cardiac rhythm in patients with cardiac arrest.

d. Anesthetics: Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of *epinephrine*. *Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. Epinephrine also reduces systemic absorption of the local anesthetic and promotes local hemostasis.
e. Intraocular surgery: Epinephrine is used in the induction and maintenance of mydriasis during intraocular surgery.

Pharmacokinetics: Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route for anaphylaxis in the outpatient setting is intramuscular (anterior thigh) due to rapid absorption. In emergencies, epinephrine is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, or by inhalation. It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and vanillylmandelic acid are excreted in urine.

Adverse effects: *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger cardiac arrhythmias, particularly if the patient is receiving *digoxin*. *Epinephrine* can also induce pulmonary edema.
Epinephrine may have enhanced cardiovascular actions in patients with hyperthyroidism, and the dose must be reduced in these individuals.
Patients with hyperthyroidism may have an increased production of adrenergic receptors in the vasculature, leading to a hypersensitive response.
Epinephrine increases the release of endogenous stores of glucose. In diabetic patients, dosages of *insulin* may have to be increased. Nonselective β-blockers prevent vasodilatory effects of *epinephrine* on β2 receptors, leaving α receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

B. Norepinephrine

Because *norepinephrine* is the neurotransmitter of adrenergic nerves, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the α-adrenergic receptor is most affected.

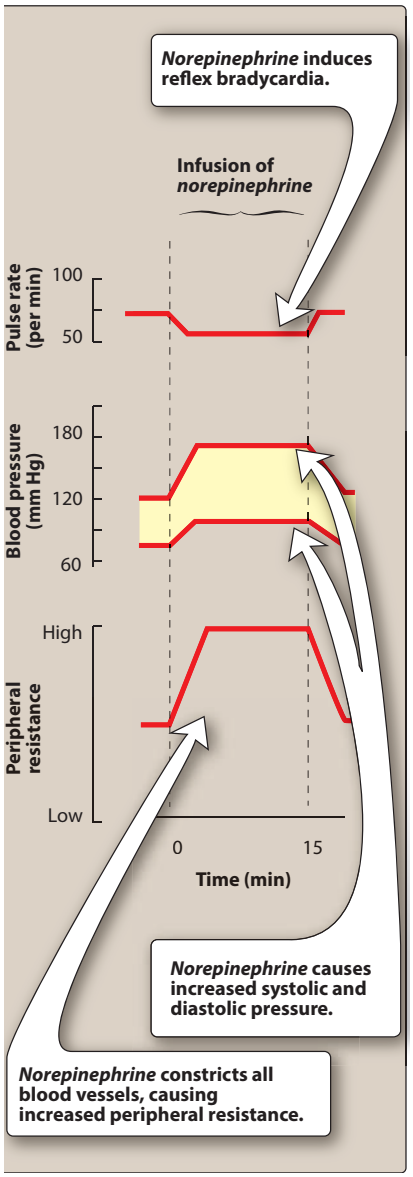


Figure 4: Cardiovascular effects of intravenous infusion of *norepinephrine*.

1. Cardiovascular actions:

a. Vasoconstriction: *Norepinephrine* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α1 effect). Both systolic and diastolic blood pressures increase (Figure 4). [Note: *Norepinephrine* causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via β2 receptors on blood vessels supplying skeletal muscles. The weak β2 activity of *norepinephrine* also explains why it is not useful in the treatment of asthma or anaphylaxis.]

b. Baroreceptor reflex: *Norepinephrine* increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia, which is sufficient to counteract the local actions of *norepinephrine* on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug (Figure 4). When *atropine*, which blocks the transmission of vagal effects, is given before *norepinephrine*, stimulation of the heart by *norepinephrine* is evident as tachycardia.

2. Therapeutic uses: *Norepinephrine* is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

C. Isoproterenol

Isoproterenol is a direct-acting synthetic catecholamine that stimulates both β1- and β2-adrenergic receptors. Its non-selectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant.

Isoproterenol produces intense stimulation of the heart, increasing heart rate, contractility, and cardiac output (Figure 4). It is as active as *epinephrine* in this action. *Isoproterenol* also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressures (Figure 4). *Isoproterenol* is a potent bronchodilator (β2 effect). The use of *isoproterenol* has largely been replaced with other drugs, but it may be useful in atrioventricular (AV) block. The adverse effects of *isoproterenol* are similar to those of *epinephrine*.

D. Dopamine

Dopamine, the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate α- and β-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors.

In addition, D1 and D2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

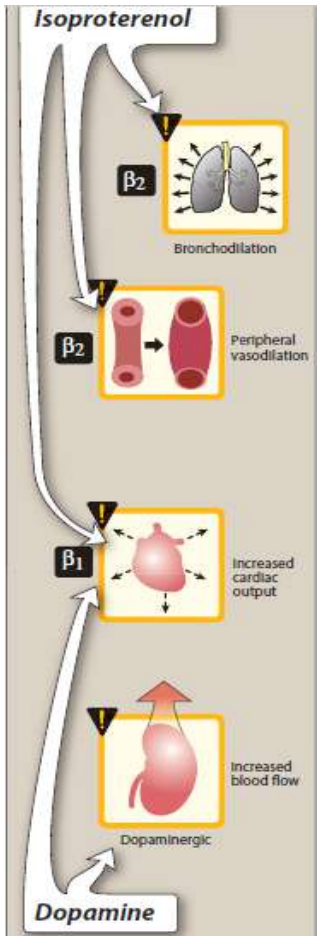


Figure 5: Clinically important actions of *isoproterenol* and *dopamine*.

1. Actions:

a. Cardiovascular: *Dopamine* exerts a stimulatory effect on the β1 receptors of the heart, having both positive inotropic and chronotropic effects. At very high doses, *dopamine* activates α1 receptors on the vasculature, resulting in vasoconstriction.

b. Renal and visceral: *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera. These receptors are not affected by α- or β-blocking drugs. Therefore, *dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

2. Therapeutic uses: *Dopamine* is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. By contrast, norepinephrine can diminish blood supply to the kidney and may reduce renal function. Dopamine is also used to treat hypotension, severe heart failure, and bradycardia unresponsive to other treatments.

E. Fenoldopam

Fenoldopam is an agonist of peripheral dopamine D1 receptors. It is used as rapid-acting vasodilators to treat sever hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. *Fenoldopam* is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed with this agent.

F. Dobutamine

Dobutamine is a synthetic, direct-acting catecholamine that is a β_1 receptor agonist. It increases cardiac rate and output with few vascular effects. *Dobutamine* is used to increase cardiac output in acute heart failure, as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs.

G. Oxymetazoline

Oxymetazoline is a direct-acting synthetic adrenergic agonist that stimulates both α1- and α2-adrenergic receptors. *Oxymetazoline* is found in many over-the-counter short-

term nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. *Oxymetazoline* directly stimulates α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion. It is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping.

Local irritation and sneezing may occur with intranasal administration. Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

H. Phenylephrine

Phenylephrine is a direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally. The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate).

Large doses can cause hypertensive headache and cardiac irregularities. *Phenylephrine* acts as a nasal decongestant when applied topically or taken orally. *Phenylephrine* is also used in ophthalmic solutions for mydriasis.

I. Midodrine: a prodrug, is metabolized to the pharmacologically active desglymidodrine. It is a selective a1 agonist, which acts in the periphery to increase arterial and venous tone. Midodrine is indicated for the treatment of orthostatic hypotension. The drug should be given three times daily, with doses at 3- or 4-hour intervals. To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

J. Clonidine

Clonidine is an **α2 agonist** that is used for the treatment of hypertension. It can also be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines. *Clonidine* acts centrally on presynaptic α2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of *clonidine* are lethargy, sedation,

constipation, and xerostomia. Abrupt discontinuance must be avoided to prevent rebound hypertension.

K. Albuterol, metaproterenol, and terbutaline

Albuterol, metaproterenol, and terbutaline are short-acting β_2 agonists (SABAs) used primarily as bronchodilators and administered by a metered-dose inhaler. Albuterol is the SABA of choice for the management of acute asthma symptoms, because it is more selective for β_2 receptors than metaproterenol. Inhaled terbutaline is no longer available in the United States, but is still used in other countries. Injectable terbutaline is used off-label as a uterine relaxant to suppress premature labor, and use for this indication should

not exceed 72 hours. One of the most common side effects of these agents is tremor, but patients tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety.

When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β_1 receptor activation), especially in patients with underlying cardiac disease. Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided.

L. Salmeterol, formoterol, and indacaterol

Salmeterol, formoterol, arformoterol (the [R,R]-enantiomer of formoterol), and indacaterol are long-acting β_2 selective agonists (LABAs) used for the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol. Unlike formoterol, however, salmeterol has a somewhat delayed onset of action. LABAs are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of asthma related deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid.

M. Mirabegron

Mirabegron is a β_3 agonist that relaxes the detrusor smooth muscle and increases bladder capacity. It is used for patients with overactive bladder. *Mirabegron* may

increase blood pressure and should not be used in patients with uncontrolled hypertension.

INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine. They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of *amphetamine* is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α1 agonist action on the vasculature, as well as β1-stimulatory effects on the heart.

Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. Thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and therapeutic uses of *amphetamine* and its derivatives are discussed under stimulants of the CNS.

B. Tyramine

Tyramine is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism.

Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor episodes. Like *amphetamines*, *tyramine* can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

C. Cocaine

Cocaine is unique among local anesthetics in having the ability to block the sodium-chloride (Na+/Cl-)-dependent norepinephrine transporter required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses

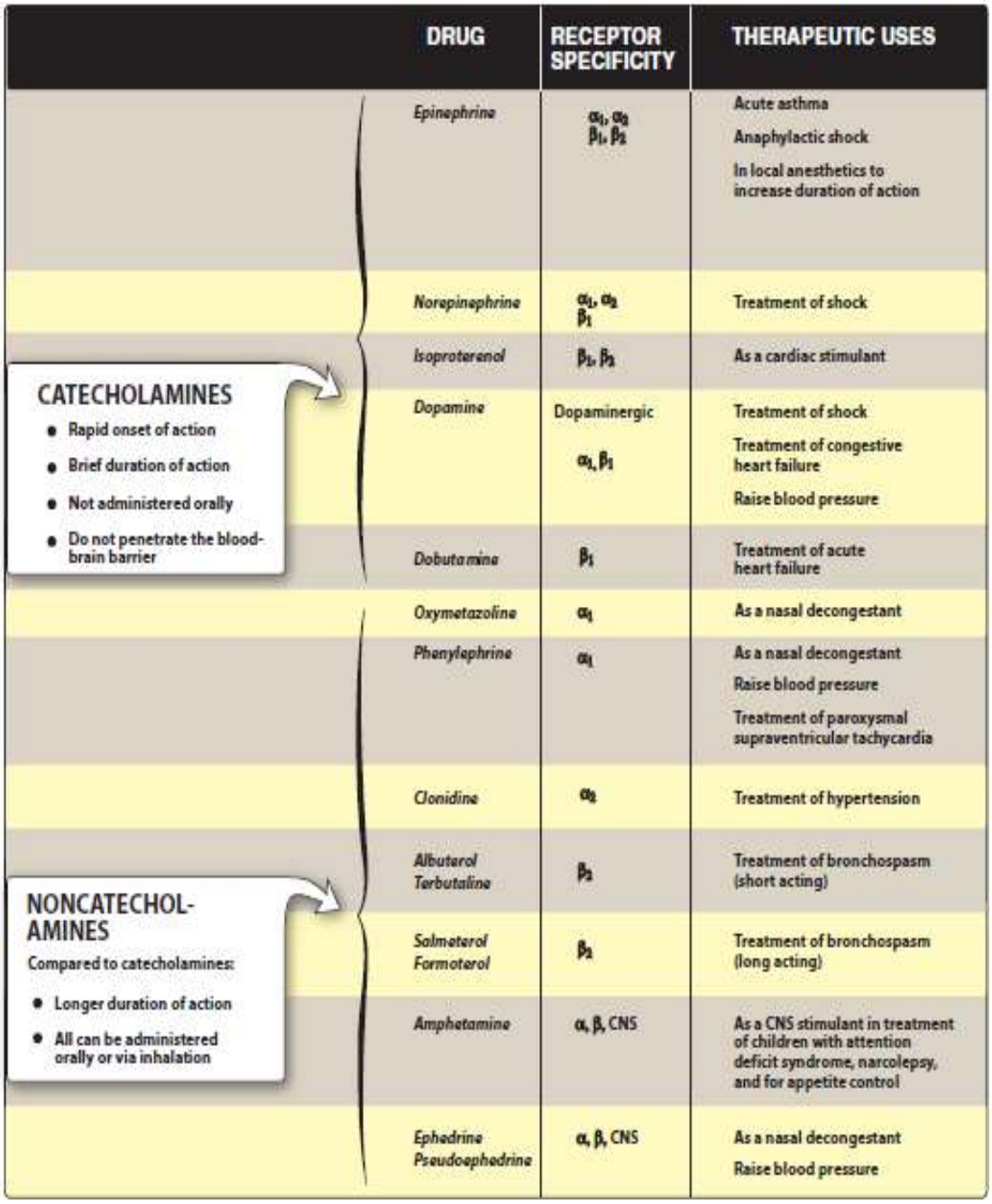
of the catecholamines produce greatly magnified effects in an individual taking *cocaine*. In addition, the duration of action of epinephrine and norepinephrine is increased. Like *amphetamines*, it can increase blood pressure by α1 agonist actions and β stimulatory effects.

MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine and *pseudoephedrine* are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent.

Ephedrine and *pseudoephedrine* are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption orally and penetrate into the CNS, but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension. *Ephedrine* produces bronchodilation, but it is less potent and slower acting than *epinephrine* or *isoproterenol*. It was previously used to prevent asthma attacks but has been replaced by more effective medications. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of *ephedrine* is declining because of the availability of better, more potent agents that cause fewer adverse effects. *Ephedrine*-containing herbal supplements (mainly ephedra-containing products) have been banned by the U.S. Food and Drug Administration because of life-threatening cardiovascular reactions.] *Pseudoephedrine* is primarily used orally to treat nasal and sinus congestion. *Pseudoephedrine* has been illegally used to produce *methamphetamine*.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin


DRUG
RECEPTOR SPECIFICITY
THERAPEUTIC USES
Epinephrine
α1, α2 β1, β2
Acute asthma
Anaphylactic shock
In local anesthetics to increase duration of action
Norepinephrine
α1, α2 β1
Treatment of shock
Isoproterenol
β1, β2
As a cardiac stimulant
CATECHOLAMINES
Rapid onset of action
Brief duration of action
Not administered orally
Do not penetrate the blood-brain barrier
Dopamine
Dopaminergic
α1, β1
Treatment of shock
Treatment of congestive heart failure
Raise blood pressure
Dobutamine
β1
Treatment of acute heart failure
Oxymetazoline
α1
As a nasal decongestant
Phenylephrine
α1
As a nasal decongestant
Raise blood pressure
Treatment of paroxysmal supraventricular tachycardia
Clonidine
α2
Treatment of hypertension
Albuterol
Terbutaline
β2
Treatment of bronchospasm (short acting)
NONCATECHOL-AMINES
Compared to catecholamines:
Longer duration of action
All can be administered orally or via inhalation
Salmeterol
Formoterol
β2
Treatment of bronchospasm (long acting)
Amphetamine
α, β, CNS
As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine
Pseudoephedrine
α, β, CNS
As a nasal decongestant
Raise blood pressure

Adrenergic Antagonists

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system.

α-ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. [Note: β receptors, including β1 adrenoceptors on the heart, are not affected by α blockade.]. The α-adrenergic blocking agents, *phenoxybenzamine* and *phentolamine*, have limited clinical applications.

A. Phenoxybenzamine

Phenoxybenzamine is nonselective, linking covalently to both α1 and α2 receptors. The block is irreversible and noncompetitive, and the only way the body can overcome the block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of *phenoxybenzamine* last about 24 hours. After the drug is injected, a delay of a few hours occurs before a blockade develops.

Actions:

a. Cardiovascular effects: By blocking α_1 receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic inhibitory α_2 receptors in the heart can contribute to an increased cardiac output. [Note: Blocking these receptors results in more norepinephrine release, which stimulates β_1 receptors on the heart, increasing cardiac output.] Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

b. Epinephrine reversal: All α-adrenergic blockers reverse the α agonist actions of *epinephrine*. For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of β2 receptors is not blocked. Therefore, in the presence of *phenoxybenzamine*, the systemic blood pressure decreases in response to *epinephrine* (Figure 1). [Note: The actions of *norepinephrine* are not reversed but are diminished because *norepinephrine* lacks significant β agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure β agonist (Figure 1).

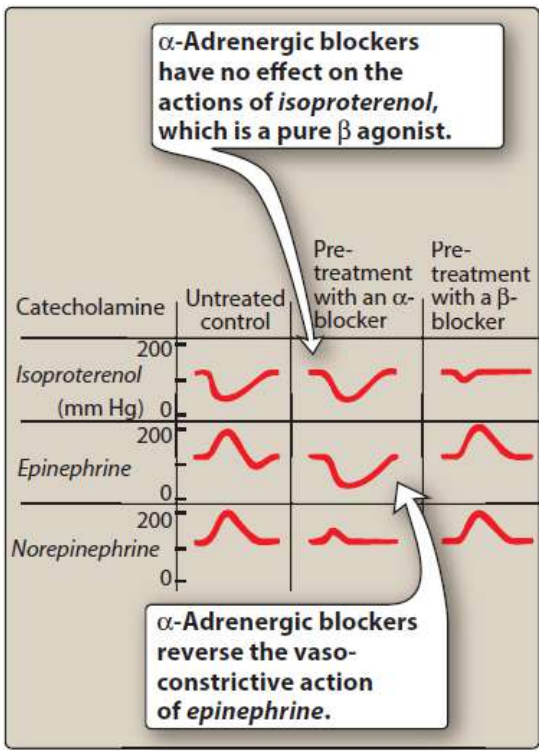


Figure 1: Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and *norepinephrine*.

2. Therapeutic uses: Phenoxybenzamine is used in the treatment of sweating and hypertension associated with pheochromocytoma, a catecholamine-secreting tumor of

cells derived from the adrenal medulla. Phenoxybenzamine is sometimes effective in treating Raynaud disease and frostbite.

3. Adverse effects: *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex. *Phenoxybenzamine* should be used with caution in patients with cerebrovascular or cardiovascular disease.

B. Phentolamine

In contrast to phenoxybenzamine, phentolamine produces a competitive block of α1 and α2 receptors. Effects last for approximately 4 hours after a single injection. Pharmacological effects of phentolamine are very similar to those of phenoxybenzamine. It is used for the diagnosis and short-term management of pheochromocytoma.

It is also used locally to prevent dermal necrosis following extravasation of norepinephrine. Phentolamine is useful to treat hypertensive crisis due to abrupt withdrawal of clonidine or ingestion of tyramine containing foods in patients taking monoamine oxidase inhibitors.

C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

Prazosin, *terazosin*, and *doxazosin* are selective competitive blockers of the α1 receptor.

In contrast to *phenoxybenzamine* and *phentolamine*, they are useful in the treatment of hypertension. *Tamsulosin* and *alfuzosin* are examples of other selective α1 antagonists indicated for the treatment of benign prostatic hyperplasia (BPH). Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

1. Mechanism of action: All of these agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Tamsulosin has the least effect on blood pressure because it is less selective for α_{1B} receptors found in the blood vessels and more selective for α_{1A} receptors in the prostate and bladder. Blockade of the α_{1A} receptors a decrease tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

2. Therapeutic uses: Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This action, termed a "first-dose" effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared to other antihypertensives, α1 antagonists are not used as monotherapy for the treatment of hypertension. The α1 receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH.

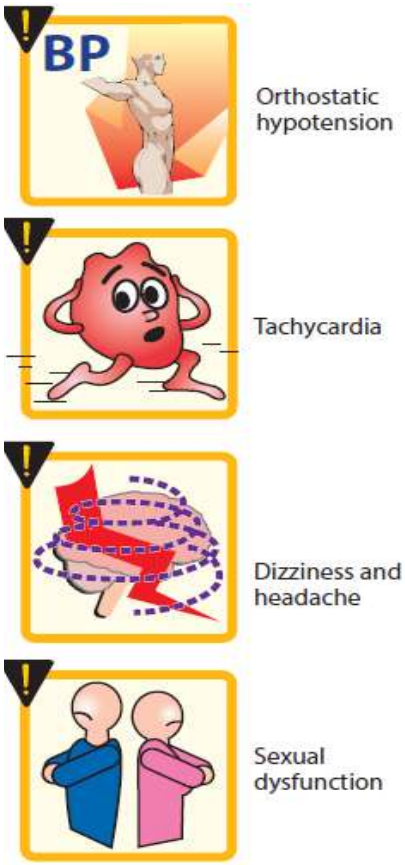


Figure 2: Some adverse effects commonly observed with nonselective α-adrenergic blocking agents.

3. Adverse effects: α1-Blockers such as prazosin and doxazosin may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with phenoxybenzamine and phentolamine)

D. Yohimbine

Yohimbine is a selective competitive α2-blocker that works at the level of the CNS to increase sympathetic outflow to the periphery. It is found as a component of the bark of the yohimbe tree (Pausinystalia yohimbe) and has been used as a sexual stimulant and in the treatment of erectile dysfunction. Its use in the treatment of these disorders is not recommended due to lack of demonstrated efficacy.

III. β-ADRENERGIC BLOCKING AGENTS

All of the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β1 and β2 receptors, whereas cardioselective β antagonists primarily block β1 receptors. [Note: There are no clinically useful β2 antagonists.]

These drugs also differ in intrinsic sympathomimetics activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics

Although all β-blockers lower blood pressure, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. B Blockers are effective in treating hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in "-olol" except for *labetalol* and *carvedilol*.]

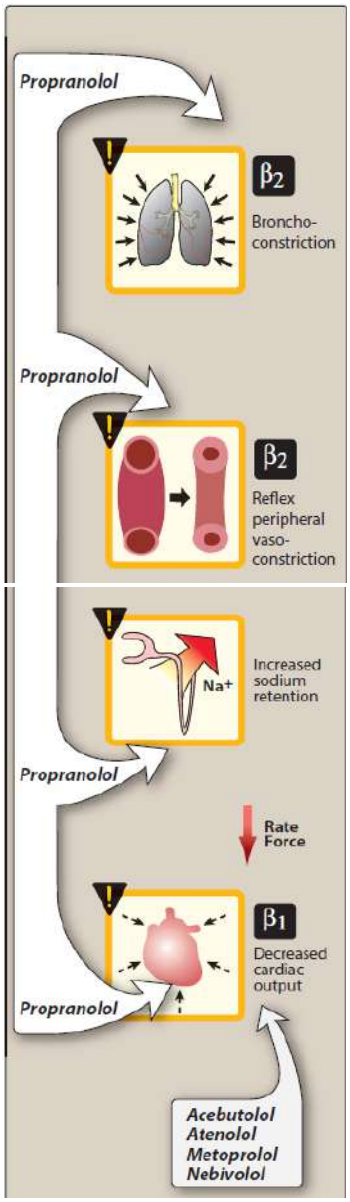


Figure 3: Actions of *propranolol* and otherβ-blockers.

A. Propranolol: A nonselective β antagonist

Propranolol is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors with equal affinity. Sustainedrelease preparations for once-a-day dosing are available.

1. Actions:

a. Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 3). It directly depresses sinoatrial and atrioventricular nodal activity.

The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina. The β-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).

b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance (Figure 3). The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of *propranolol*. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

c. Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (Figure 3). This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β-blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

d. Disturbances in glucose metabolism: β blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if *propranolol* is given to a diabetic patient receiving *insulin*, careful monitoring of blood glucose is essential, because

pronounced hypoglycemia may occur after *insulin* injection. β-blockers also attenuate the normal physiologic response to hypoglycemia.

e. Blocked action of isoproterenol: Nonselective β-blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* (β1, β2 agonist) on the cardiovascular system. Thus, in the presence of a β-blocker, *isoproterenol* does not produce cardiac stimulation (β1 mediated) or reductions in mean arterial pressure and diastolic pressure (β2 mediated).

[Note: In the presence of a nonselective β-blocker, *epinephrine* no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by α receptors) remains unimpaired. The actions of *norepinephrine* on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.]

2. Therapeutic uses:

a. Hypertension: *Propranolol* does not reduce blood pressure in people with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the antihypertensive effects.

b. Angina pectoris: *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. *Propranolol* is, thus, useful in the chronic management of stable angina.

c. Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery.

The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

d. Migraine: *Propranolol* is effective in reducing migraine episodes when used prophylactically. It is one of the more useful β-blockers for this indication, due to its lipophilic nature that allows it to penetrate the CNS. [Note: For the acute management of migraine, serotonin agonists such as *sumatriptan* are used, as well as other drugs.]

e. Hyperthyroidism: *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

3. Pharmacokinetics: After oral administration, *propranolol* is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation.

The volume of distribution of *propranolol* is quite large (4 L/kg), and the drug readily crosses the blood–brain barrier due to its high lipophilicity.

Propranolol is extensively metabolized, and most metabolites are excreted in the urine.

4. Adverse effects:

a. Bronchoconstriction: *Propranolol* has the potential to cause significant bronchoconstriction due to blockade of β2 receptors (Figure 4). Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, *propranolol* is contraindicated in patients with COPD or asthma.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

c. Sexual impairment: Because ejaculation in the male is mediated through α-adrenergic activation, β-blockers do not affect ejaculation or internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β receptor blockade.

d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β-blockers can prevent the counter regulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers.

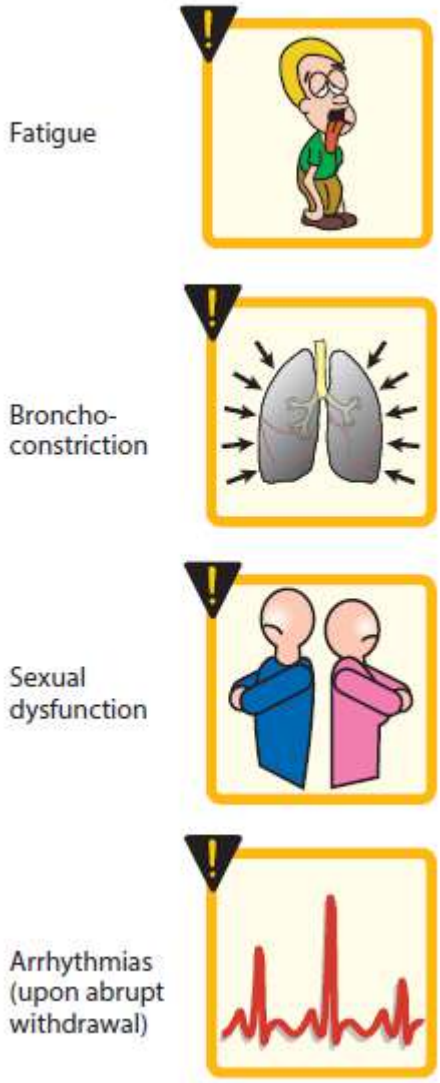


Figure 4: Adverse effects commonly observed in individuals treated with *propranolol*.

