1

Introduction to Pharmacology

1.1 Definition of Terms

Absorption	the movement of a drug from its site of administration into the systemic circulation.
Adverse drug event (ADE)	injury resulting from the use of a drug. It is an unfavorable and unintentional response resulting from an administered medication. Includes medication errors such as miscalculation of dosage or misreading a prescription by the pharmacist, doctor, and/or patient.
Adverse drug reaction (ADR) (also known as side effect)	harm to the body due to a medication that was properly prescribed (e.g., drug taken at normal doses and via the correct route of administration), or an allergic reaction to a drug. There is a causal relationship between the drug and an ADR.
Affinity	the ability of a drug to bind to the receptor to cause a therapeutic response.
Antibiotic prophylaxis	antibiotic given to prevent an infection.
Bioavailability	the amount of a drug (expressed as a percentage) that reaches the systemic circulation. For example, any drug administered intravenously has 100% bioavailability
Biologics	agents that are naturally produced in an animal or human body.
Clearance	quantitative measure of the rate of drug elimination from the body divided by the concentration.
Creatinine	a waste product in skeletal muscle produced by the breakdown of creatinine phosphate.
Creatinine clearance (CrCl)	a test that compares the level of creatinine in the urine with that of creatinine in the blood and determines normal functioning of the kidneys.
Cytochrome P450 (CYP) enzymes	found primarily in the liver and are responsible for the metabolism of many drugs. Many drug interactions occur because some drugs are inhibitors or inducers of the substrate (drug being metabolized) resulting in high or low blood levels of one or the other drug.

The Dentist's Drug and Prescription Guide, Second Edition. Mea A. Weinberg, Stuart J. Froum and Stuart L. Segelnick.

Distribution movement of a drug through the body to the various target tissues/organs (site of action) after entering the bloodstream.

Dosage the amount of drug required to produce the desired effect.

Dose the amount of drug taken at any one time.

Drug any substance which changes a physiological function or modifies a disease process.

Drug action the response of living matter to administered chemicals. Levels of drug action include cellular or molecular. Cellular site of drug action is defined as all foreign parts that enter the body will react with at least one portion of the cell. The initial reaction occurs here. At the molecular level, the molecules of the drug will react with the molecules of the body.

Efficacy the ability of a drug to stimulate the receptor and produce the maximum response achievable by the drug. Two drugs can have the same efficacy but different potencies where one drug is more potent (lower dose required to produce desired effect) than the first drug but both will have the same effect.

Elimination half-life ($t_{½}$) the time required to reduce the amount of drug in the body or concentration of drug in blood by 50%. However, once the first 50% is gone, it will take the body more time to clear 50% of the remaining medication. Usually, it takes about five half-lives to clear 99% of the medication. To determine the time it takes for a drug to be 99% eliminated from the body, multiply the half-life of the drug by five.

First-pass effect (or first-pass metabolism) before an orally administered drug enters the systemic circulation, it goes to the liver to be metabolized or biotransformed. Some oral drugs can undergo extensive first-pass effect so that they are ineffective by the time of entering the bloodstream while other drugs undergo little first-pass effect and maintain their original efficacy. Drugs that undergo extensive first-pass effect cannot be given orally because they become pharmacologically ineffective by the time they enter the general circulation. Lidocaine is an example of a drug that cannot be given orally because it undergoes extensive first-pass effect.

First-order kinetics the rate of drug elimination decreases with time. That is, the rate of drug elimination falls as the concentration falls. Most drugs are removed from the body by first-order kinetics.

Loading dose (LD) an initial higher dose of a drug that may be given at the beginning of a course of treatment (to more quickly reach adequate plasma levels) before dropping down to a lower maintenance dose (MD) afterwards. A LD is given on the first day of drug treatment.

Maintenance dose (MD) a lower drug dose that keeps the plasma drug concentration continuously within the therapeutic range. The MD is given starting after the LD on day 1 of drug therapy and is usually half the dose of the LD.

