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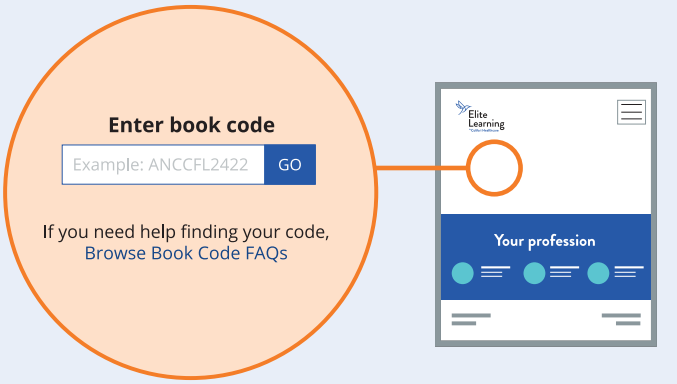

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Chapter 1: Infection Control, Cross Contamination, and Instrument Sterilization Techniques, 3rd Edition (Mandatory)

2 CE Hours

Release Date: October 31, 2022 **Expiration Date:** October 31, 2025

Faculty

Author:
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Eve Cuny has disclosed that she has no significant financial or other conflicts of interest pertaining to this course book.

Dental Planner: Karen Hallisey, DMD
The planner has disclosed that she has no significant financial or other conflicts of interest pertaining to this course book.

AGD Subject Code - 148

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INTRODUCTION

Learning objectives

After completing this course, the learner will be able to:

- Describe universal and standard precautions and protective equipment in the dental office.
- Recognize the factors governing treatment of patient care items.
- Describe infection control procedures and the steps necessary prior to sterilizing dental instruments.
- Discuss the sterilization processes most commonly used for dental instruments.

Course overview

This course is a basic-level refresher for dental healthcare personnel on infection control, cross-contamination, and instrument sterilization techniques. Areas addressed include infection control guidelines; understanding standard versus universal precautions; sterilization and disinfection of patient care items; goals for ensuring disease containment through proper instrument recirculation techniques; handling of contaminated instruments from the treatment room through precleaning, cleaning, and preparation for sterilization; the most commonly used (and accepted) methods of dental instrument sterilization; environmental infection control; dental unit waterlines, biofilm, and water quality; and other infection control considerations.

It should be noted that, with the arrival of the SARS-CoV-2 (COVID-19) pandemic, infection control has expanded to the outer office, with the advent of initial patient screening and patient masking. In the operatory, use of N95 masks and face shields became more of a standard practice (Kane, 2021). As has always been the case, it is important to follow guidelines, prescribed practices, and legal requirements.

DENTAL INFECTION CONTROL GUIDELINES

The Centers for Disease Control and Prevention (CDC) is the public health agency charged with disease surveillance and prevention in the United States. The CDC is not a regulatory agency, but it does recommend infection control precautions often used to form the basis for regulations set by state licensing boards and the Occupational Safety and Health Administration (OSHA). The CDC also works closely with other federal agencies that do have regulatory enforcement authority on issues of common interest, such as the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA; Harte, 2004).

With the advent of the *Bloodborne Pathogens Standard*, OSHA began requiring healthcare employers, including those in the dental profession to limit occupational exposure of employees to blood and other potentially infectious materials. OSHA began to require each health care facility to have an exposure control plan that provides a detailed description of how to reduce or eliminate occupational hazards. Included in the exposure control plan is a requirement to implement engineering controls (devices that isolate or remove the BBP hazard) and work practice controls (practices that reduce the likelihood of exposure by changing the way a task is performed). The exposure control plan should also include identification of job categories that involve exposure to potentially infectious materials (e.g., blood and saliva); the type and indications for the use of personal protective equipment (PPE); BBP training; exposure prevention and post-exposure management strategies; and providing HBV vaccinations for all employees with occupational exposure. Separate OSHA regulations address other safety-related items such as signs on exits, fire extinguishers, and additional safety equipment; and labels on products and chemicals used in the dental office.

In 2003, the CDC published guidelines for infection control in dental settings, providing dental professionals with comprehensive recommendations (Kohn et al., 2003). These guidelines were followed by commentary and clarifications from the American Dental Association and state dental societies (Harte, 2004; Kohn et al., 2004). In March of 2016, the CDC published a follow-up summary guide of basic infection prevention recommendations (CDC, 2016c). It is important to note that this 2016 document was not a replacement for the more extensive 2003 guidelines, but it did provide some updated information and a checklist to allow dental personnel to evaluate their compliance with the recommendations. The guidelines and summary are designed to prevent or reduce the potential for disease transmission from patient to dental healthcare personnel (DHCP), DHCP to patient, and from patient to patient. These recommendations provide the basis for preventing and reducing cross-contamination in the dental setting. The CDC believes that dental offices that follow these recommendations will strengthen their record of safe dental practice.

STANDARD VERSUS UNIVERSAL PRECAUTIONS

The concept of "universal precautions" was widely introduced in dentistry in the mid-1980s, based on the understanding that all blood and body fluids that might be contaminated with blood, should be treated as infectious for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and other bloodborne diseases (Broussard & Kahwaji, 2021; Kohn et al., 2003, 2004). The use of rubber dams to minimize blood spattering, handwashing, and the use of personal protective equipment are examples of preventive practices designed to reduce exposure to blood and other potentially infectious materials. Because of confusion among many healthcare workers concerning differences between universal precautions and body substance isolation, the CDC developed a new set of guidelines for isolation precautions in hospitals, termed "standard precautions" (Garner & The Hospital Infection Control Practices Advisory Committee, 1996; Segal, 2018).

Standard precautions expand upon universal precautions to include all body fluids, secretions, and excretions (except sweat), regardless of whether they contain blood. Standard precautions apply to percutaneous exposure, nonintact skin, and mucous membranes. As with universal precautions, DHCP should apply standard precautions for all patient encounters (CDC, 2016b; Harte, 2010).

Table 1: Standard vs. Universal Precautions

Standard precautions combine the major features of universal precautions and body substance isolation.

Universal Precautions

- This is an approach to infection control in which blood and certain body fluids are treated as if known to be infectious for:
  - HIV.
  - HBV.
  - HCV.
  - Other BBPs.
- Universal precautions were based on the concept that all blood (and body fluids that might be contaminated with blood) should be treated as infectious because patients with bloodborne infections are often asymptomatic or unaware that they are infected.

Body Substance Isolation

- Body substance isolation protects against pathogens that may exist in body substances and applies in all patient encounters regardless of the diagnosis (the same way, every day, for every patient).

Standard Precautions

- Standard precautions are the minimum infection prevention practices that apply to all patient care, regardless of suspected or confirmed infection status of the patient, in any setting in which healthcare is delivered. These practices are designed to both protect healthcare workers (HCWs) and prevent HCWs from spreading infections among patients.
- Standard precautions apply to contact with:
  - Blood.
  - All body fluids, secretions, and excretions except sweat, regardless of whether they contain blood.
  - Non-intact skin.
  - Mucous membranes.
- Standard precautions are employed in the care of all patients in the delivery of routine dental care and include:
  - Hand hygiene.
  - Use of PPE (e.g., gloves, gowns, masks, eye protection).
  - Safe injection practices.
  - Safe handling of potentially contaminated equipment or surfaces in the patient environment.
  - Respiratory hygiene/cough etiquette.

Note: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. (2003, Dec. 19). Guidelines for infection control in dental health-care settings. *Morbidity and Mortality Weekly Report, 52*(RR-17), 1-61; U.S. Department of Labor, Occupational Safety and Health Administration (1992). *Bloodborne Pathogens Standard. 29* C.F.R. §1910.1030; U.S. Department of Labor, Occupational Safety and Health Administration. *Occupational exposure to bloodborne pathogens; needlesticks and other sharps injuries; final rule*. Fed. Reg. 66:5317 (2001), 25. As amended from and includes Bloodborne Pathogens Standard. 29 CFR §1910.1030. *Occupational exposure to bloodborne pathogens; final rule*. Fed. Reg. 56:64174, 82.

HAND HYGIENE

Hand hygiene, which refers to handwashing and the use of antiseptic hand wash, antiseptic hand rub, or surgical hand antisepsis, is the most important aseptic procedure in the prevention of healthcare-associated infections (Harte, 2004; Johns Hopkins Medicine, 2020; Kohn et al., 2004; Organization for Safety and Asepsis Procedures, 2004; Sperrazza & Molinari, 2004). The purpose of surgical hand antisepsis is to eliminate transient flora and reduce resident flora for the duration of a procedure to prevent introducing organisms in the operative wound if gloves become punctured or torn. Proper hand hygiene should be performed:

- At the beginning of each workday.
- When hands are visibly soiled.
- When hands have been in contact with a patient's skin, saliva, or other body fluid.
- Immediately prior to donning gloves.
- Immediately after removal of gloves.

Several factors determine the preferred method for hand hygiene, including the intended procedure and the time that skin surface antimicrobial activity is required. Handwashing with plain or antimicrobial soap and water is adequate for routine dental examinations and nonsurgical procedures. For hands that are not soiled, clinicians can substitute alcohol-based hand rubs (Kohn et al., 2003; OSHA, 2019). Table 1 summarizes methods of hand hygiene.

Table 2: Hand Hygiene Methods and Indications

Method	Agent	Purpose	Duration (Minimum)	Indication
Routine handwash	Water and nonantimicrobial soap.	Remove soil and transient microorganisms.	15 seconds.	Before and after treating each patient. After barehanded touching of inanimate objects likely to be contaminated by blood or saliva. Before leaving the dental operatory or the dental laboratory. When visibly soiled. Before regloving after removing gloves that are torn, cut, or punctured.
Antiseptic handwash	Water and antimicrobial soap.	Remove or destroy transient microorganisms and reduce resident flora.	15 seconds.	
Antiseptic hand run	Alcohol-based hand rub.	Remove or destroy transient microorganisms and reduce resident flora.	Rub hands until the agent is dry.	
Surgical antisepsis	Water and antimicrobial soap OR water and non- antimicrobial soap, followed by an alcohol-based surgical hand-scrub product with persistent activity.	Remove or destroy transient microorganisms and reduce resident flora (persistent effect).	2-6 minutes. Follow manufacturer instructions for surgical hand-scrub product.	Before donning sterile surgeon's gloves for surgical procedures.

Note. Adapted from Table 2 in "Guidelines for Infection Control in Dental Health-Care Settings – 2003," by W. G. Kohn, A. S. Collins, J. L. Cleveland, J. A. Harte, K. J. Eklund, and D. M. Malvitz, *MMWR Recommendations and Reports, 52*(RR-17), pp. 1-61.

PERSONAL PROTECTIVE EQUIPMENT

Personal protective equipment (PPE) is designed to protect the skin and the mucous membranes of the eyes, nose, and mouth from exposure to blood or other potentially infectious materials. It also provides protection to the wearer's street clothes or work clothes. Gloves, surgical masks, protective eyewear, face shields, and protective clothing (such as long-sleeved gowns or jackets that cover the forearms) are among the primary PPE used in dentistry. On leaving patient-care areas, DHCP should remove all PPE. Cleaning reusable PPE with soap and water is recommended. These items should be disinfected between patients when visibly soiled according to the manufacturer's directions (Kohn et al., 2003).

Protection during activities likely to generate splashes or sprays of blood or body fluids should consist of protective eyewear and a surgical mask that covers both the nose and mouth. The eyewear should have solid side shields, or a face shield may be worn. The patient's eyes should be protected from spatter or debris by protective eyewear (Kohn et al., 2003). When performing dental procedures, the OSHA bloodborne pathogens standard requires sleeves of the gown or lab coat to be long enough to protect the forearms and prevent spray or splashing from dental procedures to reach the wearer's skin (OSHA, 2001). Procedures should be assessed for the likelihood of exposure, and PPE should be selected according to the type and degree of exposure that can reasonably be anticipated.

Because gloves are task-specific (Table 2), selection is based on the type of procedure to be performed:

- Patient examination gloves are indicated for routine patient care, examinations, and nonsurgical and laboratory procedures.
- Sterile surgical gloves are indicated for surgical procedures and are manufactured to meet FDA standards for assurance of sterility.
- Heavy-duty utility gloves are indicated for handling contaminated instruments or for cleaning and disinfecting operatory surfaces and instruments. These gloves are puncture-resistant and are often made of chemical-resistant materials, such as nitrile.

Exam and sterile surgical gloves may not be washed. Washing gloves may interfere with glove integrity, making the DHCP more susceptible to inadvertent contamination of the hands. In addition, patient examination and surgeon's gloves commonly contact multiple types of chemicals and materials (disinfectants and antiseptics, composite resins, and bonding agents) that can compromise the integrity of glove materials. If the integrity of a glove is compromised, it should be changed as soon as possible.

Table 3: Glove Types and Indications				
Glove	**Indication**	**Comments**	**Material**	**Attributes***
Patient examination gloves	Patient care, examinations, other nonsurgical procedures involving contact with mucous membranes, and laboratory procedures.	Medical device regulated by the FDA. Nonsterile and sterile single- use disposable. Use for one patient and discard appropriately.	Natural-rubber latex	1,2
			Nitrile-neoprene blends	2,3
			Neoprene	2,3
			Nitrile-latex blends	1,2,3
			Butadiene methyl methacrylate	2,3
			Polyvinyl chloride	4
			Polyurethane	4
			Styrene-based copolymer	4,5
Surgeon's gloves	Surgical procedures.	Medical device regulated by the FDA. Nonsterile and sterile single- use disposable. Use for one patient and discard appropriately.	Natural-rubber latex	1,2
			Nitrile	2,3
			Neoprene	2,3
			Nitrile-latex/neoprene blends	2,3
			Synthetic polyisoprene	2
			Styrene-based copolymer	4,5
			Polyurethane	4
Nonmedical gloves	Housekeeping.	Not a medical device regulated by the FDA, commonly referred to as utility, industrial, or general-purpose gloves. Should be puncture- or chemical-resistant, depending on the task. Latex gloves do not provide adequate chemical protection. Sanitize after use.	Nitrile-latex/neoprene blends	2,3
			Neoprene	2,3
			Nitrile	2,3
			Butyl rubber	2,3
			Fluoroelastomer	3,4,6
			Polyethylene and ethylene vinyl alcohol copolymer	3,4,6

* Attributes: 1, contains allergenic proteins; 2, vulcanized rubber, contains allergenic rubber processing chemicals; 3, likely to have enhanced chemical or puncture resistance; 4, nonvulcanized and does not contain rubber processing chemicals; 5, inappropriate for use with methacrylates; 6, resistant to most methacrylates.

Note. From Table 3 in "Guidelines for Infection Control in Dental Health-Care Settings – 2003," by W. G. Kohn, A. S. Collins, J. L. Cleveland, J. A. Harte, K. J. Eklund, and D. M. Malvitz, *MMWR Recommendations and Reports, 52*(RR-17), pp. 1-61.

STERILIZATION AND DISINFECTION OF PATIENT CARE ITEM

At the completion of the dental procedure, operators must safely process their reusable instruments and devices. Cleaning must precede any disinfection or sterilization process. Products and devices used to clean items or surfaces prior to disinfection or sterilization must be used in accordance with the manufacturer's instructions. Follow the manufacturer's instructions for cleaning solutions safe to use with the device, cycle times, and frequency of changing solutions. Sterilization is defined as the destruction of all forms of microbial life. The limiting requirement is the inactivation of high numbers of bacterial and mycotic endospores (often simply referred to as spores), which are produced asexually and tougher than ordinary spores (Cornell College of Agriculture and Life Sciences, 2022; Yoo, 2018). Proof of their destruction is the ultimate criterion for sterilization because these are the most heat-resistant microbial life forms (Dietz, 1992). Disinfection refers to the inhibition or killing of pathogens. Not all bacteria and mycotic spores are killed during disinfection procedures; with some classes of disinfectants, certain groups of nonsporulating pathogens also are not destroyed. Thus, disinfection represents a compromised, lower level of infectious disease control, in some cases far below the goals of sterilization. According to the CDC guidelines, heat sterilization using steam autoclaves, dry heat sterilizers, or unsaturated chemical vapor remains the standard of care (CDC, 2016a).

