وزارة التعليم العلي والبحث العمي
جامعة الفرات الاوسط التقنية/ الكوفة
كلية التقنيات الصحية والطبية

الحقيبة الدراسية لمادة الدوائيات

قسم تقنيات التجميل والليزر

المرحلة الثانية

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Introduction to Pharmacology

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes. In most cases, the drug molecule interacts as an agonist (activator) or antagonist (inhibitor) with a specific target molecule that plays a regulatory role in the biologic system. This target molecule is called a receptor.

Drugs: is a chemical substance with known biological effects on humans. In the pharmacology field, a drug is defined as a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being. Drugs interact with receptors by chemical forces or bonds. These are of three major types (covalent bond, electrostatic forces, hydrophobic forces). Drugs may be synthesized within the body (eg, hormones) or may be chemicals not synthesized in the body (ie, xenobiotics).

Toxicology is the branch of pharmacology that deals with the undesirable effects of chemicals on living systems, from individual cells to humans to complex ecosystems.

Poisons are drugs that have almost exclusively harmful effects. However, Paracelsus (1493–1541) famously stated that "the dose makes the poison," meaning that any substance can be harmful if taken in the wrong dosage.

Toxins are usually defined as poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead and arsenic.

The physical nature of drugs

To interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape, and atomic composition. Furthermore, a drug is often administered at a location distant from its intended site of action, eg, a pill given orally to relieve a headache. Therefore, a useful drug must have the necessary properties

to be transported from its site of administration to its site of action. Finally, a practical drug should be inactivated or excreted from the body at a reasonable rate so that its actions will be of appropriate duration.

1- **Drug size:** The molecular size of drugs varies from very small to very large However, most drugs have molecular weights between 100 and 1000. To have a good "fit" to only one type of receptor, a drug molecule must be sufficiently unique in shape, charge, and other properties to prevent its binding to other receptors. To achieve such selective binding, it appears that a molecule should in most cases be at least 100 MW units in size. Drugs much larger than MW 1000 do not diffuse readily between compartments of the body. Therefore, very large drugs (usually proteins) must often be administered directly into the compartment where they have their effect.

2- **Drug reactivity & Drug-receptor bonds:** Drugs interact with receptors by means of chemical forces or bonds (covalent bond, electrostatic forces, hydrophobic forces). Covalent bonds are very strong and, in many cases, not reversible under biologic conditions.

Electrostatic bonding is much more common than covalent bonding in drug-receptor interactions. Electrostatic bonds vary from relatively strong linkages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waals forces and similar phenomena. Electrostatic bonds are weaker than covalent bonds.

Hydrophobic bonds are usually quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor "pockets."

Note: drugs that bind through weak bonds to their receptors are generally more selective than drugs that bind by means of very strong bonds. This is because weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur.

3- **Drug Shape:** The shape of a drug molecule must be such as to permit binding to its receptor site via the bonds. Optimally, the drug's shape is complementary to that of the receptor site in the same way that a key is complementary to a lock. Furthermore, the phenomenon of chirality (stereoisomerism) is so common in biology that more than half of all useful drugs are chiral molecules; that is, they can exist as enantiomeric pairs.

For example, carvedilol, a drug that interacts with adrenoceptors, has a single chiral center and thus two enantiomers (Table 1). One of these enantiomers, the (S)(–) isomer, is a potent β-receptor blocker. The (R)(+) isomer is 100-fold weaker at the β receptor. However, the isomers are approximately equipotent as α-receptor blockers. Ketamine is an intravenous anesthetic. The (+) enantiomer is a more potent anesthetic and is less toxic than the (–) enantiomer. Unfortunately, the drug is still used as the racemic mixture.

Table. Dissociation constants (Kd) of the enantiomers and racemate of carvedilol

Form of Carvedilol	α Receptors (K_d, nmol/L^1)	β Receptors (K_d, nmol/L)
R(+) enantiomer	14	45
S(–) enantiomer	16	0.4
R,S(±) enantiomers	11	0.9

Classification of drugs

Drugs can be classified into groups.

1- **Therapeutic classification:** Drugs can be grouped by their principal actions, Examples

a- Analgesics: reduce pain. Nonopioid analgesics are used for mild pain. Opioid analgesics are used to treat moderate to severe pain such as acetaminophen, ibuprofen.

b- Antibiotics: treat bacterial infections such as amoxicillin and ceftriaxone.

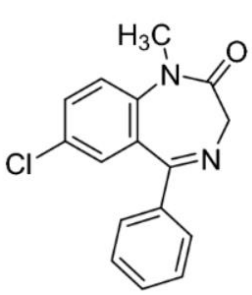
c- Anticoagulants: prevent blood from clotting such as heparin, clexane.

2- **Pharmacological classification:** categorize drugs based on how they interact with the body, primarily by mechanism of action, specific biochemical interaction with the body's systems.

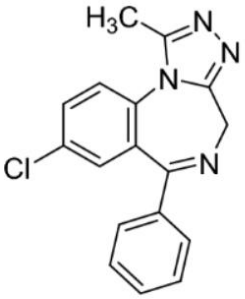
a- **Enzyme inhibitors:** block the activity of specific enzymes.

b- **Receptor antagonists:** block the binding of other molecules to receptors, preventing them from having an effect.

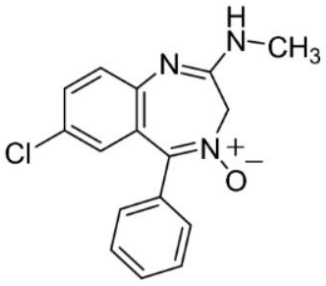
3- **Chemical Classification:** Grouping drugs by their chemical structure (e.g., benzodiazepines, central nervous system depressants).



Diazepam



Alprazolam



Chlordiazepoxide

Importance in cosmetic practice

Cosmetic practice is important for enhancing appearance, which boosts self-confidence and emotional well-being, fosters self-expression, and creates a positive professional image. Beyond aesthetics, some cosmetic treatments offer functional benefits, like skin health improvements, while others lead to social advantages through increased self-esteem.

- **Enhanced Self-Confidence**: Cosmetic practice helps individuals feel better about their appearance, which can significantly increase self-esteem and provide a positive outlook on life.
- **Improved Mood and Well-Being**: cosmetic procedures can lead to greater emotional well-being, reduced stress, and overall happiness.
- **Fostering Creativity**: Cosmetics provide a means for self-expression and creativity, allowing individuals to experiment with different looks and styles.

Pharmacokinetics

Pharmacokinetics refers to what the body does to a drug, in other words, it is the study of drug movement throughout the body, from the time it is administered until it is completely eliminated. Pharmacokinetic processes govern the absorption, distribution, metabolism and elimination as shown in figure-1.

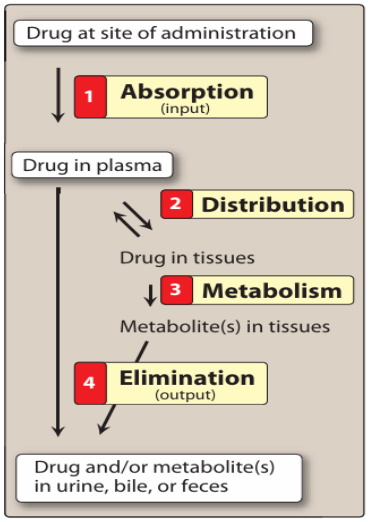


Figure 1. Schematic representation of drug absorption, distribution, metabolism, and elimination

1- **Absorption**: is considered the first property of Pharmacokinetics, is the transfer of a drug from its site of administration to the bloodstream via one of several mechanisms.

a- **Mechanisms of absorption of drugs from the GI tract**

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

1- Passive diffusion

The drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable (diffusion will continue), and shows a low structural specificity (because it does not rely on specific protein channels or carriers that selectively bind to and transport certain molecules. Instead, passive diffusion is a non-selective process where molecules cross a cell membrane based on their physicochemical properties, particularly their size and lipid solubility). Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayer.

