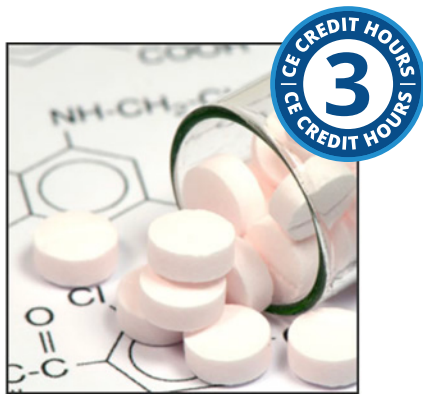


General Principles of Pharmacology



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Disclaimer: Participants must always be aware of the hazards of using limited knowledge in integrating new techniques or procedures into their practice. Only sound evidence-based dentistry should be used in patient therapy.

Conflict of Interest Disclosure Statement

- Dr. Ojeda Diaz reports no conflicts of interest associated with this course.
- Dr. Terézhalmy has done consulting work for Procter & Gamble and has served on the dentalcare.com Advisory Board.
- Dr. Ouanounou has no conflicts of interest to report. He has no relevant financial relationships to disclose.

Introduction – Pharmacology

Pharmacodynamic mechanism, i.e., drug-receptor interactions provide quantitative information that is the basis for determining efficacy, potency, and toxicity of drugs. Pharmacokinetic processes determine the ability of a drug to cross biological membranes, reach its target tissue, and to maintain steady-state concentrations at its site of action. Key points for practice to ensure effective and safe pharmacotherapy, including prescription writing, are presented.

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Overview

This course presents an overview of general pharmacological principles. It discusses (1) the conceptual basis of drug action, (2) pharmacodynamic mechanisms, (3) pharmacokinetic processes, and (4) sets forth key points to consider in clinical decision making related to pharmacotherapy and for a disciplined approach to prescription writing.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Understand the conceptual basis of drug action.
- Understand pharmacodynamic mechanisms and discuss their effects on pharmacotherapy.
- Understand pharmacokinetic processes and discuss their effect on pharmacotherapy.
- Discuss key points for practice that underlie safe and effective pharmacotherapy, including an efficient and practical approach to prescription writing.

Introduction

Until the nineteenth century, there were few standards or guidelines to protect the public from unsafe and ineffective drug, and unscrupulous purveyors. The first historical milestone in U.S. Food and Drug Laws was the publication of U.S. Pharmacopoeia (USP) in 1820, which listed standards for drug purity and strength, and directions for synthesis.¹ Today, this information is found in the **U.S. Pharmacopoeia-National Formulary** (USP-NF).

To protect the public from deceitful and unsafe practices by manufacturers and clinicians, since the early 1900s, the U.S. Congress enacted a

series of drug laws.^{1,2} The **Harrison Narcotic Act of 1914** mandated prescriptions for products containing narcotics. The **Durham-Humphrey Amendment of 1951** identified other, i.e., non-narcotic, drugs that cannot be safely used without medical supervision and prohibited their sale without a prescription by a licensed practitioner.

The **Controlled Substances Act (CSA) of 1970**, collected all legislations related to drugs with abuse potential, placed the drugs in schedules based on their accepted medical use and the potential for dependence when abused, and created a “closed” system for legitimate manufacturing, distribution, and dispensing of such drugs. The current list of controlled substances can be found in the most recent update of **Title 21, Section 1308, Code of Federal Regulations**.³

In the U. S. there are approximately 500 **Food and Drug Administration** (FDA)-approved active ingredients, i.e., therapeutic agents, available in several thousand different formulations.⁴ The FDA has specific requirements on content and format of labeling for human prescription drugs and biological products (Table 1).⁵ The labeling information must include specific headings and subheadings in a specified order, and must be updated when new information becomes available.

The **DailyMed** website, operated by the U.S. National Library of Medicine, is the official provider of FDA label information.⁶ It is a trustworthy, standard, comprehensive, up-to-date, look-up and download resource of medication content and other labeling information found in package inserts of drugs marketed in the United States. The labeling information is the most recent submitted to and approved by the FDA and includes strengthened warnings undergoing FDA review.

Clinicians and patients acknowledge the major role played by drugs in modern healthcare. However, it is also of note that therapeutic agents seldom exert their beneficial effects without also causing adverse drug effects (ADEs). ADEs range from mild to severe reactions and can lead to hospitalization, permanent disability, and even death. The

Table 1. Full Content and Format of Labeling for Human Prescription Drug and Biological Products.⁵

Warning Box	9 - Drug Abuse and Dependence 9.1 - Controlled substance 9.2 - Abuse 9.3 - Dependence 10 - Overdose 11 - Description 12 - Clinical Pharmacology 12.1 - Mechanism of action 12.2 - Pharmacodynamics 12.3 - Pharmacokinetics 13 - Nonclinical Toxicology 13.1 - Carcinogenesis, mutagenesis, impairment of fertility 13.2 - Animal toxicology and/or pharmacology 14 - Clinical Studies 15 - References 16 - How Supplied/Storage and Handling 17 - Patient Counseling Information
1 - Indications and Usage 2 - Dosage and Administration 3 - Dosage Forms and Strengths 4 - Contraindications 5 - Warnings and Precautions 6 - Adverse Reactions 7 - Drug Interactions 8 - Use in Specific Populations 8.1 - Pregnancy 8.2 - Lactation 8.3 - Females and males of reproductive potential 8.4 - Pediatric use 8.5 - Geriatric use	

inevitability of this therapeutic dilemma lends credence to the statement that there are no “absolutely” safe biologically active agents.

Hence, it is important for practitioners to have a solid foundation in pharmacology. Understanding how drugs affect physiological homeostatic mechanisms at the molecular level forms the basis for developing sound therapeutic strategies. Consequently, the use of therapeutic agents requires an understanding of basic pharmacological principles. These principles apply to all drugs and are predicated on pharmacodynamic mechanisms and pharmacokinetic processes.

Conceptual Basis of Drug Action

Drugs achieve their desirable (**therapeutic**) and undesirable (**adverse**) effects by interacting with specific molecular components of cells known as **receptors**. The various mechanisms of **drug-receptor binding** are illustrated in Figure 1.⁷ Bond strength associated with **van der Waals forces**, caused by shifting electron density in a molecule resulting in transient positive or negative charges that interact with transient areas of opposite charges on another molecule, is quite weak.

Hydrogen bonds between positively charged hydrogen atoms and negatively charged oxygen, nitrogen, or sulfur atoms and **ionic bonds**

between atoms with an excess of electrons imparting an overall negative charge and atoms with a deficiency of electrons imparting an overall positive charge, are of intermediate strength. **Covalent bonds**, resulting from the sharing of a pair of electrons between two atoms, are so strong that they are essentially irreversible.

There are six major groups of drug receptors (Figure 2).⁷ Drugs can bind to **transmembrane ion channels** and alter channel conductance. **Voltage-gated channel** conductance is regulated by the voltage across plasma membrane, e.g., action potentials in neurons permitting the selective passage of Na⁺ ions into cells, which, incidentally, may be blocked by lidocaine. **Ligand-gated channel** conductance can be controlled by endogenous ligands, e.g., acetylcholine, or exogenous drugs.

Transmembrane G protein-coupled receptors convey information provided by endogenous ligands or exogenous drugs, e.g., epinephrine, from its extracellular surface to intracellular regions and activate signaling molecules called G proteins: **G-stimulatory** (G_s) activates Ca²⁺ channels and adenylyl cyclase, **G-inhibitory** (G_i) activates K⁺ channels and inhibits adenylyl cyclase, **G_o** inhibits Ca²⁺ channels, **G_q** activates phospholipase C, and **G_{12/13}** affects diverse ion transporters.

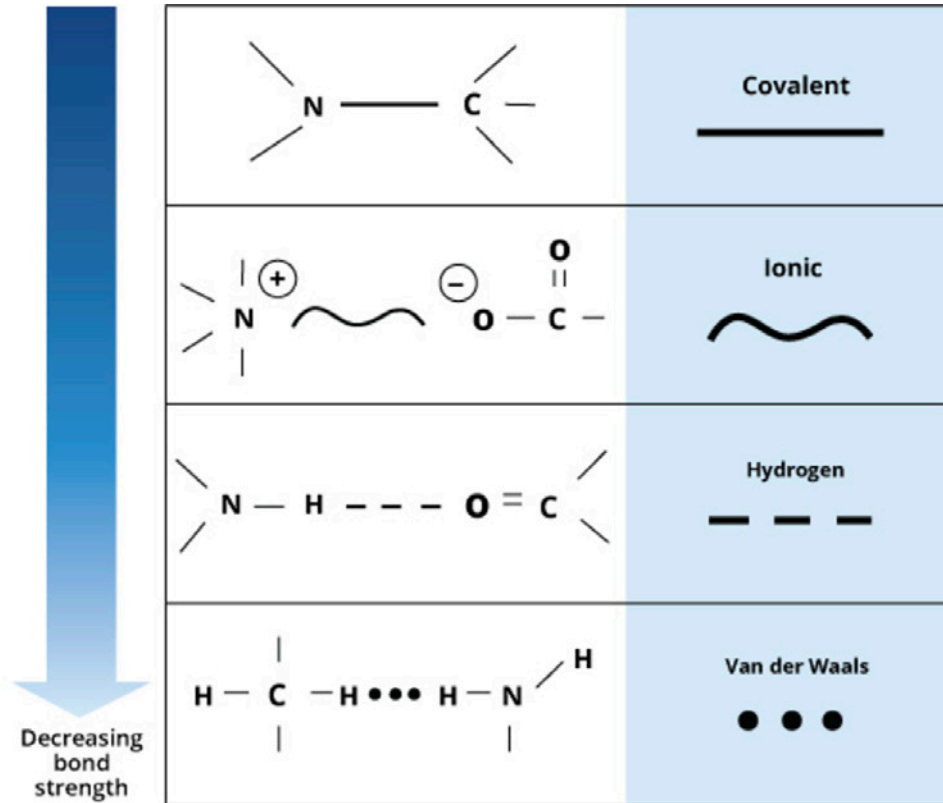


Figure 1. Hydrogen bonding and ionic bonding are the most common in drug-receptor interactions as they require little energy and may be easily broken.