Patient care items (dental instruments, devices, and equipment) are critical, semi critical, or noncritical, depending on the potential risk for infection associated with their intended use (Kohn et al., 2003; FDA, 2018b).

Critical items are those used to perform invasive procedures and that come into direct contact with soft tissues or bone of the oral cavity. Critical items confer a high risk for infection if they are contaminated by any microorganism. These include scalpels, forceps, bone chisels, and manual cutting instruments. Critical items used to penetrate soft tissue or bone should be sterilized by heat between uses or be single-use, disposable items.

Semi critical items are those not intended to penetrate oral soft or hard tissues but that may come into contact with mucous membranes and nonintact skin. These include most dental instruments, digital x-ray sensors, intraoral cameras, and x-ray positioning devices. When possible, these instruments should be sterilized. Only if the item would be destroyed by heat sterilization should it be disinfected using an EPA-registered high-level disinfectant. Although dental handpieces are considered a semi critical item, the CDC guidelines indicate that they should always be heat-sterilized between uses rather than high-level disinfected (Kohn et al., 2003). In 2018 the CDC further clarified that all reusable attachments that can be removed from air and water lines should be heat-sterilized between each use. This includes handpieces, handpiece

motors, air/water syringe tips, and ultrasonic scaler tips, among others. They further clarified that DHCP must follow the manufacturer's instructions for reprocessing, and that if there are no reprocessing instructions the item should not be used (CDC, 2018a,c).

Noncritical items are those that contact intact skin and do not come into direct contact with body fluids. Examples include blood pressure cuffs, computer equipment, and x-ray heads. Contamination of these items and surfaces may occur during patient care from contact with DHCP- contaminated gloves, and they should be cleaned followed by disinfection with an EPA-registered low- to intermediate-level disinfectant. For items visibly contaminated with blood, DHCP should use an EPA-registered hospital disinfectant with a tuberculocidal claim (an intermediate-level disinfectant).

Instrument processing

The instrument processing section of the CDC guidelines details procedures surrounding instrument processing, including designation of a central instrument processing area and procedures to follow in the event of a positive spore test (Kohn et al., 2003). Before sterilizing instruments, specific steps must be taken by dental healthcare workers to ensure that proper sterilization will occur. When contaminated instruments are transferred from the treatment area to the sterilization area, certain procedural steps must be taken to ensure that sterilization is achieved. Manufacturer instructions should always be followed for acceptable packaging materials, operating parameters, and loading procedures for sterilizers.

Precleaning and cleaning

Precleaning is a critical step in the instrument processing cycle. It reduces the number of microbes present and removes debris, including blood, saliva, and other materials that may insulate microbes from the sterilizing agent, such as heat or steam under pressure. Often it is not practical or time-efficient to prepare instruments for sterilization immediately after dismissing the patient. Thus, contaminated instruments should be submerged in a holding or presoak solution or sprayed with a cleaning product intended for this purpose if they cannot be reprocessed immediately after patient care. The spray or soak will assist in preventing the drying of debris, which can make instruments much more difficult to clean. Wearing PPE, including heavy-duty utility gloves, a mask and protective eyewear or a face shield, and a gown or lab coat, is necessary when transporting the instruments and other devices requiring reprocessing to the sterilization area. The OSHA Bloodborne Pathogens Rule requires that reusable sharp instruments and devices be transported using a container with a solid bottom and sides, labeled with the universal biohazard symbol. Covers are not required for transport, but they may be used if there is concern about an accidental puncture injury. Items may either be placed in a presoak solution, sprayed, or placed directly into an ultrasonic cleaner or instrument washer/disinfector. The solution or spray used for holding should be a product intended and labeled by the manufacturer for that purpose. All products should be used according to the manufacturer's instructions for use, including the use of PPE, dilution, and shelf life, among others.

Cleaning is the next step and typically involves automated equipment or handwashing. This step remains critical for removing all blood and other debris that may interfere with the sterilization process.

Ultrasonic scrubbing

The CDC guidelines give preference to automated equipment, such as ultrasonic cleaners and instrument washers or washer/disinfectors, to clean instruments, over the more risky hand scrubbing (Kohn et al., 2003). In comparison to manual scrubbing, ultrasonic cleaning reduces direct contact with contaminated instruments, thus decreasing the likelihood of accidental cuts and puncture wounds. Furthermore, its cavitation action makes ultrasonic cleaning more effective than hand scrubbing. Ultrasonic cleaning also frees up DHCP to perform other duties necessary in preparing for the next scheduled patient.

It is important to remember when selecting an ultrasonic instrument cleaner to:

- Purchase the necessary accessories at the same time.
- Buy a unit that meets the office's needs.
- Avoid purchasing an ultrasonic unit that has a solution heating element, as overheating may cause burning of the hands.
- Choose a unit that features a side spigot to allow for easy draining directly into the sink.
- Select a unit with a timer that automatically terminates the cleaning action.

Most dental instruments can be safely cleaned ultrasonically. High-speed and slow-speed handpieces are notable exceptions. These can be hand cleaned or cleaned and lubricated prior to sterilization in an automatic handpiece reprocessing system. The manufacturer's instructions should always be checked regarding cleaning, lubricating, and sterilization procedures. Loose hand instruments, as well as those contained in an instrument cassette, may be cleaned ultrasonically. These must be suspended in a basket within the ultrasonic solution, not touching the bottom of the chamber. The ultrasonic unit should be covered during operation. Only solutions intended for use on dental instruments in an ultrasonic cleaner should be used to prevent damage to the unit or the instruments.

The cleaning effectiveness of an ultrasonic cleaner should be monitored at the start of a workday. There are two methods for testing the cleaning efficacy of an ultrasonic unit. The aluminum foil method consists of the DHCP holding a 3-inch square piece of aluminum foil partially in the cleaning solution, running the unit for 60 to 90 seconds, then removing the foil. If significant pitting (the appearance of pinholes) occurs, the unit is operating properly. The second method of testing is the use of a commercially available ultrasonic cleaning test. These tests consist of a vial with a solution inside that has a color-change indicator to verify that cavitation was present.

To summarize, when using an ultrasonic instrument cleaner, remember the following:

- Wear PPE when handling contaminated instruments.
- Proceed slowly and carefully because handling instruments can lead to accidental cuts and puncture wounds.
- Presoak instruments before placing them into the ultrasonic cleaning unit if the instruments will need to be held for prolonged periods of time.
- Limit the number of instruments or cassettes cleaned at a time so that all are completely submerged without touching the bottom of the unit.
- Use a cleaning solution specifically designed for use in an ultrasonic cleaner and change the solutions regularly.
- Operate the ultrasonic unit with the lid in place.
- Process instruments for the period of time indicated in the manufacturer's instructions for use.
- Rinse cleaned instruments well after processing.
- Empty the cleaner tank at the end of the workday or more frequently if heavily soiled, dry it completely, and disinfect the inside, lid, and accessories.
- Perform regular tests to check for cleaning efficiency.
- Follow the manufacturer's instructions for operation and maintenance.

Instrument washing/disinfecting

Another method for cleaning instruments prior to sterilization is the use of instrument washers and washer/disinfectors. These units typically accommodate more instruments and use automated washing cycles compared to ultrasonic cleaners. They eliminate the need for manual presoaking or hand scrubbing, rinsing, and drying. Some instrument washers, called *washer/disinfectors*, have a high temperature cycle to achieve high-level thermal disinfection along with cleaning. Many instrument washer/disinfectors use a combination of chemicals to remove organic and inorganic debris during the cleaning process. It is important to only use products indicated by the unit manufacturer as safe in instrument washers and washer/disinfectors. It is also important to remember that, although these units may appear to be similar to a home dishwasher, both instrument washers and washer/disinfectors are medical devices regulated by the FDA. Therefore, a household dishwasher is not an acceptable substitute for an FDA-approved instrument washer.

Hand (manual) scrubbing

Although hand scrubbing is an effective method of removing debris from contaminated instruments, it is not the preferred method, due to concerns about safety and effectiveness (Kohn et al., 2003). Because of the risk of accidental cuts and parenteral punctures, hand scrubbing increases the risk of the dental healthcare worker being exposed to patient body fluids. Hand scrubbing also requires additional staff time that could be more effectively used performing other related tasks in the office. According to the CDC's "Guidelines for Infection Control in Dental Health-Care Settings – 2003," the following recommendations apply:

> *"Use automated cleaning equipment (e.g. ultrasonic cleaner or washer-disinfector) to remove debris to improve cleaning effectiveness and decrease worker exposure to blood."*

If hand scrubbing instruments is necessary, remember the following:

- Wear PPE when handling contaminated instruments.
- Wear heavy-duty utility gloves, a gown or lab coat, eye protection, and a mask if spatter or spray may be produced.
- Proceed slowly and carefully because hand scrubbing can lead to accidental cuts and puncture wounds.
- Place a shallow scrubbing pan that allows the instruments to be seen in the bottom of the sink.
- Use a warm detergent solution.
- Place only five or six instruments in the pan and thoroughly brush the instruments while they are fully submerged (this helps avoid splattering).
- Rinse the instruments well, avoiding splattering.
- Rinse the cleaning brush well after use and make sure it is allowed to dry thoroughly and quickly.

Drying and wrapping instruments

After manual scrubbing or ultrasonic cleaning, instruments must be rinsed and dried. In order to ensure that instruments remain sterile after processing, they must be wrapped or placed in a sterilization pouch prior to sterilization and kept sealed until ready for use. Moisture will affect the integrity of sterile packs, and therefore sterilized packs must be stored in a manner that will protect them from contact with fluids and other contaminants. A closed drawer or cabinet provides suitable storage. All instruments and devices should be cleaned, packaged, sterilized, and stored according to the manufacturer's instructions for use. If the manufacturer does not provide reprocessing instructions for critical and semi critical patient care items, the item should be considered single use and disposed after one patient use, regardless of whether the manufacturer has labeled it as single use (CDC, 2021). The CDC guidelines specify that a chemical indicator should be placed within each package, or if not visible from the outside, an external indicator should be applied to the package (Kohn et al., 2003).

To be effective, sealed instrument wraps or packs should have no punctures, staples, or other rips or tears that would allow microorganisms to penetrate them. They must also be labeled or color-coded as to the date of sterilization, the sterilization load number, the sterilizer, and expiration date, if applicable (CDC, 2018c). Instrument pouches with a clear plastic side are ideal because they allow workers to view the contents of the pack without having to open it. Either a labeling system on the outside of the wrap or color coding for each procedure is recommended.

Types of instrument wraps include nylon sterilization film (available in a variety of widths that can be heat- or tape-sealed), paper or paper and plastic pouches, and sterilization wrap for large items such as instrument cassettes or surgical trays. Plain paper or paper bags will not maintain the sterility of the contents after processing and therefore are not appropriate to use for packaging instruments. At no time should sterilized instruments be touched with bare hands.

Contaminated sharps (scalpel blades, suture needles, matrix bands, orthodontic wires, and anesthesia needles) should be properly disposed of in a puncture-resistant sharps container, positioned as close to the point of use as possible. All sharps must be disposed of as soon as feasible after use (OSHA, 2011).

Hinged items and dental handpieces may require lubrication to maintain proper function. Excess amounts of lubricant should be removed before heat processing to prevent inadequate sterilization.

Sterilization methods

The three most common methods of dental instrument sterilization are steam under pressure (autoclave), dry heat, and unsaturated chemical vapor (Chemclave®). Other methods, such as ethylene oxide and vaporized hydrogen peroxide, are used in hospital settings but are not practical for dental office use because of toxicity, long cycle time (in some cases 10 hours or more), and high cost.

Steam under pressure

The autoclave works by using steam under pressure to kill all forms of microorganisms. The autoclave is not new to dentistry and is still the most widely used method of instrument sterilization. Packages of instruments must be loaded properly to ensure that steam penetrates all areas of the instruments placed inside the chamber. The proper way to load an autoclave is with packs either in a single layer, with heavier items on the lower shelves, or with pouches packed loosely standing on their sides, plastic facing paper. This allows the steam and heat to circulate between pouches and packs, coming into full contact with each one.

In order for sterilization to occur in an autoclave, air is removed (through either gravity displacement or dynamic air removal) and a vacuum is created for pressurization of the steam. With gravity displacement, steam is injected into the closed and locked sterilization chamber, forcing air out of the chamber through vents, eventually pressurizing the chamber. With dynamic air removal, air is removed mechanically and steam is injected into the vacuum created by the air removal. Dynamic air removal is a more efficient method of creating a pressurized chamber, and the cycle times for sterilization are 3 to 5 minutes as compared to 15 minutes for gravity displacement sterilizers. Regardless of the type of autoclave, always follow the manufacturer's instructions for use and maintenance. In addition, consult the instructions for

reprocessing for instruments and devices since different devices may require varied temperatures or cycle times.

Instrument packs should remain in the sterilizer until completely dried. Removing wet packs may result in tearing of packaging material or contamination of the sterile contents.

Unsaturated chemical vapor

Unsaturated chemical vapor sterilizers use a combination of heat, chemicals, and pressure. The sterilizer's reservoir is filled with a solution provided by the manufacturer. The solution is a chemical mixture rather than water, resulting in lower humidity during the sterilization cycle. This lower humidity may reduce the risk of corrosion of sensitive instruments. The cycle time is 20 minutes plus the pressure rise time of 3 to 8 minutes. The chemical vapor sterilizer reaches the sterilization temperature of 132°C (270°F), with a minimum of 20 psi.

Advantages of the chemical vapor sterilizer include a fast turnaround time and less damage to carbon steel instruments. It should be noted that carbon steel instruments are rarely used in modern dentistry and that carbon dental burs are considered single-use devices that should not be reprocessed. Disadvantages are that the solution emits a mild odor and requires proper ventilation, and the waste product produced is a hazardous waste in most locations.

Dry heat

Dry heat provides an acceptable alternative to autoclaving and unsaturated chemical vapor sterilization. It is less preferable, however, due to the long turnaround time and greater margin for error due to uneven heat distribution. The cycle requires 1 hour at 170°C (338°F) or 2 hours at 160°C (320°F). These higher temperatures may not be suitable for some devices, such as dental handpieces and plastic reusable items.

Instruments must be completely dry before dry heat sterilization, or they will rust or corrode. Also, the solder joints of some instruments cannot tolerate the heat of a dry sterilizer.

Nylon pouches may be used with dry heat sterilizers. Paper and plastic may scorch or melt and should not be used.

Monitoring the sterilization process

Monitoring the sterilization process not only involves the use of mechanical, chemical, and biological indicators (spore tests), but also includes initial and ongoing training of all staff members involved with instrument reprocessing and the maintenance of sterilization equipment (American Dental Association [ADA], 2021; Harte, 2004; Kohn et al., 2003). The importance of the association between instrument sterilization as a fundamental component of any infection control program and sterilization monitoring cannot be overstated. The CDC's "Guidelines for Infection Control in Dental Health-Care Settings – 2003" specifically address this relationship: "Use mechanical, chemical, and biological monitors according to manufacturer's instructions to ensure the effectiveness of the sterilization process" (Kohn et al., 2003). The CDC recommends at least weekly use of a biological indicator (BI; i.e., spore) test and a matching control. With particular reference to chemical monitoring, technological advances have led to the availability of improved chemical indicators and integrators for evaluating sterilization cycles (Table 3; Molinari, 2016).