Metabolism (biotransformation) the primary mechanism of drug elimination from the body. Biotransformation will usually end the pharmacological action of the drug.

Pharmacodynamics	describes how the drug works, its mechanism of action. How a drug interacts with receptors and what happens once the drug binds to the receptor.
Pharmacogenetics	the convergence of pharmacology and genetics that deals with genetic factors that influence an organism's response to a drug.
Pharmacognosy	study of drugs derived from herbal and other natural sources.
Pharmacokinetics	study of the action of a drug once it is in the patient. It describes the absorption, distribution, metabolism, and elimination of the drug from the body
Pharmacology	the science dealing with drugs and their interaction with the body's components.
Pharmacotherapeutics	the medical use of drugs in the prevention, diagnosis, and treatment of diseases.
Polypharmacy	when many different medications including over-the-counter (OTC) and prescription drugs are taken by the patient.
Potency	strength of the drug relative to therapeutic effect.
Prodrug	a drug that becomes active only after it is ingested and metabolized in the liver. Codeine is converted from an inactive form to the pharmacologically active form morphine by first-pass metabolism.
Protein binding	attachment of a drug to proteins in the plasma. Drugs that are protein bound are inactive and become active in the free unbound form.
Steady state	the point at which the rate of drug input into the body is equal to the rate of elimination. As such, the amount or concentration in the body reaches a plateau.
Therapeutic index (TI)	a measure of the relative safety of a drug. For example, lithium has a narrow TI so if the plasma levels are slightly above the therapeutic range, toxicity can occur quickly. Patients must be on chronic lithium maintenance treatment to avoid toxicity. On the other hand, penicillin has a wide TI so that slightly more than the usual dose will not cause toxicity.
Therapeutic range	the dosage range of a drug that achieves the desired pharmacological response.
Therapeutics	branch of medicine that deals with the treatment of disease.
Toxicology	study of poisons and poisonings.
Zero-order kinetics	the drug is removed at a constant rate regardless of the drug concentration; it is linear with time. The elimination from the body of a large concentration of alcohol is an example of a drug that follows zero-order kinetics. (Gossel 1998a,b; Weinberg 2013).

1.2 Pharmacokinetics

Q. What is the definition of pharmacokinetics and why is it important to know?

A. Pharmacokinetics describes the actions of the drug as it moves through the body and how the body influences drug concentrations. It is easiest to remember pharmacokinetics by the acronym: ADME (A = absorption into the systemic circulation; D = distribution to the target tissues

and organs; M = metabolism or biotransformation; E = elimination from the body). It is important to know the basics of pharmacokinetics in order to understand the basic principles of prescribing medications (Doogue and Polasek 2013). Pharmacokinetics (e.g., absorption of the drug into the blood) may be altered when certain antibiotics prescribed in dentistry are taken with food. Instructions must be verbally expressed to the patient and documented in the patient's chart on how to take medications that are prescribed by dentists (e.g., antibiotics, antimicrobial agents, analgesics, antifungal agents, antiviral agents, fluorides).

Q. What factors affect the rate of drug absorption?

A. In the gastrointestinal tract, many factors can influence the rate of drug absorption into the systemic circulation such as acidity of the stomach and food in the stomach. Some medications used in dentistry should be taken with food to reduce gastrointestinal irritation, some medications should be taken on an empty stomach because the food could delay the absorption of the drug, and some can be taken with or without food because food does not interfere with absorption. Usually, the absorption of the total amount of drug is not reduced but rather it will just take longer to be absorbed. Usually, antibiotics have the most restrictions regarding taking with meals. Nonsteroidal antiinflammatory drugs such as ibuprofen must be taken with food to avoid gastric irritation. Specific drugs will be discussed within the relevant chapters.

Q. What does "take on an empty stomach" mean?

A. "Take on an empty stomach" means to take the drug within one hour before eating or two hours after eating. Take on an empty stomach is not interpreted as not eating.