A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated mainly by β2 and β3 receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β-blockers have increased low density lipoprotein ("bad" cholesterol), increased triglycerides, and reduced high-density lipoprotein ("good" cholesterol). These effects on the serum lipid profile may be less pronounced with the use of β1-selective antagonists such as *metoprolol*.

e. CNS effects: *Propranolol* has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects may be seen with more hydrophilic β-blockers (for example, *atenolol*), since they do not cross the blood–brain barrier as readily.

B. Nadolol and timolol: Nonselective β antagonists

Nadolol and *timolol* also block β1- and β2-adrenoceptors and are more potent than *propranolol*. *Nadolol* has a very long duration of action. *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma.

1. Treatment of glaucoma: β-blockers, such as topically applied *timolol*, *betaxolol*, or *carteolol*, are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size. When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24 hours.

The β-blockers are only used for chronic management of glaucoma. In an acute attack of glaucoma, *pilocarpine* is still the drug of choice for emergency lowering of intraocular pressure.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide*, and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: Selective β1 antagonists

Drugs that preferentially block the β1 receptors minimize the unwanted bronchoconstriction (β2 effect) seen with *propranolol* use in asthma patients. Cardioselective β-blockers, such as *acebutolol*, *atenolol*, and *metoprolol*, antagonize β1 receptors at doses 50- to 100-fold less than those required to block β2 receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Since β1 selectivity of these agents is lost at high doses, they may
antagonize β2 receptors.]

1. Actions:

These drugs lower blood pressure in hypertension and increase exercise tolerance in angina. Esmolol has a very short half-life due to metabolism of an ester linkage. It is only available intravenously and is used to control blood pressure or heart rhythm in critically ill patients and those undergoing surgery or diagnostic procedures. In addition to its cardioselective β -blockade, nebivolol releases nitric oxide from endothelial cells and causes vasodilation. In contrast to propranolol, the cardioselective β -blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism.

Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised. Because these drugs have

less effect on peripheral vascular β_2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of β -blockers, is less frequent.

2. Therapeutic uses: The cardioselective B-blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina.

Bisoprolol and the extended-release formulation of metoprolol are indicated for the management of chronic heart failure.

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. Actions:

a. Cardiovascular: *Acebutolol* (β1-selective antagonist) and *pindolol* (nonselective β-blocker) are not pure antagonists. These drugs also have the ability to weakly stimulate both β1 and β2 receptors (Figure 5) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a diminished effect on cardiac rate and cardiac output compared to that of β-blockers without ISA.

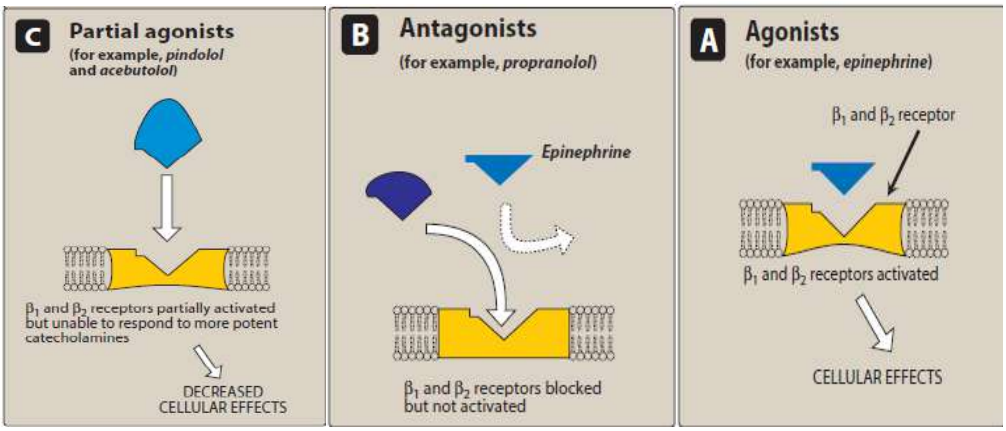


Figure 5: Comparison of agonists, antagonists, and partial agonists of β adrenoceptors.

b. Decreased metabolic effects: β-blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

2. Therapeutic use in hypertension: β-blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. [Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.].

E. Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

1. Actions: *Labetalol* and *carvedilol* are nonselective β-blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

2. Therapeutic use in hypertension and heart failure: *Labetalol* is employed as an alternative to *methyldopa* in the treatment of pregnancy- induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure. β-blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, *carvedilol* as well as *metoprolol* and *bisoprolol* are beneficial in patients with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time.

3. Adverse effects: Orthostatic hypotension and dizziness are associated with α1 blockade. Below Figure summarizes the receptor specificities and uses of the β-adrenergic antagonists.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. Reserpine is one of the remaining agents in this category.

Reserpine, a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphatedependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. Reserpine has a slow onset, a long duration of action, and effects that persist for many days after discontinuation.

It has been used for the management of hypertension but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions. It is also indicated in agitated psychotic states such as schizophrenia to relieve symptoms.

Principles of Antimicrobial Therapy

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings.

Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, *they have the ability to injure or kill an invading microorganism without harming the cells of the host*.

In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

❑ SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing

1) the organism's identity
2) the organism's susceptibility to a particular agent
3) the site of the infection
4) patient factors
5) the safety of the agent and
6) the cost of therapy.

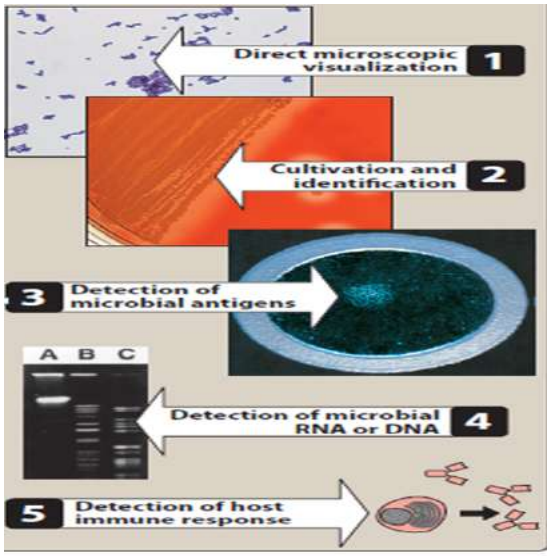


Figure 37.1
Some laboratory techniques that are useful in the diagnosis of microbial diseases.

However, some patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing)

A. Identification of the infecting organism

A rapid assessment of the nature of the pathogen can sometimes be made *on the basis of the Gram stain*, *which is particularly useful in identifying the presence and morphologic features of microorganisms* in body

fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine).

B. Empiric therapy prior to identification of the organism

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established.

1- Timing:

Acutely ill patients with infections of unknown origin

For example, a neutropenic patient (a reduction in neutrophils) or a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord) require immediate treatment. If possible, *therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available*.

2. Selecting a drug:

Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely.For example, gram-positive cocci in the spinal fluid of a newborn infant is most likely to be *Streptococcus agalactiae* which is sensitive to penicillin G.

By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be *S. pneumoniae*. This organism is frequently resistant to penicillin G and often requires treatment with a high-dose third generation cephalosporin (such as ceftriaxone) or vancomycin.

C. Determining antimicrobial susceptibility of infective organisms:

Some pathogens, such as *Streptococcus pyogenes and Neisseria meningitidis,* usually have predictable susceptibility patterns to certain antibiotics.

In contrast, most gram-negative bacilli, *enterococci, and staphylococcal* species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy. The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined.

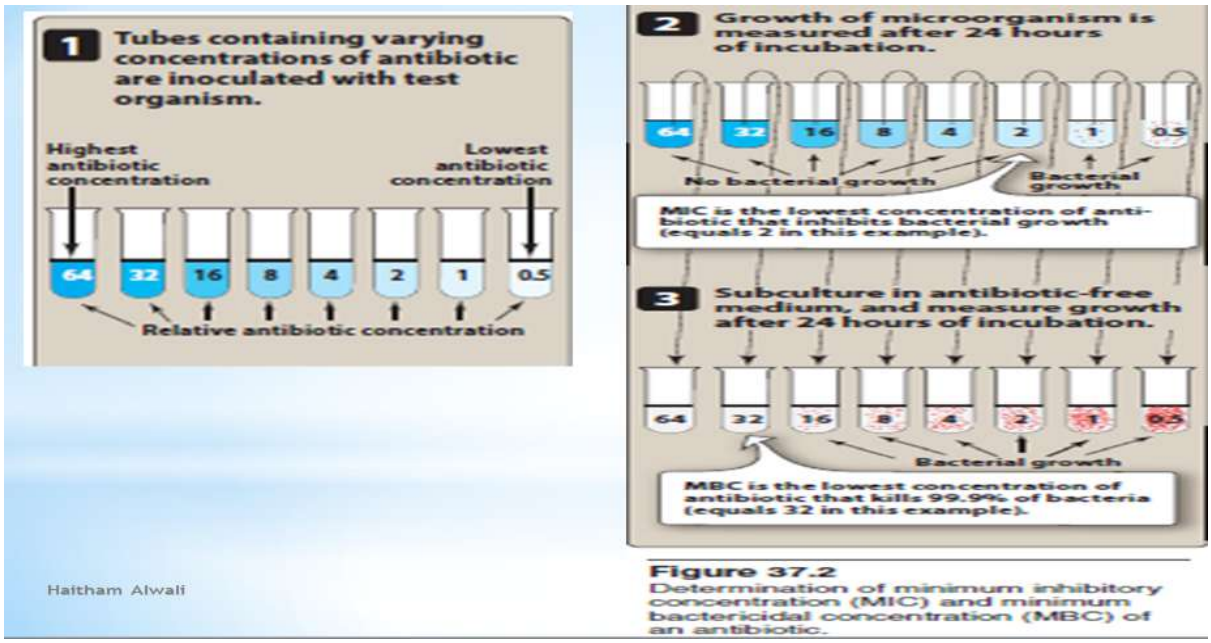


Figure 37.2
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

1. Bacteriostatic versus bactericidal drugs:

Antimicrobial drugs are classified as either bacteriostatic or bactericidal.

-Bacteriostatic drugs arrest the growth and replication of bacteria at serum(or urine) levels

-Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill and immunocompromised patients.

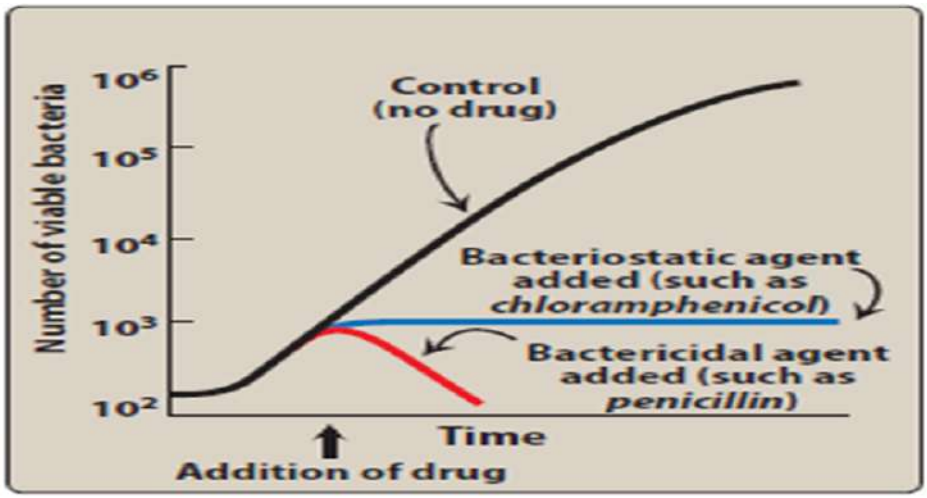


Figure 37.3
Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

2. Minimum inhibitory concentration: The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation.

3. Minimum bactericidal concentration: The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a 99.9% decline in colony count after overnight broth dilution incubations.

D. Effect of the site of infection on therapy:

The blood–brain barrier BBB: This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic.

The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:

1. **Lipid solubility of the drug:**

Lipid soluble drugs, such as chloramphenicol and metronidazole, have significant penetration into the CNS, whereas β-lactam antibiotics, such as penicillin, are ionized at physiologic pH and have low solubility in lipids.

In infections such as meningitis, the barrier does not function as effectively, and local permeability is increased. Some β-lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed.

2. **Molecular weight of the drug:**

A compounds with a high molecular weight (for example,vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

3. **Protein binding of the drug**: A high degree of protein binding of a drug restricts its entry into the CSF.

E. Patient factors

the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

1. Immune system: Alcoholism,diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, or advanced age can affect a patient's immunocompetence

High doses of bactericidal agents or longer courses of treatment may be required

2. Renal dysfunction: Poor kidney function may cause accumulation of certain antibiotics. (for eg, vancomycin, aminoglycosides)

3. Hepatic dysfunction: Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and doxycycline) must be used with caution when treating patients with liver dysfunction.

4. Poor perfusion: Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that area, making these infections difficult to treat.

5. Age: Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of *chloramphenicol and sulfonamides*.

Young children should not be treated with tetracyclines or quinolones, which affect bone growth and joints, respectively.

Elderly patients may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.

6. Pregnancy and lactation: Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

CATE-GORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with inhibitors Cephalosporins *Aztreonam* *Clindamycin* *Erythromycin* *Azithromycin* *Metronidazole* *Nitrofurantoin* Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	*Chloramphenicol* Fluoroquinolones *Clarithromycin* *Trimethoprim* *Vancomycin* *Gentamicin* *Trimethoprim-sulfamethoxazole*
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except *gentamicin*)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

Figure 37.4
FDA categories of antimicrobials and fetal risk.

F. Safety of the agent

Antibiotics such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms.

Other antimicrobial agents (for example, chloramphenicol) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient.

G. Cost of therapy

Often several drugs may show similar efficacy in treating an infection but vary widely in cost.

For example, treatment of methicillin-resistant

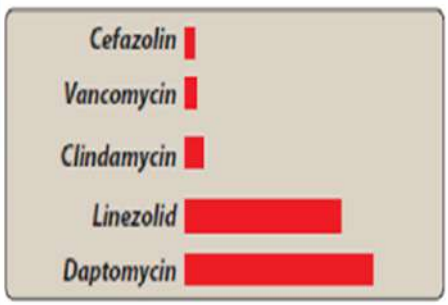


Figure 37.5
Relative cost of some drugs used for the treatment of Staphylococcus aureus.

Staphylococcus aureus (MRSA) generally includes one of the following: vancomycin, clindamycin, daptomycin, or linezolid.

❑ ROUTE OF ADMINISTRATION

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis.

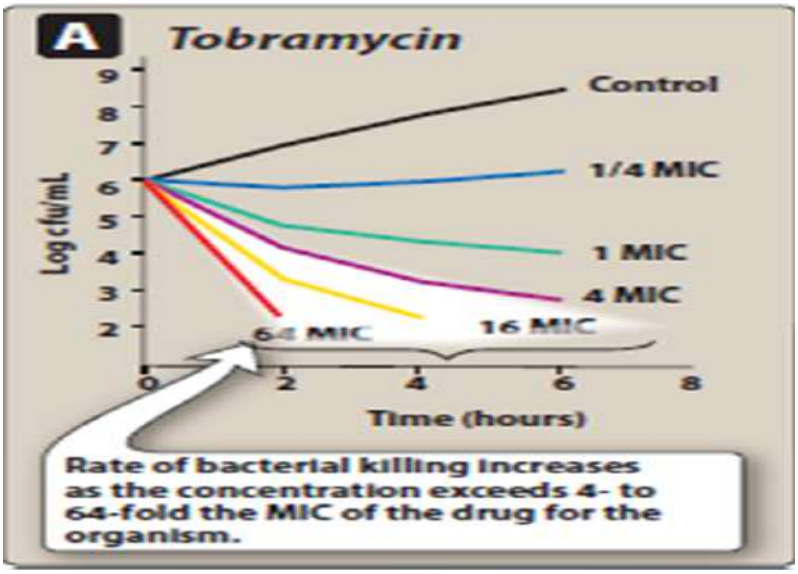
In hospitalized patients requiring intravenous therapy initially, the switch to oral agents should occur as soon as possible.

However, some antibiotics, *such as vancomycin, the aminoglycosides, and amphotericin B* are so poorly absorbed from the gastrointestinal (GI) tract that adequate serum levels cannot be obtained by oral administration.

Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections.

❑ DETERMINANTS OF RATIONAL DOSING

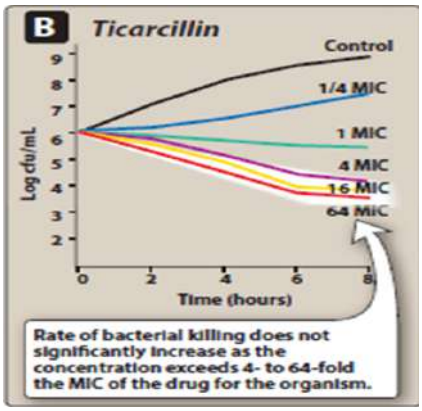
A. Concentration-dependent killing Certain antimicrobial agents, including aminoglycosides and daptomycin, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism. Giving drugs once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.



B. Time-dependent (concentration-independent) killing

In contrast, β-lactams, glycopeptides, macrolides, clindamycin, and linezolid do not exhibit concentration-dependent killing.

The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing.



C. Postantibiotic effect: PAE

The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.

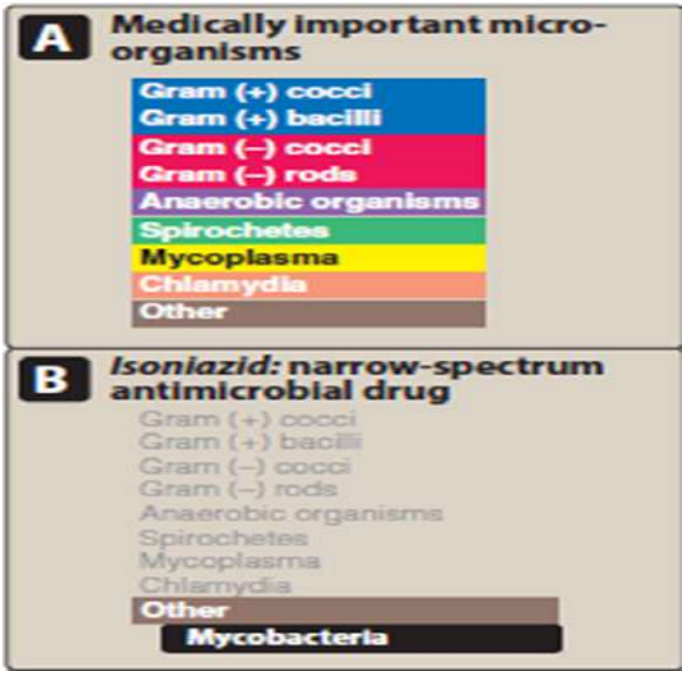
Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram negative bacteria.

❑ CHEMOTHERAPEUTIC SPECTRA

The clinically important bacteria have been organized into eight groups *based on Gram stain, morphology, and biochemical or other characteristics*. They are represented as a color-coded list (Figure 37.7A).

A. Narrow-spectrum antibiotics

Agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, isoniazid is active only against Mycobacterium tuberculosis.

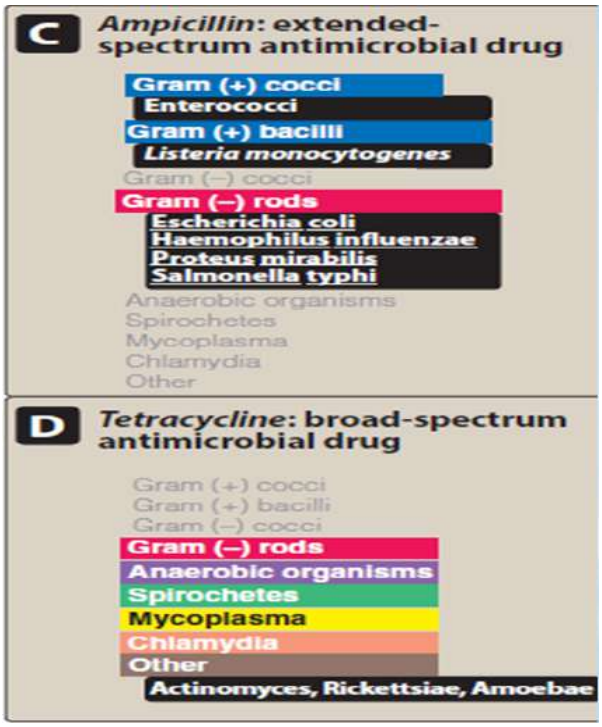


B. Extended-spectrum antibiotics

Extended spectrum is the term applied to antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, ampicillin

C. Broad-spectrum antibiotics

Drugs such as tetracycline, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics



❑ COMBINATIONS OF ANTIMICROBIAL DRUGS:

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately.

Multiple drugs used in combination are only indicated in special situations (for example, *when an infection is of unknown origin or in the treatment of enterococcal endocarditis*).

B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second.

For example, *bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins.*

Another concern is the development of antibiotic resistance by giving unnecessary combination therapy.

DRUG RESISTANCE:

Drug resistance is mediated by:

1. Modification of target sites: For example, *S.pneumoniae* resistance to β-lactam antimicrobials involves alterations in one or more of the major bacterial penicillin-binding proteins.

2. Decreased accumulation: Decreased uptake or increased efflux of an antibiotic. For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism, as seen with tetracyclines.

3. Enzymatic inactivation: The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms.

Examples of antibiotic-inactivating enzymes include

1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs.

2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating chloramphenicol or aminoglycosides; and

3) esterases that hydrolyze the lactone ring of macrolides.

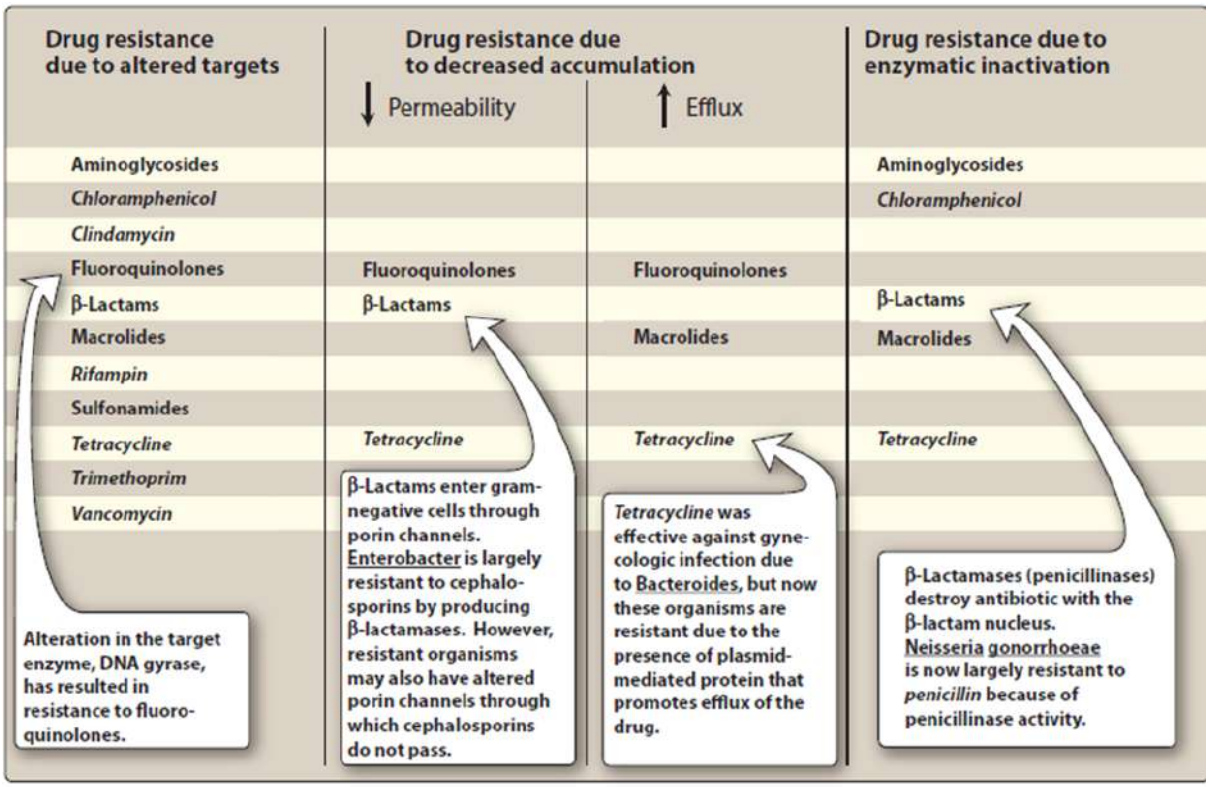


Figure 37.8 Hesham Alwali
Some mechanisms of resistance to antibiotics.

PROPHYLACTIC USE OF ANTIBIOTICS

Clinical situations, such as dental procedures and surgeries, require the use of antibiotics for the prevention rather than for the treatment of infections.

Because the unselective use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks.

The duration of prophylaxis should be closely observed to prevent the unnecessary development of antibiotic resistance.

COMPLICATIONS OF ANTIBIOTIC THERAPY

A. Hypersensitivity: the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity: For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the auditory hair cells.

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific anti-infective agents.