2- Facilitated diffusion

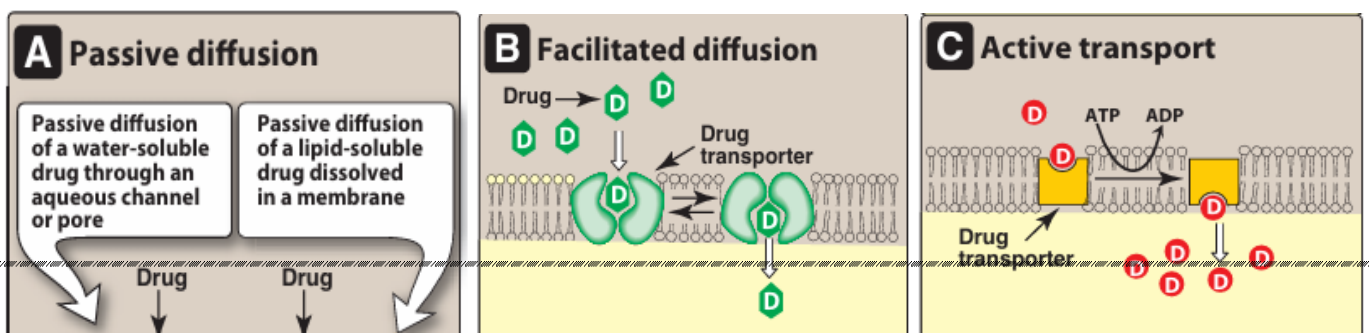
Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high con- centration to an area of low concentration. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

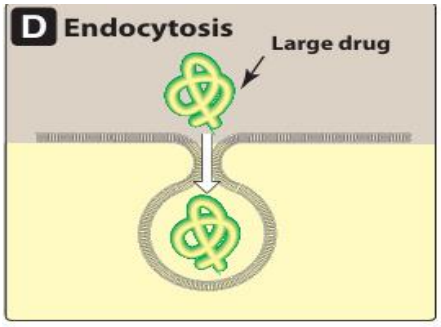
3- Active diffusion

This mode of drug entry also involves specific carrier proteins that span the membrane. It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. It is energy-dependent by the hydrolysis of adenosine triphosphate and shows saturation kinetics for the carrier protein. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

4- Endocytosis

These types of drug delivery systems transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug filled vesicle as shown in figure 2.





B- Factors influencing absorption

B- Factors influencing absorption

1- Effect of pH on drug absorption

A drug passes through membranes more readily if it is uncharged.

2- Blood flow to the absorption site

Because blood flow to the intestine is much greater than the flow to the stomach, absorption from the intestine is favored over that from the stomach.

3- Total surface area available for absorption

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

4- Contact time at the absorption surface

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

2- Distribution

In pharmacology, drug distribution is the reversible process by which a drug leaves the bloodstream and moves into the interstitium (extracellular fluid) and then the body's tissues and organs. This distribution can be influenced by several factors:

a- **Blood flow:** Tissues with high blood flow, such as the brain, liver, and kidneys, receive drugs more rapidly than those with low blood flow, like skeletal muscles this occurs depending on the unequal distribution of cardiac output to the various organs.

b- **Capillary permeability**: Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells. in the liver and spleen, a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass. This is in contrast to the brain, where the capillary structure is continuous, and there are no slit junctions. To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported as shown in figure 3.

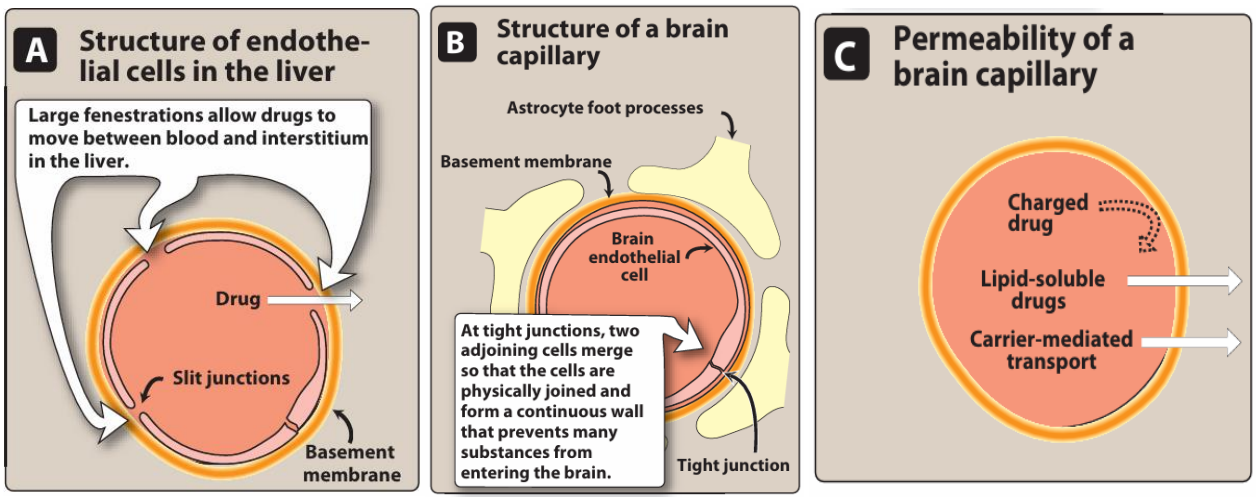


Figure 3. Cross section of liver and brain capillaries.

c- **Binding of drugs to plasma proteins and tissues**

1- **Binding to plasma proteins:** Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows their transfer out of the vascular compartment such as albumin which is the major drug-binding protein and may act as a drug reservoir (that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein). This maintains the free-drug con centration as a constant fraction of the total drug in the plasma.

2- **Binding to tissue proteins:** Numerous drugs accumulate in tissues, leading to higher concentrations of the drug in tissues than in the extracellular fluids and blood. Drugs may accumulate as a result of binding to lipids, proteins or nucleic acids. Drugs may also be actively transported into tissues. These tissue reservoirs may serve as a major source of the drug and prolong its actions, on the other hand, can cause local drug toxicity.

d- **Volume of distribution:** The apparent volume of distribution, Vd, can be thought of as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C0).

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

For example, if 10 mg of drug are injected into a patient and the plasma concentration is extrapolated back to time zero, the concentration is C0 = 1 mg/L and then Vd = 10 mg/1 mg/L = 10 L.

3- Metabolism of drugs

Once a drug enters the body, the process of elimination begins. The three major routes involved are: 1) hepatic metabolism, 2) elimination in bile, and 3) elimination in urine. Together, these elimination processes cause the plasma concentration of a drug to decrease exponentially. Most drugs are eliminated according to first-order kinetics, although some, such as aspirin in high doses, are eliminated according to zero-order kinetics. Metabolism leads to products with increased polarity, which will allow the drug to be eliminated.

