

Pharmacokinetics

PSYC 774:
Psychopharmacology

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Pharmacokinetics

- Primarily concerned with what the body does to the drug (rather than pharmacodynamics which is concerned with what the drug does to the body)

- Pharmacokinetics refers to the dynamics of the movement of drugs through the biological system, includes
 - Drug absorption
 - Distribution
 - Metabolism
 - Elimination

Drug Absorption

- In order to reach their site of action, drugs have to pass through several membranes

- The specific membranes depend on the site of action and the route of administration
 - Site of action we're interested in = brain
 - Many different routes of administration
 - Oral
 - Injection (or parenterally)
 - Inhalation
 - Absorption through the skin or membranes

Types of Absorption across Membranes

- If the drug ion is small, it can cross the membrane via aqueous channels (not most drugs)
- Occurs by dissolving in fat (lipid solubility)
- Occurs by active transport proteins with charged surfaces (positive or negative charge)

Note: Most psychoactive drugs must be somewhat soluble in water and lipid – but the higher the ratio of lipid solubility to water solubility (oil/water partition coefficient) the fastest passive absorption

Factors that affect absorption

- The particle size of the dosage form
 - Smaller is better if lipid-solubility is low
- The relative concentration of the molecule on the two sides of the membrane
 - More concentrated drugs will be absorbed better
- The pH levels

- The drug's lipid-solubility (also known as the lipophilicity)
 - Lipophilic molecules are more soluble in fats and oils. Cholesterol is lipophilic
- The drug's water-solubility (also known as hydrophilicity)
 - Hydrophilic molecules are more soluble in aqueous solutions. Salt is very hydrophilic
- Once in solution, drugs exist as a mixture of two interchangeable forms
 - Water-soluble (the ionized or electrically charged form)
 - Lipid-soluble (the nonionized, or uncharged form)

Lipid or Water Soluble?

- The more lipophilic, the better a molecule can cross membranes, especially the blood brain barrier (and placental barrier)
- The more hydrophilic, the more a drug is sequestered in the blood supply. It is less likely to enter the brain and is largely removed from the blood supply by the kidneys
 - E.g., morphine has a lower oil/water partition coefficient than Demerol and fentanyl, which results in slower onset and less intensity but a longer duration of action

- Drug molecules carrying an electrical charge (ionized) are not lipid soluble
- When dissolved in liquid, some or all of a drug's molecules become ionized; what percentage is determined by:
 - Whether the drug itself is an acid or a base
 - Whether it is dissolved in an acid or base
 - Its pKa
- The pKa of a drug is the pH at which 50% of its molecules are ionized
- pH < 7 is acidic
- pH > 7 is basic or more alkaline
- pH = 7 is neutral

- Nonionized molecules diffuse until they reach equal concentration on either side of a membrane
- If the pH differs, once the molecule diffuses over, it may be ionized
- The percentage of nonionized molecules determines the number of molecules available for absorption at any period of time (determines rate of absorption)
- Ion trapping
 - Drugs that are acids (lower pH) tend to concentrate on the side of a membrane with the higher pH
 - Drugs that are bases (higher pH) tend to concentrate on the side with the lower pH

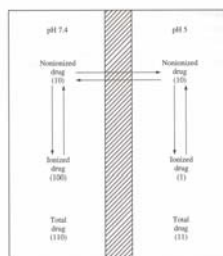
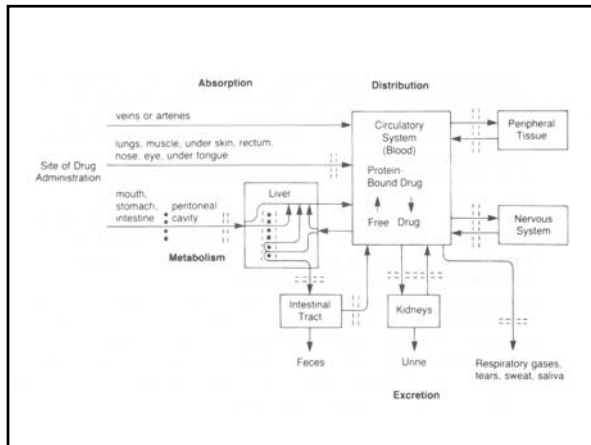


FIGURE 1.3 Distribution of a weakly acidic drug between upper intestinal fluid (pH = 7.4) and plasma (pH = 5). The solutions are separated by a cell membrane that is permeable only to the nonionized, lipid-soluble form of the drug. Note that different proportions of drug are ionized and nonionized in each of the two different pH compartments. Increased ionization traps drug in plasma. Concentrations at equilibrium are shown in brackets.