Q. What is the pharmacokinetics of an orally administered drug?

A. The pharmacokinetics of a drug administered orally such as penicillin VK is as follows (Gossel 1998a,b; Weinberg 2013).

1) An orally administered drug is swallowed and goes down the esophagus. It is important to take a tablet/capsule with a full glass of water to facilitate its passage through the esophagus into the stomach.
2) In the stomach, the tablet/capsule must be released or liberated from its formulation. Once a tablet is "broken up" and a capsule is "opened," and the active ingredients are released, there is dissolution of the drug from the liberated drug particles. Some acidic drugs are enteric coated to protect the stomach lining. Dosage forms such as syrups or solutions are liquids, which are immediately available for absorption and transport. A liquid gel capsule (Aleve®, Advil®) is formulated to dissolve quickly, allowing the liquid inside the capsule to be absorbed fast.
3) Drug goes into the upper part of the small intestine (duodenum) where most absorption into the systemic circulation occurs. This is because the small intestine has a large surface area due to microvilli, through which drugs may diffuse.
4) From the small intestine, the drug molecules are absorbed into the bloodstream. Many factors can affect the rate and extent of drug absorption, including foods and minerals. For example, tetracycline should not be given at the same time as dairy products or minerals (e.g., iron, calcium, magnesium) because insoluble complexes form in the intestinal tract, which slows down absorption. This can be avoided by taking the tetracycline 1–2 hours before or after the dairy/mineral product. Some antibiotics (e.g., tetracycline) must be taken

on an empty stomach (one hour before or two hours after meals), which increases the rate of absorption. Most antibiotics can be taken without regard to meals (with or without food) but if stomach upset occurs, these antibiotics can be taken with food (Huang et al. 2009).

5) Absorption occurs when a drug is in a nonionized or charged form and if it is more lipid soluble. Most drugs are combined with a salt to enhance absorption (e.g., lidocaine HCl, tetracycline HCl, doxycycline hyclate, amoxicillin trihydrate).
6) Before an orally administered drug reaches the systemic circulation, it goes to the liver via the portal vein whereby it is immediately exposed to metabolism by liver enzymes (Huang et al. 2009). This first exposure is referred to as the *first-pass effect*. Some drugs such as lidocaine and morphine that undergo extensive first-pass embolism will become inactive so they cannot be given orally. Diazepam (Valium®) has close to 100% bioavailability (low first-pass metabolism) so it has similar oral and intravenous doses. Alternate routes of drug administration that bypass the first-pass effect include sublingual, rectal, and parenteral (intravenous, intramuscular, subcutaneous) (Fagerholm 2007; Pond and Tozer 1984; Robertson 2017).
7) Once it reaches systemic circulation, the drug is distributed in the blood to the various organs. Many drugs are bound to circulating proteins such as albumin (acidic drugs) and glycoproteins (basic drugs). Highly protein-bound drugs are not active and only the free drug that is not bound to proteins is active.
8) Once the drug has exerted its actions, it must then be eliminated from the body. The first part of drug elimination involves *metabolism* or *biotransformation*, which occurs mostly in the liver. It may take a drug several passes through the liver before it is entirely metabolized. Biotransformation converts lipid-soluble drug molecules to metabolites or end-products that are more water soluble and therefore easier to eliminate from the body. Most of the conversion of drugs occurs in the liver by metabolizing enzymes called microsomal enzymes. These enzymes, which are also called *cytochrome P450 (CYP)* enzymes, are the primary enzymes responsible for the oxidation of many drugs. There are many different isoenzymes for different drugs (e.g., CYP3A4 is involved with many dental drugs). Many drug–drug and drug–food interactions occur via the microsomal enzymes. Some *prodrugs* have no pharmacological activity unless they are first metabolized to the active form in the body (e.g., codeine is metabolized by the liver enzyme CYP2D6 to the active morphine) (Weinberg 2013).
9) *Drug elimination*: now the more water-soluble metabolite must be eliminated from the body. The main route of drug elimination is excretion via the kidneys so diseases of the kidney can significantly prolong the duration of drug action. Therefore, dosage adjustments may be needed from the patient's physician. Some elimination occurs through the lungs, breast milk, sweat, tears, feces, and bile. Some drugs (e.g., tetracycline) undergo biliary excretion whereby the drug is eliminated in the bile and enters the small intestine and eventually leaves the body in the feces. Most bile is then circulated back to the liver by *enterohepatic recirculation* and eventually metabolized by the liver and excreted via the kidneys. This route of reabsorption is helpful in prolonging the activity (increasing the half-life) of some antibiotics (Weinberg 2013).

