

ESSENTIALS OF PHARMACOLOGY



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Essentials of Pharmacology

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Preface

Preface

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1: Introduction to Pharmacology

Learning Objectives

- Define pharmacokinetics and pharmacodynamics.
- Distinguish among a drug's chemical, generic, and trade name.
- Describe the paths a drug may take when it is free in circulation.
- Recognize and interpret a dose-response curve.
- Memorize the meaning of basic pharmacologic terminology such as agonist, antagonist, and other bolded terms.

1.0 Introduction to Pharmacology

Pharmacology is the study of the effects of drugs on the function of living systems. Drugs may be chemical agents, synthetically manufactured from plants or animals, or genetically engineered products such as biopharmaceuticals. **Pharmacokinetics** is the term for what happens to the drug within the body or the body's actions on the drug, while the action of drugs on the body is called **pharmacodynamics**.

The preparation of drugs is called pharmacy practice, with much of the practice focusing on pharmacotherapeutics and the treatment of disease. Most drugs are xenobiotics, a chemical that originates outside the body (also referred to as exogenous) and are introduced into the body by various routes of administration. For a drug to be effective, it must enter the body and be distributed to its site of action. This site of action is often a macromolecular receptor in the target tissue, but drugs may also be designed to interrupt a signaling pathway.

A common challenge in studying pharmacology is recognizing the thousands of drug names. Drugs have three different names: chemical, generic, and trade. Each drug's chemical structure and name are unique. For example, the chemical name for aspirin is 2-



acetoxybenzoic acid, and its structure is

There is only one generic name for a drug. Most organizations, including the World Health Organization (WHO) and Food and Drug Administration (FDA), usually refer to drugs by their generic name (note that generic names are not capitalized). The drug's trade name is assigned by the pharmaceutical company marketing the drug. The trade name is sometimes called the brand or proprietary name, such as Bayer's Aspirin.

1.1 Overview of Pharmacokinetics

A drug can enter the body by several different routes. Pharmacokinetics is what happens to the drug after it's in the body. Pharmacokinetics focuses on the absorption, distribution, metabolism (also referred to as biotransformation), and elimination of the concentration of a drug in the body over time. Principles of chemistry are applied while studying pharmacokinetics because the interactions between the drug and body molecules are simply a series of chemical reactions. Understanding the chemical encounters between drugs and biological environments is necessary to predict how much of a drug will be metabolized by the body. Most drug effects are temporary because the body has systems for drug detoxification and elimination. Toxicology is the branch of pharmacology focusing on drugs that produce adverse or unwanted effects.

In Chapter 1, we will consider these issues broadly and go into more depth in the following chapters. As you read, refer to Figure 1.1 below.

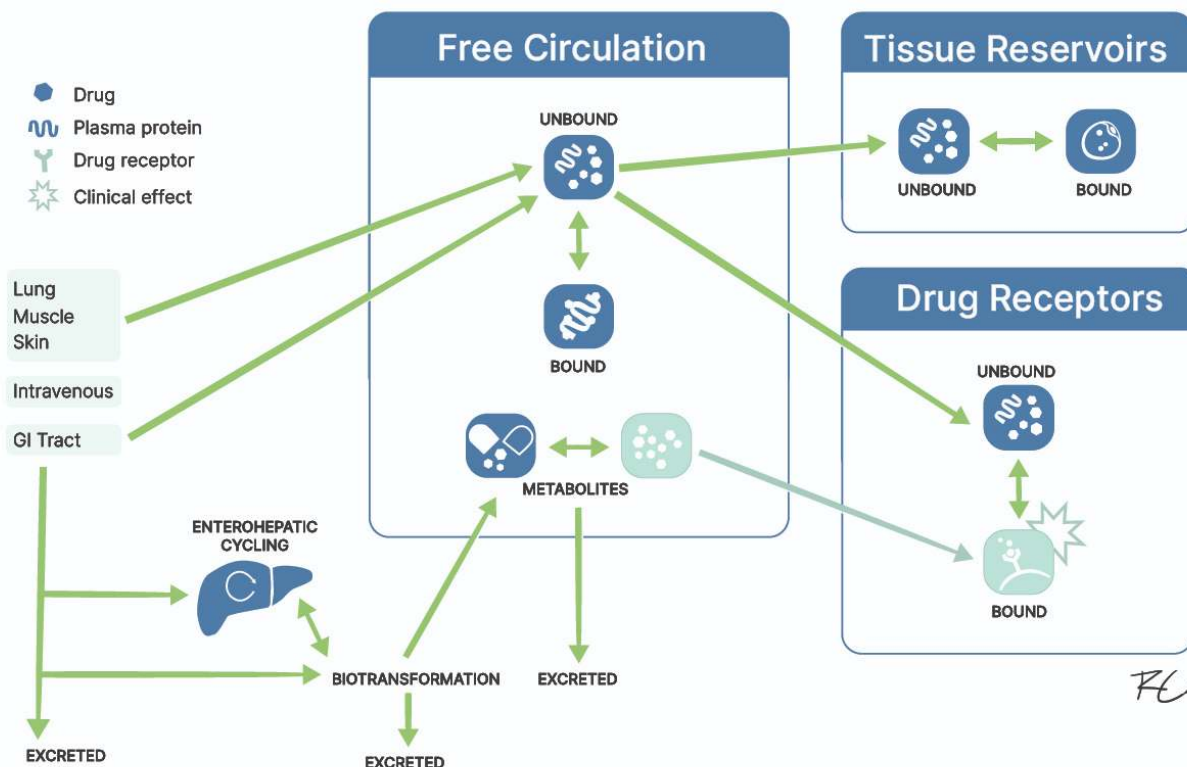


Figure 1.1: Drug Routes of Administration. (CC-BY 4.0; Riley Cutler)

1. A drug may enter the body in a variety of ways: as an oral liquid, tablet, or capsule; as an inhaled vapor or aerosol; topically absorbed through intact skin or a mucous membrane; or injected into muscle, subcutaneous tissue, spinal fluid, or intravenously (directly into the bloodstream). The physical properties of the drug and the specific way the drug is prepared greatly influence the speed or rate of its absorption. Drugs given intravenously have the quickest absorption.
2. If the drug is given orally and swallowed, it must be absorbed from the GI tract into the portal circulation (stomach → gut → portal vein → liver). If the drug is absorbed through the skin, mouth, lungs, or muscle, it will go directly into systemic circulation. If the drug is injected intravenously, 100% of the drug is “bioavailable” for distribution to tissues. This is not usually the case for other modes of administration. For example, an oral drug absorbed via portal circulation will first pass through the liver, the primary site of drug metabolism. Once a drug is metabolized, it is more likely to be excreted, causing less drug to reach the systemic circulation. This phenomenon is known as “**first-pass**” **metabolism**. First-pass metabolism reduces an oral drug’s **bioavailability** to less than 100%. Examples of drugs with a significant first-pass effect include alcohol, insulin, and morphine.
3. Once in the bloodstream, a portion of the drug may exist as a free drug, having been dissolved in plasma water and able to bind to other molecules. Some drugs will be reversibly taken up by red cells, and other drugs will be reversibly bound to plasma proteins. Reversible means the chemical bond can be broken. For many drugs, the bound form of the drug accounts for 95-98% of the total concentration of the drug in the body. This is important because the free drug is active, traversing cell membranes and producing the clinically desired effect. It is also significant because a protein-bound drug can act as a reservoir. When the chemical bonds are broken, the drug is released. Once the drug is unbound or in a free state, it can become active. The action of protein-bound drugs or binding to other reservoir sites in the body (adipose, bone) is prolonged and somewhat unpredictable.
4. An unbound drug may follow its concentration gradient and distribute into peripheral tissues. In some cases, the tissue contains the target site; in others, the tissue is unaffected by the drug.

5. The total amount of the drug within the body (in circulation and reservoir sites) reflects the **volume of distribution**. The volume of distribution determines the drug's equilibrium concentration after a specified dose. How long the drug is expected to remain in the body can be calculated using the volume of distribution.
6. Tissue-bound drug eventually reenters the bloodstream, which perfuses the liver and kidneys. The liver metabolizes most drugs into inactive or less active compounds, which are more readily excreted. These metabolites and some parent compounds (non-metabolized drugs) may be excreted in the bile and eventually pass out of the body in the feces. Alternatively, some drugs may be reabsorbed further down the GI tract (enterohepatic cycle). Any biotransformed drug not excreted in bile passes back into the systemic circulation.
7. The parent drug and metabolites in the bloodstream may be excreted through kidney filtration, where a portion undergoes reabsorption and returns to plasma. The remainder is excreted in the urine. Some drugs are actively secreted into the renal tubule. Another route of excretion is the lungs; this route eliminates alcohol and anesthetic gases. Smaller amounts of the drug are eliminated in sweat, tears, and breast milk.
8. Biotransformation of a drug may sometimes produce biologically active metabolites, which may be intended or unintended. A parent drug manufactured to be inactive until it is biotransformed after administration is referred to as a prodrug. Enalapril, clopidogrel, and codeine are examples of prodrugs.

1.2 Overview of Pharmacodynamics

Pharmacodynamics is the study of a drug's biochemical and physiologic effects on the body. A drug's specific site of action is called the mechanism of action (MOA). The MOA for most drugs is binding to particular receptors on the surface or interior of cells. However, many other cellular components and non-specific sites can serve as sites of drug action or drug targets.

1. Water can be a target. The kidney does not reabsorb osmotic diuretics such as mannitol, and the osmotic load they create in the renal tubule forces the loss of water. Laxatives like magnesium sulfate work in the intestine by the same principle.
2. Hydrogen ions can be targets. Ammonium chloride is sometimes used to acidify urine. When taken orally, the liver metabolizes the ammonium ion to urea, while the chloride is excreted in the urine. The loss of Cl^- forces the loss of H^+ in the urine, thus lowering the pH.
3. Metal ions can be targets. Chelating agents like EDTA (ethylene diamine tetra-acetic acid) may bind divalent cations like Pb^{++} . Metal ions are most frequently drug targets in cases of poisoning.
4. Enzymes are targets of many therapeutically beneficial drugs. Drugs may inhibit enzymes by competitive, non-competitive, or irreversible blockade at a substrate or cofactor binding site. Digitalis glycosides increase myocardial contractility by inhibiting the membrane enzyme $\text{Na}^+ - \text{K}^+ - \text{ATPase}$. Antimicrobial and antineoplastic drugs commonly work by inhibiting enzymes critical to the cell's functioning. These drugs must have some selective toxicities toward bacterial or tumor cells to be effective. This usually means there is a unique metabolic pathway in these cells or some difference in enzyme selectivity for a common metabolic pathway that the drug disrupts. An example of this is the inhibition of folate synthesis by sulfonamides. Sulfonamides are effective antibacterial agents because the bacteria depend on folate synthesis, whereas the host does not. This example will be covered in detail in one of our case discussions.
5. Nucleic acids are targets for antimetabolites and some antibiotics. In the case of fluorouracil (5-FU), the compound acts as a substitute for uracil and becomes incorporated into a faulty mRNA.
6. **Biologics** are drugs designed to interrupt the immune system's signaling (e.g., interleukins, $\text{TNF-}\alpha$) involved in the pathogenesis of chronic inflammatory disorders. Biologics are extracted or isolated from human, animal, or microorganism sources. They may also be produced by biotechnology.
7. Finally, some drugs act by binding to specific **receptors**. These drugs have both structural specificity and selectivity. Interacting with a drug may turn receptors on (agonist) or off (antagonist). When a specific drug binds to a receptor, the physiologic activity regulated by that receptor increases or decreases. An example is using a beta-1 adrenergic receptor blocker or antagonist to lower heart rate.

Unfortunately, no matter how effectively a drug works in a laboratory simulation, its performance in the human body will not always produce the same results, and individualized responses to drugs must be considered. Although many responses to medications may be anticipated, one's unique genetic makeup may also significantly impact one's response to a drug. Pharmacogenetics is the study of how people's genes affect their response to drugs.

Below are important concepts that we will return to repeatedly throughout the course.

- An **agonist** is a drug that binds to its "receptor" and produces its characteristic effect. Depending on the maximal effect a drug produces, that drug may be a **full** or **partial agonist**.
- An **antagonist** binds to the receptor without causing an effect, preventing an active substance from gaining access. Antagonists, like enzyme inhibitors, may be **competitive**, **non-competitive**, or **irreversible**.
- **Dose-response**. It is expected that as the dose of the drug increases, the response should increase. The curve generated is usually sigmoidal when the effect is plotted against the log dose. The effect may be measured as a graded variable (change in blood pressure, force of contraction) or a quantal variable (number dead/alive). The slope of the curve is characteristic of the particular drug-receptor interaction. We expect two parallel log-dose response curves when two drugs act by the same receptor mechanism. Figure 1.2 shows a dose-response curve for Drugs A (red) and Drug B (blue). The characteristic sigmoidal shape shows that as the dose increases, the response to the drug is greater until a plateau or maximal effect is reached. The curve for Drug A is to the left of the curve for Drug B, indicating that less (a lower dose) of Drug A is needed to elicit a response.

Dose Response Curve Comparing the Efficacy of Two Drugs

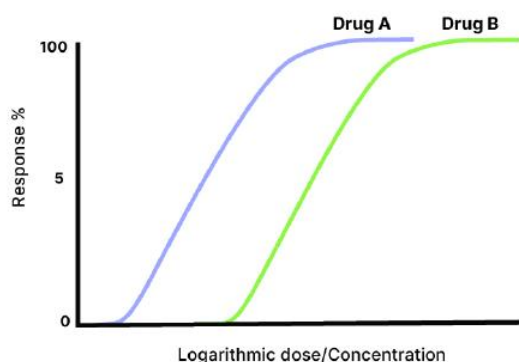


Figure 1.2: Dose Response Curve Comparing the Efficacy of Two Drugs. (CC-BY 4.0; Riley Cutler)

- **ED50**. The median effective dose is the dose that produces a response in 50% of the sample. If the response is death (known as lethality), we call it the **LD50**. Importantly, the **EC50** refers to *concentration* rather than dose.
- **Potency**. Potency is often misused to mean "effectiveness." Instead, a drug's potency refers to the dose (the molar concentration) required to produce a specific intensity of effect. If the ED50 of drugs A and B are 5 and 10 mg, respectively, the relative potency of A is twice that of B. Relative potency specifically applies to comparing drugs that act by the same mechanism and, therefore, have parallel dose-response curves.
- **Efficacy**. Also called **maximal efficacy** or intrinsic activity, this is the maximum effect the drug can produce. A potent drug may have a low efficacy, and a highly efficacious drug may have a low potency. For the clinician, efficacy is more important than potency (within limits).
- **Affinity**. The stickiness or affinity refers to the strength of the binding between the drug and the receptor. It is quantified by the dissociation constant K_d and takes into account the off-rate (unbound) divided by the on-rate (bound).
- **Selectivity**. Selectivity is the separation between a drug's desired (targeted) and undesired effects. Ideally, a drug is completely specific, and an effective dose does not elicit any undesired effect. However, that is usually not the case. Most drugs are selective, not exclusive. As a drug concentration increases, the drug can lose its selectivity for one receptor and may bind to other receptors.
- **Therapeutic window**. For every drug, there exists some concentration that is just barely effective (the **effective concentration**) and some dose that is just barely toxic (the **Toxic concentration**). Between the two is the therapeutic window where the safest and most effective treatment occurs.
- **Therapeutic index (TI)**. The ratio of toxic to effective doses: TD_{50}/ED_{50} . In animal toxicology studies, it is usually the LD_{50}/ED_{50} . A narrow TI represents a small "window" where the drug is both safe and effective.

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CHAPTER OVERVIEW

2: Pharmacokinetics

Learning Objectives

- Review the four phases of pharmacokinetics.
- Explain the process of absorption, including how drugs and other substances cross membranes.
- Compare the bioavailability and the clinical implications of the various routes of drug administration.
- Discuss factors that affect drug absorption.
- Explain the process of how drugs are distributed throughout the body.
- Describe how plasma protein binding affects distribution.
- Explain the process of metabolism and its application to pharmacotherapeutics.
- Illustrate how genetics can influence drug metabolism.
- Compare the response of metabolizing phenotypes of prodrugs vs active parent drugs.
- Explain the three major processes of drug elimination.
- Identify the factors that influence a steady state.
- Explain how a steady state of a drug is achieved and maintained.

2.0 Pharmacokinetics Overview

Pharmacokinetics is the study of how the body processes a drug. Pharmacokinetics is often organized into the four discrete processes of **absorption**, **distribution**, **metabolism**, and **excretion** (ADME). The first stage of pharmacokinetics is absorption. Absorption is the process by which a drug enters the bloodstream from its site of administration. Distribution is the movement of the drug from the blood into the target organs, tissues, and cells. Metabolism describes how the body alters the drug to make it inactive or make the drug more available for removal from the body. Distribution is the movement of the drug from the blood into the tissues and cells. Excretion is the process of the drug's removal from the body.

[2.1: Absorption](#)

[2.2: Distribution](#)

[2.3: Metabolism](#)

[2.4: Elimination](#)

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2.1: Absorption

Overview of Absorption

Drugs initially enter the body through various routes of administration (e.g., oral ingestion, injection, inhalation, absorption through the skin) and then are absorbed. The absorption process requires drug molecules to cross membranes and move into intracellular and extracellular spaces. Drugs cross membranes by diffusion, channel proteins, or active transport through the lipid bilayer. Some drugs must be transported across a membrane by a special carrier or transport protein (especially large-molecule drugs).

Routes of administration

The rate of absorption varies with the route of administration. For some drugs, the amount absorbed may be a small fraction of the dose administered by a specific route. The amount of drug absorbed into circulation divided by the total amount of drug administered equals that drug's bioavailability (F) by that route. Since intravenous drugs are administered directly into circulation, the bioavailability of any drug given intravenously equals 1.0 or 100%. Common routes of administration and characteristics are listed in Table 2.1.

Table 2.1 **Common routes of administration and characteristics**

Route	F (%)	Comment
IM (intramuscular)	75 <100	Absorption is delayed compared with IV, dependent on the site of administration. A larger volume of drug can be given than with subcutaneous administration.
inhaled	5 <100	Rapid absorption; a good route to deliver anesthetics or drugs intended for the respiratory system
IV (intravenous)	100	Immediate absorption
PO (oral)	5 <100	Absorption may be slow and influenced by first-pass effect, gastric pH, concomitant medications, and co-morbidities Oral formulations such as enteric coating and extended release affect the rate of absorption.
rectal	30 <100	Less first-pass; good for drugs with unpleasant taste or in persons who may not be able to take medications by mouth
SC (subcutaneous)	75 <100	Absorption is delayed compared with IV; a smaller volume of drug can be given than through intramuscular administration. Bioavailability depends on the site of administration, vascularity, and the person's hydration status.
SL (sublingual) or buccal (not swallowed)	varies (35% for nitroglycerin 5 mg)	
	80 <100	Slow, no first-pass effect; slow absorption, long duration; the systemic effect may be affected by site of administration or the individual's specific factors (body temperature)

As an orally or enterally administered drug moves through the gastrointestinal (GI) tract, it may be deactivated by enzymes present in the stomach and duodenum. When a drug enters circulation from the intestines, liver enzymes may break down part of it, and some drug molecules may escape to the general circulation. When a significant amount of a drug is metabolized in the intestinal wall, portal circulation, or liver before it reaches circulation, the phenomenon is known as **first-pass effect** or **metabolism**.

Please look at Figure 1.1, which shows the path a free drug can take as it travels through the circulation. Some drugs become protein-bound, rendering the drug inactive, whereas other drugs remain free in circulation and bind to a receptor site. The effects of

drug-receptor binding are further described in [Chapter 3](#). Several doses of an oral drug may be required before enough free drug stays active in the circulation (therapeutic level) to exert the desired effect or clinical response.

Drugs that undergo high first-pass metabolism have a less predictable therapeutic level. The therapeutic level, as defined above, is independent of the route of administration or first-pass effect. Importantly, a drug with a high first-pass effect, given orally, results in lower concentrations of the active drug than if the same amount were administered parenterally. To avoid the first-pass effect, some drugs may be administered using alternate routes such as dermal, nasal, inhalation, injection, or intravenous. Alternative routes of administration bypass the liver by entering circulation directly or via absorption through the skin or lungs. Notable drugs with a high first-pass effect include buprenorphine, ethanol, morphine, and tetrahydrocannabinol (THC). Nitroglycerin (NTG) and estrogen are well known to undergo first-pass metabolism and are commonly prescribed as sublingual and transdermal.

Alternative routes of medication have other patient-related problems to consider. For example, injections may be painful or difficult to administer daily, and breaks in the skin create a risk for infection. Injectable drugs can be costly and may cause localized side effects or contribute to fluctuating drug blood levels.

A transdermal route has the primary benefit of slow, steady drug delivery directly into circulation without first passing through the liver. Drugs delivered transdermally enter circulation via a meshwork of small arteries, veins, and capillaries in the skin. This makes the transdermal route particularly useful in clinical situations where the goal is to administer the drug over a long period to control symptoms. For example, a transdermal fentanyl “patch” is used to treat chronic pain, and a nitroglycerin patch is prescribed to treat chronic chest pain. Despite their advantages, skin patches have a significant drawback in that only very small drug molecules can enter the body through the skin, making this route not viable for all types of medications. Additionally, transdermal patches may come dislodged from the patient's skin, and the rate of drug dispersal may be affected by changes in body temperature or externally applied heat.

Inhaling drugs through the nose or mouth is another alternative route for rapid medication delivery that bypasses the liver. The inhalation route may also be particularly effective for medications whose site of action is in the lungs. Metered-dose inhalers have been a mainstay of asthma therapy for decades. Recently, the FDA approved the first over-the-counter prescription naloxone 4 mg nasal spray for substance abuse disorder. Inhalation is an efficient route to reverse the effects of an opioid overdose; naloxone is the standard treatment for opioid overdose.

Other Variables that Affect Absorption

In addition to the route of administration, other variables influence the rate and extent of drug absorption, including the size of the drug molecule, lipid solubility of the drug, the degree of ionization of the drug within the gastrointestinal tract, the pH of the internal environment, gastric emptying rate/motility, GI blood flow, and the presence of other drugs or food within the GI tract.

