Medication Use in Dentistry

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Faculty Disclosure

Contributing faculty, Mark J. Szarejko, DDS, FAGD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The director has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all dental professionals.

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Course Objective

As the number of medications and range of uses grow, dental prescribing has become increasingly complex. The purpose of this course is to provide dental professionals with the knowledge necessary to effectively prescribe and to monitor the effects of commonly used drugs.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the various types of local anesthetics used in dentistry.
2. Evaluate the appropriate uses of analgesics for dental pain.
3. List antibiotics and antifungal medications that may be used to prevent or treat dental infections.
4. Discuss the role of antiviral medications in dental practice.
5. Describe the effective use of anxiolytic medications in easing dental patient anxiety and fear.
6. Identify special populations for whom prescribing practices may need to be adjusted.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Each day, millions of patients undergo dental procedures, most commonly restorative, prosthetic, periodontal, endodontic, and surgical procedures. New and improved techniques and instrumentation have provided clinicians with the means to perform high-quality treatment in an efficient manner. However, successful dental treatment involves more than focused techniques and procedures. The many classifications of medications used before, during, and after dental treatment are critical adjuncts in the delivery of dental care. Local anesthetics are one of the most often used classes of medications; it is difficult to imagine restorative and surgical treatment without the use of these agents. In addition, analgesics relieve pain associated with acute dental problems and postprocedural pain after oral and periodontal surgery and endodontic treatment. Antibiotic, antifungal, and antiviral medications are necessary when microbial organisms overcome host defenses and assume a pathologic course. Many patients have fear and anxiety regarding dental procedures, and for these patients, sedative and anxiolytic medications may provide the only means by which they can undergo dental treatment.

This course will describe the most common medications used in dentistry. The indications for use, problematic side effects, interactions with other medications, and unique characteristics of each medication will be discussed. It is not the intent of this course to provide patient-specific advice for the administration of any type of medication. Each clinician should consider the medical history of the patient and his or her unique dental needs before any medication is prescribed.

LOCAL ANESTHETICS

Local anesthetics are so commonplace in the practice of dentistry today that the origin of their use may be taken for granted. In 1884, Dr. William Halstead injected cocaine into a sensory nerve trunk to induce a state of surgical anesthesia [1]. Two decades later, a synthetic analog of cocaine was developed and used as the first local anesthetic. Procaine, better known by its trade name of Novocain, was an ester-based local anesthetic created in 1904 [1]. Although a breakthrough at the time, several problems were associated with its use. Allergic reactions, delayed onset of anesthesia, and a short duration of action were the most common problems. As such, the search began for a local anesthetic that could provide profound anesthesia with minimal deleterious side effects. All current local injectable anesthetics are chemically classified as amides, with topical anesthetics the lone remaining ester-based representative [2; 4].

LIDOCAINE

Lidocaine (2%) was the first amide-based local anesthetic created in the 1940s and remains the most popular local anesthetic used in the United States today. The onset of anesthesia is usually less than five minutes, and allergic reactions are a rarity. Lidocaine is available without a vasoconstrictor but is most commonly used with a 1:100,000 concentration of epinephrine. The addition of epinephrine constricts the small blood vessels in the injection area, which decreases the systemic absorption of the local anesthetic and diminishes the potential for systemic toxicity. Decreased vascular perfusion also confines the local anesthetic at the injection site for a longer duration and potentiates the depth and duration of anesthesia. Because epinephrine is a catecholamine and can increase heart rate and blood pressure, its use in cardiac and hypertensive patients should be minimized or, in some circumstances, avoided completely. Lidocaine and all local anesthetics that contain epinephrine also include the preservative sodium bisulfite. This substance is added to delay

the oxidation of epinephrine, which would cause its deterioration. Patients with allergies to sulfites may have reactions to this component and should not be administered local anesthetics containing epinephrine and the accompanying preservative [2; 3; 4].

Lidocaine is compatible with most prescribed medications. However, cimetidine, propranolol, and protease inhibitors (e.g., ritonavir) can decrease the clearance of this local anesthetic [2].

BUPIVACAINE

Bupivacaine is a very potent local anesthetic available in 0.5% concentration, as opposed to lidocaine, which is generally produced in a 2% concentration [2]. The onset of anesthesia is approximately 10 minutes; however, the duration of soft tissue anesthesia can extend up to 12 hours [2; 7].

Among all local anesthetics, bupivacaine demonstrates the highest ability to bind to proteins within the sodium channels of the neurons that are responsible for the conduction of nerve impulses. This strong affinity extends the time during which the normal inflow and outflow of sodium through these channels is prevented and the usual propagation of the action potential along the neuron is blocked. Bupivacaine is combined with epinephrine in a 1:200,000 concentration [2; 3; 4].

The extended duration of soft tissue anesthesia makes bupivacaine an excellent anesthetic for surgical cases. Pulpal anesthesia can extend to three hours, so bupivacaine is ideal for lengthy restorative procedures. Some clinicians have used bupivacaine at the conclusion of oral or periodontal surgery to extend the duration of anesthesia and to allow time for prescribed analgesics to become effective before the anesthetic effect dissipates.

This is not the anesthetic of choice for short restorative procedures in adults or for pediatric patients. Pediatric procedures are usually accomplished quickly, which negates the need for prolonged anesthesia. The extended duration of soft tissue anesthesia can also increase the risk of self-inflicted injury from biting anesthetized tissue. Therefore, bupivacaine should be avoided in patients with cognitive impairment or mental disabilities for whom instructions to avoid traumatizing the anesthetized tissues may be difficult to comprehend [4; 7]. Similarly, patients with neuromuscular diseases such as Parkinson's disease or multiple sclerosis may be unable to control movements of the oral tissues and teeth even without the influence of a local anesthetic. The induction of a prolonged state of local anesthesia with bupivacaine in these patients could enhance the potential of self-inflicted soft tissue injury. A local anesthetic of short duration would be more appropriate.

ARTICAINE

Articaine (4%) was developed in Europe in 1969, but it has only been used in the United States since 2000. The original formulation of articaine included the preservative methylparaben, which had been removed from all anesthetic cartridges in North America. The concern with the potential allergic response to methylparaben delayed the distribution of articaine in the United States until another preservative (sodium metabisulfite) was substituted [2; 7]. This is the only amide-type local anesthetic with an ester group within its chemical composition. This allows the amide portion to be metabolized in the liver while the ester portion is metabolized by plasma esterases [7; 9]. The onset of action is rapid, at one to two minutes for infiltration anesthesia and one to three minutes for a mandibular (inferior alveolar nerve) block. Unlike other local anesthetics, articaine has a sulfur-containing thiophene ring, which confers upon it a higher degree of lipid solubility and a more rapid absorption by the nerve membrane [3]. Some clinicians have claimed that buccal infiltration with articaine on maxillary teeth provides palatal anesthesia without any further independent injection of the palatal tissues [10]. However, controlled studies have offered differing opinions on its ability to do so [11; 12; 13]. Soft tissue anesthesia extends for three to six hours for articaine with 1:100,000 epinephrine or two to three hours when a 1:200,000 concentration of epinephrine is utilized. Pulpal anesthesia lasts for 75 minutes with the higher epinephrine concentration and for approximately one hour when the lesser concentration is used.