NOTE: Clearance (CL) estimates the amount of drug cleared from the body per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as:

$$CL = 0.693 \times V_d / t_{1/2}$$

where $t_{1/2}$ is the drug's elimination half-life, Vd is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, Vd is a constant.

a- Kinetics of metabolism

1- First-order kinetics: The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics.

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

$$K_m >>> [C]$$

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

The rate of drug metabolism and elimination is directly proportional to the concentration of free drug, and first-order kinetics are observed. First-order kinetics is sometimes referred to clinically as linear kinetics.

2- Zero-order kinetics: With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. Therefore, [C] is much greater than K_m ($[C]>>>K_m$), and the velocity equation becomes.

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time. This is called zero order kinetics (sometimes referred to clinically as nonlinear kinetics). A constant amount of drug is metabolized per unit of time, and the rate of elimination is constant and does not depend on the drug concentration.

b- Reactions of drug metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents must first be metabolized into more polar (hydrophilic) substances in the liver using two general sets of reactions, called Phase I and Phase II as shown in figure 3.

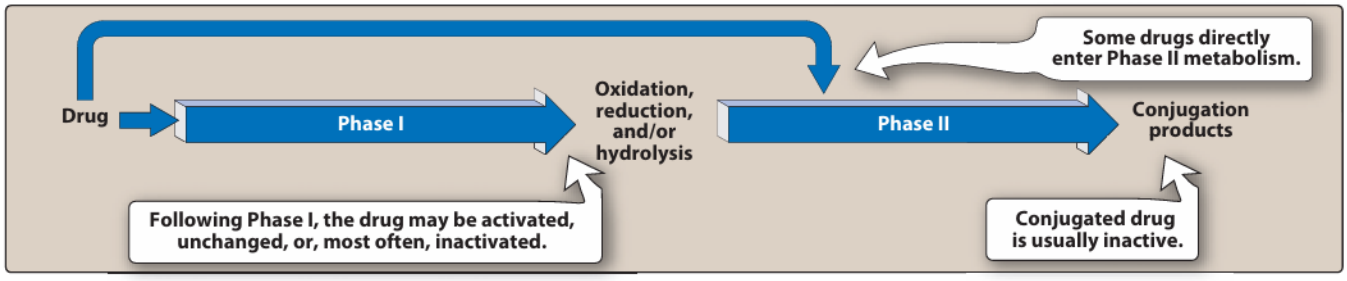


Figure 3. The biotransformation of

1- Phase I: Phase I reactions convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as –OH or –NH_2. Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

a- Phase I reactions utilizing the P450 system: The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed-function oxidases) which designated as CYP. There are likewise many different P450 isoforms Four isozymes are responsible for the vast majority of P450 catalyzed reactions. They are CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2. There are two affected on P450 enzymes.

1- **Inducers:** Many drugs may induce the activity of The CYP450–dependent enzymes by inducing the expression of the genes encoding the enzyme or by stabilizing the enzymes. for example, phenobarbital, rifampin, and carbamazepine are capable of increasing the synthesis of one or more CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes with concurrent loss of pharmacologic effect. Figure 4 lists some of the more important inducers for representative CYP isozymes.

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	*Carbamazepine*
Cyclosporine	*Dexamethasone*
Erythromycin	*Phenobarbital*
Nifedipine	*Phenytoin*
Verapamil	*Rifampin*

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin	*Phenobarbital*
Phenytoin	*Rifampin*
Ibuprofen	
Tolbutamide	

Figure 4. lists some of the more important inducers for representative CYP isozyme

2- **Inhibitors:** The metabolism of drugs cannot obtain because the inhibiting of CYP isozyme activity by many medications. Numerous drugs have been shown to inhibit one or more of the CYP-dependent biotransformation pathways of warfarin. For example, omeprazole is a potent inhibitor of three of the CYP isozymes responsible for warfarin metabolism. If the two drugs are taken together, plasma concentrations of warfarin increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions. The more important CYP

inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes. Cimetidine blocks the metabolism of theophylline, clozapine, and warfarin.

b- Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of pravastatin in liver), and hydrolysis (for example, of procaine).

2- Phase II: This phase consists of conjugation reactions. If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many Phase I metabolites are too lipophilic to be retained in the kidney tubules. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive. Glucuronidation is the most common and the most important conjugation reaction. Drugs already possessing an –OH, –NH2, or –COOH group may enter Phase II directly and become conjugated without prior Phase I metabolism. The highly polar drug conjugates may then be excreted by the kidney or in bile.

4- Drug Elimination

Elimination of drugs from the body requires the agents to be sufficiently polar for efficient excretion. Removal of a drug from the body occurs via a number of routes including renal excretion, biliary excretion and pulmonary excretion, the most important being through the kidney into the urine.

- **Renal (Kidney) Excretion:** water-soluble drugs and their metabolites are filtered from the blood and eliminated in the urine as shown in figure 5.
- **Biliary (Bile) Excretion:** Some drugs and metabolites are excreted into bile by the liver and then eliminated in the feces.
- **Pulmonary (Lung) Excretion:** Volatile anesthetic drugs are an example of drugs that can be exhaled unchanged by the lungs.

Factors Affecting Drug Elimination

- **Drug Properties:** Intrinsic characteristics of the drug, such as its polarity (fat-soluble vs. water-soluble) and size, influence how it is metabolized and excreted.

- **Organ Function:** The efficiency of the liver and kidneys is crucial. Dysfunction in these organs can lead to drug accumulation and toxicity.
- **First-Pass Metabolism:** Some drugs are extensively metabolized by the liver after being absorbed from the digestive tract, which can significantly affect the amount of active drug reaching the bloodstream.
- **Genetic Variations:** Differences in an individual's genetic makeup can affect the enzymes involved in metabolism, influencing drug elimination rates.

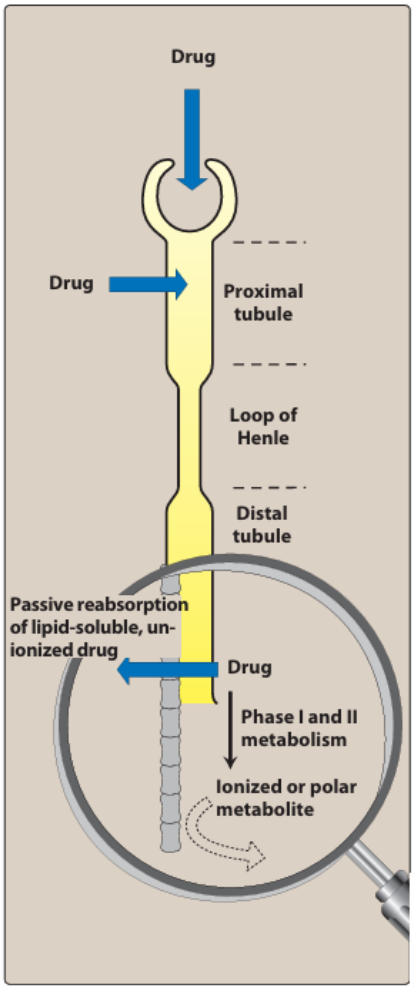


Figure 5. Effect of drug metabolism on reabsorption in the distal tubule.

Pharmacodynamic

Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors present on the cell surface or

within the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction.