Size of the Drug Molecule

Drugs vary in size and molecular weight. Drugs with a large molecular weight (MW greater than 1000) are poorly absorbed. Large molecular weight drugs (for example, heparin) are often administered by parenteral or intravenous routes to increase absorption.

Lipid Solubility Drug

The lipid solubility of a drug determines how easily the drug will pass through a membrane. Lipid-soluble drugs pass through membranes readily (including the blood-brain barrier) and are absorbed more quickly than water-soluble drugs. Lipid-soluble drugs often undergo first-pass metabolism. These drugs tend to accumulate in fatty tissues and may be difficult to excrete. Water-soluble drugs tend to stay within the circulation.

Ionization of Drugs

Drugs are either weak acids or weak bases and may be ionized (charged) or not ionized. The pH of the environment determines the number of drug molecules that become ionized. Ionized drugs are more polar and water-soluble and are more easily excreted.

pH

The pH of the gut changes from an acidic environment in the stomach to an alkaline environment in the duodenum. Drugs can influence the pH of the gastric environment. For example, an antacid changes the gastric environment to be more alkaline and can

affect the absorption of other drugs. A weak acid is more lipid soluble in an acidic environment, and a weak base is more lipid soluble in an alkaline environment. When a drug is more lipid soluble, it can move readily through membranes.

Gastric motility

The rate and extent of absorption following oral drug administration are highly variable. Gastric pH can influence absorption and how quickly the drug moves through the gut. Most orally administered drugs are primarily absorbed in the small intestine.

Blood flow

Blood flow influences how well a cutaneous or intramuscular injection is absorbed. In hypoperfusion or shock states where blood flow is compromised, drugs may not be well absorbed, and the intravenous route is the best option. Drugs are absorbed more rapidly in areas where blood flow is high.

Presence of other drugs or food in the GI tract

As mentioned previously, other drugs a person is taking can change the pH, gastric motility, and pre-systemic metabolism of a medication. Some drug absorption may vary depending on the person's fasting or fed state (the body digests and absorbs nutrients, and insulin levels are high).

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2.2: Distribution

2.2 Overview of Distribution

After a drug has been absorbed or administered intravenously, the second phase of pharmacokinetics, distribution, begins. In this phase, the drug is distributed throughout the body and gains exposure to its target site via the circulatory system.

A medication's distribution can also cause unintended adverse or side effects, as described in [Chapter 6](#). Drugs are designed to be **selective**, binding to one specific receptor and primarily causing one effect. Often, that is not the case. The likelihood of a drug binding to another receptor increases as the amount of drug in circulation increases. Side effects may occur when a drug binds to other sites in addition to the intended target. These side effects can range from tolerable to unacceptable, resulting in discontinuation of the medication (a drug given to treat a disease state). For example, a person might take ibuprofen (Advil®) for muscle soreness in their leg, and the pain may be relieved, but the side effect of gastric irritation may cause the person to stop taking the medication.

As a drug is circulated throughout the body, it crosses membranes to be dispersed into interstitial and intracellular fluids. There is often no direct way to measure the drug concentration in the target tissue. Instead, blood plasma levels are used as a surrogate to determine the concentration of a drug within the body. The amount of drug that reaches the target molecule or tissue depends upon many factors that determine how easily a drug can move through the body and cross membranes (including the blood–brain barrier and the placental barrier). These factors include blood flow, plasma protein binding, lipid solubility, drug concentration gradients, and permeability. Other factors include capillary permeability, differences between blood/tissue, and volume of distribution.

Blood Flow

Blood flow is a major regulating factor in the rate of drug uptake at a particular distribution site. Drug uptake is quicker in well-perfused tissues such as the brain, heart, kidneys, and splanchnic organs. Poor perfusion to the target organ can affect medication delivery, such as decreased blood flow in dehydration, heart failure, shock states, or other clinical scenarios involving compromised circulation. For example, when administering an antibiotic to a patient with diabetes who has an infected toe, it may be difficult for the antibiotic to reach a therapeutic concentration within the cells of the infected toe. This is because the same processes that contribute to the development of the infection, poor circulation to the foot/toe, also affect the distribution to that site.

Protein-Binding

One factor impacting the medications' distribution is the presence of plasma proteins in the blood, including albumin and glycoproteins. Albumin is the most abundant plasma protein, and its levels are decreased by malnutrition, liver dysfunction, and aging. A certain percentage of almost every drug is bound to plasma proteins once it reaches circulation. The portion of the drug that becomes “protein-bound” will be inactive while it is bound. The portion of the unbound or “free” drug is available to bind to the target tissue or target molecule and exerts its effect or blocks an action. The binding of a drug to plasma proteins is usually reversible, meaning that as a drug concentration decreases, the drug is released from the plasma protein. In contrast, an irreversibly bound drug is not released as concentration levels decrease. The drug's **affinity** for a specific plasma protein or a receptor determines the probability of the drug binding to plasma proteins or a receptor.

A patient taking several highly protein-bound medications may experience a greater risk of side effects from each of these drugs. The affinity among the prescribed medications for a plasma protein (often albumin) varies. Suppose more than one medication that binds to plasma proteins is in circulation. In that case, the medications compete for the binding site, and the medication with the highest affinity will bind to the plasma protein. This action prevents other medications in the circulation from binding to plasma proteins, which float freely in the circulation and are available to bind to receptors, increasing the risk of side effects and toxicities.

Blood–Brain Barrier

Medications destined for the central nervous system (the brain and spinal cord) face an even larger obstacle than protein-binding; they must also pass through a nearly impenetrable barricade called the blood–brain barrier. This barrier is formed from a tightly woven mesh of capillaries that protects the brain from potentially dangerous substances such as microbes (viruses) and foreign molecules (drugs). Only lipid-soluble medications or medications that bind to a “carrier” or transport protein can cross the blood–brain barrier.

Pharmacologists and research scientists involved in designing and manufacturing drugs have devised ways for certain medications to penetrate the blood–brain barrier. An example is the brand-named medication Sinemet®, which is a combination of two drugs, carbidopa and levodopa, used to treat Parkinson’s Disease. Levodopa is lipid-soluble and crosses the blood–brain barrier, where it enters the brain and is converted into dopamine to exert its effect on Parkinson’s disease symptoms. However, if levodopa is given alone without carbidopa, it is degraded in the peripheral circulation, and only a small fraction of the original dose of levodopa reaches the brain. Carbidopa prevents the degradation of levodopa in peripheral circulation, allowing a larger amount of the levodopa to enter the brain and exert a therapeutic effect. This is an example of a **synergistic** drug combination.

Some lipid-soluble medications bypass the blood–brain barrier and impact an individual’s central nervous system function (CNS depressants). For example, diphenhydramine (Benadryl®) is an antihistamine that decreases allergy symptoms. However, because it crosses the blood-brain barrier and depresses the central nervous system, diphenhydramine causes drowsiness. This drowsy side effect may benefit a person who has difficulty falling asleep. Still, it may be problematic for another person as they try to carry out daily activities safely.

Placental Barrier

Consider the effects of medication on individuals who are or may become pregnant. The placenta is known to be permeable to substances such as alcohol, cocaine, caffeine, and certain prescription medications that cross the fetal–placental barrier. Some drugs can cause harm to the unborn fetus during any trimester, while others are teratogenic during a specific trimester. Further information is found in Chapter 7.

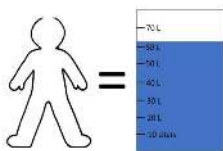
Tissue Differences in Rates of Drug Uptake

How quickly an organ or target tissue takes up a drug depends on the surface area of the organ or tissue. The larger the surface area, the faster the drug will be distributed to that tissue.

Capillary permeability is also tissue-dependent. Distribution rates are relatively slower or non-existent in the CNS because of the tight junction between capillary endothelial cells, the blood-brain barrier, and the presence of P-glycoproteins. These efflux proteins expel foreign molecules from the brain. Capillaries of the liver and kidneys are fenestrated or more porous, allowing for greater permeability.

Apparent Volume of Distribution

The **volume of distribution (Vd)** is not an actual anatomical space but a theoretical space. The volume of distribution (Vd) is the concentration of a drug spread across fluid compartments: plasma, extracellular water, and total body water. The volume of distribution is the pharmacokinetic parameter that relates the dose to the plasma concentration. Clinically, it is essential for accurately predicting how much medication we need to administer to achieve the desired therapeutic concentration in the plasma. Vd helps clinicians calculate that dose. Vd is depicted below. In the figure below (Figure 2.2.1), the Vd for the human figure on the left equals approximately 60 ml of fluid in the beaker on the right.



Vd is calculated by using the amount of the drug in the body divided by the plasma concentration of the drug ($Vd = \text{total amount of drug} / \text{plasma drug concentration}$).

Every drug has a different Vd and pattern of distribution. Some drugs are widely distributed in the body and cross cellular membranes to disperse into adipose tissue or bone (Figure 1.1). These drugs have a wide or large Vd. In contrast, some drugs may not distribute extensively throughout the body but stay in the plasma compartment. Such drugs may have relatively small Vd, and relatively low doses are necessary to achieve a target concentration. Other drugs may bind to plasma proteins. In this case, plasma drug levels may not accurately reflect the pharmacologic effect the drug may exert. Figure 2.2.2 below illustrates how a drug may bind and distribute throughout tissues and the subsequent relationship to the plasma concentration of a drug in circulation.

Figure 2.2.2 depicts drug binding between the vascular and extracellular compartments under various hypothetical clinical conditions. In panel A, Drug A

Drug Binding & Volume of Distribution

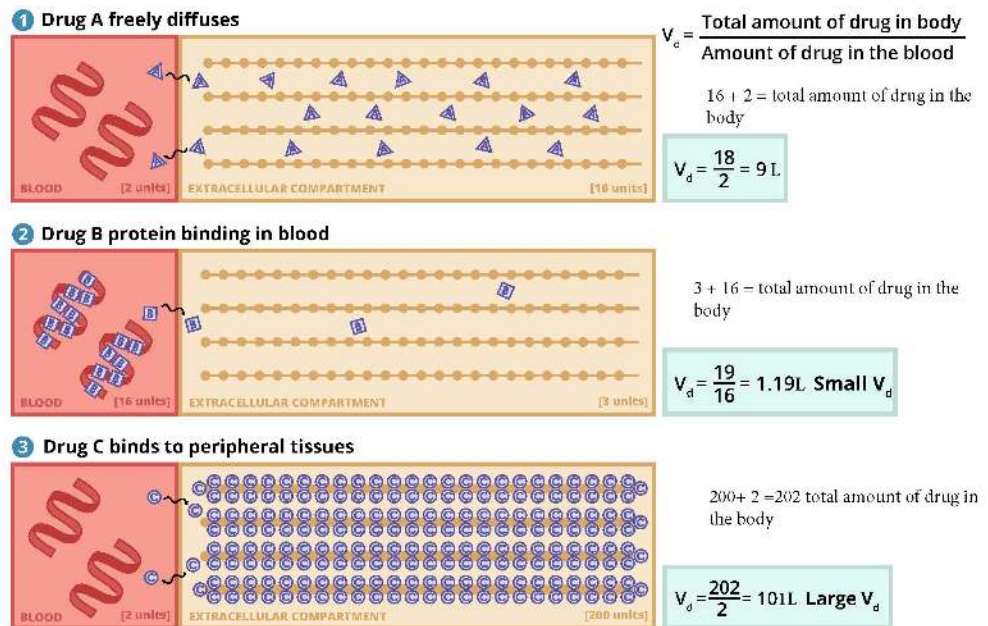
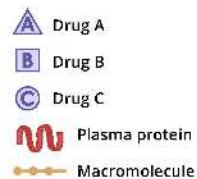


Figure 2.2.2: Drug binding and distribution. (CC-BY 4.0; Amy Hoang)

diffuses freely across the membrane between the two compartments. As a drug freely diffuses, it will reach equilibrium or steady state. At equilibrium, 20 mg of the drug is in the body. With 20 mg of the drug in the body, the steady-state distribution leaves a 2 mg/L plasma concentration.

In panel B, Drug B binds plasma proteins in the vascular compartment. At equilibrium, only 2 mg of the total drug is present in the extravascular compartment, while the remaining 18 mg is still in the vascular compartment. For the conditions in panels A and B, the total amount of drug in the body is the same (20 mg), but the apparent V_d is very different.

Finally, in panel C, Drug C exits the vascular compartment and strongly binds to molecules in peripheral tissues. For Drug C to reach a plasma concentration of 2 mg/L, a larger total dose of 200 mg must be given to achieve the desired plasma concentration. At equilibrium, 198 mg are bound in the peripheral tissues and only 2 mg in the plasma, so the calculated volume of distribution is greater than the physical volume of the system.

Clinicians use V_d to calculate how much drug or dose is needed to achieve a therapeutic concentration of a drug in the plasma. Another important point about understanding V_d is that it helps explain the limitations of plasma drug levels. As demonstrated in Figure 2.21, a plasma drug level doesn't accurately reflect how much drug may be in the body. Clinicians need to be aware of the pharmacokinetic properties of individual drugs, including drugs that bind to plasma proteins such as digoxin, amiodarone, and ibuprofen. The V_d of drugs that bind to plasma proteins (albumin) can be altered by liver disease through reduced protein synthesis and kidney disease through protein loss in the urine. On the other hand, if a drug is avidly bound in peripheral tissues, the drug's concentration in plasma may drop to very low values even though the total amount in the body is large. As a result, the V_d may greatly exceed the total physical volume of the body. For example, 50,000 liters is the average V_d for the drug quinacrine, also known as mepacrine, in persons whose average physical body volume is 70 liters.

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2.3: Metabolism

2.3 Overview of Metabolism

The next pharmacokinetic phase is metabolism. Drug metabolism or biotransformation is the chemical alteration or breakdown of the drug's structure. Although most drug metabolism occurs in the liver, the enzymes responsible for metabolizing drugs and other foreign substances (**xenobiotics**) are found in most tissues within the body.

As mentioned above, most biotransformation reactions take place in the liver. These biotransformation reactions are categorized into two phases: Phase I and Phase II. Phase I reactions introduce or uncover a functional group on the drug molecule, which makes it more amenable to phase II metabolism. Phase II metabolism then makes the drug molecule more water soluble to allow its free extraction from the body in the urine.

2.3.1 Phase I reactions

Phase I reactions work by modifying drug molecules through an interaction with enzymes in the liver. The primary Phase I metabolizing enzymes are in the Cytochrome P450 enzyme family, which has many subtypes. Once the metabolic pathway for a medication is known (i.e., the metabolizing subtype of Cytochrome P450 has been identified), clinicians can understand and better manage how a medication may interact with other medications, food, and herbal supplements the individual is taking. Such interactions are the underlying mechanisms for many unintended medication outcomes and may influence enzyme activity by inhibition or induction.

2.3.2. Induction and Inhibition

Enzyme Inhibition Drug Interactions:

Often, when patients take multiple medications that undergo Phase I metabolism, there can be competition for the active site of a P450 enzyme, which can reduce the rate of metabolism and lead to the accumulation of one or both enzyme substrates. This process is known as competitive inhibition. Another type of enzyme inhibition is called non-competitive enzyme inhibition. In contrast to competitive inhibition, non-competitive inhibition does not involve direct competition for a finite number of active sites on the enzyme for metabolism. Instead, it occurs when one medication causes a conformational change to an enzyme structure after binding to a separate site of the enzyme. Panel A of Figure 2.3.2 shows the standard binding of substrate to an enzyme. Panels B and C illustrate competitive and non-competitive enzyme inhibition. Panel 2B/C demonstrates the effect of adding an inhibitor (either competitive or non-competitive) on the blood concentration of an enzyme substrate.

Enzyme Induction Drug Interactions:

In enzyme induction drug interactions, one medication increases the transcription of an enzyme responsible for the metabolism of another drug. When this occurs, the rate of drug metabolism can be increased, reducing the plasma concentration and effectiveness of the medication. Enzyme induction processes and their effect on plasma concentration of the enzyme substrate (other medication) are depicted in Figure 2.3.1, Panels A and D, respectively. Of note, the effect of enzyme induction on the substrate concentration may be gradual or delayed, as it takes time for the increased transcription of new enzymes to occur.

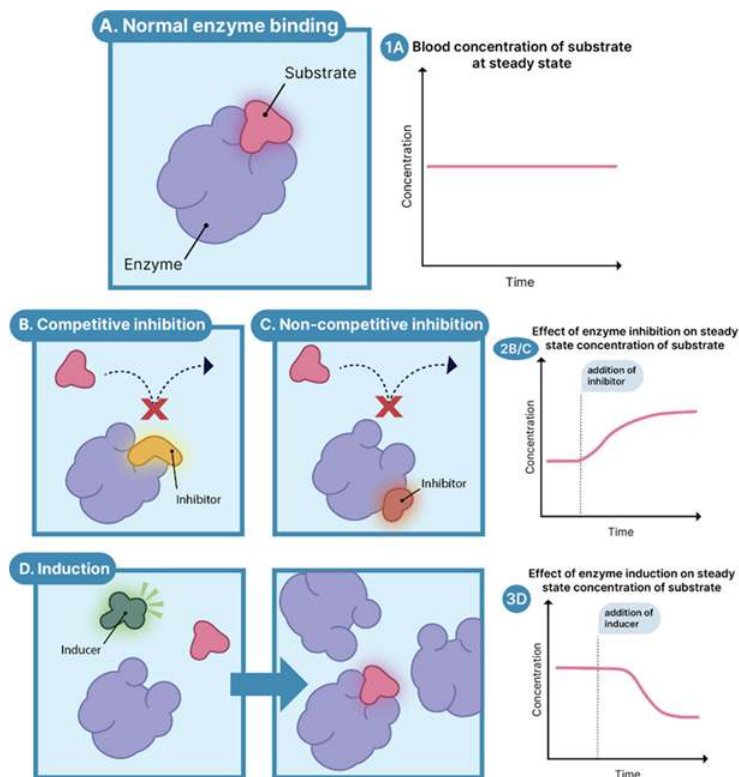


Figure 2.3.2: Enzyme Induction Drug Interactions. (CC-BY 4.0; Riley Cutler and Delilah Przybyla)

2.3.3 Phase II Reactions

In Phase II metabolism, various enzymes catalyze the conjugation of endogenous molecules to the enzyme substrate drug. These reactions include glucuronidation, acetylation, or sulfation. The metabolite of this phase of metabolism is transformed into a more water-soluble molecule that is more readily excreted from the body.

2.3.4 Saturability of Metabolic Processes

The body's ability to metabolize medications depends on the availability of the metabolizing enzymes. If the drug's concentration exceeds the availability of the metabolizing enzymes, the metabolic process is said to be saturated. When enzymatic saturation is reached, patients can be at high risk for adverse effects as drug concentrations may rise rapidly with additional intake, and the half-life can be exceedingly prolonged as the elimination of the drug is significantly compromised.

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2.4: Elimination

2.4 Overview of Elimination

Elimination is the combined process of metabolism and excretion. **Renal excretion** is the primary method by which drugs are removed from the body.

2.4.1 Renal excretion

Along with hepatic metabolism, renal excretion is the other process that eliminates or attenuates the therapeutic action of an absorbed drug. Renal excretion occurs in the kidney as water-soluble compounds are filtered and excreted in the urine. In addition to eliminating water-soluble compounds via passive renal excretion, some compounds are actively transported into the urine by transport proteins that line the tubules of the nephron, which is the functional unit of the kidney. As shown in Figure 2.4.1 below, a simple diagram of a nephron, glomerular filtration takes place in Bowman's capsule, which is the first step of the process. Drugs with a low molecular weight will be freely filtered from the plasma to the glomerulus. An individual's glomerular filtration rate (GFR) determines how much plasma is filtered per unit of time and potentially how quickly a drug is renally eliminated. Another process of renal elimination is tubular reabsorption. Reabsorption of unionized drugs that are weak acids and bases can occur by passive diffusion. Reabsorption may be affected by alterations in urinary pH and ionization. For example, alkalinization of the urine will result in less of the ionized form of an acidic drug being reabsorbed and hence eliminated. Tubular secretion involves two systems to transport organic acids (OAT) and bases (OBT) that may secrete drugs into the ultrafiltrate. The transporters can bind to multiple drugs and other molecules. Thus, they are a site for potential drug-drug interactions because they may compete with each other for binding sites on the transporter.

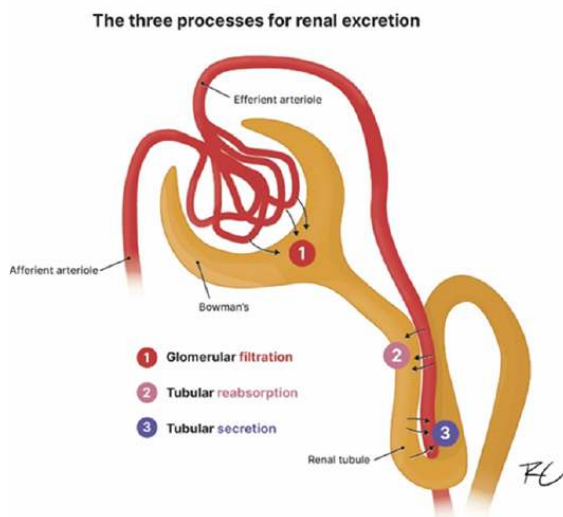


Figure 2.4.1: Renal Excretion. (CC-BY 4.0; Riley Cutler)

2.4.2. Other pathways of drug elimination

Renal excretion accounts for the vast majority of the elimination of drugs from the body. Other excretion pathways include biliary, respiratory, and mammary excretion, or excretion via sweat or saliva. These non-renal pathways account for a minority of drug elimination from the body and, with only a few exceptions, are relatively insignificant in excretion.

Pharmacokinetic patterns of drug elimination can follow a few different patterns: zero-order, first-order, Michaelis-Menten, and half-life. Each pattern is described visually and in the text.

Zero-order kinetics: A drug following a zero-order pharmacokinetic elimination pattern is eliminated at a constant rate, independent of plasma drug concentration. Drugs that follow zero-order kinetics include aspirin, fluoxetine, thiopental, and

omeprazole. Figure 2.4.2.1 demonstrates a zero-order pattern of elimination, which is simply a horizontal line across drug concentrations.