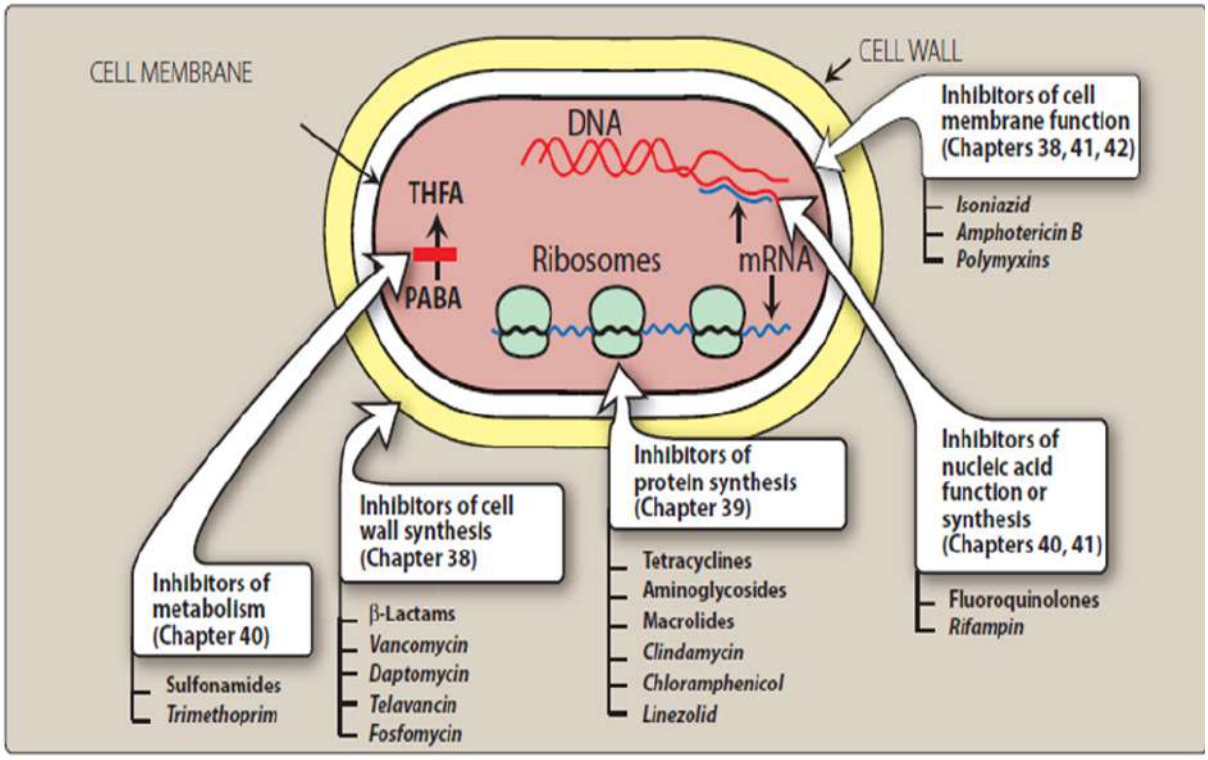


Figure 37.10
Haitham Alwali
Classification of some antimicrobial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.)

Cell Wall Inhibitors

Penicillins and cephalosporins are the major antibiotics that inhibit bacterial cell wall synthesis. They are called beta-lactams because of the unusual 4-member ring that is common to all their members .The beta-lactams include some of the most effective, widely used, and well-tolerated agents available for the treatment of microbial infections.

- Synthetic Production of Penicillin Professor Alexander Fleming, holder of the Chair of Bacteriology at London University, who first discovered the mould *Penicillium notatum*.
- Here in his laboratory at St Mary's, Paddington, London.

PENICILLINS

- *Amoxicillin* AMOXIL
- *Ampicillin* PRINCIPEN
- *Dicloxacillin* DYNAPEN
- *Nafcillin*
- *Oxacillin*
- *Penicillin G* PFIZERPEN
- *Penicillin V*
- *Piperacillin*
- *Ticarcillin*

CEPHALOSPORINS

- *Cefaclor* CECLOR
- *Cefadroxil* DURACEF
- *Cefazolin* KEFZOL
- *Cefdinir* OMNICEF
- *Cefepime* MAXIPIME
- *Cefixime* SUPRAX
- *Cefotaxime* CLAFORAN
- *Cefotetan* CEFOTAN
- *Cefoxitin* MEFOXIN
- *Cefprozil* CEFZIL
- *Ceftaroline* TEFLARO
- *Ceftazidime* FORTAZ
- *Ceftibuten* CEDAX
- *Ceftizoxime* CEFIZOX
- *Ceftriaxone* ROCEPHIN
- *Cefuroxime* CEFTIN
- *Cephalexin* KEFLEX

CARBAPENEMS

- *Doripenem* DORIBAX
- *Ertapenem* INVANZ
- *Imipenem/cilastatin* PRIMAXIN
- *Meropenem* MERREM

MONOBACTAMS

- *Aztreonam* AZACTAM

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

- *Clavulanic acid + amoxicillin* AUGMENTIN
- *Clavulanic acid + ticarcillin* TIMENTIN
- *Sulbactam + ampicillin* UNASYN
- *Tazobactam + piperacillin* ZOSYN

OTHER ANTIBIOTICS

- *Colistin* COLOMYCIN, COLY-MYCIN M
- *Daptomycin* CUBICIN
- *Fosfomycin* MONUROL
- *Polymyxin B* AEROSPORIN
- *Telavancin* VIBATIV
- *Vancomycin* VANCOCIN

PENICILLINS

Classification

All penicillins are derivatives of *6-aminopenicillanic acid* and contain a beta-lactam ring structure that is essential for antibacterial activity.

Penicillin subclasses have additional chemical substituents that confer differences in antimicrobial activity, susceptibility to acid and enzymatic hydrolysis, and biodisposition.

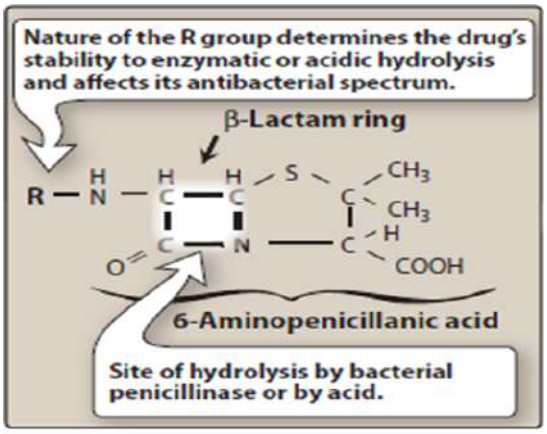


Figure 38.2
Structure of β-lactam antibiotics.

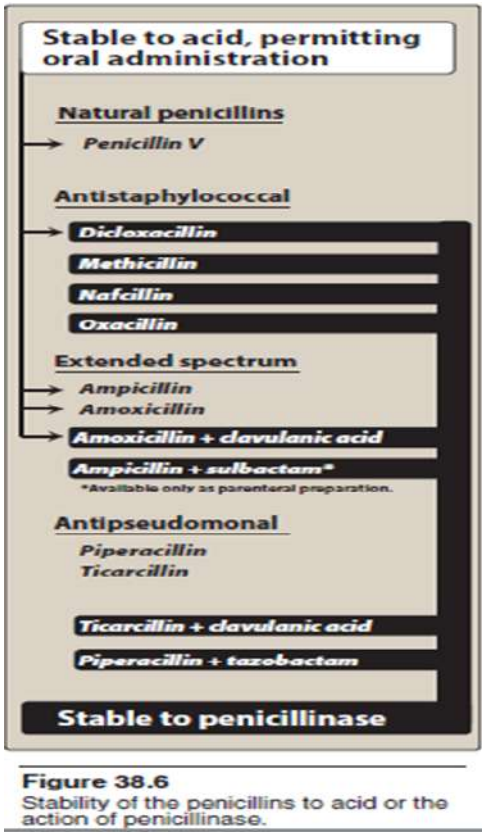


Figure 38.6
Stability of the penicillins to acid or the action of penicillinase.

Pharmacokinetics

A. Routes of administration:

1-The combination of *ampicillin with sulbactam*, *ticarcillin with clavulanic acid*, and *piperacillin with tazobactam*, and the antistaphylococcal penicillins *nafcillin and oxacillin* must be administered intravenously (IV) or intramuscularly (IM).

Penicillin V, amoxicillin, and dicloxacillin are available only as oral preparations. Others are effective by the oral, IV, or IM routes.

2- Depot forms:

Procaine penicillin G and benzathine penicillin G

are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

B. Absorption:

Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora.

Food decreases the absorption of all the penicillinase-resistant penicillins because as gastric emptying time increases, the drugs are destroyed by stomach acid. Therefore, they should be taken on an empty stomach.

C. Distribution:

All the penicillins distribute well & cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or (CSF) is insufficient for therapy unless these sites are inflamed.

D. Excretion:

The primary route of excretion is by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Nafcillin and oxacillin are metabolized in the liver.

Probenecid inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels.

Mechanisms of Action and Resistance

Beta-lactam antibiotics are bactericidal drugs. They *act to inhibit cell wall synthesis* by the following steps:

(1) Binding of the drug to specific enzymes (penicillin-binding proteins [PBPs]) located in the bacterial cytoplasmic membrane;

(2) inhibition of the transpeptidation reaction that cross-links the linear peptidoglycan
chain constituents of the cell wall; and

(3) activation of autolytic enzymes that cause lesions in the bacterial cell wall.

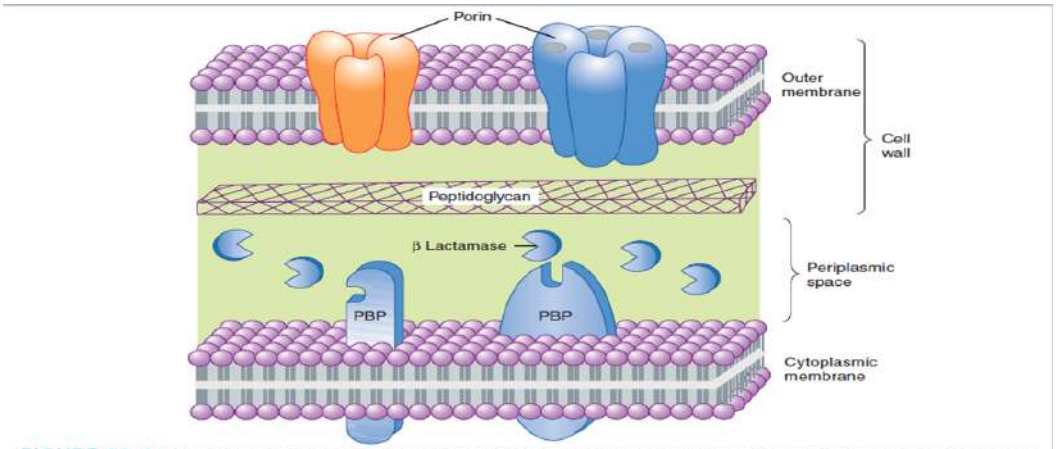


FIGURE 43–1 Beta-lactams and bacterial cell wall synthesis. The outer membrane shown in this simplified diagram is present only in gram-negative organisms. It is penetrated by proteins (porins) that are permeable to hydrophilic substances such as beta-lactam antibiotics.

Mechanism of bacterial resistance:

- The formation of beta-lactamases (penicillinases) by most staphylococci and many gram-negative organisms.
- ✓ Inhibitors of these bacterial enzymes (eg, clavulanic acid, sulbactam, tazobactam) are often used in combination with penicillins to prevent their inactivation.
- Structural change in target PBPs is responsible for methicillin resistance in staphylococci (MRSA) and for resistance to penicillin G in pneumococci (eg, PRSP, penicillin resistant *Streptococcus pneumoniae*) and *enterococci*.
- In some gram-negative rods (eg, *Pseudomonas aeruginosa*), changes in the porin structures in the outer cell wall membrane may contribute to resistance by impeding access of penicillins to PBPs.

Clinical Uses

1. Narrow-spectrum penicillinase-susceptible agents— Penicillin G is the prototype of a subclass of penicillins.

Clinical uses include therapy of infections caused by common streptococci, meningococci, gram-positive bacilli, and spirochetes.

Many strains of pneumococci (penicillin-resistant *S. pneumoniae* [PRSP] strains). *Staphylococcus aureus* and *Neisseria gonorrhoeae* are resistant via production of beta-lactamases.

penicillin G remains the drug of choice for syphilis. Activity against enterococci is enhanced by coadministration of aminoglycosides.

Penicillin V is an oral drug used mainly in oropharyngeal infections.

2. Very-narrow-spectrum penicillinase-resistant drugs—

This subclass of penicillins includes methicillin (the prototype, but rarely used owing to its nephrotoxic potential), nafcillin, and oxacillin.

Their primary use is in the treatment of known or suspected staphylococcal infections.

Methicillin-resistant (MR) staphylococci (*S. aureus* [MRSA] and *S. epidermidis* [MRSE]) are resistant to all penicillins and are often resistant to multiple antimicrobial drugs.

3. Wider-spectrum penicillinase-susceptible drugs

a. Ampicillin and amoxicillin has a wider spectrum of antibacterial activity than penicillin G. Their clinical uses include indications similar to penicillin G as well as infections resulting from *enterococci, Listeria monocytogenes, Escherichia coli, Proteus mirabilis, Haemophilus influenzae, and Moraxella catarrhalis*, although resistant strains occur.

When used in combination with inhibitors of penicillinases (eg, clavulanic acid), their antibacterial activity is often enhanced. In enterococcal and listerial infections, ampicillin is synergistic with aminoglycosides.

b. Piperacillin and ticarcillin

These drugs have activity against several gram-negative rods, including *Pseudomonas, Enterobacter,* and in some cases *Klebsiella species*.

Most drugs in this subgroup have synergistic actions with aminoglycosides against such organisms.

Piperacillin and ticarcillin are susceptible to penicillinases and are often used in combination with penicillinase inhibitors (eg, tazobactam and clavulanic acid) to enhance their activity.

E. Adverse effects

1. Allergy—Allergic reactions include urticaria, severe pruritus, fever, joint swelling, hemolytic anemia, nephritis, and anaphylaxis.

Methicillin causes interstitial nephritis, and nafcillin is associated with neutropenia.

Complete cross-allergenicity between different penicillins should be assumed.

2. Gastrointestinal disturbances— Nausea and diarrhea may occur with oral penicillins, especially with ampicillin. Gastrointestinal upsets may be caused by direct irritation or by overgrowth of gram-positive organisms or yeasts.

CEPHALOSPORINS:

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins.

Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to *7-aminocephalosporanic acid*.

Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be *more resistant than the penicillins to certain β-lactamases*.

Pharmacokinetics:

Several cephalosporins are available for oral use, but most are administered parenterally.

Cephalosporins with side chains may undergo hepatic metabolism, but the *major elimination mechanism* for drugs in this class is *renal excretion via active tubular secretion.*

Cefoperazone and ceftriaxone are excreted mainly in the bile.

Most *first- and second-generation cephalosporins* do *not enter the cerebrospinal fluid* even when the meninges are inflamed.

Mechanisms of Action and Resistance

Cephalosporins bind to PBPs on bacterial cell membranes to inhibit bacterial cell wall synthesis by mechanisms similar to those of the penicillins. *Cephalosporins are bactericidal* against susceptible organisms.

Cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of *other betalactamases* that can inactivate cephalosporins.

Resistance can also result from decreases in membrane permeability to cephalosporins and from changes in PBPs.

Methicillin-resistant staphylococci are also resistant to cephalosporins.

Clinical Uses

1. **First-generation drugs**—Cefazolin (parenteral) and cephalexin (oral) are examples of this subgroup.

They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E coli* and *K pneumoniae* are also sensitive.

Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in selected conditions.

2. **Second-generation**

have slightly less activity against gram-positive organisms than the first-generation drugs but *have an extended gram-negative coverage*.

Marked differences in activity occur among the drugs in this subgroup. Examples of clinical uses *include infections caused by the anaerobe Bacteroides fragilis* (cefotetan, cefoxitin) and sinus, ear, and respiratory infections caused by *H influenzae or M catarrhalis* (cefamandole, cefuroxime, cefaclor).

3. **Third-generation drugs**: (eg, ceftazidime, cefoperazone, cefotaxime)

include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate the blood-brain barrier (EXCEPT cefoperazone and cefixime).

- Most are active against *Providencia, Serratia marcescens*, and beta-lactamase producing strains of *H influenzae and Neisseria*.
- Ceftriaxone and cefotaxime are currently the most active cephalosporins against penicillin-resistant pneumococci (PRSP strains)
- Also have activity against *Pseudomonas* (cefoperazone, ceftazidime) and *B fragilis* (ceftizoxime)
- Ceftriaxone (parenteral) and cefixime (oral), currently drugs of choice in gonorrhea.

4. Fourth-generation drugs

- Cefepime is more *resistant to beta-lactamases* produced by gram-negative organisms, including *Enterobacter, Haemophilus, Neisseria*, and some *penicillin resistant pneumococci*.
- Cefepime combines the gram-positive activity of first-generation agents with the wider gram-negative spectrum of third-generation cephalosporins.
- Ceftaroline has activity in infections caused by methicillin-resistant staphylococci.

Adverse effects

1. Allergy—Cephalosporins cause a range of allergic reactions from skin rashes to anaphylactic shock. These reactions occur *less frequently with cephalosporins than with penicillins*.

Complete cross-hypersensitivity between different cephalosporins should be assumed. Cross-reactivity between penicillins and cephalosporins is incomplete (5–10%).

2- Cephalosporins may cause *pain at intramuscular* injection sites and *phlebitis* after I.V administration.

3-They may *increase the nephrotoxicity of aminoglycosides* when the two are administered together.

OTHER BETA-LACTAM DRUGS:

A. Aztreonam

- Aztreonam is a monobactam that is *resistant to beta-lactamases* produced by certain gram-negative rods, including *Klebsiella, Pseudomonas, and Serratia*. *The drug has no activity against gram positive bacteria or anaerobes*.
- Aztreonam is administered intravenously and is eliminated via renal tubular secretion. Its half-life is prolonged in renal failure.
- *Adverse effects include* gastrointestinal upset with possible superinfection, vertigo and headache, and rarely hepatotoxicity, skin rash (NO cross allergenicity with penicillins).

B. Imipenem, Doripenem, Meropenem, and Ertapenem: parenterally

- These drugs are carbapenems (chemically different from penicillins but retaining the beta-lactam ring structure)
- They have wide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes.
- For *pseudomonal infections*, they are often used in combination with an aminoglycoside.
- MRSA strains of staphylococci are resistant.
- Imipenem is rapidly *inactivated by renal dehydropeptidase-I* and is administered in fixed combination with cilastatin, an inhibitor of this enzyme. *Cilastatin increases the plasma half life of imipenem and inhibits the formation of potentially nephrotoxic metabolite*.

- Adverse effects of imipenem-cilastatin include *gastrointestinal distress, skin rash*, and, at very high plasma levels, CNS toxicity (confusion, encephalopathy, seizures).

- *There is partial cross allergenicity with the penicillins.*

C. Beta-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins.

- They are most active against plasmid-encoded beta-lactamases such as those produced by *gonococci, streptococci, E coli*, and *H influenzae*.

- They are NOT good inhibitors of inducible chromosomal beta-lactamases formed by *Enterobacter, Pseudomonas, and Serratia.*

OTHER CELL WALL OR MEMBRANE-ACTIVE AGENTS:

A. Vancomycin

- Vancomycin is a bactericidal glycoprotein that binds to the *d-Ala-d-Ala* terminal of the nascent peptidoglycan pentapeptide side chain and *inhibits transglycosylation*. This action prevents elongation of the peptidoglycan chain and interferes with crosslinking.

- Resistance in strains of enterocci (vancomycin-resistant enterococci [VRE]) and staphylococci (vancomycin-resistant S aureus [VRSA]) involves a decreased affinity of vancomycin for the binding site.

- Vancomycin has a narrow spectrum of activity and is *used for serious infections caused by drug-resistant gram-positive* organisms, including methicillin-resistant staphylococci (MRSA) and in combination with ceftriaxone for treatment of (PRSP). Vancomycin is a backup drug for treatment of infections caused by *Clostridium difficile*.

- ❑ Toxic effects of vancomycin include chills, fever, phlebitis, ototoxicity, and nephrotoxicity. Rapid intravenous infusion may cause diffuse flushing ("red man syndrome") from histamine release.

B. Fosfomycin

- Fosfomycin is an *antimetabolite inhibitor of cytosolic enolpyruvate transferase*. This action prevents the formation of N-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation.
- Fosfomycin is *excreted by the kidney*, with urinary *levels exceeding the minimal inhibitory concentrations* (MICs) ,So It is indicated for urinary tract infections caused by *E. coli* or *E. faecalis*. It maintains high concentrations in the urine over several days, allowing for a one-time dose
- adverse effects include diarrhea, vaginitis, nausea, and headache.

C. Daptomycin

- Daptomycin is a bactericidal, a novel cyclic lipopeptide with spectrum similar to vancomycin but active against vancomycin-resistant strains of enterococci and staphylococci.
- Daptomycin is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus.
- Daptomycin is inactivated by pulmonary surfactants; thus, it should *never* be used in the treatment of pneumonia.
- Creatine phosphokinase should be monitored since daptomycin may cause myopathy.

D. POLYMYXINS

- Are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and ultimately cell death.
- Polymyxins are concentration-dependent bactericidal agents with activity against P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter species, and Enterobacter species.
- Only two forms of polymyxin are in clinical use today, polymyxin B and colistin (polymyxin E). Polymyxin B is available in parenteral, ophthalmic, otic, and

topical preparations. Colistin is only available as a prodrug, colistimethate sodium, which is administered IV or inhaled via a nebulizer.

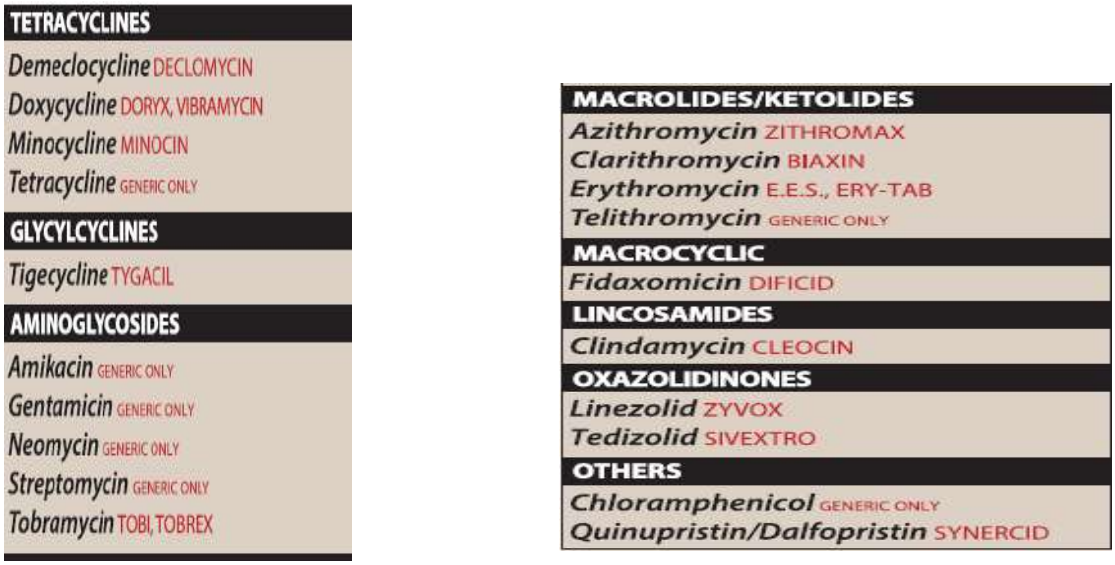
- The use of these drugs has been limited for a long time, due to the increased risk of nephrotoxicity and neurotoxicity (slurred speech, muscle weakness) when used systemically.

Protein Synthesis Inhibitors

A number of antibiotics exert their antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis. Most of these agents exhibit bacteriostatic activity. Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits).

In general, selectivity for bacterial ribosomes minimizes Potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells.

However, high concentrations of drugs such as *chloramphenicol* or the *tetracyclines* may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.



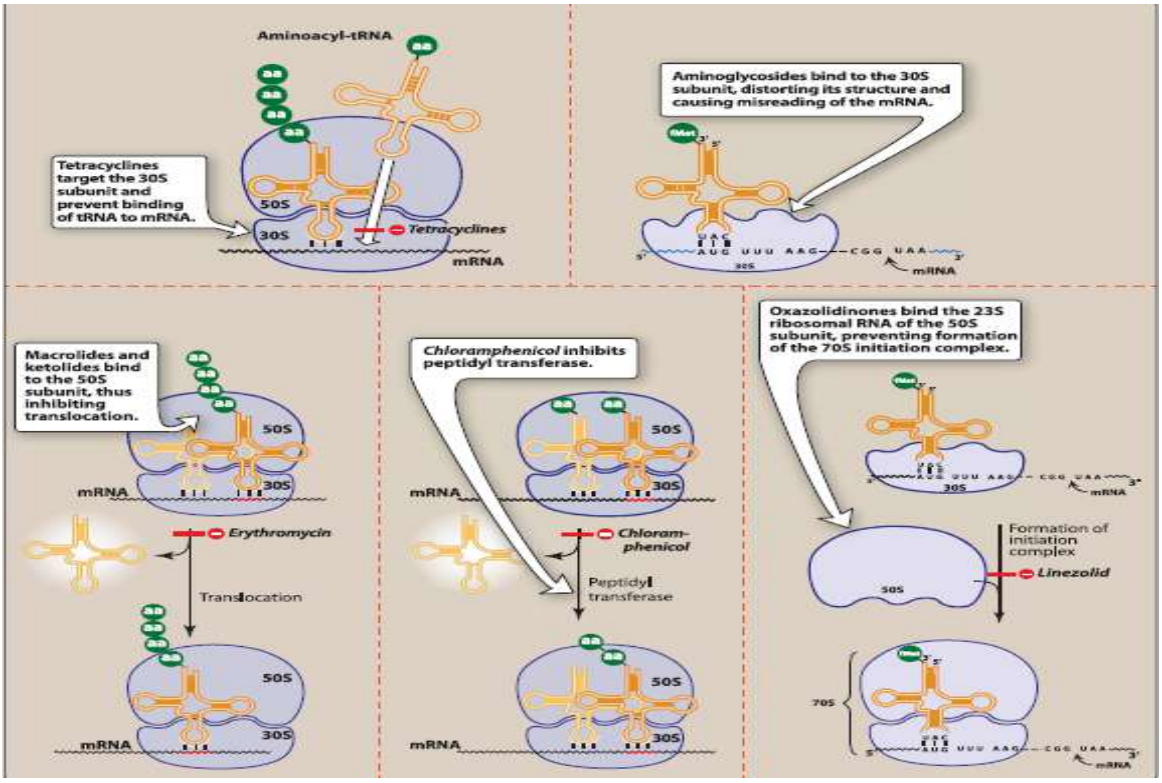
Summary of protein synthesis inhibitors.