Routes of Administration

- Oral
- Injection
 - Intravenous
 - Subcutaneous
 - Intramuscular
 - Intraperitoneal
- Transdermal (patch)
- Mucous membranes of mouth or nose (includes nasal sprays)
- Inhalation
- Rectal or vaginal



Oral = (per os or P.O.) through mouth, into stomach, into upper intestine, into blood

- | <u>Pros</u> | <u>Cons</u> |
|--|--|
| <ul style="list-style-type: none"> • Relatively Fast • Painless (usually) • Easy • Safe • No need for equipment or help • Most drugs can be given orally • E.g., medications in pill form, barbiturates, LSD, caffeine, alcohol | <ul style="list-style-type: none"> • Not very fast • Some drugs don't withstand stomach/GI conditions (insulin, cocaine) • Drug absorption more variable • May cause GI distress • Not suitable for uncooperative, vomiting, unconscious • FIRST PASS through liver |

Factors influencing absorption through the GI tract

- Ionization (a state in which an atom or molecule has a net electrical charge) reduces an ion's solubility in cellular membranes because the proteins in the membrane have a mix of positive and negative charges that tend to repel charged particles.
 - Ionized = water soluble; nonionized = lipid soluble
- Local pH or Alkalinity and acidity is what controls the ratio of ionized to nonionized drug
- Higher concentrations of drug and slow movement through the GI tract favors absorption
- Food can bind to the drug or dilute it to slow it down

Injection, in general

Pros

- Fast
- Bypasses first pass
- Bypasses digestion
- More accurate dose
- Can be done by person with training

Cons

- Painful
- Too fast to respond if bad reaction or overdose
- Potential for infection
- Unless planning IV, must be careful to avoid veins
- No recall of drug

Intravenous = (I.V.) directly into bloodstream via vein

Pros

- Very rapid method (15 sec to brain)
- Dose can be precise
- Can start and stop injection, or do it slow
- Can give large volume with small concentrations of drug (avoid irritation)
- Smaller doses needed
- E.g., PCP, heroin, morphine

Cons

- Much care needed if reaction or allergy possible
- Overdose can't be corrected unless there is an antidote on hand
- Infection can be devastating
- Repeated injection can damage veins
- Drug must be completely water soluble

Intramuscular = (I.M.) inject into muscle

Pros

- If skeletal muscle, fairly rapid
 - Slower than I.V., faster than P.O.
- Can put drug in slow-release suspension (repository preparations)
- Can give drugs that can't be given IV

- E.g., inoculations, antibiotics, insulin

Cons

- Painful
- Must be very careful to avoid artery or vein
- Should be water soluble
- Infection possible

Subcutaneous = (S.C., pronounced sub-q) just beneath skin, into body fat

Pros

- Slowest of injection routes, but is still rapid
- Easy
- Can most reasonably be done by person
- Suspension or pellets possible (repository preparation)

- E.g., birth control, heroin

Cons

- Can be irritating to local tissue
- Large volumes may not be appropriate
- Distribution not always controlled
- Infection possible

Other Injection types

- Intraperitoneal = (I.P.) into stomach cavity (between organs). Faster than P.O.
- Intrathecal = into subdural spaces of the spinal cord; bypasses blood brain barrier but invasive
- Intracerebroventricular = into the ventricles (where cerebrospinal fluid is produced) in the brain; bypasses blood-brain barrier but extremely invasive
- Intracerebral = into the brain itself

Transdermal = diffusion through the skin

Pros

- Easy
- Not painful
- Slow, sustained release
- Bypasses GI tract & first pass
- Only have to change every few days / weeks
- E.g., estrogen, motion-sickness medications, nicotine, fentanyl, LSD

Cons

- Can fall off
- Potential toxicity to children and pets
- Very few drugs absorbed sufficiently, low permeability of skin
- Local irritation possible
- Toxicity if additional drug consumed

Transdermal: through the skin

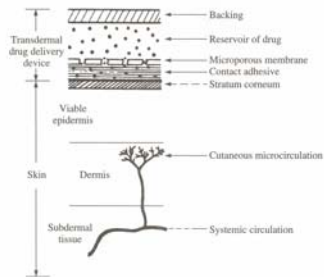


FIGURE 1.5 Diagrammatic representation of a transdermal fentanyl "patch" delivery system placed on the skin.