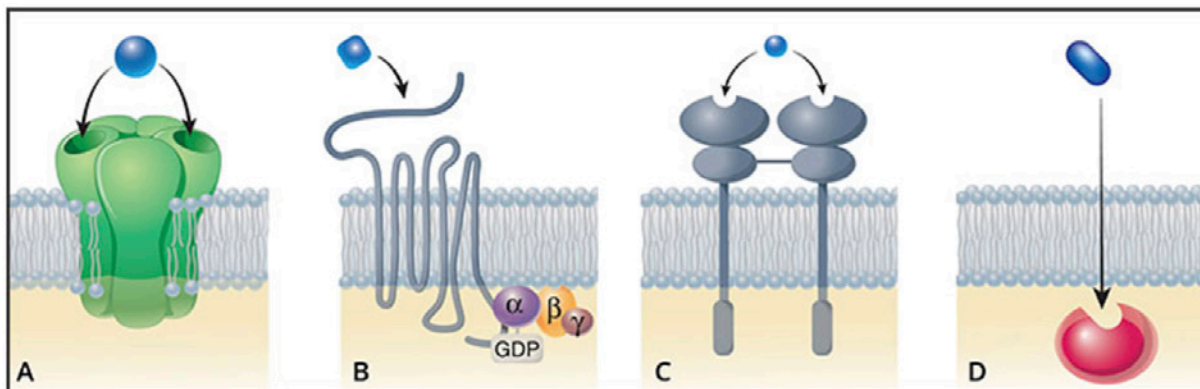


Figure 2. Major types of drug-receptor interactions. Drugs can bind to (A) transmembrane ion channels, (B) transmembrane G protein-coupled receptors, (C) transmembrane receptors with linked enzymatic domains, or (D) following diffusing across the plasma membrane, to cytoplasmic or nuclear receptors. Additionally, drugs can target extracellular and adhesion receptors (not shown).

Phosphorylation is a ubiquitous mechanism of protein signaling. **Transmembrane receptors with linked enzymatic domains** modify proteins by adding or removing phosphate groups to or from amino acids. The largest group of transmembrane receptors with enzymatic domains is the **receptor tyrosine kinases** family. These receptors transduce signals from many hormones and growth factors by phosphorylating tyrosine residues on the cytoplasmic side of the receptor.

Small, lipophilic (lipid-soluble) drugs that can cross the plasma membrane, along the concentration gradient, by passive diffusion and other drugs that are transported into the cell by facilitated transport or active transport target **intracellular receptors**. There are many such drugs that by activating or inhibiting **intracellular enzymes and signal transduction molecules, transcription factors, structural proteins, and nucleic acids**, have profound effects on cellular function.

Some drug receptors are located outside the plasma membrane. **Extracellular receptors** may be structural proteins, signaling molecules, or soluble cytokines such as TNF- α . Cells also interact directly; for example, when immune cells interact with cells in an inflamed tissue. The region of contact between two cells is called an **adhesion**. Cell-to-cell adhesion interactions are mediated by pairs of **adhesion receptors**, which may be inhibited by a class of drugs known as integrins.

Pharmacodynamic mechanisms

Pharmacodynamic mechanisms regulate the effects of drugs on the human body.⁸ As noted earlier, drug-receptor binding results in multiple, complex chemical interactions. The site on the receptor at which a drug binds is called its **binding site**. The reactivity of a drug and that of a binding site determines how tightly two molecules will bind to each other. The favorability of a drug-receptor interaction is referred to as the **affinity** of the drug for its binding site on the receptor.

Affinity, predicated on the intrinsic properties of any given drug-receptor pair, is expressed by the **dissociation constant** (K_d). K_d is defined as that concentration of a drug at which 50%

of the available receptors are occupied. When a sufficient number of receptors are occupied on or in a cell, the cumulative effect of receptor occupancy may become apparent in that cell. It follows that the **drug-receptor binding relationship** is closely related to the **dose-response relationship**.

There are two major types of dose-response relationships: graded and quantal. The **graded dose-response curve** (Figure 3) demonstrates the effect (E) of various doses or concentrations ([L]) of a drug on an individual from which two important parameters can be deduced: potency and efficacy. **Potency** (EC_{50}) of a drug is defined as the [L] at which the drug elicits 50% of its maximal response. **Efficacy** (E_{max}) is the maximal effect of a drug when all available receptors are occupied.

The **quantal dose-response curve** (Figure 4) demonstrates the average effect of a drug, as a function of its dose, in a population of individuals from which three important parameters can be deduced: effectiveness, toxicity, and lethality. Responses are qualified as either present or absent. The doses that produce these responses in 50% of a population are defined as the **median effective dose** (ED_{50}), **median toxic dose** (TD_{50}), or **medial lethal dose** (LD_{50}), respectively.

The **therapeutic window** is a range of doses of a drug that elicits a therapeutic response in a population of individuals without unacceptable toxic (adverse) effects. The therapeutic window can be quantified by the **therapeutic index** (TI): $TI = TD_{50}/ED_{50}$. A large TI represents a wide therapeutic window, e.g., a hundred-fold difference between TD_{50} and ED_{50} . A small TI represents a narrow therapeutic window, e.g., a two-fold difference between TD_{50} and ED_{50} .

Drug receptors exist in two conformational states in equilibrium with one another: an **active state** and an **inactive state**. The pharmacological properties of drugs can be based on their effects on the state of their receptors. A drug that favors binding to its active receptor, stabilizes its active conformation, and produces a pharmacological effect is called an **agonist**. A drug that causes an intrinsically active receptor to become inactive is called an **inverse agonist**.

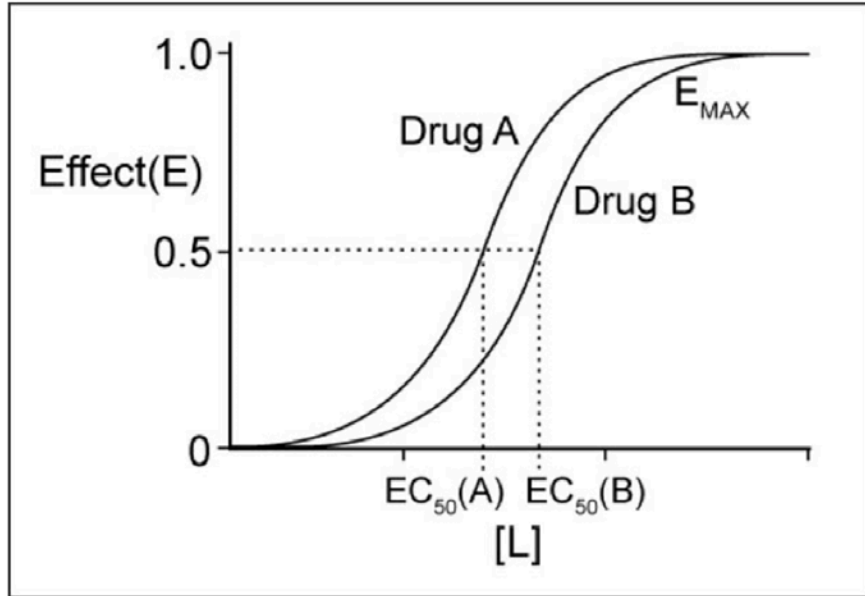


Figure 3. Graded dose-response curves for two drugs. Note that Drug A is more potent than Drug B; however, in this example, Drug A and Drug B exhibit the same efficacy.

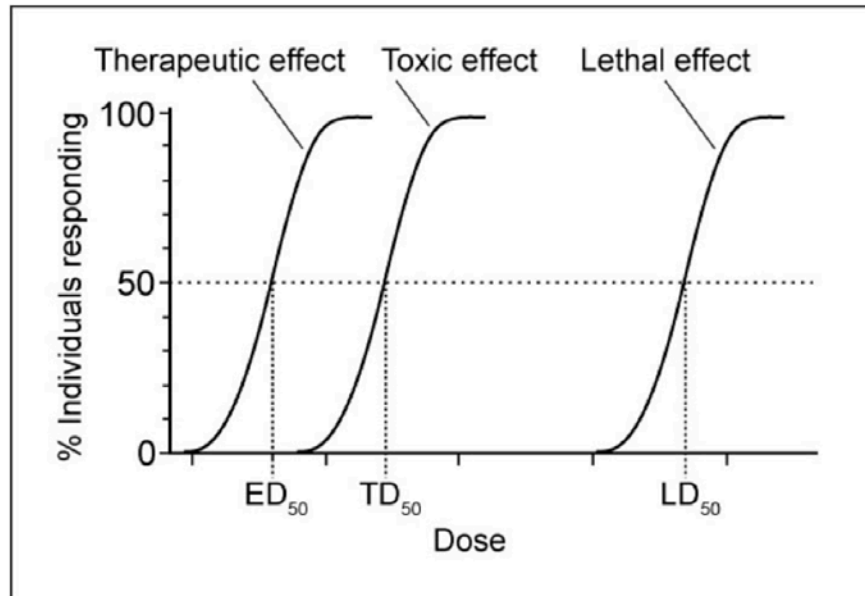


Figure 4. Quantal dose-response curve. Note that ED_{50} is the dose at which 50% of the subjects respond to the drug, whereas EC_{50} (see Figure 3) is the dose at which a drug elicits a half-maximal effect in an individual.