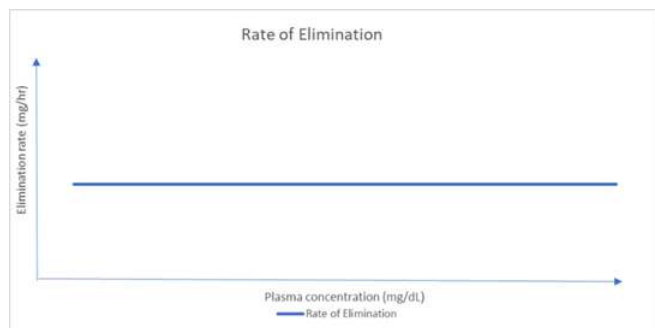


Figure 2.4.2.1: Graph Illustrating Zero-order Kinetics Rate of Elimination Pattern. (CC-BY 4.0; Riley Cutler)

First-order kinetics: When a drug follows a first-order elimination pattern, the rate of elimination depends on the plasma concentration. As the drug plasma concentration increases, so does the rate of elimination. Most medications follow a first-order kinetics pattern of elimination. Figure 2.4.2.2 demonstrates a first-order pattern, which shows that a constant fraction or proportion of the drug is eliminated per unit of time.

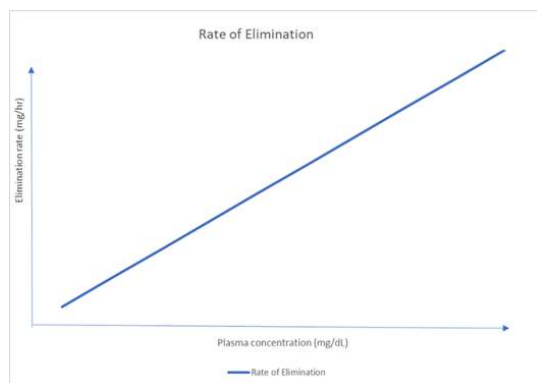


Figure 2.4.2.2: Graph Illustrating First-order Kinetics Rate of Elimination Pattern. (CC-BY 4.0; Riley Cutler)

Michaelis-Menten kinetics: In this pattern of pharmacokinetics, the drug's elimination follows a first-order pattern up to a point, and then it follows a zero-order pattern. The Michaelis-Menten pattern is observed when processes involved in eliminating a drug from the body are saturable. When these processes are saturated, metabolism or excretion can no longer increase to accommodate higher drug concentrations, as demonstrated by the straight line or plateau on the graph. Usually, the number of available transport proteins affects saturation as a transport protein is needed for the drug to move from the circulation into the lumen of the nephron. This pattern is less commonly observed. Note that, as Figure 2.4.2.3 demonstrates, drugs following this type of elimination pattern will take longer to eliminate at higher concentrations. Phenytoin is an example of a medication that follows this pattern.

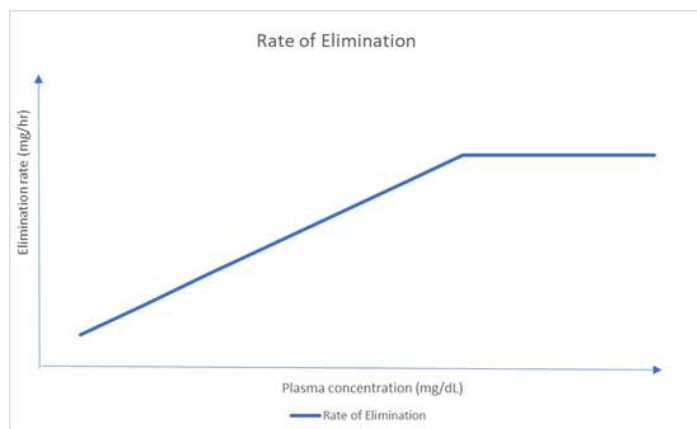


Figure 2.4.2.3: Graph Illustrating Michaelis-Menten Kinetics Rate of Elimination Pattern. (CC-BY 4.0; Riley Cutler)

Elimination half-life ($t_{1/2}$): A drug's half-life ($t_{1/2}$) is a measure of time. Specifically, it is the time it takes for the concentration of a drug to be reduced by half. This parameter helps determine medication dosing intervals and understand how long a drug may remain at physiologically important plasma concentrations. Figure 2.4.2.4 illustrates how a clinician can use the half-life parameter of a drug to estimate how much medication may remain after a dose. After one half-life, 50% of the original concentration remains; after two half-lives, 25% of the original concentration remains; after three half-lives, 12.5% of the original concentration remains. The concentration continues to decrease by half each time the drug's half-life has elapsed.

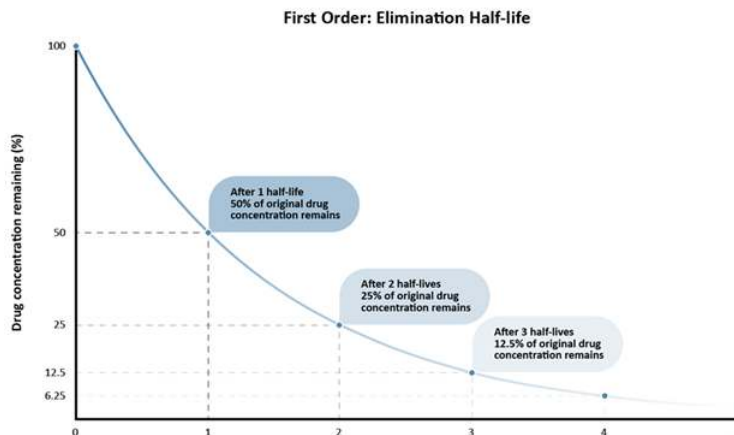
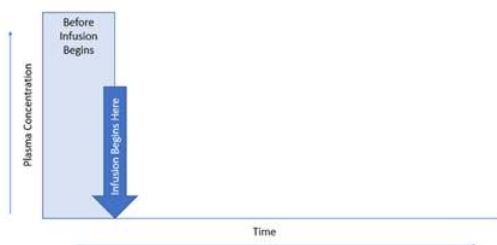


Figure 2.4.2.4: Graph Illustrating First-order Kinetics Elimination Half-Life ($t_{1/2}$). (CC-BY 4.0; Amy Hoang)

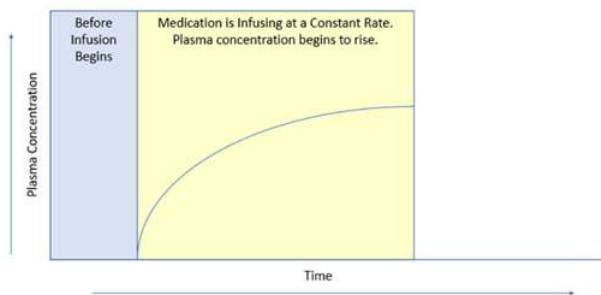
2.4.3 Steady State

The **steady-state concentration** is achieved when the amount of drug coming into the body equals the amount cleared from the body. The plasma concentration is consistent at steady-state concentration, neither rising nor falling. The time it takes for a drug to reach a steady state concentration depends on its elimination pharmacokinetics. One of the simplest ways to conceptualize the time it takes to get to steady-state concentration is to relate this time to the drug's half-life. The series of figures shown in Figure 2.4.3 panels A-F below depicts a continuous drug infusion starting at time zero through achieving a steady-state concentration. The graphs show the change in plasma concentration over time until a steady state is reached and drug concentration plateaus as the same amount of drug is being administered and leaving the body.

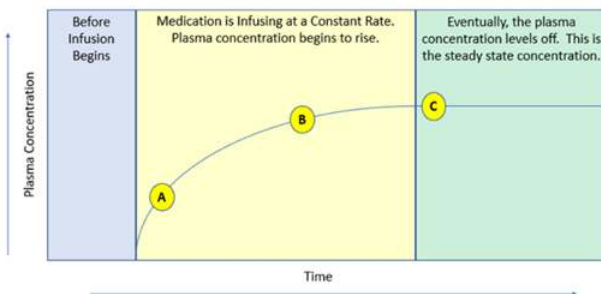
A. The medication concentration is zero before starting an intravenous infusion medication.



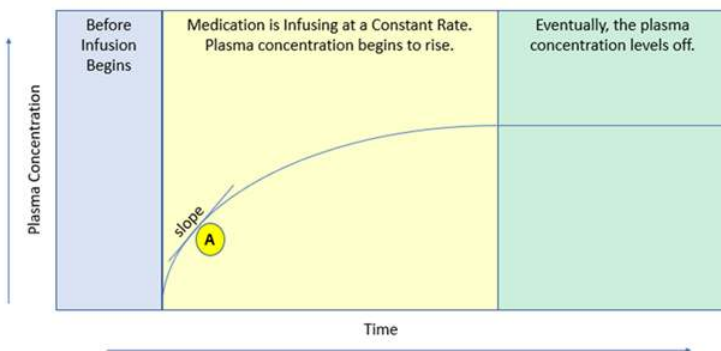
B. The plasma concentration rises once the medication infuses (yellow area).



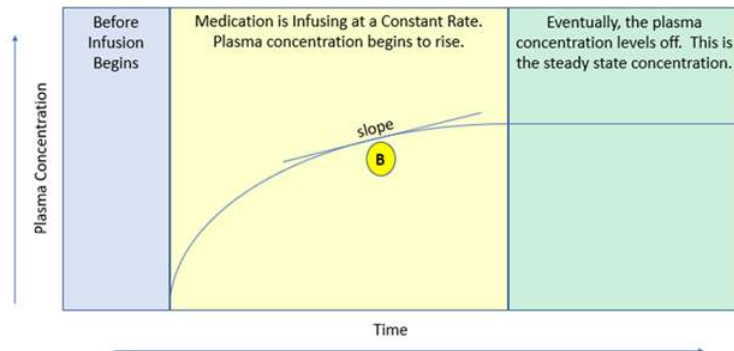
C. The plasma concentration levels off when the drug reaches a “steady state” (green area).



D. Consider points A, B, and C. At point A, the slope of the curve is a steep incline. The plasma concentration is relatively low. The rate of absorption/administration greatly exceeds the rate of elimination.



E. At point B, the slope of the curve is less steep. The plasma concentration is higher, and the elimination rate is closer to the rate of absorption/administration.



F. At point C, the slope of the curve is flat. At this higher plasma concentration, the elimination rate is equal to the rate of absorption/administration. At this stage, the plasma concentration will stay constant unless there is a change in the administration

rate or the body's ability to clear the drug.

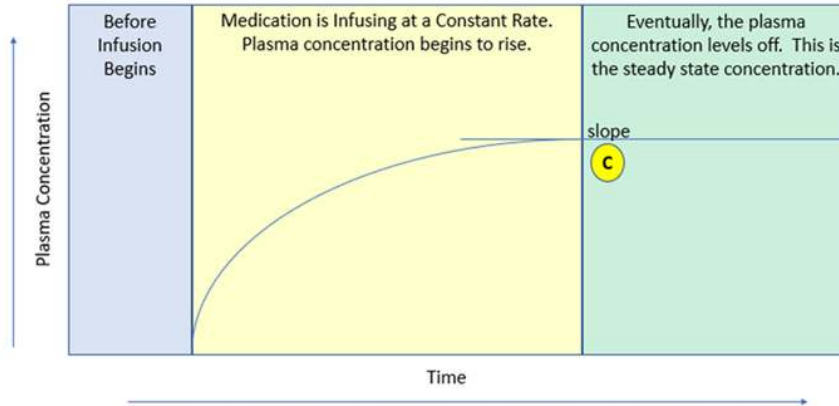


Figure 2.4.3.1 Panels A-F: Graph series illustrating achieving a steady state over time. (CC-BY 4.0; Riley Cutler)

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3: Pharmacodynamics

Learning Objectives

- Explain the relationship between drug action (mechanism of action) and the various types of drug receptors.
- Compare and contrast the terms potency, efficacy, and affinity.
- Distinguish among an agonist, a partial agonist, a mixed agonist-antagonist, and an antagonist.
- Explain the significance of a drug's therapeutic index to its lethal dose and margin of safety.
- Recognize the components and significance of dose-response curves and quantal dose-response curves.
- Relate the relationship of K_D to affinity (think about the calculation for K_D).
- Discuss the clinical implications of an agonist or an antagonist drug that binds irreversibly.

3.0 Overview of Pharmacodynamics

Pharmacodynamics is the study of a drug's biochemical and physiologic effects on the body. The biochemical interactions through which a medication exerts its clinical or pharmacological effect are called the **mechanism of action** (MOA). The MOA includes the specific drug target, such as receptors, enzymes, proteins, hormones, or drug pathways.

3.1 Drug Binding Sites

Receptors are proteins found on the cell surface or within the cell. Substances that interact with receptors are called ligands. Ligands can be endogenous substances (produced inside the body), such as epinephrine, or exogenous substances (produced outside the body), such as a drug manufactured to mimic epinephrine. In both cases, the endogenous or exogenous epinephrine molecule binds to the alpha and beta receptors of the autonomic nervous system. Traditionally, most drugs have been manufactured to bind to specific receptors on the cell surface or within a targeted cell type. However, many other cellular components and non-specific sites can serve as drug targets to create a clinical response. For example, the osmotic laxative magnesium citrate attracts and binds with water molecules, pulling water into the bowel to increase the likelihood of a bowel movement.

An agonist is a drug that binds to a receptor and produces a biological effect. A medication that exerts a strong biological effect is classified as a full agonist. Other types of agonist drug-receptor interaction describe medications that produce an effect weaker than the response of a full agonist and are called partial agonists.

Other medications may bind to a receptor site but block the receptor's activity. This type of drug-receptor interaction is inhibitory, and the drug is called an antagonist. For example, antimicrobial and antineoplastic drugs commonly work by inhibiting enzymes critical to the cell's function. With blockage of the enzyme binding site, the cell, microbe, or neoplastic cell is no longer viable, and cell death occurs. Antagonists and agonists often compete for the same binding sites.

Finally, some drugs have a mixed response depending on the cell type and tissue location. A drug may act as an agonist at one receptor type, whereas at another receptor type, the same drug acts as an antagonist. For example, the opioid receptor system includes multiple receptor types (mu and kappa) that interact differently with opioid drugs. Buprenorphine binds to mu and kappa receptors and is classified as a mixed agonist-antagonist: a partial agonist at the mu receptor and an antagonist at the kappa receptor. Figure 3.1.1 below shows the range of clinical responses from agonism (full activation) to antagonism (full inhibition).

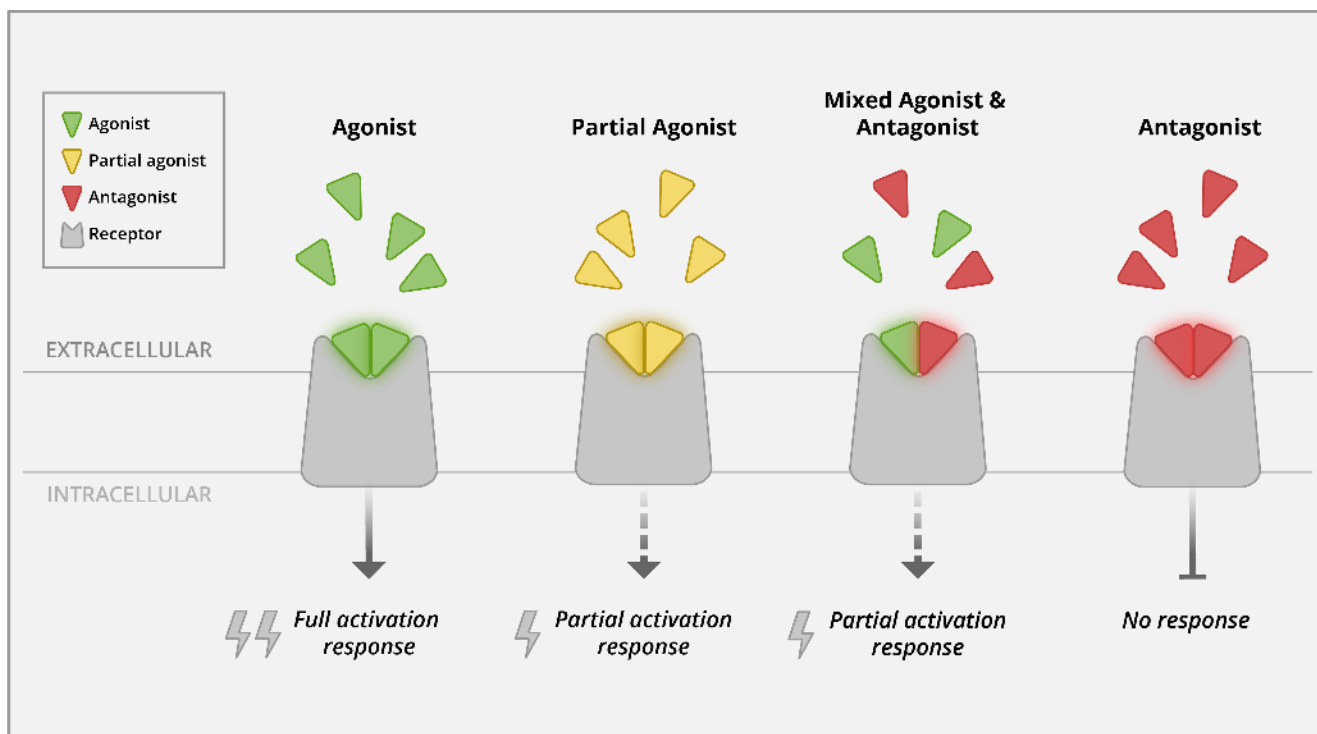


Figure 3.1.1: Drug-Receptor Binding and the Range of Drug Responses. (CC-BY 4.0; Riley Cutler)

Receptor or drug targets are often proteins and can be divided into four broad classes, shown below in Figure 3.1.2 Panels A–D. Panel A shows two different drugs that are binding to a receptor. Receptors play an important role in the communication pathway that coordinates the function of various cells within the body. Agonist medications may bind to numerous receptor types (see panels A–D below). Once an agonist binds to a receptor, a physiologic mechanism is activated. Currently, in the largest group of drug-receptor interactions, the medication is present in the extracellular space, and the physiologic or effector mechanism resides within the cell; signaling occurs across the membrane. Once bound, the drug modifies some intracellular process, often involving a sequence of second messenger events. This is why receptors are sometimes described as endogenous mediators. Panels B–D describe receptor types in more detail.

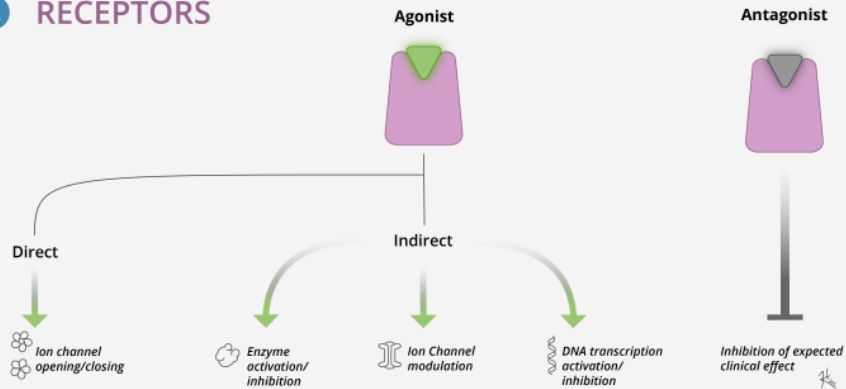
Panel B depicts **ion channels**. Ion channels are gates that open and close to selectively allow an ion or drug to pass through a cell membrane. There are two types of ion channels: ligand-gated and voltage-gated. Ligand-gated ion channels open when an agonist is bound and are classified as receptors. Voltage-gated ion channels respond to a change in the transmembrane potential rather than molecular binding. Medications can interact with an ion channel in several ways. A medication may directly bind to the channel protein. For example, local anesthetics bind to and block voltage-gated sodium channels, inhibiting signal transmission. Allosteric binding, that is, the drug binds to a site on the channel other than the binding site for the molecule that activates the channel, includes the neurotransmitter, gamma-aminobutyric acid or GABA (in the case of benzodiazepines), dihydropyridines, and sulfonylureas. Other medications may indirectly interact with an ion channel by activating a G protein-coupled receptor. Finally, some drugs may alter the level of expression of ion channels on the cell surface. For example, gabapentin reduces the number of active presynaptic calcium channels and the subsequent release of excitatory neurotransmitters. Yet other antagonists modulate the opening and closing of a channel, whereas other medications block the channel's entry or the channel from within, as shown in panel B.

Panel C shows **enzymes** or proteins, which many medications target. Enzymes are biological catalysts that speed up essential chemical reactions for life. Often, enzymes are proteins with the ending *ase*. Clinically, a critical case to understand is when a medication is a **prodrug**. Prodrugs are medications that require metabolism or degradation to be converted to their biologically active form. Understanding prodrugs is essential because they are associated with drug toxicity and treatment failures. One of the first prodrugs used was aspirin. Aspirin is metabolized into salicylic acid; salicylates inhibit the activity of cyclooxygenases (COX-1 and COX-2), reducing inflammation. An individual who has a variant of P450 metabolizing enzymes required to convert a drug

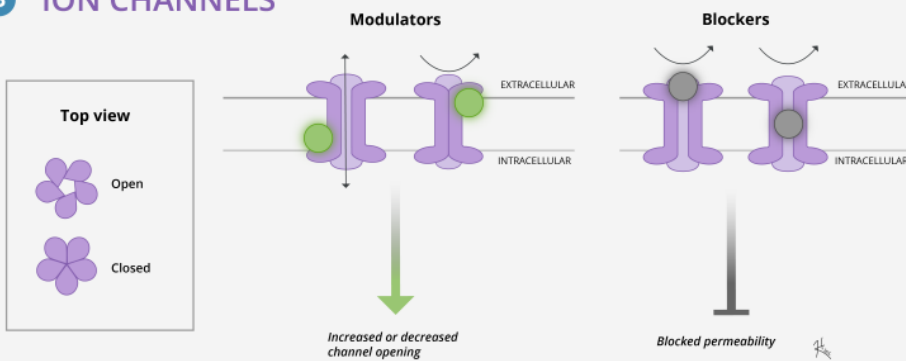
to a prodrug may experience treatment failure. Other medications act as a substrate analog or decoy that competes with the target enzyme. For example, captopril acts on the angiotensin-converting enzyme. Medications are also made to act as false substrates and produce an abnormal product that disrupts the normal metabolic pathway. An example is fluorouracil (5-FU), which replaces uracil in purine biosynthesis, ultimately disrupting DNA synthesis and cell division.