Receptor binding: is the process in which **ligand** (a molecule like a hormone or drug) attaches to a **receptor**, a protein on or in a cell, which triggers a biological response. This interaction is fundamental to cell signaling and is characterized by the ligand's affinity.

The mechanism of action (MOA): is how a drug produces its effects in the body at a molecular level, often by binding to specific molecular targets like enzymes, receptors, ion channels, or carrier molecules. This binding causes a biochemical interaction by signal transduction that leads to a pharmacological effect, such as increasing or decreasing a cellular function.

Signal Transduction: Drugs act as signals, and their receptors act as signal detectors. Many receptors signal their recognition of a bound ligand by initiating a series of reactions that ultimately result in a specific intracellular response.

a- The drug–receptor complex: Cells have different types of receptors, each of which is specific for a particular ligand and produces a unique response. The magnitude of the response is proportional to the number of drug–receptor complexes. the receptor not only has the ability to recognize a ligand, but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect.

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

b- Receptor states: Classically, the binding of a ligand was thought to cause receptors to change from an inactive state (R) to an activated state (R*). The activated receptor then interacts with intermediary effector molecules to produce a biologic effect.

c- Major receptor families: In pharmacology, receptors are defined as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can be considered to be pharmacologic receptors. the richest sources of therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses. These receptors may be divided into four families as shown in figure 1.

1- Ligand-gated ion channels
2- G protein–coupled receptors
3- Enzyme–linked receptors
4- Intracellular receptors

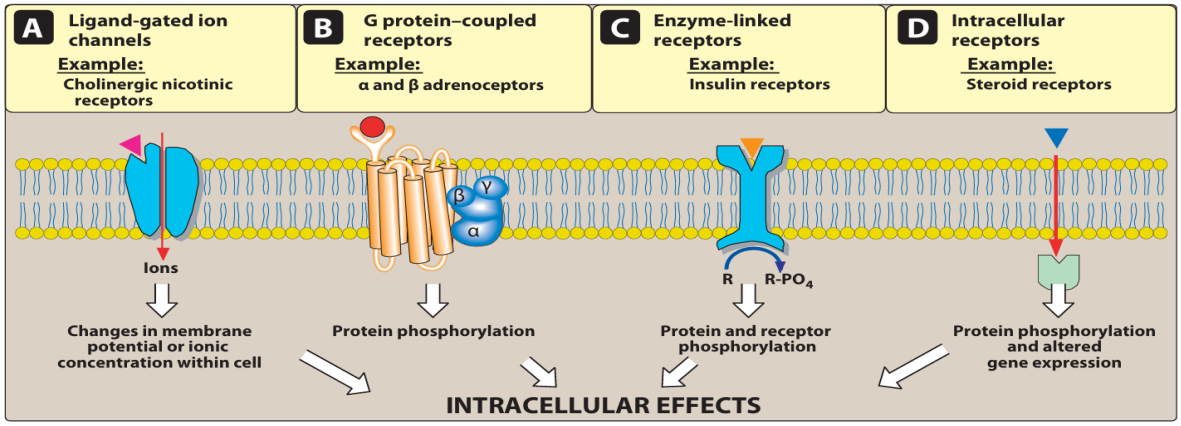


Figure 1. Transmembrane signaling mechanisms.

The type of receptors a ligand will interact with depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface (Figures 1 A, B, C). In contrast, hydrophobic ligands can enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 1D).

d- Some characteristics of signal transduction

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

1- **The ability to amplify small signals:** A characteristic of many receptors, particularly those that respond to hormones, neurotransmitters, and peptides, is their ability to amplify signal duration and intensity. Two phenomena account for the amplification of the ligand–receptor signal. First, a single ligand–receptor complex can interact with many G proteins, thereby multiplying the original signal manyfold. Second, the activated G proteins persist for a longer duration than the original ligand–receptor complex.

2- **Desensitization and down-regulation of receptors:** Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor. To prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death), several mechanisms have evolved to protect a cell from excessive stimulation. When repeated administration of a drug results in a diminished effect, the phenomenon is called tachyphylaxis. The receptor becomes desensitized to the action of the drug.

Dose response relationships

An agonist is defined as an agent that can bind to a receptor and elicit a biologic response. The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

a- Graded dose–response relations: As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases. The response is a graded effect, meaning that the response is continuous and gradual. Two important properties of drugs, potency and efficacy, can be determined by graded dose response curves.

1- Potency: The first property is potency, a measure of the amount of drug necessary to produce an effect of a given magnitude. The con centration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the EC_{50}. In Figure 2, the EC50 for Drugs A and B are indicated. Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect. Thus, therapeutic preparations of drugs will reflect the potency

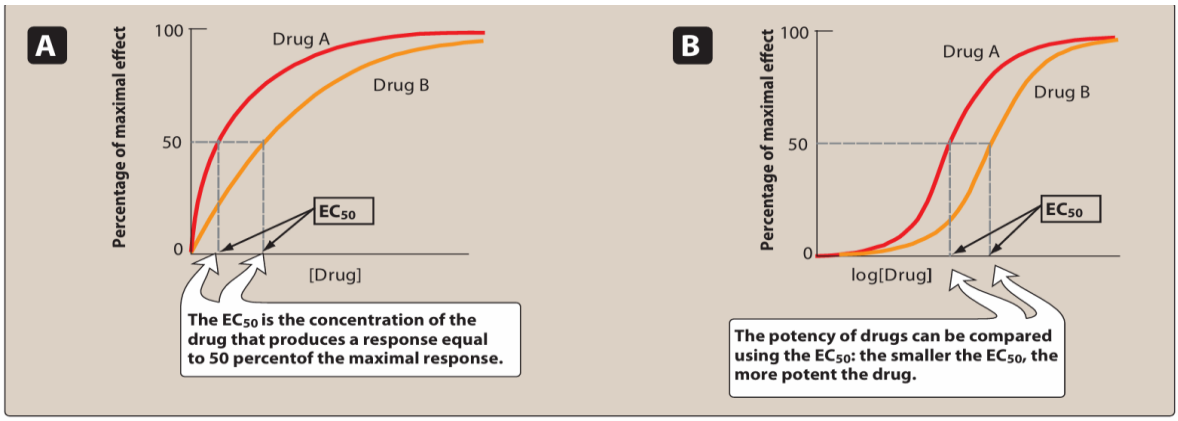


Figure 2. The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semi logarithmic plot of the same data. EC50 = drug dose that shows 50 percent of maximal response.

2- Efficacy: The second drug property that can be determined from graded dose–response plots is the efficacy of the drug. This is the ability of a drug to elicit a response when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the efficiency of the coupling of

receptor activation to cellular responses. The maximal response or efficacy, is more important than drug potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent. Maximal efficacy of a drug assumes that all receptors are occupied by the drug, and no increase in response will be observed if more drugs are added.

Agonist: it binds to a receptor and produces a biologic response. An agonist may be

1- **Full agonist:** If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is known as a full agonist as illustrated in figure-3.

2- **Partial agonists:** Partial agonists have efficacies (intrinsic activities) greater than zero but less than that of a full agonist. Even if all the receptors are occupied, partial agonists cannot produce an E_{max} of as great a magnitude as that of a full agonist.

3- **Inverse agonists:** some receptors show a spontaneous conversion from R to R* in the absence of agonist (that is, they can be active without the presence of agonist). These receptors, thus, show a constitutive activity that is part of the baseline response measured in the absence of drug.