There is some concern that the use of articaine may result in damage to the nerves being anesthetized, especially the inferior alveolar and lingual nerves of the mandible. A retrospective study in the United States did not duplicate studies from Canada and Denmark that suggested an increase in the incidence of nerve-related injuries after the administration of articaine [14]. Specifically, the international studies indicated an increased risk of paresthesia within tissues previously anesthetized with articaine. Paresthesia is characterized by burning, tingling, or occasional sharp pain, the duration of which can be variable. However, a direct cause and effect relationship has not been established between articaine and paresthesia [15]. It has been suggested that the condition may develop when the needle from an anesthetic syringe contacts a nerve directly, as the problem has not developed when infiltration anesthetic techniques are utilized. It has also been attributed to the use of articaine following the administration of a nerve block injection [16]. Clinicians who use articaine should remain abreast of the research regarding this issue.

MEPIVACAINE

Mepivacaine (3%) does not share the vasodilating qualities of other local anesthetics, so its formulation does not contain epinephrine or the associated preservative sodium bisulfite. Thus, dental professionals treating patients with sulfite allergies or for whom epinephrine should be avoided may find mepivacaine suitable for their anesthetic needs, pending no other contraindications [2; 3]. It is not an ideal choice for longer procedures, as pulpal anesthesia is only maintained for 20 minutes when mepivacaine is infiltrated or 40 minutes when an inferior alveolar nerve block is used. Soft tissue anesthesia can linger for two to three hours [2; 7]. Mepivacaine is best utilized for shorter restorative appointments, pediatric patients, and patients with an increased risk of accidental self-inflicted trauma in anesthetized tissues.

PRILOCAINE

Like many of the other local anesthetics, prilocaine (4%) is often combined with epinephrine to improve its efficacy and extend its duration of action. With the addition of 1:200,000 epinephrine, pulpal anesthesia can last about 1.5 hours, while soft tissue anesthesia can linger for up to 8 hours [4; 7; 9]. These durations are suitable for procedures of intermediate lengths and for the prolonged anesthesia necessary after surgical procedures.

Without epinephrine, prilocaine is best utilized for shorter procedures. With prilocaine alone, pulpal anesthesia extends about 15 minutes with an infiltration technique and 60 minutes when a nerve block is used [9]. When the same injection techniques are used, soft tissue anesthesia lasts for two or four hours, respectively. Because prilocaine is supplied as a 4% solution, about twice the amount of anesthetic molecules will reach the neurons when compared to lidocaine or mepivacaine. However, one anesthetic cartridge of 4% prilocaine is also more toxic then either lidocaine or mepivacaine, and fewer cartridges of prilocaine may be used before systemic toxicity ensues.

The use of prilocaine has also been linked to the development of methemoglobinemia as a result of its metabolism into o-toluidine. Methemoglobinemia occurs when red blood cells contain more than 1% methemoglobin, with resulting headache, fatigue, and bluish coloring of the skin. Doses of up to 600 mg are generally considered safe, but methemoglobinemia can develop with lower doses in some patients [2; 7].

GENERAL CONSIDERATIONS

The frequent use of local anesthetics in dentistry should not instill a sense of complacency with their use. These drugs are capable of causing deleterious systemic reactions. Allergic reactions to the amide type of local anesthetics are possible, but rare. Inadvertent intravascular injections can cause seizures and even cardiovascular collapse. Package inserts included with local anesthetics advise clinicians of these potential problems and the need for the dental staff to be adequately trained to treat patients who experience medical emergencies resulting from the use of a local anesthetic.

Vasovagal syncope (fainting) remains the most frequent medical emergency in dental offices. Some of these episodes occur because of the fear and psychogenic response that many patients harbor toward dental treatment, especially injections [2]. This possibility should be considered for patients being administered a local anesthetic.

The U.S. Food and Drug Administration (FDA) has assigned risk categories to all medications for their potential to cause birth defects in the developing fetus. While these categories can be a guide to the choice of a local anesthetic for pregnant patients, it would be prudent to consult with the patient's obstetrician prior to the use of any local anesthetic. All clinicians should have a thorough knowledge of the patient's current medical history before the initiation of any dental treatment, the injection of any local anesthetic, or the dispensation of any prescribed medication.

State laws vary as to the degree of staff training and the type of emergency supplies that are necessary to address medical emergencies in the dental setting. Many states require dental offices to have an automated external defibrillator (AED) and for staff to be trained in its proper use. All dental offices should have periodic mock emergency drills in which each staff member is assigned a role to assume during a real medical emergency. The ability to use portable oxygen tanks and to retrieve and use the appropriate supplies from a medical emergency kit should be a part of the training for medical emergencies. The staff has the responsibility of treating the patient until emergency medical services arrive.

ANALGESICS

The relief of pain in dentistry is usually associated with short-term situations, such as the initiation or exacerbation of pain from teeth with carious pulpal involvement, postsurgical pain, or postendodontic procedure pain. This pain can be treated with a wide variety of analgesic medications. This section will highlight the most commonly used analgesics in dentistry, their indications and contraindications, and the most frequent interactions with other medications. The dosage and frequency of administration of any medication should be determined by the individual clinician, taking into consideration a patient's history, age, weight, systemic illnesses, and use of other medications. These factors can influence the distribution, absorption, metabolism, and excretion of medications, and clinicians may need to consult the patient's physician if a complex medical history complicates their ability to prescribe routine medications.

ACETAMINOPHEN

Acetaminophen was first approved for use by the FDA in 1951, and it is both an analgesic and antipyretic (fever reducer). It is used in dentistry for the treatment of mild-to-moderate pain and can be dispensed by itself or in combination with narcotic medications such as codeine, hydrocodone, or oxycodone. This analgesic works by decreasing the synthesis of prostaglandins, chemical mediators of inflammation and pain, in the central nervous system and by peripherally blocking the generation of pain impulses. Because the primary metabolism of acetaminophen occurs in the liver, patients with impaired liver function can have difficulty metabolizing this medication properly and can cause further damage to the hepatocytes (liver cells) by ingesting even small doses. The use of alcohol can exacerbate the hepatotoxic potential of acetaminophen, and therefore it should not be consumed concurrently with this medication. Concomitant use of carbamazepine, isoniazid, and rifampin can increase the hepatotoxic potential of acetaminophen [4; 7].

However, acetaminophen does have advantages over some other analgesics. It is better tolerated in some patients, with fewer gastrointestinal side effects compared to nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen is also safe to take with antihypertensive drugs, unlike long-term NSAID use, which decreases the efficacy of these medications.

NSAIDs

Ibuprofen

Ibuprofen is an over-the-counter NSAID that was originally approved by the FDA in 1974. It is available both by itself and in combination with a narcotic such as hydrocodone. Ibuprofen's mechanism of action is based on the inhibition of the enzyme cyclo-oxygenase, which converts arachidonic acid to the progenitor prostaglandin H2, from which several other prostaglandins are formed. It is used for mild-to-moderate pain associated with dental treatment or odontogenic causes [4; 7].

Ibuprofen can have deleterious effects on the gastrointestinal tract and can increase the risk of gastrointestinal irritation, ulceration, bleeding, or perforation. Renal function can also be compromised [7].

Ibuprofen is associated with several drug interactions, some of which can be dangerous. The clearance of lithium, a medication used to treat bipolar disorders, can be reduced by simultaneous use of ibuprofen. The efficacy of medications used to treat hypertension, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics (e.g., hydrochlorothiazide), can be decreased by the extended use of ibuprofen. The anticoagulant effects of warfarin and the antiplatelet effects of clopidogrel can be enhanced by the simultaneous use of ibuprofen, with the potential for internal bleeding. Although it is available over-the-counter, ibuprofen is contraindicated in the last trimester of pregnancy as it may cause closure of fetal ductus arteriosus, fetal renal damage, inhibited clotting, and delayed labor and birth [4; 7].