One question concerning monitoring is how to check autoclave cycles between weekly BIs. As shown in Table 3, a Class 5 integrating indicator (integrator) contains a chemical that reacts with the three parameters of sterilization: temperature, pressure, and time. Movement of chemical ink in the strip into the "safe" or "accept" zone of a test strip serves as an immediate visual indication of the success of the sterilization cycle.

Heat-sensitive semi critical instruments

The CDC guidelines cover the use of liquid chemical germicides to either high-level disinfect or sterilize heat-sensitive semi critical instruments, whichever is appropriate (Kohn et al., 2003). According to the guidelines, heat-sensitive critical and semi critical instruments should be reprocessed by using FDA-cleared sterilants or high-level disinfectants or an FDA-cleared low-temperature sterilization method (such as ethylene oxide). DHCP should follow the manufacturer's instructions for use of these chemical sterilants and high-level disinfectants. The use of these products, particularly those containing glutaraldehyde, has raised safety concerns. Always use proper PPE and ventilation when using high-level disinfectants (OSHA, 2006).

Table 4: Types and Applications for Use of Sterilization Monitoring Devices

Monitor	Frequency of Use	Application (Release of Sterilizer, Package, Load)
Physical Monitors		
Mechanical monitors, including digital gauges, printouts of sterilization load parameters, etc.	Used for every sterilization load.	• Identification of mechanical failure/possible need for maintenance and reprocessing of load contents.
Chemical Indicators (CIs)		
Type 1 External indicators measuring single parameter of sterilization, such as heat.	Should be used on outside of every package unless the internal CI is visible.	• Failure indicates sterilization failure, which may be due to mechanical issues or operator error (e.g., overloading).
Type 2 Bowie-Dick type indicators	For testing of most dynamic air removal sterilizers. Consult sterilizer manufacturer's instructions for use to determine if a Type 2 test is indicated. If used, should be run, within a test pack, each day in an empty sterilizer before the first processed load.	• Test of sterilizer for efficacy of air removal and steam penetration; part of release criteria for using sterilizer for the day. • Part of release criteria for placing sterilizer into service after qualification testing.

Table 4: Types and Applications for Use of Sterilization Monitoring Devices		
Monitor	**Frequency of Use**	**Application (Release of Sterilizer, Package, Load)**
Type 3 Single critical process variable indicator	May be used to meet internal CI recommendations.	• Failure indicates either mechanical failure or operator error. Indicates need for load reprocessing and investigation
Type 4 Multi critical process variable	May be used to meet internal CI recommendations.	• Failure indicates either mechanical failure or operator error. Indicates need for load reprocessing and investigation.
Type 5 Integrating indicator	May be used to meet internal CI recommendations. Within a process challenge device (PCD), may be used to monitor sterilizer loads.	• Part of package release criteria at use site. • Part of load release criteria for nonimplant loads. • Part of release criteria for loads containing implants. • Implants should be quarantined until BI results are known, except in emergency situations.
Type 6 Emulating indicator	May be used to meet internal CI recommendations. Only used for specific types of loads. Not generally used in dental office settings.	• Part of package release criteria at use site. • Part of load release criteria for nonimplant loads. • Part of release criteria for loads containing implants. • Implants should be quarantined until BI results are known, except in emergency situations.
Biological Indicator (BI)	Should be run in a full load for sterilizers larger than 2 cubic feet; for table-top sterilization, should be run in a fully loaded chamber; for Immediate Use Steam Sterilization (IUSS), should be run in an empty chamber.	• Part of load release criteria. • Failure indicates mechanical issues or operator error.
Note. Adapted from AAMI (2017), ANSI/AAMI ST79:2017 Comprehensive guide to steam sterilization and sterility assurance in health care facilities.		

NEEDLES AND SHARPS SAFETY

Injuries with contaminated sharp instruments and needles pose a risk of bloodborne disease transmission to dental healthcare personnel. In a review of national surveillance data collected between 1995 and 2004, researchers examined occupational exposures among dental healthcare personnel in healthcare settings, including the types of injuries that occurred, the circumstances surrounding the injuries, and the individuals involved. General practice dentists sustained the greatest number of injuries during that time, followed by oral surgeons (Cleveland, et al., 2007). Attempts to reduce percutaneous or "sharps" injuries in dental settings have included reducing the use of needles, eliminating or isolating injury hazards by using sharps containers, needle-recapping devices, or self-sheathing needles, and instituting workplace controls (e.g., placing sharps containers closer to the point of use, recapping needles with one hand, and not passing unsheathed needles) (Cleveland, et al., 2007).

Because the majority of injuries involve needles, reducing or preventing these injuries is an important goal of an infection control program, and protocols for handling contaminated sharps are emphasized. Strict regulations by OSHA and other agencies address the use, handling, and disposal of sharps.

In the event that an injury does occur, a plan for managing occupational exposures must be in place and noted in the written protocol (CDC, 2017). Figures 1 through 3 outline the current OSHA Bloodborne Pathogens Standard and CDC protocols for occupational exposure. It should be noted that compressing a puncture wound to encourage bleeding is not recommended. Caustic agents such as bleach should not be used to cleanse a wound. Washing skin around an injury with soap and water or flushing mucous membranes with water is recommended to cleanse the area or remove debris.

The rates of seroconversions for bloodborne diseases following exposures is very low. On average, the risk after a percutaneous injury involving blood from a person infected with a bloodborne disease is 0.03% for HIV, 1.8% for HCV, and between 6% and 30% for HBV if the worker is unvaccinated (CDC, 2017). When new clinical employees are hired, they should receive training regarding the transmission of bloodborne pathogens, the wearing of PPE as protection, the tasks that place them at risk, and information on how to manage an occupational exposure. All training should be documented in the written protocol. Because HBV is the most easily transmitted of all the bloodborne pathogens (CDC, 2017; NIOSH, 2016), employees with occupational exposure to blood or OPIM should be offered HBV vaccination (Kuhar, et al., 2014).

Figure 1: Post-Exposure Management, Part 1

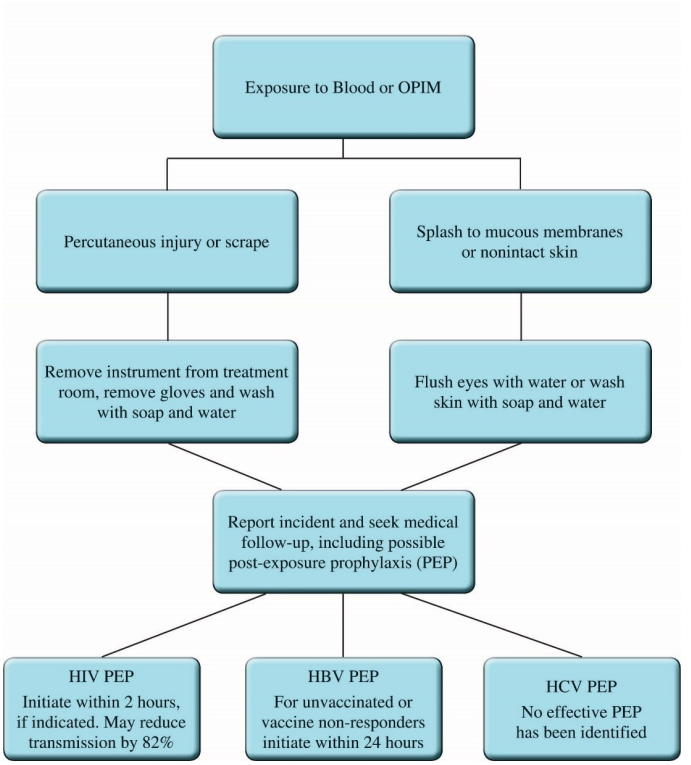
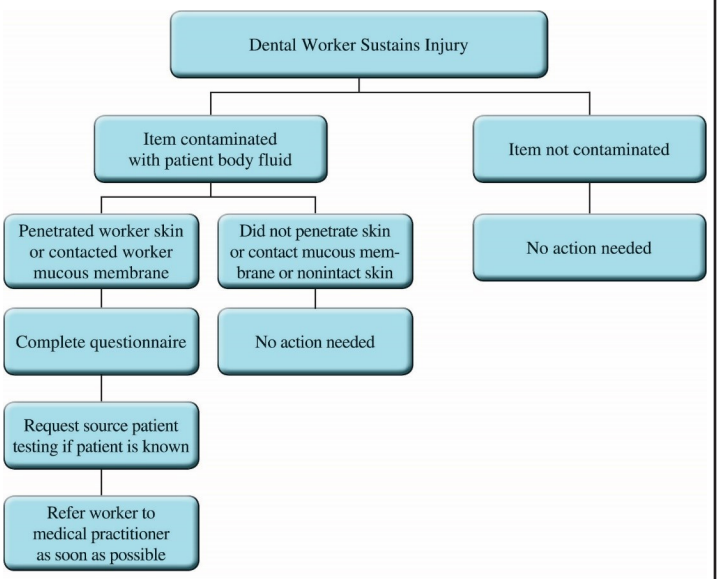
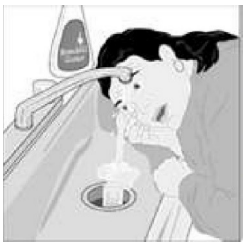


Figure 2: Post-Exposure Management, Part 2



Note. Adapted from "Guidelines for Infection Control in Dental Settings – 2003," by the Centers for Disease Control and Prevention, 2003, *MMWR Recommendations and Reports, 52*(RR-17), 1-68; and "Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis," by D. T. Kuhar, D. K. Henderson, K. A. Struble, W. Heneine, V. Thomas, L. W. Cheever, … A. L. Panlilio, 2014, *Infection Control and Hospital Epidemiology, 34*(9), 875-892.

Figure 3: Eye Exposures



Is this an acceptable method?

The OSHA Regulations state "a mechanism for flushing the eyes must be available to operators."

- It's hard to control the forces of the water with this method.
- Eyewash stations or sterile water in flush bottles are safer options.
- Irrigate the mucous membranes with sterile normal saline or water.

Treat occupational exposures as a medical emergency.

Note. Adapted from "Bloodborne Infectious Diseases: HIV/AIDS, Hepatitis B, Hepatitis C: Emergency Needlestick Information," by the National Institute for Occupational Safety and Health, 2014. Retrieved from http://www.cdc.gov/niosh/topics/bbp/emergnedl.html

ENVIRONMENTAL INFECTION CONTROL

In the dental operatory, environmental surfaces – surfaces or pieces of equipment that do not directly contact the patient – become contaminated during the delivery of care via contact with sprays and aerosols and DHCP's hands. Environmental surfaces include housekeeping surfaces and clinical contact surfaces. Housekeeping surfaces, such as floors, walls, and sinks, are not involved in the direct delivery of dental care. Clinical contact surfaces are those that are touched by contaminated hands, instruments, devices, or other items while providing healthcare-related activities.

Clean housekeeping surfaces with detergent and water. If blood or other body fluids are present, clean housekeeping surfaces followed by an application of a low-level disinfectant or dilute bleach.

Clinical contact surfaces may be cleaned and disinfected between patients, or impervious FDA-cleared surface barriers may be used to protect surfaces (CDC, 2019; Kohn et al., 2003). Barrier-protected surfaces do not need to be cleaned and disinfected between patients as long as barriers are changed, and the underlying surface is not inadvertently contaminated. Difficult-to-clean surfaces are good candidates for the use of surface barriers (Hill, 2020). DHCP should use gloved hands to remove contaminated surface barriers. The exam gloves worn during patient treatment provide an acceptable level of protection because there is no risk of sharps injury or chemical exposure in removing a surface cover. After disposing of the contaminated barrier, remove gloves and perform hand hygiene. A clean barrier can then be placed on the surface. Unless a barrier has been torn or punctured, or unless the exposed, "dirty" side of the barrier contacted the underlying surface, cleaning and disinfection of the underlying surface is not necessary between patients. It is generally sufficient to perform cleaning and disinfection at the end of the clinic day.

If barriers are not used, an EPA-registered nontuberculocidal hospital disinfectant can be used to disinfect surfaces that are not visibly contaminated if the germicide has an HIV and HBV kill claim. However, in the dental practice setting, tuberculocidal (intermediate-level) hospital disinfectants may be a more flexible

option. Surfaces with or without visible contamination can be disinfected with intermediate-level agents after the surfaces are cleaned according to label instructions (Organization for Safety and Asepsis Procedures, 2004). Precleaning must precede disinfection. If the manufacturer of the disinfectant indicates that the product may also be used as a cleaner, only one product will be necessary. For disinfectants that do not contain a cleaning agent, a separate product is necessary to first clean the surface of any debris that could interfere with the disinfection process.

DENTAL UNIT WATERLINES, BIOFILM, AND WATER QUALITY

The CDC guidelines recommend discharging water and air, for a minimum of 20 to 30 seconds after each patient, from any device connected to the dental water system that enters the patient's mouth (handpieces, ultrasonic scalers, air/water syringes, and so on; FDA, 2018; Kohn et al., 2003). The CDC has recommended that, during dental procedures, treatment water should contain no more than 500 colony-forming units (CFU) of bacteria per milliliter (Kohn et al., 2003). Standards established by the EPA set limits of no more than 500 CFU/mL for drinking water (ADA, 2022), and the CDC recommends that dental unit water also meet this standard (except for oral surgical procedures that require sterile water). Some form of treatment, such as filtration, disinfection, or a combination of the two, is required to meet the goal of 500 CFU/mL. Only products approved by the FDA or EPA are suitable for disinfection of dental treatment water.

In rare instances, dental patients have contracted life-threatening bacterial infections that were traced to dental water used to treat them (Peralta et al., 2016; Ricci et al., 2012; Ross, 2016). These cases reinforce the principle that untreated or unfiltered dental unit water is unlikely to meet the drinking water standard (Guritzky, 2016; Offner & Musset, 2021; Spagnolo et al., 2020; Walker et al., 2000). However, effective methods for improving the quality of this water include self-contained water systems combined with chemical treatment, in-line microfilters, and combinations of these treatments. The removal or inactivation of dental waterline biofilms requires the use of chemical cleaners and germicides. The CDC advises dentists to consult with the dental unit manufacturer for appropriate methods and equipment to maintain the recommended quality of dental water (CDC, 2018b; Kohn et al., 2003). For monitoring water quality, dentists should also follow recommendations of the manufacturer of the unit or waterline treatment product.

SPECIAL CONSIDERATIONS

The CDC guidelines contain a "Special Considerations" section, which includes a variety of topics (Kohn et al., 2003). Four of these are considered here.

Dental radiology

For dental radiology, the CDC guidelines recommend that DHCP wear gloves when exposing radiographs and handling contaminated film packets and use other PPE as appropriate if spattering of blood or other body fluids is likely. Intraoral devices (such as film holders and positioning devices) should be heat-tolerant or disposable whenever possible. Heat-tolerant devices should be cleaned and heat-sterilized between patients. At a minimum, semi critical heat-sensitive devices should be high-level disinfected according to the manufacturer's instructions.

The sensors used in digital radiology present a challenge in infection control. According to the CDC guidelines, they should be cleaned and ideally heat-sterilized or high-level disinfected between patients because they contact mucous membranes. However, these devices differ in their ability to withstand sterilization or high-level disinfection. If the item cannot tolerate these procedures, then, at a minimum, it should be protected with an FDA-cleared barrier and cleaned and disinfected with an EPA-registered hospital disinfectant with intermediate-level activity between patients. The manufacturer should provide information on appropriate disinfection methods and compatible products.