Panel D shows **transporters**. Ions and small molecules move across cell membranes through channels or with the help of transporters. Many molecules are too polar (a weak lipid-soluble molecule) to penetrate the lipid bilayer independently. Several different types of transporters have been identified. Transporters of pharmacologic importance are ion transporters in the renal tubule, the intestinal epithelium, the blood-brain barrier, and those that transport $\text{Na}^+/\text{Ca}^{2+}$ out of cells. A transporter often requires energy in the form of adenosine triphosphate (ATP) to transport substances against the electrochemical gradient and maintain cell functioning. Examples include the sodium pump and the multidrug resistance (MDR) transporter, also called the P-glycoprotein (PGP) transporter. The PGP ejects cytotoxic substances from the cell, including medications. For example, the PGP ejects cytotoxic cancer drugs from cancer and microbial cells, conferring resistance to these therapeutic agents. Sometimes, the transport of organic molecules is coupled to the transport of ions (often Na^+), as in the transport of neurotransmitters. Transporters are becoming increasingly recognized as a source of individual variation in the pharmacokinetics associated with certain medications, such as azithromycin.

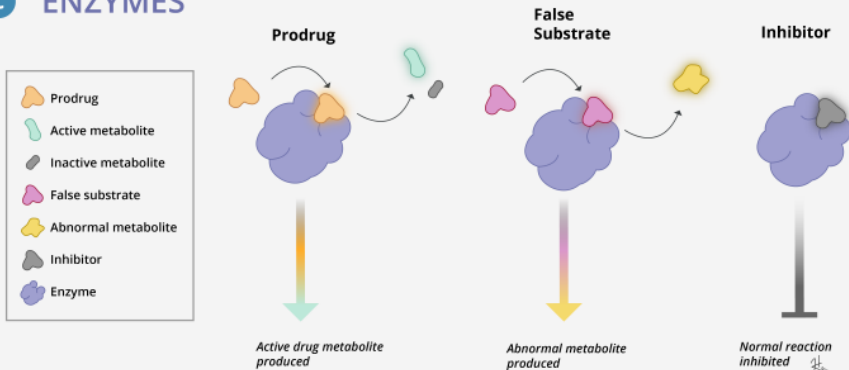
A RECEPTORS



B ION CHANNELS



C ENZYMES



D TRANSPORTERS

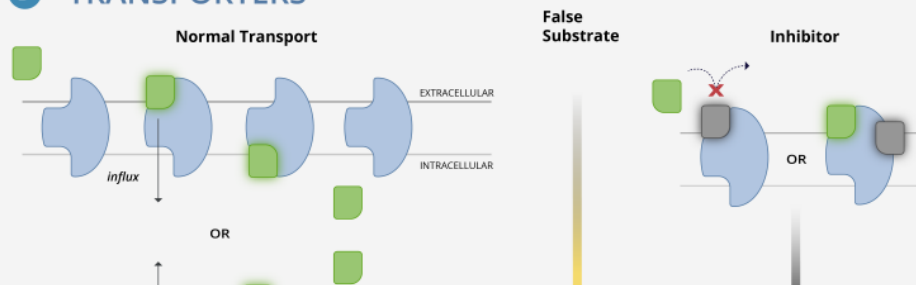


Figure 3.1.2: Drugs Binding to Receptors, Enzymes, Ion Channels, and Transporters. Description in text. (CC-BY 4.0; Hannah Koffman and Riley Cutler)

Not all drugs bind directly to the active site on the target molecule. Some drugs bind to a receptor allosterically, meaning the drug binds to a distinct site from the active site. Figure 3.1.3 below depicts allosteric binding, also called allosteric modulation, which can be positive or negative. The classic example of this type of binding is the binding of the neurotransmitter GABA to the GABA receptor in the presence of a benzodiazepine (BZD), which is shown below. When GABA binds, it opens the channel and allows for the influx of Cl ions. Benzodiazepines also bind to the GABA receptor, but at a different site than GABA. In the presence of the BZD, the neurotransmitter GABA still binds to its site on the GABA receptor. However, the BZD causes the channel to stay open longer, allowing more Cl ions to enter. This is an example of a positive allosteric modulator because the BZD enhances the regular activity of the receptor.

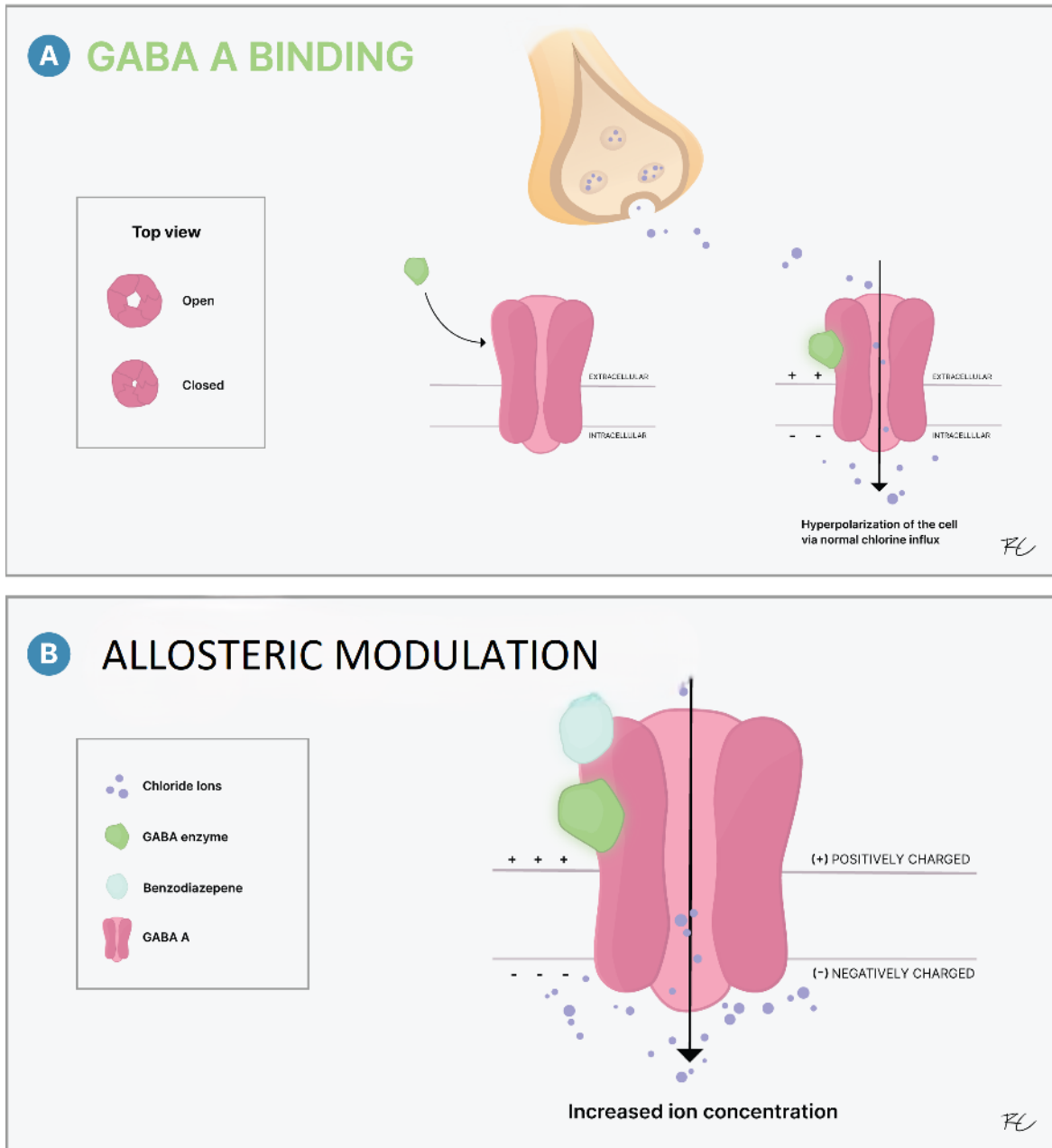


Figure 3.1.3: GABA A Binding & Allosteric Modulation (CC-BY 4.0; Riley Cutler)

3.2 Dose-Response Curves (Graded)

When a drug or medication attaches to its target, it forms a complex. The drug-target complex causes a biological response. The biological response and the medication's concentration in circulation are expressed through dose-response curves. The dose-response curve describes the relationship between drug concentration on the x-axis and the biological response on the y-axis, sometimes called graded dose-response curves. The **minimum effective concentration (MEC)** is the lowest dose at which the desired biological effect is noted. For example, the **MEC** for antimicrobials is the lowest dose at which microbial growth is suppressed. The same dose of a medication can result in different plasma concentrations in other individuals. That difference is related to the pharmacokinetics of the individual and the dose of the medication.

The drug's **affinity** and **efficacy** characterize drug-receptor interactions. The occupation of a drug on a receptor is governed by its affinity, or the strength of the bond between the drug and the receptor. Affinity can be expressed as the K_D or equilibrium constant. K_D is calculated as the K_{off}/K_{on} . A drug's off and on rates are specific, and a drug with a high affinity for a receptor may spend more time attached or bound to the receptor than unattached or off. Thus, K_D is the reciprocal or inversely related to affinity. Dose-response curves can estimate efficacy and **potency**. Potency is the concentration at which the medication elicits 50% of the maximal response (EC50). The lower the EC50, the greater the potency of the medication. Efficacy is the maximal response or effectiveness a medication can produce at a tolerable dose (E_{max}). In Figure 3.2.1, the graph shows the dose-response curves for three drugs, A, B, and C. Drug C is the most potent, and E_{max} is reached at the lowest drug concentration. However, the response to Drug C is not as great as the response to Drugs A and B. The drug concentration increases as you move to the right along the x-axis. Drugs A and B are less potent than Drug C; the ranking of the three drugs for potency from highest to lowest is $C > A > B$. Look at the dotted line representing the EC50 on the graph. Drugs A and B have similar efficacy; both curves plateau or flatten almost at the same point along the y-axis, and Drug A is slightly higher. The ranking of efficacy of the three drugs from highest to lowest is $A > B > C$. Efficacy can be expressed numerically from zero to one, on a continuum. A full agonist drug has an efficacy of one, whereas a full antagonist has an efficacy of zero.

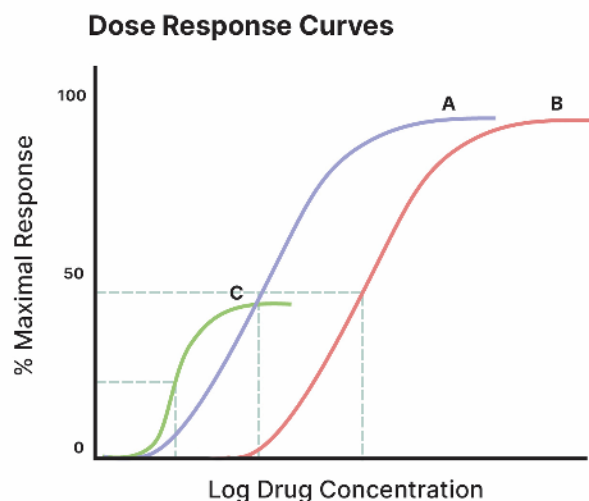


Figure 3.2.1: Dose-Response Curves for Three Different Drugs to Compare Potency and Efficacy. (C-BY 4.0; Riley Cutler)

Agonist and antagonist drugs compete for binding sites with other drugs, hormones, neurotransmitters, and other substances. Whatever molecule has the strongest affinity will out-compete and bind to the receptor. Usually, binding is reversible; the drug-receptor complex separates depending on the drug's affinity to its target molecule or receptor. Binding can also be irreversible. Irreversible antagonists may bind covalently so that the receptor is deactivated. Once deactivated, the cell internalizes and recycles the non-functional receptor. For example, succinylcholine binds irreversibly to the nicotinic acetylcholine receptor, and aspirin binds irreversibly to its target molecule, platelets. The duration of the binding and the drug's action depends on the body's ability to metabolize succinylcholine into butyrylcholine and, in the case of aspirin, the body's ability to make new platelets.

When two drugs competing for the same receptor are given simultaneously, there is always the potential for drug interactions. Figure 3.2.2 below shows what happens to a full agonist, Drug A, in the presence of two different antagonists. The broken line labeled Drug A' shows the change in the dose-response curve for Drug A with the addition of a *competitive* antagonist. The broken line "Drug A" shows the dose-response curve for the agonist, Drug A, when a *non-competitive* antagonist is added. Note, with the addition of a competitive antagonist, *increasing* the amount of agonist allows the agonist to reach the maximal possible response observed in the absence of the antagonist (same point on the y-axis for A and A"). The agonist competes with the competitive antagonist for binding sites; adding more or increasing the concentration of the agonist allows the agonist to overcome the competitive antagonist. However, with the addition of a non-competitive antagonist, the agonist Drug A can never reach its maximal possible response, and the biological response is blunted.

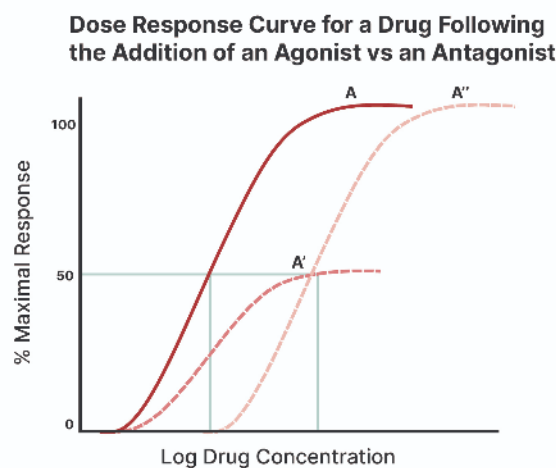


Figure 3.2.2: Full Agonist in the Presence of a Competitive vs. Non-Competitive Antagonist. (CC-BY 4.0; Riley Cutler)

3.3 Quantal Dose Response Curves

The dose required to produce a therapeutic effect varies from individual to individual; a quantal dose-response curve determines the effective doses for a group of individuals or a population. The dose in the middle of the distribution is the ED50, defined as the dose needed to produce the intended therapeutic effect for 50% of the population. This is the standard dose, but some individuals will be under-treated, whereas others will be over-treated. Because you cannot predict an individual's response to the drug, you must monitor the patient for their response and adjust dosing. High responders will need less drug, and low responders will need more.

Individual Variability in Drug Response

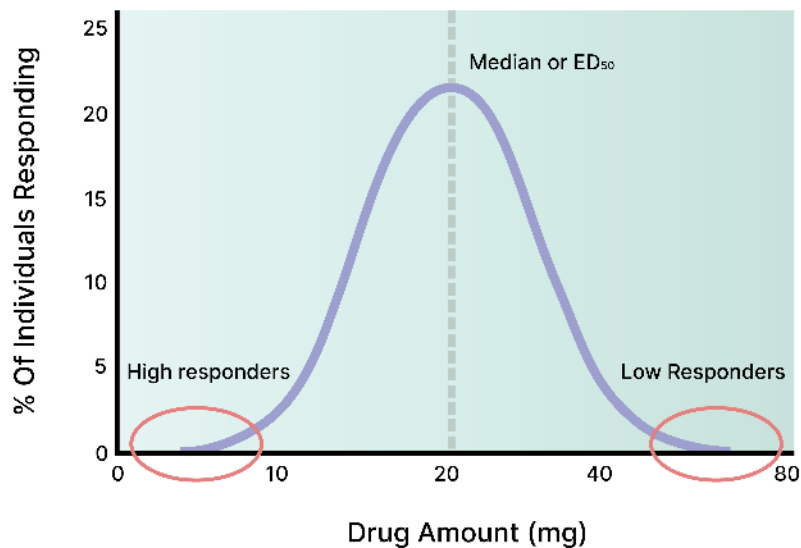


Figure 3.3.1: Frequency Distribution Showing the Percent of Individuals' Response to a Range of Drug Doses. (CC-BY 4.0; Riley Cutler)

Quantal dose-response curves are also used to determine a drug's therapeutic index or window. The therapeutic index (TI) measures a drug's safety. The larger the difference between a drug's effective and lethal dose, the greater the TI and the safer the drug. In Figure 3.3.2, the TI for two drugs is shown below. Both drugs have similar ED₅₀ values but different LD₅₀ values. When the gap between the ED₅₀ and LD₅₀ doses is close or narrow, such as the drug in the bottom panel, that drug has a narrow safety margin. Drugs with a narrow TI often have specific monitoring recommendations, such as periodic serum drug levels. Carbamazepine, lithium, warfarin, and phenytoin all have a narrow TI and are subject to therapeutic monitoring.

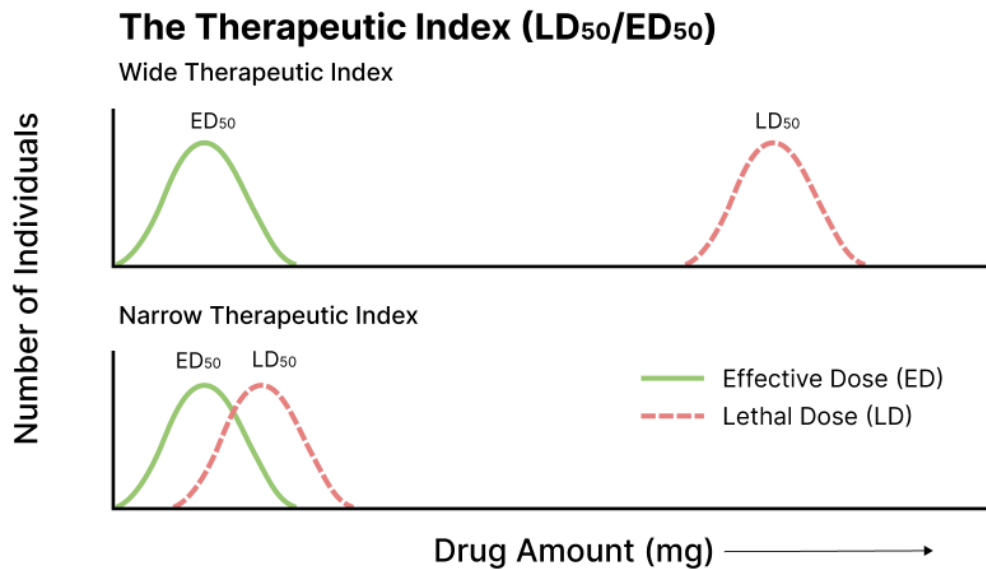


Figure 3.3.2: Comparison of a Wide vs. Narrow Therapeutic Index. (CC-BY 4.0; Riley Cutler)

3.4 Area Under the Curve (AUC)

A drug's safety profile is related to its pharmacokinetic parameters. The area under the curve, or AUC, represents the entire time a drug is in the body or the total exposure of the body to a drug over time. Although AUC is a pharmacokinetic concept, it is mentioned here because of its importance to pharmacodynamics. The relationship between AUC and pharmacodynamics is the understanding that the concentration of a drug at its site of action influences its effectiveness and safety profile. In Figure 3.4.1, AUC and its safety at a given concentration are depicted. The y-axis is drug concentration, the x-axis is time, and the minimum effective concentration, therapeutic range, and toxicity are shown on the right. Ideally, a drug's level will be in the therapeutic range. The AUC is a critical concept in antimicrobial prescribing.

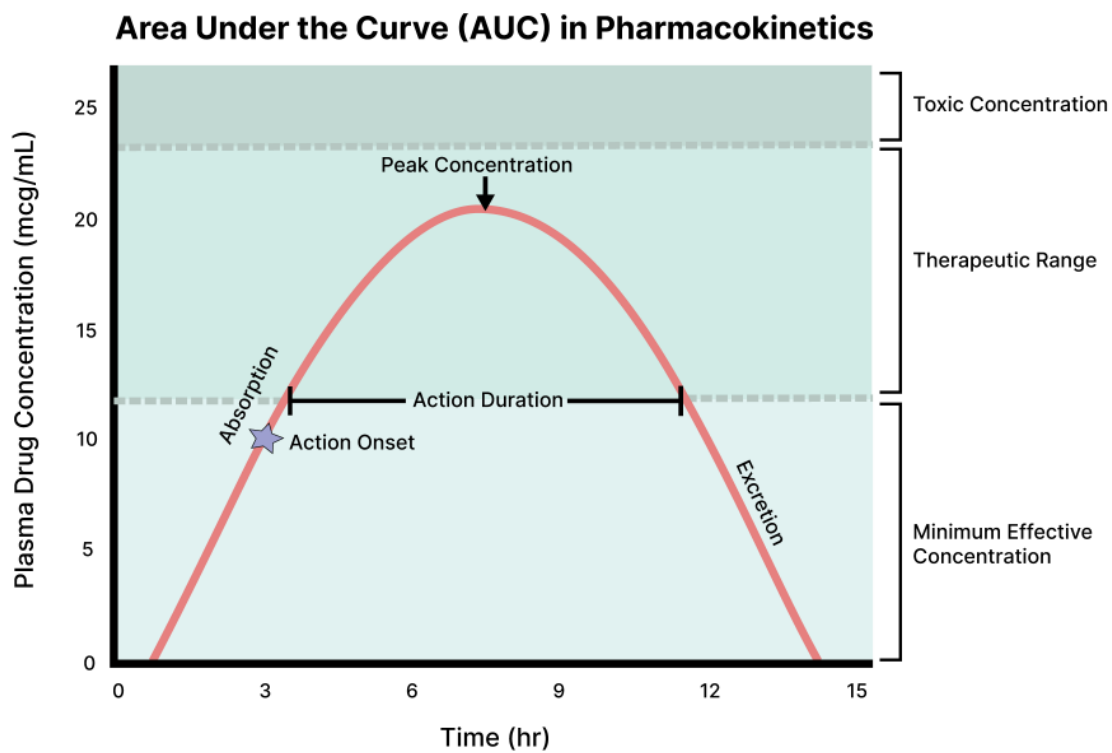


Figure 3.4: Relationship Between AUC and Therapeutics. (CC-4 BY; Riley Cutler)

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4: Pharmacogenomics and Variation in Drug Response

Learning Objectives

- Name 3 gene polymorphisms that increase or decrease drug efficacy or toxicity.
- Differentiate among the five types of metabolizing phenotypes.
- Compare therapeutic benefits and treatment failure for active parent drug vs prodrug.
- Explore the genetic consortiums' websites for clinical recommendations for prescribing.