A drug that binds to a receptor at its active site and produces maximal response when all receptors are occupied is called a **full agonist**. A drug that binds to a receptor at its active site, but produces only a partial response, even when all receptors are occupied is called a **partial agonist**. A drug that can inhibit the action of an agonist, but has no effect in the absence of that agonist, is called an **antagonist**. Antagonists can be divided into two classes: receptor and nonreceptor antagonists.

A **receptor antagonist** can bind the agonist binding site or an **allosteric site**, i.e., a site different from the agonist site, on a receptor. Binding of an antagonist to the active site prevents the binding of the agonist to the receptor. Binding of an antagonist to an allosteric site either alters the agonist's affinity for its binding site or prevents the conformational change required for receptor activation. Antagonism at an agonist and an allosteric binding site may be competitive or noncompetitive.

An antagonist that competes with an agonist for the agonist binding site is referred to as a **competitive antagonist**. High concentrations of the agonist can overcome competitive antagonism, which is therefore, reversible. A **noncompetitive antagonist** binds covalently or with very high affinity to the agonist binding site. Consequently, high concentrations of the agonist are unable to overcome noncompetitive antagonism, which is therefore, irreversible.

A **nonreceptor antagonist** inhibits the ability of an agonist to initiate a response by chemical or physiological means. A **chemical antagonist** inactivates an agonist by modifying or sequestering it before it has the opportunity to act. For example, protamine binds to heparin, an anticoagulant, and inactivates it. A **physiologic antagonist** causes an effect opposite to that of an agonist. For example, β_1 -adrenoceptor antagonists counter tachycardia caused by excess thyroid hormone.

Pharmacokinetic Processes

To elicit an effect on its target, a drug must be absorbed and then distributed to its binding

site before being metabolized and excreted.⁹⁻¹¹ These **pharmacokinetic processes** affect the amount of free drug that ultimately will reach its binding site on a receptor. At all times, free drug in the systemic circulation is in equilibrium with its protein-, tissue reservoir-, and receptor-bound fractions (Figure 5). Only the receptor-bound fraction will have a pharmacologic effect.

All human cells have a lipid bilayer cytoplasmic membrane consisting mainly of phospholipids, sterols, and glycolipids. The membrane's semipermeable lipid bilayer presents the major barrier to drugs. Nonetheless, most small, nonpolar, lipophilic molecules are able to diffuse through lipid bilayer membranes along the concentration gradient by **passive diffusion** until equilibrium is reached. However, passive diffusion is ineffective for the transport of large, polar molecules.

Since only the nonpolar fraction of a drug can diffuse across biological membranes, net diffusion of acidic and basic drugs is affected by a charge-based phenomenon known as **pH trapping**, which depends on a drug's **acid dissociation constant** (pKa) and the pH of the biological environment (Figure 6). The pKa of a drug is defined as that pH of a biological medium at which 50% of the drug is protonated (i.e., electrically neutral) and 50% is deprotonated (i.e., electrically negative).

This charge-based phenomenon can be illustrated with the use of lidocaine (pKa 7.8). When administered into a healthy extracellular environment, which is more acidic (pH 7.4) in relation to lidocaine's pKa of 7.8, the protonated, electrically neutral form of lidocaine, which can diffuse into a neuron, represents about 28% of the dose administered. When lidocaine is administered into an inflamed/infected area (pH <7.4), its neutral fraction is further reduced and anesthesia fails.

Lipid bilayer plasma membranes also contain transmembrane proteins of the **human solute carrier** (SLC) superfamily, which can transport some polar drugs across biological membranes. Protein channels or carrier proteins may facilitate the transport of some drugs down their concentration gradient by energy-independent

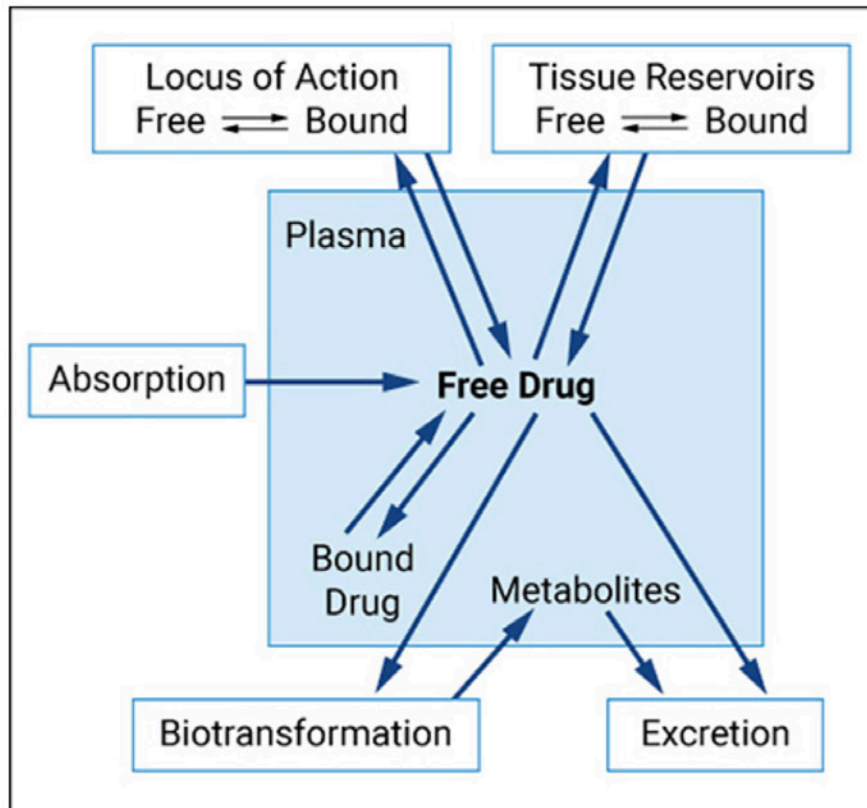


Figure 5. To elicit an effect on its target, a drug must be absorbed and then distributed to its binding site before being metabolized and excreted.

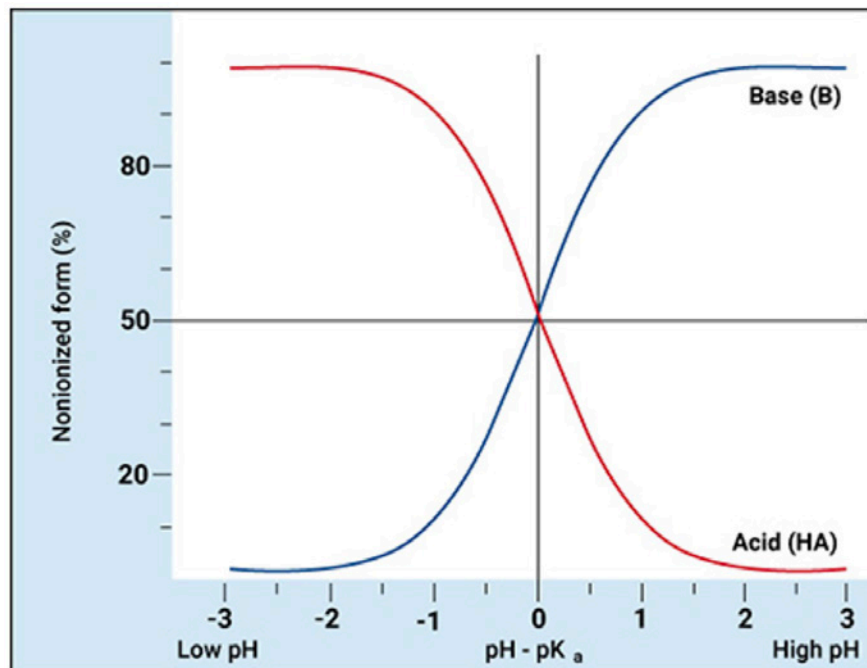


Figure 6. The relationship between the pKa of an acidic (AH) and a basic (B) drug and the pH of the biological medium. Note that at low pH the predominant fraction of a basic drug is ionized; conversely, the predominant fraction of an acidic is nonionized.

facilitated transport. The transport of drugs against their concentration gradient may be accomplished by energy-dependent **active transport.**

Unlike other anatomic regions, the central nervous system (CNS) presents a special challenge to pharmacotherapy. The **blood-brain barrier** is characterized by specialized tight junctions to prevent passive diffusion of most drugs from the systemic to the cerebral circulation. Drugs designed to act on the CNS must either be sufficiently small and lipophilic to cross the blood-brain barrier or use existing transport proteins in the blood-brain barrier to penetrate the CNS.