Naproxen

Originally a prescription medication, naproxen was approved by the FDA for over-the-counter use in 1994. It is available in formulations as naproxen base or naproxen sodium, with 200 mg of the base form equivalent to 220 mg of the sodium form. It is generally prescribed for mild-to-moderate pain associated with dental procedures or from an odontogenic origin. The extended analgesic and anti-inflammatory effects of naproxen can reduce the frequency of administration of this medication [4; 7].

Categorized as an NSAID, naproxen's mechanism of action against prostaglandin synthesis is similar to that of ibuprofen. As such, potential drug-drug interactions with lithium, ACE inhibitors, beta-blockers, and hydrochlorothiazide are the same as those described for ibuprofen. The potential to enhance the effects of warfarin and clopidogrel is also a concern, especially for dental patients who cannot discontinue these medications prior to oral surgery.

Gastrointestinal and renal side effects are another concern. An enteric-coated version of naproxen is available that can alleviate, but not eliminate, the potential for gastrointestinal irritation.

OPIOID ANALGESICS

Opioids are a class of analgesic medications prescribed for the relief of mild-to-severe pain. In dentistry, oral or periodontal surgery, orthognathic surgery, endodontic procedures, and oral and maxillofacial trauma are among the situations for which opioid analgesics may be prescribed. The acute pain associated with these procedures and problems is generally of a short duration, with a commensurate schedule for the administration of these medications. However, even short-term use of opioid analgesics can cause complications such as respiratory depression, constipation, dizziness, and sedation [23]. Physical dependence, tolerance, and withdrawal symptoms may develop with extended use. Due diligence must be utilized when these medications are prescribed because of the potential for addiction. Opioid analgesics act by mimicking the naturally occurring endogenous opioid peptides or endorphins in the brain [23].

Aside from physicians, dentists are the most frequent prescribers of immediate-release opioids (e.g., codeine, hydrocodone, oxycodone). While most patients use these for the analgesic purpose for which they are intended, abuse of prescribed opioid medications heavily contributed to the second wave of the opioid crisis in the United States that began between 2010 to 2013. However, increased education, awareness campaigns, and regulatory efforts have proven to reduce opioid prescribing

rates among dentists. One study showed that 60% of dentists reduced their opioid prescribing rates by 30% to 83% between 2016 and 2019. However, 3.4% of dentists consistently prescribed at high rates. It is essential that all clinicians prescribe opioid medications in a responsible fashion [26].

A web-based survey of dentists was conducted to assess their pain management prescribing practices and risk-mitigation strategies, including risk screening, prescription drug monitoring program (PDMP) use, and patient education [27]. Of the 822 dentists who completed the survey, a minority reported prescribing opioids alone or in combination with an NSAID or acetaminophen (11% and 18%, respectively). The respondents also reported that 50% or more of their patients required acute pain management, yet most dentists reported infrequent PDMP use and patient counseling regarding risks, storage, and disposal of opioids. Higher levels of opioid prescribing were associated with less consistent risk mitigation implementation and patient education [27]. In a separate survey of 87 dental practitioners, 75.8% reported prescribing opioids; 44% reported regularly screening patients for current prescription drug misuse; 5.8% reported requesting prior medical records; 38% reported ever accessing a PDMP; and 4.7% consistently used a PDMP [28].

Codeine

Codeine is a prototype opioid medication. When used in dentistry, it is most frequently combined with acetaminophen and less frequently with aspirin or ibuprofen. When used in combination with acetaminophen the amount of codeine per tablet can vary from 7.5 mg to 60 mg [7]. This medication is used for mild-to-moderate pain of odontogenic or postprocedural origin. About 10% of codeine is converted to the active metabolite of morphine [23]. The remaining significant metabolites of codeine are codeine-6-glucuronide (70%), norcodeine (10%), and hydromorphone (1%) [4; 7]. Codeine's active metabolite of morphine can be transmitted through breast milk in levels great enough to cause potentially fatal respiratory depression in infants [7]. Respiratory depression among opioid medications is dose-related and a potentially serious adverse effect. The respiratory depression and sedative effects of codeine can be enhanced by alcohol or other medications, in some cases resulting in profound sedation. Clinicians who prescribe opioid medications should first obtain a thorough patient history, particularly a list of other medications currently being taken by the patient that could potentiate these reactions. This includes over-the-counter medications and herbal supplements. Some herbal medications, such as kava kava and St. John's wort, have sedating qualities that can work synergistically with those of codeine or any opioid.

Hydrocodone

Hydrocodone was approved for use in the United States by the FDA in 1943. This semi-synthetic opioid can be derived from either codeine or thebaine, each a naturally occurring opiate. It is used for the treatment of moderate-to-severe pain and is stronger than codeine but not as potent as morphine. For dental use, it is usually combined with either acetaminophen or ibuprofen. There are numerous brand name and generic versions of hydrocodone/acetaminophen formulations [4; 7].

Hydrocodone is a central nervous system depressant and must not be taken with alcohol, benzodiazepines, barbiturates, or any other medication(s) that can cause central nervous system depression; concurrent use may result in respiratory compromise, sedation, or coma. Because acetaminophen is metabolized solely by the liver, there is a risk for liver damage or failure with this combination. The simultaneous use of alcohol with this compound can increase the hepatotoxic potential [7].

Among the most common adverse effects associated with hydrocodone are dizziness, drowsiness, nausea, and vomiting [7]. The potential for abuse, physical dependence, addiction, and withdrawal symptoms is also a concern. This medication should be prescribed for the shortest duration possible and should not be utilized for patients who have had opioid dependence problems in the past. Alternative analgesics such as those in the NSAID category should be considered first.

Oxycodone

Oxycodone is another opioid used for the treatment of moderate-to-severe acute pain among dental patients. It can be combined with aspirin, acetaminophen, or ibuprofen. Oxycodone binds with opioid receptors in the cerebral cortex, causing a decrease in the synaptic transmissions throughout the central nervous system and blocking pain signals. Oral oxycodone is quickly absorbed systemically and reaches peak plasma levels approximately one hour after administration. Relief of pain can begin as quickly as 15 minutes after oral administration [4; 7].

Oxycodone is reserved for patients who have had extensive surgical procedures or severe oral and maxillofacial trauma, as it is 1.5 to 2 times as potent as morphine in oral form. Physical and psychologic dependence can develop, so it should be used for the shortest duration possible. The most common side effects of oxycodone use are nausea, vomiting, constipation, xerostomia, dizziness, and confusion. The simultaneous use of antidepressants, antihistamines, muscle relaxants, sedatives, and other narcotics can potentiate the sedative effects of oxycodone. Withdrawal symptoms can precipitate a medical emergency [4; 7].

ANTIBIOTICS

Although the use of local anesthetics and analgesics in dentistry has been critical in providing comfort and alleviating the aftermath of pain associated with many dental procedures and dental pathologies, antibiotics are also essential for the practice of dentistry. The oral environment is composed of hundreds of bacterial species, most of which do not assume a pathologic role. However, dental caries and periodontal disease both have bacterial etiologies. Bacterial contamination of the dental pulp can extend into the alveolar bone and the adjacent soft tissue. Bacteria within periodontal pockets can also cause infections in the surrounding soft tissue.