4.0 Overview of Pharmacogenomics

Pharmacogenomics is the study of how genes affect a person's response to drugs. This field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications that can be prescribed based on a person's genetic makeup. This development suggests that "personalized medicine" may be a possibility.

Many currently available drugs are presented as "one size fits all," but significant genetic variations in drug metabolism exist between individuals. It can be challenging to predict who will benefit from a medication, who will not respond at all, and who will experience adverse side effects or an unintended drug event. Unintended drug reactions are a significant cause of hospitalizations and deaths in the United States, as discussed in Chapter 6.

Genetic variations (polymorphisms) impact an individual's response to drugs, such as the variants in Phase I and Phase II drug metabolizing enzymes and drug transporters. Data regarding these genetic differences is used to predict whether a drug will be effective for an individual and which dose will help prevent unintended drug reactions. Knowledge about an individual's genetic makeup and subsequent response to certain drugs includes clopidogrel resistance, warfarin sensitivity, warfarin resistance, malignant hyperthermia, Stevens-Johnson syndrome/toxic epidermal necrolysis, and thiopurine S-methyltransferase deficiency.

Pharmacogenomics is being used to develop tailored drugs to treat a wide range of health problems, including cancer, depression, cardiovascular disease, Alzheimer's disease, and asthma.

The field of pharmacogenomics is growing, and researchers have identified common types of genetic variation called single-nucleotide polymorphisms (SNPs), which are responsible for variations in drug response.

4.1 Single-nucleotide polymorphisms

Single-nucleotide polymorphisms, or **SNPs**, are the most common type of genetic variation among humans. Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, an SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a particular stretch of DNA, as shown in Figure 4.1.

The highlighted area shows a strand of DNA with an SNP. Instead of C paired with G as expected, C is paired with T, representing a single nucleotide substitution.

Example of an SNP

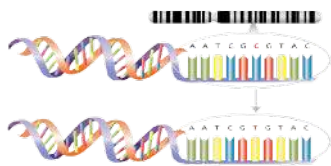


Figure 4.1: DNA Strand with a SNP. (CC-BY 4.0; Riley Cutler)

SNPs occur normally throughout a person's DNA. On average, SNPs occur almost once in every 1,000 nucleotides, meaning roughly 4 to 5 million SNPs in a person's genome. A variant must be found in at least 1% of the population to be classified as an SNP. Scientists have found more than 600 million SNPs in populations around the world.

Most SNPs do not affect health or development. However, some genetic differences have proven very important in studying human health. Some SNPs are associated with a gain of function in an enzyme or transport protein, whereas others are associated with a loss of function in an enzyme or transport protein. SNPs help predict susceptibility to environmental factors such as toxins, the risk of developing diseases, and an individual's response to certain drugs. SNPs in drug-metabolizing enzymes, drug transporters, and drug targets significantly contribute to the individual variation in response to a drug.

An audio definition of SNPs is available from the National Human Genome Research Institute's [Talking Glossary of Genetic Terms](#), available from the National Institutes of Health.

4.2 Phase I Enzymes, Genetic Variation, and Drug Metabolism

Phase I reactions convert a drug to a more polar form; polarized drugs are more easily excreted. Phase I enzymes include the important and carefully studied cytochrome P450 (CYP450) superfamily. These enzymes are found in high concentrations in the liver's endoplasmic reticulum and other cells throughout the body. CYP450 enzymes are not very selective for their substrate (molecules or drugs the enzyme acts on), so a relatively small number of isoforms metabolize most drugs. CYP2D6, CYP2C19, and CYP3A4/5 metabolize over 75% of the drugs acted on by this superfamily and are among the isoenzymes best studied.

Multiple enzyme polymorphisms may contribute to a drug's efficacy and tolerability. One well-studied example is warfarin. Warfarin is manufactured as S and R-isomers. The isomers differ in their chemical properties. CYP2C9 and **vitamin K reductase epoxide complex subunit 1 (VKORC1)** inactivate the S-isomer. Polymorphisms and mutations in the genes that code for these enzymes may cause individuals to have spontaneous bleeding or increased warfarin levels. Patients may be screened for genetic variants in these genes to optimize drug selection and clinical efficacy.

The CYP2D6 gene is highly polymorphic, with over 100 polymorphisms identified; nine variants are common. CYP2D6 polymorphisms are significant clinically as commonly used drugs, such as sedatives (midazolam, diazepam, diphenhydramine), anti-depressants (fluoxetine, amitriptyline), anti-arrhythmics (amiodarone), beta-blockers (carvedilol, metoprolol), and pain medications (codeine, tramadol). Polymorphisms are important in individuals who are prescribed codeine because it is a prodrug. Please remember that prodrugs are inert chemicals that need to be converted to their active form in the body. In the case of codeine, the 2D6 enzyme converts the drug to its active metabolite, morphine. Figure 4.2.1 depicts the differences between a parent drug (starting compound) and a prodrug.

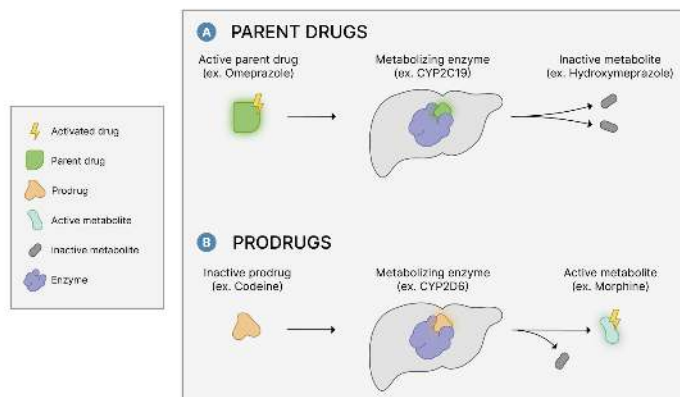


Figure 4.2.1: Comparison of the Metabolism of Parent Drugs vs Prodrugs. (CC-BY 4.0; Riley Cutler)

CYP2C19 metabolizes a few clinically significant drugs, including clopidogrel, propranolol, omeprazole, and diazepam. Again, clopidogrel is a prodrug, and individuals who cannot metabolize it to its active metabolite will not experience antiplatelet benefits.

CYP3A4 and CYP3A5 are responsible for metabolizing many of the drugs currently in use. Polymorphisms of 3A4 and 3A5 are not common, but these enzymes are important because so many drugs are metabolized by these enzymes. While the polymorphisms

of 2D6 and 2C19 significantly influence the clinical efficacy and management of drugs used for chronic conditions, 3A4 and 3A5 are important because of the potential drug-drug interactions due to the high number of drugs metabolized by these enzymes.

4.3 Phase II Enzymes, Genetic Variation, and Drug Metabolism

Phase II enzyme reactions, which include reactions to make a drug more water soluble—such as glucuronation, acetylation, and methylation—also have polymorphism in other enzyme families. Making a drug more water soluble allows it to be excreted.

Enzymes that regulate Phase II reactions also have polymorphisms. Uridine 5′-diphospho (UDP) glucuronosyltransferase (UGT1A1) and thiopurine S-methyltransferase (TPMT) are important in the treatment of cancer. These enzymes metabolize chemotherapeutic drugs; polymorphisms may alter therapeutic efficacy and toxicities.

4.4 Transport Proteins and Polymorphisms

The **SLCO1B1** gene codes for the organic anion transporter (OATP), transports drugs and other compounds from blood into hepatocytes. Substrates for OATP include statins and methotrexate. Numerous SNPs in the SLCO1B1 gene are associated with elevated statin levels, especially simvastatin, and increased risk of skeletal myopathy.

The **ABCB1** gene codes for P-glycoproteins (PGPs), an efflux protein found on blood-tissue interfaces such as the blood–brain barrier, intestines, and placenta. The PGP performs an essential function, expelling foreign compounds from the cell. Sometimes described as promiscuous, the PGPs can bind to many drugs and compounds. It is associated with expelling cytotoxic drugs from resistant cancer cells.

4.5 Human Leukocyte Antigen (HLA) and Polymorphisms

Human leukocyte antigen (HLA) genes code for proteins responsible for identifying self from non-self. They play a significant role in immune defense/transplant rejection and are highly variable. HLA polymorphisms are associated with immunological responses to drugs such as liver injury, Stevens-Johnson syndrome, and toxic epidermal necrosis. Carbamazepine has been associated with HLA polymorphisms.

Phase I and Phase II enzymes, transport proteins, and HLA all have polymorphisms, contributing to the variation in response to drug efficacy and tolerability. Personalized medicine considers the person's genetic factors or genotype that may potentially contribute to the response to a drug and drug efficacy. Much is known about the identification of specific genes that affect drug pharmacokinetics. Although this knowledge is incomplete and continues to unfold, our understanding of the relationship between genotype and phenotype has allowed the development of guidelines to direct prescribing based on the person's genotype. To fully comprehend this process, we need to discuss metabolizing phenotypes.

4.6 Drug Metabolizing Phenotypes

We inherit one gene from each parent. The variation in the DNA sequence of a gene is called an allele. Individuals may be homozygous (two identical alleles) or heterozygous (two different alleles). Alleles coding for the CYP450 superfamily enzymes and the other metabolizing enzymes are named with standardized * nomenclature. The *1 designation (wild type) is the referent to which all alleles are compared and codes for the “normally” functioning enzyme. The enzyme activity of each allele is assessed and categorized using the function of the *1 allele as a reference. Some alleles have less activity (loss of function), whereas others confer increased activity (gain of function). The functional phenotype or metabolizer status results from the combined effect of both alleles and is categorized using standardized nomenclature. Poor, intermediate, normal (wild type), rapid, and ultrarapid phenotypes describe the spectrum of possible enzyme activity.

Recall Figure 4.2.1, which illustrated the metabolism of a parent drug compared to a prodrug. Prodrugs require conversion to an active form by metabolizing enzymes. Knowing whether a prescribed medication is a prodrug or not helps clinicians anticipate the clinical effects of altered enzyme metabolism and the risk of unintended drug events, drug-drug interactions, and therapeutic failures. Figure 4.6.1 illustrates the relationship between parent drugs, prodrugs, and metabolizer status. The categories and definitions of the metabolizing phenotypes are: (1) normal metabolizers with two fully functional alleles; (2) rapid metabolizers with gain of function alleles and high enzyme activity; (3) ultrarapid metabolizers have higher enzyme activity than rapid metabolizers; (4) intermediate metabolizers with decreased enzyme activity compared to normal metabolizers; and (5) poor metabolizers with loss of function alleles with little to no enzyme activity. The relationship between drug concentration and enzyme

phenotype is opposite in the parent drug vs a prodrug that must be converted into an active metabolite. Normal metabolizers are most likely to experience therapeutic benefits, but persons with other metabolizing phenotypes may experience a range of benefits and toxicities.

Parent Drugs, Prodrugs, and Metabolizer Status

 Diagram Description automatically generated with low confidence

Figure 4.6.1: Parent Drugs, Prodrugs, and Enzyme Metabolizer Status. (CC-BY 4.0; Riley Cutler)

Ideally, identifying a person's metabolizing phenotype may help avoid therapeutic failures and unintended events. Many healthcare systems are implementing pharmacogenomic testing and strategies. Genetic testing may be embedded in the person's electronic health record (EHR), which is then available to all clinicians. Consortia have been developed that curate and centralize pharmacogenetic information to support and facilitate pharmacogenetic testing. PharmVar, the Pharmacogene Variation Consortium, and PharmGKB are resources supported by the National Institutes of Health for this purpose. The Clinical Pharmacogenetic Implementation Consortium (CPIC) produces evidence-based guidelines on actionable gene-drugs, including statements for adults and pediatrics. The Food and Drug Administration (FDA) lists detailed additional data supporting management recommendations and how drug labels have incorporated pharmacogenetic data.

Clinical implementation of pharmacogenetic data is a challenge. Many questions remain unanswered regarding best practices for selecting genetic testing, interpreting test results, and maintaining confidentiality.

Related websites:

[CPIC](#)

[ClinGen Pharmacogenomic Working Group](#)

[Royal Dutch Pharmacists Association-Pharmacogenetics Working Group](#)

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5: Drug Development for Traditional Drugs and Biologics

Learning Objectives:

- Explain the phases of the drug development process.
- Compare and contrast the drug development process between traditional drugs and biologics.
- Identify the role of the Food and Drug Administration (FDA) in ensuring that drugs are safe and effective.
- Explain why the FDA may expedite drug approval or encourage the development of certain drugs.
- Describe the role of the health care team in post-marketing surveillance.

5.0 Introduction to the Drug Development Process

In the United States, the drug development process occurs within a structured framework to determine that a candidate drug has proven benefits that outweigh known and potential risks for the intended patient population. This process includes several stakeholders, including the pharmaceutical company (sponsor) developing the candidate drug and the Food and Drug Administration (FDA). The Center for Drug Evaluation and Research (CDER) is the FDA division responsible for regulating the approval and use of drug products as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, including prescription and over-the-counter medications, certain biological therapeutics, and generic drugs.^{1,2} In addition, CDER considers products such as fluoride toothpaste, antiperspirants, dandruff shampoos, and sunscreens to be drugs and, therefore, is also responsible for regulating their approval and use.² The Center for Biologics Evaluation and Research (CBER) is the FDA division responsible for the regulation of biological products under the authority of the Public Health Services (PHS) Act and the FD&C Act.³⁻⁵ Examples of products regulated by CDER and CBER are provided in Table 1.

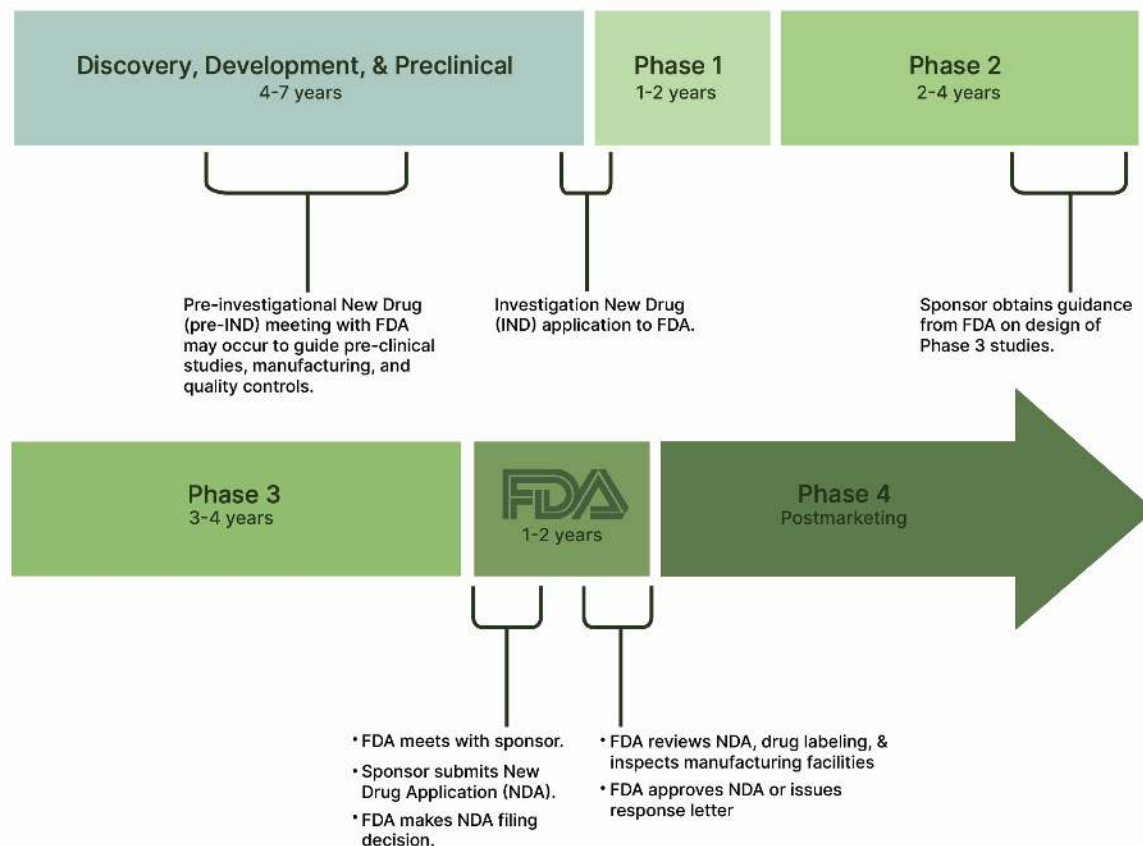
Table 5.1 CDER and CBER Product Regulatory Responsibility^{4,5}

CDER and CBER Product Regulatory Responsibility

CDER Responsible	CBER Responsible
Naturally occurring substances from mineral or plant source materials (excluding vaccines or allergenics)	Vaccines and vaccine-associated products
Products produced from nonhuman animal or human solid tissue sources	In vivo diagnostic allergenic products
Chemically synthesized molecules, including those that bind to the receptors for biological products and mononucleotide or polynucleotide products (e.g., cytokines, thrombolytics, monoclonal antibodies, immunomodulators)	Human blood or human blood-derived products, animal-derived procoagulant products, and animal- or cell culture-derived hemoglobin-based products (e.g., red blood cell substitutes)
Antibiotics	Immunoglobulin products
Hormone products (e.g., insulin, human growth hormone, pituitary hormones)	Products composed of or intended to contain intact cells or intact microorganisms, including bacteria, fungi, viruses, or virus pseudotypes, or viral vectors (e.g., gene therapy products)
Certain substances produced by fungi or bacteria (e.g., disaccharidase inhibitors, HMG-Co-A reductase inhibitors)	Protein, peptide (40 or fewer amino acids), or carbohydrate products produced by cell culture, except antibiotics, hormones, and products previously derived from human or animal tissue and regulated as approved drugs
	Animal venoms or constituents of venoms
	Synthetically-produced allergenic products are intended to specifically alter the immune response to a specific antigen or allergen
	Certain drugs used in conjunction with blood banking and/or transfusion

The drug development process includes 5 phases: 1) discovery and development, 2) preclinical research, 3) clinical research, 4) FDA review, and 5) post-marketing safety monitoring. For most drugs, the typical duration from discovery to FDA approval is between 10 and 15 years (Figure 5.1) and may cost more than \$1 billion.⁶ Each of these phases is described below in more detail.

Drug Development Timeline



FL

Figure 5.1: Drug Development Timeline. (CC-BY 4.0; Riley Cutler)

5.1 Discovery, Development, and Preclinical Research

The discovery, development, and preclinical research phases (Figure 5.2) encompass the drug development work before investigational drugs are tested in humans. This process may take 4 – 7 years to complete, with several steps occurring simultaneously (Figure 5.1).⁷

5.1.1 Discovery and Development

During the discovery phase, scientists identify disease-related mechanisms and processes (e.g., disease pathways, genes, proteins) that may serve as targets for developing drugs to stop, reverse, or prevent the disease of interest. These discoveries are made in a laboratory setting.