Mucous Membranes

Pros

- Quick absorption
- Easy and discreet
- Little chance of infection or tissue harm (except with vasoconstrictors)

Cons

- Can taste bad or irritate membranes
- Not all drugs absorbed readily
- Ease and speed exacerbate abuse liable drugs' potential for abuse

Various Types of Absorption via Mucous Membranes

- Sublingual = through the oral mucosa under the tongue; e.g., nitroglycerin
- Buccal = through the oral mucosa between the cheek and gum; e.g., chewing tobacco
- Intranasal = snorting it into the nose; e.g., cocaine
- Rectal = inserting it into the anus; good for person vomiting or unconscious but absorption iffy; e.g., meds for constipation
- Vaginal = inserting it into the vagina; e.g., meds for yeast infection

Inhalation = inhale gas or vapor into lungs

Pros

- Painless and quick
- Easy and discreet
- Very rapid; comparable to I.V. injection or faster
- 5 - 8 sec to brain
- Intense effects

Smoke Examples:

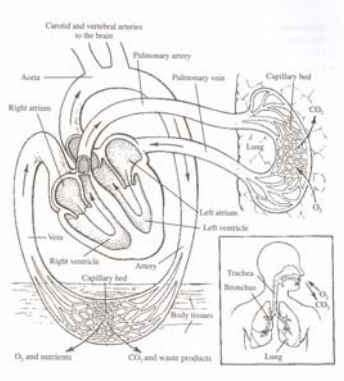
- Nicotine, opium, marijuana, free-base cocaine, crystalline methamphetamine

Vapor examples:

- Paint thinners, gasoline, glues, anesthetics

Cons

- Potential harm to lungs
 - Short term = pneumonia
 - Long term = cancer
- Exacerbation of abuse liability
- Only viable for volatile forms of drugs or that can be in very tiny particles
- Drug is sometimes destroyed in process



The diagram illustrates the heart and circulatory system. It shows the right and left atria and ventricles, the pulmonary artery and vein, and the aorta. Blood flows from the right ventricle to the lungs, where it is oxygenated. From the lungs, it returns to the left atrium and is pumped to the body tissues. In the body tissues, it releases oxygen and nutrients and picks up carbon dioxide and waste products. The trachea and bronchi are also shown in the lung section.

Heart & Circulatory System

- "Used" blood flows from right ventricle to the lungs
- Blood is oxygenated in the lungs and returned to the left atrium
- "Fresh" blood is then pumped from the left ventricle into the aorta and from there directly to the brain and other tissues

Drug Distribution

- Once in the bloodstream, a drug is distributed throughout the body,
- Very little of the drug is in contact with receptors at any given time
- Most of the drug is in areas remote from the site of action (of interest), such as
 - Plasma binding sites
 - Muscle tissue
 - Adipose tissue (fat)
 - Liver
 - Kidneys

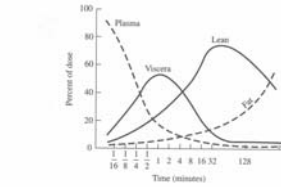


FIGURE 1.9 Diagrammatic representation of the distribution of a lipid-soluble drug (thiopental, a barbiturate discussed in Chapter 5) in blood plasma, body fat, lean body mass (muscle), and visceral tissues at various times after intravenous injection of the drug. Time scales (in minutes) progress geometrically.