Since most drugs reach their sites of action directly from the systemic circulation, drug **absorption** can limit the drug's **bioavailability**, i.e., the fraction of administered drug that reaches the systemic circulation. Drug formulations and routes of administration such as enteral (oral), parenteral (subcutaneous, intramuscular, intravenous, intrathecal), mucous membrane, and transdermal, are chosen to take advantage of transport and other mechanisms that permit the drug to enter the body.

The **enteral route** is the most common, convenient, economical, and painless method of drug administration. It is also the least predictable. A drug administered orally must be stable until absorbed from the gastric environment. Furthermore, a drug's rate of absorption is greatly influenced by such factors as the pH of the gastrointestinal tract, gastric motility, splanchnic blood flow, the presence of food in the stomach, and patients' adherence to the prescribed drug regimen.

Another important determinant of bioavailability, unique to the oral administration of a drug, is **first-pass metabolism**, a process by which liver enzymes inactivate a fraction of the drug. A drug given enterically that is subject to significant first-pass metabolism must be administered in a quantity sufficient to ensure that an effective concentration of the active drug is reached in the systemic circulation. Drugs administered non-enterically are not subject to first-pass metabolism.

The **subcutaneous** (SC) route allows for the administration of small volumes of oil-based drugs and provides for a slow rate of drug absorption to maintain steady-state concentrations. Local tissue irritation such as sloughing, necrosis, and severe pain may occur. The **intramuscular** (IM) route allows for rapid absorption of aqueous solutions, while oil-based formulations provide for slow, constant absorption. This route may be painful and cause intramuscular hemorrhage.

The **intravenous** (IV) route provides for rapid onset of action and allows for controlled drug delivery into the systemic circulation. The dose can be adjusted to patient response. Administering drugs by the IV route too rapidly or in incorrect doses can result in increased toxicity. Local irritation and thromboembolic complications may occur with some drugs. Drugs administered by the **intrathecal** (IT) route bypass the blood-brain barrier and reach their target the fastest.

Mucous membrane routes such as sublingual, ocular, pulmonary, nasal, and rectal, because of the highly vascular nature of these tissues, allow for rapid absorption of drugs by passive diffusion as a function of concentration, molecular size, lipid solubility, and pKa of the drug. The **transdermal** route allows for slow absorption of lipophilic drugs across skin and subcutaneous tissues into the systemic circulation and is ideal for drugs that require prolonged administration.

Once a drug has been absorbed into the systemic circulation (vascular compartment), it is then capable of reaching any target organ by the process of **distribution**. The **volume of distribution** (V_d) reflects the extent to which a drug is partitioned between plasma and various other tissue compartments. Thus, the V_d is low for drugs that are retained within the vascular compartment and high for drugs that are highly distributed to adipose tissue and various other tissue compartment.

As an illustration, consider the effect of two drugs of equal potency administered to a patient. The drug that is more highly distributed among the various body tissues requires a higher initial dose to establish a therapeutic plasma concentration than does a drug that is less highly distributed. The capacity of tissues to absorb drugs increases

the tendency of drugs to diffuse from the vascular compartment. This tendency, however, is counteracted by the **plasma protein binding** of drugs.

Albumin is responsible for most drug-plasma protein binding. Plasma protein binding reduces the availability of free drug for diffusion or transport into other tissues because, in general, only the free or unbound fraction of a drug is capable of crossing biological membranes. The administration of two drugs that bind to plasma proteins result in a higher than expected plasma concentration of the free fraction of either or both drugs as they compete for the same plasma protein binding site.

Most drugs are **xenobiotics**, substances that are not naturally found in the body. Some of these are inherently **active drugs** used to modulate bodily functions for therapeutic ends. Others are inherently **inactive prodrugs** that must be converted to active drugs. Active drugs may be further converted to **active, inactive or toxic metabolites**. Finally, **unexcretable drugs** and unexcretable **active, inactive or toxic metabolites** of drugs must be converted to **excretable metabolites**.

These processes are called **drug metabolism** or **drug biotransformation** and are classified as **oxidation/reduction reactions** and conjugation/hydrolysis reactions. The most common pathway of **oxidation/reduction reactions** that modify the structure of drugs involve the hepatic **microsomal cytochrome P450 enzyme system**. Oxidation/reduction reactions can convert a prodrug to its active form; they can also transform drugs to more polar, excretable metabolites.

Conjugation/hydrolysis reactions can also result in the metabolic activation of prodrugs. More commonly, these reactions convert drugs to large, polar molecules in order to inactivate them and to enhance their clearance. The conjugation/hydrolysis enzymes are located in both the cytosol and the endoplasmic reticulum of hepatocytes. Many drugs induce or inhibit enzymes associated with biotransformation, a phenomenon important in understanding **drug-drug interactions**.

Oxidation/reduction and conjugation/hydrolysis reactions enhance the water solubility of drugs, which facilitates their elimination from the body. A small number of drugs are excreted in the bile, or through the respiratory and dermal routes. Most drugs are eliminated through **renal excretion**. Drugs may be filtered at the renal glomerulus, secreted into the proximal tubule, reabsorbed from the tubular lumen and transported back into the blood, and excreted into the urine.

The rate of drug metabolism and excretion by an organ is limited by the rate of blood flow to that organ. Most drugs demonstrate **first-order kinetics**, i.e., the amount of drug that is metabolized and excreted in a given unit of time is directly proportional to the concentration of the free drug in plasma at that time. A small number of drugs demonstrate **saturation** or **zero-order kinetics**, i.e., metabolic and clearance rates fail to increase with increasing plasma drug concentrations.

The **distribution half-life** of a drug is the time required to distribute 50% of a drug from plasma to tissue reservoirs. The amount of time over which a drug's concentration in plasma decreases to one-half of its original value because of metabolism and excretion kinetics is known as the **elimination half-life** ($t_{1/2}$) of the drug. Knowing a drug's $t_{1/2}$ allows the clinician to establish the frequency of dosing required to maintain a drug's plasma concentration within therapeutic range.

Therapeutic dosing seeks to maintain the trough (lowest) drug concentration above the minimally effective dose and the peak (highest) plasma drug concentration below the toxic concentration. It takes four $t_{1/2}$ for tissue distribution and plasma concentration of a drug to reach **steady-state** (Figure 7). A **loading dose**, i.e., a much higher initial dose than would be required if the drug were retained in plasma, may be used to achieve therapeutic levels with only one or two doses of drug.

However, continued excessive drug dosing may saturate the body's capacity to eliminate the drug, e.g., overwhelm the hepatic cytochrome P450 enzyme system. When the elimination rate of the drug does not increase with increasing

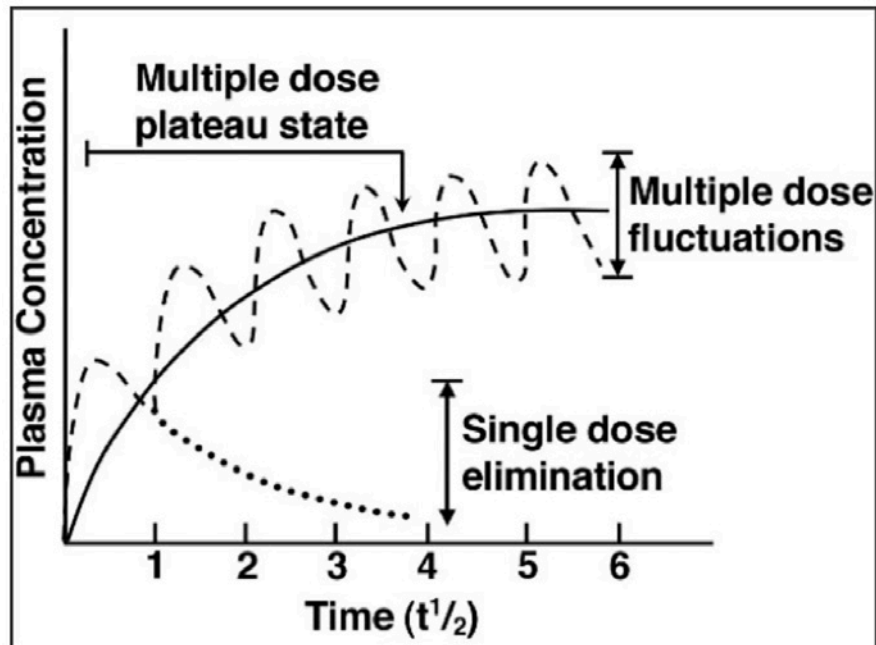


Figure 7. At optimal dosing, steady-state plasma concentration remains within the therapeutic range.

plasma drug concentrations, it may reach toxic levels. Once steady-state concentration of a drug is achieved, subsequent doses, i.e., **maintenance doses** need to replace only the amount of drug that is lost through metabolism and excretion.

Key Points for Practice

Pharmacotherapy, i.e., the use of drugs in the prevention and treatment of disease, is predicated on the clinical application of pharmacodynamic and pharmacokinetic principles as influenced by patient-related variables. Many factors affect the drug response phenotype, e.g., age, gender, underlying disease, and genetic variations, and determine the individual effective dose of a drug required to produce a specific response and determine the success or failure of therapy.¹²

Genetic polymorphism can result in altered drug-receptor interactions or signaling pathways once a drug-receptor complex is formed causing inter-individual **pharmacodynamic variations**. Genomic variations can also affect oxidation/reduction and conjugation/hydrolysis reactions causing inter-individual **pharmacokinetic variations**. Furthermore, pharmacogenetic variations related to rare, unpredictable, i.e.,

idiosyncratic adverse effects have also been reported.