Oral surgical procedures

In the guidelines, the CDC clarifies the definition of an oral surgical procedure as any procedure involving the incision, excision, or reflection of tissue that exposes normally sterile areas in the oral cavity (Kohn et al., 2003). Examples include biopsy, periodontal surgery, apical surgery, implant surgery, and surgical extractions of teeth.

The CDC recommendations for oral surgical procedures include performing surgical hand hygiene before donning sterile surgeon's gloves and using sterile irrigating solutions during oral surgical procedures (Kohn et al., 2003). Sterile saline or sterile water should be used as a coolant/irrigant when performing oral surgical procedures, employing devices designed for delivering sterile irrigating fluids (such as a bulb syringe, single-use disposable products, and sterilizable tubing). The CDC guidelines recommend disposal of extracted teeth as regulated medical waste unless they are returned to the patient. Extracted teeth containing amalgam must not be disposed of in regulated medical waste intended for incineration. In most cases, extracted teeth may be given to the patient or used in educational settings after appropriate disinfection or sterilization.

Dental laboratory

DHCP are advised to use PPE when handling items received in the laboratory until they have been decontaminated (Kohn et al., 2003). Before they are handled in the laboratory, all dental prostheses and prosthodontic materials (impressions, bite registrations, occlusal rims, extracted teeth) should be cleaned, disinfected, and rinsed using an EPA-registered intermediate-level disinfectant. Consult with manufacturers regarding the stability of specific materials relative to disinfection procedures. Specific information regarding disinfection, including the solution used and the duration of use, should be included when laboratory cases are sent offsite and upon their return.

The CDC guidelines indicate that heat tolerant items used in the mouth, such as metal impression trays and face-bow forks, should be cleaned and heat-sterilized. The manufacturer's instructions should be followed for cleaning and sterilizing or disinfecting contaminated items that do not normally contact the patient, such as burs, polishing points, rag wheels, articulators, case pans, and lathes. If instructions are unavailable, clean and heat-sterilize heat-tolerant items. Heat-sensitive materials can be cleaned and disinfected with an EPA-registered hospital disinfectant with low- to intermediate-level activity, depending on the degree of contamination.

Program evaluation

The CDC guidelines offer recommendations on how to evaluate an infection control program. A successful program depends on establishing routine evaluation of the program, including evaluation of performance indicators, at an established frequency.

Dental offices should develop standard operating procedures, evaluate practices, routinely document adverse outcomes (such as occupational exposures to blood) and work-related illnesses in DHCP, and monitor healthcare-associated infections in patients. Strategies and tools to evaluate the infection control program can include periodic observational assessments, checklists to document procedures, and routine reviews of occupational exposures to bloodborne pathogens.

Conclusion

As dental professionals, we must be aware of the proper techniques to protect our patients and ourselves from disease and infection. We learned in this course specific guidelines for dental infection control; the difference between standard versus universal precautions; sterilization and disinfection of patient care items; proper handling of contaminated instruments from the treatment room through precleaning, cleaning, and preparation for sterilization; environmental infection control; proper cleaning of dental unit waterlines and biofilms; and other special considerations in relation to cross-contamination and infection control in the dental office.

Resources

- Association for Professionals in Infection Control and Epidemiology https://apic.org
- Centers for Disease Control and Prevention: Advisory Committee on Immunization Practices https://www.cdc.gov/vaccines/acip/index.html
- Centers for Disease Control and Prevention: Infection Prevention & Control in Dental Settings https://www.cdc.gov/oralhealth/infectioncontrol/index.html
- Immunization Action Coalition https://www.immunize.org/acip
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- Occupational Safety and Health Administration: Quick Reference Guide to the Bloodborne Pathogens Standard https://www.osha.gov/bloodborne-pathogens/quick-reference
- Occupational Safety and Health Administration: Dentistry https://www.osha.gov/dentistry
- Organization for Safety, Asepsis and Prevention https://www.osap.org
- S. Environmental Protection Agency: Selected EPA-Registered Disinfectants https://www.epa.gov/pesticide-registration/selected-epa-registered-disinfectants

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INFECTION CONTROL, CROSS CONTAMINATION, AND INSTRUMENT STERILIZATION TECHNIQUES, 3RD EDITION

Final Examination Questions

Select the best answer for each question and mark your answers on the Final Examination Answer Sheet found on page 60, or complete your test online at **EliteLearning.com/Book**

1. Standard precautions expand upon universal precautions to include all body fluids, secretions, and excretions except:
   a. Saliva.
   b. Blood.
   c. Sweat.
   d. Tears.

2. Proper hand hygiene should be performed:
   a. Immediately after removing gloves.
   b. Immediately after donning gloves.
   c. Immediately before removing gloves.
   d. Within an hour of surgery.

3. For routine dental examinations and nonsurgical procedures, hand hygiene can be adequately achieved by using:
   a. Hand cream with alcohol.
   b. Antimicrobial soap and water followed by alcohol.
   c. Plain soap and water or antimicrobial soap and water.
   d. High-level disinfectant.
4. Sleeves on protective clothing such as gowns or lab coats should be:
   a. Short to avoid contamination.
   b. Long enough to cover the forearms.
   c. Made of cotton.
   d. Dipped in disinfectant daily.
5. The selection of gloves to be used is based on:
   a. The patient's own flora.
   b. The patient and healthcare personnel's comfort.
   c. The manufacturer of the gloves.
   d. The type of procedure to be performed.
6. For laboratory procedures, the proper gloves are:
   a. Patient examination gloves.
   b. Surgical gloves.
   c. Nonmedical gloves.
   d. Medical gloves.
7. Disinfection differs from sterilization in not requiring:
   a. Destruction of free-living organisms with living cell walls.
   b. Removal of viruses such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV).
   c. Destruction of the tuberculosis pathogen.
   d. Killing of all bacterial and mycotic spores.
8. Critical patient care items should be:
   a. Disinfected with an intermediate-level disinfectant after use.
   b. Sterilized or high-level disinfected between uses.
   c. Heat-sterilized between uses or be single-use/ disposable.
   d. Low-level disinfected.
9. Semicritical patient care items should:
   a. Always be sterilized.
   b. Be heat-sterilized whenever possible or high-level disinfected using an EPA-registered product.
   c. Be disinfected whenever possible and sterilized otherwise.
   d. Always be disinfected.
10. According to the Centers for Disease Control and Prevention (CDC) guidelines, dental handpieces should always be:
    a. Low-level disinfected between uses.
    b. Intermediate-level disinfected between uses.
    c. High-level disinfected between uses.
    d. Heat-sterilized between uses.
11. Noncritical items that are visibly contaminated should be:
    a. Cleaned before reuse.
    b. Cleaned and disinfected with a low- to intermediate-level disinfectant before reuse.
    c. Cleaned and sterilized before reuse.
    d. Discarded.
12. The Occupational Safety and Health Administration Bloodborne Pathogens Rule requires that reusable sharp instruments and devices be transported using a container:
    a. Labeled with the standard precautions symbol.
    b. With a slotted bottom for easy drainage.
    c. With a solid bottom and sides.
    d. With a sealed cover at all times.
13. The CDC guidelines on instrument cleaning methods give preference to:
    a. Ultrasonic cleaning.
    b. Hand scrubbing.
    c. Manual scouring.
    d. Chemical disinfection.
14. Which dental instruments should be hand cleaned because they cannot be safely cleaned ultrasonically?
    a. Loose hand instruments.
    b. High-speed handpieces.
    c. Nonmetallic instruments.
    d. Contaminated instruments.
15. Steam under pressure is used for dental instrument sterilization to kill all forms of microorganisms in:
    a. The autoclave.
    b. Unsaturated chemical vapor.
    c. The ultrasonic cleaner.
    d. Dry heat.
16. Sterilization by dry heat may damage:
    a. Stainless-steel instruments.
    b. Large containers.
    c. Semicritical patient care items.
    d. Instruments with solder joints.
17. The CDC recommends monitoring the sterilization process using a weekly:
    a. Rinse with a sodium nitrite solution in the autoclave.
    b. Spore test and a matching control.
    c. Pressure check.
    d. Foil test.
18. Surfaces that are touched by contaminated hands, instruments, devices, or other items while providing healthcare are classified as:
    a. Housekeeping surfaces.
    b. Clinical contact surfaces.
    c. Maintenance surfaces.
    d. Medical surfaces.
19. Housekeeping surfaces can generally be cleaned with:
    a. Tuberculocidal hospital disinfectants.
    b. Detergent and water.
    c. Intermediate-level disinfectants.
    d. Hospital disinfectants with HBV and HIV kill claim.
20. According to the CDC guidelines, any device connected to the dental water system that enters a patient's mouth must be run after each patient to discharge water and air for a minimum of:
    a. No more than 5 seconds.
    b. 10 seconds.
    c. 12 to 15 seconds.
    d. 20 to 30 seconds.

Course Code: DNJ02IC

Chapter 2: Prescription Drug Abuse Among Dental Patients: Scope, Prevention, and Management Considerations (Mandatory)

5 CE Hours

Release Date: December 31, 2020

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Faculty

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The authors and peer reviewer have disclosed that they have no significant financial or other conflicts of interest pertaining to this course.

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AGD Subject Code - 134

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INTRODUCTION

Learning objectives

After completing this course, the learner will be able to:

- Describe the history and scope of prescription drug abuse and the role of the dental professional.
- Define the terminology used in discussing prescription drug abuse.
- Explain the pharmacology, physiology, and regulatory control of the prescription drugs that are most commonly abused and the extent and impact of their nonmedical use.
- Describe the populations most at risk for abusing prescription drugs and their access to these drugs.
- Discuss the tactics and resources available to manage and prevent prescription drug abuse in the dental practice.

Course overview

National concern is growing regarding the rise in prescription drug abuse in the United States. Addressing the abuse of drugs in general has been a long-standing battle for healthcare providers and law enforcement agencies, but the increased nonmedical use of therapeutic agents is particularly disturbing. Abuse of prescription drugs has increased so dramatically that in 2017 the United States Department of Health and Human Services (HHS) declared a public health emergency (HHS, 2019b). Prescription drugs carry an *aura of acceptability* because they are legal and prescribed by professionals, yet the repercussions of using them for other than their intended purpose are often neither recognized by the user nor discussed by the prescriber. Prescription drug abuse, like other forms of drug abuse, spares no one; it crosses boundaries of gender, age, race, and socioeconomic status. The abuse of prescription drugs is both an individual and a public health concern, costing individuals and the nation in terms of lost productivity and resulting healthcare costs, in addition to the devastating effects on families and significant others.

Dental providers frequently prescribe medications for their patients, especially for the control of pain. Although initially prescribed to help alleviate pain, their pleasurable side effects cause these drugs to be among those that carry the highest risk of abuse. Pain is often an unavoidable sequela to invasive dental procedures and untreated or long-standing oral disease. Balancing the desire to alleviate pain against the suspicion that the patient may be a drug seeker is just one of the issues that confront dental providers. The patient's past medical, dental, and social history; current history; chief complaint; and history of prescription drug use all contribute to the impression received by the dental provider. How the dental provider manages this information is critical to the result of the visit and subsequent outcome for the patient.

Diversion of prescription drugs is another part of the growing abuse problem. *Diversion* refers to the illegal use of legal drugs; it is seen most frequently with those drugs used to relieve pain (Coalition Against Insurance Fraud [CAIF], 2007). Diversion of drugs can occur when drugs are stolen or prescriptions are forged, as in the submission of fraudulent prescription claims to insurance companies, which is a significant portion of the problem (CAIF, 2007; U.S. Drug Enforcement Administration [DEA], n.d.b). Diversion also occurs when healthcare providers sell prescriptions to known abusers, or when pharmacists falsify records and sell the drugs involved (DEA, n.d.b). These forms of diversion all involve blatant criminal activity, but diversion can also occur when medications are shared with others for nonmedical use – actions that are also illegal. In fact, the primary source of prescription drugs for nonmedical users is through family and friends (Lipari & Hughes, 2017). "Doctor shopping," the practice of going to multiple healthcare providers to obtain prescription drugs for nonmedical use, is also considered to be a form of diversion (National Institute on Drug Abuse [NIDA], 2018c).

Over-the-counter (OTC) medications, although not the focus of this course, are also part of the problem of prescription drug abuse. These readily available medications, particularly cough and cold preparations, are often among the first drugs abused by adolescents. It is estimated that 1 in 11 teens have abused cough medicine or other OTC products (Stanford Children's Health, 2019). As dental providers explore their patients' histories of prescription drug use, they should also consider OTC preparation use and abuse (NIDA, n.d.e).

Although prescription drugs have been identified as essential tools to treat a myriad of illnesses as well as manage various levels of pain, it has been their recent "misuse" and its relation to the opioid overdose epidemic that has caught the attention of the nation (Blanco et al., 2007; Office of National Drug Control Policy [ONDCP], n.d.c). People across all demographics can appreciate the pleasurable side effects of these drugs and can be at risk for addictive behaviors. Additionally, life-threatening complications can occur when an individual other than the intended recipient takes these medications, or when the intended recipient takes them in a manner outside of their prescribed purpose. From 1999 to 2017, almost 218,000 people died in the United States from overdoses related to prescription opioids. Overdose deaths involving prescription opioids were five times higher in 2017 than in 1999 (Centers for Disease Control and Prevention [CDC], 2018d). In March of 2007, in response to these trends, and in recognition of this problem as a serious healthcare issue facing our nation, NIDA, a component of the National Institutes of Health, initiated its first large-scale national study related to prescription drug abuse (NIDA, 2007). Focused education and collaborative efforts are required to properly position healthcare professionals to help manage and prevent continued abuse of prescription drugs (Riggs, 2008).

The information provided in this course is applicable to all dental team members, regardless of their practice setting or scope of practice. The information is of interest to dental team members in private practice, academic institutions, military service positions, hospitals, and community health centers.

The purpose of this basic-level course is to provide dental practitioners with an appreciation of the scope of the problem of prescription drug abuse and a realization that the misuse and abuse of these drugs likely take place among the patient populations they serve. By becoming familiar with the pharmacology of the most commonly abused drugs, the risk factors for developing addictive behaviors, and the manner in which these medications are commonly acquired, dental providers will be positioned to curb prescribing practices that contribute to this growing problem and will be better able to serve their patients and their communities as informed prevention advocates.

THE ROLE OF PRESCRIPTION DRUGS

Prescription drugs have undoubtedly contributed to both the life expectancy and quality of life of countless individuals in the United States. However, use of prescription drugs is not without hazards. Some carry a significant risk for abuse and a potential for addiction. The three most commonly abused prescription drug categories – opioids, central nervous system (CNS) depressants, and stimulants – play an important role in mitigating the devastating manifestations of the diseases they treat and are used responsibly by most people (Mayo Clinic, 2018b; National Institute on Drug Abuse [NIDA], 2011b, 2018i). Opioids are prescribed to relieve pain that ranges from mild to severe and, when taken as prescribed, can be very effective.

Central nervous system depressants, such as sedatives and tranquilizers, are used for treating anxiety and sleep disorders. Due to their high abuse potential, stimulants are currently employed for only a few conditions, including for narcolepsy and attention-deficit/hyperactivity disorder (ADHD; Mayo Clinic, 2018b; NIDA, 2018h). Because the abuse and addiction potential for these drugs is high, the benefits from prescribing them must outweigh the associated risks for the patient.

