The Dentist's Drug and Prescription Guide

Second Edition

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Preface

The Dentist's Drug and Prescription Guide, 2nd edition, is a much-needed update to the first edition. Change has occurred in both the dental and pharmacology field and we have striven to imbue this edition with the same scientific basis for the sensible and appropriate use of drugs in the dental patient.

Keeping this book in easy reach will enable you to answer the most common and uncommon questions the dental professional has. Whether you are a dentist, dental specialist, dental hygienist, dental assistant, or dental lab technician, this drug guide will make a valuable addition to your knowledge base.

Today, the dental provider interacts with an increasing population of medically treated and possibly medically compromised patients. According to the US Department of Health and Human Services Centers for Disease Control and Prevention National Center for Health Statistics, "During 2015–2016, almost one-half of the U.S. population used one or more prescription drugs in the past 30 days (45.8%)." Dentists will surely be faced with daily decisions on treating people on medications. The importance of understanding potential drug interaction with our health care is essential for dental practice.

The proliferation of computer software programs providing drug interaction advice is helpful but we do not recommend thoughtlessly basing your treatment decisions on these algorithms. In this new edition, we have built for you a solid foundation allowing you to interact with the most up-to-date techniques and technologies in the dental and pharmacological world.

We have thoroughly updated most sections, including the most recent peer-reviewed publications. We have added completely new sections on the new classification of periodontal disease including antimicrobial treatment, the opioid crisis in dentistry, and HIV/AIDS research and medications.

Features of the book still include the following.

- Readability: short, easy question and answer format linking pharmacy theory to clinical dental practice.
- Need-to-know information: the content of this book was written in regard to the many questions practitioners have about prescribing drugs to patients.
- Drug tables: there are many tables in the book which not only summarize the main pharmacological features of the different disciplines but also allow the reader to review the key drugs and theories at a quick glance.

We sincerely hope you enjoy *The Dentist's Drug and Prescription Guide,* 2nd edition, and that it becomes a highly useful addition in your professional practice.

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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2

The Prescription and Drug Names

2.1 Parts of a Prescription

Q. What are the different parts of a written prescription?

A.
- Heading:
  - Prescriber's name, address, phone number, license number, Drug Enforcement Administration (DEA) number and NPI (national provider identifier) (the DEA number can also be located at the bottom of the prescription by the prescriber's signature)
  - Patient's information (name, address, age, weight)
  - Date of the order (must be written or it is not legal).
- Body:
  - Rx symbol
  - Medication prescribed (drug name, strength, and formulation) and quantity to be dispensed
  - Instructions to the pharmacist. For example: Dispense 10 capsules.
- Closing:
  - Signature (Sig): directions to the patient
  - Signature of prescriber
  - Whether or not substitution is permissible
  - Number of refills
  - Label (informs the pharmacist how to label the medication).

Q. What does "Rx" mean?

A. Rx is a symbol referring to "prescription." Rx stands for the Latin word "recipe" or "take thou" or "take thus" or "to take." Essentially, it is a command to take a specific compound.

Q. What does "Sig" mean?

A. Sig is an abbreviation for the Latin *signatura*, meaning "write," "make" or "label." These should always be written in English; however, prescribers sometimes use Latin abbreviations, e.g., "1 cap tid pc," which the pharmacist translates into English as "take one capsule three times daily after meals."

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

Q. Does the age of the patient need to be written on the prescription?
A. Yes. Generally, it is helpful to write in the age (in years) of the patient. For pediatric prescriptions, it is recommended to write in the age of the child if the patient is less than 12 years of age and the age in years and months if less than 5 years of age. Including the weight of the child is also helpful. For Schedule II drugs, it is mandatory to include the age of the patient on the prescription. The reason for writing the age of the patient is that in some cases dose adjustments may be needed.

Q. What is the NPI?
A. NPI stands for national provider identifier. It is an identification number given to healthcare providers by the CMS (Centers for Medicare and Medicaid Services). Healthcare providers must apply for an NPI number through an application process on the CMS website. Health practitioners need to have this number in order to receive reimbursement from insurance companies and to prescribe medicines.