Once a disease-related target has been identified, hundreds to thousands of chemical and/or biological compounds are screened using *in silico*, or computational, testing to evaluate their ability to interact with the disease-related target and potentially treat or prevent the disease of interest.^{7,8} The goal of this process is to identify a small number of compounds—and ultimately a lead compound—that offer the most promise for further development. Promising compounds are further evaluated using *in silico* and *in vitro* models to predict physicochemical parameters, pharmacokinetics, and drug metabolism.^{8,9}

Once a lead compound is identified, the preclinical development includes analytical and bioanalytical methods development and validation, dosage form design, and establishment of good manufacturing processes for the active ingredient (e.g., lead compound)

Pre-Clinical

Discovery & Development

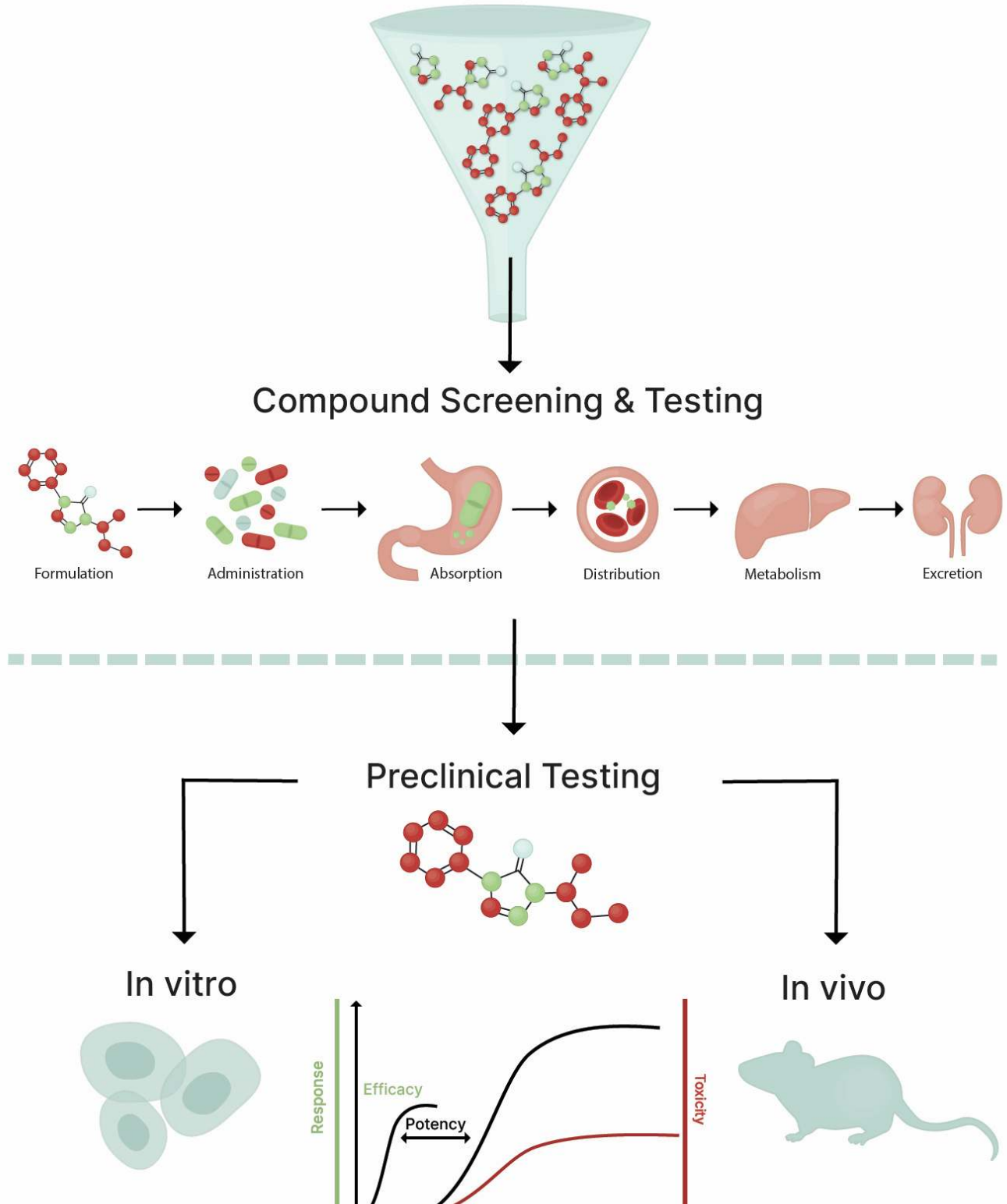


Figure 5.1.2: Preclinical Research (CC-BY-NC) Riley Cutler

and final investigational drug product to be used in clinical research phases.^{8,9} Additionally, *in vivo* studies are performed on the investigational drug using one or more animal models to evaluate basic pharmacology (e.g., metabolism, pharmacokinetics), perform dose range-finding, and assess experimental toxicology.⁹

5.1.2 Preclinical Research

Before an investigational drug can be tested in humans, definitive, *in vivo* preclinical studies in one or more animal models are required to assess the safety and toxicology (LD_{50}) of candidate drugs using good laboratory practices (GLP), good manufacturing practice (GMP) in the dosage form and maximally tolerated dose from dose range-finding studies.^{9,10} Additional *in vitro* studies are also performed to assess organ system toxicity (e.g., central nervous, cardiovascular, respiratory, and immune systems) and genetic toxicology (e.g., DNA, cellular genetic processes).⁹ Investigational drugs that exhibit potentially beneficial pharmacological activity to treat the disease of interest and have demonstrated reasonable safety in preclinical research may proceed to the clinical research phase once the sponsor receives approval for an **investigational new drug (IND)** application (described further in 5.3.1). Only about 1 in 1,000 potential drugs evaluated in the discovery, development, and preclinical phase proceed to the clinical research phase.⁶

5.2 Clinical Research

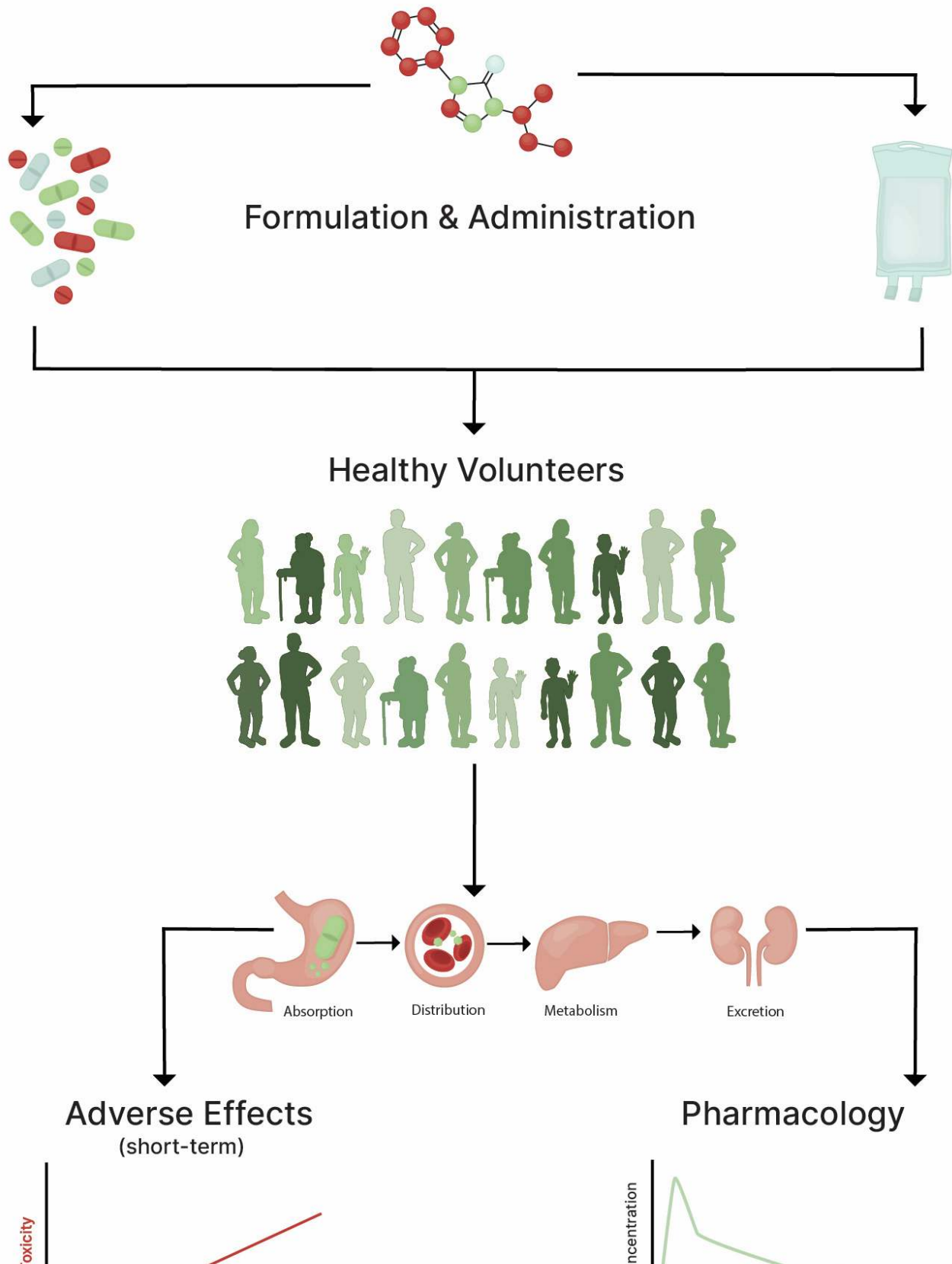
Once the FDA approves an **IND** application, a three-step clinical research phase begins, during which the investigational drug is tested in humans. The goal of the clinical research phase is to establish the safety, efficacy, and effectiveness of new drugs in humans.

5.2.1 Phase 1

The first step of the clinical research phase is to conduct Phase 1 studies (Figure 5.3). The primary focus of Phase 1 studies is to determine a safe dosage range and administration method and evaluate the investigational drug's toxicity profile. Part of the determination of a safe dosage range includes evaluations of the drug's pharmacokinetic properties.

Phase 1 studies are typically conducted in a relatively small number (20 – 80 subjects) of healthy volunteers. However, Phase 1 studies evaluating drugs to treat cancer are typically conducted in patients with the targeted type of cancer.^{1,7,11} Phase 1 studies may take 1 – 2 years or more to complete (Figure 5.1) and inform the design of Phase 2 studies.^{7,11,12}

Phase 1



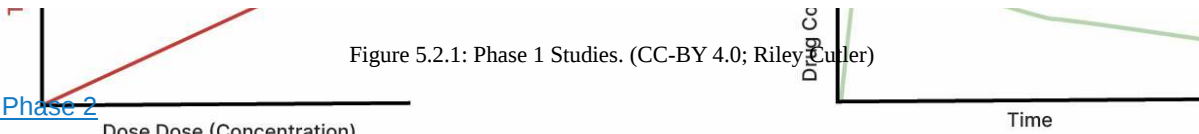


Figure 5.2.1: Phase 1 Studies. (CC-BY 4.0; Riley Cudler)

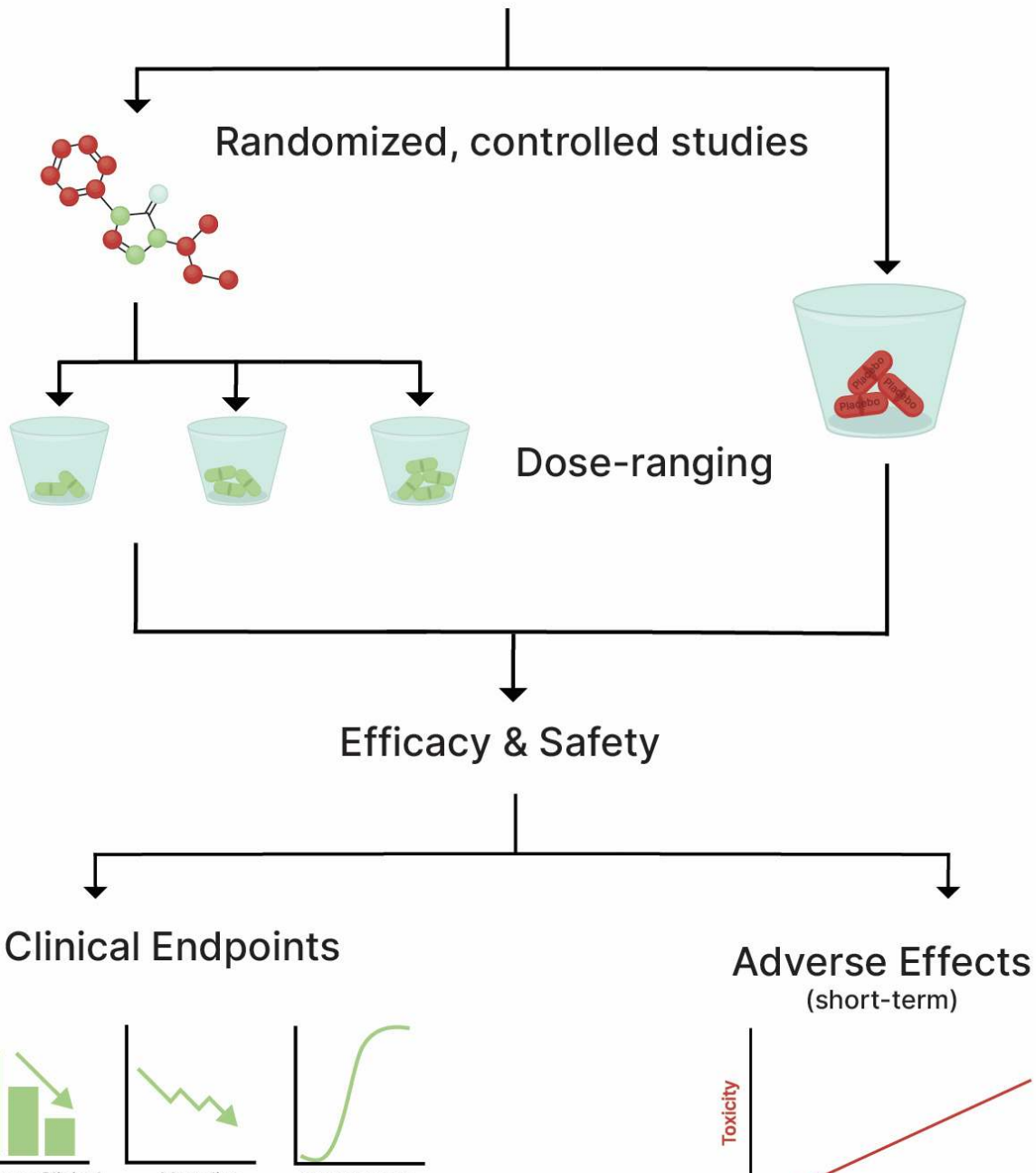
5.2.2 Phase 2

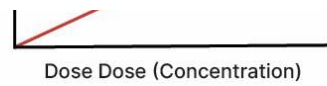
Approximately 40 – 70% of investigational drugs tested in Phase 1 demonstrate a reasonable safety profile and move on to Phase 2 studies (Figure 5.2.2).^{11,12} The purpose of Phase 2 studies is to evaluate the efficacy of the investigational drug to treat the condition of interest while gaining additional safety data. Phase 2 studies often incorporate dose-ranging evaluations to explore the investigational drug's therapeutic range.^{6,7,11}

Because Phase 2 studies are designed to evaluate efficacy, they are conducted in patients with the condition of interest. Furthermore, the number of patients studied in Phase 2 studies is larger (100 – 300) compared to Phase 1 studies. Phase 2 studies are generally randomized, controlled studies utilizing a placebo or alternative treatment (e.g., standard of care) and study patients for up to 2 years.¹¹ Efficacy endpoints often relate to symptom relief, pharmacodynamic/physiologic changes expected based on the pharmacology (e.g., blood pressure), and/or biomarker changes indicative of alterations in the disease course. Phase 2 studies serve as a “proof-of-concept” to inform the design of Phase 3 studies.⁷ Overall, it may take 2 – 4 years for Phase 2 studies to be completed (Figure 5.2.2).^{6,11,12}

Phase 2

People with the condition being studied





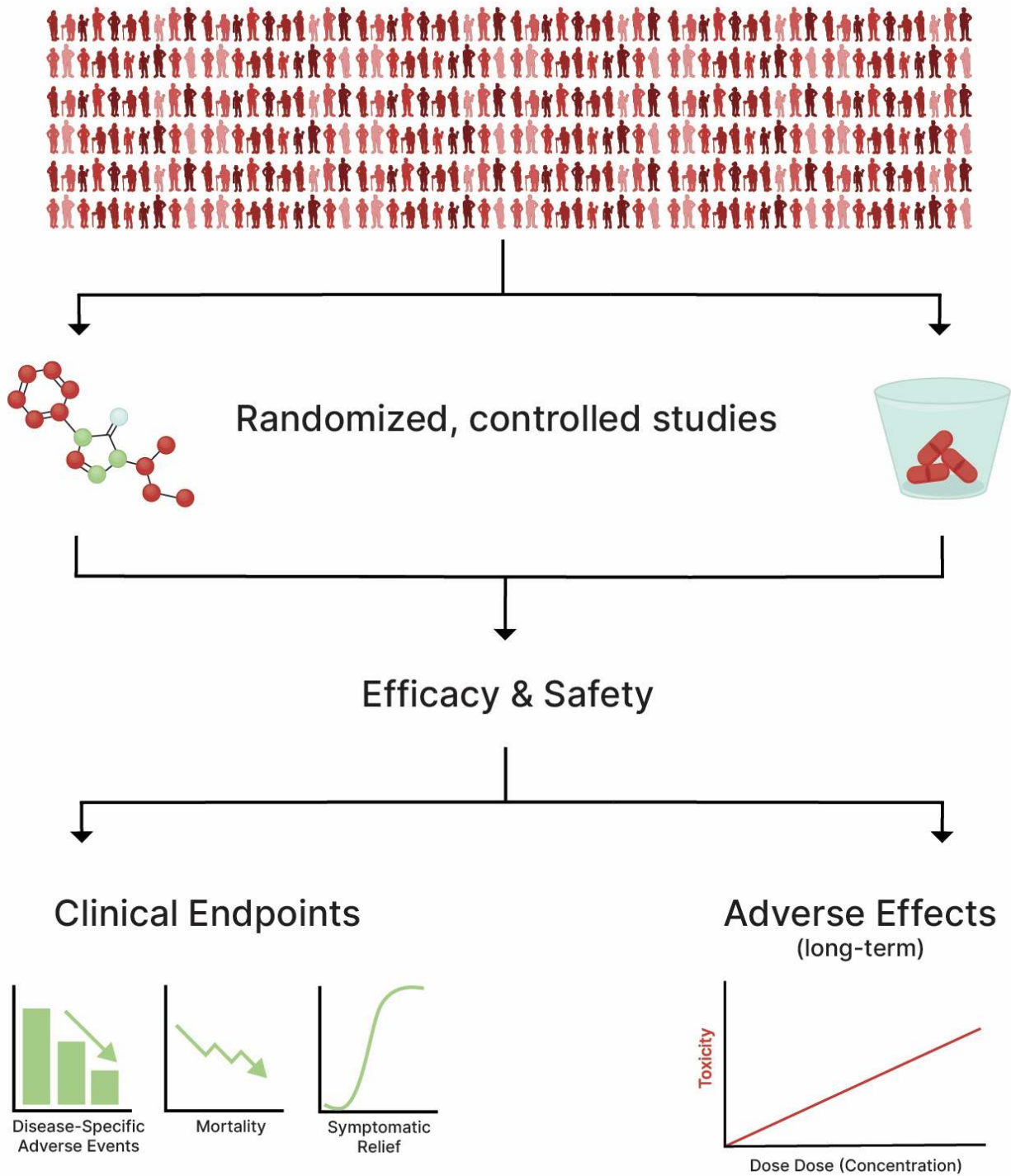
5.2.3 Phase 3

Approximately 30% of investigational drugs tested in Phase 2 demonstrate efficacy and a reasonable safety profile, enabling them to proceed to Phase 3 studies.^{11,12} The purpose of Phase 3 studies is to confirm that the investigational drug is both effective and safe in patients with the disease of interest.

To accomplish these goals, Phase 3 studies include much larger (300–3,000 or more) cohorts of patients with the disease of interest and longer durations of follow-up, providing a better assessment of serious, long-term, and/or rare adverse effects.^{6,7,11} Like Phase 2 studies, Phase 3 studies compare the investigational drug to a control group, typically a placebo. Efficacy endpoints may also include more robust clinical endpoints such as disease-specific adverse events, including mortality. Phase 3 often takes 1–4 years to complete (Figure 5.1).^{6,7,11,12}

Phase 3

People with the condition being studied



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5.3 Regulatory Process and Timeline

The FDA and CDER have a clearly defined structure to guide sponsors and regulate the drug development process, including timelines and deadlines related to formal reviews and approvals. Two critical components of this structure are the IND application and New Drug Application (NDA) or Biologics License Application (BLA), which are described below and incorporated into the timeline depicted in Figure 5.1. While sponsors must follow the IND and NDA/BLA processes, they are encouraged to seek guidance from the FDA throughout the drug development process. In particular, sponsors are encouraged to have a pre-IND meeting with the FDA to review guidance documents, share their proposed drug development plan with the FDA, and solicit FDA feedback on strategies to address specific questions related to the investigational drug's development.^{6,9,11} Sponsors are also encouraged to seek guidance from the FDA following completion of Phase 2 studies to guide the design of the pivotal Phase 3 studies.^{1,11}

5.3.1 Investigational New Drug Application

For investigational drugs that show promise in preclinical studies, a critical step in the drug development process is the IND application, the approval of which allows research of the investigational drug in humans to proceed. The IND application is submitted upon completion of the Preclinical Phase. The IND application must include data from preclinical studies (e.g., pharmacology, safety/toxicology); data from previous human experience (if any); chemistry, manufacturing, and control information; protocols for the conduct of each study proposed during the clinical research phase, and information about the investigator(s).^{9,11}

Once submitted, the FDA will notify the sponsor of the date it was received. The FDA may place the IND application on a Clinical Hold or request additional information before permitting the Clinical Research Phase to proceed.^{9,13} If the sponsor does not receive notification of a Clinical Hold or request for more information within 30 days of receiving the application, the IND may go into effect. The IND may go into effect earlier if notified by the FDA that the IND may begin. The manufacturer may ship the investigational new drug to investigators who may administer the drug to human subjects participating in the clinical studies once the IND goes into effect. For more information regarding the components, format, and other details related to the IND application, readers are referred to the [Code of Federal Regulations Title 21 Part 312](#).

5.3.2 New Drug Application & Biologics License Application

For investigational drugs shown to be safe and effective in Phase 3 clinical studies, the sponsor must submit an NDA (or BLA if the drug is a biologic) to the FDA formally requesting approval to market the drug. Before submitting the NDA, the sponsor may meet with the FDA to obtain guidance on the application. The NDA (or BLA) provides the FDA comprehensive information and data regarding the manufacturing process and facilities, quality control, and assurance; complete product description, including the chemical formula/structure, specifications, pharmacodynamics, and pharmacokinetics; data from all preclinical and clinical studies; indications; labeling including directions for use and patient information; safety updates and proposed risk evaluation and mitigation strategies (REMS) that may be applicable; drug abuse information; and institutional review board compliance.^{6,14}

Once received from the sponsor, the FDA has 60 days to decide to accept it for review.^{1,6} Once accepted for review, the FDA aims to complete its comprehensive review and render a decision within 6 – 10 months.^{1,6,14} In addition to reviewing the data contained within the NDA (or BLA), the FDA review also includes inspection of production facilities and clinical study sites. Additionally, the FDA review may include review by one or more of the FDA Advisory Committees to get additional, independent advice from experts, including patient representatives.¹⁴ The NDA/BLA review process often takes 1–2 years to complete before the FDA renders a decision (Figure 5.1).^{6,12} For more information regarding the details and requirements for submission, readers are referred to the [Code of Federal Regulations Title 21 Part 314](#) for an NDA or [Code of Federal Regulations, Title 21 Part 601](#) for a BLA.

The FDA estimates that approximately 25–30% of drugs entering Phase 3 move on to the next phase: NDA.¹¹ However, a recent analysis of clinical drug development between 2011 – 2020 reported a much higher success rate (57.8%) for investigational drugs moving from Phase 3 to NDA.¹² In this same analysis, the approval rate of NDAs was approximately 90%.