Antibiotics are a means by which oral bacterial infections can be managed, so definitive therapy can be completed to eliminate the source of the infection. Prescribing antibiotics must be done in a responsible fashion, as the imprudent use of these medications has caused multiple strains of bacteria to become resistant to several conventional antibiotics. The potential for allergic reactions, gastrointestinal upset, and drug-drug interactions also support the need for a judicious approach to the use of these medications. According to the American Dental Association (ADA), reports from 2017 through 2019 suggest that 30% to 85% of dental antibiotic prescriptions are "suboptimal or not indicated" [32; 33; 34]. To help prevent a postantibiotic era, in 2019 the ADA published a guideline on antibiotic use [35]. The stated aim of the guideline is to move the dental profession from a "just in case" approach of antibiotic prescribing to a "when absolutely needed" approach [36].

This section will only address the oral preparations of the most common antibiotics; a full discussion of all available antibiotics is beyond the scope of this course. As always, it is up to the independent clinical judgment of the practicing clinician to determine which antibiotic is compatible with a patient's medical history, is appropriate for the extent and virulence of the existing infection, and is compatible with any other medications utilized by the patient.

PENICILLIN AND PENICILLIN DERIVATIVES

Penicillin V Potassium

Originally noted by a French medical student in 1896 and rediscovered by Sir Alexander Fleming in 1928, it was not until the 1940s that penicillin became commercially available in the United States. Chemically, penicillin and its derivatives all share a similar structure, including a beta-lactam ring; this structure is also the core of cephalosporin and monobactam antibiotics. Penicillins remain the antibiotic of choice for orofacial infections caused by aerobic, gram-positive streptococci and anaerobes. The bactericidal effect of penicillin is derived from its ability to interfere with the synthesis of components of the bacterial cell wall. The resultant decrease in the tensile strength of the bacterial cell wall causes weakening and cell rupture through osmotic lysis [7; 35; 37].

Penicillin is compatible with most medications, with a few noteworthy exceptions. The anticoagulant effects of warfarin may be increased with the simultaneous use of penicillin, potentially leading to coagulation difficulties. This could be a concern for patients who cannot discontinue warfarin prior to oral surgery and who are prescribed penicillin to treat or prevent odontogenic infection. In addition, the efficacy of oral contraceptives may be decreased in patients taking penicillin [7]. An alternative means of contraception or an alternative antibiotic is necessary for these women. Probenecid, which is used to treat hyperuricemia associated with gout or gouty arthritis, can decrease the excretion of penicillin and cause the plasma levels of the drug to rise [7].

Penicillins are generally well-tolerated medications, but up to 10% of the population is documented to have an allergy to this class of antibiotics. Long-term use has also led to the resistance in several strains of bacteria. These bacterial species can produce a substance called beta-lactamase, which breaks the beta-lactam ring and renders penicillin useless [7; 37].

Side effects of penicillin are usually gastrointestinal and can include nausea, vomiting, and diarrhea. Because penicillin decreases a portion of the oral microbial population, competitive inhibition among the remaining microbes decreases. This can result in the development of opportunistic infections such as oral and/or vaginal candidiasis. In these cases, antifungal medications may be required to alleviate the problem. Probiotics have been suggested as a possible preventive option for candidiasis in patients taking antibiotics [38]. More research into the efficacy of probiotics is necessary, but initial studies are promising.

Amoxicillin

The addition of one amine group and one hydroxyl group and the deletion of one oxygen molecule is all that differentiates amoxicillin from penicillin V. The addition of the hydroxyl group allows for amoxicillin to be absorbed faster than penicillin V, with more diffuse distribution through infected tissue and organic fluids. Food will not delay the absorption of amoxicillin, as it does with other penicillin medications. This improvement has resulted in amoxicillin replacing penicillin as the antibiotic of choice for prophylaxis of bacterial endocarditis. Compared with penicillin V, amoxicillin has a broader spectrum of microbial activity [7; 29].

Adverse drug interactions associated with amoxicillin parallel those of penicillin. Additionally, the simultaneous use of allopurinol in patients treated for gout can increase the potential for the development of a rash [7].

Potential side effects are similar to those described for penicillin; however, gastrointestinal problems can be more severe and can even include the development of hemorrhagic or pseudomembranous colitis [7]. Patients who are allergic to penicillin will also experience reactions to amoxicillin.

Amoxicillin and Clavulanic Acid

Although penicillin and amoxicillin are good empiric choices for the treatment of many oral and maxillofacial infections, these medications do not always resolve the infection. Due to developed resistance or natural defenses, many bacteria produce beta-lactamase, making treatment with a penicillin ineffective. The addition of clavulanic acid addresses this issue.

Alone, clavulanic acid has low antibacterial activity. However, when combined with amoxicillin, it extends the spectrum of bactericidal activity to include organisms that produce beta-lactamase. Infections that do not resolve with this medication generally require another class of antibiotic medications altogether. Available under the brand name Augmentin or Amoclan, this combination can be prescribed in various dosage forms, including an 875 mg tablet taken once every 12 hours [7]. Possible interactions and side effects are the same as for those of amoxicillin, with the additional concern of clavulanic acid allergy.

CEPHALOSPORINS

Cephalexin

Cephalexin is a semi-synthetic medication that shares the beta-lactam structure of both penicillin and amoxicillin. Cephalexin and other first-generation cephalosporins are less susceptible to beta-lactamase as compared to penicillin and amoxicillin and provide reasonable coverage against pathogenic oral flora [30]. It is most effective against aerobic, gram-positive bacteria. First introduced in 1967, cephalexin remains among the most frequently prescribed antibiotics in North America. It can be utilized as antibiotic prophylaxis for bacterial endocarditis for those allergic to amoxicillin or clindamycin. Patients who are allergic to penicillin have a potential cross-reactivity to cephalexin. In particular, if the reaction to penicillin was immediate and anaphylactic, there is a 20% chance that there will be a cross reactivity between these two medications; in these cases, cephalexin is absolutely contraindicated. If the reaction to penicillin had a delayed onset, the risk that the patient is also allergic to cephalexin is only 1% [7; 30; 37].

The most common adverse effects are similar to those described for penicillin and amoxicillin. Additionally, central nervous system symptoms such as dizziness, confusion, and fatigue can occur [7]. A unique drug interaction not seen with other beta-lactam antibiotics is seen with cephalexin and the oral hypoglycemic medication metformin, commonly used in patients with type 2 diabetes. The simultaneous use of these drugs can decrease the renal clearance of metformin, thereby increasing its plasma concentration. This can result in a decrease in blood glucose levels to a range that could precipitate a hypoglycemic crisis, especially if the patient has not eaten [7].

Cefuroxime

Cefuroxime is a second-generation cephalosporin used in the treatment of susceptible dental infections. Unlike the first-generation cephalosporins, the second-generation medications have improved efficacy against certain anaerobes. Cefuroxime is a drug of choice for the treatment of Lyme disease. Although FDA approved for the treatment of uncomplicated and disseminated gonococcal infections, clinical practice guidelines do not recommend cefuroxime for the treatment of gonorrhea because of widespread resistance, inferior efficacy, and less favorable pharmacodynamics. Possible side effects include diarrhea, vaginitis, nausea/vomiting, and eosinophilia. When taken concurrently, cefuroxime diminishes the therapeutic effect of the antitubercular vaccine bacille Calmette-Guérin; these therapies should never be administered at the same time [7; 28].