Because of these genomic variations, an individual may be **hyporeactive**, i.e., a drug's usual effect is produced at an unexpectedly high dose or **hyperreactive**, i.e., the usual effect of a drug is produced at an unexpectedly low dose. An individual may also develop a **tolerance** following repeated exposure to a drug requiring higher doses to maintain efficacy. Tolerance that develops rapidly, following the administration of only a few doses of a drug, is referred to as **tachyphylaxis**.

The individual effective dose of a drug intended to produce a specific effect is usually expressed in terms of milligram per kilogram of **body weight**. Manufacturers' **maximum recommended dose (MRD)**, by definition, is for a 75 kg (165 lbs.) healthy adult. Ultimately, in determining the optimum therapeutic dose of a drug for an individual one must consider the patient's weight, as well as other factors such as dynamic and kinetics variables related to a specific patient.

Pregnancy. Pregnancy is accompanied by various physiological changes that may affect multiple organs. These changes are important

for adaptation and to facilitate fetal growth and survival. These physiological changes should not be mistaken with pathological ones and thus dentists must recognize them. The most important alterations involve the cardiovascular system (CVS), hematological system, gastrointestinal (GI) system, respiratory system and renal system. In this section we will review these changes and link them to the effects on drug pharmacokinetics.

When treating the pregnant patient, special considerations may be needed. These include changes that may be required in administering and prescribing drugs. The concern that all clinicians have is the potential adverse teratogenic effects that some drugs display. In pregnancy, it is assumed that all drugs can cross the placenta and thus affect the developing fetus. During the first 90 days (first trimester), organogenesis occurs and thus the fetus is most susceptible to teratogenesis. Therefore, avoiding medications during this time is desirable, although not always possible. Similarly, the approach of not prescribing any drugs to the pregnant patient carries its own risks. For instance, inadequately managed persistent pain may be harmful. Likewise, an untreated apical abscess may lead to systemic infection. Thus, failure to manage these conditions may harm the mother and/or the fetus. In pregnancy, drugs should be prescribed when the benefit to the mother is maximized and when the risk to the developing fetus is minimal. To determine the risks associated with the use of drugs in pregnancy, the United States Food and Drug Administration (FDA) has classified drugs based on the level of risks they pose to the fetus. Drugs in category A and B are considered safe as no adverse effects have been shown in humans. Drugs in category C are ones in which adverse effects on the fetus have been shown in some animal studies, but there are no adequate and well-controlled studies in humans. In this category drugs may still be used if the benefits outweigh the risks. Drugs in category D should be avoided as some studies demonstrated clear teratogenic effects in humans. Nonetheless, in rare circumstances, drugs in this category may be used. Finally, drugs in category X clearly should be avoided as studies in humans or animals have demonstrated fetal abnormalities and positive evidence of human fetal risk.

Lactation and the neonate. Milk is generally more acidic (pH 6.8) than plasma (pH 7.4); therefore, basic drugs become more concentrated in milk because of the phenomenon of pH trapping, while acidic drugs are limited in their ability to enter milk. Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions,” and “Adverse Effects” sections, and “Lactation” subsection of specific drug labeling.⁶

Females and males of reproductive potential.

The FDA requires pregnancy testing or contraception before, during, or after therapy with some drugs and warnings about possible drug-related fertility effects. Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions,” and “Adverse Effects” sections, and “Females and Males of Reproductive Potential” subsection of specific drug labeling.⁶

Pediatric patients. Often there is a paucity of specific pharmacokinetic and pharmacodynamic data for the pediatric population. Dosage forms designed with the adult population in mind and the dosages cannot easily be individualized for children. Even when appropriate dosage forms for children are available palatability, resistance to taking medications, and adherence issues related to parent/guardian/caregiver may further hinder optimal therapy.

Although there are many rules and formulae to calculate drug dosages for children, weight-based dosing recommendations by manufacturers provide the most reasonable approach.⁶ The maximum safe dose of a drug should be carefully calculated for each child. Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions,” and “Adverse Effects” sections, and “Lactation” subsection of specific drug labeling.⁶

Geriatric. The aging process includes 3 types of physiological changes: changes in cellular homeostatic mechanisms, which may include regulation of body temperature, as well as blood and extracellular fluid volumes; those related to a decrease in organ mass; and those involving a decline in, and loss of, the functional reserves of the body's systems. The

prescription and use of multiple drugs to deal with concomitant multiple diseases is known as polypharmacy. Numerous studies have shown that the elderly take more prescription and over-the-counter (OTC) medications than younger adults. The most commonly used classes of OTC medications include analgesics, laxatives, vitamins and minerals. At any given time, an elderly patient takes, on average, 4 or 5 prescription drugs and 2 or 3 OTC medications.

Herbal supplements have long been used by older people as a substitute for high-cost prescription medications as well as because of their overall popularity. The unmonitored use of herbal supplements can be a serious risk in this population, who are commonly given prescription medications to control multiple disorders. For instance, many herbal preparations, such as ginkgo, ginseng, garlic and ginger, have anti-platelet and anticoagulation properties and, thus, may potentiate the effects of other anticoagulation drugs, such as warfarin. Synergistic interactions may also occur between herbal medicines and other anti-platelets drugs, such as ASA and nonsteroidal anti-inflammatory drugs (NSAIDs). Thus, geriatric patients who take warfarin and other anti-platelet medications should be advised about these interactions with herbal products.

The high prevalence of polypharmacy among the elderly may lead to inappropriate drug use, medication errors, drug interactions and adverse drug reactions. Adverse drug reactions and drug interactions are common reasons for admission to hospital of older people, are common in elderly patients in hospital and are an important cause of morbidity and mortality. The incidence of adverse drug reactions in the elderly is 3-4 times that seen in young adults. The medications most often associated with adverse reactions and interactions are anticoagulants, anticonvulsants and cardiovascular agents. The most consistent risk factor for adverse drug reactions is number of drugs being taken, i.e., the risk rises exponentially as the number of drugs increases. Other factors that contribute to the incidence of adverse drug reactions are changes in pharmacokinetics and pharmacodynamics and comorbidities associated with the elderly

patient. The symptoms of adverse drug reactions may be harder to detect in the elderly and may be misinterpreted as symptoms of a disease or even "normal aging."

Although polypharmacy is acceptable in many cases of multiple comorbidities, prescribers must consider older adults' physiology. For instance, many elderly patients are prescribed warfarin concurrently with an NSAID, a selective serotonin reuptake inhibitor (SSRI) or a lipid-lowering agent, which may increase the risk of bleeding (already increased by use of warfarin alone).

To avoid adverse drug reactions and drug interactions, the dentist should regularly review the patient's medical history and medication list and carefully assess the need for and consequences of pharmacologic intervention. Finally, close monitoring and thorough evaluation of pharmacotherapy is important in preventing adverse drug reactions and drug interactions.

Patients with liver disease. In the presence of liver disease, adverse drug effects are primarily related to altered pharmacokinetic processes. To estimate the ability of the liver to metabolize drugs, determine the patient's **Child-Pugh score** (Table 2).¹³⁻¹⁵ Prescribing precautions can be found in the "Dosage and Administration," "Contraindications," "Warning and Precautions" and "Adverse Effects" sections of specific drug labeling.⁶

Patients with chronic renal disease. Drug dosages are most commonly based on the **estimated creatinine clearance** determined by the **Cockcroft-Gault equation**, i.e., $eCrCl \text{ in mL/min} = (140 - \text{age} \times \text{weight in kg} \times 0.85 \text{ (for females)}) \div S_{cr} \text{ in mg/dL} \times 72$.¹⁶ The normal range for men and women ≥ 40 years of age is 107-139 mL/min and 87-107 mL/min, respectively. It is of note that after 20 years of age, eCrCl is reduced by 6.5 mL/min every 10 years. The eCrCl is used as a surrogate of GFR (Figure 8). In general, if the eCrCl is >50 mL/min, no dosage adjustment is required; if it is 10-50 mL/min, some drugs should be reduced by 25-50%; if it is <10 mL/min, some drugs should be reduced by up to 75%, while others should

Table 2. Child-Pugh Classification for Chronic Liver Disease.

Tests/Symptoms	Score 1 point each	Score 2 points each	Score 3 points each
Total bilirubin in mg/dL	< 2.0	2.0-3.0	> 3.0
Serum albumin in mg/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time in seconds over control or the INR	< 4 (INR: < 1.7)	4-6 (INR: 1.7-2.3)	> 6 (INR: > 2.3)
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

✓ A score of 5 indicates normal liver function, whereas a score of 15 indicates extreme dysfunction.
 ✓ A score of ≤ 7 requires no modification in the daily dose.
 ✓ A score of 8 to 9 is grounds for a moderate decrease ($\approx 25\%$) in the daily dose.
 ✓ A score of ≥ 10 indicates a need for significant decrease ($\approx 50\%$) in daily dosing.