The potential for misuse and abuse of prescription drugs

The prescription drug abuse problem has become an epidemic in the United States (McHugh, Nielsen, & Weiss, 2015), and in 2017 the United States Department of Health and Human Services declared it a public health emergency (HHS, 2019b). A number of possible reasons for the rise in prescription drug abuse in this country have been postulated. The volume of prescriptions written for the drugs in the most-abused categories increased substantially since the 1990s; between 1992 and 2002, as the U.S. population rose by 13%, prescriptions for controlled drugs rose 154% (Coalition Against Insurance Fraud, 2007). The overall opioid prescribing rate in the United States peaked and leveled off from 2010 to 2012 and has been declining since 2012, but the amount of opioids in morphine milligram equivalents (MME) prescribed per person is still around three times higher than it was in 1999 (CDC, 2018d). In spite of awareness of the problem, Medicare paid for more such prescriptions in 2012 than it had in 2011 (Ornstein & Jones, 2014). Pain relievers, the most abused category of drugs, have become both stronger and more effective, increasing their medical utility, but also their allure and street value. Adding to the problem of prescription drug abuse is our nation's culture of believing that a "pill" will cure all and that these pills' legal prescription status makes them somehow more acceptable or less harmful. Insufficient training of healthcare professionals and inadequate initiatives in educating the public are also factors that may contribute to the growing abuse problem.

The perception that prescription drugs are safe is also promoted when drugs are advertised or labeled misleadingly. For example, the manufacturer originally labeled OxyContin as "less addictive, less subject to abuse, and less likely to cause withdrawal symptoms" than other pain medications – claims that were unsupported by the findings of the U.S. Food and Drug Administration (FDA), but resulted in the drug becoming popular with narcotic users. In 2007, the drug's manufacturer pleaded guilty to felony misbranding (Chasan, 2007). About the time that OxyContin was first marketed, pain was gaining wider acceptance as a genuine medical condition, and the medical community increasingly recognized that patients, and chronic pain sufferers in particular, should not suffer needlessly when effective narcotic pain medications were available. Reflective of this thinking was the phrase coined by the American Pain Society and adopted in 2000 by the Veterans Health Administration: "Pain is the fifth vital sign." The unintended result of this shift in thinking regarding pain management was a surge in the number of prescriptions for opioid pain relievers and the proliferation of "pill mills" – clinics, pharmacies, and doctors' offices where narcotics are prescribed in large quantities or for nonmedical use under the pretense of legitimate pain relief (Coalition Against Insurance Fraud, 2007; Ling, Mooney, & Hillhouse, 2011). Researchers following this campaign to assist chronic pain sufferers found that their pain management was no more effective than before (Mularski et al., 2006).

All of the three most abused categories of drugs – opioids, stimulants, and CNS depressants – have a high potential for abuse and addiction, but their pharmacological effects vary. Opioids, for example, reduce the intensity of pain, but can also produce a euphoric effect in some individuals who might then seek to increase the intensity of the experience through repeated or enhanced use of the drug. Stimulants, which increase attention, alertness, and energy, are more widely prescribed than ever despite the limited conditions they are used to treat. These effects, their broad availability, and the perception that they are safe because they are legal, have resulted in an upsurge in their use by diverse populations, including high school and college students, athletes, performers, and older adults (NIDA, 2018h). Around 6 million Americans (approximately 2% of the U.S. population aged 12 and older) misused prescription stimulants in 2016 (CDC, 2018d). Central nervous system depressants can be abused for their relaxing effects or to counter or enhance the use of other drugs (NIDA for Teens, 2019a).

History of prescription drug abuse

The use and abuse of drugs is not new. Narcotics and related drugs are known to have been used from as early as 3400 BC for relaxation, stimulation, or euphoria (History.com, 2019a). Addiction problems in the United States were recognized as early as 1875, when San Francisco outlawed opium dens (History.com, 2019a). It was not until the twentieth century, however, that national drug laws were enacted, with the Pure Food and Drug Act of 1906 (U.S. House of Representatives, n.d.) and the Harrison Narcotics Tax Act of 1914 (History.com, 2019a). These laws required labeling of medications containing opium and certain other drugs and forbade the sale of such drugs except by designated professionals; in 1920, a Supreme Court decision also made it illegal for physicians to knowingly prescribe narcotics to "cater to the appetite or satisfy the craving of one addicted to the use of the drug" (Schaffer Library of Drug Policy, n.d.).

Drug abuse was recognized as a problem that often started at an early age and therefore required early intervention for prevention. Efforts by public school systems to introduce and require drug abuse education occurred as early as the 1930s, but were thwarted by fears that education would encourage experimentation; as a result, these efforts soon died out. At the same time that efforts by public schools began, other attempts to control drug abuse were being made by the federal government; however, by the 1950s, the use of marijuana, as well as amphetamines and tranquilizers, was increasing. In 1970, Congress enacted the Uniform Controlled Substances Act (CSA), which attempted to rank addictive drugs according to their abuse potential (Cornell University Law School, Legal Information Institute, n.d.). The result was the classification of drugs into the five schedules that we use today, with Schedule I being drugs with no accepted medical use, such as heroin and LSD, and Schedule V being controlled substances with a low potential for abuse, such as the antitussives, antidiarrheal, and analgesic preparations. In between, and ranked by abuse potential, Schedule II drugs include pain relievers such as oxycodone and stimulants such as amphetamines, Schedule III drugs include anabolic steroids and the anesthetic ketamine, and Schedule IV consists of some of the CNS depressants such as diazepam and alprazolam (U.S. Drug Enforcement Agency [DEA], n.d.a). (See Table 1.) The Uniform Controlled Substances Act will be further discussed in a later section.

In 1973, the Drug Enforcement Administration (DEA) was created to oversee enforcement of all controlled substance laws in the country. One year later, the National Institute on Drug Abuse (NIDA) was established as a federal agency for "research, treatment, prevention, training, services, and data collection on the nature and extent of drug abuse" (National Institutes of Health [NIH], 2018b). Fear that education would result in increased experimentation was finally countered by President Nixon's "War on Drugs" in 1971, which included a call to increase awareness through education (History.com, 2019b).

In 1988, the Anti-Drug Abuse Act was enacted to send a clear message of zero tolerance to the public, now including the user as well as the seller in the criminal and civil penalties that could

be imposed (U.S. Department of Justice, n.d.). It also provided for the establishment of the Office of National Drug Control Policy, which works to reduce drug use and its consequences by leading and coordinating the development, implementation, and assessment of U.S. drug policy (Executive Office of the President, Office of National Drug Control Strategy [ONDCS], n.d.a). Today, government continues to focus on drug abuse in general, but has become increasingly aware of the problem of prescription drug abuse in particular. In addition, nongovernmental organizations such as the National Coalition Against Prescription Drug Abuse (NCAPDA), founded in 2010, work to further raise awareness of this growing national problem (NCAPDA, n.d.).

The scope of the problem

In 2017, an estimated 6% of U.S. adults older than age 26 had used prescription drugs for nonmedical purposes for the first time within the past year. Also in 2017, statistics showed that as many as 14% of young adults aged 18 to 25 were currently using prescription psychotherapeutic drugs for reasons other than those intended (NIDA, n.d.f).

Table 1: Definition of Controlled Substance Schedules

Drugs and other substances that are considered controlled substances under the Controlled Substances Act (CSA) are divided into five schedules. An updated and complete list of the schedules is published annually in **Title 21 Code of Federal Regulations (C.F.R.) §§ 1308.11 through 1308.15**. Substances are placed in their respective schedules based on whether they have a currently accepted medical use in treatment in the United States, their relative abuse potential, and likelihood of causing dependence when abused. Some examples of the drugs in each schedule are listed here.

Schedule I Controlled Substances	• Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse. • Some examples of substances listed in Schedule I are heroin, lysergic acid diethylamide (LSD), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine ("Ecstasy").
Schedule II Controlled Substances	• Substances in this schedule have a high potential for abuse that may lead to severe psychological or physical dependence. • Examples of Schedule II narcotics include hydromorphone, methadone, meperidine, oxycodone, and fentanyl. Other Schedule II narcotics include morphine, opium, and codeine. • Examples of Schedule II stimulants include amphetamine, methamphetamine, and methylphenidate. • Other Schedule II substances include amobarbital, glutethimide, and pentobarbital.
Schedule III Controlled Substances	• Substances in this schedule have less potential for abuse than substances in Schedules I or II, and abuse may lead to moderate or low physical dependence or high psychological dependence. • Examples of Schedule III narcotics include combination products containing not more than 90 milligrams of codeine per dosage unit and buprenorphine. • Examples of Schedule III non-narcotics include benzphetamine, phendimetrazine, ketamine, and anabolic steroids.
Schedule IV Controlled Substances	• Substances in this schedule have a low potential for abuse relative to substances in Schedule III. • Examples of Schedule IV substances include alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, and triazolam.
Schedule V Controlled Substances	• Substances in this schedule have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics. • Examples of Schedule V substances include cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams and ezogabine.

Note. Adapted from "Controlled Substance Schedules," by the U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control, n.d.a.. Retrieved from https://www.deadiversion.usdoj.gov/schedules/

Emergency room visits involving prescription drug abuse have seen alarming increases. Approximately 1.2 million emergency room visits in 2011 were attributed to misuse of prescription drugs. Narcotic pain reliever-related emergency room visits involving nonmedical use increased 117% from 168,379 visits in 2005 to 366,181 visits in 2011 (Crane, 2015). These numbers do not include hospital visits and deaths resulting from the effects of driving while impaired by prescription drug abuse, a number that still remains largely unknown. Admission to treatment facilities for prescription drug abuse and addiction has also increased more than for most other drug admissions. According to the 2017 Treatment Episode Data Sets Annual Report on Admissions to and Discharges from Publicly-Funded Substance Use Treatment, the most frequently reported primary substances abused in 2017 were opiates (34%), alcohol (29%), marijuana/hashish (13%), stimulants (12%), and cocaine (5%), accounting for 93% of all admissions of patients aged 12 years and older. Additionally, the proportion of admissions aged 12 years or older for primary use of opiates other than heroin increased from 5% in 2007 to 10% in 2011 and 2012, before declining to 7% in 2017 (HHS, 2017).

The most frequently abused prescription drugs are those used for the control of pain, particularly opioids (NIDA, 2018b). The United States makes up only 4.6% of the world's population but uses 80% of the global supply of opioid pain relievers (Institute of Addiction Medicine, n.d.). Drug overdose deaths from opiates rose from 8,048 in 1999 to 47,600 in 2017. Deaths from opioid overdoses alone now outnumber deaths due to heroin and cocaine combined, and have increased six-fold in the past 20 years (NIDA, 2019a).

Populations at risk for prescription drug abuse cross all demographic sectors, although the drug of choice may differ. Colleges, for example, have seen abuse of prescription stimulants. Nonmedical use of Adderall increased between 2009 and 2013, but decreased from 2013 to 2017 (NIDA, 2018i). Certain populations may be more at risk than others, including youth, women, and older adults; people between the ages of 18 and 25 have the highest reported rate of abuse of prescription drugs (NIDA, 2018i). Early prescription drug use for nonmedical reasons, particularly prior to age 21, is a predictor of future abuse (McCabe et al., 2007; NIDA, 2018i). Older adults, particularly women, are more likely to abuse prescription pain relievers than any other substances (Hemsing, 2016). The number of pregnant women with opioid use disorder (OUD) at labor and delivery more than quadrupled from 1999 to 2014, according to an analysis by the CDC. The babies born to these

women may exhibit neonatal abstinence syndrome (NAS), and are more likely to have a developmental delay or speech or language impairment in early childhood compared with children born without NAS (CDC, 2018a,b). Patients with comorbidities (defined as two or more conditions that occur at the same time but for which there is not necessarily a cause-and-effect relationship), particularly psychiatric disorders, are significantly more likely to also abuse prescription drugs. Individuals who abuse other substances (for example, alcohol or illicit drugs) may also be more likely to abuse prescription drugs alone or in combination (NIDA, 2018b; Regier et al., 1990).

The prescription drug abuse epidemic affects society as well as individuals. Economic costs in the form of lost productivity, healthcare expenses, and law enforcement costs, to name a few, amount to tens of billions of U.S. dollars annually (NIDA, 2017). Inadequate or insufficient treatment of individuals suffering from abuse or addiction exacerbates this drain on the country's resources.

The role of the dental professional

Dentists are mentioned less frequently than other healthcare providers in the literature or on websites addressing the prescription drug abuse problem, yet dental providers can contribute to both the scope and prevention of this growing epidemic. Although there are fewer indications for dentists to prescribe stimulants or CNS depressants, the use of prescription pain relievers such as opioids is quite common in dental practices. Opioids are frequently used for the relief of acute pain resulting from infection or following invasive treatment procedures such as the extraction of third molars. In addition, the dental office can be a target for patients seeking prescription drugs for nonmedical use, including patients who engage in "doctor shopping" as a source of drugs.

The dental provider can take steps to avoid becoming an unwitting participant in the growth of the prescription drug abuse epidemic, including reviewing current prescribing practices and considering alternative medications for the control of pain. Working together, the dentist and office staff can effectively prevent abuse through awareness of the scope of the problem and identification of patients who are at risk for abuse or addiction, or who are currently abusing prescription medications. Education of both patients and staff can raise awareness, and identification of at-risk patients can result from the collaborative efforts of dentists, staff, physicians, and pharmacists. A thorough history that includes specific questions regarding past use of prescription drugs (California Dental Association, 2015) can identify potential abuse, yet research has shown that these questions are not frequently asked during the health history interview (Brown University, 2011). The use of screening tools in the dental office and frank conversations with the patient's network of healthcare providers when abuse is suspected or identified can curtail the problem of abuse. Having knowledge of the common characteristics and tactics of drug-seeking patients helps dental professionals identify these patients in their practice.

Definitions

The terminology surrounding drug abuse requires some standardization to enable practitioners to communicate effectively with patients and colleagues. In this course, the term *prescription drugs* refers to those controlled substances that are prescribed and dispensed legally by dental providers. In contrast, the term *illicit drugs* refers to those drugs that are not legally permitted and includes references to street drugs. The terms *prescription drug abuse* and *nonmedical use* have the same meaning for the purposes of this discussion and are in keeping with accepted terminology in the literature. These terms are defined as "the intentional use of an approved medication either without a prescription, in a manner other than how it was prescribed, for purposes other than prescribed, or for the experience or feeling the medication can produce" (Volkow, 2010). This includes a teenager sharing his narcotic pain reliever prescribed following third molar extractions with his best friend, for example, or this same patient continuing to use his medication for its pleasurable effects long after the need for pain management has ceased. This is in contrast to the term *misuse*, which generally refers to the *unintentional* and incorrect use of a medication by patients who may use a drug for other than the prescribed purpose, take too little or too much, take it too often, or take it for too long. The term "misuse" is also sometimes employed to refer to the behavior of dentists or other healthcare providers who prescribe medications for the wrong indication, at too high a dose, or for too long (Volkow, 2010).

Clarification of terminology regarding *addiction* and *physical dependence* is also important, particularly to avoid overdiagnosis of addiction when discussing issues of pain management. Addiction and physical dependence can occur together (NIDA, 2018d) or can be independent from each other. Addiction is compulsive drug use despite harmful consequences and is characterized by an inability to stop using a drug; failure to meet work, social, or family obligations; and sometimes (depending on the drug), tolerance and withdrawal (NIDA, 2018b). Therefore, a patient with chronic pain who is physically dependent on her medication in order to perform the necessary daily activities that allow her to get to work may not necessarily crave the medication or exhibit other signs of addiction; however, she may exhibit withdrawal symptoms if her medication regimen is significantly altered.