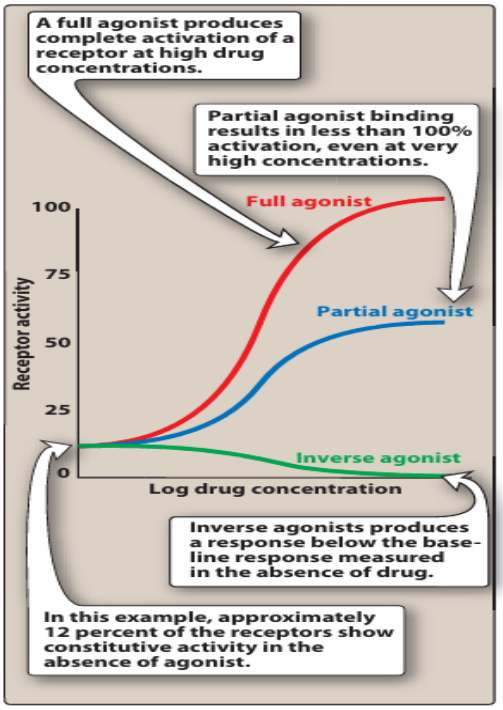


Figure 3. Effects of full agonists, partial agonists, and inverse agonist on receptor activity.

Antagonists are drugs ther drug or endogenous ligand. An a sent. they are able to bind avidly to target receptors because they possess strong affinity.

1- Competitive antagonists: If both the antagonist and the agonist bind to the same site on the receptor, they are said to be "competitive." The competitive antagonist will prevent an agonist from binding to its receptor and maintain the receptor in its inactive conformational state.

2- Non-competitive antagonist: is a compound that reduces the maximum possible effect of an agonist but does not compete with the agonist for its binding site on the receptor. It binds to a different site, either an allosteric site or the active site through irreversible bond, and changes the receptor's shape so the agonist can't activate it. There are two mechanisms by which an agent can act as a noncompetitive antagonist, first, the antagonist can bind covalently or with very high affinity to the active site of the receptor causing the reduces the amount of receptors available to the agonist. Second, antagonist binds to a site ("allosteric site") other than the agonist binding site. This allosteric antagonist prevents the receptor from being activated even when the agonist is attached to the active site.

Note: An irreversible antagonist causes a downward shift of the maximum, with no shift of the curve on the dose axis unless spare receptors are present as shown in figure 4. The effects of competitive antagonists can be overcome by adding more agonist. Irreversible antagonists, by contrast, cannot be overcome by adding more agonist. Competitive antagonists increase the ED50, whereas irreversible antagonists do not (unless spare receptors are present).

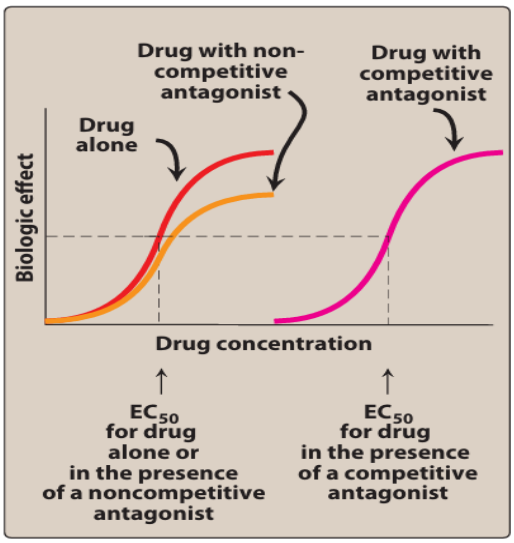


Figure 4. Effects of drug antagonists. EC_{50} = drug dose that shows 50 percent of maximal response.

b- Quantal-dose response relationships

Another important dose–response relationship is that of the influence of the magnitude of the dose on the proportion of a population that responds. These

responses are known as quantal responses, because, for any individuals, the effect either occurs or it does not.

Therapeutic index: The therapeutic index (TI) of a drug is the ratio of the dose that pro duces toxicity to the dose that produces a clinically desired or effective response in a population of individuals (The therapeutic index is a measure of a drug's safety). As the drugs have a large therapeutic index, they become more safety than those that have narrow therapeutic index, for example, Warfarin and Penicillin as shown in figure-5.

$$\text{Therapeutic index} = TD_{50}/ED_{50}$$

where TD_{50} = the drug dose that produces a toxic effect in half the population, and ED_{50} = the drug dose that produces a therapeutic or desired response in half the population.

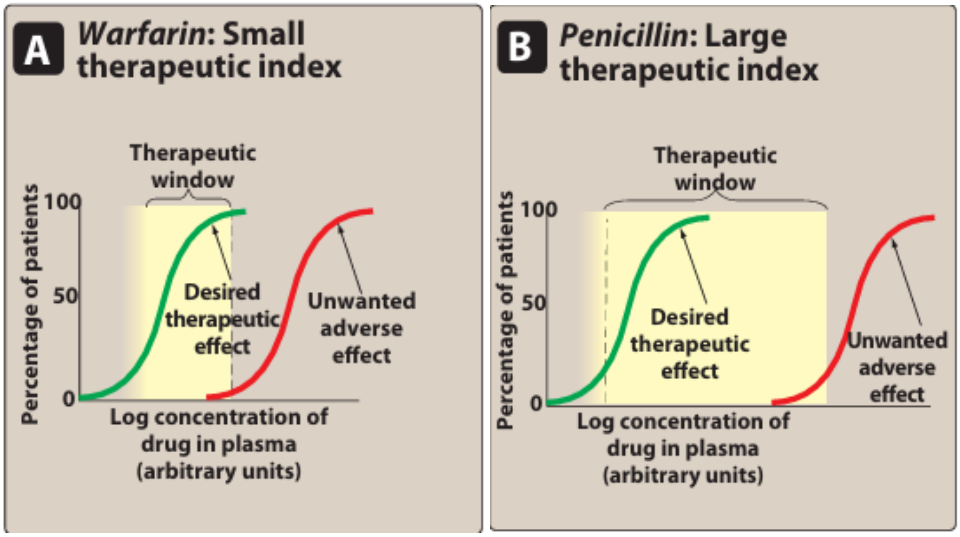


Figure 5. Cumulative percentage of patients responding to plasma levels of warfarin and penicillin.

Topical Agents

Topical agents: are drugs applied to the body's surface (skin and mucous membranes) for a localized effect. Topical agents include antibiotics, antiseptic, corticosteroids, antineoplastics, local anesthetics.

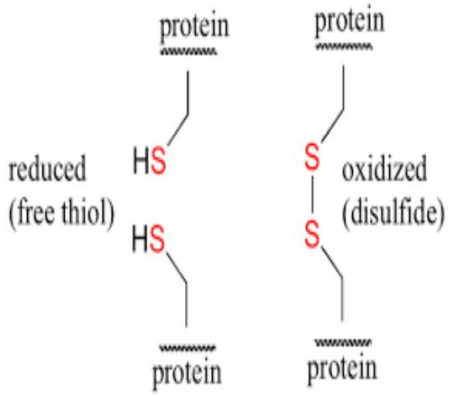
Classification of Topical agents

Topical agents can be classified into three categories s based on their usual action or use.

1- **Protectives**: These are substances which tend to form a coating and protect the exposed skin or mucous membrane from harmful stimuli such as irritants, moisture, or mechanical friction. This protection is achieved either through physical or chemical means. They should be insoluble and chemically as well as biologically inert. Ex. Dusting powder like Zinc oxide, talc, calamine.