TETRACYCLINES:

A. Mechanism of action

Tetracyclines enter susceptible organisms via passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Tetracyclines concentrate intracellularly in susceptible

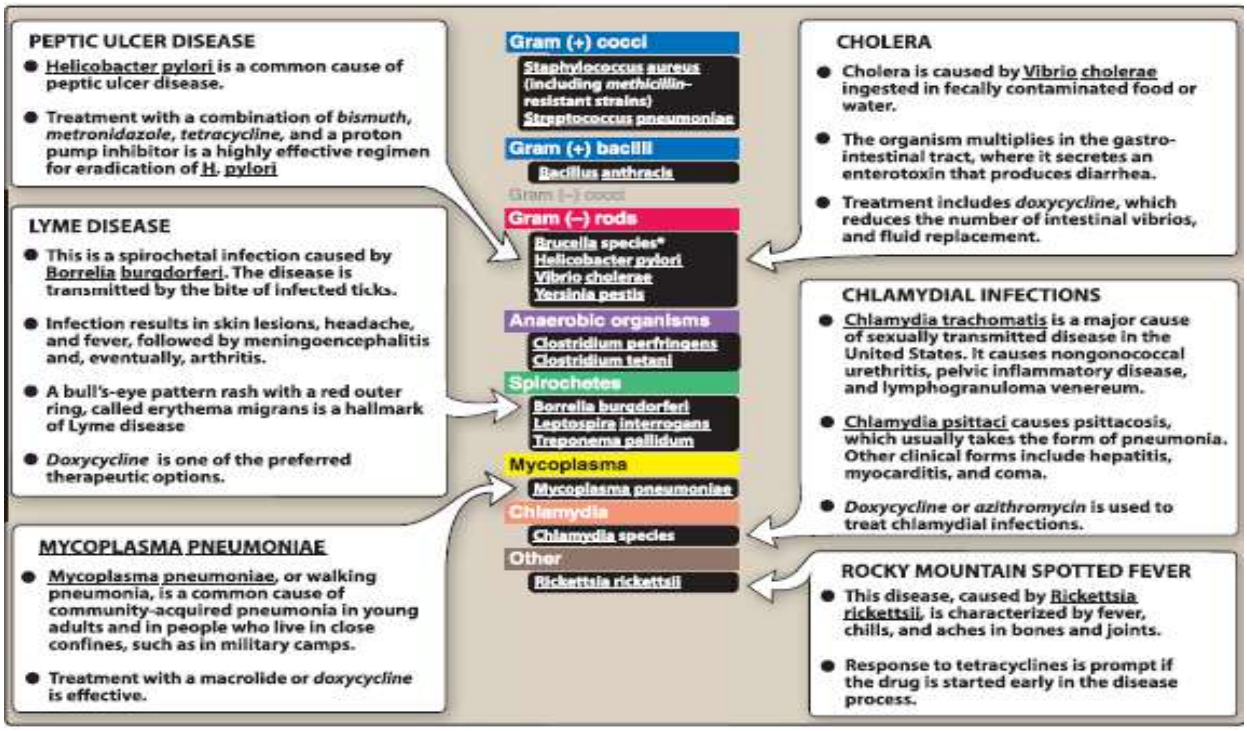
organisms. The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mANA-ribosome complex, thereby inhibiting bacterial protein synthesis.



Mechanisms of action of the various protein synthesis inhibitors. aa = amino acid.

B. Antibacterial spectrum

The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species. They are commonly used in the treatment of acne and Chlamydia infections.



Typical therapeutic applications of tetracyclines. *A *tetracycline+ gentamicin.*

C. Resistance

The most commonly encountered naturally occurring resistance to tetracyclines is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation. Other mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Resistance to one tetracycline does not confer universal resistance to all tetracyclines, and the development of cross-resistance may be dependent on the mechanism of resistance.

D. Pharmacokinetics

1. Absorption: Tetracyclines are adequately absorbed after oral ingestion. Administration with dairy products or other substances that contain divalent and trivalent cations {for example, magnesium, calcium and aluminum antacids, or iron supplements} decreases absorption, particularly for *tetracycline*, due to the formation of non-absorbable chelates. Both *doxycycline* and *minocycline* are available as oral and intravenous {IV} preparations.

2. Distribution: The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification {for example, teeth and bones} or to tumors that have high calcium content. Penetration into most body fluids is adequate. Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid {CSF}. *Minocycline* also achieves high concentrations in saliva and tears, rendering it useful in eradicating the meningococcal carrier state. All *tetracyclines* cross the placental barrier and concentrate in fetal bones and dentition.

3. Elimination: *Tetracycline* is primarily eliminated unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. *Doxycycline* is preferred in patients with renal dysfunction, as it is primarily eliminated via the bile into the feces.

E. Adverse effects

1. Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through coadministration with food {other than dairy products) or fluids and the use of capsules rather than tablets. [Note: *Tetracycline* should be taken on an empty stomach.]

2. Effects on calcified tissues: Deposition in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth. For this reason, the use of tetracyclines is limited in pediatrics.

3. Hepatotoxicity: Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.

4. Phototoxicity: Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with *tetracycline* and *demeclocycline*. Patients should be advised to wear adequate sun protection.

5. Vestibular dysfunction: Dizziness, vertigo, and tinnitus may occur particularly with *minocycline,* which concentrates in the endolymph of the ear and affects function.

6. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

7. Contraindications: The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

GLYCYLCYCLINES

Tigecycline, a derivative of *minocycline,* is the first member of the glycylcycline antimicrobial class. It is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

A. Mechanism of action

Tigecycline exhibits bacteriostatic action by reversibly binding to the 305 ribosomal subunit and inhibiting bacterial protein synthesis.

B. Antibacterial spectrum

Tigecycline exhibits broad-spectrum activity that includes *methicillin- resistant* staphylococci (MRSA), multidrug-resistant streptococci, vancomycin-resistant enterococci (VRE), extended-spectrum P-lactamase--producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms.

Tigecycline is not active against Morganella, Proteus, Providencia. or Pseudomonas species.

C. Resistance

Tigecycline was developed to overcome the emergence of tetracycline class-resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. Resistance to *tigecycline* has been observed and is primarily attributed to overexpression of efflux pumps.

D. Pharmacokinetics

Following IV infusion, *tigecycline* exhibits a large volume of distribution. It penetrates tissues well but achieves low plasma concentrations. Consequently, *tigecycline* is a poor option for bloodstream infections. The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment; however, a dose reduction is recommended in severe hepatic dysfunction.

E. Adverse effects

Tigecycline is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported with therapy. Elevations in liver enzymes and serum creatinine may also occur. All-cause mortality in patients treated with *tigecycline* is higher than with other agents. A boxed warning states that *tigecycline* should be reserved for use in situations when alternative treatments are not suitable. Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy. *Tigecycline* may decrease the clearance of *warfarin.* Therefore, the international normalized ratio should be monitored closely when *tigecycline* is coadministered with *warfarin.*

AMINOGLYCOSIDES:

A. Mechanism of action

Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. Inside the cell, they bind the 30S ribosomal subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code.

Aminoglycosides have concentration-dependent bactericidal activity; They also exhibit a postantibiotic effect (PAE), which is continued bacterial suppression after drug concentrations fall below the MIC. Because of these properties, high-dose extended-interval dosing is commonly utilized. This dosing strategy also reduces the risk of nephrotoxicity and increases convenience.

B. Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram-negative bacilli, including those that may be multidrug resistant, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter sp. Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect, particularly in the treatment of Enterococcus faecalis and Enterococcus faecium infective endocarditis.

C. Resistance

Resistance to aminoglycosides occurs via: 1) efflux pumps, 2) decreased uptake, and/or 3) modification and inactivation by plasmid- associated synthesis of enzymes. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed. [Note: *Amikacin* is less vulnerable to these enzymes than other antibiotics in this group.]

D. Pharmacokinetics

1. Absorption: The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration; therefore, all aminoglycosides (except *neomycin* must be given parenterally to achieve adequate serum concentrations [Note: *Neomycin* is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally to decontaminate the gastrointestinal tract prior to colorectal surgery.]

2. Distribution: Because of their hydrophilicity, aminoglycoside tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable. Concentrations achieved in CSF are inadequate, even in the presence of inflamed meninges.

For central nervous system infections, the intrathecal or intraventricular routes may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. Elimination: More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine . Accumulation occurs in patients with renal dysfunction; thus, dose adjustments are required. *Neomycin* is primarily excreted unchanged in the feces.

E. Adverse effects

The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. Ototoxicity: Ototoxicity (vestibular and auditory) is directly related to high peak plasma concentrations and the duration of treatment. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics, are particularly at risk. Vertigo (especially in patients receiving *streptomycin)* may also occur.

2. Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis.

3. Neuromuscular paralysis:high doses infused over a short period or concurrent administration with neuromuscular blockers. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block that causes neuromuscular paralysis.

4. Allergic reactions: Contact dermatitis is a common reaction to topically applied *neomycin.*

MACROLIDES AND KETOLIDES:

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* was the first of these drugs to have clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals with an allergy to β-lactam antibiotics. *Clarithromycin* (a methylated form of *erythromycin)* and *azithromycin* (having a larger lactone ring) have some features in common with, and others that improve upon, *erythromycin. Telithromycin* a semisynthetic derivative of *erythromycin,* is a "ketolide" antimicrobial agent.

A. Mechanism of action

The macrolides and ketolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis. They

may also interfere with other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical to or in close proximity to that for *clindamycin* and *chloramphenicol.*

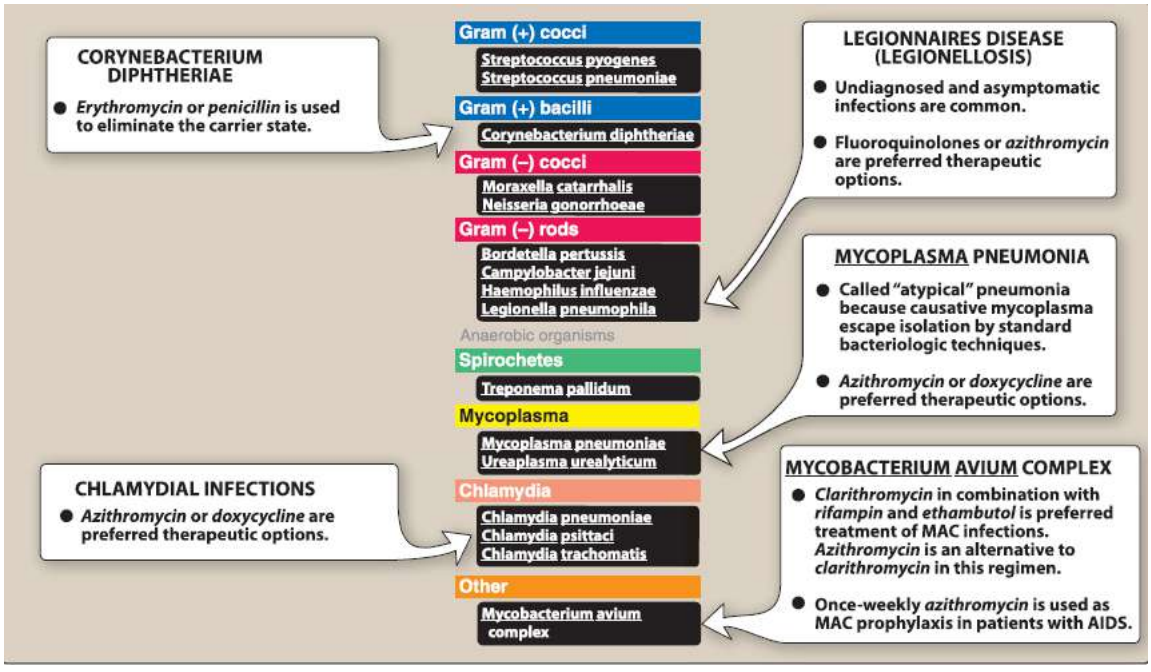
B. Antibacterial spectrum

1. Erythromycin: This drug is effective against many of the same organisms as *penicillin G* ; therefore, it may be considered as an alternative in patients with *penicillin* allergy.

2. Clarithromycin: *Clarithromycin* has activity similar to *erythromycin,* but it is also effective against *Haemophilus influenzae* and has greater activity against intracellular pathogens such as *Chlamydia, Legionella, Moraxella, Ureaplasma species*, and *Helicobacter pylori*

3. Azithromycin: Although less active than *erythromycin* against streptococci and staphylococci, *azithromycin* is far more active against respiratory pathogens such as *H. influenzae* and *Moraxella catarrhalis*.

Typical therapeutic applications of macrolides



4. Telithromycin: *Telithromycin* has an antimicrobial spectrum similar to that of *azithromycin.* Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms that render *macrlides* ineffective.

C. Resistance

Resistance to macrolides is associated with: 1) the inability of the organism to take up the antibiotic, 2) the presence of efflux pumps, 3) a decreased affinity of the 50S ribosomal subunit for the antibiotic due to methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms, and 4) the presence of plasmid-associated *erythromycin* esterases in gram-negative organisms such as the Enterobacteriaceae. *Erythromycin* has limited clinical use due to increasing resistance. Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin. Telithromycin* may be effective against macrolide-resistant organisms.

D. Pharmacokinetics

1. Absorption: The *erythromycin* base is destroyed by gastric acid; thus, either enteric-coated tablets or esterified forms of the antibiotic are administered and all have adequate oral absorption . *Clarithromycin, azithromycin,* and *telithromycin* are stable in stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin. Telithromycin* is administered orally without regard to meals. *Erythromycin* and *azithromycin* are available in IV formulations.

2. Distribution: *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuse into prostatic fluid, and it also accumulates in macrophages. All four drugs concentrate in the liver. *Clarithromycin, azithromycin,* and *telithromycin* are widely distributed in the tissues. *Azithromycin* has the largest volume of distribution of the four drugs

3. Elimination: *Erythromycin* and *telithromycin* undergo hepatic metabolism. They inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system. Interference with the metabolism of drugs such as *theophylline,* statins, and numerous antiepileptics has been reported for *clarithromycin.*

4. Excretion: *Azithromycin* is primarily concentrated and excreted in the bile as active drug. *Erythromycin* and its metabolites are also excreted in the bile. In contrast, *clarithromycin* is hepatically metabolized, and the active drug and its metabolites are mainly excreted in the urine. The dosage of this drug should be adjusted in patients with renal impairment.

E. Adverse effects

1. Gastric distress and motility: Gastrointestinal upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with *erythromycin).* Higher doses of *erythromycin* lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes employed for the treatment of gastroparesis or postoperative ileus.

2. Cholestatic jaundice: This adverse effect occurs most commonly with the estolate form of *erythromycin* (not used in the United States); however, it has been reported with other formulations and other agents in this class.

3. Ototoxicity: Transient deafness has been associated with *erythromycin,* especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.

4. QTc prolongation: Macrolides and ketolides may prolong the OTc interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.

5. Contraindication: Patients with hepatic dysfunction should be treated cautiously with *erythromycin, telithromycin,* or *azithromycin,* because these drugs accumulate in the liver. Severe hepatotoxicity with *telithromycin* has limited its use.

6. Drug Interactions: *Erythromycin, telithromycin,* and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds. An interaction with *digoxin* may occur. One theory to explain this interaction is that the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin,* leading to greater reabsorption of *digoxin* from the enterohepatic circulation.

FIDAXOMICIN

Fidaxomicin is a macrocyclic antibiotic with a structure similar to the macrolides; however, it has a unique mechanism of action. *Fidaxomicin* acts on the sigma subunit of RNA polymerase, thereby disrupting bacterial transcription, terminating protein synthesis and resulting in cell death in susceptible organisms.

Fidaxomicin has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes. While it possesses activity against staphylococci and enterococci, it is used primarily for its bactericidal activity against Clostridium difficile. Because of the unique target site, cross-resistance with other antibiotic classes has not been documented.

Following oral administration, *fidaxomicin* has minimal systemic absorption and primarily remains within the gastrointestinal tract. This is ideal for the treatment of C. difficile infection, which occurs in the gut.

The most common adverse effects include nausea, vomiting, and abdominal pain. Anemia and neutropenia have been observed infrequently. Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred. *Fidaxomicin* should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.

CHLORAMPHENICOL

The use of chloramphenicol, a broad-spectrum antibiotic, is restricted to life-threatening infections for which no alternatives exist.

A. Mechanism of action

Chloramphenicol binds reversibly to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction . Because of some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating *chloramphenicol* concentrations, producing bone marrow toxicity. [Note: The oral formulation of *chloramphenicol* was removed from the US market due to this toxicity.]

B. Antibacterial spectrum

Chloramphenicol is active against many types of microorganisms including chlamydiae, rickettsiae, spirochetes, and anaerobes. The drug is primarily bacteriostatic, but it may exert bactericidal activity depending on the dose and organism.

C. Resistance

Resistance is conferred by the presence of enzymes that inactivate *chloramphenicol.* Other mechanisms include decreased ability to penetrate the organism and ribosomal binding site alterations.

D. Pharmacokinetics

Chloramphenicol is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF. *Chloramphenicol* primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine. Dose reductions are necessary in patients with liver dysfunction or cirrhosis. *Chloramphenicol* is also secreted into breast milk and should be avoided in breastfeeding mothers.

E. Adverse effects

1. Anemias: Patients may experience dose-related anemia, hemolytic anemia (observed in patients with glucose-6-phosphate dehydrogenase deficiency), and aplastic anemia. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

2. Gray baby syndrome: Neonates have a low capacity to glucuronidate the antibiotic, and they have underdeveloped renal function, which decreases their ability to excrete the drug. This leads to drug accumulation to concentrations that interfere with the function of mitochondrial ribosomes, causing poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death. Adults who have received very high doses of *chloramphenicol* may also exhibit this toxicity.

3. Drug Interactions: *Chloramphenicol* inhibits some of the hepatic mixed-function oxidases, preventing the metabolism of drugs such as *warfarin* and *phenytoin,* which may potentiate their effects.

CLINDAMYCIN

Clindamycin has a mechanism of action that is similar to that of the macrolides. *Clindamycin* is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and streptococcus, and anaerobic bacteria.

Resistance mechanisms are the same as those for *erythromycin,* and cross-resistance has been described. C. difficile is resistant to *clindamycin,* and the utility of *clindamycin* for gram-negative anaerobes (for example, Bacteroides sp.) is decreasing due to increasing resistance.

Clindamycin is available in both IV and oral formulations, but use of oral *clindamycin* is limited by gastrointestinal intolerance. It distributes well into all body fluids but exhibits poor entry into the CSF. *Clindamycin* undergoes extensive oxidative metabolism to active and inactive products and is excreted into bile and urine. Low urinary excretion of active drug limits its clinical utility for urinary tract infections. Accumulation has been reported in patients with either severe renal impairment or hepatic failure. In addition to skin rash, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of C. difficile. Oral administration of either *metronidazole* or *vancomycin* is usually effective in the treatment of C. difficile infection.

QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin is a mixture of two streptogramins in a ratio of 30 to 70, respectively. Due to significant adverse effects, this combination drug is normally reserved for the treatment of severe infections caused by *vancomycin-resistant* Enterococcus faecium (VRE) in the absence of other therapeutic options.

A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome. *Dalfopristin* disrupts elongation by interfering with the addition of new amino acids to the peptide chain. *Quinupristin* prevents elongation similar to the macrolides and causes release of incomplete peptide chains. Thus, they synergistically interrupt

protein synthesis. The combination drug has bactericidal activity against most susceptible organisms and has a long PAE.

B. Antibacterial spectrum

Quinupristinldalfopristin is active primarily against gram-positive cocci, including those resistant to other antibiotics. Its primary use is for the treatment of E. faecium infections, including VRE strains, against which it is bacteriostatic. The drug is not effective against E. faecalis.

C. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 238 ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid associated acetyltransferase inactivates *dalfopristin.* An active efflux pump can also decrease levels of the antibiotics in bacteria.

D. Pharmacokinetics

Quinupristinldalfopristin is available intravenously. It does not achieve therapeutic concentrations in CSF. Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

E. Adverse effects

Venous irritation commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line.

Hyperbilirubinemia occurs in about 25% of patients, resulting from a competition with the antibiotic for excretion. Arthralgia and myalgia have been reported when higher doses are administered. *Quinupristin/dalfopristin* inhibits the cytochrome P450 CYP3A4 isoenzyme, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

OXAZOLIDINONES

Linezolid and *tedizolid* are synthetic oxazolidinones developed to combat gram-positive organisms, including resistant isolates such as *methicillin-resistant* Staphylococcus aureus, VRE, and *penicillin-resistant* streptococci.

A. Mechanism of action

Linezolid and *tedizolid* bind to the bacterial 23S ribosomal RNA of the 50S subunit, thereby inhibiting the formation of the 70S initiation complex and translation of bacterial proteins.

B. Antibacterial spectrum

The antibacterial action of the oxazolidinones is directed primarily against gram-positive organisms such as staphylococci, streptococci, and enterococci, Corynebacterium species and Listeria monocytegenes. It is also moderately active against Mycobacterium tuberculosis. The main clinical use of *linezolid* and *tedizolid* is to treat infections caused by drug-resistant gram-positive organisms.

Like other agents that interfere with bacterial protein synthesis, *linezolid* and *tedizolid* are bacteriostatic; however, *linezolid* has bactericidal activity against streptococci. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. Because they are bacteriostatic, the oxazolidinones are not recommended as first-line treatment for MRSA bacteremia.

C. Resistance

Resistance primarily occurs via reduced binding at the target site. Reduced susceptibility and resistance have been reported in S. aureus and Enterococcus sp. Cross-resistance with other protein synthesis inhibitors does not occur.

D. Pharmacokinetics

Linezolid and *tedizolid* are well absorbed after oral administration. IV formulations are also available. These drugs distribute widely throughout the body. Although the metabolic pathway of *linezolid* has not been fully determined, it is known that it is metabolized via oxidation to two inactive metabolites. The drug is excreted

both by renal and non-renal routes. *Tedizolid* is metabolized by sulfation, and the majority of elimination occurs via the liver, and drug is mainly excreted in the feces. No dose adjustments are required for either agent for renal or hepatic dysfunction.

E. Adverse effects

The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash. Thrombocytopenia has been reported, usually in patients taking the drug for longer than 10 days.

Linezolid and *tedizolid* possess nonselective monoamine oxidase activity and may lead to serotonin syndrome if given concomitantly with large quantities of tyramine-containing foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. The condition is reversible when the drug is discontinued. Irreversible peripheral neuropathies and optic neuritis causing blindness have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

I- Fluoroquinolone

The discovery of quinolone antimicrobials led to the development of numerous compounds utilized in clinical practice. Following the synthesis of nalidixic acid in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance. Due to these enhancements, quinolone antimicrobials were rapidly integrated into human and agricultural medicine. Unfortunately, overuse resulted in rising rates of resistance in gram-negative and gram-positive organisms, increased frequency of Clostridium difficile infections, and identification of numerous untoward adverse effects. Consequently, these agents have been relegated to second-line options for various indications.

Summary of drugs described in this lecture

Mechanism of action

Most bacterial species maintain two distinct type II topoisomerases that assist with deoxyribonucleic acid (DNA) replication, (DNA gyrase), and topoisomerase IV. DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA and introducing negative supercoils. Topoisomerase IV assists in separating daughter chromosomes once replication is completed. fluoroquinolones bind to these enzymes and interfere with DNA ligation. This interference increases the number of permanent chromosomal breaks, triggering cell lysis. In general, fluoroquinolones have different targets for gram-negative (DNA gyrase) and gram-positive organisms (topoisomerase IV), resulting in rapid cell death.

Antimicrobial spectrum

Fluoroquinolones are bactericidal and exhibit area-under-the-curve/minimum inhibitory concentration (AUC/MIC)-dependent killing. A major facet of their development centered on improving microbiologic coverage. Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration. These changes enhanced activity against a variety of pathogens including Aerobic gram-negative and gram-positive organisms, atypical organisms (for example, chlamydia, legionella, and mycoplasma spp.), and Anaerobes. Based on the impact of these structural changes, fluoroquinolones are often classified according to the spectrum of activity.

First-generation compounds (for example, nalidixic acid) were narrow-spectrum agents with activity against aerobic gram-negative bacilli, mostly Enterobacteriaceae.

Second-generation compounds (for example, ciprofloxacin) exhibit improved intracellular penetration and broadened coverage, which includes Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp.

Third-generation compounds (for example, levofloxacin) maintain the bacterial spectrum of second-generation agents, with improved activity against Streptococcus spp., including S. pneumoniae, methicillin-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia, and Mycobacterium spp.

Fourth-generation compounds (moxifloxacin, gemifloxacin, and delafloxacin) have enhanced gram-positive activity, including Staphylococcus and Streptococcus spp. Delafloxacin has activity against methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcus faecalis. Further, delafloxacin and moxifloxacin have activity against Bacteroides fragilis and Prevotella spp., while maintaining activity against Enterobacteriaceae and Haemophilus influenzae. From this group, only delafloxacin has activity against Pseudomonas aeruginosa. Lastly, these agents maintain atypical coverage, with moxifloxacin and delafloxacin showing activity against Mycobacteria spp. Common therapeutic applications of fluoroquinolones are shown in Figure 31.2.

Resistance

Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens. High-level fluoroquinolone resistance is primarily driven by chromosomal mutations within topoisomerases, decreased entry, efflux systems, and modifying enzymes play a role.

Mechanisms responsible for resistance include the following:

1. Altered target binding

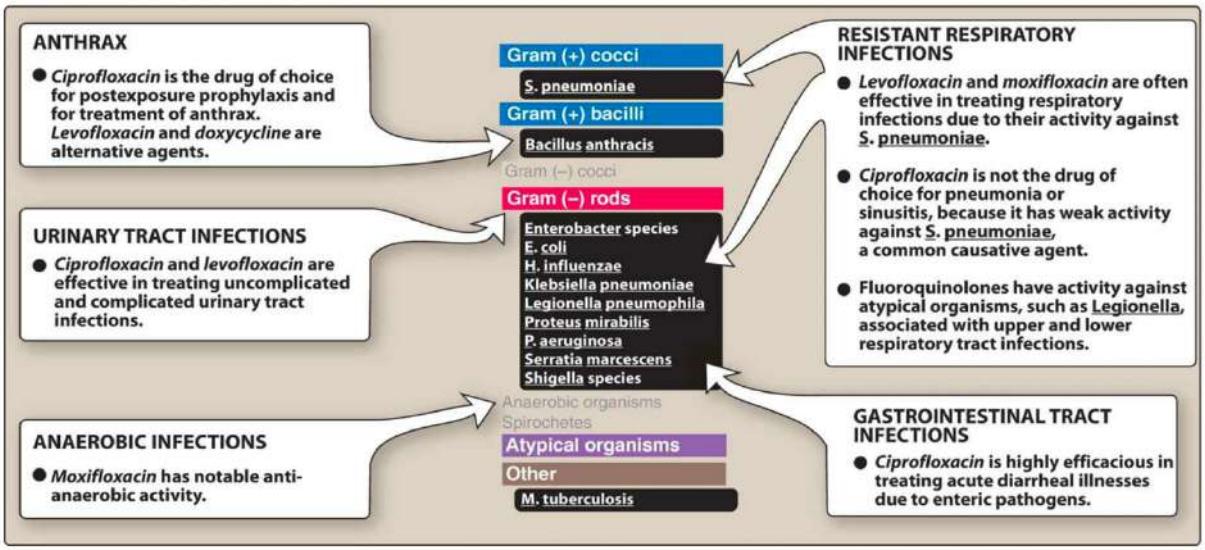


Figure 31.2 Typical therapeutic applications of fluoroquinolones.