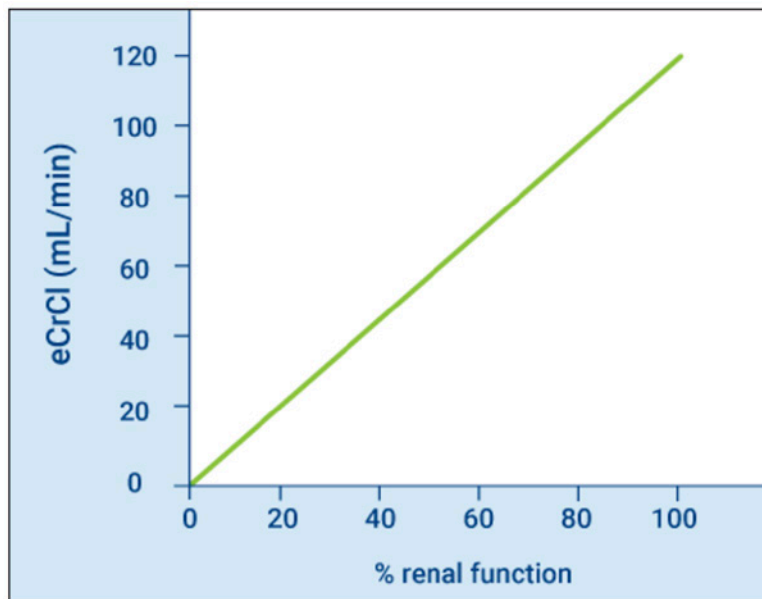


Figure 8. eCrCl, a surrogate for glomerular filtration rate (GFR), and estimated percent renal function.

be avoided.¹⁶ Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions” and “Adverse Effects” sections of specific drug labeling.⁶

Non-adherence. It is a generally accepted that many patients do not adhere to their prescribed therapeutic regimen.¹⁷⁻²⁰ Non-adherence can be intentional (actively choosing not to adhere) or unintentional (e.g., passively inconsistent medication-taking behavior including forgetfulness or carelessness). Determinants of non-adherence include the disease, the patient, the practitioner, the treatment regimen, economic factors, and the interaction of each of these factors.

A patient’s trust in the clinician and/or the treatment protocol as established during the office visit is important. Patients tend to be adherent if they have a good understanding of the illness and the therapy. Therefore, good communication between clinicians and patients is a major factor affecting adherence. A positive experience during the office visit, along with individualized regimens and good follow-up on the part of clinicians, improve adherence.

When an illness is serious or disabling, the patient will likely follow the therapeutic regimen. The longer the duration of treatment, the less likely it is that the patient will adhere to the regimen over time. This is especially true if symptoms are relieved before drug therapy is to be discontinued. The regimen itself may also be discouraging or confusing because of multiple drug use, scheduling of dosages, and side effects. Finally, cost may be a major contributing factor.

In children, the major reason for non-adherence is a dislike for the taste or smell of the medication. If it is frustrating to the parent/guardian/caregiver to give the medication, they are more likely to skip doses or discontinue the medication with the disappearance of symptoms. If the child is attending school, the regimen should be convenient and coordinated with the school schedule. Consider recommending specific times rather than generalize.

Common causes of non-adherence in elderly patients include failure to fill prescriptions due to transportation problems and expense. Other factors include a lack of trust or confidence in the doctor or therapy and poor comprehension of the regimen. Difficulty in opening packages or swallowing pills, poor memory, visual or hearing impairment may also contribute to non-adherence. Repetition of directions with written instructions and clear labeling are helpful.

Prescriptions. Drugs fall into two major categories: **non-prescription**, i.e., over-the-counter, and **prescription drugs**.¹⁻³ Prescription drugs are further divided into legend drugs and scheduled drugs. **Legend drugs** require a prescription because they are considered to be potentially harmful if not used under supervision by a licensed practitioner. Legend drugs are known as such because their labels bear the legend “Caution: Federal Law Prohibits Dispensing Without a Prescription.”

The prescription of **scheduled drugs**, i.e., controlled substances, is even more strictly controlled by Federal regulations. A licensed practitioner who administers, prescribes, or dispenses controlled substances must register under **Controlled Substances Act of 1970** with the Drug Enforcement Administration (DEA) and obtain a DEA number, which must be included on every prescription for a controlled substance.¹⁻³ Many States have additional, sometimes more strict requirements.

A prescription is a written, verbal, or electronic order (1) from a licensed practitioner, (2) to a licensed pharmacist, (3) for a particular medication, (4) for a specific patient, (5) at particular time. It has three components: a heading, a body, and a closing (Figure 9). These elements identify the prescriber and the patient; inform the pharmacist of the name, strength, and formulation of the drug to be dispensed; and provide instructions to the patient for self-administration of the drug. As noted earlier, while drugs have the capacity to enhance health, they all have the potential to cause harm if prescribed or taken inappropriately. For this reasons it is recommended that healthcare professionals

Heading	Prescriber's Name, Address, and Telephone Number	
	Date _____	
Body	Patient's name _____ Gender ____ Age _____ DOB _____	
	Address _____ Phone number _____	
	R _x Name, strength or concentration of the drug Disp: Quantity of the drug to be dispensed Sig: Directions for the patient	
Closure	Refill _____ times	Prescriber's signature _____
	Generic substitution allowed: Y or N	
	Other instructions: _____	DEA # _____

Figure 9. Essential Elements of a Prescription.

who prescribe medications exercise critical thinking skills to ensure the safe and effective use of therapeutic agents. The following steps, along with ongoing self-directed learning, reflect a disciplined approach to prescription writing and avoiding errors.²¹⁻²³

Step 1- Be clear about the reasons for prescribing

- Establish an accurate diagnosis whenever possible; although, at times one may prescribe medications based on a presumptive or working diagnosis.
- Set a clear therapeutic objective.

Step 2 - Consider the patient's drug history before prescribing

- Obtain an accurate list of current and recent medications (including over-the-counter and alternative medicines) and a history of prior adverse drug reactions.

Step 3 - Identify other factors that might alter the benefits and risks of treatment

- Consider individual risk factors that might influence therapy, e.g., weight of the patient, physiological changes with age and pregnancy, or impaired hepatic and renal function.

Step 4 - Take into consideration the patient's expectations

- Seek to form a partnership with the patient when selecting treatments, making sure patient understands and agrees with the reasons for taking the medication.

Step 5 - Select efficacious, safe, and cost-effective drugs appropriate for the patient

- The likely beneficial effects of a drug should outweigh any potential harms and, whenever possible, this decision should be based on published evidence.
- Choose the best formulation, dose, route of administration, frequency of dosing, and duration of treatment.

Step 6 - Adhere to guidelines

- Be aware of evidence-based recommendations developed by Federal and state agencies, and professional organizations, e.g., opioid prescribing guidelines.
- Prescribe only the necessary quantity of a drug to a patient.
- Balance specific drug selection considering the needs of the patient and cost.
- Use reliable informational resources, e.g., DailyMed.

Step 7 - Write unambiguous prescriptions

- Write the strength of a drug's unit dose in the metric system, e.g., in grams (g) or milligrams (mg) for solid formulations and in milligram per milliliter (mg/ml) for liquid formulations.
- When the unit dose is 1 gram or more it should be written in grams, e.g., write 2 g, not 2000 mg.
- When the unit dose is 1 milligram or more, but less than 1 gram, it should be written in milligrams, e.g., write 200 mg, not 0.2 g.
- When writing dosage strength, always use leading zeros, e.g., write 0.5 ml versus .5 ml, which can be mistaken for 5 ml.
- Avoid trailing zeroes, e.g., write 5 mg versus 5.0 mg, which can be mistaken for 50 mg.
- Under directions for the patient it may be necessary to convert milliliters to a convenient household measurement.
- When prescribing a controlled substance, in addition to writing the number of tablets or capsules to be dispensed, the amount must also be written-out longhand, e.g., Disp #20 (twenty) tablets.
- Avoid using abbreviations and write-out instructions in full; for example, "Take two tablets four times a day for 5 days".

Step 8 - Monitor the beneficial and adverse effects of therapeutic agents

- Know what to look for.
- Understand how to alter the therapeutic regimen as a result of this information.
- Know how to report adverse drug reactions.

Step 9 - Communicate the reasons for and document prescribing decisions

- Communicate clearly with the patient as well as the pharmacist.
- Inform the patient about how to take the medicine, what benefits might arise, and what potential adverse effects they may experience.

- Document prescribing decisions in the health record accurately.

Step 10 - Prescribe within limitations of knowledge, skills, and experience

- Always keep relevant knowledge and skills up to date.
- Be prepared to seek the advice and support of qualified professional colleagues.
- Verify all information on prescriptions.

Adverse drug effects (ADE). As noted earlier, there are no "absolutely" safe biologically active agents. Whether a drug will do harm to an individual depends on the patient's age, genetic makeup, and preexisting conditions; and other drugs that the patient may be taking. A discussion of mechanisms of ADEs, common ADEs associated with drugs dispensed by U.S. community pharmacies, and less common ADEs in the head and neck area is presented elsewhere.²⁴⁻²⁶

Summary

Pharmacodynamic mechanisms relate to drug-receptor interactions and provide quantitative information that is the basis for determining efficacy, potency, and toxicity of drugs. Pharmacokinetic processes underlie the fate of drugs within the body, i.e., provide the basis for understanding how drugs reach their receptors and factors essential to maintain therapeutic steady-state concentration for optimum efficacy and safety.