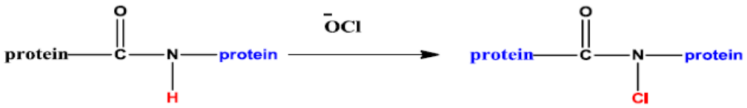
2- **Antimicrobial**: Agents that inhibit or kill the growth of microorganisms e.g. bacteria, fungi, etc. It can be classified according to their mechanism of action into oxidation, hydrogenation and protein precipitation.

a- **Oxidation:** Those compounds (oxidizing agents) act as antimicrobial agents by liberating oxygen causing oxidation of active function groups such as (the thiol group (-SH)) of the protein enzymes of microorganisms and inactivating them. oxidizing agents include hydrogen peroxide H_2O_2, potassium permanganate $KMnO_4$, zinc peroxide ZnO2, povidone-iodine, etc..
The liberated oxygen from H_2O_2 by enzyme (catalase) acts as an oxidizing agent on bacteria, providing antiseptic action.



b- Halogenations: It involves destruction to the function of protein because substations of halogen as chlorine atom for the hydrogen (mainly for primary and

secondary amide R-C=O-NH2), cause a conformational change of protein, subsequently inactivating it.



Inactive

c- Protein precipitation: This type of mechanism involves the interaction of the protein with metallic ions having large charge\ radius ratios or strong electrostatic fields such as Cu(II), Ag(I), Zn(II), and Al(III).

3- Astringent: are substances that cause a dry, puckering sensation in the mouth by causing proteins in saliva and oral tissues to precipitate and contract. For example, aluminum or zinc salts. An astringent is a substance that draws water out of tissues, causing them to shrink. In skin care, using astringent products after cleansing can temporarily tighten the skin, shrink pores, and remove oil.

The protein precipitation caused by astringent due to the presence of metallic ions having large charge or strong electrostatic fields. The metal forms complex with various polar groups presents on the protein.

Astringents have a variety of uses which include: -

- To arrest hemorrhage by coagulation of the blood.
- To reduce inflammation of the mucous membrane.
- To decrease sweating and to make skin tougher.
- To promote healing process.
- Astringent also possesses deodorant properties

Note: topical agents my be ointment, cream, gel, lotion or spray.

Emollients are ingredients in skin creams, lotions, moisturizers or ointments that form a film on your skin. These ingredients can relieve dryness, itching and scaling. Emollients can help your skin feel more comfortable if you have eczema, psoriasis, dry or sensitive skin. There are two main types of emollients

1- Occlusives: it is formed a thick and greasy coating the skin and don't dissolve in water. Examples of occlusives include petroleum jelly, mineral oil, lanolin and liquid paraffin. Occlusives don't add moisture to your skin but help it hold onto the moisture it already has.

2- Humectants: they are attracted and bind water to your skin, increasing its moisture. These ingredients feel less thick and greasy than occlusives but wash off more easily in water. Examples of humectants are glycerin, hyaluronic acid, propylene glycol and urea.

Retinoids: Retinoids are a class of compounds derived from vitamin A or showing structural and/or functional similarities to vitamin A. According to the latter definition, retinoids are molecules that can bind to and activate the appropriate nuclear receptors and to induce transcription of relevant genes either directly or after metabolic transformation. Retinoids are widely applied in cosmetics being a potent dermatological agent used in acne, psoriasis as well as other skin diseases**.** Retinoids can be synthetic and natural.

- **Natural Retinoids:** include retinol, retinaldehyde and retinoic acid which metabolites to retinol.
- **Synthetic Retinoids:** include Tretinoin (all-*trans* retinoic acid), adapalene, tazarotene, trifarotene, alitretinoin, and bexarotene.
- **Tretinoin:** is indicated in the treatment of acne vulgaris and photoaging/rhytides and hyperpigmentation.
- **Tazarotene:** is a topical retinoid indicated in acne vulgaris and the only retinoid indicated in the use of plaque psoriasis.
- **Adapalene**: is a topical retinoid indicated in acne vulgaris. Off-label it is also used in the treatment of hyperpigmentation and actinic keratosis, and due to its tolerability, it is often used off-label for photoaging/rhytides.

Topical retinoids mechanism of action

Retinoids are defined as a molecule that binds to and activates retinoic acid receptors through direct ligand-receptor binding, thereby eliciting transcription of retinoic acid-responsive genes. Retinoids influence the proliferation and differentiation of cells. Their biological effects are mediated and regulated by cytosolic binding proteins and nuclear hormone receptors. Retinoids normalize abnormal desquamation in acne by increasing follicular epithelial turnover and accelerating the shedding of corneocytes, leading to the expulsion of mature comedones and the suppression of microcomedone formation as shown in figure 1.

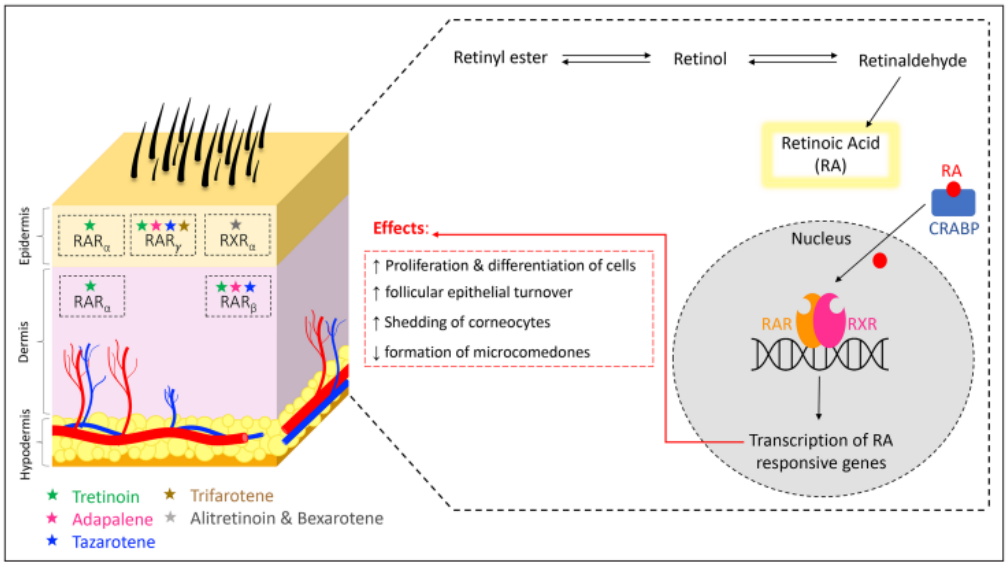


Figure 1. Biological pathway of natural retinoids and target sites of synthetic retinoids**.**

Corticosteroids: topical corticosteroids are a form of medicine applied directly to the skin which helps reduce inflammation, redness and irritation. The type of steroid is similar to those produced naturally in the body. Topical corticosteroids come in many preparations: ointments, creams, lotions. The well-known indications are for diseases such as psoriasis, limited areas of vitiligo, eczema, atopic dermatitis, phimosis, acute radiation dermatitis, lichen planus, lichen simplex chronicus, discoid lupus erythematosus, lichen sclerosis, and alopecia areata.