Mutations in bacterial genes encoding DNA gyrase or topoisomerase IV (for example, gyrA or parC) alter target site structure and reduce the binding efficiency of fluoroquinolones.

2. Decreased accumulation

Reduced intracellular concentration is linked to 1) a reduction in membrane permeability or 2) efflux pumps. Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus limiting drug access to topoisomerases. Efflux pumps actively remove fluoroquinolones from the cell.

3. Fluoroquinolone degradation

An aminoglycoside acetyltransferase variant can acetylate fluoroquinolones, rendering them inactive.

Pharmacokinetics

1. Absorption

Fluoroquinolones are well absorbed after oral administration, with levofloxacin and moxifloxacin having a bioavailability that exceeds 90% (Figure 31.3). Ingestion of fluoroquinolones with sucralfate, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents (Figure 31.4).

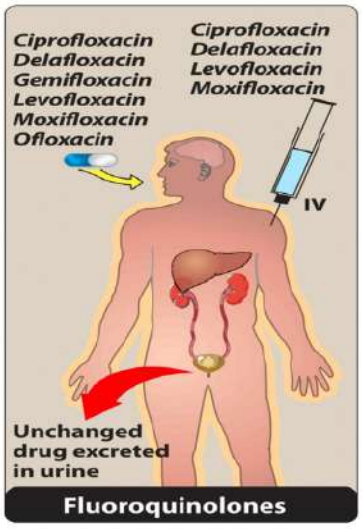


Figure 31.3 Administration and fate of the fluoroquinolones.

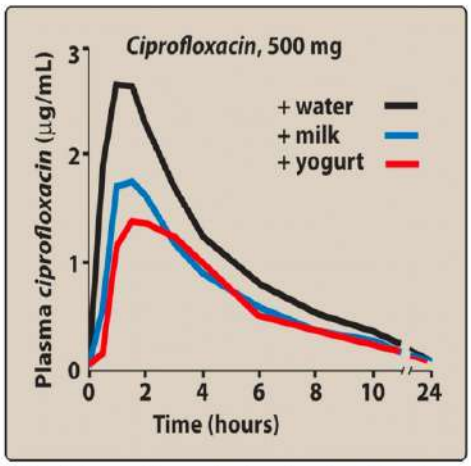


Figure 31.4 Effect of dietary calcium on the absorption of *ciprofloxacin*.

2. Distribution

Binding to plasma proteins ranges from 20% to 84%. Fluoroquinolones distribute well into all tissues and body fluids. Concentrations are high in bone, urine (except moxifloxacin), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum. Penetration into cerebrospinal fluid is good, and these agents may be considered in certain central nervous system (CNS) infections. Accumulation in macrophages and polymorphonuclear leukocytes results in activity against intracellular organisms such as Listeria, Chlamydia, and Mycobacterium.

3. Elimination

Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction. Moxifloxacin is metabolized primarily by the liver, and

while there is some renal excretion, no dose adjustment is required for renal impairment (see Figure 31.3).

Adverse Reactions

In general, fluoroquinolones are well tolerated (Figure 31.5). Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness. These agents carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and CNS effects (hallucinations, anxiety, insomnia, confusion, and seizures). Patients taking fluoroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions. Patients should use sunscreen and avoid excessive exposure to ultraviolet (UV) light. Arthropathy is uncommon, but arthralgia and arthritis are reported with fluoroquinolone use in pediatric patients.

Use in the pediatric population should be limited to distinct clinical scenarios (for example, cystic fibrosis exacerbation). Hepatotoxicity or blood glucose disturbances (usually in diabetic patients receiving oral hypoglycemic agents or insulin) have been observed.Identification of any of these events should result in prompt removal of the agent.

Fluoroquinolones may prolong the QTc interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. Ciprofloxacin inhibits P450 1A2- and 3A4-mediated metabolism. Serum concentrations of medications such as theophylline, tizanidine, warfarin, ropinirole, duloxetine, caffeine, sildenafil, and zolpidem may be increased (Figure 31.6).

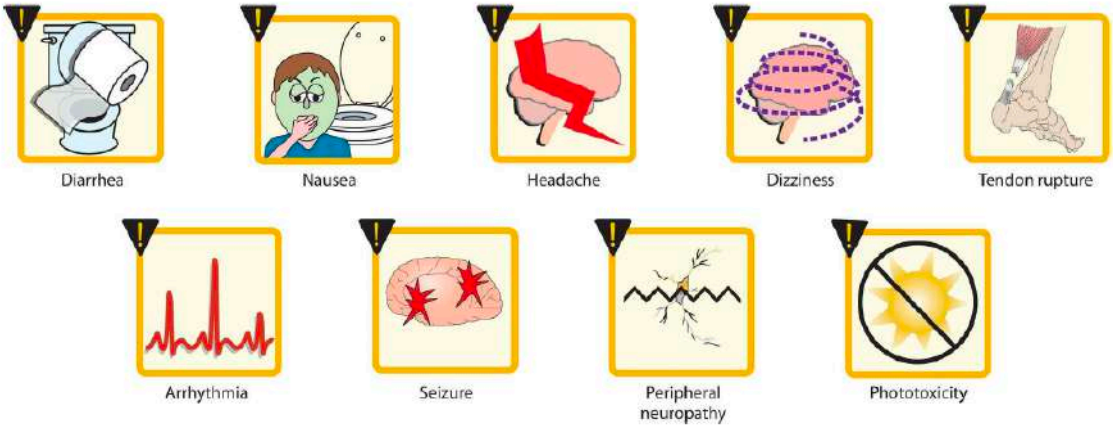


Figure 31.5 Some adverse reactions to fluoroquinolones.

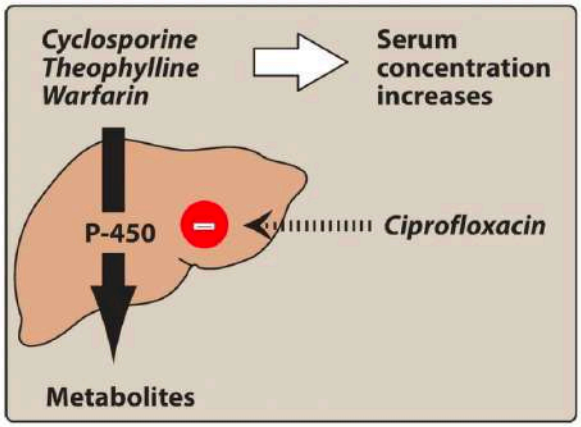


Figure 31.6 Drug interactions with *ciprofloxacin*.

Examples of clinically useful fluoroquinolones

Due to increasing resistance and boxed warnings, fluoroquinolones should be used with caution in select circumstances. They may be considered in patients who do not tolerate other agents (for example, severe beta-lactam allergies) or as definitive therapy once susceptibilities are available.Listed below are potential indications for these agents:

1. Ciprofloxacin

Ciprofloxacin has good activity against gram-negative bacilli, including P. aeruginosa. Ciprofloxacin is used in the treatment of traveler's diarrhea, typhoid fever, and anthrax. It is a second-line agent for infections arising from intra-abdominal, lung, skin, or urine sources. Of note, high-dose therapy should be employed when treating Pseudomonas infections.

2. Levofloxacin

Levofloxacin has similar activity to ciprofloxacin and they are often interchanged when managing gram-negative bacilli, including P. aeruginosa. Levofloxacin has enhanced activity against S. pneumonia and is first-line therapy for community-acquired pneumonia (CAP). It is a second-line agent for the treatment of S. maltophilia.

3. Moxifloxacin

Moxifloxacin has enhanced activity against gram-positive organisms (for example, S. pneumoniae), gram-negative anaerobes, and Mycobacterium spp. The drug may be used for CAP, but not hospital-acquired pneumonia due to poor coverage of P. aeruginosa. It may be considered for mild-to-moderate intra-abdominal infections but should be avoided if patients have fluoroquinolone exposure within the previous three months, due to increasing B. fragilis resistance. Moxifloxacin may be considered a second-line agent for the management of drug-susceptible tuberculosis.

4. Gemifloxacin

Gemifloxacin is indicated for the management of community-acquired respiratory infections. Unlike the other compounds, it is only available as an oral formulation.

5. Delafloxacin

Delafloxacin has improved activity against gram-positive cocci, including MRSA and Enterococcus spp. Due to its spectrum of activity, it is an option for managing acute bacterial skin and skin structure infections. It is available as an intravenous and oral formulation.

II- Folate Antagonists

Folic acid is a coenzyme essential in the synthesis of ribonucleic acid (RNA), DNA, and certain amino acids. In the absence of folate, cells cannot grow or divide. Humans use dietary folate to synthesize the critical folate derivative, tetrahydrofolic acid. By contrast, many bacteria are impermeable to folate derivatives and rely on their ability to synthesize folate de novo (Figure 31.7).

Sulfonamides (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate. A second type of folate antagonist, trimethoprim, prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid. Thus, both sulfonamides and trimethoprim interfere with the ability of an infecting bacterium to perform DNA synthesis and other essential cellular functions. The combination of the sulfonamide sulfamethoxazole with trimethoprim (the generic name for the combination is cotrimoxazole) provides a synergistic effect.

III. Sulfonamides

Sulfa drugs were among the first antibiotics used in clinical practice. Today, they are seldom prescribed alone except in developing countries, where they are employed because of low cost and efficacy.

Mechanism of action

Microorganisms use the enzyme dihydropteroate synthetase to create dihydrofolic acid from the precursor molecule p-aminobenzoic acid (PABA). Sulfonamides are synthetic analogs of PABA. Because of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and the genesis of bacterial dihydrofolic acid (see Figure 31.7). These agents, including cotrimoxazole, are bacteriostatic.

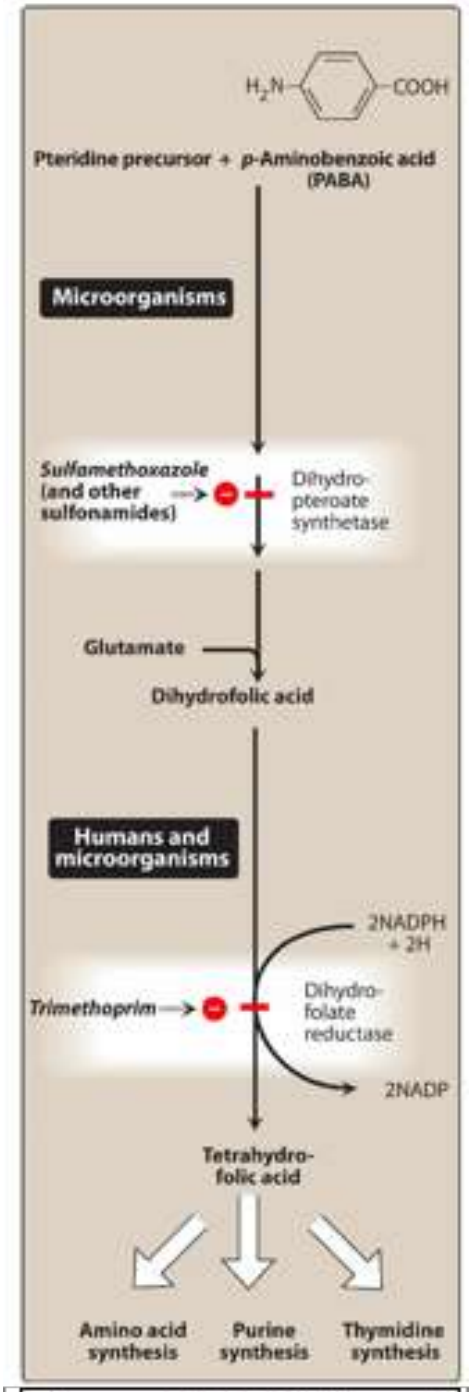


Figure 31.7 Inhibition of tetrahydrofolate synthesis by sulfonamides and trimethoprim

Antibacterial spectrum

Sulfa drugs have in vitro activity against gram-negative and gram-positive organisms. Common organisms include Enterobacteriaceae, Haemophilus influenzae, Streptococcus spp., Staphylococcus spp., and Nocardia. Additionally, sulfadiazine [sul-fa-DYE-a-zeen] in combination with the

dihydrofolate reductase inhibitor pyrimethamine [py-ri- METH-a-meen] is the preferred treatment for toxoplasmosis.

Resistance

Bacteria that obtain folate from their environment are naturally resistant to sulfa drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. Resistance may be due to 1) altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA. [Note: Organisms resistant to one member of this drug family are resistant to all.]

Pharmacokinetics

1. Absorption

Most sulfa drugs are well absorbed following oral administration (Figure 31.8). An exception is sulfasalazine. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for the treatment of chronic inflammatory bowel diseases. [Note: Intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect. Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations or have severe infections. Because of the risk of sensitization, sulfa drugs are not usually applied topically.

However, in burn units, silver sulfadiazine or mafenide acetate (α-amino-p-toluenesulfonamide) creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. [Note: Silver sulfadiazine is preferred because mafenide produces pain on application and its absorption may contribute to acid–base disturbances.]

2. Distribution

Sulfa drugs are bound to serum albumin in circulation and widely distributed throughout body tissues. Sulfa drugs penetrate well into cerebrospinal fluid (even in the absence of inflammation) and cross the placental barrier to enter fetal tissues.

3. Metabolism

Sulfa drugs are acetylated and conjugated primarily in the liver. The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria (“stone formation”; see below) and potential damage to the kidney.

4. Excretion

Unchanged sulfa drugs and metabolites are eliminated via glomerular filtration and secretion, requiring dose adjustments with renal impairment. Sulfonamides may be eliminated in breast milk.

Adverse effects

1. Crystalluria

Nephrotoxicity may develop as a result of crystalluria (Figure 31.9). Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

2. Hypersensitivity

Hypersensitivity reactions, such as rashes, angioedema, or Stevens-Johnson syndrome, may occur. When patients report previous sulfa allergies, it is paramount to acquire a description of the reaction to direct appropriate therapy.

3. Hematopoietic disturbances

Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.Granulocytopenia and thrombocytopenia can also occur. Fatal reactions have been reported from associated agranulocytosis, aplastic anemia, and other blood dyscrasias.

4. Kernicterus

Bilirubin-associated brain damage (kernicterus) may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood–brain barrier is not fully developed.

5. Drug potentiation

Sulfamethoxazole potentiates the anticoagulant effect of warfarin due to inhibition of CYP2C9, resulting in reduced clearance of warfarin. Sulfonamides may also displace warfarin from binding sites on serum albumin. Serum methotrexate levels may rise through protein binding displacement. Other CYP2C9 substrates, such as phenytoin, may have increased concentrations when given with sulfonamides.

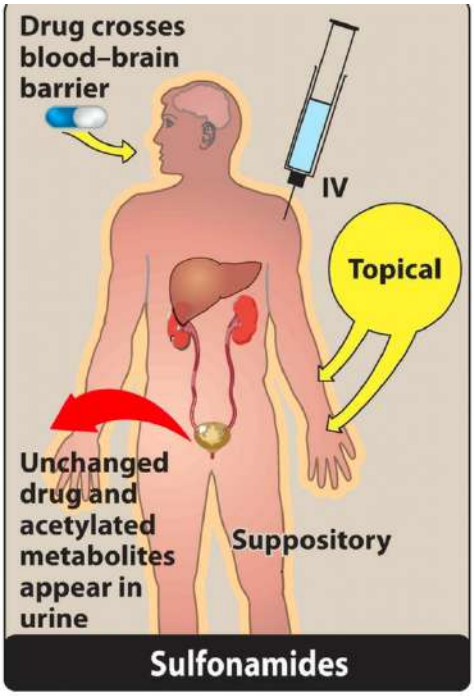


Figure 31.8 Administration and fate of the sulfonamides.

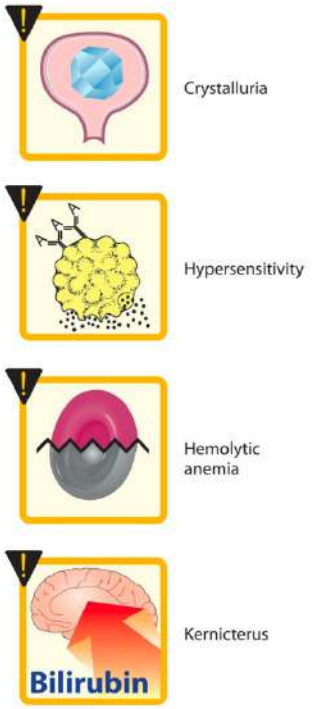


Figure 31.9 Some adverse reactions to sulfonamides.

6. Contraindications

Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age, as well as in pregnant women at term. Sulfonamides should not be given to patients receiving methenamine, since they can crystallize in the presence of formaldehyde produced by this agent.

IV. Trimethoprim

Trimethoprim, a potent inhibitor of bacterial dihydrofolate reductase, was initially available in combination with the sulfonamide sulfamethoxazole [sul-fa-meth-OX-a-zole], and later approved for use as a single agent. Today, trimethoprim is most commonly used in combination with sulfamethoxazole.

Mechanism of action

Trimethoprim is a potent inhibitor of bacterial dihydrofolate reductase (see Figure 31.7). Inhibition of this enzyme prevents the formation of the metabolically active form of folic acid, tetrahydrofolic acid, and thus, interferes with normal bacterial cell functions. Trimethoprim binds to bacterial dihydrofolate reductase more readily than it does to human dihydrofolate reductase, which accounts for the selective toxicity of the drug.

Antibacterial spectrum

The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole. However, trimethoprim is 20- to 50-fold more potent than the sulfonamides. Trimethoprim may be used alone in the treatment of urinary tract infections (UTIs) and in the treatment of bacterial prostatitis (although fluoroquinolones and cotrimoxazole are preferred).

Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for trimethoprim. Efflux pumps drug may play and decreased permeability to the drug may play a role.

Pharmacokinetics

Trimethoprim is rapidly absorbed following oral administration. Because the drug is a weak base, higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids. The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid. Trimethoprim undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.

Adverse effects

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those with nutrient-poor diets. These blood disorders may be reversed by simultaneous administration of folinic acid (also known as leucovorin), which does not enter bacteria. Trimethoprim has a potassium-sparing effect and may cause hyperkalemia, especially at higher doses and when administered with other medication that causes hyperkalemia (for example, angiotensin-converting enzyme inhibitors).

V. Cotrimoxazole

The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole, shows greater antimicrobial activity than equivalent quantities of either drug used alone (Figure 31.10). The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

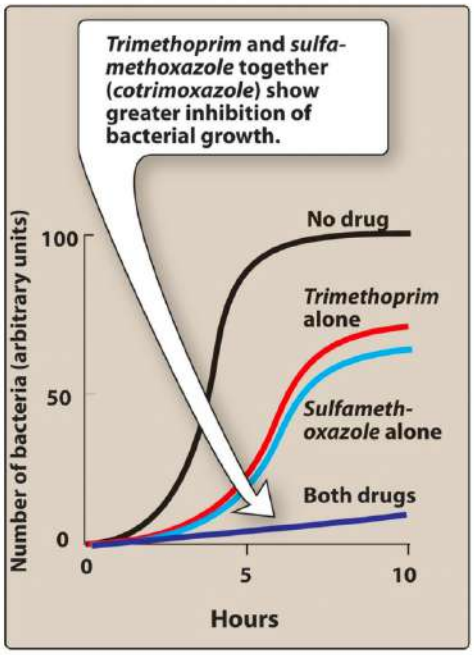


Figure 31.10 Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of E. coli.

Mechanism of action

The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid. Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents the reduction of dihydrofolate to tetrahydrofolate (Figure 31.7).

Antibacterial spectrum

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone (Figure 31.11). It is effective in treating UTIs and respiratory tract infections, as well as Pneumocystis jirovecii, toxoplasmosis, Listeria monocytogenes, and Salmonella infections. It has activity against methicillin-resistant S. aureus and can be particularly useful for skin and soft tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible Nocardia spp. and Stenotrophomonas maltophilia.

Resistance

Resistance to the trimethoprim–sulfamethoxazole combination is encountered less frequently than resistance to either of the drugs alone, because it requires bacterium to maintain simultaneous resistance to both drugs. Significant resistance has been documented in a number of clinically relevant organisms, including E. coli.

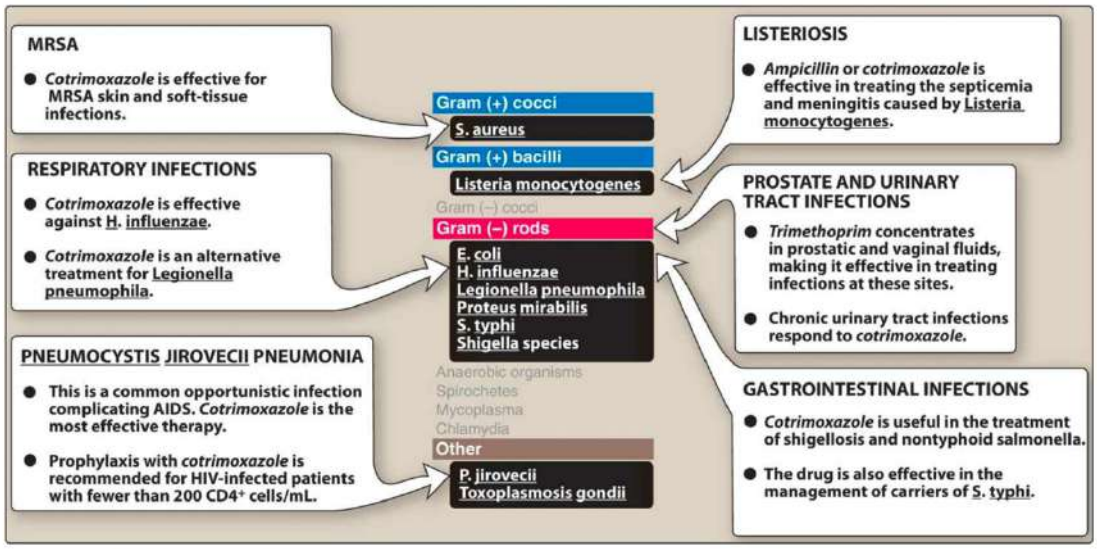


Figure 31.11 Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

Pharmacokinetics

Cotrimoxazole is generally administered orally (Figure 31.12). Intravenous administration may be utilized in patients with severe pneumonia caused by Pneumocystis jirovecii. Both agents are distributed throughout the body. Trimethoprim concentrates in the relatively acidic milieu of prostatic fluids, and this accounts for the use of trimethoprim–sulfamethoxazole in the treatment of prostatitis. Cotrimoxazole readily crosses the blood–brain barrier. Both parent drugs and their metabolites are excreted in the urine.

Adverse effects

Adverse reactions and drug interactions related to cotrimoxazole are similar to those expected with each of the individual components, sulfamethoxazole and trimethoprim (Figure 31.13). The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.

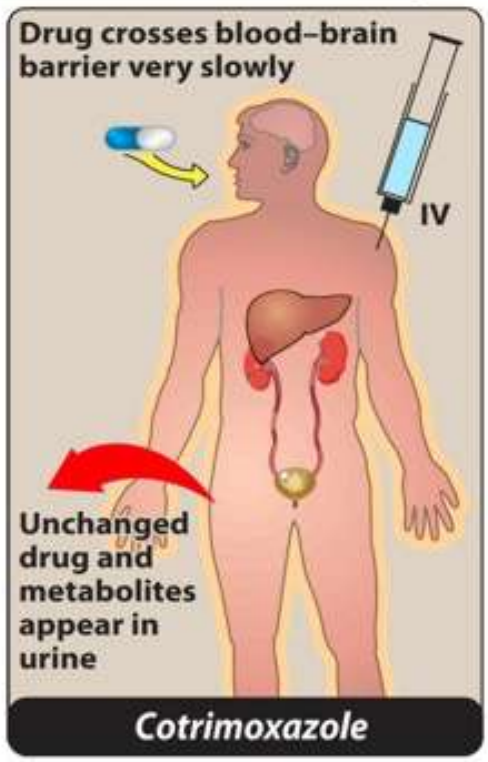


Figure 31.12 Administration and fate of cotrimoxazole

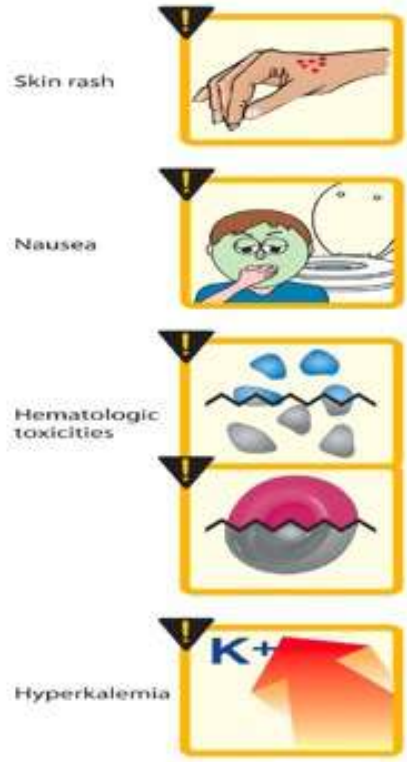


Figure 31.13 Some adverse reactions to cotrimoxazole

VI. Urinary Tract Antiseptics/Antimicrobials

UTIs are one of the most common bacterial infections in the world, primarily impacting women and the elderly. Historically, fluoroquinolones and cotrimoxazole have been the first-line therapy for the treatment of UTIs. Unfortunately, resistance has increased among common pathogens (for example, E. coli). As a result, methenamine, nitrofurantoin, and fosfomycin can be considered for treatment or suppression of recurrence, due to their efficacy against common pathogens and high concentrations in the urine.

A. Methenamine

Mechanism of action

Methenamine salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH $\leq$ 5.5). Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death. Methenamine is combined with a weak acid (for example, hippuric acid) to maintain urine acidity and promote the production of formaldehyde (Figure 31.14).