MACROLIDE ANTIBIOTICS

Clindamycin

Clindamycin is a derivative of lincomycin and acts to inhibit bacterial protein synthesis by binding to the 50S ribosomal RNA (rRNA) subunit of susceptible bacteria; thus, it is bacteriostatic rather than bactericidal [7; 31]. Clindamycin is readily absorbed from the gastrointestinal tract and is distributed effectively to most tissues. It is actively transported into macrophages and leukocytes, both of which are highly concentrated in abscesses. The 2021 update from the American Heart Association Scientific Statement on the prevention of infective endocarditis no longer recommends clindamycin as an oral or parenteral alternative for patients who are allergic to amoxicillin or ampicillin [39]. This update reflects the concern that clindamycin has been associated with more frequent and severe reactions, including *Clostridioides difficile* infection. Azithromycin or clarithromycin have replaced clindamycin in this capacity [39].

It is also used in the treatment of orofacial infections that are not resolved with beta-lactam antibiotics, especially orofacial infections caused by susceptible anaerobic bacteria. The most significant adverse effect of clindamycin is the development of pseudomembranous colitis, which is caused by the overgrowth of *C. difficile*, a component of the gastrointestinal flora that is resistant to clindamycin. The development of this condition can be potentially lethal, so immediate medical attention is required and patients with a history of colitis should not take

this medication. Clindamycin may extend the effect of neuromuscular blocking drugs such as tubocurarine and pancuronium [7; 31].

Azithromycin

Azithromycin is a macrolide antibiotic derived from erythromycin. For many years, erythromycin was the antibiotic of choice for prophylaxis against bacterial endocarditis. However, gastrointestinal side effects, bacterial resistance, and interactions with several medications have led to erythromycin being used sparingly in the dental setting and discontinued in the antibiotic prophylaxis of bacterial endocarditis, except in certain patients at high risk for adverse outcomes [7].

Azithromycin is a bacteriostatic antibiotic that inhibits protein synthesis in susceptible bacteria. It is an alternative antibiotic for some patients with orofacial infections who cannot take beta-lactam antibiotics or clindamycin, and it is also an approved antibiotic for the prevention of bacterial endocarditis. Nausea, cramping, and vomiting are among the most common side effects associated with azithromycin. It also has potential to interact with several other medications. Azithromycin can decrease the metabolism and increase the anticoagulant effect of warfarin. Antacids taken concurrently can bind with azithromycin and prevent its absorption. Azithromycin may also interfere with the efficacy of oral contraceptive medications, so an alternative form of contraception is required for its duration [7].

TETRACYCLINES

Tetracyclines are generally not used in the treatment of acute orofacial infections or for prophylaxis of bacterial endocarditis. Instead, formulations of tetracycline are used as pharmacologic adjuncts in the definitive treatment of periodontal disease.

The decision to use antibiotics as adjunctive treatment for periodontal disease depends upon the patient's medical history and the extent of the periodontal disease. Patients should be informed that these medications are not substitutes for good oral hygiene, recall appointments, root planing and curettage, or periodontal surgery. The most common tetracyclines used in the treatment of periodontal disease are tetracycline, doxycycline, and minocycline. The benefits accrued through these medications extend beyond their bacteriostatic effect. They reduce inflammation and reduce matrix metalloproteinases such as collagenase, a protein that is associated with periodontal pathogens that damages connective tissue and bone [17].

Tetracycline can be administered systemically or locally. Doxycycline is also available in different formulations developed for various delivery systems. A systemic but subantimicrobial dose of doxycycline (20 mg) may be used as an adjunctive treatment for periodontal disease. At a dose of 20 mg, the therapeutic benefit is anticollegenase and anti-inflammatory rather than antibacterial, allowing the medication to be used daily for several months without the risk of developing resistance [40]. Doxycycline is also available in a controlled-release 10% gel formulation applied into periodontal pockets. This application is active for more than 21 days, and it is completely bioabsorbable, so no removal is required [7; 31].

Minocycline is most frequently administered via a local subgingival delivery system. It is supplied in unit dose cartridges, with 1 mg of minocycline base per cartridge. The minocycline dose is incorporated into a bioresorbable polymer, which is then placed into the periodontal pocket, where the therapeutic minocycline concentrations are maintained for 21 days [7; 31].

Each clinician must decide which tetracycline, if any, is appropriate for their patients. Periodontal disease can be refractory to conventional forms of definitive treatment with or without adjunctive pharmacotherapeutic support, and referral to a periodontist may be required.

One of the most notable side effects of tetracycline and its derivatives is irreversible staining of the developing permanent teeth. Therefore, tetracyclines should not be taken by women who are pregnant or nursing or children 8 years of age or younger [7]. As with the other antibiotics, drug interactions include an increase in the anticoagulant effect of warfarin and decreased efficacy of oral contraceptives.

ANTIFUNGAL MEDICATIONS

Antifungal medications are prescribed much less frequently in dentistry than conventional antibiotics or analgesics. However, each clinician should have a familiarity with the most common antifungal medications and indications for their use.

In dental patients, antifungals are mainly used to treat oral candidiasis, an infection that can develop secondary to various underlying causes. *Candida albicans* is the primary fungal organism among the oral flora that proliferates to cause oral and pharyngeal candidiasis. The Centers for Disease Control and Prevention has listed oral candidiasis as an acquired immunodeficiency syndrome (AIDS)-defining illness. An estimated 80% to 90% of patients with AIDS will develop oral candidiasis at some time during the progression of their disease [18]. In addition, patients taking oral antibiotics can develop an opportunistic case of oral candidiasis due to imbalances in the oral flora. Patients with other forms of immunosuppression, such as those taking chemotherapy, organ or bone marrow transplants recipients who require immunosuppressive medications for life, poorly controlled diabetics, and postradiotherapy oral cancer patients with a permanent reduction in salivary flow, are all susceptible to initial and recurring cases of oral candidiasis. This section will discuss the most common antifungal medications used to treat oral candidiasis. Some cases can be refractory to conventional oral antifungal medications and require more intensive treatment. Disseminated fungal infections among immunocompromised patients are associated with a high morbidity rate and even fatal termination. Oropharyngeal candidiasis that does not resolve with polyene or azole antifungal agents should be referred to a medical professional immediately.

NYSTATIN

Polyene antifungal medications such as nystatin act by combining with ergosterol, an important and unique constituent of the fungal cell membrane, to cause porosities in the membrane. This results in an outflow of the potassium ion and ultimately the death of the fungal organism [7]. Nystatin is most commonly prescribed as an oral suspension, dissolvable troches, or a topical ointment.

Typically, the adult dose of the oral suspension of nystatin for the treatment of oral candidiasis is 400,000–600,000 units four times every day [7; 19]. A swish-and-swallow protocol is utilized, as fungal organisms that have extended toward the esophagus can be treated as the oral suspension is swallowed. This regimen is followed for an average of 7 to 10 days. Nystatin is also available as a dissolvable troche that contains 200,000–400,000 units of the drug, usually taken four to five times daily [7; 19]. Patients using this formulation should be advised to remove any oral prosthesis to allow adequate contact between the oral mucosa and the dissolving troche. The ability of the nystatin troche to work properly depends on an adequate salivary medium, so any medication or condition that diminishes salivary gland output can decrease the efficacy of this formulation.

A topical ointment formulation of nystatin can be used to treat the mucocutaneous candidal infection angular cheilitis, which occurs at the corners of the mouth. The oral suspension and troche formulations will have inadequate access and contact time with this area. The topical version of nystatin can be combined with triamcinolone, a synthetic corticosteroid, to reduce the inflammation associated with this condition.