Drug distribution

- Factors that affect absorption also affect storage or accumulation in tissue
- Drugs will accumulate greatly in adipose or fat tissue (18-28% of body is fat)
 - Usually are not active in fat unless person begins using the fat tissue (dieting, starving); will slowly reenter the bloodstream
 - E.g., thiopental, an anesthetic is very lipid soluble
 - Enters brain quickly, has rapid onset
 - Enters muscle tissue quickly too, & follows its concentration gradient out of the brain back into circulation
 - Enters fat tissue and is stored there
 - Therefore, effect is short, but may linger for many hours
- Women have less water (54 vs. 60%) and more fat (28 vs. 18%) than men: drug action differs

Body Membranes that Affect Drug Distribution

- Cell membranes
 - Stomach/GI tract into bloodstream
 - Fluid around tissue cells into the cell
 - Interior of cells back into fluid around them
 - Kidneys back into the bloodstream
- Cell membranes are permeable to
 - Small molecules
 - Lipid-soluble molecules

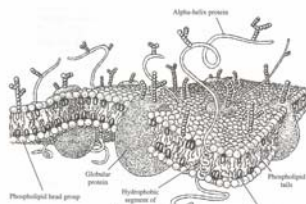


FIGURE 1.7 Diagrammatic representation of the cell membrane, a phospholipid bilayer in which cholesterol and protein molecules are embedded. Both globular and helical kinds of protein traverse the bilayer. Cholesterol molecules tend to keep the tails of the phospholipids relatively fixed and orderly in the regions close to the hydrophilic phospholipid heads; the parts of the tails close to the core of the membrane move about freely (from M. S. Bretscher, "The Molecules of the Cell Membrane," Scientific American 233 (1985): 104).

Body Membranes that Affect Drug Distribution

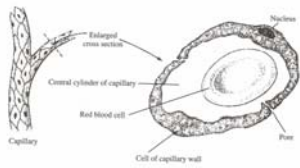


FIGURE 1.8 Cross section of a blood capillary. Within the capillary are the fluids, proteins, and cells of the blood, including the red blood cells. The capillary itself is made up of cells that completely surround and define the central cylinder (or lumen) of the capillary. Water-filled pores form channels, allowing free flow of blood plasma and extracellular fluid.

- Capillaries
 - Drugs enter all body tissues via the capillaries
 - Rate that drug enters tissue depends on blood flow to that area and ease of passing through capillary membranes
- Permeability
 - Drug molecules pass easily through the pores in the membranes (but not red blood cells or proteins)
 - Independent of lipid solubility
 - Drugs that bind to proteins won't pass out of capillaries

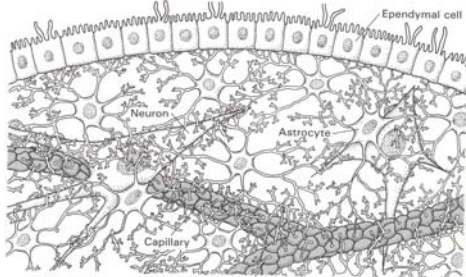
Tissue of interest for psychoactive drugs is the BRAIN

- Brain is 2% of body by mass but uses 25% of energy and 20% of blood flow from the heart
- With that much blood flow, mechanism needed to protect the brain from nonnutritive substances: the blood brain barrier (BBB)
- Even nutritive substances could be disruptive to the brain if flow rate not controlled

Body Membranes that Affect Drug Distribution: the Blood-Brain Barrier (BBB)

- The BBB is located in the specialized endothelial cells of the capillaries that deliver blood to the brain
- The walls of the capillaries, which are lipid endothelial cells, are the last membrane into the brain
- Liquid diffuses through brain capillaries or via choroid plexus in the ventricular system (which makes CSF) into the fluid surrounding the brain cells or into the astrocyte processes
- Foot processes of the astrocyte cells surround the capillaries and line the ependymal cells of the ventricles, and make contact with neurons
- Astrocytes are glial cells in the brain and do much of the "housekeeping"

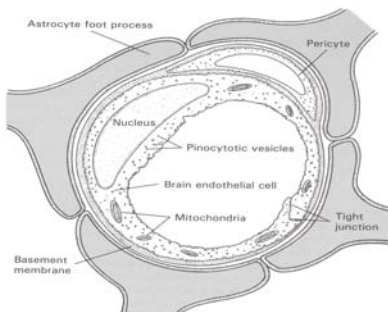
Astrocyte processes in contact with neurons, ependymal cells of ventricle, and brain capillaries



Endothelial cells of brain capillaries are different from those in other organs

- Brain endothelial cells have tight junctions of high electrical resistance which provide a barrier even to ions (whereas peripheral endothelial cells are fenestrated or have tight junctions with low electrical resistance)
- Brain endothelial cells rarely have pinocytotic vesicles and little transcellular transport of compounds (whereas peripheral endothelial cells move molecules across the cells via fluid-phase and receptor-mediated endocytosis)
- Brain endothelial cells have more mitochondria
- Brain capillaries are surrounded by astrocyte foot processes whereas peripheral ones are not