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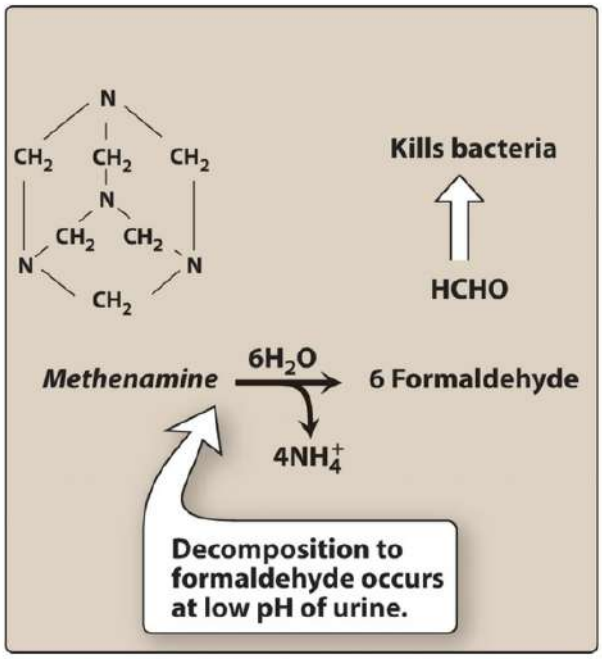

Figure 31.14 Formation of formaldehyde from *methenamine* at acid pH.

Antibacterial spectrum

Methenamine is primarily used for chronic suppressive therapy to reduce the frequency of UTIs. Methenamine is active against E. coli, Enterococcus spp., and Staphylococcus spp. It has some activity against Proteus spp. and Pseudomonas aeruginosa, but urine pH must be kept acidic to achieve bactericidal activity. The main benefit of methenamine is the lack of selection for resistant organisms.

Pharmacokinetics

Methenamine is orally absorbed, with up to 30% decomposing in gastric juices, unless protected by enteric coating. It reaches the urine through tubular secretion and glomerular filtration. Concentrations are sufficient to treat susceptible organisms. Due to ammonia formation, use should be avoided in hepatic insufficiency.

Adverse effects

The major adverse effect of methenamine is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. Methenamine mandelate is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. The methenamine hippurate formulation should be used instead. [Note:

Sulfonamides, such as cotrimoxazole, react with formaldehyde and must not be used concomitantly with methenamine. The combination increases the risk of crystalluria and mutual antagonism.]

B. Nitrofurantoin

Nitrofurantoin was introduced into clinical practice for the management of cystitis in the early 1950s. For decades, it was rarely used, but was resurrected due to increasing antibiotic resistance among Enterobacteriaceae and is considered first-line therapy for uncomplicated cystitis. Nitrofurantoin works by inhibiting DNA and RNA synthesis. Susceptible organisms include E. coli, Klebsiella spp., Enterococcus spp., and Staphylococcus spp. Following oral administration, it is rapidly absorbed, with nearly 40% excreted unchanged in the urine. Overall, nitrofurantoin is well tolerated.

Common adverse events include nausea, vomiting, and diarrhea. The use of the microcrystalline formulation decreases the incidence of gastrointestinal toxicity. Rare complications of therapy include pulmonary fibrosis, neuropathy, and autoimmune hepatitis. These events are observed with prolonged exposure greater than 1 month. Additionally, patients with impaired renal function should not receive nitrofurantoin due to an increased risk of adverse events.

Antimycobacterial Drugs

Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro. Their cell walls contain mycolic acids, which give the genus its name. Mycolic acids are long-chain, β-hydroxylated fatty acids. Mycobacteria produce highly lipophilic cell walls that stain poorly with Gram stain. Once stained, the bacilli are not decolorized easily by acidified organic solvents. Hence, the organisms are called "acid-fast bacilli." Mycobacterial infections classically result in the formation of slow-growing, granulomatous lesions that cause tissue destruction anywhere in the body.

DRUGS USED TO TREAT TUBERCULOSIS
- *Ethambutol* MYAMBUTOL
- *Isoniazid* GENERIC ONLY
- *Pyrazinamide* GENERIC ONLY
- *Rifabutin* MYCOBUTIN
- *Rifampin* RIFADIN
- *Rifapentine* PRIFTIN

DRUGS USED TO TREAT TUBERCULOSIS (2ND LINE)
- Aminoglycosides
- *Aminosalicylic acid* PASER
- *Bedaquiline* SIRTURO
- *Capreomycin* CAPASTAT
- *Cycloserine* SEROMYCIN
- *Ethionamide* TRECATOR
- Fluoroquinolones
- Macrolides

DRUGS USED TO TREAT LEPROSY
- *Clofazimine* LAMPRENE
- *Dapsone* GENERIC ONLY
- *Rifampin (Rifampicin)* RIFADIN

Mycobacterium tuberculosis can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB). [Note: In LTBI, the patient is infected with M. tuberculosis without signs or symptoms of active TB disease.] TB is the leading infectious cause of death worldwide, and a quarter of the world's population is infected with TB. Increasing in frequency are diseases caused by nontuberculous mycobacteria (NTM).

These species include M. avium-intracellulare, M. chelonae, M. abscessus, M. kansasii, and M. fortuitum. Finally, M. leprae causes leprosy.TB treatment generally includes four first-line drugs (Figure 32.1). Second-line drugs are typically less effective, more toxic, and less extensively studied. They are used for patients who cannot tolerate first-line drugs or who are infected with resistant TB. No drugs are specifically developed for NTM infections. Macrolides, rifamycins, and aminoglycosides are frequently included, but NTM regimens vary widely by organism.

II. Chemotherapy for Tuberculosis

M. tuberculosis is slow-growing and requires treatment for months to years. LTBI can be treated for 9 months with isoniazid (INH) monotherapy or with 12 once-weekly

higher doses of INH and rifapentine. In contrast, active TB disease must be treated with several drugs. Treatment for drug-susceptible TB lasts for at least 6 months, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.

A. Strategies for addressing drug resistance

Populations of M. tuberculosis contain small numbers of organisms that are naturally resistant to a particular drug. Under selective pressure from inadequate treatment, especially from monotherapy, these resistant organisms can emerge as the dominant population. Figure 32.2 shows that resistance develops rapidly in TB patients given only streptomycin.

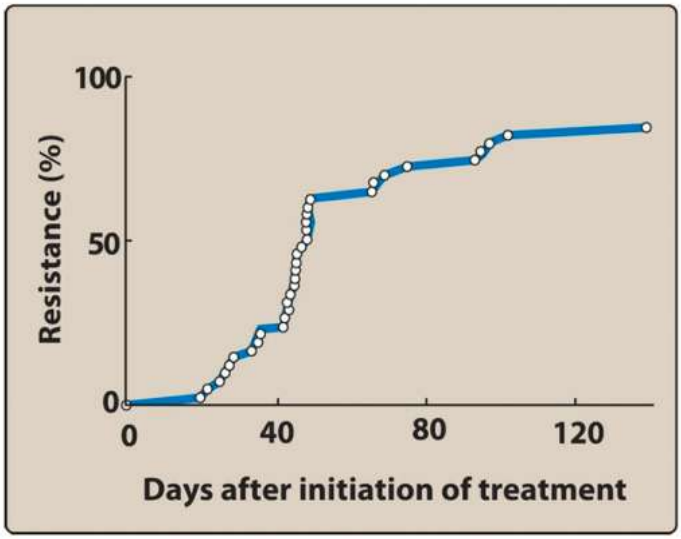

Figure 32.2 Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to *streptomycin*.

Multidrug therapy is employed to suppress these resistant organisms. The first-line drugs isoniazid, rifampin, ethambutol, and pyrazinamide are preferred because of their high efficacy and acceptable incidence of toxicity. Rifabutin or rifapentine may replace rifampin under certain circumstances. Active disease always requires treatment with multidrug regimens, and preferably three or more drugs with proven in vitro activity against the isolate. Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate persistent organisms and to prevent relapse. Standard short-course chemotherapy for tuberculosis includes

isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (the intensive phase), followed by isoniazid and rifampin for 4 months (the continuation phase; Figure 32.3).

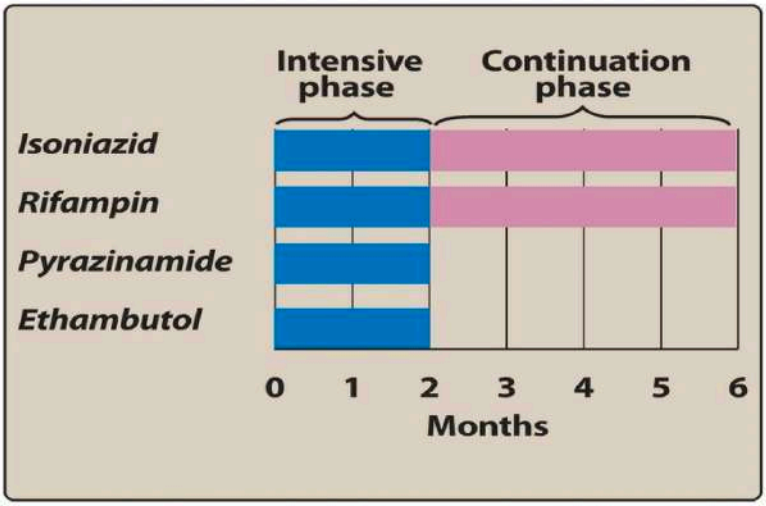

Figure 32.3 One of several recommended multidrug schedules for the treatment of tuberculosis.

Once susceptibility data are available, the drug regimen can be individually tailored. Second-line regimens for MDR-TB (TB resistant to at least isoniazid and rifampin) normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (all injectable agents), a fluoroquinolone (typically levofloxacin or moxifloxacin), any first-line drugs that remain active, and one or more of the following: cycloserine, ethionamide, or p-aminosalicylic acid. For extensively drug-resistant TB (XDR-TB), other drugs such as clofazimine and linezolid may be employed empirically. Patient adherence can be low when multidrug regimens last for 6 months or longer. One successful strategy for achieving better treatment completion rates is directly observed therapy (DOT). Patients take the medications under the observation of a member of the health care team. DOT decreases drug resistance and improves cure rates. Most public health departments offer DOT services.

B. Isoniazid

Isoniazid, along with rifampin, is one of the two most important TB drugs.

Mechanism of action

Isoniazid is a prodrug activated by a mycobacterial catalase–peroxidase (KatG). Isoniazid targets the enzymes acyl carrier protein reductase (InhA) and β-ketoacyl-ACP

synthase (KasA), which are essential for the synthesis of mycolic acid. Inhibiting mycolic acid leads to a disruption in the bacterial cell wall.

Antibacterial spectrum

Isoniazid is specific for the treatment of M. tuberculosis, although M. kansasii may be susceptible at higher drug concentrations. Most NTM are resistant to INH. The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms.

Resistance

Resistance follows chromosomal mutations, including 1) mutation or deletion of KatG (producing mutants incapable of prodrug activation), 2) varying mutations of the acyl carrier proteins, or 3) overexpression of the target enzyme InhA. Cross-resistance may occur between isoniazid and ethionamide.

Pharmacokinetics

Isoniazid is readily absorbed after oral administration. Absorption is impaired if isoniazid is taken with food, particularly high-fat meals. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tuberculous lesions). Drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum. Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products. Isoniazid acetylation is genetically regulated, with fast acetylators exhibiting a 90-minute serum half-life, as compared with 3 to 4 hours for slow acetylators (Figure 32.4). Excretion is through glomerular filtration and secretion, predominantly as metabolites (Figure 32.5). Slow acetylators excrete more of the parent compound.

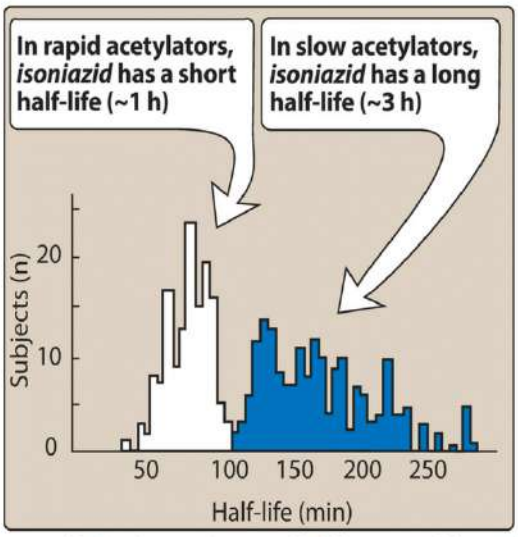

Figure 32.4 Bimodal distribution of *isoniazid* half-lives caused by rapid and acetylation of the drug.

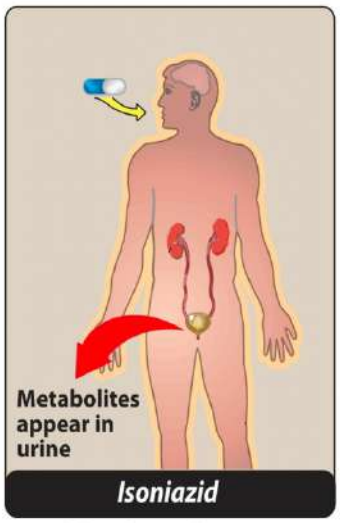

Figure 32.5 Administration and fate of *isoniazid*.

Adverse effects

Hepatitis is the most serious adverse effect associated with isoniazid. If hepatitis goes unrecognized, and if isoniazid is continued, it can be fatal. The incidence increases with age (greater than 35 years old), among patients who also take rifampin, or among those who drink alcohol daily. Peripheral neuropathy, manifesting as paresthesia of the hands and feet, appears to be due to a relative pyridoxine deficiency caused by isoniazid. This can be avoided by daily supplementation of pyridoxine (vitamin B6) Central nervous system (CNS) adverse effects can occur, including convulsions in patients prone to seizures.

Hypersensitivity reactions with isoniazid include rashes and fever. Because isoniazid inhibits the metabolism of carbamazepine and phenytoin, isoniazid can potentiate the adverse effects of these drugs (for example, nystagmus and ataxia).

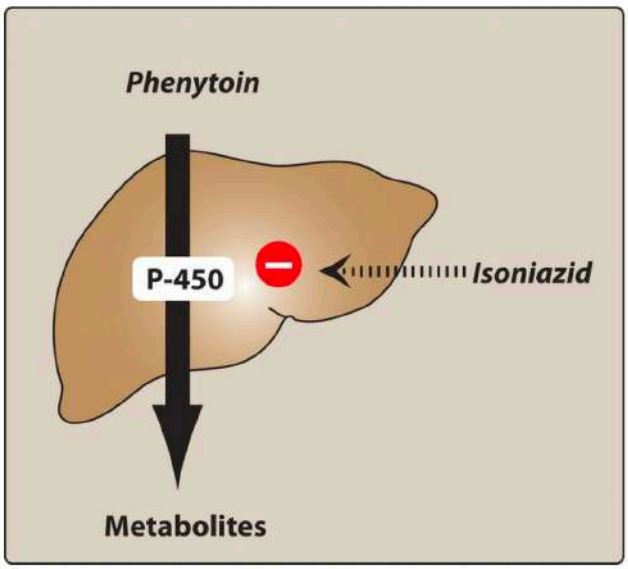

Figure 32.6 *Isoniazid* potentiates the adverse effects of *phenytoin*.

C. Rifamycins: rifampin, rifabutin, and rifapentine

Rifampin, rifabutin, and rifapentine are all considered rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line oral agents for tuberculosis.

1. Rifampin

Rifampin has broader antimicrobial activity than isoniazid and can be used as part of treatment for several different bacterial infections. Because resistant strains rapidly emerge during monotherapy, it is never given as a single agent in the treatment of active tuberculosis.

Mechanism of action

Rifampin blocks RNA transcription by interacting with the β subunit of mycobacterial DNA-dependent RNA polymerase.

Antimicrobial spectrum

Rifampin is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and NTM, such as M. kansasii and Mycobacterium avium complex (MAC). It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by

meningococci or Haemophilus influenzae. Rifampin also is highly active against M. leprae.

Resistance

Resistance to rifampin is caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

Pharmacokinetics

Absorption is adequate after oral administration. Distribution of rifampin occurs to all body fluids and organs. Concentrations attained in the CSF are variable, often 10% to 20% of blood concentrations. The drug is taken up by the liver and undergoes enterohepatic recycling. Rifampin can induce hepatic cytochrome P450 enzymes and transporters, leading to numerous drug interactions. Unrelated to its effects on cytochrome P450 enzymes, rifampin undergoes autoinduction, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing. Elimination of rifampin and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine (Figure 32.7). [Note: Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.]

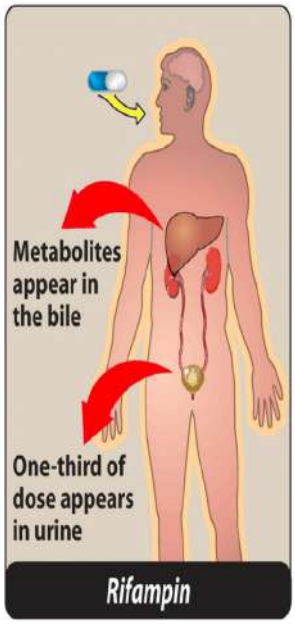

Figure 32.7 Administration and fate of *rifampin*. [Note: Patient should be warned that urine and tears may turn orange-red in color.]

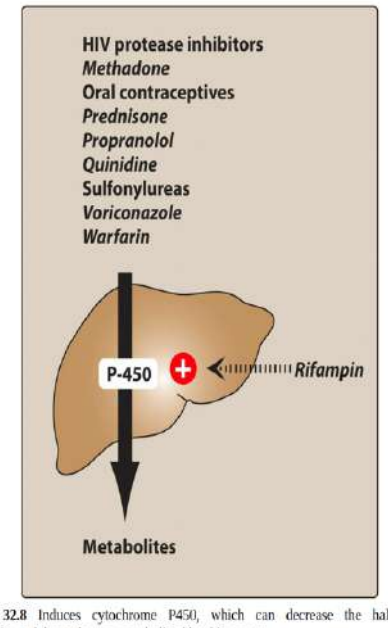

Figure 32.8 Induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system.

Adverse effects

Rifampin is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease. There is a modest increase in the incidence of hepatic dysfunction when rifampin is coadministered with isoniazid and pyrazinamide. When rifampin is dosed intermittently, especially with higher doses, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

Drug interactions

Because rifampin induces a number of phase I cytochrome P450 enzymes and phase II enzymes, it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes (Figure 32.8). This may necessitate higher dosages for coadministered drugs, a switch to drugs less affected by rifampin, or replacement of rifampin with rifabutin.

2. Rifabutin

Rifabutin, a derivative of rifampin, is preferred for TB patients coinfected with the human immunodeficiency virus (HIV) who are receiving protease inhibitors or several of the nonnucleoside reverse transcriptase inhibitors. Rifabutin is a less potent inducer (approximately 40% less) of cytochrome P450 enzymes, thus lessening drug interactions. Rifabutin has adverse effects similar to those of rifampin but can also cause uveitis, skin hyperpigmentation, and neutropenia.

3. Rifapentine

Rifapentine has a longer half-life than that of rifampin. In combination with isoniazid, rifapentine may be used once weekly in patients with LTBI and in select HIV-negative patients with minimal pulmonary TB.

D. Pyrazinamide

Pyrazinamide is a synthetic, orally effective short-course agent used in combination with isoniazid, rifampin, and ethambutol. The precise mechanism of action is unclear.

Pyrazinamide must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase enzyme. Pyrazinamide is active against tuberculosis bacilli in acidic lesions and in macrophages.

The drug is distributed throughout the body, penetrating the CSF. Pyrazinamide may contribute to liver toxicity. Uric acid retention is common but rarely precipitates a gouty attack. Most of the clinical benefit from pyrazinamide occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen.

E. Ethambutol

Ethambutol is bacteriostatic and specific for mycobacteria. Ethambutol inhibits arabinosyl transferase—an enzyme important for the synthesis of the mycobacterial cell wall. Ethambutol is used in combination with pyrazinamide, isoniazid, and rifampin pending culture and susceptibility data. [Note: Ethambutol may be discontinued if the isolate is determined to be susceptible to isoniazid, rifampin, and pyrazinamide. Ethambutol distributes well throughout the body. Penetration into the CNS is variable, and it is questionably adequate for tuberculous meningitis. Both the parent drug and its hepatic metabolites are primarily excreted in the urine. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. The risk of optic neuritis increases with higher doses and in patients with renal impairment. Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter. Uric acid excretion is decreased by ethambutol, and caution should be exercised in patients with gout. The figure below summarizes some of the characteristics of first-line drugs.

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with *phenytoin* and *carbamazepine*.
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

F. Alternate second-line drugs

Streptomycin, para-aminosalicylic acid, capreomycin, cycloserine, ethionamide, bedaquiline, fluoroquinolones, and macrolides are second-line TB drugs. In general, these agents are less effective and more toxic than the first-line agents. The figure below summarizes some of the characteristics of second-line drugs.

DRUG	ADVERSE EFFECTS	COMMENTS
Fluoroquinolones	GI intolerance, tendonitis, CNS toxicity including caffeine-like effects	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.
Aminoglycosides, *Capreomycin*	Nephrotoxicity, ototoxicity	Not available orally. Monitor for vestibular, auditory and renal toxicity.
Macrolides	GI intolerance, tinnitus	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except *azithromycin*).
Ethionamide	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with *isoniazid* is possible.
Para-aminosalicylic acid (PAS)	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. Patients with G6PD deficiency are at increased risk of hemolytic anemia.
Cycloserine	CNS toxicity	Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.

Figure 32.10 Some characteristics of second-line drugs used in treating tuberculosis. BUN = blood urea nitrogen; CNS = central nervous system; CYP = cytochrome; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone.

1. Streptomycin

Streptomycin, an aminoglycoside antibiotic, was one of the first effective agents for TB. Its action appears to be greater against extracellular organisms. Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin, to which these bacilli usually remain susceptible.

2. Para-aminosalicylic acid

Para-aminosalicylic acid (PAS) works via folic acid inhibition. While largely replaced by ethambutol for drug- susceptible TB, PAS remains an important component of many regimens for MDR-TB.

3. Capreomycin

This is a parenterally administered polypeptide that inhibits protein synthesis similar to aminoglycosides. Capreomycin is primarily reserved for the treatment of MDR-TB. Careful monitoring of renal function and hearing is necessary to minimize nephrotoxicity and ototoxicity, respectively.

4. Cycloserine

Cycloserine is an orally effective, tuberculostatic drug that disrupts D-alanine incorporation into the bacterial cell wall. It distributes well throughout body fluids, including the CSF. Cycloserine is primarily excreted unchanged in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances (for example, lethargy, difficulty concentrating, anxiety, and suicidal tendencies), and seizures may occur.

5. Ethionamide

Ethionamide is a structural analog of isoniazid that also disrupts mycolic acid synthesis. The mechanism of action is not identical to isoniazid, but there is some overlap in the resistance patterns. Ethionamide is widely distributed throughout the body, including the CSF. Metabolism is extensive, most likely in the liver, to active and inactive metabolites. Adverse effects that limit its use include nausea, vomiting, and hepatotoxicity. Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.

6. Fluoroquinolones

The fluoroquinolones, specifically moxifloxacin and levofloxacin, have an important place in the treatment of multidrug-resistant tuberculosis. Some NTM also are susceptible.

7. Macrolides

The macrolides azithromycin and clarithromycin are included in regimens for several NTM infections, including MAC. Azithromycin may be preferred for patients at greater risk for drug interactions, since clarithromycin is both a substrate and inhibitor of cytochrome P450 enzymes.

8. Bedaquiline

Bedaquiline, a diarylquinoline, is an ATP synthase inhibitor. It is approved for the treatment of MDR-TB. Bedaquiline is administered orally, and it is active against many types of mycobacteria. Bedaquiline has a boxed warning for QT prolongation, and monitoring of the electrocardiogram is recommended. Elevations in liver enzymes have also been reported and liver function should be monitored during therapy. This agent is metabolized via CYP3A4, and administration with strong CYP3A4 inducers (for example, rifampin) should be avoided.

III. Drugs for Leprosy

Leprosy (or Hansen disease) is uncommon in the United States; however, worldwide, it is a much larger problem (Figure 32.11). Leprosy can be treated effectively with dapsone and rifampin (Figure 32.12).

A. Dapsone

Dapsone is structurally related to the sulfonamides and similarly inhibits dihydropteroate synthase in the folate synthesis pathway. It is bacteriostatic for M. leprae, and resistant strains may be encountered. Dapsone also is used in the treatment of pneumonia caused by Pneumocystis jirovecii in immunosuppressed patients. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high concentrations in the skin. The parent drug undergoes hepatic acetylation. Both parent drug and metabolites are eliminated in the urine. Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

B. Clofazimine

Clofazimine is a phenazine dye. Its mechanism of action may involve binding to DNA, although alternative mechanisms have been proposed. Its redox properties may lead to the generation of cytotoxic oxygen radicals that are toxic to the bacteria. Clofazimine is bactericidal to M. leprae, and it has potentially useful activity against M. tuberculosis and NTM. The drug is recommended by the World Health Organization as part of a shorter regimen (9 to 12 months) for MDR-TB. Following oral absorption, clofazimine accumulates in tissues, allowing intermittent therapy but does not enter the

CNS. Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance. Eosinophilic and other forms of enteritis, sometimes requiring surgery, have been reported. Clofazimine has some anti-inflammatory and anti-immune activities. Thus, erythema nodosum leprosum may not develop in patients treated with this drug.

Fig.32.12 Patient with leprosy

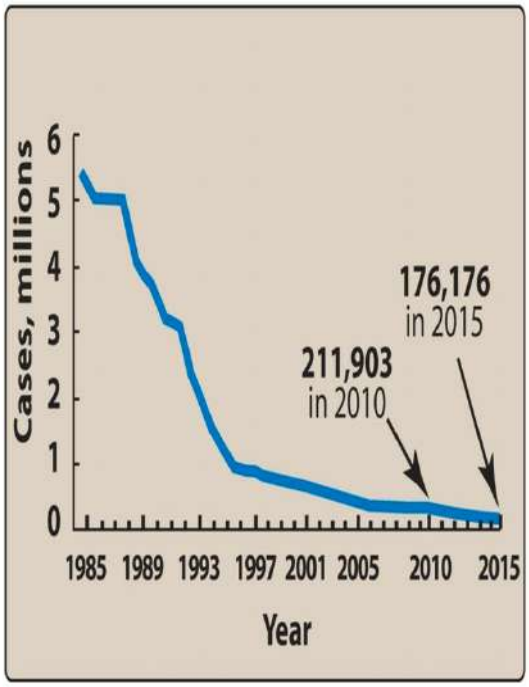

Figure 32.11 Reported prevalence of leprosy worldwide.