Q. What does the label box at the bottom of the prescription mean?
A. Any information about the medication to be dispensed is provided on the label that is affixed to the drug container.

2.2 Generic Substitution

Q. When does a brand name drug become generic?
A. A brand name drug can become generic when the patent for that drug expires. Once the brand name drug goes off-patent, several drug companies can begin to manufacture a generic equivalent drug. In the United States, one company is given 180 days of exclusivity to manufacture a generic version of a drug. After 180 days, other manufacturers of generic medications can then start to make their own generic form of the drug. For example, the patent on Celebrex® expired in 2013. Until 2013, Celebrex was not available in a generic form (www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm).

Q. At the bottom of the prescription there is a section that says "dispense as written" or "substitution permissible." What is the difference between a generic drug and a brand name drug?
A. A generic drug is manufactured and distributed usually without a patent. However, the generic drug may still have a patent on the entire formulation but not on the active ingredient. A drug that has a trade (brand) name is protected by a patent whereby it can only be manufactured and sold by the company holding the patent. Once the patent expires (between seven and 12 years) on a brand name drug, the generic form becomes available (Welage et al. 2001).

Q. What is generic equivalency?
A. Generic equivalency was developed to save consumers and insurance companies high costs. Generic drugs are much cheaper because of competition between drug manufacturers once the patent has expired. Also, it costs less to manufacture generic drugs. Many brand name drugs have less expensive generic substitutes that according to the FDA are therapeutically and biochemically equivalent to the brand name drug. The FDA requires the bioequivalence of the generic drug (active ingredient) to be between 80% and 125% of that of the brand name drug.

Generics are considered by the FDA to be identical in dose, strength, safety, efficacy, and intended use (Balthasar 1999; Greene et al. 2001; Meridith 2003).

Q. Is a generic drug always equivalent to a brand name drug?
A. According to the law, drug companies are required to prove bioavailability. Many drugs that are available generically are equally efficacious with the equivalent brand name (Birkett 2003).

Q. What is generic substitution and how do I know if a generic drug substitute is available?
A. Generic substitution is the process by which a brand name drug is dispensed by a different form of the same active substance (Posner and Griffin 2011). There is a book called the "Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations" that all pharmacies have, and since February 2005, there has been a daily Electronic Orange Book (EOB) product information for new generic drug approvals. The downloaded Annual Edition and Cumulative Supplements are also available in a paper version (Approved Drug Products with Therapeutic Equivalence Evaluations, ADP 2008) from the US Government Printing Office: http://bookstore.gpo.gov; toll free telephone number 866-512-1800.

Q. How do I write for a generic substitute on a prescription?
A. Prescriptions have instructions on whether the prescriber will allow the pharmacist to substitute a generic version of the drug. This instruction is communicated in several different ways which differ among states. Usually, the prescription contains two signature lines. One line has "substitution permitted" or "substitution permissible" printed at the bottom of the prescription and the other line has "dispense as written" or "do not substitute." The prescriber signs either line. Some states have a "daw" (dispense as written) box printed at the bottom of the prescription. This means that the prescription will be filled generically unless the prescriber writes "daw" in the box, in which case the prescription will be filled the way it is written by the prescriber. For example, if you write a prescription for the trade name of a drug such as Vibramycin® (the patient only wants to take a brand name drug) and sign the line "do not substitute" or write "daw" in the box, the prescription will be dispensed with the brand name drug rather than the generic substitute (doxycycline) (Meridith 2003).

Q. When should a generic drug rather than a brand name drug be prescribed?
A. Any time. It is the decision of the patient. Most drugs today are dispensed as generic. Generic substitution is intended for the pharmacist to use a form of the drug which may be less expensive to the patient. It is usually the cheaper drug yet still has the same FDA guidelines in manufacturing and should be equal in efficacy to the brand name drug. However, if the prescriber writes a prescription for the brand name drug and signs "do not substitute," the patient cannot request the generic (Food and Drug Administration [FDA] – Center for Drug Evaluation and Research [CDER]. Statistical approaches to Establishing Bioequivalence 2001).