Pharmacotherapy relates to the use of drugs in the prevention and treatment of disease predicated on the application of pharmacodynamic and pharmacokinetic principles. It requires critical thinking skills forged during long hours of clinical practice and a life-long commitment to the disciplined study of drug- and patient-related variables. Fostered by a sincere desire to maximize therapeutic benefits, clinicians should prescribe drugs with great care.

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: www.dentalcare.com/en-us/ce-courses/ce580/test

- 1. All of the following statements related to important historical milestones in U.S. Food and Drug Laws are correct EXCEPT for one? Which is the exception?**
 - A. The Harrison Narcotic Act of 1914 mandated standards for drug purity and strength, and directions for synthesis.
 - B. The Durham-Humphrey Amendment of 1951 identified non-narcotic drugs that cannot be safely used without medical supervision and prohibited their sale without a prescription by a licensed practitioner.
 - C. The Controlled Substances Act (CSA) of 1970, collected all legislations related to drugs with abuse potential, placed the drugs in schedules and created a “closed” system for legitimate manufacturing, distribution, and dispensing of such drugs.
 - D. The current list of controlled substances can be found in the most recent update of Title 21, Section 1308, Code of Federal Regulations.
- 2. The FDA has specific requirements on content and format of labeling for human prescription drugs and biological products.**
 - A. True
 - B. False
- 3. The passive diffusion rate of lipid-soluble drugs depends on all of the following EXCEPT for one. Which is the exception?**
 - A. The concentration or dose of the drug.
 - B. The oil/water partition coefficient of the drug.
 - C. The amount of the drug present in a charged form.
 - D. ATP-dependent transport.
- 4. All of the following statements related to drug-receptor binding are correct EXCEPT one. Which is the exception?**
 - A. Drugs achieve their desirable (therapeutic) and undesirable (adverse) effects by interacting with specific molecular components of cells known as receptors.
 - B. Drug-receptor bonding associated with van der Waals forces is of intermediate strength.
 - C. Hydrogen bonding and ionic bonding are the most common in drug-receptor interactions as they require little energy and may be easily broken.
 - D. Covalent bonds, resulting from the sharing of a pair of electrons between two atoms, are so strong that they are essentially irreversible.
- 5. All of the following statements related to drugs-receptor interactions are correct EXCEPT for one. Which one is the exception? Drugs can interact with _____.**
 - A. transmembrane ion channels, which may be voltage-gated or ligand-gated.
 - B. transmembrane G protein-coupled receptors and transmembrane receptors with linked enzymatic domains.
 - C. intracellular receptors known as cytoplasmic or nuclear adhesion receptors.
 - D. extracellular receptors, which may be structural proteins, signaling molecules, or soluble cytokines such as TNF- α .

6. **All of the following statements related to Phase I biotransformation are correct EXCEPT one. Which one is the exception?**
- A. Requires specific transfer-enzymes and conjugation to endogenous substances.
 - B. Requires participation of NADPH-reductase to reduce ferric (Fe³⁺) to ferrous (Fe²⁺) iron.
 - C. Is increased in the elderly.
 - D. Metabolites are usually active.
7. **The graded dose-response curve demonstrates the average effect of a drug, as a function of its dose, in a population of individuals from which three important parameters can be deduced: effectiveness, toxicity, and lethality.**
- A. True
 - B. False
8. **A drug that favors binding to its active receptor, stabilizes its active conformation, and produces a pharmacological effect is called _____.**
- A. an agonist.
 - B. an inverse agonist.
 - C. a full agonist.
 - D. a partial agonist.
9. **All of the following statements related to an antagonist are correct EXCEPT for one. Which one is the exception?**
- A. A receptor antagonist can bind the agonist binding site or an allosteric site, i.e., a site different from the agonist site, on a receptor.
 - B. Binding of an antagonist to the active site prevents the binding of the agonist to the receptor.
 - C. Binding of an antagonist to an allosteric site either alters the agonist's affinity for its binding site or prevents the conformational change required for receptor activation.
 - D. A physiologic antagonist inactivates an agonist by modifying or sequestering it before it has the opportunity to act.
10. **All of the following statements related to the ability of drugs to diffuse through lipid bilayer membranes is correct EXCEPT for one. Which is the exception?**
- A. Most small, nonpolar, lipophilic molecules are able to diffuse through lipid bilayer membranes along the concentration gradient by passive diffusion until equilibrium is reached.
 - B. Net diffusion of acidic and basic drugs is affected by a charge-based phenomenon known as pH trapping, which depends on a drug's acid dissociation constant (pKa) and the pH of the biological environment.
 - C. The pKa of a drug is defined as that pH of a biological medium at which 50% of the drug is protonated (i.e., electrically neutral) and 50% is deprotonated (i.e., electrically negative).
 - D. Protein channels or carrier proteins may facilitate the transport of some drugs down their concentration gradient by energy-independent active transport.
11. **During the first 90 days (first trimester), organogenesis occurs and thus the fetus is most susceptible to teratogenesis.**
- A. True
 - B. False

- 12. All of the following statements related to the fate of drugs in the vascular compartment are correct EXCEPT for one. Which is the exception?**
- A. Once a drug has been absorbed into the systemic circulation (vascular compartment), it is then capable of reaching any target organ by the process of distribution.
 - B. The volume of distribution (V_d) reflects the extent to which a drug is partitioned between plasma and various other tissue compartments.
 - C. The V_d is high for drugs that are retained within the vascular compartment and low for drugs that are highly distributed to adipose tissue and various other tissue compartment.
 - D. Plasma protein binding reduces the availability of free drug for diffusion or transport into other tissues because, in general, only the free or unbound fraction of a drug is capable of crossing biological membranes.
- 13. All of the following statements related to xenobiotics, substances that are not naturally found in the body EXCEPT for one. Which is the exception?**
- A. Unexcretable drugs and unexcretable active, inactive or toxic metabolites of drugs must be converted to excretable metabolites by processes called drug metabolism.
 - B. The most common pathway of oxidation/reduction reactions that modify the structure of drugs involve the hepatic microsomal cytochrome P450 enzymes.
 - C. Oxidation/reduction reactions more commonly convert drugs to large, polar molecules in order to inactivate them and to enhance their clearance.
 - D. Many drugs induce or inhibit enzymes associated with biotransformation, a phenomenon important in understanding drug-drug interactions.
- 14. All of the following statements related to the elimination of drugs from the body are correct EXCEPT for one. Which is the exception?**
- A. A small number of drugs are excreted in the bile, or through the respiratory and dermal routes; however, most drugs are eliminated through renal excretion.
 - B. Most drugs demonstrate first-order kinetics, i.e., metabolic and clearance rates fail to increase with increasing plasma drug concentrations.
 - C. The amount of time over which a drug's concentration in plasma decreases to one-half of its original value because of metabolism and excretion kinetics is known as the elimination half-life ($t_{1/2}$) of the drug.
 - D. It takes four $t_{1/2}$ for tissue distribution and plasma concentration of a drug to reach steady-state.
- 15. A loading dose, i.e., a much higher initial dose than would be required if the drug were retained in plasma, may be used to achieve therapeutic levels with only one or two doses of drug.**
- A. True
 - B. False
- 16. All of the following statements related to the individual effective dose are correct EXCEPT for one. Which is the exception?**
- A. Factors such as age, gender, underlying disease, and genetic variations determine the individual effective dose of a drug required to produce a specific response and determine the success or failure of therapy.
 - B. Genomic variations can affect oxidation/reduction and conjugation/hydrolysis reactions causing inter-individual pharmacodynamic variations.
 - C. Because of genomic variations, an individual may be hyporeactive, i.e., a drug's usual effect is produced at an unexpectedly high dose or hyperreactive, i.e., the usual effect of a drug is produced at an unexpectedly low dose.
 - D. Tolerance that develops rapidly, following the administration of only a few doses of a drug, is referred to as tachyphylaxis

- 17. Which of the following statements related to determining the optimum therapeutic dose of a drug for an individual is correct?**
- A. The individual effective dose of a drug intended to produce a specific effect is usually expressed in terms of milligram per kilogram of body weight.
 - B. Manufacturers' maximum recommended dose (MRD), by definition, is for a 75 kg (165 lbs.) healthy adult.
 - C. In determining the therapeutic dose of a drug for an individual one must consider such as dynamic and kinetics variables related to a specific patient.
 - D. All of the above.
- 18. Milk is generally more acidic (pH 6.8) than plasma (pH 7.4); therefore, acidic drugs become more concentrated in milk because of the phenomenon of pH trapping, while basic drugs are limited in their ability to enter milk.**
- A. True
 - B. False
- 19. All of the following statements related to drugs and the pediatric patient population are correct EXCEPT one. Which is the exception?**
- A. Often there is a paucity of specific pharmacokinetic and pharmacodynamic data for the pediatric population.
 - B. Dosage forms designed with the adult population in mind and the dosages can be easily be individualized for children.
 - C. Although there are many rules and formulae to calculate drug dosages for children, weight-based dosing recommendations by manufacturers provide the most reasonable approach.
- 20. If drug "X" has a half-life of 12 hours, how long does it take for it to be eliminated from the body?**
- A. 10 hour
 - B. 14 hour.
 - C. 24 hours
 - D. 2.5 hours
- 21. All of the following statements related to drugs and the patient with liver disease are correct EXCEPT one. Which is the exception?**
- A. In the presence of liver disease, adverse drug effects are primarily related to altered pharmacokinetic processes.
 - B. To estimate the ability of the liver to metabolize drugs, determine the patient's Child-Pugh score.
 - C. A Child-Pugh score of 5 indicates normal liver function, whereas a score of 15 indicates extreme dysfunction
 - D. A score of ≤ 7 is grounds for a moderate decrease ($\approx 25\%$) in the daily dose of a drug.
- 22. All of the following statements related to drugs and the patient with chronic renal disease are correct EXCEPT for one. Which is the exception?**
- A. Drug dosages are most commonly based on the estimated creatinine clearance determined by the Cockcroft-Gault equation, i.e., the eCrCl.
 - B. It is of note that after 20 years of age, eCrCl is increased by 6.5 mL/min every 10 years.
 - C. If the eCrCl is >50 mL/min, no dosage adjustment is required.
 - D. If the eCrCl is <10 mL/min, some drugs should be reduced by up to 75%, while others should be avoided.