Antifungal Drugs

Fungi are eukaryotic and have rigid cell walls composed largely of chitin rather than peptidoglycan, which is a characteristic component of most bacterial cell walls. The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. Fungal infections are generally resistant to antibiotics, and, conversely, bacteria are resistant to antifungal agents. Fungal infection is termed mycosis.

Types of fungal infections:

■ **Mucocutaneous** (superficial) infections

- Dermatophytes: cause infection of skin, hair, and nails: eg. tinea capitis (scalp), tinea cruris (grain), tinea pedis (foot), onychomycosis (nails).

- Yeasts cause infections of moist skin and mucous membranes: e.g. Candida albicans causing oral, pharyngeal, vaginal, & bladder Infections.

■ **Systemic mycoses**: are fungal infections affecting internal organs. It occurs in immune-compromised patients e.g. cryptococcosis, and aspergillosis (Lung).

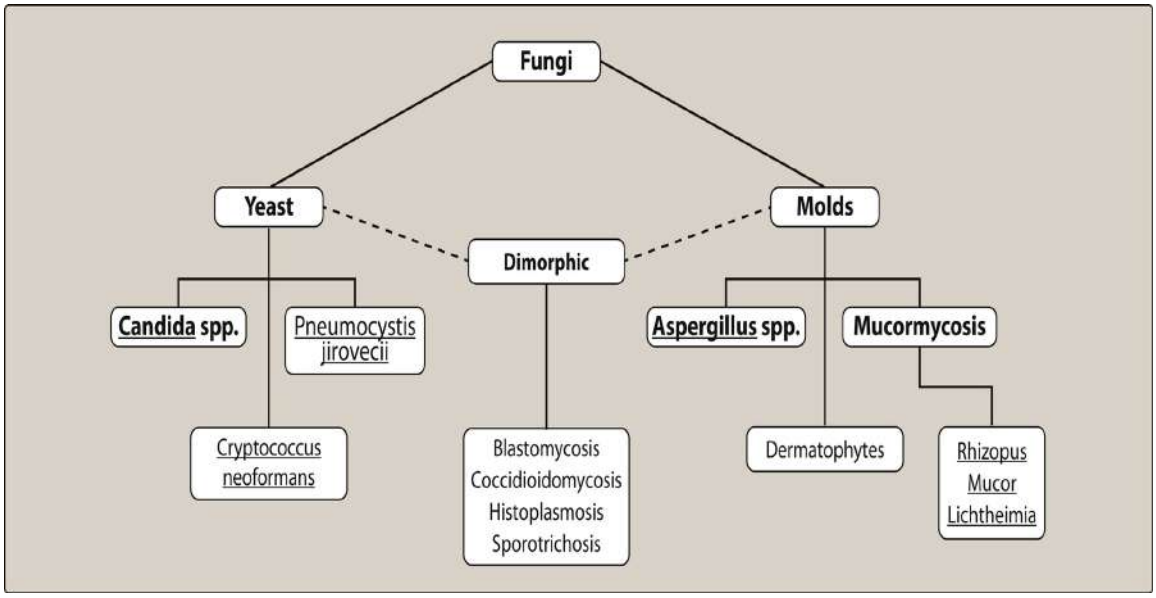

Figure-1 The common pathogenic organisms of the Kingdom Fungi

Classification of antifungal drugs

Antifungals can be grouped into three classes based on their site of action:

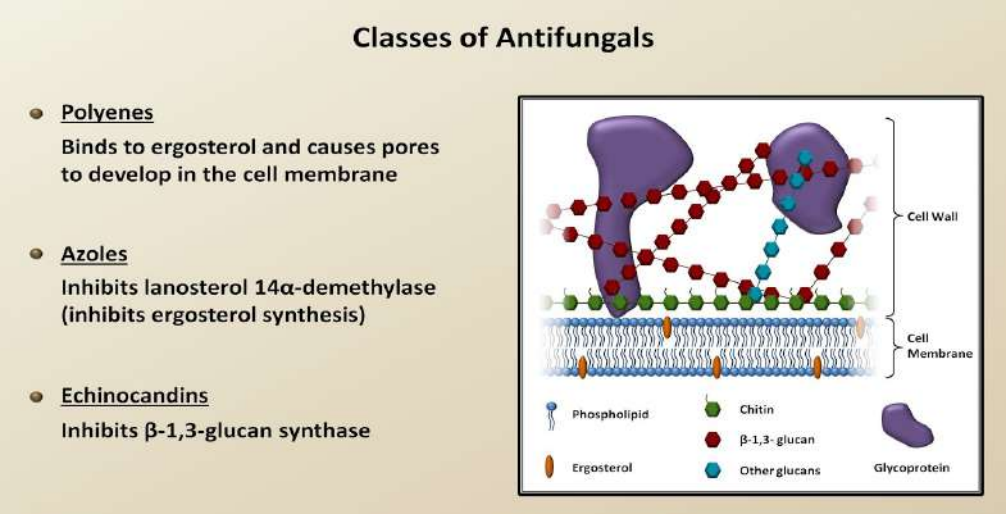

Figure 2: Classification of antifungal drugs **(**Polyenes such as amphotericin B bind to ergosterol in the fungal membrane causing disruption of membrane structure and function. Azoles inhibit the synthesis of ergosterol in the endoplasmic reticulum of the fungal cell. Flucytosine is converted within the fungal cell to 5-fluorouracil which inhibits DNA synthesis.)

DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

A. Amphotericin B

Amphotericin B, a naturally occurring polyene antifungal, is derived from Streptomyces nodosus. Drug for life-threatening mycoses.

The mechanism of action involves binding to ergosterol in fungal cell membranes, forming pores that disrupt membrane function, leading to the leakage of electrolytes and small molecules and ultimately causing cell death. Amphotericin B exhibits both fungicidal and fungistatic properties , It is effective against a broad spectrum of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and various strains of Aspergillus. Additionally, it is utilized in treating leishmaniasis.

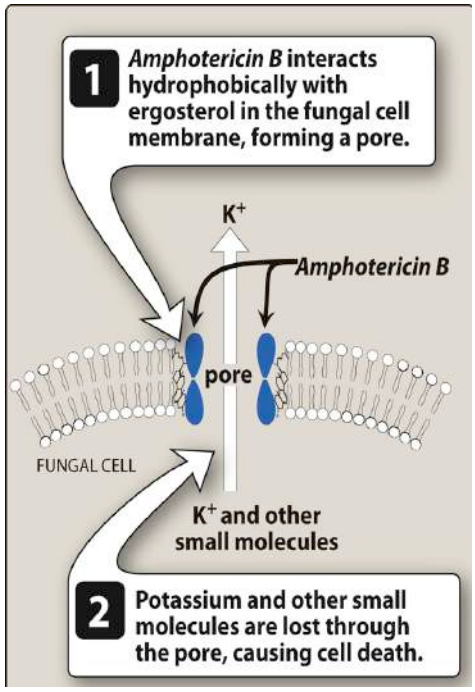

Figure-3-(Amphotericin B) mechanism of action

Resistance: Reduced ergosterol content in the fungal membrane.

Pharmacokinetics:

Administered through slow IV infusion, amphotericin B is insoluble in water and requires co-formulation with sodium deoxycholate or artificial lipids. The drug is extensively bound to plasma proteins, distributed throughout the body, and excreted primarily in the urine over an extended period, with limited penetration into certain body fluids.

Adverse Effect

low therapeutic index. Fever and chills: These occur most commonly 1-3 hours after starting the IV administration to mitigate these effects, premedication with a corticosteroid or antipyretic is recommended. Renal impairment: Azotemia is exacerbated by other nephrotoxic drugs, such as aminoglycosides, cyclosporine, and vancomycin, although adequate hydration can decrease its severity. Hypotension companied by hypokalemia; potassium fluctuations may occur in patients taking digoxin requiring potassium supplementation. Thrombophlebitis: Adding *heparin* to the infusion can alleviate this problem.

B. Antimetabolite antifungals

Flucytosine (5-FC) is a synthetic pyrimidine antimetabolite that is often used in combination with other antifungal agents.

Mechanism of action: 5-FC enters the fungal cell via a cytosine-specific permease, an enzyme not found in mammalian cells. It is subsequently converted to a series of compounds, including 5-fluorouracil (5-FU) and 5-fluorodeoxyuridine 5′-monophosphate, which disrupt nucleic acid and protein synthesis **([Note: Amphotericin increases cell permeability, allowing more 5-FC to penetrate the cell leading to synergistic effects**.].

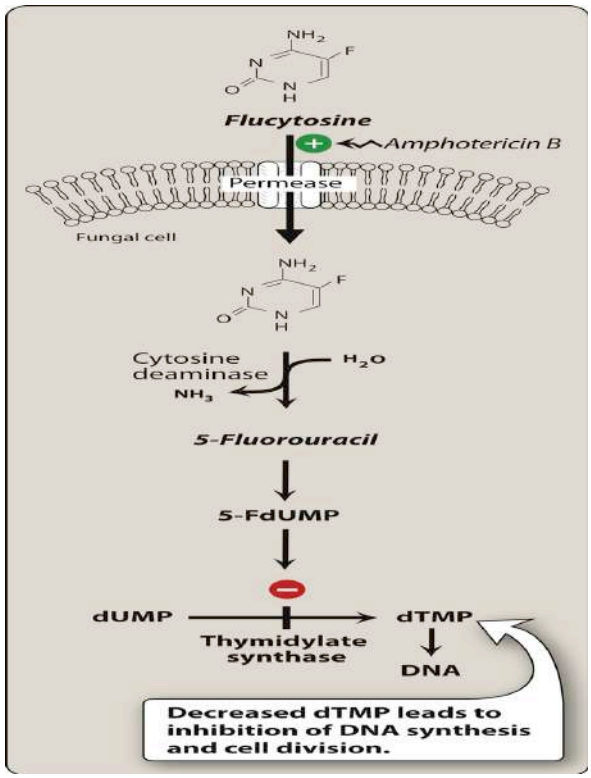

Figure-4- Flucytosine mechanism of action

Antifungal spectrum: 5-FC is fungistatic. It is effective in combination with itraconazole for treating chromoblastomycosis. It is also used in combination with amphotericin B for the treatment of systemic mycoses and for meningitis caused by C. neoformans and C. lbicans

Flucytosine is an alternative treatment for Candida urinary tract infections when fluconazole is not suitable, although resistance may develop with repeated use. Resistance is linked to decreased enzyme levels in the conversion of flucytosine to active metabolites. Combining flucytosine with another antifungal agent lowers the emergence of resistant fungal cells, emphasizing that it is not employed as a standalone antifungal drug.

Pharmacokinetics: 5-FC is efficiently absorbed orally and widely distributed in the body water, with good penetration into the cerebrospinal fluid (CSF). The presence of 5-FU in patients is likely due to the metabolism of 5-FC by intestinal bacteria. Both the parent drug and its metabolites are excreted through glomerular filtration, necessitating dose adjustments in individuals with impaired renal function.

Adverse effects: *5-FC* causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Reversible hepatic dysfunction with elevation of serum transaminases has been observed. Nausea, vomiting, and diarrhea are common, and severe enterocolitis may occur.

C. Azole antifungals

Azole antifungals consist of two classes—imidazoles and triazoles—with similar mechanisms of action and spectra of activity. However, their pharmacokinetics and therapeutic uses differ. Imidazoles are typically used topically for cutaneous infections, while triazoles are administered systemically for treating or preventing both cutaneous and systemic mycoses. The systemic triazole antifungals include *fluconazole*, *itraconazole*, *posaconazole*, *voriconazole*, and *isavuconazole*.

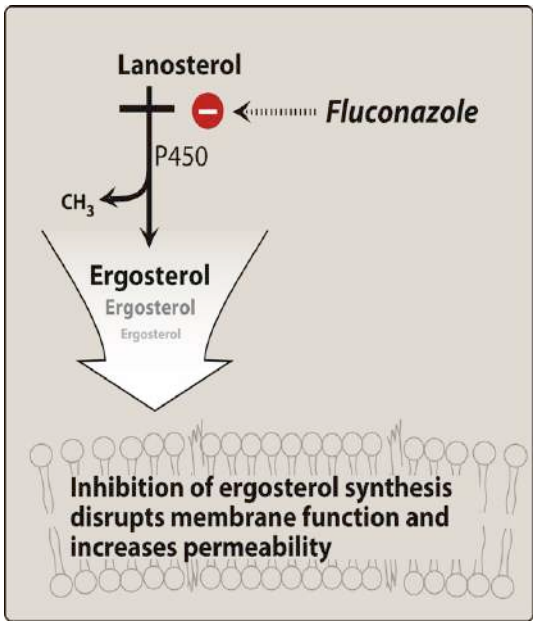

Figure 5: ***Mode of action of azole antifungals.***

Mechanism of action: Azoles function as fungistatic agents by inhibiting 14-α-demethylase, a cytochrome P450 enzyme. This inhibition prevents the demethylation of lanosterol to ergosterol, disrupting the biosynthesis of ergosterol. Consequently, this disruption compromises the structure and function of the fungal membrane, leading to the inhibition of fungal cell growth.

Resistance

Mutations in the14-α-demethylase gene that lead to decreased azole binding and efficacy. efflux pumps that pump the drug out of the cell or have reduced ergosterol in the cell wall.

Contraindications: Azoles are considered teratogenic, and they should be avoided in pregnancy unless the potential benefit outweighs the risk to the fetus.

D. Fluconazole

Fluconazole, the initial triazole antifungal, exhibits the lowest activity among its counterparts, primarily targeting yeasts and certain dimorphic fungi. Notably, it is ineffective against aspergillosis or mucormycosis. The drug demonstrates high efficacy against C. neoformans and specific Candida species like C. albicans and Candida parapsilosis. Nevertheless, resistance is a concern, particularly with other species such as Candida krusei and Candida glabrata.

Uses: Fluconazole is employed in bone marrow transplant recipients to prevent invasive fungal infections. It is the preferred treatment for C. neoformans following initial therapy with amphotericin B and flucytosine. Additionally, fluconazole is utilized for treating candidemia, coccidioidomycosis, and various forms of mucocutaneous candidiasis. For vulvovaginal candidiasis, it is commonly administered as a single oral dose.

Fluconazole is available in oral and IV dosage formulations. It is well absorbed after oral administration and distributes widely to body fluids and tissues. The majority of the drug is excreted in urine, and doses must be reduced in patients with renal dysfunction.

Adverse effects: nausea, vomiting, headache, and skin rashes.

E. Itraconazole

Itraconazole, a synthetic triazole, exhibits a broad antifungal spectrum compared to fluconazole. It is the preferred treatment for blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Available in capsule or oral solution form, the capsule is best taken with food and an acidic beverage for enhanced absorption, while the solution is more effective on an empty stomach. The drug distributes well in various tissues, including bone and adipose tissues. Extensively metabolized by the liver, both the drug and its inactive metabolites are excreted in urine and feces.

Itraconazole: potent inhibitor of CYP3A4 and coadministration of other agents metabolized by CYP3A4 should be avoided, if possible.

Adverse effects

Nausea, vomiting, diarrhea, rash (more pronounced in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Liver toxicity is a concern, particularly when administered concurrently with other hepatotoxic drugs. Itraconazole has a negative inotropic effect, making it unsuitable for patients with evidence of ventricular dysfunction, such as those with heart failure.

F. Posaconazole

Posaconazole, a synthetic triazole similar to itraconazole, is a broad-spectrum antifungal available in oral suspension, tablet, and IV formulations. Treating and preventing invasive Candida and Aspergillus infections in severely immunocompromised patients, it also demonstrates efficacy against infections caused by Scedosporium and Mucorales due to its broad spectrum. **Posaconazole** has low oral bioavailability and requires administration with food. Unlike other azoles, it is not metabolized by CYP450 but is eliminated via glucuronidation. Drugs that increase gastric pH (for example, proton pump inhibitors) may decrease the absorption of oral posaconazole and should be avoided. Concomitant use of posaconazole with various agents, including ergot alkaloids, atorvastatin, alprazolam, citalopram, and risperidone, is contraindicated due to posaconazole's potent inhibition of CYP450 3A4.

G. Voriconazole

Voriconazole, a synthetic triazole related to fluconazole, serves as a broad-spectrum antifungal agent available in IV and oral forms. It has replaced amphotericin B as the preferred treatment for invasive aspergillosis and is approved for invasive candidiasis, as well as serious infections caused by Scedosporium and Fusarium species. **Voriconazole** exhibits high oral bioavailability, effective tissue penetration, and undergoes extensive metabolism by CYP2C19, CYP2C9, and CYP3A4 isoenzymes, with the metabolites primarily excreted via urine.

Side Effect

High concentrations of the drug have been linked to adverse effects such as visual and auditory hallucinations, an increased risk of hepatotoxicity, hypokalemia, and reversible visual impairment upon discontinuation. Voriconazole is **contraindicated** with many drugs that are inducers of CYP450 (for example, *rifampin*, *rifabutin* and carbamazepine,

H. Isavuconazole

Isavuconazole is a broad-spectrum antifungal agent available in both intravenous and oral forms, supplied as the prodrug isavuconazonium. The prodrug rapidly converts to isavuconazole in the blood. Isavuconazole is effective against invasive aspergillosis and invasive mucormycosis, sharing a similar spectrum of activity with voriconazole. It exhibits high bioavailability orally and distributes well into tissues. Metabolism involves CYP3A4, CYP3A5, and uridine-diphosphate-glucuronosyltransferases. Coadministration with potent CYP3A4 inhibitors and inducers is contraindicated due to drug interactions. Additionally, Isavuconazole inhibits the CYP3A4 isoenzyme, leading to increased concentrations of drugs that are substrates of CYP3A4.

Side Effect: Nausea, vomiting, diarrhea, and hypokalemia.

	Fluconazole	*Itraconazole*	*Isavuconazole*	*Voriconazole*	*Posaconazole*
Spectrum of activity	+	++	+++	+++	++++
Route(s) of administration	Oral, IV	Oral	Oral, IV	Oral, IV	Oral, IV
Oral bioavailability (%)	95	55 (solution)	98	96	Variable
Drug levels affected by food or gastric pH	No	Yes	No	No	Yes
Protein binding (%)	10	99	99	58	99
Primary route of elimination	Renal	Hepatic CYP3A4	Hepatic CYP3A4, UGT	Hepatic CYP2C19, 2C9, 3A4	Hepatic glucuronidation
Cytochrome P450 enzymes inhibited	CYP3A4, 2C9, 2C19	CYP3A4	CYP3A4	CYP2C19, 2C9, 3A4	CYP3A4
Half-life ($t_{1/2}$)	25 h	30–40 h	130 h	Dose dependent	20–66 h
CSF penetration	Yes	No	Yes	Yes	Yes
Renal excretion of active drug (%)	>90	<2	45	<2	<2
TDM recommended (rationale)	No	Yes (efficacy)	No	Yes (efficacy and safety)	Yes (efficacy)

Figure 6: Major different between azole drugs.

I. Echinocandins (*Caspofungin*, *micafungin*, and *anidulafungin*)

Echinocandins, such as caspofungin, micafungin, and anidulafungin, disrupt fungal cell wall synthesis by inhibiting β(1,3)-d-glucan synthesis, leading to cell lysis and death. These drugs, administered intravenously once daily, are particularly effective against Aspergillus and various Candida species, even those resistant to azoles. Micafungin stands out for not requiring a loading dose. Despite minimal activity against other fungi, they can induce adverse effects like fever, rash, nausea, and phlebitis. Slow IV infusion is recommended to prevent histamine-like reactions, especially flushing, associated with rapid administration.

1. Caspofungin: is a first-line treatment for invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients unable to tolerate amphotericin B or an azole. Dosing adjustments are necessary for moderate hepatic dysfunction, and caution is advised when co-administering with CYP450 enzyme inducers. Concurrent use with cyclosporine is discouraged due to a high risk of elevated hepatic transaminases.

2. Micafungin and anidulafungin:

Micafungin and anidulafungin are recommended as first-line treatments for invasive candidiasis, including candidemia. Micafungin also serves for prophylaxis against invasive Candida infections in patients undergoing hematopoietic stem cell transplantation. Notably, both drugs are not substrates for CYP450 enzymes and do not pose any associated drug interactions.

DRUGS FOR CUTANEOUSMYCOTIC INFECTIONS

Cutaneous infections caused by mold-like fungi are known as dermatophytes or tinea. These infections, classified by the affected site (e.g., tinea pedis for feet infections), are commonly referred to as "ringworm" when presenting as round red patches with clear centers. The primary fungi responsible for cutaneous infections are Trichophyton, Microsporum, and Epidermophyton. Additionally, skin infections can be caused by yeasts such as Malassezia and Candida.

A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane (Figure-7). Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

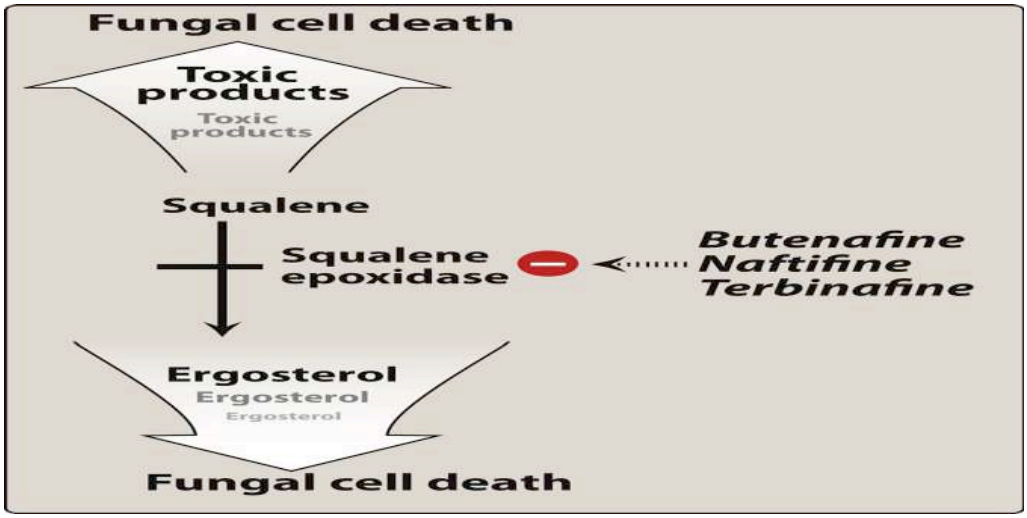

Figure-7- Mode of action of squalene epoxidase inhibitors.

1. Terbinafine:

Oral terbinafine is the preferred treatment for dermatophyte onychomycoses (nail fungal infections), offering better tolerance, shorter therapy duration (usually around 3 months), and increased effectiveness compared to itraconazole or griseofulvin, particularly against Trichophyton. This oral antifungal is also applicable for tinea capitis (scalp infection), requiring systemic therapy. Conversely, topical terbinafine in various forms is employed for treating tinea pedis, tinea corporis, tinea cruris, and tinea versicolor caused by Malassezia furfur, with a typical treatment duration of 1 week.

Antifungal spectrum

Terbinafine is effective against Trichophyton and Malassezia. While it may potentially work against Candida, Epidermophyton, and Scopulariopsis.

Pharmacokinetics:

Terbinafine, available for oral and topical use, exhibits 40% bioavailability orally due to first-pass metabolism. It is highly protein-bound and accumulates in the skin, nails, and adipose tissue, leading to a prolonged half-life of 200 to 400 hours. Metabolized by various CYP450 isoenzymes, primarily excreted through urine, it should be avoided in patients with significant renal or hepatic impairment. Terbinafine inhibits CYP2D6 isoenzyme, posing a risk of adverse effects when used concurrently with CYP2D6 substrates.

Adverse effects:

The oral formulation of the medication is associated with common adverse effects such as diarrhea, dyspepsia, nausea, headache, and rash. Additionally, taste and visual disturbances may occur, along with elevated levels of serum hepatic transaminases. On the other hand, the topical formulations are generally well tolerated.

2. Naftifine:

Naftifine is effective against Trichophyton, Microsporum, and Epidermophyton. It is utilized topically in the form of cream and gel for treating tinea corporis, tinea cruris, and tinea pedis, with a typical treatment duration of 2 to 4 weeks.

3. Butenafine:

Butenafine is effective against Trichophyton rubrum, Epidermophyton, and Malassezia. It is employed topically, in cream form, similar to naftifine, for the treatment of tinea infections.

B. Griseofulvin

Griseofulvin disrupts the mitotic spindle and inhibits fungal mitosis, making it effective for dermatophytosis of the scalp and hair. However, it has been largely replaced by oral terbinafine for onychomycosis treatment. Griseofulvin is fungistatic, necessitating a prolonged treatment duration (e.g., 6-12 months for onychomycosis), determined by the rate of healthy skin and nail replacement. The drug is absorbed well with high-fat meals, concentrating in skin, hair, nails, and adipose tissue. Griseofulvin induces hepatic CYP450 activity, impacting drug metabolism, contraindicating its use in pregnancy and porphyria patients.

C. Nystatin

Nystatin, a polyene antifungal similar to amphotericin B in structure, chemistry, mechanism of action, and resistance profile, is employed for treating cutaneous and oral Candida infections. Due to minimal absorption from the gastrointestinal tract and potential systemic toxicity, it is not administered parenterally. Instead, it is given orally for oropharyngeal candidiasis, intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis, using methods such as "swish and swallow" or "swish and spit."

D. Imidazoles,

Imidazoles a class of azole derivatives, includes various agents like butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole, terconazole, and tioconazole. These topical agents exhibit

broad activity against Epidermophyton, Microsporum, Trichophyton, Candida, and Malassezia. They are utilized for treating conditions such as tinea corporis, tinea cruris, tinea pedis, oropharyngeal and vulvovaginal candidiasis. However, their topical use may lead to contact dermatitis, vulvar irritation (with vaginal preparations), and edema. Clotrimazole and miconazole are available in troche and buccal tablet forms, respectively, for treating thrush. While oral ketoconazole is rarely used due to severe side effects, topical formulations are effective against conditions like tinea versicolor and seborrheic dermatitis.

E. Efinaconazole

Efinaconazole is a topical triazole antifungal agent designed for treating toenail onychomycosis caused by T. rubrum and Trichophyton mentagrophytes, with a prescribed treatment duration of 48 weeks.

F. Ciclopirox

Ciclopirox, a pyridine antimycotic, disrupts the synthesis of DNA, RNA, and proteins by inhibiting the transport of essential elements in fungal cells. Ciclopirox exhibits activity against various fungi, including Trichophyton, Epidermophyton, Microsporum, Candida, and Malassezia. It comes in multiple formulations, such as shampoo for seborrheic dermatitis, and cream, gel, or suspension for conditions like tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor. Additionally, onychomycosis can be addressed with the nail lacquer formulation of ciclopirox.