Q. What is the definition of drug absorption?

A. Drug *absorption* is the movement of a drug from the site of administration to the systemic circulation.

Q. What does it mean when a drug has 100% bioavailability?

A. *Bioavailability* describes the portion of an administered drug that reaches the systemic circulation. It is the rate and extent of absorption and how fast and how much of the drug is absorbed. It indicates that the drug is 100% absorbed into the blood. Only intravenously administered drugs have 100% bioavailability because 100% of the drug enters directly into the blood. A drug administered orally that undergoes extensive first-pass metabolism (or first-pass effect) by traveling first to the liver, where it is metabolized, and can become almost inactive by the time it reaches the systemic circulation, is a drug with low bioavailability.

Q. What is the first step involved in drug absorption?

A. The first step before a drug can be absorbed in the small intestine is disintegration of the dosage formulation into a formulation that can easily be absorbed. The stomach might be expected to be the first site of absorption but in reality, very little absorption occurs in the stomach because the surface area is very small. A tablet must break up to expose the active ingredient, which takes some time. A capsule must open up, which takes less time than a tablet. A solution is already in a liquid, easily absorbed form and takes the least time for disintegration and absorption. The order of bioavailability is oral solution > oral suspension > capsule > tablet (Lloyd et al. 1978).

Q. Is there any systemic absorption of a topical anesthetic applied on the surface of the gingiva?

A. Yes. The purpose of topical agents is to maximize the concentration of the drug at the target site while minimizing potential systemic adverse effects. Although drug absorption is not desired, there could be some systemic absorption, especially if the agent is applied on abraded gingiva or skin. Because of its lipophilic nature, the stratum corneum of the skin may act as a reservoir for many drugs. Consequently, the local effects of the drug may persist long enough to allow once-daily application. For example, once-daily application of corticosteroid preparations is as effective as multiple applications in most circumstances. Direct access to the skin may predispose the patient to frequent topical applications, increasing the risk of systemic adverse effects.

Q. How does a drug get absorbed into the systemic circulation?

A. A drug must pass through many cell membranes to get into the blood. A drug must have some water solubility to go through aqueous fluids and some lipid solubility to get through the cell membrane, which is composed of two layers of phospholipids.

Q. What is the purpose of epinephrine added to local anesthetics?

A. Epinephrine is a vasoconstrictor that acts to constrict blood vessels to decrease blood flow in the submucosal area via activating alpha-1 receptors (Becker and Reed 2012). This allows the anesthetic solution to stay at the site of action longer, which slows absorption of the anesthetic solution.

Q. What is drug distribution and what factors affect distribution?

A. Drug *distribution* is the movement of an agent through the blood or lymph to various sites of action in the body. An important factor affecting drug distribution is *protein binding*. Many drugs in the blood are bound to circulating proteins such as albumin for acidic drugs (e.g., penicillin, barbiturates, aspirin, vitamin C) and acid glycoproteins and lipoproteins for basic

drugs (e.g., narcotic analgesics, erythromycin). When drugs are bound to plasma proteins, they are inactive while circulating in the blood. This binding to proteins is temporary, reversible, and can convert to free drug. Only drugs that are not bound to plasma proteins are "freely active" and bind to specific receptors on the target tissue/organ. Another factor that affects drug distribution is blood flow to the target organs.

