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. Terézhalmay has done consulting work for Procter & Gamble and has served on the dentalcare.com Advisory Board.

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 the 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. 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. 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.

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. The FDA has specific requirements on content and format of labeling for human prescription drugs and biological products (Table 1). 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. 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
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
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).
intracellular regions and activate signaling molecules called G proteins: **G-stimulatory** \( (G_s) \) activates \( Ca^{2+} \) channels and adenyl cyclase, **G-inhibitory** \( (G_i) \) activates \( K^+ \) channels and inhibits adenyl cyclase, \( G_o \) inhibits \( Ca^{2+} \) channels, \( G_a \) activates phospholipase C, and \( G_{12/13} \) affects diverse ion transporters.

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. 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 \( ED_{50} \).
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.
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.

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, β1-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. 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 faction 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%
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.
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 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 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 developed **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 and the fetus.** Each drug appears to have a threshold concentration above which fetal abnormalities can occur and below which no adverse effects are discernible. Whether a drug reaches threshold concentrations in the fetus depends on a drug's ability to translocate across the placental barrier. Genetic determinants of both the mother and the fetus will influence the extent to which a drug will affect the developing fetus.

Malformations are usually the result of fetal exposure to a drug during the first trimester. Exposure during the second and third trimesters primarily affects organ function. However, it is paramount to recognize that human teratogenicity is not predictable. Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions”, and “Adverse Effects” sections, and “Pregnancy” subsection of specific drug labeling.

**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.

**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.

**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. 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 “Pediatric” subsection of specific drug labeling.

**Geriatric patients.** The use of drugs in elderly patients is another challenging area of clinical practice. The pharmacokinetics and pharmacodynamics of drugs are altered by age-related physiologic changes. The increased incidence of multiple chronic illnesses, the disproportionately high use of prescription and over-the-counter medications, inadequate nutrition, and poor adherence also contribute to the problem and lead to more adverse drug effects among the elderly.

Therapeutic target concentrations of drugs in the elderly population are also difficult to define because of marked inter-individual variations. Conservative dosing and close monitoring for dose-related effects is imperative. Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions” and “Adverse Effects” sections, and “Geriatric use” subsection of specific drug labeling.
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 be avoided.

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

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

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 in mL/min = (140 - age x weight in kg x 0.85 (for females) ÷ Scr in mg/dL x 72). 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 be avoided. Prescribing precautions can be found in the “Dosage and Administration,” “Contraindications,” “Warning and Precautions” and “Adverse Effects” sections of specific drug labeling.

Non-adherence. It is a generally accepted that many patients do not adhere to their prescribed therapeutic regimen. 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, the patient's health beliefs, the patient's social support, the patient's medication-related beliefs, and the patient's medication-related behaviors.

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

<table>
<thead>
<tr>
<th>Tests/Symptoms</th>
<th>Score 1 point each</th>
<th>Score 2 points each</th>
<th>Score 3 points each</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin in mg/dL</td>
<td>&lt; 2.0</td>
<td>2.0-3.0</td>
<td>&gt; 3.0</td>
</tr>
<tr>
<td>Serum albumin in mg/dL</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombin time in seconds over control or the INR</td>
<td>&lt; 4 (INR: &lt; 1.7)</td>
<td>4-6 (INR: 1.7-2.3)</td>
<td>&gt; 6 (INR: &gt; 2.3)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Moderate</td>
<td>Severe</td>
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- 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 (≥25%) in the daily dose.
- A score of ≥ 10 indicates a need for significant decrease (≥50%) in daily dosing.
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/caretaker 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.

**Prescriptons.** Drugs fall into two major categories: non-prescription, i.e., over-the-counter, and prescription drugs. 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. 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 a particular time. It has three components: a heading, a body, and a closing (Figure 9).