Tolerance refers to the need to use a higher dose of a drug to achieve the same effects previously achieved by a lower dose (Volkow, 2010). Tolerance occurs as the drug is used over time and, depending on the drug, can result from different physiological mechanisms. Tolerance to a drug is not synonymous with addiction, although the drug being used may also have addictive potential (Volkow, 2010). A patient with chronic pain, for example, may require an increase in the dosage of medication over time in order to provide adequate pain relief without exhibiting signs of addiction. It is important to note, however, that tolerance can occur alongside addiction.

HISTORY OF UNITED STATES DRUG LAW

Throughout this course, reference is made to *scheduled* or *controlled* drugs. Scheduled or controlled drugs are drugs whose use and distribution are tightly controlled because of their potential or risk of abuse. These drugs are classified into one of five schedules (see Table 1) based on whether they are otherwise useful in medical treatment. This drug scheduling system was first promulgated under the Uniform Controlled Substances Act of 1970, which was later superseded by the Uniform Controlled Substances Act of 1990. The 1990 Act attempted to:

- Establish uniformity between federal and state law, and uniformity among states, in the control of scheduled drugs.
- Classify *all* currently available substances into appropriate schedules.
- Anticipate the classification of drugs not yet available, such as newer "designer drugs" that might be developed in the future (Braun, 1991).

Terms such as *analogues* and *immediate precursor* were included in the legislation in an attempt to keep abreast of and deal with chemical derivatives of controlled drugs, which are synthesized to circumvent scheduling and hence not be considered illegal. Another component of the 1990 legislation was the provision of emergency scheduling as a method of combating emerging designer drugs. If a drug or chemical is deemed to be an imminent hazard to public safety, the substance can be scheduled without administrative delay. This provision of the bill has been invoked many times, for example when chemical modifications of "bath salts" chemicals and synthetic marijuana made their way into the drug abuse world.

The Uniform Controlled Substances Acts are actually successors to earlier laws such as the Harrison Narcotics Tax Act of 1914 and the Uniform State Narcotic Drug Act of 1934, which dealt with what we now refer to as controlled substances. In reality, the first government attempt to regulate drugs in the United States occurred with passage of the Pure Food and Drug Act of 1906 (FDA, 2019b). The act was designed to prevent the manufacturing, selling, and transporting of adulterated, misbranded, poisonous, or deleterious foods, drugs, medicines, and liquors. Prior to the Pure Food and Drug Act, labels on patent medicines were full of glowing endorsements of what these medicines could cure, but disclosed no information about their ingredients. Such patent medicines or "nostrums" often contained unregulated amounts of cocaine, opium, morphine, and even heroin. These early examples of legislation regulating food and drugs were essentially the beginnings of the FDA in the United States (FDA, 2019b). Although, technically speaking, drug regulation was first begun under the Pure Food and Drug Act, this legislation was primarily a "labeling law." It did not address two important subjects: drug safety and efficacy. These important subjects were not addressed until much later under the Food, Drug and Cosmetic Act of 1938 (drug safety; FDA, 2018b) and the Kefauver-Harris Amendments of 1962 (efficacy; Greene & Podolsky, 2012).

The first legislation dealing with what are now called *controlled drugs* was the Harrison Narcotics Tax Act of 1914. The purpose of the act was:

> *To provide for the registration of, with collectors of internal revenue, and to impose a special tax upon all persons who produce, import, manufacture, compound, deal in, dispense, sell, distribute, or give away opium or coca leaves, their salts, derivatives, or preparations, and for other purposes (Harrison Narcotics Tax Act, 1914a).*

Far from being a prohibition law, the Harrison Narcotics Tax Act was instead a law for the orderly marketing of opium, morphine, heroin, and other drugs – in small quantities over the counter and in larger quantities on a physician's prescription. Indeed, the right of a physician to prescribe was spelled out in apparently unambiguous terms:

> *Nothing contained in this section shall apply … to the dispensing or distribution of any of the aforesaid drugs to a patient by a physician, dentist, or veterinary surgeon registered under this Act in the course of his professional practice only (Harrison Narcotics Tax Act, 1914b).*

Registered physicians were required only to keep records of drugs dispensed or prescribed. Because the Harrison Narcotics Tax Act was primarily a revenue-producing act, the Conference of Commissioners on Uniform State Laws developed the Uniform State Narcotic Drug Act in 1934. This act was written to make the law uniform in various states with respect to controlling the *sale* and *use* of narcotic drugs. The commissioners intended to effectively safeguard and regulate narcotic drugs throughout all the states. Until passage of the Uniform Controlled Substances Act of 1970, the use, taxing, and distribution of narcotic drugs was regulated by the legislative acts of 1914 and 1934.

Two important laws were enacted between 1934 and 1970 that did not deal specifically with controlled substances, but rather with the safety and efficacy of drug products. The Food, Drug, and Cosmetic Act of 1938 extended the labeling requirements of earlier laws to include proof that the drug was safe. After years of legislative turmoil in the 1930s, a series of deaths attributed to elixir of sulfanilamide helped to bring this legislation to fruition (Wax, 1995; West, 2018). Sulfanilamide, an early sulfa drug, was safe. However, a concoction designed for pediatric consumption used a toxic chemical, diethylene glycol, to dissolve the drug. The provisions of the 1938 legislation were quite extensive, but still did not require a drug to be effective; it needed only to be safe. In 1962, in response to the birth defects caused by thalidomide in several countries, the passage of the Kefauver-Harris Amendments was accomplished (FDA, 2012; Tantibanchachai, 2018). These amendments stated that a drug had to be safe and effective for the specific disorder for which it was marketed. Moreover, the amendments essentially established the FDA as the government entity that had to grant approval before any human trials of a drug could be approved.

Although a discussion of all the legislation enacted in the past century to control prescription drugs is beyond the scope of this course, one final item relating to controlled substances should be mentioned. The Anabolic Steroids Control Act of 1990 added anabolic steroids to the list of controlled substances as Schedule III drugs in response to extensive abuse of these drugs in sports. The Anabolic Steroid Control Act of 2004 added prohormones (hormone precursors) as Schedule III drugs. The Designer Anabolic Steroid Control Act of 2014 added new designer anabolic steroids to the list (Council for Responsible Nutrition, n.d.).

PHYSIOLOGY AND PHARMACOLOGY OF DRUG ABUSE

The brain is a communication center consisting of billions of neurons. Neuronal networks pass messages back and forth to different structures within the brain, the spinal cord, and the peripheral nervous system. Communication between neurons is accomplished by release of neurotransmitters from presynaptic neurons that pass through a cleft or gap (*synaptic cleft*) and bind to receptors on the postsynaptic neuron. Neurotransmitter activity is terminated by synaptic enzymes or by reuptake into the presynaptic neuron. Virtually all drugs that work in the brain do so by affecting this system in one way or another.

Drugs may stimulate or inhibit neurotransmitter release, mimic neurotransmitter action, block receptors, inhibit metabolizing enzymes, or block presynaptic reuptake. Drug abuse (including abuse of prescription drugs) often involves interactions in various "reward systems" in the brain, often involving the neurotransmitter dopamine. The three most commonly abused prescription drug categories produce activity in one or more of the reward areas of the brain (as do nonpharmacological rewards such as food, music, and sex).

Stimulants

Pharmacologically, stimulant drugs are classified as *sympathomimetics*. These agents mimic the effects of the sympathetic nervous system, which causes the *fight* or *flight* response in the body (e.g., increased heart rate, pupil dilation). They mimic both central and peripheral effects of adrenergic agonists such as norepinephrine and dopamine, either directly or indirectly. Direct-acting agents specifically interact with and activate adrenergic receptors. Indirect-acting agents either displace stored neurotransmitters from adrenergic nerve endings or they inhibit the reuptake of neurotransmitters already released – either way increasing synaptic residence time and the amount of adrenergic receptor interactions. For the most part, therapeutically available stimulants are indirect-acting agents that *displace* stored neurotransmitters. In contrast, the most common illicit stimulant, cocaine, is an indirect-acting chemical that *inhibits* neurotransmitter reuptake.

Amphetamine and methamphetamine are contained in several products that are marketed for three purposes: weight loss and the treatment of narcolepsy and attention-deficit/hyperactivity disorder (ADHD). From a regulatory viewpoint, amphetamines are classified as Schedule II drugs, whereas "diet drugs" such as phendimetrazine (Prelu-2) are classified as Schedule III.

Adderall is a mixture of two amphetamine salts and two dextroamphetamines that is marketed for the treatment of ADHD. Methylphenidate (Ritalin, Concerta), also indicated for ADHD, differs structurally from amphetamines, but has similar indirect sympathomimetic activity.

Amphetamine abuse often involves altering oral dosage forms to prepare solutions for injection or powder for inhalation. The pleasurable experience and urge to continue drug use are primarily related to increased dopamine levels in the pleasure centers of the brain. As levels become excessive, the pleasurable effects can transform into hallucinations and delusions. Excessive levels of dopamine in the brainstem can lead to salivation, burning tongue, and nausea, whereas excessive levels in the motor areas of the brain can lead to involuntary muscle twitches and odd posturing. An amphetamine *high* is invariably associated with a noticeable *crash*, and tolerance develops with continued amphetamine use.

With the increased prescription use of methylphenidate (Ritalin, Concerta) for treatment of ADHD over the past decade, the incidence of its nonmedical use (via snorting and injecting) has also grown. The pharmacological effects of injected or snorted methylphenidate are qualitatively the same as amphetamines, although structurally different. Because it is easily accessible from siblings and classmates, methylphenidate is increasingly becoming a gateway drug for many adolescents. It is also in demand on college campuses for appetite suppression and late-night studying. The Monitoring the Future survey of substance use and attitudes in teens found that about 6% of high school seniors reported past-year nonmedical use of the prescription stimulant Adderall in 2017 (NIDA, 2018e). The total number of stimulant prescriptions in the United States grew by more than 500% from 2002 to 2013 (Schwartz, 2013). Although nonmedical use of Adderall increased between 2009 and 2013, it decreased between 2013 and 2017 (NIDA, 2018e).

Central nervous system (CNS) depressants

In general, CNS depressants produce dose-dependent pharmacological actions, including sedative/hypnotic, anticonvulsant, and anesthetic effects. All tend to produce similar adverse effects, such as respiratory depression, but to varying degrees. All CNS effects result from various interactions with actions of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The three main classes of CNS depressants are barbiturates, benzodiazepines (BZDs), and selective BZD agonists.

Barbiturates

The oldest of the CNS depressants, barbiturates have been used in clinical practice since the beginning of the twentieth century. It is currently hypothesized that barbiturates bind near postsynaptic GABA receptors in the CNS and prolong chloride channel opening in response to GABA binding. This increases postsynaptic chloride influx, which causes the neuron to hyperpolarize, resulting in generalized CNS depression. This dose-dependent depression can produce effects ranging from mild sedation to sleep, unconsciousness, and, in extreme cases, death due to respiratory depression. Like many other centrally acting drugs, tolerance develops to the therapeutic effects of barbiturates (e.g., sedation and sleep). Tolerance to the respiratory depressant effects develops more slowly, however; as patients increase the dose to overcome tolerance, blood drug levels rapidly approach toxicity.

Although their use as daytime sedatives has been largely replaced by the use of benzodiazepines, barbiturates still have limited use as anticonvulsants and anesthetics. Phenobarbital (Luminal, Solfoton) continues to be used in the treatment of seizure disorders, and the "ultra" short-acting injectable barbiturates, such as thiopental (Pentothal) and methohexital (Brevital), are used as adjuncts in surgical anesthesia.

The prevalence of barbiturate abuse is low relative to other classes of abused substances. Unfortunately, this is not the result of recognition of the dangers of barbiturates, but rather of their decreased availability. Prescriptions for barbiturates as daytime sedatives or nighttime hypnotics have been steadily declining since the introduction of the benzodiazepines in the early 1960s. From a practical viewpoint, barbiturate abuse is not a significant problem today; it has been replaced by benzodiazepine abuse.

Benzodiazepines

Benzodiazepines (BZDs) were first introduced with the release of chlordiazepoxide (Librium, Libritabs) in 1960, followed 4 years later by diazepam (Valium, Diastat). These drugs rapidly replaced the barbiturates, and by the mid-1970s were being enthusiastically prescribed (Skolniek & Poul, 1982; Wick, 2013). BZDs also act on the GABA system of the CNS. Unlike the barbiturates, BZDs are hypothesized to bind to specific BZD receptors in the brain that increase the affinity of GABA for its postsynaptic receptors. This results in neuronal hyperpolarization at lower release levels of GABA. More importantly, this mechanism imparts a "ceiling effect" on the central actions of BZDs, compared with the more direct actions of the barbiturates. Accordingly, BZDs were safer and less toxic than their predecessors. In 1970, the Upjohn Company (later acquired by Pfizer) introduced the first triazolo-benzodiazepine, known as *alprazolam* (Xanax, Nivravam). These derivatives were considerably more potent than diazepam and were heavily marketed. Although they supplanted diazepam in sales, partially due to the company's contention that they did not cause dependence, they in fact produced far more intense dependence than other BZDs. At least 10% of patients prescribed with Xanax became addicted (Skolniek & Poul, 1982).

Early BZDs, such as diazepam, and those that followed, such as alprazolam, were marketed as *anxiolytics* (anxiety-reducing agents). In the early 1970s, flurazepam (Dalmane) was introduced as the first of several BZDs to treat insomnia. Another BZD, midazolam (Versed), is one of the most common intravenous anesthetics in use. Despite their drawbacks, BZDs turned out to be safer than barbiturates for all these uses and essentially signaled the end of the clinical use of barbiturates.

Benzodiazepines are Schedule IV controlled substances. Because of this designation, they are more readily prescribed than many other prescription drugs of abuse. As many as one third of drug-related emergency room visits involve the use of BZDs (DEA, 2013). Virtually all such admissions involve the presence of one or more other drugs and/or alcohol. Although BZD abuse as a sole agent occurs, most BZD abuse occurs in combination with other abused substances. For example, in 2015, 23% of people who died of an opioid overdose also tested positive for benzodiazepines (NIDA, 2018a). A 2016 report by the Philadelphia Department of Public Health found benzodiazepine involvement in 90% of opioid overdose deaths in that city (Philadelphia Department of Behavioral Health and Intellectual Disability Services, 2018). This situation is discussed further in the section on drug combinations.

Selective benzodiazepine agonists

The BZD receptors of the CNS are classified into several subtypes depending on the responses to their binding and their substrate specificity. According to this scheme, BZD-1 receptors are hypothesized to mediate the sedative-hypnotic effects of BZD, whereas BZD-2 receptors are hypothesized to mediate adverse effects such as respiratory depression. Based on this thinking, a series of BZD-1 selective agonists were introduced in the 1980s that were supposedly more effective hypnotics with reduced respiratory depression and addiction potential.

The BZD-1 selective agonists include zolpidem (Ambien, Edluar), zaleplon (Sonata), and eszopiclone (Lunesta). They are marketed as "safer" alternatives to classic BZDs as treatments for insomnia. However, time has shown that these drugs are no less addictive than their earlier counterparts. Addiction to zolpidem (Ambien, Edluar) can occur accidentally among people taking it as a sleep aid. It acts rapidly and provides relief for anxiety and insomnia, but it also has a seductive euphoric effect that is enhanced when people resist going to sleep after taking it.

Another drug that deserves mention as a CNS depressant is the drug meprobamate (Miltown, Equanil). In the 1950s and early 1960s, meprobamate was marketed as a safer alternative to existing anti-anxiety drugs and remained quite popular until the introduction of chlordiazepoxide (Librium, Libritabs) and diazepam (Valium, Diastat). It has sedative and muscle relaxant effects with a poorly defined mechanism of action. Although now essentially obsolete, meprobamate is a metabolite of carisoprodol (Soma, Vanadom), which is a widely used muscle relaxant, and is a popular *co-drug* used in drug combinations.