Q. What is the minimum effective concentration (MEC) of a drug?

A. The *minimum effective concentration (MEC)* is the amount of drug required to produce a therapeutic effect. This is important to know because a drug should not be given above the MEC as this will produce toxic concentrations. The ideal concentration of a drug should be between the MEC and the toxic concentration. This is referred to as the *therapeutic range*. For example, after periodontal surgery, it is recommended that the patient take ibuprofen (Motrin®, Nuprin®). If the patient decides to take only one 200 mg tablet during the day, they will still experience pain because the therapeutic range was not reached. The patient should take two or three tablets which will increase the plasma level of ibuprofen into the therapeutic range. If the patient takes five or more tablets at one time, then adverse effects may occur because the plasma level of ibuprofen is outside the therapeutic range and the maximum dose has been exceeded. Beyond the maximum dose, the analgesic effect does not increase.

Q. What does the term "dose" mean?

A. The *dose* of a drug is the amount of drug taken at any one time. Dose is expressed as the weight of drug (e.g., 500 mg), the number of dosage forms (e.g., one capsule), or the volume of liquid (e.g. two drops).

Q. What is the elimination half-life of a drug?

A. The *elimination half-life ($t_{½}$)* of a drug is essentially the duration of action of a drug. Also, it is used to determine the dosing of a drug. The elimination half-life of a drug is the amount of time required for a drug to decrease its original concentration by 50%. The second half-life is when it removes another 50%, leaving 25% in the blood. The third half-life is when it removes another 50%, leaving 12.5% in the blood. Drugs have different predetermined half-lives. As repeated doses of a drug are administered, the plasma concentration builds up and reaches "steady state." Steady state occurs when the amount of drug in the plasma builds up to a level considered therapeutically effective. In order to achieve steady state, the amount of drug administered must balance the amount being cleared from the body. It usually takes about between four and five half-lives to reach clinical steady state and about six half-lives before 98% of the drug is eliminated from the body (Ito 2011). For example, if a drug has a $t_{½}$ of 2 hours, it will take about 8–10 hours to reach clinical steady state (Ito 2011).

Drugs with a short $t_{½}$ are eliminated faster than drugs with a long $t_{½}$. For example, tetracycline HCl has a $t_{½}$ of 6–12 hours and doxycycline hyclate has a $t_{½}$ of 14–24 hours. Thus, tetracycline dosing is one capsule every four hours while doxycycline is dosed 100 mg every 12 hours on day 1, then 100 mg every day. On average, doxycycline's half-life is around 19 hours. By multiplying 19 hours by six hours (average $t_{½}$ to be 98% eliminated from the body) ($19 \times 6 = 114$ hours), it takes 114 hours, or about five days, before 98% of the doxycycline has been removed from the body. Penicillin VK has a $t_{½}$ of 30 minutes and amoxicillin's $t_{½}$ is 1–1.3 hours. Thus, penicillin is given every six hours and amoxicillin is dosed every eight hours (Thomson 2004a,b).

Ibuprofen has a short $t_{½}$ and is cleared from the body more rapidly than a drug with a longer $t_{½}$. Ibuprofen requires a more frequent, regular dosing regimen of 200–400 mg (OTC strength) q4–6h or prescription ibuprofen 600–800 q6–8h in order to build up and maintain a high enough concentration in the plasma to be therapeutically effective.

Q. What is the volume of distribution (V_D)?

A. *Apparent volume of distribution (V_D)* refers to the amount of drug in the various tissues of the body. Volume of distribution is a calculated value referring to the volume of fluid (e.g., plasma, interstitial fluid [fluid between the cells], and lymph) in which a drug is able to distribute to the organs. The volume of distribution can be used to calculate the LD, MD, and clearance of a drug (Aki et al. 2010; Thomson 2004a, b; Wesolowski et al. 2016).