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 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:

**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). A 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 drugs-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/professional-education/ce-courses/ce580/start-test

1. **All of the following statements related to important historical milestones in U.S. Food and Drug Laws are correct EXCEPT which one?**
   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. **Which of the following statements related to the DailyMed website is correct?**
   A. The DailyMed website, operated by the U.S. National Library of Medicine, is the official provider of FDA label information.
   B. The DailyMed website 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.
   C. The labeling information on the DailyMed website is the most recent submitted to and approved by the FDA and includes strengthened warnings undergoing FDA review.
   D. All of the above.

4. **All of the following statements related to drug-receptor binding are correct EXCEPT which one?**
   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 which one? 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. Which of the following statements related to the favorability of a drug-receptor interaction is correct?
   A. The favorability of a drug-receptor interaction is referred to as the affinity of the drug for its binding site on the receptor.
   B. Affinity, predicated on the intrinsic properties of any given drug-receptor pair, is expressed by the dissociation constant ($K_d$).
   C. $K_d$ is defined as that concentration of a drug at which 50% of the available receptors are occupied.
   D. All of the above.

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 which one?
   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 which one?
    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. A drug's bioavailability, i.e., the fraction of administered drug that reaches the systemic circulation may be affected by ____________.
    A. a drug's formulation.
    B. route of drug administration.
    C. first-pass metabolism.
    D. All of the above.
12. All of the following statements related to the fate of drugs in the vascular compartment are correct EXCEPT which one?
   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 (Vd) reflects the extent to which a drug is partitioned between plasma and various other tissue compartments.
   C. The Vd 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 which one?
   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 which one?
   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 (t1/2) of the drug.
   D. It takes four t1/2 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 which one?
   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. All of the following statements related to pregnancy and the effects of drugs on the fetus are correct EXCEPT which one?
   A. Each drug appears to have a threshold concentration above which fetal abnormalities can occur and below which no adverse effects are discernible.
   B. Whether a drug reaches threshold concentrations in the fetus depends on a drug's ability to translocate across the placental barrier.
   C. Malformations are usually the result of fetal exposure to a drug during the second and third trimesters primarily affects organ function.
   D. It is paramount to recognize that human teratogenicity is not predictable.

19. 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

20. All of the following statements related to drugs and the pediatric patient population are correct EXCEPT which one?
   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.

21. Which of the following statements related to drugs and the elderly is correct?
   A. The pharmacokinetics and pharmacodynamics of drugs are altered by age-related physiologic changes.
   B. The increased incidence of multiple chronic illnesses, the disproportionately high use of prescription and over-the-counter medications, inadequate nutrition, and poor adherence lead to more adverse drug effects among the elderly.
   C. Therapeutic target concentrations of drugs in the elderly population are difficult to define because of marked inter-individual variations.
   D. All of the above.
22. All of the following statements related to drugs and the patient with liver disease are correct EXCEPT which one?
   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 $\leq 7$ is grounds for a moderate decrease ($\approx 25\%$) in the daily dose of a drug.

23. All of the following statements related to drugs and the patient with chronic renal disease are correct EXCEPT which one?
   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.

24. All of the following statements related to non-adherence are correct EXCEPT which one?
   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.

25. 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

26. A prescription ____________.
   A. 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 a particular time
   B. has three major components: a heading, a body, and a closing
   C. identifies 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
   D. All of the above.

27. 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
28. **When prescribing a drug** ___________.
   A. be aware of evidence-based recommendations developed by Federal and state agencies, and professional organizations, e.g., opioid prescribing guidelines
   B. prescribe only the necessary quantity of a drug to a patient and balance specific drug selection considering the needs of the patient and cost
   C. use reliable informational resources, e.g., DailyMed
   D. All of the above.

29. **Which of the following statements related to the writing of unambiguous prescriptions is correct?**
   A. When the unit dose is 1 gram or more it should be written in grams, e.g., write 2 g, not 2000 mg.
   B. 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.
   C. When writing dosage strength, always use leading zeros, e.g., write 0.5 ml versus .5 ml, which can be mistaken for 5 ml. and avoid trailing zeroes, e.g., write 5 mg versus 5.0 mg, which can be mistaken for 50 mg.
   D. All of the above.

30. **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

Additional Resources
• No Additional Resources Available

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