Strength, Classification, and Administration

The potency of topical corticosteroids refers to the amount of medication required to achieve the desired therapeutic effect. The gold standard for determining potency is the vasoconstrictor assay, which measures vasoconstrictive properties based on cutaneous vasoconstriction. The United States classification consists of 7 classes: class I superpotent and class VII least potent.

- **Class I** are superpotent corticosteroids: clobetasol propionate 0.05% in any vehicle, augmented betamethasone dipropionate 0.05% gel or ointment, diflorasone diacetate 0.05% ointment, fluocinonide 0.1% cream, and halobetasol propionate 0.05% cream or ointment.

- **Class II** are high-potency corticosteroids: amcinonide 0.1% ointment, augmented betamethasone dipropionate 0.05% cream or lotion, betamethasone dipropionate 0.05% ointment, desoximetasone cream or gel or ointment, diflorasone diacetate 0.05% cream, fluocinonide 0.05% cream or gel or ointment, and halcinonide 0.1% cream or ointment or solution.
- **Class III** are medium- to high-potency corticosteroids: amcinonide 0.1% cream, betamethasone dipropionate 0.05% cream, fluticasone propionate 0.005% ointment, and triamcinolone acetonide 0.5% cream or ointment.
- **Class IV and V** are medium-potency corticosteroids: betamethasone valerate 0.1% cream or lotion or foam, desoximetasone 0.05% cream, fluocinolone acetonide 0.025% cream or ointment, fluticasone propionate 0.05% cream, hydrocortisone butyrate 0.1% ointment, hydrocortisone probutate 0.1% cream, hydrocortisone valerate 0.2% cream or ointment, mometasone furoate 0.1% cream or lotion or ointment, triamcinolone acetonide 0.025% cream or lotion or ointment, and triamcinolone acetonide 0.1% cream or lotion or ointment
- **Class VI** are low-potency corticosteroids: alclometasone dipropionate 0.05% cream or ointment, fluocinolone 0.01% cream, and hydrocortisone butyrate 0.1% cream.
- **Class VII** are least-potent corticosteroids: hydrocortisone 1% and 2.5% cream lotion or ointment.

Antibiotics: topical antibiotics are medications applied directly to the skin in the form of creams, ointments, or sprays to treat localized bacterial infections. They are used for mild to moderate skin conditions like cuts, scrapes, burns, and secondary infections from conditions like eczema. Common examples include bacitracin, mupirocin, silver sulfadiazine, neomycin, clindamycin,…etc.

Antibiotics and Antiseptics

Antibiotics: - are substances which often derived from microorganisms, combat bacterial infections within the body. They prevent bacteria from multiplying or kill them directly. Types include penicillin, tetracyclines, and macrolides. These drugs are essential in treating bacterial infections like strep throat and urinary tract infections. Misuse or overuse may lead to antibiotic resistance, a significant public health concern. Responsible use, based on medical prescriptions, ensures effective infection control and minimizes resistance development.

Antiseptics: - are chemical agents applied to living tissues such as skin, inhibit microbial growth and prevent infection. They play an essential role in reducing microorganisms at surgical sites and during routine skin cleaning. Common examples include alcohol, iodine, and hydrogen peroxide. Hospitals and clinics utilize antiseptics to maintain sterile environments and prevent infections from wounds or surgical procedures. Antiseptics significantly reduce infection rates and promote safer healthcare practices.

Antibiotics and Antiseptics use in acne

Antibiotics and antiseptics are common and effective treatments for **inflammatory acne** (red, swollen pimples and pustules), working to reduce bacteria and inflammation. Current guidelines strongly recommend using them in combination with non-antibiotic agents like **benzoyl peroxide** (an antiseptic) to maximize effectiveness and minimize the development of antibiotic resistance.

Antibiotics

Mechanism of Action:

Antibiotics primarily work in two ways:

- **Reducing Bacteria:** They kill or inhibit the growth of *Cutibacterium acnes* (previously *Propionibacterium acnes*), the bacteria that live in hair follicles and contribute to acne development.
- **Anti-inflammatory Effects:** They help reduce the redness and swelling associated with inflamed lesions, a key component of moderate to severe acne.

Antiseptics

Mechanism of Action:

Antiseptics have a broad spectrum of activity and generally use non-specific mechanisms to kill or inhibit microorganisms.

- **Benzoyl Peroxide (BPO):** The most common antiseptic used for acne. It releases oxygen into the pore, creating an environment where *C. acnes* bacteria cannot thrive. It also has a mild anti-inflammatory and comedolytic (unclogs pores) effect.
- **Azelaic Acid:** A naturally occurring acid with antibacterial, anti-inflammatory, and exfoliating properties.
- **Salicylic Acid:** Works as an exfoliant to unclog pores and has some antibacterial properties.

Antibiotics and Antiseptics – Use in wound care

Antiseptics are used to cleanse wounds and prevent infection by killing microorganisms on the skin's surface, **while antibiotics** are used to treat an existing, deeper wound infection, ideally systemically. For preventing infection, antiseptics are preferred because they have broad-spectrum activity and do not contribute to the development of antibiotic-resistant strains like topical antibiotics can. Systemic antibiotics are recommended for clear, established wound infections, but topical antibiotics are generally not recommended for routine wound care due to low effectiveness and resistance concerns.

Antiseptics in wound care

- **Use:** For cleansing and preventing infection in acute and chronic wounds.
- **Action:** Kill or inhibit the growth of microorganisms on the skin's surface, including bacteria, viruses, and fungi.
- **Benefits:**

1- Reduce bacterial load. 2- Support wound healing.
3- Do not contribute to antibiotic resistance.

Examples: Hydrogen peroxide, povidone-iodine, and chlorhexidine gluconate (CHG).

Antibiotics in wound care

- **Use:** To treat a diagnosed, systemic wound infection.
- **Action:** Kill bacteria by targeting specific parts of the bacterial cell, such as the cell wall, cell membrane, or protein synthesis.
- **Benefits:** Effective for established infections when administered appropriately (usually systemically).
- **Risks of topical use:**

1- Minimal effectiveness bacteria. 2-Contribute to the development of antibiotic-resistant 3- Can cause sensitization

Antibiotics and Antiseptics use in infection control

Antibiotics treat internal bacterial infections, while antiseptics prevent microbial growth on surfaces and living tissues like skin. Antibiotics work by killing or inhibiting specific bacteria within the body, often taken orally or systemically. **Antiseptics** are applied externally to cleanse wounds, surgical areas, or skin to reduce microbial load, and they can target a broader range of microorganisms, including bacteria, fungi, and viruses.

Antibiotics

- Purpose: To fight bacterial infections already present inside the body.
- Mechanism: Kill or prevent the multiplication of specific types of bacteria.
- Application: Administered systemically (orally, intravenously) or sometimes topically.
- Considerations: Overuse can contribute to antibiotic resistance.

Antiseptics

- Purpose: To prevent infection by inhibiting microbial growth on living surfaces.
- Mechanism: Broad-spectrum action against a wide range of microorganisms.
- Application: Applied topically to the skin, wounds, and surgical sites.
- Considerations: Modern antiseptics have good tissue compatibility, and resistance to them is uncommon.

Analgesics and Anesthetics

Analgesics relieve pain without affecting consciousness, while anesthetics temporarily block all sensation, which may or may not include loss of consciousness. Analgesics work by blocking or interfering with pain signals, while anesthetics can be local, regional, or general, and work by completely blocking nerve function.