Cross section of a brain capillary. Endothelial cells of brain capillaries differ from other capillaries



Penetrating into the Brain

- Getting into the brain
 - Drugs that are small molecules
 - Lipid-soluble
 - Active transport systems (require energy: mitochondria)
 - For getting nutritive but not lipid substances into the brain, e.g., minerals, glucose, vitamins
 - Carrier-mediated transport systems (don't need energy)
 - Pinocytotic vesicles
- Other factors that affect absorption into the CNS
 - Drugs that are highly bound to plasma proteins are less likely to penetrate the BBB
 - Drugs that are weak acids (are highly ionized at the pH of blood, 7.4) are less likely to penetrate (have low lipid-solubility); e.g., penicillin

The blood-brain barrier is not always uniform

- The BBB is relatively permeable in several places
 - area postrema in 4th ventricle (area that controls vomiting so more permeable in order to detect toxins in blood)
- BBB can be weakened by injury (e.g., concussion) or by illness (e.g., meningitis)

Body Membranes that Affect Drug Distribution: the Placental Barrier

- Psychoactive drugs taken by a pregnant woman are easily distributed to the fetus through the placenta
- Psychoactive drugs are generally excreted through the umbilical cord and back into the bloodstream

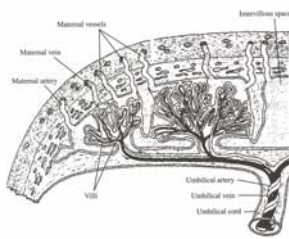


FIGURE 1.11 Placental network separating the blood of mother and fetus. Note the close relationship between fetal and maternal blood in the villi.

A Fetus is more susceptible to toxic effects of drugs

- The BBB of an infant is not complete until about 1 to 2 years of age
- A fetus has fewer plasma proteins (to bind drugs, which keeps them out of the brain)
- A fetus has a greater proportion of blood flow to the brain
- A fetus has a lower level of hepatic enzymes for metabolism
- A fetus has slower drug excretion

Risks to fetus from drug exposure

- Teratogenic effects = abnormal development
 - Immediate: spontaneous abortion, malformation, or altered fetal growth
 - Alcohol, Nicotine, marijuana, cocaine and opiates result in low birth weight and/or shorter gestational periods
- Long term behavioral effects
- Direct toxic effects

Metabolism

- Metabolism = biotransformation
 - any process which results in a chemical change in a drug in the body
 - Catabolism = when complex compounds are broken down into simpler ones
 - Anabolism = when simpler compounds or molecules are combined into more complex ones

- Metabolism may go in stages, and generally goes from more lipophilic to increasingly hydrophilic
- A drug may have several metabolites (by-products or waste products)
 - Metabolites may be inactive or active

Metabolic processes can occur in any tissue, but are most likely to occur in liver, kidneys, lungs, & GI tract

- Cleavage = splitting of the molecule into 2 or more simpler molecules
- Oxidation = combining the molecule with oxygen, or increasing the electropositive charge by the loss of hydrogen or of one or more electrons
- Conjugation = the combining of the molecule with glucuronic or sulfuric acid
- Reduction = the molecule gains 1 or more electrons and becomes more negatively charged

- Some drugs are excreted intact with minimal metabolic changes
- Before any significant elimination of a drug occurs it must become more water-soluble (because excretion occurs via water-based routes for the most part, e.g., urine)
 - Most psychotropic drugs are lipid soluble

- Metabolism begins in the G.I. tract for orally administered drugs
- Drugs that pass through the stomach/small intestine end up in the hepatic portal vein and visit the liver first – referred to as first-pass metabolism
- For most drugs first-pass metabolism is primarily hepatic (liver), although metabolism of alcohol occurs predominantly at an upper G.I. site
- The liver is the organ most responsible for metabolizing drugs regardless of administration route

What is first-pass metabolism?