Q. What is drug biotransformation?

A. *Drug biotransformation* (or metabolism, as it is sometimes called) terminates the action of a drug. It is a process by which a substance changes from one chemical form to another via a reaction in the body. Usually, biotransformation occurs in the liver but can also occur in the plasma and kidney.

Q. What is the importance of drug clearance?

A. *Clearance* refers to the volume of fluid (e.g., plasma) that would be completely cleared of drug if the entire drug being excreted were removed from that volume of fluid. Essentially, clearance is the removal of a drug from the plasma. It is a calculated value and measured in liters/hour. Clearance indicates the ability of the liver and kidney to eliminate a drug from the body (Doogue and Polasek 2013). Clearance may be reduced in the elderly. Both clearance and V_D are important values in determining the half-life of a drug (Gossel 1998a,b).

Q. What must happen to a drug in the body in order for a drug effect to occur?

A. The rate of absorption must be greater than the rate of elimination for the drug to have an effect on the body. Usually, the rate of elimination is slower than the rate of absorption so that the rate of elimination is the controlling factor in the presence of the drug in the body (Fujimoto 1979).

1.3 Pharmacodynamics

Q. What is the definition of pharmacodynamics and what is its significance in dentistry?

A. *Pharmacodynamics* deals with the mechanism of action of drugs or how the drug works in the body to produce a pharmacological response and the relationship between drug concentration and response. It is important to know the mechanism of action of drugs because it will help with understanding the reason for prescribing the drug.

Q. What is the definition of drug affinity?

A. *Affinity* is the ability of a drug to bind to the receptor to elicit a therapeutic response. If one drug has a greater affinity than another drug, it means that drug binds more readily to the receptor. If a drug has a high affinity, this means that a smaller dose can produce a therapeutic effect compared to a drug with a lower affinity for the same receptor.

Q. Do drugs bind strongly to a receptor?

A. Most drugs bind weakly to their receptors via hydrogen, hydrophobic and ionic bonds. Because these are relatively weak bonds, the drug can bind and unbind the receptor. Some drugs do bind strongly to the receptor via covalent bonds.

Q. Can drugs bind to other receptors besides their specific receptors?

A. Yes. For example, atypical antipsychotic drugs bind to dopamine receptors for their antipsychotic response but also bind to alpha receptors which cause adverse effects such as weight loss while binding to muscarinic receptors causes xerostomia.

Q. How do most drugs cause a therapeutic response?

A. Most drugs have an affinity for a specific receptor. Most receptors are proteins. Once the drug binds to the receptor, a therapeutic response occurs. Receptors have a steric or three-dimensional structure so when the substrate or drug binds to that receptor, the receptor undergoes steric realignment which allows the drug to bind more precisely to the receptor with better efficacy.

Q. Do all drugs interact with receptors to cause a therapeutic response?

A. No. Epinephrine binds to alpha and beta receptors on the organs but also produces some of its effects by activating an enzyme called adenyl cyclase. Also, anesthetic gases do not bind to receptors in the central nervous system. Antacids do not work by interacting with receptors.

Q. What are drug agonists and antagonists?

A. Drugs produce their effects by altering the function of cells and tissues in the body or organisms such as bacteria. Most drugs have an affinity for a target receptor, which is usually a protein on the cell surface. Once a drug binds to a receptor, it can act as either as an *agonist* (produces a stimulatory response) or an *antagonist* (sits on the receptor site and prevents an agonist from binding to the receptor; an antagonist does not produce a therapeutic response).

For example, epinephrine in low doses as used in dentistry is an agonist that binds to and activates beta-2 receptors, resulting in vasodilation of systemic arterioles (Becker and Reed 2012). This vasodilation tends to reduce peripheral resistance and therefore diastolic blood pressure. At the same time, the beta-1 receptors in the heart are activated to increase cardiac output and systolic blood pressure. These two influences cancel each other out regarding mean blood pressure (Becker and Reed 2012).