Opioids

The term *opiate* refers to analgesics with a chemical structure analogous to morphine (i.e., drugs with a phenanthrene chemical nucleus). Opiates include morphine, codeine, oxycodone, hydrocodone, oxymorphone, and even the antagonist naloxone. *Opioid* is a broader term that encompasses centrally acting analgesics of any chemical structure. Opioids include the opiates (phenanthrenes), methadone (and other phenylheptylamines), and fentanyl (and other phenylpiperidines).

The opioid drugs have the potential to produce profound analgesia, mood changes, physical dependence, tolerance, and hedonic (rewarding) effects that may lead to compulsive drug use. They produce their effects by binding to opiate (opiopeptin) receptors that are found in both the CNS and the periphery. The most well-characterized receptors have been cloned and are designated mu, delta, and kappa. They all belong to a large family of receptors that possess seven transmembrane-spanning domains of amino acids (coupled to intracellular mechanisms via G-proteins). The specific pharmacological profile of an opioid depends on which receptor type the drug binds to and whether it acts as an agonist, a partial agonist, or an antagonist. Opioids produce analgesia by mimicking the natural opiopeptins, such as the enkephalins, beta-endorphin, dynorphin, and others. The opioids and the natural compounds produce analgesia by binding to presynaptic sites in pain pathways to inhibit release of excitatory neurotransmitters such as substance P (via effects on calcium channels), or by direct postsynaptic inhibitory mechanisms (via effects on potassium channels). Most opioids act at the mu and delta receptors to produce analgesia, euphoria, respiratory depression, and physiological dependence. Kappa receptors are more likely involved in producing spinal analgesia.

The principal therapeutic use for the opioids is treatment of moderate to severe pain. Activation of certain central receptors is the basis for their use as antitussives, whereas activation of receptors in the gastrointestinal tract is the basis for their use in treating diarrhea. Virtually all the clinically used opioids can be classified as full agonists capable of producing equal maximal reactions. The primary difference among the opioids is in the potency of each agent. Although a number of algorithms exist to convert doses of drugs into "morphine equivalents," care must always be taken when switching from one opioid to another. Such switching, or rotating, of opioids may be beneficial in certain instances due to differences in the receptor profile of individual opioids or due to genetic variability in opioid receptors across the population.

Tolerance and dependence are induced by chronic opioid exposure more than is the case for any other group of drugs (Kosten & George, 2002). Tolerance simply means that higher doses of the drug are gradually needed to produce a given effect (Mayo Clinic, 2018a; Volkow, 2014). When tolerance is fully developed, the maximum response attainable with the opioid is also reduced. Evidence suggests that tolerance may result from a gradual separating of opioid receptors from their G-proteins, thus uncoupling receptors from their effector system. Tolerance does not develop for certain opioid effects such as miosis (pupil constriction) and constipation. Accordingly, "pinpoint" pupils are diagnostic for opioid use (abuse) regardless of tolerance to other effects, and constipation is an issue in individuals using or abusing opioids chronically. The one exception is meperidine (Demerol), which in high doses does not cause miosis because of its anticholinergic activity and ability to block opioid effects on the oculomotor nerve. Although dependence usually accompanies tolerance, they are distinct phenomena. Dependence is not revealed until the drug is removed from its receptors, either by stopping administration or administering an opioid antagonist such as naloxone. This sets in motion a complex brain response characterized by the classic physical symptoms of withdrawal. Dependence generally occurs much more rapidly than tolerance.

A number of specific opioids are available for pain treatment, as well as a number of dosage forms for delivering these drugs (see Table 2). The most commonly prescribed products for chronic pain treatment are oxycodone and hydrocodone. Typical oxycodone regimens include a sustained-release baseline product (e.g., OxyContin, Percolone) and various immediate-release products to be taken as needed for breakthrough pain. Oxycodone products are available as single-component products or fixed combinations, usually with acetaminophen; all are classified as Schedule II drugs. Hydrocodone combinations (e.g., hydrocodone with acetaminophen [Vicodin, Lorcet]), which had been classified as Schedule III, are now classified as Schedule II (DEA, 2014). A more recent trend in sustained delivery involves use of skin patches. Fentanyl (Duragesic, Actiq) and buprenorphine (Butrans, Norspan) are examples of such products.

A number of pharmacological approaches are available to treat opioid addiction and overdose. Substitution or chemical detoxification through methadone maintenance programs have been a mainstay for decades. More recently, buprenorphine substitution, in an outpatient physician's office environment, has gained popularity. The principal product used in these programs is buprenorphine/naloxone (Suboxone and generics) sublingual film. Naloxone, an opioid antagonist, is not substantially absorbed by the sublingual route, but is present to prevent abuse by dissolving the films for intravenous injection. Injection of naloxone neutralizes the effects of the buprenorphine and may actually precipitate withdrawal in an opioid-tolerant patient. Opioid antagonists also have other roles in opioid abuse and overdose. Intranasal preparations of naloxone have been successfully shown to reverse respiratory depression in cases of opioid overdose (NIDA, 2018f). Significant public interest currently exists to examine methods for more widely distributing this life-saving therapy. Depending on the state, friends, family members, and others in the community may give the auto-injector and nasal spray formulation of naloxone to someone who has overdosed. Some states require a physician to prescribe naloxone; in other states, pharmacies may distribute naloxone in an outpatient setting without bringing in a prescription from a physician (NIDA, 2018b). In addition, depot injections (deep intramuscular injections of a dosage form that slowly releases active drug) of naltrexone (Vivitrol, ReVia) are available for detoxified patients to block opioid effects in the case of a drug relapse.

Table 2: Common Opioid Analgesics							
Generic Name	Receptor Effects1			Approximately Equivalent Dose (mg)	Oral: Parenteral Potency Ratio	Duration of Analgesia (hours)4	Maximum Efficacy
	Mu	Delta	Kappa				
Morphine2	+++		+	10	Low	4 to 5	High
Hydromorphone	+++			1.5	Low	4 to 5	High
Oxymorphone	+++			1.5	Low	3 to 4	High
Methadone	+++			10	High	4 to 6	High
Meperidine	+++			60 to 100	Medium	2 to 4	High
Fentanyl	+++			0.1	Low	1 to 1.5	High
Sufentanil	+++	+	+	0.02	Parenteral only	1 to 1.5	High
Alfentanil	+++			Titrated	Parenteral only	0.25 to 0.75	High
Remifentanil	+++			Titrated3	Parenteral only	0.054	High
Levorphanol	+++			2 to 3	High	4 to 5	High
Codeine	±			30 to 60	High	3 to 4	Low
Hydrocodone5	±			5 to 10	Medium	4 to 6	Moderate
Oxycodone[2,6]	++			4.5	Medium	3 to 4	Mod-High
Pentazocine	±		+	30 to 50	Medium	3 to 4	Moderate
Nalbuphine	—		++	10	Parenteral only	3 to 6	High
Buprenorphine	±	—	—	0.3	Low	4 to 8	High
Butorphanol	±		+++	2	Parenteral only	3 to 4	High

1 +++, ++, +, strong agonist; ±, partial agonist; —, antagonist.

2 Available in sustained-release forms, morphine (MS Contin); oxycodone (OxyContin).

3 Administered as an infusion at 0.025-0.2 mcg/kg/min.

4 Duration is dependent on a context-sensitive half-time of 3-4 minutes.

5 Available in tablets containing acetaminophen (Norco, Vicodin, Lortab, others).

6 Available in tablets containing acetaminophen (Percocet); aspirin (Percodan).

Drug combinations

Prescription drug abuse often involves combinations of drugs intended to intensify the abuse experience. The best known combination is called the *holy trinity*, which includes an opioid, alprazolam (Xanax, Nivravam), and carisoprodol (Soma, Vanadom). Alprazolam is a BZD sedative, and carisoprodol is a muscle relaxant that is metabolized to form meprobamate, a CNS depressant. This mixture is much sought after by drug abusers and has been implicated in the overdose deaths of drug-naïve teenagers (Fudin, 2014; Seay, 2014). Compulsive seeking of alprazolam or carisoprodol, even in the absence of opioid seeking, should be monitored by practitioners. Teens have been reported to combine drugs at *pharming* or *skittles* parties, at which prescription drugs, stolen from the home medicine cabinet, are randomly mixed and taken by the handful (Levine, 2007; Contemporary Pediatrics, 2014). It is a concerning risky behavior that allows for the ability to get high without regard for the type of drug that is being ingested, often along with alcohol (Contemporary Pediatrics, 2014).

Prescription drug abuse is a societal problem that will not magically go away. Careful prescribing of controlled substances and timely communication among healthcare practitioners can go a long way in alleviating the problem.

EFFORTS TO PREVENT NONMEDICAL USE OF PRESCRIPTION DRUGS

Executive office efforts

Evidence of the concern surrounding prescription drug abuse has been mounting in the past decades. Recognizing the seriousness of this epidemic and its impact on individuals and society, the U.S. government has invested attention and resources into its prevention and resolution. The government's dedicated efforts can best be seen in the Executive Office of the President of the United States, in which the Office of National Drug Control Policy (ONDCP) was established as a result of the Anti-Drug Abuse Act of 1988 (ONDCP, n.d.a). The ONDCP positions itself as a group that "works to reduce drug use and its consequences by leading and coordinating the development, implementation, and assessment of U.S. drug policy" (ONDCP,

n.d.a). The ONDCP Director is the principal advisor to the president on drug control issues. The ONDCP coordinates the drug control activities and related funding of 16 federal departments and agencies. The ONDCP also produces the National Drug Control Strategy, which outlines Administration efforts for the nation to reduce illicit drug use, manufacturing, and trafficking; drug-related crime and violence; and drug-related health consequences (New England High Intensity Drug Trafficking Area, n.d.).

In October of 2017, the White House declared the opioid crisis a public health emergency. In 2018, the Initiative to Stop Opioid Abuse was unveiled. According to the White House, the initiative was meant to confront "the driving forces behind the opioid crisis." Actions were intended to reduce "demand and over-prescription" and to educate Americans about the dangers of opioid misuse, cut down on the availability of illicit drugs "by cracking down on the international and domestic drug supply chains that devastate American communities," and help people "struggling with addiction through evidence-based treatment and recovery support services" (ONDCP, 2018).

Congressional efforts

In 2018, Congress passed the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act (the SUPPORT Act). This was a bipartisan bill aimed at addressing the nation's opioid overdose epidemic. The Act included provisions to teach addiction medicine and standardize the delivery of addiction medicine, while expanding access to high-quality, evidence-based care. Importantly, the Act also addressed coverage of payment for such care (American Society of Addiction Medicine [ASAM], 2018).

NATIONAL ORGANIZATIONS

The White House and Congress are not alone in their crusade against prescription drug abuse. Prescription drug abuse is the focus of several nationwide organizations that have joined forces to leverage each other's strengths and maximize their collective efforts. Organizations that exemplify the dedication and efforts being made to curb prescription drug abuse include NCAPDA, the NIH's NIDA, and the HEAL (Helping to End Addiction Long-term) Initiative (NIDA 2019b).

National Coalition Against Prescription Drug Abuse

In response to their son Joey's death on December 18, 2009, April and Joseph Rovero committed themselves to reducing the number of deaths attributed to prescription drug misuse and abuse by raising public awareness. Joey Rovero was a student at Arizona State University who died from an overdose combination of prescription drugs and alcohol; he had planned to come home for winter break the day after his death. April Rovero founded the National Coalition Against Prescription Drug Abuse (NCAPDA) in March 2010 and spreads its message concerning the dangers of prescription drug abuse through a nationwide campaign that includes ongoing collaborations with community organizations, healthcare representatives, law enforcement, schools, and other agencies. Through its slogan *One Pill Can Kill!*, NCAPDA is committed to sharing best practices, information, statistics, stories, and resources targeted to helping those afflicted and the loved ones searching for answers and guidance related to prescription drug abuse and learning about treatment and recovery options (NCAPDA, n.d.).

National Institute on Drug Abuse

A government entity dedicated to reducing prescription drug abuse is the National Institute on Drug Abuse. NIDA is "the lead federal agency supporting scientific research on drug use and its consequences." The Institute's 2016-2020 mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health through "strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved," as well as "ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder" (NIDA, n.d.g).

The NIDA comprehensive website (https://www.drugabuse.gov) offers wide-ranging educational materials; statistics; information on more than 16 of the most commonly abused drugs; fact sheets; podcasts; e-newsletters; and data regarding related topics, including addiction, comorbidities, criminal justice, drugged driving, drug testing, global health, medical consequences, and research on drug prevention and treatment. The Institute's organizational structure and funding reflect its dedication to this cause, and its approach suggests an understanding of its target audience. The Institute recognizes that prescription drug addiction is a topic of interest not only to parents, teachers, politicians, military leaders, and healthcare providers, but also to the broader general public (NIDA, n.d.a).

Helping to end addiction long-term

The National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) Initiative was launched in 2018, to be "an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis." The Initiative was to:

> *Build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with Medication-Assisted Treatment (MAT) for opioid use disorder (OUD). Successes from this research include the development of the nasal form of naloxone, the most commonly used nasal spray for reversing opioid overdose, the development of buprenorphine for the treatment of OUD, and evidence for the use of nondrug and mind/body techniques such as yoga, tai chi, acupuncture, and mindfulness meditation to help patients control and manage pain (NIH, 2019).*

Economic impact

In response to the level of national attention on prescription drug abuse, the National Rx Drug Abuse Summit (now the National Rx Drug Abuse & Heroin Summit) held its first annual conference in April of 2012, as a national collaboration of professionals from local, state, and federal agencies; business; and academia, along with clinicians and advocates affected by prescription drug abuse (National Rx Drug Abuse & Heroin Summit, n.d.).

One focus of this event and other related discussions across the country has been the national economic impact of the prescription drug abuse crisis, which includes costs associated with health care, crime, and lost productivity. In February of 2012, the website CNNMoney reported in an article titled "How Prescription Drug Abuse Costs You Money" that in 2006 as a nation we had spent $8.2 billion on the criminal justice bill and incurred $42 billion in lost productivity related to nonmedical use of prescription opioids (O'Toole, 2012). In addition, each patient

who engages in the act of "doctor shopping" – going from doctor to doctor, complete with expensive diagnostic tests and emergency room visits, for the purpose of acquiring prescription drugs – costs an insurer from $10,000 to $15,000 annually (CAIF, 2007; Hansen et al., 2011).

According to the Pew Charitable Trusts (2017), annual costs of prescription opioid misuse, overdose, and dependence include $28.9 billion in health care costs (with patients with an OUD incurring annual additional costs of approximately $18,000). Society pays another $7.6 billion in criminal justice costs (with 96% of these costs falling on state and local governments). The estimated annual cost of lost productivity is $41.8 billion with 7 in 10 employers experiencing "issues associated with prescription drug misuse, such as employee absenteeism, decreased job performance, and injury."

The remarks of an addict, posting under the pseudonym punkin0201 in reaction to the CNNMoney article, are troubling:

> *I am a recovering addict (from prescription pain pills) and I currently have 2 years clean. What I still say to this day is that it is sad that not only are these prescriptions given out like candy (I was being prescribed 360 Percocet [pills] a month), but insurance companies will only charge you the copay to get them. So pretty much for $5, my copay for generic, I was getting all of those pills. But the truly sad part is that when I needed to go to rehab to try to arrest my addiction, that same insurance that let me pay $5, would only pay for and allow me to stay in rehab for 8 days, when it was recommended that I stay 45 days (O'Toole, 2012).*

The CAIF report compared the 2007 retail price and street value of several prescription drugs known to be most commonly abused. The report noted that retail prices were supplied by Walgreens.com, whereas street values were obtained from a group of sources (including information gathered from police representatives; the Office of the Attorney General of Kentucky; and the Warren County, Ohio, Drug Task Force). According to this report, several drugs – including: oxycodone 40mg, Ritalin, Adderall, Vicodin, hydrocodone/APAP (with acetaminophen), Valium, diazepam, Adipex, Xanax 2mg, and alprazolam – could be bought on the streets for less than $10 a pill (CAIF, 2007). A CNN Money report of 2011 revealed that prices had not changed substantially (Kavilanz, 2011).