- Drugs metabolism occurs primarily in the liver through its enzymes, particularly the cytochrome P450 family of enzymes
 - Enzymes are catalysts that induce chemical changes in other substances, but not themselves (proteins)
 - These cytochrome P450 enzymes have diversified to accomplish the metabolism (detoxification) of environmental chemicals, food toxins, and drugs that are foreign to our needs
 - There are several cytochrome P450 families, designated CYP (e.g., CYP1 or CYP-3A4)

Role of the liver in drug metabolism

- Drugs diffuse out of the blood into liver cells (hepatocytes) where they are acted on by the cytochrome P450 enzymes
- Metabolites and the drug will diffuse back into the blood plasma and/or be secreted into the bile
- Metabolites that are sufficiently water-soluble will be excreted via urine, if not water-soluble they will recirculate and may be further metabolized in the liver
- Metabolites in the bile that are water-soluble will be excreted via feces, if not water-soluble they will be re-absorbed, and undergo further metabolism

- Liver cells (hepatocytes) biotransform some drug molecules into metabolites that are less fat-soluble
- The metabolites are carried to the kidneys via blood, and those that are water-soluble will be excreted via urine
- Metabolites that are still fat-soluble will be reabsorbed into blood and circulate back to the liver again

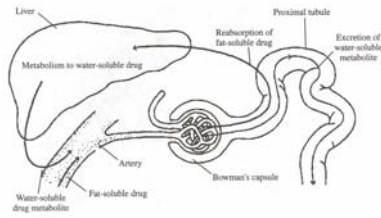


FIGURE 1.13 How the liver and kidneys interact to eliminate drugs from the body. Drugs may be filtered into the kidney, reabsorbed into the bloodstream, and carried to the liver for metabolic transformation to a more water-soluble compound that, having been filtered into the kidney, cannot be reabsorbed and is therefore excreted in urine.

Factors affecting drug metabolism

- Drug Dose
 - The higher the plasma concentration of a drug the higher the rate of metabolism (first-order kinetics) for most drugs (but not alcohol)
 - A drug that is easily hepatically metabolized must be given in higher doses
- If a person's liver is altered or damaged, the effectiveness of a drug given orally may be greatly changed
- Enzyme changes
 - Many drugs cause induction of liver enzymes (increases due to continued use); this reduces the effectiveness of those drugs and other drugs that are metabolized by those enzymes (one aspect of tolerance)
 - Some drugs inhibit the activity of enzymes, which will increase the effect of all drugs metabolized by that enzyme
- Some drugs have direct effects on rate of metabolism of other drugs
 - E.g., they may compete for the same enzyme
- Individual differences
 - Sex, Age, Species, Past experience with drugs

Elimination: Role of the Kidneys

- Renal (kidney) excretion is the primary removal mechanism for drugs
- Major functions of kidneys
 - Excrete most of the products of body metabolism
 - Closely regulate the levels of most of the substances found in body fluids
- Kidneys filter about 1 liter (1000 cubic cm) of plasma per minute
 - Only 1 cubic cm of urine is formed per minute, so most of the filtered fluid is reabsorbed
 - Lipid-soluble drugs are reabsorbed back into plasma along with the other 99% of filtered fluid

The Nephron is the functional unit of the Kidneys

- Blood flows into the glomerulus
- Pressure causes fluid (water) to flow into the Bowman's capsule
- Fluid flows through tubules and some will go into a duct which collects fluid from several nephrons
- Fluid in ducts will collect in ureters and then flow into the urinary bladder
- Rest of fluid diffuses back into capillaries and recirculates

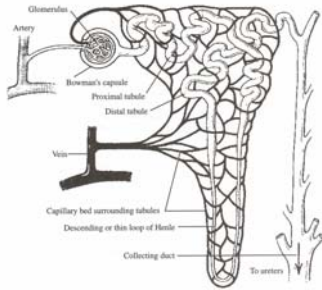


FIGURE 1.12 Nephron within a kidney. Note the complexity of the structure and the intimate relation between the blood supply and the nephron. Each kidney is composed of more than a million such nephrons.

Other forms of drug excretion

- Many drugs and their metabolites may be found in other secretions, but their concentrations are generally low
 - Excretion of drugs via sweat, tears, or salivation is minuscule
 - Small amounts are excreted in breast milk, but small amounts may be too much for babies
 - Excretion occurs from the lungs with some drugs (e.g., alcohol). Lungs can excrete volatile substances (which may not be water-soluble)
 - Bile (feces)

Time Course of Drug Distribution and Elimination: Concept of Drug Half-Life

- Dose response function- expresses relationship between the dose administered and the response observed

Plasma or drug half-life

- A huge determinant of a drug's effects is the length of time for a dose to be metabolized, and presence of active metabolites (breakdown products).
- The **plasma half-life** is the time it takes for half of a dose of a drug to be eliminated from the bloodstream.
- Metabolites have half-lives also. They can be inactive, more active than the parent drug, or somewhere in between.
- Prozac (fluoxetine) has a half life of 1 to 3 days; its primary metabolite (norfluoxetine) is even more active and the metabolite's half-life can be 7 to 15 days!!!