G. Tavaborole

Tavaborole is a topical solution used to treat toenail onychomycosis by inhibiting an aminoacyl-transfer ribonucleic acid synthetase, thereby preventing fungal protein synthesis. It is effective against T. rubrum and T. mentagrophytes, requiring a 48-week treatment period.

H. Tolnaftate

Tolnaftate, a topical thiocarbamate, disrupts hyphae and inhibits mycelial growth in susceptible fungi, specifically targeting Epidermophyton, Microsporum, and Malassezia furfur. However, it is not effective against Candida. Tolnaftate is employed

in the treatment of conditions such as tinea pedis, tinea cruris, and tinea corporis, and is available in solution, cream, and powder forms.

Antiprotozoal Drugs

Protozoan parasites causing human diseases are widespread in underdeveloped tropical and subtropical regions due to inadequate sanitary conditions and vector control. Global travel has expanded the reach of protozoal diseases beyond specific geographic areas. Protozoal cells share metabolic processes with human hosts, making treatment more challenging compared to bacterial infections. Many antiprotozoal drugs have serious toxic effects, especially on highly metabolically active cells, and are generally unsafe for pregnant patients.

Chemotherapy for Amebiasis

Amebiasis (amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. E. histolytica is endemic in developing countries and is mainly transmitted via the fecal–oral route or through ingestion of contaminated food or water. Most infected individuals are asymptomatic but can exhibit varying degrees of illness depending on host factors and formation of trophozoites. The diagnosis is established by isolating E. histolytic from feces. Therapeutic agents for amebiasis are classified as luminal, systemic, or mixed amebicides according to the site of action.

A. Mixed amebicides (Metronidazole and Tinidazole)

1. Metronidazole:

Metronidazole, a nitroimidazole, is the preferred mixed amebicide for treating amebic infections. It is also utilized in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, anaerobic gram-negative bacilli (e.g., Bacteroides species), and anaerobic gram-positive bacilli (e.g., Clostridioides difficile*)*.

Mechanism of action:

Amebas contain electron transport proteins with low-redox potential similar to ferredoxin. Metronidazole, through its nitro group, acts as an electron acceptor in

amebas. This process leads to the formation of cytotoxic compounds that bind to proteins and DNA, causing the death of E. histolytica trophozoites.

Pharmacokinetic Metronidazole, when orally administered, is rapidly and completely absorbed, with widespread distribution in body tissues and fluids, including vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid. Metabolized in the liver, the drug accumulates in severe hepatic disease and is excreted in urine.

Adverse effects include nausea, vomiting, epigastric distress, abdominal cramps, and a metallic taste. It may lead to oral yeast infections and potentially prolong the QT interval, requiring caution when used with drugs that increase QT prolongation. Combining metronidazole with alcohol can trigger a disulfiram-like reaction.

2. Tinidazole:

Tinidazole, a second-generation nitroimidazole, shares a similar spectrum of activity and absorption with metronidazole. It is employed in treating amebiasis, amebic liver abscess, giardiasis, and trichomoniasis, demonstrating efficacy comparable to metronidazole but at a higher cost. Metabolized by CYP3A4, tinidazole concentrations can be influenced by strong inducers or inhibitors of this enzyme. Common adverse effects include gastrointestinal upset and a metallic taste, and alcohol consumption is advised against during therapy.

B. Luminal amebicides (luminal agent, such as *iodoquinol*, *diloxanide furoate*, or *paromomycin*,)

1. Iodoquinol:

Iodoquinol is an amebicidal medication effective against luminal trophozoite and cyst forms of E. histolytica. However, its use comes with potential adverse effects such as rash, diarrhea, and dose-related peripheral neuropathy, including rare optic neuritis. Due to these risks, long-term usage of iodoquinol is advised against.

2. Paromomycin:

Paromomycin, an aminoglycoside antibiotic, is specifically effective against luminal forms of E. histolytica as it is poorly absorbed from the gastrointestinal tract. Its direct amebicidal action and reduction of intestinal flora contribute to its anti amebic effects. The main adverse effects include gastrointestinal distress and diarrhea.

C. Systemic amebicides

Chloroquine, a systemic amebicide, is effective in treating extraintestinal amebiasis, including liver abscesses and intestinal wall infections caused by amebas. It is often combined with metronidazole or used as a substitute for nitroimidazoles in cases of intolerance to treat amebic liver abscesses. Chloroquine eliminates trophozoites in liver abscesses but is not effective against luminal amebiasis, necessitating follow-up with a luminal amebicide. Additionally, chloroquine is effective in treating malaria.

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *paromomycin*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *iodoquinol* or *paromomycin*
Amebic liver abscess	*Metronidazole* (or *tinidazole*) plus *iodoquinol* or *paromomycin*

Figure 1: Therapeutic options for the treatment of amebiasis.

Antimalarial drugs

Four species of plasmodium typically cause human malaria:

1. Plasmodium falciparum

2. P vivax.

3. P malariae.

4. P ovale.

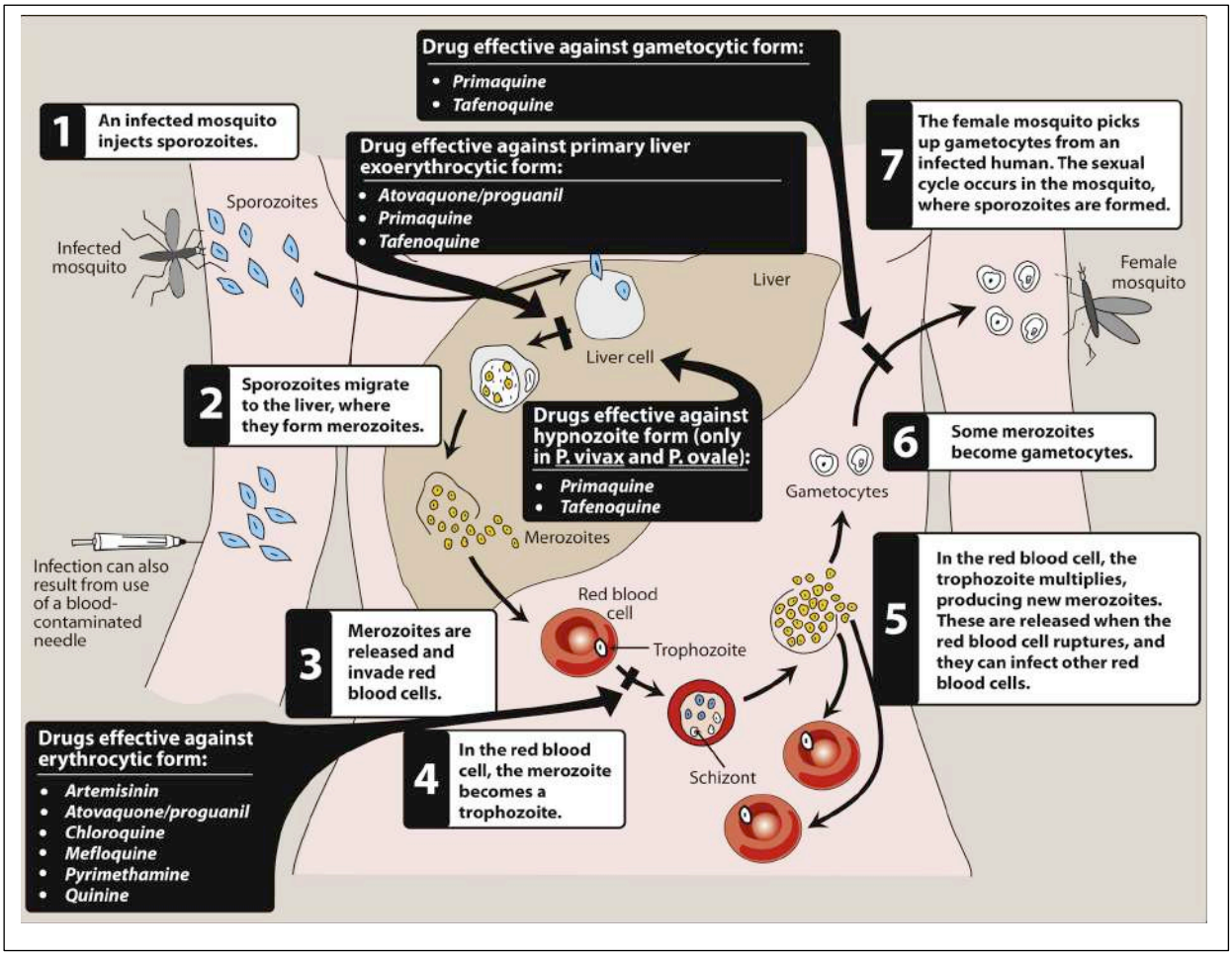

Figure 2: Life cycle of the malarial parasite, Plasmodium falciparum, showing the sites of action of antimalarial drugs

Classification of Drug

1. Tissue schizonticide

2. a blood schizonticide tissue schizonticide primaquine

• Eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale).

• Lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver in the exoerythrocytic form after the erythrocytic form of the disease is eliminated.

• The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thus interrupting the transmission of the disease.

Primaquine is not effective against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as chloroquine, quinine, mefloquine, or pyrimethamine.

Mechanism of action of primaquine

Metabolites of primaquine are believed to act as oxidants that are responsible for the schizonticidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities.

Pharmacokinetics of Primaquine:

- Primaquine is well absorbed on oral administration
- It is rapidly oxidized to metabolites which appear in the urine

Adverse effects of Primaquine

- Hemolytic anemia (in patient's low levels of glucose-6- phosphate)
- Abdominal discomfort (with large doses) especially when administered in combination with chloroquine
- Methemoglobinemia
- Granulocytopenia (rarely)
- Primaquine is contraindicated during pregnancy.
- All Plasmodium species may develop resistance to primaquine

Blood schizonticide

Chloroquine

• The mainstay of antimalarial therapy, and it is the drug of choice in the treatment of erythrocytic P. falciparum malaria,

• Chloroquine is less effective against P. vivax malaria.

• It is highly specific for the asexual form of plasmodia.

• Chloroquine is also effective in the treatment of extraintestinal amebiasis

Pharmacokinetics of Chloroquine

Chloroquine is rapidly and completely absorbed following oral administration. 4 days of therapy suffice to cure the disease. The drug concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes.

Some metabolic products have antimalarial activity. The excretion by urine rate is enhanced as is acidified.

Adverse effect of Chloroquine

Higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurring of vision. Discoloration of the nail beds and mucous membranes may be seen on chronic administration. Electrocardiographic changes (because it has a quinidine-like effect). Dermatitis produced by gold or phenylbutazone therapy.

Patients with psoriasis or porphyria should not be treated with chloroquine, because an acute attack may be provoked.

Mefloquine

An effective single agent for suppressing and curing infections caused by multidrug-resistant forms of P. falciparum. Its exact mechanism of action remains to be determined, but like quinine, it can apparently damage the parasite's membrane, is absorbed well after oral administration and concentrates in the liver and lung, It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems., The drug undergoes extensive metabolism. Its major excretory route is the feces, Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Electrocardiographic abnormalities and cardiac arrest are possible if mefloquine is taken concurrently with quinine or quinidine.

Quinine and quinidine

Interfere with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. For These drugs are reserved severe infestations and for malarial strains that are resistant to other agents, such as chloroquine.

Taken orally, quinine is well distributed throughout the body and can reach the fetus. Alkalinization of the urine decreases its excretion.

The major adverse effect of quinine

1. Cinchonism (syndrome causing nausea, vomiting, tinnitus, and vertigo).

2. Positive Coombs' test for hemolytic anemia occurs (Quinine)

3. Quinine is fetotoxic

Drug interactions of quinine

- Potentiation of neuromuscular-blocking agents
- Elevation of digoxin levels if taken concurrently with quinine
- Quinine absorption is retarded when the drug is taken with aluminum-containing antacids.

Pyrimethamine

- Inhibits plasmodial dihydrofolate reductase at much lower concentrations than those needed to inhibit the mammalian enzyme.
- The inhibition deprives the protozoan of tetrahydrofolate cofactor required in the de-novo biosynthesis of purines and pyrimidines
- It is also used against P. malariae and toxoplasma gondii.
- If megaloblastic anemia occurs with pyrimethamine treatment, it may be reversed with leucovorin

Chemotherapy for Trypanosomiasis

Only four drugs are available for the chemotherapy of human African trypanosomiasis or sleeping sickness; Suramin, pentamidine, melarsoprol and eflornithine.

African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease) are two chronic and, eventually, fatal diseases caused by species of Trypanosoma. In African sleeping sickness, Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense initially live and grow in the blood. The parasite later invades the CNS, causing inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas disease is caused by Trypanosoma cruzi and is endemic in Central and South America

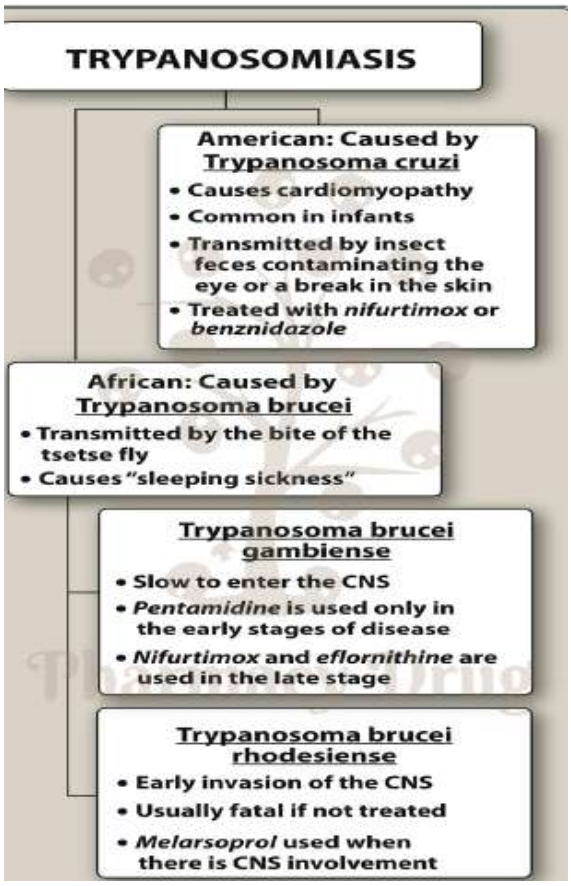

Figure-3- Summary of trypanosomiasis.

CNS = central nervous system

Pentamidine

Pentamidine is utilized to treat African trypanosomiasis caused by T. brucei gambiense in the early hemolymphatic stage without CNS involvement and is an alternative for preventing or treating infections caused by the atypical fungus P. jirovecii, especially in immunocompromised individuals. It is considered in cases where sulfonamides are contraindicated and is an alternative for treating leishmaniasis. The drug's mechanism of action involves concentration in T. brucei through an energy-dependent uptake system, potentially interfering with parasite synthesis of RNA, DNA, phospholipids, and proteins. Pentamidine is administered intravenously or intramuscularly for trypanosomiasis and P. jirovecii pneumonia. However, it carries

risks of serious reversible renal dysfunction upon discontinuation, as well as adverse effects such as hyperkalemia, hypotension, pancreatitis, ventricular arrhythmias, and hyperglycemia. Monitoring plasma glucose is crucial due to the potential for life-threatening hypoglycemia.

Suramin

Suramin is primarily employed in the early stage of African trypanosomiasis caused by T. brucei rhodesiense, especially when there is no central nervous system (CNS) involvement. Its mechanism of action involves inhibiting various enzymes, particularly those related to energy metabolism, which contributes to its trypanocidal activity. Administered intravenously, suramin binds to plasma proteins, poorly penetrates the blood-brain barrier, and exhibits a prolonged elimination half-life (over 40 days), primarily excreted unchanged in urine. Adverse reactions, though rare, may encompass nausea, vomiting, shock, loss of consciousness, acute urticaria, blepharitis, and neurologic issues such as paresthesia, photophobia, and hyperesthesia of the hands and feet. Renal insufficiency, if present, tends to resolve upon discontinuation of treatment, and acute hypersensitivity reactions are also possible.

Melarsoprol

Melarsoprol, a trivalent arsenical compound, is the primary treatment for late-stage African trypanosome infections with CNS involvement from T. brucei rhodesiense. The drug interacts with sulfhydryl groups, affecting pyruvate kinase enzymes in both the organism and host. Administration through slow IV injection is crucial to reduce the risk of resistance, potentially associated with decreased transporter uptake. However, melarsoprol is associated with CNS toxicity, particularly reactive encephalopathy, resulting in a 10% fatality rate. Co-administration of corticosteroids can help mitigate the risk of encephalopathy. Adverse effects include peripheral neuropathy, hypertension, hepatotoxicity, albuminuria, hypersensitivity reactions, and febrile reactions post-injection. Individuals with glucose-6-phosphate dehydrogenase deficiency may experience hemolytic anemia as a side effect

Eflornithine

Eflornithine is a crucial component in the treatment of late-stage African trypanosomiasis when combined with nifurtimox. The intravenous form is used, but frequent dosing is required due to its short half-life. Additionally, topical eflornithine is employed to manage unwanted facial hair in women. Potential adverse reactions include anemia, thrombocytopenia, seizures, and temporary hearing loss.

Nifurtimox

The drug, when combined with eflornithine, is employed to treat advanced infections of T. brucei gambiense and T. cruzi (Chagas disease). Functioning as a nitroaromatic compound, it undergoes reduction, generating toxic oxygen radicals that are detrimental to T. cruzi. Administered orally, the drug excreted through urine. adverse effects including hypersensitivity reactions, gastrointestinal problems, and peripheral neuropathy.

Benznidazole

Benznidazole, a nitroimidazole derivative akin to nifurtimox, is the preferred treatment for Chagas disease due to its improved tolerability compared to nifurtimox. Adverse effects, such as dermatitis, peripheral neuropathy, insomnia, and anorexia, are common. Both benznidazole and nifurtimox are cautioned against during pregnancy due to the potential risk of harm to the fetus.

Chemotherapy for Leishmaniasis

Leishmaniasis, caused by various Leishmania species and transmitted by infected sand flies, presents in three forms: cutaneous, mucocutaneous, and visceral (potentially fatal if untreated). Treatments for visceral leishmaniasis include **amphotericin B,** pentavalent antimonials (**sodium stibogluconate or meglumine antimoniate**), pentamidine, and paromomycin. **Miltefosine**, an orally active agent, is also effective.

Sodium stibogluconate, administered parenterally, is a prodrug with an unknown mechanism of action, and resistance has developed. Miltefosine interferes with parasitic cell membrane components and induces apoptosis, but its use is cautioned during pregnancy due to teratogenic effects. Adverse reactions for both treatments

include various side effects such as injection site pain, gastrointestinal upset, and cardiac arrhythmias.

Chemotherapy for Toxoplasmosis

Toxoplasmosis, a common human infection caused by the protozoan T. gondii, is transmitted through consumption of raw or undercooked infected meat, contaminated water, or accidental ingestion of oocysts from cat feces. Pregnant women can transmit the infection to their fetus, and immunocompromised patients may develop severe disseminated disease. Current treatments focus on the tachyzoite stage, with pyrimethamine, particularly in combination with sulfadiazine, being the most effective. Leucovorin is often administered to prevent folate deficiency. Alternative treatments include pyrimethamine with clindamycin or trimethoprim/sulfamethoxazole. Prophylaxis against toxoplasmosis in immunocompromised patients involves the use of trimethoprim/sulfamethoxazole. Discontinuation of pyrimethamine is advised at the first sign of a rash due to potential severe hypersensitivity reactions.

Chemotherapy for Giardiasis

Giardia lamblia, the most commonly diagnosed intestinal parasite in the United States, is typically contracted through fecally contaminated water or food. Infections involve trophozoites in the small intestine, occasionally forming cysts passed in stools. While some cases are asymptomatic, severe diarrhea, particularly in immunocompromised individuals, can occur. The preferred treatment is a single oral dose of tinidazole, with oral metronidazole as an alternative for 5 days. Nitazoxanide, approved for giardiasis and cryptosporidiosis, is administered as a 3-day oral therapy for giardiasis. Albendazole and paromomycin may also be effective, with paromomycin considered for pregnant patients.

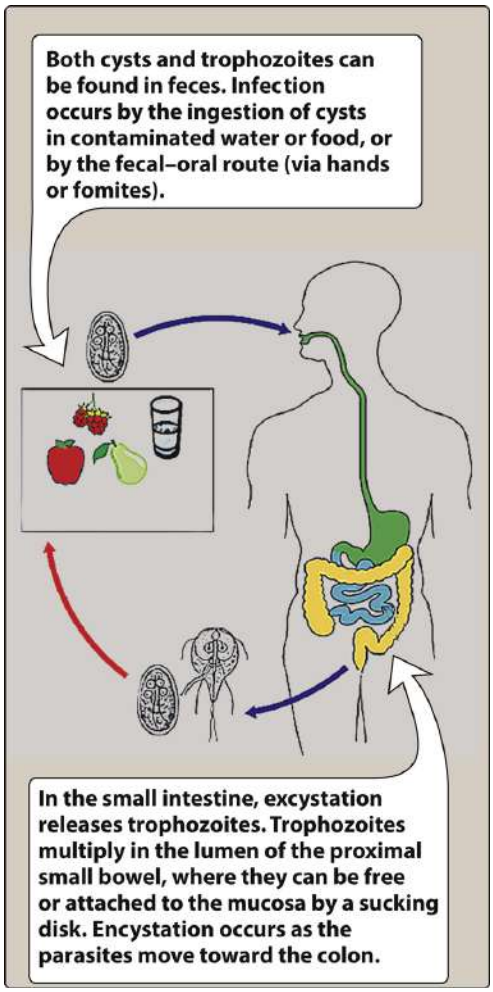

Figure: Life cycle of *Giardia lamblia*.

Anthelmintic Drugs

The three primary groups of helminths (nematodes, trematodes, and cestodes) that infect humans. Anthelmintic drugs are designed to target metabolic processes present in the parasites but not in the host. The goal of these drugs is to eliminate the organisms from the host and control the spread of infections.

DRUGS FOR THE TREATMENT OF NEMATODES

Nematodes, elongated roundworms with a complete digestive system, cause infections in the intestines, blood, and tissues.

A. Mebendazole, a synthetic benzimidazole compound, is a first-line treatment for whipworms, pinworms, hookworms, and roundworms. It acts by binding to parasite β-tubulin, inhibiting microtubule polymerization, and expelling affected parasites in feces.

Adverse effects include abdominal pain and diarrhea, with rare but serious effects like convulsions in infants and an increased risk of Stevens–Johnson syndrome or toxic epidermal necrolysis when combined with metronidazole. Mebendazole is **contraindicated i**n pregnancy.

B. Pyrantel pamoate

Pyrantel pamoate is an effective treatment for pinworm and hookworm infections, particularly in the intestines. It functions as a depolarizing neuromuscular blocking agent, causing acetylcholine release and cholinesterase inhibition, resulting in worm paralysis and expulsion. Due to its poor absorption after oral administration, it mainly acts locally.

Adverse effects are generally mild and include nausea, vomiting, and diarrhea.

C. Ivermectin

Ivermectin is the drug of choice for cutaneous larva migrans, strongyloidiasis, and onchocerciasis (river blindness). It also finds efficacy in treating scabies and head lice through a topical formulation. Effective by targeting glutamate-gated chloride channel receptors, enhances chloride influx, leading to hyperpolarization, paralysis, and

death of the worm. Administered orally, it does not easily cross the blood–brain barrier and is **contraindicated** in pregnancy due to potential risks. Its use in onchocerciasis may induce a Mazzotti reaction, with symptoms alleviated by antihistamines or steroids, .

D. Moxidectin

Is an alternative to ivermectin for treating onchocerciasis, sharing a similar mechanism of action without affecting adult worms. Its safety in pregnancy is not confirmed, and its use can lead to the Mazzotti reaction due to the death of microfilaria in onchocerciasis.

E. Diethylcarbamazine

Diethylcarbamazine is the preferred treatment for filariasis caused by Wuchereria bancrofti, Brugia malayi, or Brugia timori. It effectively kills microfilariae and targets adult worms. Administered orally with meals, the drug is rapidly absorbed and primarily excreted through urine.

Adverse effects: include fever, nausea, vomiting, arthralgia, and headache.

Drugs for the Treatment of Trematodes

Trematodes, or flukes, are flatworms with a leaf-shaped structure, and they are identified based on the tissues they infect, such as the liver, lung, intestine, or blood.

A. Praziquantel

Is the preferred treatment for various parasitic infections, including schistosomiasis, most trematode infections (excluding fascioliasis), and certain cestode infections like taeniasis. Its mechanism involves inducing contracture and paralysis in parasites by enhancing cell membrane permeability to calcium. The drug is rapidly absorbed orally and should be taken with food. Metabolized extensively, inactive byproducts are primarily excreted through urine. **Common** side effects include dizziness, malaise, headache, and gastrointestinal disturbances. phenytoin is contraindicated, Notably, praziquantel should not be used to treat ocular cysticercosis due to the risk of irreversible damage to the eye.

B. Triclabendazole

Is a benzimidazole derivative used to treat fascioliasis caused by liver flukes (Fasciola hepatica and Fasciola gigantica). It is inhibiting tubulin function, protein synthesis, and enzyme synthesis**. Common** side effects include abdominal pain, hyperhidrosis, and nausea. Its use in pregnancy should be approached with caution due to limited available data.

Drugs for the Treatment of Cestodes

Cestodes, commonly known as "true tapeworms," are characterized by a flat, segmented body that attaches to the host's intestine. Similar to trematodes, tapeworms lack a mouth and digestive tract throughout their life cycle.

A. Niclosamide

No longer available in the United States, serves as an alternative to praziquantel for treating taeniasis, diphyllobothriasis, and other cestode infections. Its mechanism involves inhibiting mitochondrial phosphorylation of adenosine diphosphate in the parasite, causing lethality for the cestode's scolex and segments, but not for the ova. To enhance efficacy, a laxative is administered before oral intake to purge the bowel of dead segments and improve ova liberation. It is recommended to avoid alcohol within 1 day of niclosamide use.

B. Albendazole

Albendazole, a benzimidazole derivative, is effective against a broad spectrum of nematodes by inhibiting microtubule synthesis and glucose uptake. Its primary therapeutic use is in treating cestodal infestations, particularly cysticercosis and hydatid disease caused by the larval stage of Echinococcus granulosus. Additionally, Albendazole is effective against microsporidiosis, a fungal infection. Despite erratic absorption, its uptake is improved with a high-fat meal. Prolonged treatment for hydatid disease carries a risk of hepatotoxicity, agranulocytosis, or pancytopenia, necessitating regular monitoring of blood counts and liver function tests every two weeks.