5.3.3 Accelerated Approval & Drug Development Designations

For some candidate drugs, the FDA has several mechanisms in place to expedite drug approval and encourage the development of certain drugs. These mechanisms can abbreviate the typical drug development timeline to as little as ~9 years.¹⁵

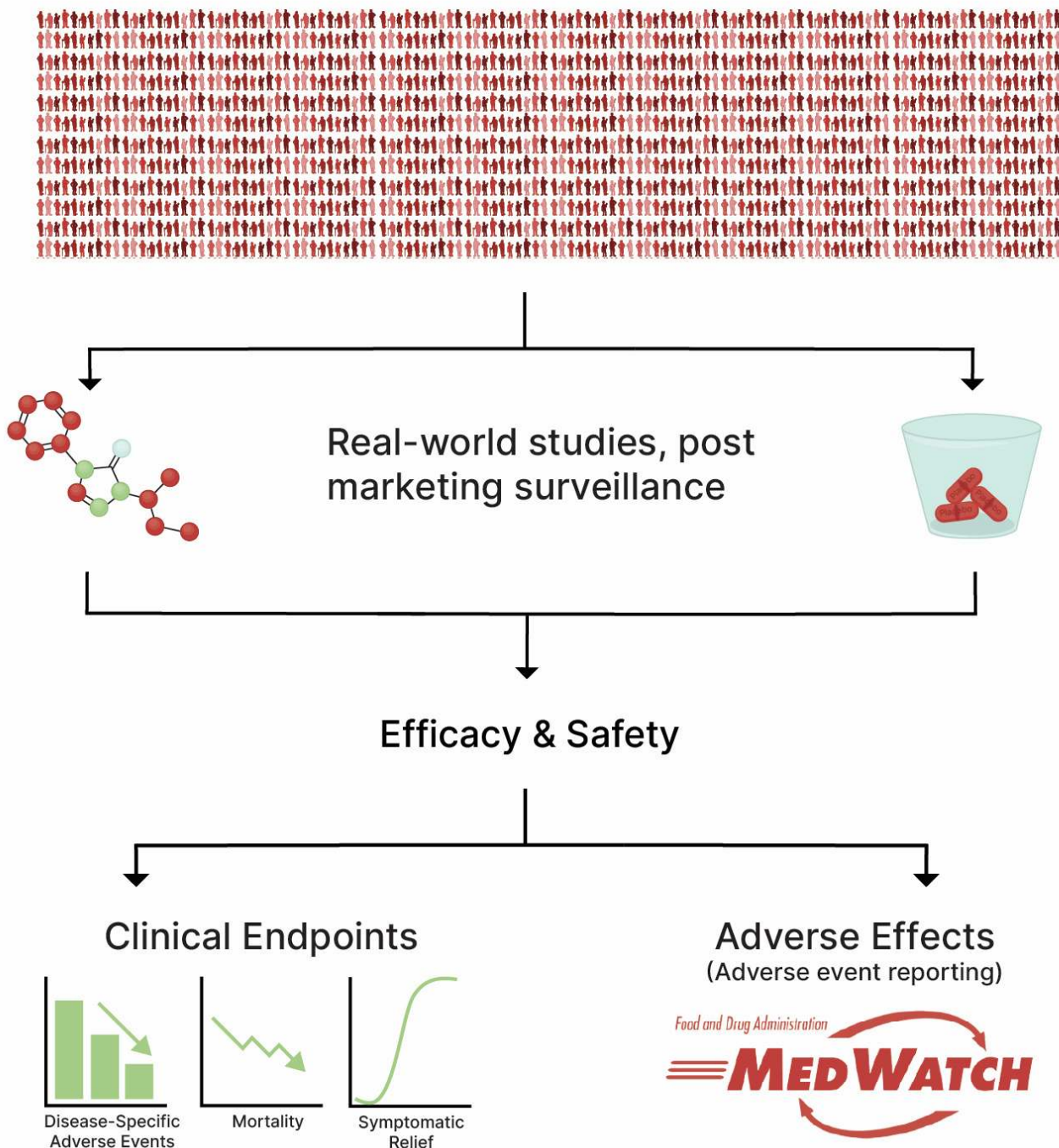
- **Accelerated Approval:** Promising candidate drugs that treat serious or life-threatening conditions and provide greater benefit and/or lower risk over currently available therapies can be granted accelerated approval.^{1,16} Drugs granted accelerated approval must demonstrate improvements in surrogate endpoints likely to predict clinical benefit or intermediate clinical endpoints less robust than standard endpoints.¹⁶ For drugs granted accelerated approval, the sponsor is required to conduct Phase 4 post-marketing studies to verify and further elucidate the drug's benefits.^{1,16} Approval of a drug granted accelerated approval can be withdrawn if Phase 4 studies fail to verify clinical benefits outweigh the risks associated with the drug.¹⁶
- **Fast Track:** Candidate drugs that treat serious conditions and fill an unmet medical need, based on preclinical and/or early clinical research, may be designated as fast track to expedite the approval process and make the drug available to patients sooner.¹⁷ The sponsor must request the fast track process.
- **Breakthrough Therapy:** Similarly, candidate drugs intended to treat serious conditions for which preliminary evidence has demonstrated substantial benefit over currently available therapies may be designated as breakthrough therapy.¹⁸ Like fast-track drugs, the sponsor must request breakthrough therapy designation. Drugs designated as breakthrough therapy may also be eligible for fast-track designation.
- **Priority Review:** Drugs that significantly improve the treatment, diagnosis, or prevention of serious illnesses may be designated for priority review, which seeks to reduce the time for the FDA to take action on the NDA from 10 months to 6 months or less.^{1,19}

5.4 Phase 4: Post-Marketing Surveillance

Phase 4 of drug development research refers to the post-marketing evaluation of newly approved drugs. These studies are designed to provide additional information related to the safety, increasing pharmacovigilance, and efficacy of the new drug.^{1,7,11} Phase 4 studies are conducted in much larger populations (e.g., thousands of patients) with the disease of interest, often in “real-world” settings.¹¹ These studies may be required by the FDA as conditions of approval or conducted voluntarily as part of the long-term scientific evaluation by the sponsor or investigators. Importantly, during Phase 4, the evaluation of adverse events voluntarily reported by health professionals, patients, and consumers using the FDA's [MedWatch](#) program is also done. Reporting adverse events is an expectation for all healthcare workers.

Phase 4

People with the condition being studied



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Figure 5.4: Phase 4 Studies. (CC-BY 4.0; Riley Cutler)

References:

1. Gibofsky A. The FDA and the Drug Development Process. In: Lockshin MD, Crow MK, Barbhuiya M, eds. *Diagnoses Without Names*. Springer International Publishing; 2022:69-74. doi:10.1007/978-3-031-04935-4_7
2. U.S. Food & Drug Administration. Center for Drug Evaluation and Research | CDER. Published August 14, 2023. Accessed September 18, 2023. [FDA website\(opens in new window\)](https://www.fda.gov) [www.fda.gov] [www.fda.gov] [www.fda.gov]
3. Van Norman GA. Drugs, Devices, and the FDA: Part 1. *JACC: Basic to Translational Science*. 2016;1(3):170-179. doi:10.1016/j.jacbts.2016.03.002
4. BioStock. Drug development: the four phases. Published January 2, 2023. Accessed September 19, 2023. [NA\(opens in new window\)](https://www.biostock.se) [www.biostock.se]
5. U.S. Food & Drug Administration. Step 1: Discovery and development. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
6. Steinmetz KL, Spack EG. The basics of preclinical drug development for neurodegenerative disease indications. *BMC Neurol*. 2009;9(Suppl 1):S2. doi:10.1186/1471-2377-9-S1-S2
7. U.S. Food & Drug Administration. Step 2: Preclinical research. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
8. U.S. Food & Drug Administration. Step 3: Clinical research. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
9. Thomas D, Chancellor D, Micklus A, et al. *Clinical Development Success Rates and Contributing Factors 2011-2020*. Biotechnology Innovation Organization | Informa Pharma Intelligence | QLS Advisors LLC; 2021. [NA\(opens in new window\)](https://go.bio.org) [go.bio.org]
10. U.S. Food & Drug Administration. Investigational New Drug (IND) application. Published July 20, 2022. Accessed September 19, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
11. U.S. Food & Drug Administration. Step 4: FDA drug review. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
12. Brown DG, Wobst HJ, Kapoor A, Kenna LA, Southall N. Drug development times for innovative drugs. *Nat Rev Drug Discov*. 21:793-794. doi:10.1038/d41573-021-00190-9
13. U.S. Food & Drug Administration. Accelerated Approval. Published February 24, 2023. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
14. U.S. Food & Drug Administration. Fast track. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
15. U.S. Food & Drug Administration. Breakthrough therapy. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]
16. U.S. Food & Drug Administration. Priority review. Published January 4, 2018. Accessed September 18, 2023. [NA\(opens in new window\)](https://www.fda.gov) [www.fda.gov]

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6: Unintended Medication Outcomes

Learning Objectives

- Define an unintended drug outcome.
- Name factors that contribute to medication errors.
- Explain why a patient's medication non-adherence may not be intentional.

6.0: Overview of Unintended Medication Outcomes

When considering the occurrence or prevention of unintended outcomes of medication use, error taxonomy and classification can help to guide follow-up actions and prioritize efforts for improvement, when applicable. The classification system for untoward medication-related events is not mutually exclusive. Events may be classified into more than one event category.

6.1. Medication Errors

Medication errors refer to preventable events that lead to inappropriate medication use or harm to a patient. Medication errors can occur at any stage of the medication use process, including prescribing, verifying/preparing, dispensing, administering, or monitoring. Examples of medication errors at each step of the medication use process are described in the table below. One important note about medication errors is that the majority of errors do not result in harm to the patient.

Medication Use Process Step	Example of Medication Error
Prescribing	Prescribing a medication at a dose that is inappropriate for their weight, height, gender, or end-organ (renal/liver) function.
Verifying/Preparing	Reconstituting a medication in the incorrect volume of fluid, results in an unintended concentration.
Dispensing	Giving or dispensing a medication to the incorrect person.
Administering	Administering a medication via the incorrect route.
Monitoring	Failure to perform required monitoring for a high-alert medication.

6.2 Near Misses

A near-miss medication error is a subclassification that refers to the inappropriate use of a medication that did not reach the patient. Such events, often also described as “good catches”, can significantly contribute to the understanding of important process gaps that could lead to patient harm if not identified/remedied before the medication reaches the patient.

6.3 Adverse Drug Events

Adverse Drug Events (ADEs) are injuries that result from the use of the medication. ADE's may or may not be related to medication errors. When ADEs are not related to a medication error, they are considered non-preventable. The terms “Non-preventable ADE” and “Adverse Drug Reaction (ADR)” refer to such occurrences.

Preventable Adverse Drug Events involve injury/harm that results from inappropriate medication use. They are medication errors that result in injury or harm. This is a particularly important classification of unintended medication outcomes for medical-legal reasons, and because the circumstances that lead to the event have proven, by definition, to be capable of causing injury.

6.4 Medication Non-Adherence

Medication adherence is a critical aspect of pharmacotherapeutic care that can be easily overlooked or underappreciated by healthcare providers. Non-adherence, also referred to as non-compliance, can be detrimental to patient care. It is important to remember that non-adherence may not be intentional.

Factors that can lead to medication non-adherence include:

- *Complexity of medication regimens:* When medication regimens are complex, patients may find it difficult to remember to take all their medications at the right time or in the correct way (e.g., with food).
- *Side effects:* Some medications can cause unpleasant side effects, which can lead a person to stop taking their medications. Some may believe that the benefits of the medication do not outweigh the side effects. Fear of side effects may also lead to non-adherence.
- *Cost:* Medications can be expensive, and some patients may not be able to afford the cost of their medications. This may include medications for which insurance companies or other payors have created administrative barriers to insurance coverage (e.g., prior authorization) to prevent inappropriate use.
- *Lack of understanding or education:* Individuals may not understand the importance of their medications or how to take them properly.
- *Mental health or cognitive issues:* Patients with mental health or cognitive issues may have difficulty remembering to take their medications, understanding the importance of their medications, or unable to follow complex instructions.
- *Lack of social support:* Patients who lack social support may have difficulty adhering to their medication regimens. They may not have anyone to remind them to take their medications or provide transportation to procure their prescriptions from a pharmacy.
- *Cultural or language barriers:* Patients from different cultures or with limited English proficiency may have difficulty understanding the instructions for their medications or may have beliefs that are not consistent with the medication regimen.

To promote medication adherence, clinicians should identify which of the above factor(s) may be contributing to non-adherence on a case-by-case basis, and work to resolve the root causes. For instance, if cost is a barrier, the provider may be able to help the patient enroll in a manufacturer support assistance program, or consider alternative therapies that may be available to the patient at a lower cost.

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7: Pharmacologic Issues Across the Lifespan

Learning Objectives

- Name three physiologic pharmacokinetic issues affecting drug response in neonates and infants.
- Discuss the pharmacologic variables associated with each pediatric age group (neonate, infant, and child).
- Name the four considerations for increasing medication compliance for the elderly.
- Describe the physiologic changes in pregnancy that may affect the absorption, distribution, metabolism, and excretion of medications.
- Summarize the Pregnancy and Lactation Rule endorsed by the Food and Drug Administration (FDA).

7.0 Overview

Pharmacokinetic and pharmacodynamic processes vary with age. These differences are due to the normal physiologic changes that occur over a normal lifespan, especially in infants and older people. A critical difference across the lifespan is the amount of total body water, which changes with age and condition.

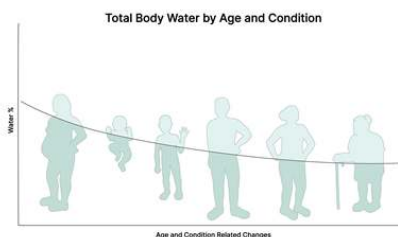


Figure 7.0: Total Body Water by Age and Condition. (CC-BY 4.0; Riley Cutler)

7.1 Neonates, Infants, Children

Drug treatment for neonates (less than one month of age) and infants (less than one year of age) is complicated by the lack of evidence in this age group. Instead, data from adult clinical trials is applied to determine dosing and efficacy. The dose-response relationship may change in the first few weeks after birth, making it a challenge to establish guidelines.

7.1.1 Absorption

Some physiologic changes associated with the first few months of life that affect absorption include a higher-than-normal gastric pH. In neonates and pediatric patients, the stomach's acid-producing cells are immature until around the age of one to two years. They also experience prolonged and irregular gastric emptying until 6-8 months of age.

7.1.2 Distribution

Changes that affect distribution include lower adipose tissue, decreased plasmin albumin, and higher total body water. The developing blood-brain barrier allows more drugs to enter the brain.¹

7.1.3 Metabolism

The developing liver in neonates and infants produces decreased levels of microsomal enzymes. This may decrease the ability to metabolize medications, necessitating lower drug doses. As an infant's liver matures and liver metabolism increases, the infant may require higher doses of medications. Age (in weeks) is important when prescribing for neonates and infants, as liver function may change weekly. Hepatic function reaches maturity at about two years old.

7.1.4 Elimination

Neonates, infants, and children have immature kidneys with decreased glomerular filtration, reabsorption, and tubular secretion. As a result, medications are not cleared as efficiently from the body. Dosing for most medications used to treat infants and pediatric

patients is commonly based on weight in kilograms, and a smaller dose is usually prescribed. In addition, pediatric patients may have higher levels of free circulating medication than anticipated and may become toxic quickly.

7.2 Overview of Older Adults

The rationale use of drugs in persons over 65 years of age is complicated by physiologic changes, increased incidence of chronic disease and co-morbidities, and polypharmacy. Financial issues, limited resources, and poor nutritional status may all influence an older adult's ability to comply.

Cardiac output starts declining by 1% at about age 30, and in older people, there is a redistribution of blood flow favoring the brain, heart, and kidneys. Lean body mass declines with age, and total body water decreases. Plasma albumin levels may decrease, especially in the poorly nourished. Glomerular filtration rate and plasma renal blood flow steadily decline with aging.

7.2.1 Absorption

As a natural result of aging, older adults will experience decreased blood flow to tissues within the GI tract. In addition, changes in the gastric pH may alter the absorption of certain medications. Older adult patients may also experience variations in available plasma proteins, which can impact drug levels of highly protein-bound medications. Consideration must also be given to using subcutaneous and intramuscular injections in older patients experiencing decreased cardiac output. Decreased drug absorption of medications can occur when peripheral circulation is reduced. Finally, as adults age, they often have less body fat, resulting in reduced absorption of drugs from transdermal patches that require adequate subcutaneous fat stores for proper absorption.

7.2.2 Distribution

The aging adult patient will experience a decrease in total body water, muscle mass, and serum albumin while total body fat increases. As these parameters change with aging, the volume of distribution (V_d) of a drug may be affected. Recall that V_d is the volume of total body fluid into which a drug appears to distribute after it reaches equilibrium or steady state. In older adults, lipid-soluble drugs such as diazepam and lidocaine have a larger V_d , whereas water-soluble drugs such as acetaminophen and ethanol have a smaller V_d . Serum albumin often also decreases, resulting in more active free drug within the body. This is one reason why many older adult patients require lower medication levels. Be aware that a person who has taken medication for a chronic condition for many years may need a dosage adjustment as they age.

7.2.3 Metabolism

Hepatic metabolism may significantly decline in older adults. As a result, dosages should be adjusted according to the patient's liver function and anticipated metabolic rate. First-pass metabolism is also decreased with aging; therefore, older adults may have higher "free" circulating drug concentrations and be at higher risk for side effects and toxicities.

7.2.4 Elimination

Kidney and liver function often decreases with age, leading to reduced medication excretion. Subsequently, medication may have a prolonged half-life with a greater potential for toxicity from elevated circulating drug levels. Two important principles need to be applied to dosing for older people. First, most elderly patients do not have "normal" renal function despite having a serum creatinine level that appears normal. Second, most elderly persons require a dose adjustment for a medication or drug metabolite eliminated through the kidneys. Smaller doses of medications are often recommended for older patients because of these factors, commonly called "start low and go slow."

7.3 Overview of Pregnancy and Breastfeeding

Drug use during pregnancy is common: many people take at least one medication. Indications may include pregnancy-related issues such as nausea, constipation, and pre-eclampsia, or chronic conditions such as epilepsy and asthma. When drugs are used during pregnancy, there is a risk to the fetus as well. However, most drugs are not tested during pregnancy, and the risk to the fetus remains unknown. Therefore, the provider should initiate a shared decision approach and weigh the risks and benefits.

For some chronic conditions, such as asthma, the risk to the fetus is clearly greater when the pregnant person stops the asthma medications. The incidence of stillbirth is high among pregnant persons who do not take medications for asthma. Note that due to the lack of data from clinical trials, evidence for the medication safety and risk is derived from histories of women who have delivered children with and without congenital disabilities.

During pregnancy, changes in the kidney, liver, and GI tract affect drug disposition. These changes may be associated with a specific trimester. During the third trimester, renal blood flow doubles, causing an increase in glomerular filtration and an accelerated clearance of drugs, such as lithium, that are eliminated by this process.

In December 2014, the FDA passed the Pregnancy and Lactation Labeling Rule (PLLR). This rule supersedes the Pregnancy Risk Categories and was enacted on June 30, 2015. By 2020, all drugs will cease using lettered categories. The PLLR requires labeling for (1) pregnancy, (2) lactation, and (3) females and males of reproductive potential. More information is available at [fda.gov](https://www.fda.gov) [fda.gov] [www.fda.gov] under pregnancy and lactation labeling resources.

From a pharmacological perspective, the greatest concern during pregnancy is exposing the fetus to a **teratogen**. A teratogen is any substance, organism, or physical agent that causes a permanent malformation of an embryo. The risk is dependent upon the dose of the drug and the time during gestation at which the exposure occurred. In general, clinicians should assume all drugs cross the placenta and may reach the fetus.

7.3.1 Absorption

Hormonal changes and abdominal pressure as the uterus expands may affect absorption. Gastric tone and motility slow during pregnancy, requiring a longer time to absorb drugs. This may require a reduction in drug dose.

7.3.2 Distribution

The increase in blood volume and decrease in plasma proteins in a pregnant person cause dilution of drug levels. In addition, increased cardiac output and plasma volume alter regional blood flow. Blood flow to the uterus, kidneys, and skin is increased. Changes in lipid levels may alter distribution, especially in the third trimester. Fat-soluble drugs readily distribute into breast milk.

7.3.3. Metabolism

Drug metabolism may increase during pregnancy, requiring a higher dose for certain drugs, such as anticonvulsants. Carbamazepine, phenytoin, and valproic acid may require higher doses during pregnancy.

7.3.4 Elimination

Blood flow through the kidneys is increased by the third trimester by over 50%. Because drug excretion rates are increased, medication doses may need to be adjusted.

7.4 Lactation

A large number of drugs are secreted into breast milk, but few are contraindicated. The potential effects of drugs on the infant are influenced by the amount of drug that reaches the infant's circulation. Some drugs may not be absorbed or may be destroyed in the infant's GI system. General recommendations for pharmacotherapy during lactation are: (1) postponing therapy until the infant is weaned, (2) administering the medication immediately after breastfeeding to maximize time in between feedings, (3) prescribing medications with a short half-life to reduce the drug exposure to the infant, (4) avoiding breastfeeding when the medication is at its peak, (5) selecting medications with high protein-binding properties as they are less likely to be secreted into breast milk, and (6) avoiding herbals and supplements that have not been reviewed with a provider.

References:

Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between the pediatric population and adults. *Pharmaceutics*, 3(1), 53–72. [NA](#) [doi.org]

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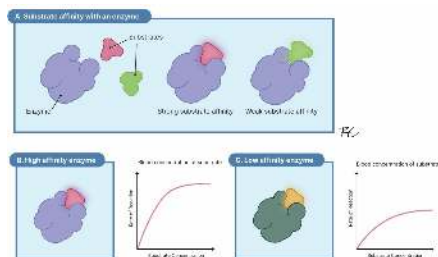
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Glossary

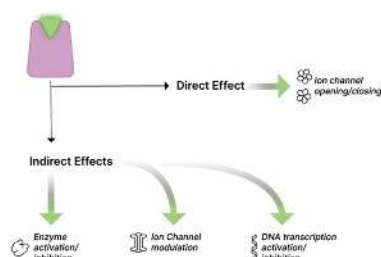
Absorption: The first stage of pharmacokinetics, when medications enter the body and travel from the site of administration into the body's circulation, crossing membranes in the process.