Time-Concentration Relationship

- Redistribution: spread of drug into tissues
- Tangent line A shows rate of redistribution
- Tangent line B shows rate of metabolism

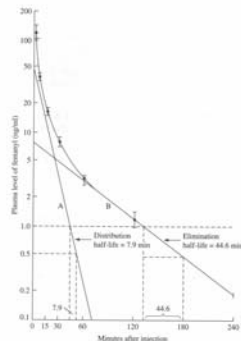


FIGURE 1.15 Plasma levels of a narcotic drug (fentanyl) injected intravenously into a rat. The elimination half-life is shown as 44.6 minutes. The horizontal line drawn at 1 nanogram per milliliter plasma concentration is the level needed for analgesic effect. Thus, analgesia would be lost about 130 minutes after drug injection. (Data from C. C. Hug, Jr., and M. R. Murphy, "Tissue Redistribution of Fentanyl and Termination of Its Effects in Rats," *Anesthesiology* 55 (1981): 369-373.)

Plasma half-life

- A drug's half-life (measured in time) determines how often it must be taken and how long it takes for the drug to wear off and to leave one's system.

# of Half-lives	Percent eliminated
0	0
1	50
2	75
3	87.5
4	93.8
5	96.9
6	98.4

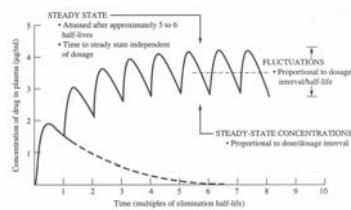
- This assumes normal liver and kidney function. Older, younger, or sick people may clear drugs more slowly.

Therapeutic window

- The relationship between the concentration levels of a drug in the blood plasma and the response to the drug is often curvilinear or biphasic
- The optimal therapeutic effect will be obtained only when the concentration levels in the plasma are within a certain range, called the therapeutic window
- Therefore, one must keep the drug concentration at that level constantly: steady-state concentration

- The time to reach steady-state concentration is ~6 times the drug's elimination half-life

- Steady-state concentration is achieved when the amount of drug administered per unit time equals the amount eliminated per unit time



- Variables:
 - Dose
 - The dose interval
 - The half-life of the drug
 - Complex factors affecting elimination

FIGURE 1.17 Plasma drug concentrations during repeated oral administration of a drug at intervals equal to its elimination half-life. The dashed line illustrates the elimination curve if only a single dose is given. Because only 50 percent of each dose is eliminated before the next dose is given, the drug accumulates, reaching steady-state concentration in five to six half-lives. The sinusoidal curve shows the maximal and minimal drug concentrations at the beginning and end of each dosage interval, respectively. The dotted line illustrates the average concentration achieved at steady state.

Tolerance

- Tolerance is decreased sensitivity to a drug that comes from its continued use; the drug user must take larger and larger amounts of the drug in order for it to be effective
- Once tolerance develops, the user will often suffer withdrawal symptoms if they stop taking the drug

Mechanisms for Tolerance

- **Metabolic tolerance**
 - Increased synthesis of liver enzymes resulting in faster metabolism, requiring more drug in order to maintain same level of drug in body
- **Decrease in the effectiveness of the drug as a neuromodulator**
 - (e.g., receptors become less sensitive or there are fewer of them = down regulation)
- **Behavioral conditioning processes**
 - Classical conditioning of the body's homeostatic compensatory mechanism

Dependence

- **Physical dependence**
 - Drug is needed to avoid physiological withdrawal symptoms
- **Psychological dependence**
 - Drug is needed to avoid psychological, not physical, withdrawal symptoms
 - Psychological withdrawal symptoms are not outwardly measurable
 - Therefore, psychological dependence may be used to refer to excessive use of a drug that cannot be explained by physical dependence and fear of physical withdrawal symptoms