Q. Who decides to choose a generic substitute?
A. The patient makes the decision as long as the prescription is signed by the prescriber to allow for substitution. If the prescriber does not sign the appropriate place to allow for generic substitution, the pharmacist must dispense the generic.

2.3 Controlled Drugs

*Note: Always confirm any drug laws with your state regulations because *the most restrictive clause will prevail, whether state or federal*.

Q. What are controlled substances?
A. Controlled substances come under the jurisdiction of the Controlled Substances Act of 1970. The federal agency is the DEA and the State agency is the Division of Narcotics and Dangerous Drugs of the DHHR. The Controlled Substances Act 1970 was developed to educate and monitor the prescribing and dispensing of potentially addictive substances into five Schedules according to their potential for abuse or physical or psychological dependence.

Q. What is the schedule for marijuana?
A. Even though marijuana is legal in some states and many groups want it rescheduled, the government says it is still a dangerous drug and should not be rescheduled. However, Epidiolex® (a drug derived from cannabidiol which is contained in the marijuana plant and indicated for Lennox–Gastaut syndrome) has been rescheduled to a Schedule V controlled substance.

Q. What is the definition of physical dependence?
A. Physical dependence is a physiological state characterized by the development of an abstinence syndrome on abrupt withdrawal of the medication. Physical dependence does not imply abuse or addiction.

Q. Sometimes controlled substances are written as Schedule III or "C-III." Is there a difference?
A. No. The *C* refers to controlled substance. Drugs which are subject to control under the Controlled Substances Act are assigned to one of five schedules, referred to as controlled substance schedules: Schedule I controlled substance, Schedule II controlled substance, Schedule III controlled substance, Schedule IV controlled substance and Schedule V controlled substance, depending on the abuse potential. These schedules are commonly shown as C-I, C-II, C-III, C-IV, and C-V.

Q. What are the different controlled (scheduled) drugs?
A. Refer to Table 2.1.

Q. Is a DEA number required to prescribe an opioid?
A. Yes. A dentist is required by law to register with the DEA in Washington, to dispense, store or prescribe controlled drugs. A DEA number will be issued to the prescriber in the state where they are practicing dentistry. If the state requires that the dentist have a State Controlled Substance Number, in addition to the DEA number, then the DEA will require that this number be issued before the DEA number can be issued. Twenty-six states that require a Controlled Substance Number and a DEA number are New Jersey, Alabama, South Carolina, Nevada, Iowa, District of Columbia, Utah, Oklahoma, Massachusetts, Michigan, Illinois, Connecticut, South Dakota, Louisiana, Guam, Wyoming, Puerto Rico, Rhode Island, Missouri, Indiana, Delaware, Texas, New Mexico, Maryland, Hawaii, and Idaho. There must be a space on the prescription to write in the DEA number.

Table 2.1 Controlled drugs

Schedule	Abuse potential	Examples
C-I	Highest	Not accepted for medical purposes: heroin, lysergic acid diethylamide (LSD), methaqualone, peyote, 3,4,methylenedioxymethamphetamine ("Ecstasy"), marijuana
C-II	High	Oxycodone/acetaminophen (Percocet®, Tylox®), hydrocodone/acetaminophen (Vicodin®, Lorcet®), meperidine (Demerol®), codeine, cocaine, morphine, oxycodone (OxyContin®), methadone (Dolophine®)
C-III	Less potential than C-II	Acetaminophen w/codeine, phenobarbital
C-IV	Less potential than C-III	Zolpidem (Ambien®), diazepam (Valium®), alprazolam (Xanax®)[a]
C-V	Limited abuse	Cough syrups with codeine, antidiarrheals such as diphenoxylate/atropine (Lomotil®)

[a] In certain states like New York, Schedule IV benzodiazepines (e.g., Valium, Xanax) are treated as Schedule II.