Adverse effect: An unintended and potentially dangerous pharmacological effect when medication is administered correctly.

Affinity: The strength of binding between a drug and a receptor.



Agonist: A drug or ligand that binds to a receptor and produces a direct or indirect effect. Agonists may be full or partial.

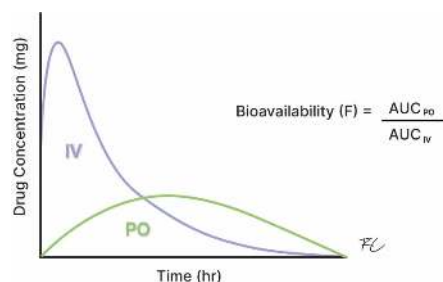


Antagonist: A molecule that prevents the action of other molecules, often by competing for a cellular receptor; opposite of agonist. Antagonists may be further described as competitive, non-competitive, or irreversible. Drug (red triangle) binds to the receptor, but there is no clinical effect.

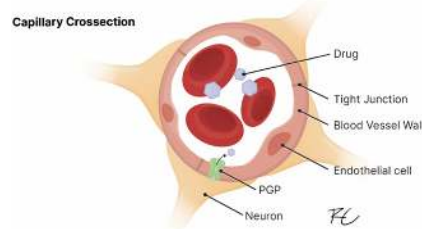


Bioavailability: The amount or presence of a drug in the bloodstream after it is administered. Bioavailability varies with the route of administration and is usually expressed as a percentage. The bioavailability of an intravenous drug

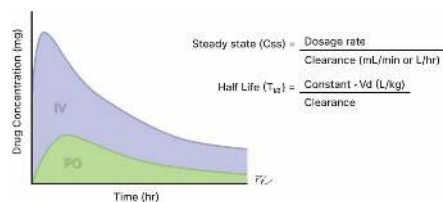
(IV) is 100% or 1. Any other route of administration is less than 100% or 1. Bioavailability is described as the area under the curve (AUC).



Blood-brain barrier (BBB): A nearly impenetrable barricade built from a tightly woven mesh of capillaries tightly woven together to protect the brain from potentially dangerous substances such as poisons, viruses, or drugs. The figure of the capillary cross section of the BBB shows the tight junctions between endothelial cells and the location of the P-glycoproteins (PGP). Notice that the PGP effluxes molecules from the neuron into the bloodstream.

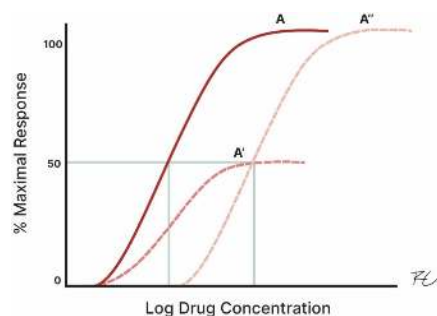


Clearance: The ratio of the rate of elimination of a drug to the plasma concentration of the drug. Clearance has an inverse relationship to half-life.

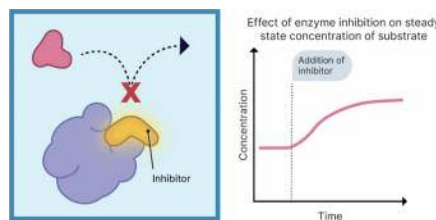


Competitive antagonists: the dose-response curve for an agonist alone is labeled A. The curve for an agonist plus a competitive antagonist is labeled A'. The competitive antagonist shifts the agonist curve to the right. An irreversible, also

called non-competitive, antagonist is labeled A'. A non-competitive antagonist shifts the agonist curve downward, decreasing the maximal response.



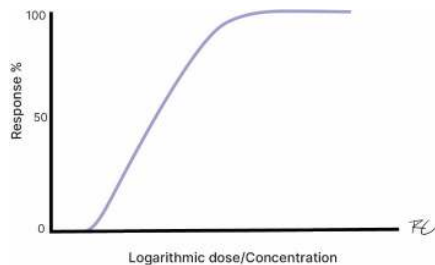
Competitive inhibition: The drug competes with a substrate for an active binding site.,



CYP (Cytochrome) P450 family: Enzymes responsible for the metabolism of most drugs; there are many isoforms of CYP enzymes.

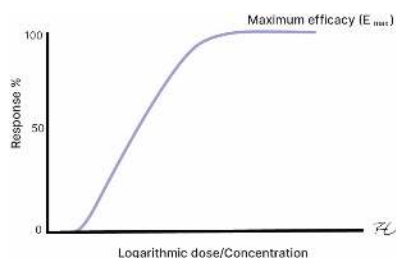
Distribution: The second stage of pharmacokinetics is the process by which a medication moves from the site of administration to tissues throughout the body.

Dose-response curve: Graph showing the relationship between a dose or drug concentration and its effectiveness, often measured as a clinical response. As the dose of a drug increases, ideally, the response to the drug should also increase until saturation is reached. The slope and shape of the curve are characteristic of the particular drug-receptor interaction. The drug concentration is expressed as a logarithmic dose.



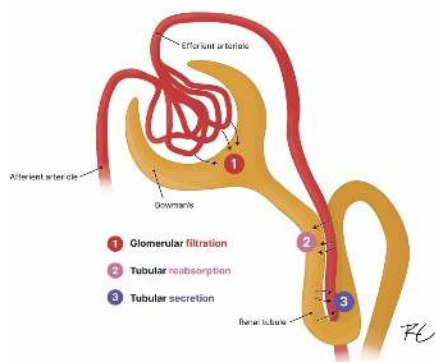
Duration: The length of time a medication produces its desired therapeutic effect.

Efficacy: The ability of a drug to produce a particular effector response. The plateau represents the maximum effect achieved with a drug, no matter how much of the drug is given.



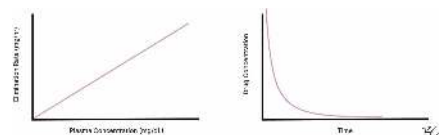
Excretion: The final stage of pharmacokinetics, the process whereby drug byproducts and metabolites are eliminated from the body. Renal and liver excretion are the most common forms of drug removal, but drugs may also be excreted through the lungs (exhalation), skin (sweat), and mammary glands (breast milk).

The three processes for renal excretion



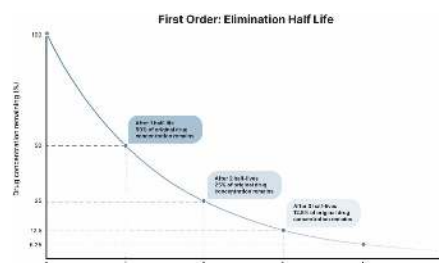
First-order kinetics: When a drug follows a first-order pattern of elimination pharmacokinetics, the elimination rate depends on the plasma concentration. As the plasma concentration increases, so

does the rate of elimination, as demonstrated by the graph on the left.

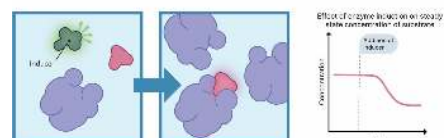


First-pass effect: The inactivation of orally or enterally administered drugs in the liver and intestine. Blood containing the absorbed drug passes through the liver and goes through chemical reactions that can deactivate a substantial amount of the drug, thus decreasing its bioavailability and efficacy.

Half-life: A drug's half-life ($t_{1/2}$) is the measure of time it takes for the concentration of a drug in the body to be reduced by half. Half-life is related to the kinetics (first-order or zero-order) elimination pattern of the drug.



Induction: Increased synthesis and/or activity of drug-metabolizing enzymes. In the illustration below, the inducer is the green molecule (another drug or ligand), the purple shape is a drug metabolizing enzyme, and the drug is the pink triangle. When the inducer is present, more drug-metabolizing enzymes are produced, which decreases the steady state of the drug as depicted in the graph on the right, showing a decline in drug concentration after adding an inducer.

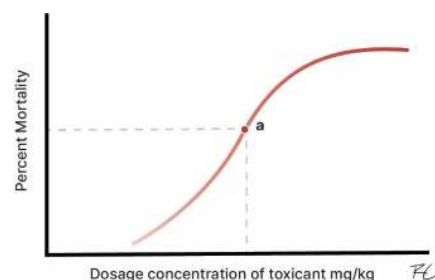


Inhibition: Decreased synthesis of drug-metabolizing enzymes or interference with how an enzyme works. The effects of the inhibitor are the opposite of an inducer. When an inhibitor is added, the

number or activity of the drug-metabolizing enzymes decreases, and the steady state rises. The increase in drug concentration in the body can lead to adverse events, toxicity, and potentially lethal effects.

Intermediate metabolizer: One of the categories of metabolizing phenotypes, displaying slightly reduced metabolic activity.

Lethal dose or LD50: Lethal dose of a drug for 50% of the population in an animal study. The graph below shows the drug concentration that causes 50% mortality.

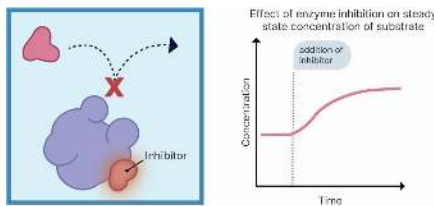


Mechanism of action (MOA): How a medication works at the molecular or cellular level within the body to achieve a desired biological response or outcome. The molecular interaction may include how a drug binds to its target receptor (beta blockers), inhibits an enzyme or protein (immunosuppressants), or interacts with DNA or RNA (antimicrobials). These interactions may cause changes in cellular function, such as cell growth, division, or the production/inhibition of specific molecules. Ultimately, the MOA should lead to the drug's desired biological response or therapeutic effect.

Metabolism: The breakdown of a drug molecule via enzymes in the liver (primarily) or intestines (secondarily).

Non-competitive antagonists: A drug that binds to a non-agonist site on the receptor but still prevents activation of the receptor. The illustration on the right shows a drug (pink) that cannot interact with its binding site due to the presence of an inhibitor bound to the target

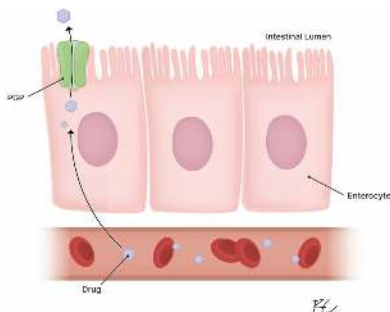
molecule at a different site. A corresponding concentration vs. time graph shows loss of steady state once the inhibitor is added. Concentration increases over time.



Normal metabolizer: The reference metabolizing phenotype with two functioning alleles.

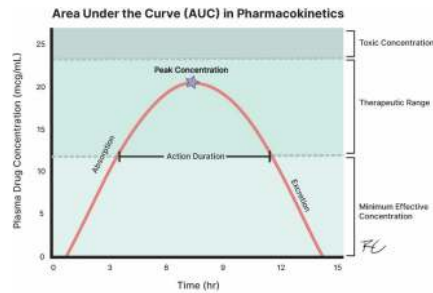
Onset: The time it takes for a medication to begin to work and exert a therapeutic effect after administration. Onset will vary depending on the route of administration.

P-glycoprotein (PGP): An efflux transmembrane protein that transports various substances, including drugs, across epithelial membranes. The protein protects against xenobiotics and is found in intestines, liver, kidney, placenta and blood brain barrier. The illustration below shows the location and activity of PGP for an enterocyte (location varies by tissue type). The drug moves from the bloodstream or circulation into the enterocyte. The PGP, located on the brush border side of the cell, "escorts" it into the intestinal lumen where it is excreted.



Peak: When a drug reaches its maximum concentration in the bloodstream. The graph below shows the AUC (time vs plasma drug concentration) as a bell-shaped curve with the maximum concentration at the midpoint. The AUC varies by drug and route of

administration. Three important concentration parameters are labeled on the right-hand side of the graph: minimum effective concentration, therapeutic range, and toxic concentration.

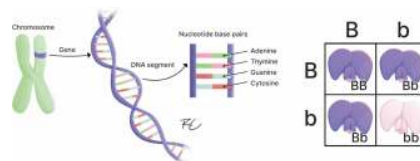


Phase I reactions: CYP450 enzyme reactions convert the parent drug into a more polar, water-soluble metabolite, making the drug easier to eliminate. These enzymes are not highly selective for their substrate, so a few isoforms metabolize thousands of drugs.

Phase II reactions: Reactions that increase the water solubility of a drug.

Pharmacodynamics: The study of how drugs act at target sites of action in the body.

Pharmacogenetics: A branch of pharmacology that studies individual variation in the DNA sequence in drug metabolism and response. The diagram below reviews key genetic concepts from genotype, nucleotide base sequencing, and phenotype using Punnett's square.



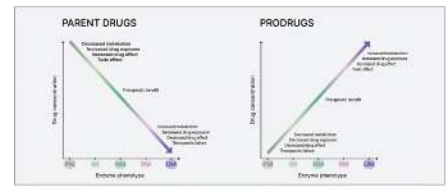
Pharmacogenomics: A branch of pharmacology that studies population variation in the DNA sequence in drug metabolism and response.

Pharmacokinetics: The study of how the body absorbs, distributes, metabolizes, and eliminates drugs.

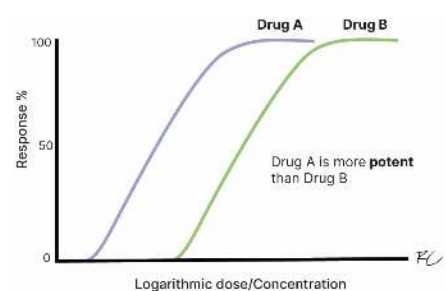
Pharmacology: The science dealing with the actions of drugs on the body.

Pharmacy: The science of the preparation of drugs.

Poor metabolizer: An individual who displays little to no functional metabolic activity for prodrugs and toxicity for parent drugs.



Potency: The drug dose required to produce a specific intensity of effect. The graph of dose-response curves for different drugs shows the difference in potency. The more potent drug requires a lower dose of drug concentration to elicit a response.



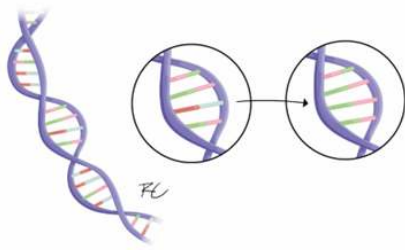
Rapid metabolizer: A metabolizing phenotype that shows increased metabolic activity.

Selectivity: A "selective" drug binds to a primary and predictable site to create one desired effect. A "non-selective" drug is less predictable, binding to multiple receptor sites with potentially more side effects.

Side effect: Effect of a drug, other than the desired effect, sometimes in an organ other than the target organ. Side effects are also called unintended medication outcomes.

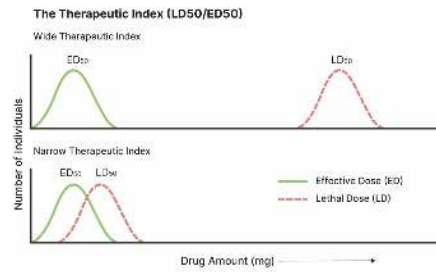
Single nucleotide polymorphism (SNP): a variation of a nucleotide (A, T, C, and G) at a single position in a DNA sequence among individuals. SNPs are common and found in at least 1% of the population. SNPs can influence how individuals respond to drugs. The

illustration below shows a single nucleotide substitution in the DNA strand.



Steady state: When the rate of drug elimination equals the rate of administration.

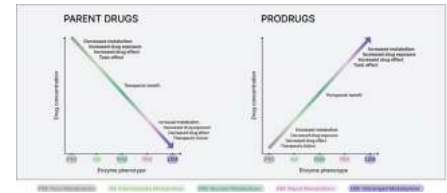
Therapeutic index (TI): A quantitative measurement of the relative safety of a drug that compares the amount of drug that produces a therapeutic effect (ED₅₀) with the amount of drug that produces a toxic effect (LD₅₀). A medication with a large therapeutic index is safer than a medication with a small therapeutic index. $TI = LD_{50}/ED_{50}$.



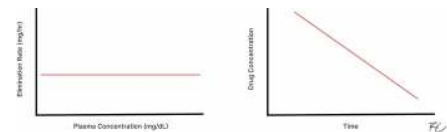
Therapeutic window: The dosing window is the safe range between the minimum therapeutic concentration and the minimum toxic concentration of a drug; the range in which the most effective treatment will occur.

Ultra-rapid metabolizer: Metabolizing phenotype of individuals with substantially increased metabolic activity. Ultra-rapid metabolizers (UM) may experience a therapeutic failure when taking parent drugs (the drug does not have to be metabolized into a biologically active metabolite). Conversely, UMs may

develop toxicities when prescribed a prodrug.



Zero-order kinetics: A process that describes how a drug's metabolism or elimination rate remains constant, regardless of the drug's concentration. In the graphs below, the figure on the right is a straight line. It reflects that the same amount of drug is eliminated across plasma concentrations. The second graph, showing drug concentration vs time, is a diagonal line with drug concentration decreasing over time.



Figure

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Supplemental Materials - Extra Credit Exercises

Medication Adherence Case Study #1

AW is 50-year-old with heart failure (HFrEF Stage C NYHA Class II) is taking metoprolol, furosemide and lisinopril. AW continues to work as a court reporter and cannot leave the proceedings once court is in session. Create a medication plan for frequency and timing of medications around AW's work schedule yet optimizing the pharmacotherapy. Please consider that during the incident hospitalization for heart failure, AW had an episode of hypotension. Also, AW has carpal tunnel syndrome and has a long commute to work (no available restroom). AW has been skipping the furosemide and taking metoprolol and lisinopril together on route to work; sometimes arriving to the courthouse feeling lightheaded as AW goes through the metal detector.

Assigned Student Task #1.1:

Suggest a schedule for AW to take their medications that will allow AW to take all medications daily, safely arrive at work, and minimize hypotensive episodes. Write a brief description of the pharmacokinetics of the various drugs that you considered when creating the medication schedule.

Assigned Student Task #1.2:

Design a pillbox! AW requested a pillbox that would be small enough to fit in a pocket. You can be creative with the features you would like to include that may help adherence.

Medication Adherence Case Study #2

CZ is 30-year-old with heart failure post COVID infection (HFrEF Stage C NYHA Class II) is taking metoprolol, furosemide, and sacubitril/valsartan (Entresto). CZ has returned to work and bikes about 3 blocks to the office. Previously on the weekends CZ rode about 10 miles on a bike trail and wants to gradually try resuming longer bike rides. Create a medication plan for frequency and timing of medications around to optimize the pharmacotherapy and limit skipped or missed doses. CZ has been missing the furosemide and then taking metoprolol and Entresto together at work.

Assigned Student Task #2.1:

Suggestion a schedule for CZ to take their medications that will allow AW to take all medications daily, safely bike to work, minimize hypotensive episodes, and resume biking. Write a brief description of the pharmacokinetics of the various drugs CZ is taking, which will help you to create the medication schedule.

Assigned Student Task #2.2:

Design a pillbox! CZ requested a pillbox that would be small enough to fit into biking clothes. You can be creative with the features you would like to include that may help adherence. Also, a bioengineering student is available for consultation.

Supplemental Materials - Instructor Notes for Extra Credit Exercises

Medication Adherence Case Study #1

AW is a 50-year-old with heart failure (HFrEF Stage C NYHA Class II) who is taking metoprolol, furosemide, and lisinopril. AW continues to work as a court reporter and cannot leave the proceedings once the court is in session. Create a medication plan for the frequency and timing of medications around AW's work schedule while optimizing the pharmacotherapy. Please consider that during the incident hospitalization for heart failure, AW had an episode of hypotension. Also, AW has carpal tunnel syndrome and has a long commute to work (no available restroom). AW has been skipping the furosemide and taking metoprolol and lisinopril together on the way to work; sometimes arriving at the courthouse feeling lightheaded as AW goes through the metal detector.

Assigned Student Task #1.1:

1.1. Suggest a schedule for AW to take their medications that will allow AW to take all medications daily, safely arrive at work, and minimize hypotensive episodes. Write a brief description of the pharmacokinetics of the various drugs you considered when creating the medication schedule.

Notes for Instructor:

- Encourage students to refer to the most recent guidelines for heart failure.
- Consider switching AW to a sodium-glucose co-transporter 2 inhibitor (SGLT2i), such as dapagliflozin or empagliflozin. These drugs have a mild diuretic effect and may allow AW to stop the furosemide (loop diuretic).

Assigned Student Task #1.2:

1.2. Design a pillbox! AW requested a pillbox that would be small enough to fit in a pocket without any metal. You can be creative with the features you would like to include that may help adherence.

Notes for Instructor:

- This assignment can be enhanced using a 3D printer. Students can compete for the best design. Search for free software to print a pillbox, such as <https://cults3d.com/en/tags/pillbox?>.

Medication Adherence Case Study #2

CZ is a 30-year-old with heart failure post-COVID infection (HFrEF Stage C NYHA Class II), is taking metoprolol, furosemide, and sacubitril/valsartan (Entresto). CZ has returned to work and bikes about three blocks to the office. Previously, on the weekends, CZ rode about 10 miles on a bike trail and wants to try resuming longer bike rides gradually. Create a medication plan for the frequency and timing of medications to optimize the pharmacotherapy and limit skipped or missed doses. CZ has been missing the furosemide and taking metoprolol and Entresto together at work.

Assigned Student Task #1.1:

1. Suggest a schedule for CZ to take their medications that will allow AW to take all medications daily, safely bike to work, minimize hypotensive episodes, and resume biking. Write a brief description of the pharmacokinetics of the various drugs CZ is taking, which will help you to create the medication schedule.

Notes for Instructor:

You can easily change this assignment to a pediatric case with a child with a chronic problem, such as congenital heart disease.

Assigned Student Task #1.2:

2. Design a pillbox! CZ requested a pillbox that would be small enough to fit into biking clothes. You can be creative with the features you would like to include that may help with adherence. Also, a bioengineering student is available for consultation.

Notes for Instructor:

Pairing a nursing student with a bioengineering student may allow for greater creativity. Together, the students may be able to create and print a pillbox that a patient can use. Be aware of the type of resin that may be required.

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