Nystatin formulations have high sugar content, so oral hygiene should be meticulous for the duration of its administration. Patients with diabetes should consult with their physician prior to its use. Because the oral suspension is not absorbed from the gastrointestinal mucosa, nystatin is not intended to be used for systemic fungal infections and usually will not interact with other medications. Side effects are generally mild and involve the gastrointestinal tract. A systemic antifungal agent should be considered if empiric therapy with nystatin does not resolve the initial fungal infection, as resistance to oral fungal organisms is a growing problem.

The successful treatment of oral candidiasis must also include the treatment of any oral prostheses in addition to the oral cavity. The acrylic of partial or complete dentures, orthodontic appliances, and night guards contain numerous microscopic porosities in which fungal organisms may reside. Without the elimination of this reservoir of fungal contaminants, a cycle of re-inoculation of the oral tissue can occur. The acrylic and metallic components of prostheses can vary considerably, so any substance designed to treat fungal organisms on appliances should follow manufacturers' guidelines.

AZOLE ANTIFUNGAL AGENTS

Azole antifungal agents are used for systemic fungal infections in addition to localized treatment of oropharyngeal candidiasis. These agents interact with enzymes necessary for the conversion of lanosterol to ergosterol. When this important fungal cell membrane constituent is lacking, increased fungal cell permeability causes the death of the fungal organism. Azole antifungals used in dentistry include fluconazole, ketoconazole, and clotrimazole [7; 18; 19].

Fluconazole

Fluconazole is available in both oral tablets and IV formulations, with oral administration most commonly used in the treatment of oropharyngeal candidiasis. It is indicated to treat oral candidal infections that have not responded to nystatin, candidiasis in patients with impaired immunocompetence, or infections with suspicion of antifungal resistance. Fluconazole is well distributed to all tissues, and food does not preclude its absorption. If hepatic or renal problems exist, fluconazole can exacerbate these issues [7].

The most common side effects of fluconazole are diarrhea, nausea, vomiting, headache, and dizziness. Fluconazole is taken once daily, and the duration of therapy and the strength of the prescribed dose will vary with the extent of fungal involvement and the patient's response to therapy. For typical, uncomplicated oropharyngeal candidiasis, the usual initial dose in adults is 100–200 mg daily for 7 to 14 days [7; 19].

Many medications can interact adversely with fluconazole, and a discussion of all possible drug interactions is beyond the scope of this course; only the most common will be discussed here. Fluconazole can enhance the anticoagulant effect of warfarin, so patients' international normalized ratios should be monitored if these medications are used simultaneously. The serum concentration of calcium channel blockers, a class of medications used to treat hypertension, can rise when taken concurrently with fluconazole [7]. This can result in excessive reduction in blood pressure and hypotension. If neither medication can be changed, consult a physician to determine if a temporary dose reduction of the calcium channel blocker can be prescribed. In addition, the serum concentrations of anxiolytic medications such as triazolam and diazepam are increased with the concomitant use of fluconazole, which can result in excessive sedation [7; 19]. Before fluconazole is prescribed, it is imperative that the clinician is aware of the potential interactions to medications the patient is already taking.

Ketoconazole

Like fluconazole, ketoconazole is a systemic antifungal medication that can also be used to treat oral candidiasis, but the pharmacodynamics of this medication are not as favorable as those of fluconazole. It is also available for a once daily dosing schedule at a dose of 200–400 mg, depending on the virulence of the fungal infection [7]. Ketoconazole depends on a high acidity level in the stomach for absorption, so onset of action will be delayed if antacids are used simultaneously. It has a high affinity for lipophilic tissues and accumulates in adipose tissue, which results in more toxic potential compared to fluconazole [7]. Patients with hepatic impairment should have the approval of their physician prior to the use of this medication.

There are numerous potential adverse interactions with other medications, many of which are identical to those noted for fluconazole. Additionally, the efficacy of oral contraceptives may be diminished with the concomitant use of ketoconazole. The macrolide antibiotics erythromycin and clarithromycin, which have occasional use for orofacial infections, can increase its serum concentration.

In 2013, the FDA limited the approved use of ketoconazole to certain fungal infections only when alternative antifungal medications are not available or tolerated [20]. This change was prompted by cases of severe liver injuries and adrenal gland problems in addition to potentially harmful drug interactions. Ketoconazole contains a boxed warning regarding its association with hepatotoxicity [7].

Clotrimazole

Clotrimazole is an azole antifungal available as a topical cream or troches. The troches, manufactured as a 10-mg dose, must be dissolved slowly in the mouth for the treatment of oropharyngeal candidiasis, as there is no systemic absorption if it is swallowed [7]. The usual dose is four or five troches per day for up to 14 days, with the extent of the oral candidiasis dictating the cumulative daily dose and duration [7; 19]. The troches contain a significant amount of sugar, so adherence to good oral hygiene practices should be emphasized while they are being used.

Clotrimazole is present in the saliva for several hours after its dissolution, as it is slowly released from the oral mucosa with which it initially binds. Patients who take any medication or have any condition that causes a reduction of salivary flow may be unable to use this medication properly and should consider an oral suspension of an another antifungal agent.

The side effects associated with clotrimazole are minor and consist of oral mucosal irritation and gastrointestinal upset. The lack of systemic absorption minimizes adverse interactions with other medications.

ANTIVIRAL MEDICATIONS

Diseases of viral origin span the spectrum in their virulence and associated degree of morbidity. All tissues and organ systems can be infected by viral organisms, with varying degrees of severity ranging from the annoyance of the common cold to the devastating immunosuppression caused by the human immunodeficiency virus (HIV). Viral disease can be particularly difficult to treat, and many viral diseases are incurable. Antiviral medications are often used to manage the virulence of viral outbreaks affecting the oral and maxillofacial structures.

Acyclovir and valacyclovir are the most common antiviral medications used to treat viral pathologies of the oral and maxillofacial complex. Other antiviral medications, such as ganciclovir, penciclovir, and famciclovir, are used in some cases, and each has its own spectrum of activity, side effects, and drug interactions. While it is uncommon to use these medications in the routine practice of dentistry, clinicians should have a solid knowledge of the underlying problems for which these medications are prescribed as well as their side effects and drug interactions.

ACYCLOVIR

The most common oral lesion of viral origin, recurrent herpes labialis, is caused by a reactivation of the herpes simplex virus-1 (HSV-1), which can lie dormant for years in a regional nerve ganglion. Illness, sunlight, emotional stress, and immunosuppression are among the most common factors to trigger a reactivation of HSV-1 from dormancy. The classic presentation of herpes labialis is the development of small, fluid-filled vesicles laden with viral particles, usually at the mucocutaneous junction of the skin and lips. The vesicles fuse to form larger lesions that ulcerate, crust, and heal within two weeks in healthy patients. Patients with herpes can experience mild discomfort and malaise, but systemic involvement is rare. Immunosuppressed patients, such as those with HIV/AIDS, may experience a more virulent course, longer healing times, systemic involvement, and overlapping recurrent episodes of successive outbreaks with a lack of complete healing.

Unlike antibiotic or antifungal medications, which target the cell wall or cell membrane, acyclovir becomes incorporated into the viral DNA and prevents further viral replication. Acyclovir and its derivatives are highly selective for viral DNA, so collateral damage to the host mammalian cells is spared [30]. The bioavailability of oral acyclovir is low, ranging from 10% to 20% [7]. While oral and topical formulations are prescribed most frequently, intravenous acyclovir is also available for patients whose immunosuppression is conducive to a longer and more virulent HSV-1 course. The topical form of acyclovir decreases viral shedding and can be applied directly to the lesion with a special applicator. Patients should be advised to avoid direct contact between the fingertips and the viral lesions. Viral inoculation of the finger can result in the development of recurrent herpetic outbreaks of the finger known as herpetic whitlow. Oral acyclovir is taken in either 200- or 400-mg doses three to five times per day [7]. The duration of treatment is determined by the extent of viral involvement. The medication may also be used to suppress future outbreaks.