Q. Are prescription writing rules for controlled substances state or federal regulated?
A. Both. Regulations can be under state or federal law. The prescriber must review individual laws in their state. For example, under federal law, a prescription for Schedule II substances must be filled within 30 days of writing. *A state could establish rules tighter than the federal rules and the most restrictive clause will prevail, whether state or federal.*

Q. According to state and federal law, are there limits to the quantity of controlled drugs that can be prescribed?
A. While states may have more restrictive rules, the federal law does not limit the amount prescribed. *The most restrictive clause will prevail, whether state or federal.*

Q. Can Schedule I substances be prescribed by a private practitioner?
A. No. Schedule I substances have the highest abuse potential and no medical uses, thus no indications to be prescribed, and are not legally available to the public. This is a federal law and does not vary from state to state.

Q. Can Schedule II substances be prescribed by a private practitioner?
A. Yes. Schedule II drugs have a high abuse potential and include narcotics and amphetamines. There cannot be any refills and prescriptions are invalid after a certain number of days which is state regulated. For example, in New Jersey any controlled substance prescription can be filled in a pharmacy within 30 days of writing the prescription. After the limit, a new prescription is required. A Schedule II drug can be phoned into the pharmacy only in emergency situations and must be followed up by a written prescription within 72 hours. Only a three-day supply can be dispensed.

Q. What are the regulations for Schedule III drugs?
A. Schedule III drugs have a lower abuse potential than Schedule II drugs. Prescriptions for Schedule III substances expire six months after the date written. Refills are allowed but only five refills within six months. A practitioner may issue a new prescription for the Schedule III substance within a six-month period if necessary.

Q. What is the refill regulation for Schedule IV and V drugs?
A. Five refills in six months.

Q. Can the prescriber presign prescriptions for controlled substances?
A. No. Federal law prohibits prescribers from presigning prescriptions. All prescriptions for controlled substances must be dated and manually signed on the day the prescription was written.

Q. What are prescription drug monitoring programs (PDMPs)?
A. Diversion of controlled substances that have a high potential for abuse or profit when sold illegally is a serious problem. Different methods of diversion include illegal selling of controlled substance by physicians, dentists, and pharmacists; prescription theft; and inappropriate prescribing by physicians and dentists to themselves, family members or others. Drug monitoring programs were developed to control diversion. The program is run via an electronic database that tracks controlled substance prescriptions in a state. These monitoring programs are intended to improve opioid prescribing and protect patients at risk. Some states that have a drug monitoring system include California, Hawaii, Idaho, Illinois, Indiana, Massachusetts, Michigan, New York, Oklahoma, Rhode Island, Texas, New York, and New Jersey. Information on controlled drugs, primarily Schedule II substances, prescribing, dispensing, and purchasing is sent via electronic means to the state and analyzed. New York State also has extended its program to include benzodiazepines that are federally scheduled as C-IV controlled substances. Therefore, in New York State, all benzodiazepines, such as alprazolam (Xanax®) or diazepam (Valium®) require a new prescription every month and no refills.

2.4 Principles of Prescription Writing

Q. What is a legend drug?
A. A legend drug is a drug that can only be dispensed by a pharmacist with a prescription. Labels on these medications carry the legend: "Caution! Federal law prohibits dispensing without a prescription."

Q. What is the chemical name of a drug?
A. The chemical name describes the chemical make-up of a drug. For example, the chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol.

Q. What is the proprietary name of a drug?
A. Other terms for proprietary name are brand or trade name and refer to the drug name assigned by the specific manufacturer which is protected by copyright. For example, one of the brand names for ibuprofen is Motrin® (McNeil).

Q. How long is a prescription valid until it is filled?
A. Every state has different rules which apply to prescriptions. A nonnarcotic prescription is valid for 365 days (one year) from the date on the prescription. Check with the local state boards for state-specific laws.