An example of an antagonist is flumazenil (Romazicon®), which is a benzodiazepine receptor antagonist used as rescue medication in the event of benzodiazepine overdose. It will bind the benzodiazepine receptor (BZR) and prevent the benzodiazepine from attaching. Naloxone (Narcan®) is a narcotic receptor antagonist.

Q. What is the difference between drug potency and efficacy?

A. *Potency* is the relationship between the dose of a drug and the therapeutic effect; it is the strength of drug required to produce the desired response. *Efficacy* refers to the ability of a drug to exert an effect. For example, 500 mg of acetaminophen and 200 mg of ibuprofen

both produce the same analgesia and have the same efficacy, but ibuprofen is more potent because it requires a lower dosage.

Q. What is the TI of a drug?

A. The *therapeutic index* (TI) is the dose range within which the drug is effective without causing adverse events/effects (Tamargo et al. 2015). The TI or ratio equates the blood level at which a drug causes a therapeutic effect compared to the dose that causes death. To determine drug safety, the drug's TI is calculated by dividing LD_{50} by ED_{50}. The ED_{50} is the median effective dose, which is the dose required to produce a specific therapeutic response in 50% of patients. The median lethal dose (LD_{50}) refers to the dose of drug that will be lethal in 50% of a group of animals, not humans. Some drugs (e.g., lithium, digoxin) have a narrow TI so that routine blood tests are necessary to assure the plasma drug level is within the therapeutic range.

Q. What is an ADR and why is it important to know?

A. An *adverse drug reaction* (ADR) is defined by the World Health Organization (WHO) as any response to a drug that is noxious, unintended, and *occurs when a drug is properly prescribed at doses normally* used in humans for the prophylaxis, diagnosis, or therapy of disease. Medical errors are not included in this definition. Bisphosphonate-induced osteonecrosis of the jaws is an ADR. Other examples of ADRs include drug interactions, allergic reactions and irritating adverse effects of a drug such as gastrointestinal problems (nausea, diarrhea). A drug interaction occurs when the effects of one drug are altered by the effects of another drug, resulting in an increase or decrease in the blood levels of the drug. An allergic reaction due to a drug is an abnormal and unwanted response that ranges from a mild rash to life-threatening anaphylaxis. An allergic reaction does not often happen the first time you take a medication but is much more likely to occur the next time you take that medication (Shamna et al. 2014). ADRs have a great effect on quality of life and continue to be challenging in prevention and treatment because of the increased use of alternative medications and an increase in the elderly population (Coleman and Pontefract 2016; Rieder and Ferro 2015).

Q. How does an ADR differ from an adverse effect or allergy?

A. An adverse effect is a type of ADR mediated by an immune response and is not the intended therapeutic outcome. It has been suggested to avoid using the term "side effect" and use the term "adverse effect" or "adverse drug reaction" instead (Riedl and Casillas 2003; VA Center for Medication Safety and VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel 2006).

Q. What is an ADE and is it the same as an ADR?

A. An *adverse drug event* (ADE) is an unfavorable and unintended response to a drug that includes medical errors (e.g., miscalculations, misinterpretation of handwritten prescriptions). The dentist has the responsibility to report any ADE that occurs through the FDA's Adverse Event Reporting System (MedWatch; www.fda.gov/Safety/MedWatch/default.htm) (Mayer et al. 2010). The terms ADE and ADR are often used interchangeably but should not be (Leheny 2017). Adverse drug events are not desired and usually require medical intervention. On the other hand, the majority of ADRs are undesirable but are usually predictable. The majority of cases resolve on their own (Leheny 2017).

Q. What is the definition of tolerance?

A. *Tolerance* is the development of resistance to the effects of a drug. Therefore, in order to achieve the desired response, more of the drug must be taken. Overdose is very common. Narcotics and alcohol are common examples of drugs that produce tolerance.

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