Possible side effects of oral acyclovir include abdominal cramping, nausea, and vomiting. Simultaneous use of the antiviral medication zidovudine, which is used to treat HIV/AIDS patients, or probenecid, used to treat gout, can lead to adverse central nervous system effects [7].

Oral acyclovir may also be used to treat oral hairy leukoplakia, characterized by bilateral lesions on the lateral surfaces of the tongue. These corrugated white lesions are painless and fixed to the underlying tissue and arise as a result of reactivation of the Epstein-Barr virus in immunosuppressed patients. These lesions will regress with acyclovir therapy but often return upon its cessation.

Acyclovir can also be used for the treatment of the oral and cutaneous lesions caused by the reactivation of varicella zoster virus, also known as shingles [7]. Varicella zoster virus is the etiologic agent of chickenpox in children and young adults, and after this initial infection, the virus migrates to a cranial nerve or dorsal root ganglia, where it remains dormant until reactivation (often decades later). Immunosuppression, physical conditions or trauma, and emotional stress can prompt the reactivation of varicella zoster virus, causing shingles. Shingles lesions are usually found on the skin of the back, stomach, chest, or buttocks, but some may be facial or intraoral. In the oral and maxillofacial complex, lesions follow the distribution of the divisions of the facial and the trigeminal nerves and have a protracted course compared to recurrent herpes labialis.

The dosage and the route of administration of acyclovir for shingles is commensurate with the severity of the outbreak, with some cases in need of intravenous acyclovir. These patients are usually managed by a physician.

VALACYCLOVIR

Valacyclovir is an ester of acyclovir and is converted to acyclovir in the liver and gastrointestinal tract. It is only available in an oral formulation and is predominantly used to treat infections caused by the herpes simplex viruses, with limited activity against Epstein-Barr virus. It has much higher bioavailability (55%) compared to acyclovir [7].

The adverse drug interactions and gastrointestinal side effects of valacyclovir are similar to those of acyclovir. Caution should be exercised if this medication is used in immunocompromised patients, as rare but serious adverse incidents, such as thrombocytopenic purpura or hemolytic uremic syndrome, can occur [7]. Consult a physician if this medication is to be used for patients who are immunosuppressed, as an alternative antiviral medication may be required.

ANXIOLYTIC MEDICATIONS

Even in the modern era of dentistry, many people harbor conscious and subconscious fears of dental treatment and seek dental care only when an emergency occurs. These fears are exacerbated for patients with anxiety disorders and those who experience panic attacks in stressful situations. Previous negative experiences during dental treatment, fear of injections, dislike of the sight and sounds of varied dental handpieces (e.g., drills) and instruments, and the fear of pain are among the many reasons individuals may fear dental treatment.

Dental professionals may administer anxiolytic medications to calm patients and reduce the anxiety and fear associated with dental treatment. This section will highlight some of the most common oral and inhaled anxiolytic medications used by general dentists. Intravenous sedation and general anesthesia used by oral surgeons and for dental procedures performed in a hospital setting are beyond the scope of this discussion.

State regulations vary as to the type and combination of anxiolytic medications that can be used for each patient. Sedation at any level is associated with certain risks, including respiratory depression and allergic reactions, and clinicians who use any of these medications must be capable of managing emergency situations that develop pursuant to their use. Emergency training for all staff members is essential. State laws also vary as to the level of vital sign monitoring and cardiopulmonary resuscitation (CPR) training required for dentists and staff members. Used properly, anxiolytic medications can be an excellent adjunct in the treatment of dental patients, but their risks, side effects, and interactions with other medications should be considered before their use.

DIAZEPAM

Diazepam was the second benzodiazepine medication ever developed, first becoming available in 1963. Today, it is one of the core medications in the World Health Organization's Model List of Essential Medicines [21]. The bioavailability after oral administration is 90%, and peak plasma levels occur 15 minutes to 2.5 hours after oral administration, allowing for a rapid onset of action. When used as an anxiolytic medication before dental treatment, it may be taken both the night prior and one hour before the appointment. The dose depends upon the degree of anxiety, the patient's weight, concurrent use of other medications, and pertinent factors in the patient's medical history. The degree of sedation varies among individuals, so patients should not drive to or from their dental appointments if this drug is used. Diazepam has a lengthy half-life of 44 to 48 hours; the half-life of its active major metabolite, desmethyldiazepam, is 100 hours [7]. This extended half-life results in a protracted period of varying degrees of sedation, and any activity that would endanger the patient during this interval (e.g., operating heavy machinery) should be avoided.

Among the most common medical conditions that preclude the use of diazepam for sedation are severe respiratory disorders, alcohol or drug dependence, liver disorders, and renal disorders [7]. Hepatic pathologies such as hepatitis and cirrhosis impede the metabolism of diazepam and can allow accrual of the drug, causing excessive sedation and potential toxic accumulation. Similarly, renal impairment can decrease the excretion of diazepam and allow serum drug levels to remain high. Gastrointestinal side effects, such as nausea, vomiting, and constipation, can occur. Possible adverse central nervous system effects include amnesia, confusion, excessive sedation, and paradoxical excitement [7].

Diazepam has the potential for many adverse interactions with other medications, including some medications prescribed for oral health issues. Diazepam increases the depressive effect of narcotic analgesics and can exacerbate respiratory depression [7]. Simultaneous use of ketoconazole can decrease the elimination of diazepam and prolong its effect [22]. Patients who consume alcoholic beverages while taking diazepam can experience advanced sedation and hypotension. Before diazepam is administered for anxiolytic purposes, patients should be informed of its potential side effects and adverse medication interactions.

TRIAZOLAM

Triazolam, also a benzodiazepine drug, has been available in the United States since 1982. Triazolam has a rapid onset of action and a significantly shorter half-life (two to five hours) compared to diazepam. Therefore, there is a decreased potential for protracted sedation with this medication. Triazolam can be administered sublingually the night before a dental appointment to promote good sleep and one hour before the appointment for anxiolytic purposes, although this use is off label. The usual dose is 0.25 mg, with a maximum cumulative dose of 0.5 mg/day [7]. Unlike diazepam, triazolam has no active metabolites and does not cause extended sedation. In fact, the sedative effect of an initial dose of triazolam may not be sufficient for longer appointments. However, extreme caution must be used in the administration of additional doses of this medication. At least 90 minutes should elapse before even the lowest second dose (0.125 mg) is provided [7]. Given the variability in action among patients based on the degree of anxiety, weight, and medical history, excess sedation can occur in some patients even before the maximum cumulative dose is reached. The lowest possible initial and cumulative doses necessary to attain the desired sedative effect should be used.

Possible side effects of triazolam use include nausea, vomiting, drowsiness, dizziness, and in some cases, psychiatric disturbances [7]. Many medications have problematic interactions with triazolam, including drugs regularly used in dental care. Azole antifungal medications such as ketoconazole and antibiotics such as erythromycin can increase the blood plasma levels and effects of triazolam. Simultaneous use of narcotic analgesics and triazolam can cause enhanced respiratory depression. Hepatic impairment can decrease the metabolism of triazolam, while renal problems can decrease its excretion, both of which can cause increased plasma drug levels and enhanced sedation.