Anesthetics are drugs that cause a temporary loss of feeling (sensation) or awareness, preventing pain during medical procedures like surgery. They work by blocking nerve signals from reaching the brain and are categorized as either local (for a small area), regional (for a larger part of the body), or general (causing unconsciousness for a complete loss of sensation and awareness).

Types of anesthetics

- **General anesthetics:** Cause a reversible loss of consciousness, along with analgesia (pain relief) and muscle relaxation, making the patient unaware of the procedure.
- **Regional anesthetics:** Block pain in a specific part of the body, such as an arm or leg, without causing general unconsciousness.
- **Local anesthetics:** Cause a loss of feeling in a very small, specific area, like the site of a dental filling or a minor skin procedure.

Local anesthetics: - are medications that numb a specific area of the body to prevent pain during medical, dental, or surgical procedures, while the patient remains awake. They work by blocking nerve signals to the brain and can be administered as injections, creams, sprays, or ointments. Unlike general anesthesia, they do not cause unconsciousness and have fewer side effects.

Pain management in aesthetic procedures

Pain management for aesthetic procedures involves a combination of topical anesthetics, cooling, vibrational devices, oral pain medications, and sometimes inhaled analgesics like Pro-Nox (50% oxygen 50% nitrous oxide) he best approach depends on the specific procedure and the patient's individual needs, and it is essential to discuss options with the practitioner to ensure both comfort and safety.

Anti-inflammatory and Immunomodulatory Drugs Steroids

Anti-inflammatory steroids: - also known as corticosteroids, are drugs that reduce inflammation and suppress the immune system. These synthetic hormones mimic cortisol, which is naturally produced by the body, and are used to treat inflammatory and autoimmune diseases by reducing pro-inflammatory chemicals and white blood cell activity. Common examples include prednisone, prednisolone, and dexamethasone.

Examples of corticosteroids

- **Prednisone:** An oral medication that must be converted by the liver into its active form, prednisolone.
- **Prednisolone:** Has strong anti-inflammatory properties and is used for systemic treatment.
- **Dexamethasone:** Has high anti-inflammatory action with very low sodium retention, making it suitable for patients who must limit sodium intake.
- **Hydrocortisone:** A functional steroid the body produces naturally, often used topically for mild inflammation due to its low potency and high sodium-retaining activity.

Immunomodulatory drugs and steroids:- are used together to treat inflammatory conditions, with steroids providing rapid relief from symptoms while immunomodulators work over time to reduce the long-term need for steroids. Steroids, such as prednisone, work by suppressing the immune system and reducing inflammation, but can cause side effects with long-term use. Immunomodulators, like azathioprine, are "steroid-sparing" drugs that modify the immune response to allow for the use of lower doses of steroids or their eventual discontinuation.

Hormonal therapy

Hormonal therapy is a treatment that changes the body's hormones to stop or slow the growth of hormone-sensitive cancers, such as breast and prostate cancer. It can involve taking synthetic hormones, using drugs to block hormone receptors, or surgically removing endocrine glands to reduce hormone production.

Androgens are a group of steroid hormones that are the main sex hormones in men and are also present in smaller amounts in women. Their primary role is to develop and maintain masculine characteristics, such as muscle and bone growth, and male reproductive tissues and secondary sexual characteristics like facial hair and a deeper

voice. The most well-known androgen is testosterone. Androgens also affect other bodily functions, including metabolism, insulin sensitivity, and are involved in the reproductive cycles of both sexes.

Estrogens are a group of female sex hormones that are essential for the development and regulation of the female reproductive system and secondary sex characteristics. They are produced primarily by the ovaries, adrenal glands, and fat cells, and are also created synthetically for medical uses like birth control and hormone replacement therapy. Key functions of estrogens include regulating the menstrual cycle, affecting the urinary tract, heart, blood vessels, bones, skin, and brain, and influencing the growth of pubic and armpit hair.

Primary functions and effects

- **Reproduction:** Estrogens play a crucial role in the normal sexual and reproductive development of females, including regulating the menstrual cycle and influencing fertility.
- **Secondary sex characteristics:** They are responsible for the development of secondary sex characteristics, such as breast growth and the widening of the hips.
- **Bone health:** Estrogens help maintain bone density by suppressing the activity of bone-resorbing cells (osteoclasts), which is why a drop in estrogen levels during menopause can lead to increased risk of osteoporosis.
- **Other systems:** Estrogens also affect the urinary tract, heart and blood vessels, skin, hair, and mucous membranes. They also have important functions in the brain.
- **Pregnancy:** During pregnancy, the placenta produces significant amounts of estrogen to help maintain the pregnancy and prepare the breasts for lactation.

Oral contraceptives in skin and hair disorders

Combined oral contraceptives are often prescribed for acne and hirsutism (excessive hair growth) because the estrogen component decreases oil production, while the overall effect of estrogen and progestin in these formulations is to lower androgen levels. However, certain progestins can worsen acne, and progestin-only methods may exacerbate acne or hirsutism in some individuals. In rare cases, combined oral contraceptives have been linked to other skin or hair issues like scarring hair loss (frontal fibrosing alopecia), especially in genetically predisposed individuals.

Drugs for pigmentation and hair disorders

Drugs for pigmentation disorders include topical agents like **hydroquinone**, **retinoids**, and **azelaic acid** for hyperpigmentation. For hair disorders, some medications are used to treat the underlying cause, like anti-inflammatory or other agents for certain types of hair loss, while other treatments focus on stimulating repigmentation.

Hydroquinone is an organic compound primarily used in topical creams, gels, and solutions to lighten dark spots on the skin by decreasing melanin production. It treats conditions like melasma, chloasma, and post-inflammatory hyperpigmentation.

Uses Hydroquinone

- **Treating hyperpigmentation:** Hydroquinone is used to treat dark spots caused by hormonal changes, sun exposure, or inflammation.
- **Lightening skin:** It is used cosmetically and therapeutically to lighten the skin's color.
- **Specific conditions:** It helps treat conditions such as melasma, chloasma, freckles, and solar lentigines.

Minoxidil is a medication used to treat two distinct conditions: **high blood pressure** (hypertension) and **pattern hair loss** (androgenetic alopecia). It functions as a potent vasodilator, meaning it widens blood vessels and improves blood flow.

Uses and Formulations

- **High Blood Pressure:** Minoxidil was originally developed as an oral tablet (brand name Loniten) for severe, symptomatic high blood pressure that did not respond well to other medications.
- **Hair Loss:** A significant side effect of the oral medication was unexpected hair growth (hypertrichosis), which led to the development of a topical formulation (brand name Rogaine) to be applied directly to the scalp. It is widely used to stimulate hair growth and slow balding in both men and women.

Finasteride is an oral prescription medication primarily used to treat **male pattern hair loss** (androgenetic alopecia) and **benign prostatic hyperplasia (BPH)**, also known as an enlarged prostate. It belongs to a class of drugs called 5-alpha reductase inhibitors and is available under brand names such as Propecia (for hair loss) and Proscar (for BPH), as well as in generic form.

Finasteride works by blocking the enzyme 5-alpha reductase, which is responsible for converting testosterone into dihydrotestosterone (DHT). DHT is the hormone that causes the prostate gland to grow larger and also causes hair follicles on the scalp to shrink, leading to hair loss in men. By lowering DHT levels, finasteride can reduce prostate size, improve urinary symptoms, slow or stop hair loss, and in some cases, promote hair.