- 23. All of the following statements related to non-adherence are correct EXCEPT one. Which is the exception?**
- A. Non-adherence can be intentional (actively choosing not to adhere) or unintentional (e.g., passively inconsistent medication-taking behavior including forgetfulness or carelessness).
 - B. Determinants of non-adherence include the disease, the patient, the practitioner, the treatment regimen, economic factors, and the interaction of each of these factors.
 - C. The longer the duration of treatment, the more likely it is that the patient will adhere to the regimen over time.
 - D. Common causes of non-adherence in elderly patients include failure to fill prescriptions, difficulty in opening packages or swallowing pills, poor memory, visual or hearing impairment, transportation problems, and expense.
- 24. Legend drugs require a prescription because they are considered to be potentially harmful if not used under supervision by a licensed practitioner who must be registered under Controlled Substances Act of 1970 with the Drug Enforcement Administration**
- A. True**
 - B. False
- 25. Before prescribing a drug, a licensed practitioner must establish an accurate diagnosis whenever possible; although, at times one may prescribe medications based on a presumptive or working diagnosis.**
- A. True
 - B. False
- 26. All of the following statements regarding polypharmacology are true EXCEPT one, which is the exception?**
- A. It is defined as taking at least nine prescription medications.
 - B. Its incidence is significantly higher in the elderly population.
 - C. It is only due to self-medications (e.g., over the counter medications)
 - D. It can result in a gradual accumulation of side effects and/or adverse drug reactions.
 - E. It may be due to multiple physicians and pharmacies.
- 27. Which of the following statements regarding prescribing during pregnancy is correct?**
- A. Drugs in category A are considered safe.
 - B. Drugs in Category B are to be prescribed cautiously.
 - C. Drugs in category C can never be prescribed.
 - D. Drugs in category D are considered safe.
- 28. When prescribing a controlled substance, in addition to writing the number of tablets or capsules to be dispensed, the amount must also be written-out longhand, e.g., Disp #20 (twenty) tablets.**
- A. True
 - B. False

References

1. FDA. Milestones in U.S. Food and Drug Law History. 2018 Feb 01. Accessed March 21, 2019.
2. FDAReview.org. History of Federal Regulation: 1902-Present. Independent Institute. Accessed March 21, 2019.
3. U.S. Department of Justice. DEA. Office of Diversion Control. Controlled Substance Schedules. Accessed March 21, 2019.
4. ClinCalc DrugStats Data Base. Accessed March 21, 2019.
5. FDA. CFR - Code of Federal Regulations Title 21, Part 201. Labeling. Revised April 1, 2018. Accessed March 21, 2019.
6. NIH. U.S. National Library of Medicine. DailyMed. Accessed March 21, 2019.
7. Alenghat FJ, Golan DE. Drug-receptor interactions. Principles of Pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 2-16.
8. Baca QJ, Golan DE. Pharmacodynamics. Principles of Pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 17-26.
9. Baca QJ, Golan DE. Pharmacokinetics. Principles of Pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 27-42.
10. Ersoy BA, Hoffmaster KA. Drug transporters. Principles of Pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 56-68.
11. Guengerich FP. Drug metabolism. Principles of Pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 43-54.
12. Dahlin A, Tantisira K. Pharmacogenomics. Principles of Pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 87-95.
13. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-649.
14. Cholongitas E, Papatheodoros GV, Vangeli M, et al. Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther*. 2005 Dec;22(11-12):1079-89. doi: 10.1111/j.1365-2036.2005.02691.x.
15. Boursier J, Cesbron E, Tropet AL, et al. Comparison and improvement of MELD and Child-Pugh score accuracies for the prediction of 6-month mortality in cirrhotic patients. *J Clin Gastroenterol*. 2009 Jul;43(6):580-5. doi: 10.1097/MCG.0b013e3181889468.
16. NIH. CKD and Drug Dosing: Information for Providers. Estimation of Kidney Function for Prescription Medication Dosage in Adults. 2015 Apr. Accessed on March 21, 2019.
17. Mukhtar O, Weinman J, Jackson SH. Intentional non-adherence to medications by older adults. *Drugs Aging*. 2014 Mar;31(3):149-57. doi: 10.1007/s40266-014-0153-9.
18. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: How unintentional is it really? *BMC Health Serv Res*. 2012 Jun 14;12:98. doi: 10.1186/1472-6963-12-98.
19. Clark N, Jones P, Keller S, et al. Patient factors and compliance with asthma therapy. *Respir Med*. 1999 Dec;93(12):856-62.
20. Gellad WF, Grenard JL, Marcum ZA. A Systematic Review of Barriers to Medication Adherence in the Elderly: Looking Beyond Cost and Regimen Complexity. *Am J Geriatr Pharmacother*. 2011 Feb;9(1):11-23. doi: 10.1016/j.amjopharm.2011.02.004.
21. Master list of medical abbreviations. Accessed March 21, 2019.
22. Pollock M, Bazaldua OV, Dobbie AE. Appropriate prescribing of medications: an eight-step approach. *Am Fam Physician*. 2007 Jan 15;75(2):231-6.
23. British Pharmacological Society. Ten Principles of Good Prescribing. Accessed March 21, 2019.
24. Conner MW, Dorian-Conner C, Vaidya VS, et al. Drug toxicity. Principles of pharmacology: The pathophysiologic basis of drug therapy, 4th edition. David E. Golan (Ed). Philadelphia, PA. Wolters Kluwer. 2017. 70-86.

25. Williams KA, Taifour ML. Adverse Drug Reactions - Part I. dentalcare.com. Accessed on March 21, 2019.
26. Williams KA, Taifour ML. Adverse Drug Reactions - Part II. dentalcare.com Accessed on March 21, 2019.
27. Ouanounou, A. & Haas, D. A. Pharmacotherapy for the Elderly Dental Patient. *J Can Dent Assoc* 80 (2015).
28. Nobili, A, Garattini S, Mannucci PM. Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. *J Comorbidity*. 2011;1(1):28-44
29. Wawruch M, Kuzelova M, Foltanova T, Ondriasova E, Luha J, Dukat A, et al. Characteristics of elderly patients who consider over-the-counter medications as safe. *Int J Clinical Pharm*. 2013;35(1):121-8.
30. de Souza Silva JE, Santos Souza CA, da Silva TB, Gomes IA, Brito G de C, de Souza Araújo AA, et al. Use of herbal medicines by elderly patients: a systematic review. *Arch Gerontol Geriatr*. 2014;59(2): 227-33.
31. Pasina L, Djade CD, Nobili A, Tettamanti M, Franchi C, Salerno F, et al. Drug-drug interactions in a cohort of hospitalized elderly patients. *Pharmacoepidemiol Drug Saf*. 2013;22(10):1054-60.
32. Hofer-Dueckelmann C, Prinz E, Beindl W, Szymanski J, Fellhofer G, Pichler M, et al. Adverse drug reactions (ADRs) associated with hospital admissions — elderly female patients are at highest risk. *Int J Clin Pharmacol Ther*. 2011;49(10):577-86.
33. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patient. *Br J Clin Pharmacol*. 2004;57(2):121-6.
34. Lynn SJ. Adverse drug reactions in the elderly: can we stem the tide? *Am Nurs Today*. 2012;7(1):34-40.
35. Ouanounou, A and Haas, D. Drug therapy during pregnancy: implications for dental practice. *Br Dental J*. 2016. volume 220, pages413-417.
36. Maged M C . Physiologic and pharmacokinetic changes in pregnancy. *Front Pharmacol* 2014; 5: 1-5.
37. Mitchell A A, Hernadez-Diaz S, Louik C et al. Medication use in pregnancy. *Pharmacoepidemiol* 2001; 10: S146.
38. Andrade S E, Gurwitz J H, Davis R L et al. Prescription drug use in pregnancy. *Am J Obstet Gynecol* 2004; 191: 398-407.
39. Yanamandra N, Chandraharan E . Anatomical and physiological changes in pregnancy and their implications in clinical practice. In Chandraharan E, Arulkumaran S (eds) *Obstetric and Intrapartum Emergencies*. Cambridge: Cambridge University Press, 2012.
40. Giglio, J A, Lanni S M, Laskin D M et al. Oral health for the pregnant patient. *JCDA* 2009; 75: 43-48.
41. Dawes M, Choiencyk P J . Pharmacokinetics in pregnancy. *Clin Obst Gyna* 2001; 15: 819-826.

Additional Resources

- No Additional Resources Available

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