LORAZEPAM

Lorazepam has poor solubility in lipids, and its more hydrophilic nature accounts for its onset of action after oral administration. It has a half-life of approximately 10 to 20 hours in adults, which makes its duration of action shorter than diazepam but longer than triazolam [7; 22]. Compared with other members of the benzodiazepine group, lorazepam can produce better amnesic effects, but the extended length of sedation may be undesirable for patients. It can be administered the night before a dental appointment to promote sleep and two hours before the dental appointment to reduce anxiety. As with all anxiolytic medications, a responsible driver should transport the sedated patient to and from the dental appointment.

Interactions between lorazepam and other medications prescribed for oral health concerns can occur. As described for the other benzodiazepines, the concomitant use of narcotic analgesics can enhance respiratory depression. The potential drug interactions associated with lorazepam are numerous and beyond the scope of dental practice. If questions regarding appropriate use arise, a physician should be consulted. When lorazepam is used as a short-term anxiolytic for dental treatment, the side effects are usually confined to gastrointestinal upset. However, patients must be monitored carefully, as excessive sedation may occur with anxiolytic doses.

NITROUS OXIDE/OXYGEN INHALATION SEDATION

Nitrous oxide was first used in dentistry in the 1840s to minimize the discomfort patients experienced during the extraction of teeth [24]. While this formulation was comprised entirely of nitrous oxide without oxygen, it is the forerunner of the modern nitrous oxide/oxygen systems used today.

Also known as "laughing gas" or "sweet air," nitrous oxide/oxygen is used for its anesthetic and analgesic effects. Whether used alone or combined with an oral anxiolytic medication, state regulations exist defining the degree of training and certification required for the dentist and staff involved in administering this medication [25].

Unlike the first uses of pure nitrous oxide, conventional dental use of this gas today is combined with varying percentages of oxygen. A typical mixture is 30% nitrous oxide and 70% oxygen, with other proportionate combinations also used. This combination of gases rapidly diffuses into the bloodstream and is eliminated at the end of the session when pure oxygen is inhaled for five minutes; it is not metabolized by the body and is secreted essentially unchanged via the lungs. There are no known significant drug interactions, although there is some evidence that nitrous oxide may increase the risk of methotrexate-associated toxicity. Common side effects are postprocedural nausea and vomiting. Absolute contraindications to nitrous oxide use include emphysema, pneumothorax, middle ear surgery, air embolus, elevated intracranial pressure, and methionine synthase pathway enzyme deficiencies. Renal, hepatic, and neurologic problems may be noted, and fertility issues can develop in women exposed to multiple doses of nitrous oxide [5; 7].

To protect staff, scavenger systems are available to recover nitrous oxide that escapes from the system. All components of these delivery systems should be inspected on a regular basis, as chronic exposure to nitrous oxide can be hazardous. During the administration of nitrous oxide/oxygen, patients should only speak when there is an issue relative to their dental treatment in order to minimize the amount of nitrous oxide exhaled into the room. Properly fitted inhalation masks should be worn by the patient to decrease the amount of nitrous oxide leaked into the office.

The American Dental Association asserts that because sedation and general anesthesia are a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to diagnose and manage the physiologic consequences (rescue) for patients whose level of sedation becomes deeper than initially intended.

(https://www.ada.org/-/media/project/ada-organization/ada/ada-org/files/resources/research/ada_sedation_use_guidelines.pdf. Last accessed August 22, 2024.)

Strength of Recommendation/Level of Evidence: Strong recommendation, moderate quality of evidence

SPECIAL CONSIDERATIONS

Many factors can influence the absorption, distribution, metabolism, and excretion of medications, and before any medication is administered, these factors must be considered. The patient's weight, health issues, other prescribed medications, and current condition will influence the dose, frequency of administration, and duration of use of medication(s). The medical history should be updated with each patient visit, including information about any problematic experience that the patient has had with the use of prescribed or over-the-counter medications.

Systemic health issues will influence the choice of medications as well. Patients with hepatic problems, such as hepatitis or cirrhosis, often have decreased liver function and impaired ability to metabolize medications. Similarly, renal pathology can decrease the excretion of medications and allow a detrimental drug accumulation. In these patients, dose, frequency of administration, and the duration of treatment should be adjusted to prevent toxic accumulation or overdose of a given medication. Patients taking multiple medications for complex medical problems face the challenges of adverse drug interactions, inadequate drug metabolism, and impaired drug excretion. Consult the patient's physician if there are any concerns about prescribing additional medications for these patients.

Medication use may also be modified for pregnant or breastfeeding women. In 1979, the FDA established drug risk categories (lettered A, B, C, D, and X) for all medications according to the potential harm to the developing fetus or the mother. These categories were substantially updated in 2006 under the FDA's Physician Labeling Rule. Effective June 2015, the Pregnancy and Lactation Labeling Rule (PLLR) replaced the product letter categories with three detailed labeling subsections [6]:

- Pregnancy: The pregnancy subsection will provide information relevant to use of the drug in pregnant women (e.g., dosing, potential risk to fetus). It must also provide information about whether a registry exists that collects/maintains date on the drug's effect on pregnant women.
- Lactation: This subsection will provide information about use of the drug during breastfeeding (e.g., amount of drug in breast milk, potential effect on the child).
- Females and males of reproductive potential: This subsection will include information about pregnancy testing, contraception, and infertility as it relates to the drug.

The PLLR is intended to provide a more consistent way to include relevant information about the risks and benefits for the patient, the fetus, and the breastfeeding child. It will apply to all "newly approved" drug and biologic product applications. The labeling of previously approved products will be phased in gradually [6]. Any concerns about the use of a medication for a pregnant patient should be directed to the patient's obstetrician.

In 2020, the FDA announced the availability of a draft guidance entitled *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format* [8]. The draft guidance is intended to assist applicants in complying with the content and format requirements of the "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" subsections of labeling for human prescription drug and biological products described in the PLLR. The revisions provide clarification and additional information on recommendations in response to public comments and the FDA's regulatory experience implementing the PLLR [8].

Age is yet another factor to consider, as both the pediatric and geriatric populations have altered abilities to absorb, metabolize, and excrete medications. Both anatomic and physiologic differences in these patient populations require alterations in dosage and more extensive monitoring.

CONCLUSION

The vast array of medications available in dentistry has done much to improve the health of patients and the quality of dental care. However, because the use of medications has become so common, the risks associated with their use are often minimized. Allergic reactions, adverse drug interactions, and deleterious side effects are all issues that must be considered before prescribing or administering medications. The unique dental problems of each patient coupled with concurrent health issues, the use of any prescribed or over-the-counter medications, and the patient's status, age, and weight should be used to guide clinicians to select the medication(s) most appropriate for the circumstances.

This course has provided an overview of the most frequently used medications before, during, and after dental treatment, but it is by no means an exhaustive list. Textbooks and drug handbooks may be consulted for more extensive information. This discussion should heighten clinicians' awareness of the most frequently prescribed medications adjunctive to definitive dental treatment and the risks and benefits associated with their use.

A safe and responsible approach to prescribing and administering can minimize, but not eliminate, the occurrence of adverse medication-related events. All clinicians should strive to use medications that will combine safety and efficacy. This will improve the oral health and overall health of each patient and also ensure that individuals experience the best possible quality of life.

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Evidence-Based Practice Recommendation Citation

American Dental Association. *Guidelines for the Use of Sedation and General Anesthesia by Dentists*. Chicago, IL: American Dental Association; 2007. Available at https://www.ada.org/-/media/project/ada-organization/ada/ada-org/files/resources/research/ada_sedation_use_guidelines.pdf. Last accessed August 22, 2024.