The website StreetRx.com uses crowdsourcing to identify and track the street value of prescription as well as illicit drugs. The site shows current prices for each drug in various parts of the country (StreetRx.com, n.d.). Table 3 shows an example of a StreetRx display for Adderall. For comparison, as of late June 2019, one website was showing that a single 30 mg Adderall capsule, sold in a bottle of 60, was selling in pharmacies around the country for approximately $7.50. A 10 mg capsule in a bottle of 7 was being sold for approximately $8.50 (PharmacyChecker.com, n.d.).

StreetRx users can anonymously post, view, and rate submissions. This site offers an inside look at the black market. By providing invaluable information about the preferences of users, health communication specialists can adapt outreach efforts to the needs of their communities (StreetRx.com, n.d.). As of 2016, the prices reported on this site had been validated by two separate sites, one governmental and the other illicit (Dart et al., 2016).

Table 3: Example of a StreetRx Display for Adderall Pricing

Prices for Adderall - USA
□ Include products with the same active ingredient

$5 Jun 16, 2019	Adderall, 5mg pill New Jersey	Rate: $ $ $ $ $ $
$5 Jun 16, 2019	Adderall, 10mg pill Houston, Texas	Rate: $ $ $ $ $ $
$25 Jun 16, 2019	Adderall, 15mg pill Los Angeles, California	Rate: $ $ $ $ $ $
$4 Jun 16, 2019	Adderall, 20mg pill Missouri	Rate: $ $ $ $ $ $
$10 Jun 16, 2019	Adderall, 20mg pill Kentucky	Rate: **$ $ $** $ $ $
$5 Jun 16, 2019	Adderall, 30mg pill North Dakota	Rate: **$** $ $ $ $ $
$15 Jun 16, 2019	Adderall, 30mg pill Meridianville, Alabama	Rate: **$ $ $ $ $** $
$10 Jun 16, 2019	Adderall, 30mg pill Ohio	Rate: **$ $ $** $ $ $
$10 Jun 16, 2019	Adderall, 10mg pill Poughkeepsie, New York	Rate: **$ $ $ $ $** $

The economic impact of opioid abuse has also been studied. In 2005, White and colleagues examined the medical and pharmacy claims of 16 self-insured employer health plans from 1998 to 2002. Their study included data from more than 2 million people; their findings concluded that:

> *Opioid abusers, compared with nonabusers, had significantly higher prevalence rates for a number of specific comorbidities, including nonopioid drug poisoning, hepatitis (A, B, or C), psychiatric illnesses, and pancreatitis, which were approximately 78, 36, 9, and 21 ($p < 0.01$) times higher, respectively, compared with nonabusers (White et al., 2005).*

These higher prevalence rates translated into increased hospital costs to treat these patients; treatment costs for opioid abusers were 12 times higher than for those who had no abuse activity for the same drug (White et al., 2005).

One cost of prescription drug abuse that has come under increasing scrutiny is the role of prescription drugs as gateway drugs to heroin abuse. For people who have become addicted to prescription opioids and now find that they are difficult to access or too expensive, heroin may become the alternative (CDC, 2014; Muhuri et al., 2013; NIDA, 2018g; Sacco et al., 2018).

As the U.S. epidemic of prescription drug abuse expands, so do its estimated societal costs. Until the root of the cause is sufficiently addressed, these costs will continue to escalate, placing a huge burden on our nation's future (Birnbaum et al., 2011).

Prescription drug acceptability

Use of illicit or street drugs conjures up images of abandoned houses in questionable neighborhoods, violent crimes, police raids, assorted weaponry, and unsavory characters lurking in dark alleys. In contrast, abuse of prescription drugs often occurs in an entirely different world. Prescription medicines are perceived to be high in benefit and low in risk (Slovic et al., 2007). As a part of this thought process, abusers will note that these drugs are FDA-approved, prescribed by a licensed doctor, and dispensed by pharmacists. Although some abusers choose to inject or crush their prescription drug of choice, many can simply wash it down with a beverage right out in the open – in "public." Their drug use produces no smoke, no residual smell, requires no needles or "paraphernalia" – just some liquid to help those abusers who cannot "dry swallow" the pill(s) that were likely taken from or given to them by a friend or family member. Raiding an elderly relative's medicine cabinet is far safer than meeting a drug dealer on a street corner.

Populations at risk

The behaviors that lead to prescription drug abuse do not discriminate. Everyone is at risk of abusing prescription drugs, regardless of geographic location, socioeconomic status, or ethnicity. Despite this universal danger, however, studies have shown that certain groups of people are more at risk than others for abusing or misusing prescription drugs. The following populations are particularly vulnerable to the risk of prescription drug abuse: teens, college students, military personnel and families, the elderly, Native Americans and Alaska Natives, people with disorders in addition to drug abuse, and those with abusive tendencies. Gender differences also affect the likelihood of abuse.

Teens

According to NIDA (2018i), among adolescents aged 12 to 17 in the year 2017, 4.9% reported the nonmedical use of prescription drugs in the past year. After alcohol, marijuana, and tobacco, prescription drugs were the most commonly used substances by seniors in high school, and 6% of high school seniors reported the nonmedical use of Adderall.

The rate of prescription drug abuse among teens has the attention of parents, teachers, law enforcement, politicians, and government officials. The National Institute on Drug Abuse maintains a branch called *NIDA for Teens* (https://teens.drugabuse.gov/) that can help young people get the information they need on prescription drug abuse (NIDA for Teens, 2019b) as well as a variety of other drug-related topics.

The report *Teen Prescription Drug Abuse: An Emerging Threat*, developed by the Community Anti-Drug Coalitions of America (CADCA) in collaboration with the ONDCP's National Youth Anti-Drug Media Campaign, states:

> *Teens say they abuse prescription painkillers because they believe they are safer to use than illicit drugs (41%), there is less shame attached to using them (37%), there are fewer side effects than illicit drugs (31%), and parents don't care as much if you get caught (20%) (CADCA, 2008).*

Teens also experience challenges unique to their age group that may contribute to their vulnerability to behaviors leading to prescription drug abuse. Some difficulties encountered by teens include experiencing physical and psychological changes, attempting to develop an acceptable identity and peer group acceptance, facing academic and sports-related pressures to succeed, and the ongoing emergence of new life experiences. Adolescents with a history of exposure to various traumatic events such as physical assault, sexual assault, witnessing violence, or the presence of family members with drug or alcohol use problems appear to be at an increased risk for substance abuse/dependence behaviors (Carliner et al., 2016; NIDA, 2014b). Finally, an anatomical consideration unique to teens is that the prefrontal cortex, responsible for judgment and decision-making activity, is the last part of the brain to fully develop and mature (American Academy of Child and Adolescent Psychiatry, 2016; Volkow, 2008; Winters & Arria, 2011). These elements contribute to the increased risk among the teenage population for experimentation of all kinds, sometimes opening the path for first-time drug use and future patterns of drug abuse behavior.

It is worth noting that, according to the U.S. Department of Health and Human Services (HHS), prescriptions issued by dentists account for almost a third of U.S. adolescents' first exposure to opioids (HHS, 2019a).

College students

Young adults in their college years also present as a population at risk for the perils of prescription drug abuse. Like the teenagers discussed above, these students face a variety of stressors that may cloud their decision-making process and make them more susceptible to risky behaviors. These stressors may include high-stakes examinations, escalation of the need for peer acceptance in the face of social independence, irregular sleeping habits, stress-relieving bingeing activity, limited finances, and pressures to select and pursue a lifelong career path.

Faced with these issues, some college students turn to stimulants to gain an edge over their classmates. Some students may begin this behavior by consuming energy drinks. Arria and colleagues (2010) reported that students who turn to energy drinks are more likely to turn to prescription drugs for similar effects in the next year. Some college students believe that stimulants will allow them to stay awake for longer periods of time and increase their powers of concentration, leading to the ultimate goal: a better grade (Arria, O'Grady, et al., 2008; Prudhomme White et al., 2016). Unfortunately, they may discover that the perceived *magic pill* to get a better grade has other, undesirable, outcomes. Not only are these students at greater risk for drug abuse behaviors, but a study found that students who used stimulants and analgesics for nonmedical purposes also skipped 21% of their classes, whereas their non-using counterparts skipped 9% of classes (Arria, O'Grady, et al., 2008; United Nations Office on Drugs and Crime, 2011). In fact, symptoms of ADHD, particularly inattentiveness, have been linked to nonmedical use of prescription stimulants – a consequence opposite of the perceived intent (Arria, Caldeira, et al., 2008). As a result, it is not surprising that the abusing students are reported to have lower grades than their non-using counterparts (Arria & DuPont, 2010).

Students who are Caucasian, live in fraternities or sororities, attend more competitive colleges, and use other illicit drugs are more likely to use prescription stimulants and analgesics for nonmedical purposes (McCabe, Knight, et al., 2005; McCabe, Teter, et al., 2005). In a presentation at a 2012 National Collegiate Athletic Association conference, Dr. Amelia Arria raised concern that nonprescription drug use may be a "gateway" to other drugs and alcohol. In her study, of those who reported a nonmedical use of stimulants, "93.5 percent also reported use of marijuana, 89.4 percent used tobacco products, and 100 percent used alcohol" (Hendrickson, 2012). The mix of alcohol and stimulants is another "cocktail" that appears to appeal to college students. People using this combination say that they are able to drink more for a longer period of time (American Addiction Centers, 2019). These college students forget or are unaware that stimulants mask the depressive effects of alcohol, increasing the risk of overdose and even death. The combination may cause liver damage and increased risk of heart problems (NIH, 2018a; National Institute on Alcohol Abuse and Alcoholism, 2014).

Military personnel and families

Many people would use terms such as *discipline*, *rules*, and *commanding oversight* to describe the environment of the U.S. armed forces. Such a description may make it difficult to understand how the same climate could foster an atmosphere conducive to prescription drug abuse. According to the 2015 Department of Defense Health Related Behaviors Survey of Active Duty Military Personnel, across all branches of the military, 4.1% of active duty personnel reported misuse of prescription drugs within the past 12 months (Mendez, 2018). Several factors unique to a service member's life can cause the type of stress that may create the perfect environment for risky behavior involving prescription drug abuse. These issues include multiple and long deployments resulting in family separation and relationship strain, participation in and witnessing of traumatic events, posttraumatic stress disorder (PTSD), and traumatic brain injury.

Not surprisingly, deployed military service members tend to be more at risk for abusing prescription medications than their nondeployed comrades (NIDA, 2013). The Army was the military branch with the most men and women deployed in the most recent wars in Iraq and Afghanistan. According to one study, one in four Army soldiers deployed in those wars admitted to abusing prescription drugs during a one-year period (Bray

et al., 2010). These numbers led to collaborative action on the part of the Institute of Medicine (IOM; now the National Academy of Medicine) and the Department of Defense (DoD). Their plan included the following actions for active duty military personnel and their families: providing accessible information regarding recent trends and evidence-based prevention behaviors, ensuring proper testing, developing methods to ensure proper diagnosis of those affected, and addressing the long-lived stigma that exists for those seeking treatment in this "zero-tolerance policy" climate (i.e., the Army is experimenting with confidential counseling programs; IOM, 2012; Military OneSource, 2018; NIDA, 2016).

In 2010, in response to increased prescription drug abuse among military personnel, a $6 million federal grant was presented to NIDA, other institutions within the NIH, and the U.S. Department of Veterans Affairs to address this crisis. In 2012, the Department of Defense responded to abuse of prescription drugs by expanding drug testing requirements for service members to include "some of the most abused prescription drugs containing hydrocodone and benzodiazepine." It also set a 6-month limit on prescriptions for commonly abused drugs (Davis, 2015). The Millennium Cohort Study is following a sample of military personnel through the year 2022 (DoD, n.d.). Researchers hope to identify patterns that may lead to relapse of abuse by documenting via smartphones and wireless devices the real-time stresses of veterans with trauma and addiction histories.

Older adults

As a group, the elderly have distinctive characteristics regarding their health status and drug use that put them at a higher risk for misuse behaviors. These characteristics add to their vulnerability and may increase unwanted and unexpected dependence and abuse. These factors include a decline in cognitive and motor skills; the use of multidrug therapies, including many OTC remedies (traditionally termed *polypharmacy*); the presence of complicated health histories requiring treatment from several physicians (often leading to duplicate prescriptions); and potentially delayed metabolism of medications (Oakley et al., 2011). As a result, these individuals are at risk for unpredictable drug interactions and resulting complications from these interactions that may necessitate additional changes to their already complicated drug regimens.

More than 80% of older patients (ages 57 to 85 years) use at least one prescription medication on a daily basis, with more than 50% taking more than five medications or supplements daily. This can potentially lead to health issues resulting from unintentionally using a prescription medication in a manner other than how it was prescribed or from intentional nonmedical use. The high rates of multiple (comorbid) chronic illnesses in older populations, age-related changes in drug metabolism, and the potential for drug interactions make medication (and other substance) misuse more dangerous in older people than in younger populations (NIDA, 2018i).

Native Americans/Alaska natives

A 2009 survey reported that 6.2% of Native American and Alaska Native populations had abused prescription drugs in the past month (ONDCP, n.d.b). Statistics show that prescription drug abuse impacts American Indian/Alaska Native communities at a higher rate than any other racial group. In response, the National Indian Health Board has implemented programs such as prescription drug take-back days, proper drug disposal, and outreach and education programs (National Indian Health Board, n.d.)

Gender differences

According to NIDA, 19.5 million females (or 15.4%) aged 18 or older have used illicit drugs in the past year; "illicit" refers to the use of illegal drugs, including marijuana, and misuse of prescription medications (NIDA, 2019c). Recent evidence suggests that gender differences may deserve consideration when evaluating those most at risk for prescription drug abuse (SAMHSA, 2014a). Women exhibit abuse behaviors for reasons that are different from men. Psychological or emotional distress may contribute to opioid abuse for women, whereas social or behavioral issues, such as having difficulty with personal interactions, contribute to opioid abuse among men (Jamison et al., 2020. Prescribing healthcare professionals, including dentists, are in a position to consider these differences when making decisions related to drug therapies, advising patients regarding the proper use of medications, and referring patients to colleagues to treat underlying issues that may contribute to drug dependence and abuse behaviors.

Individuals with other health-related conditions

Individuals, including athletes, who have other health-related conditions, such as emotional or psychiatric disorders, chronic pain, or who are recovering from surgery, are often prescribed highly addictive pain or mood-altering medications as part of comprehensive therapy to treat their condition (American Academy of Orthopaedic Surgeons, 2015; Jenkins & Maese, 2013). Access to these medications, coupled with the issues underlying these health-related conditions, elevates this group's risk for abusing prescription drugs. Chronic use can lead to drug dependence, which can in turn lead to unintentional misuse, thus paving the way for future abuse. Attention should be focused on prescribing safe yet effective quantities to these patients to avoid precipitating misuse and subsequent abuse patterns.

Individuals with abusive tendencies

Certain abusive tendencies represented by a past history of drug abuse or familial history of drug abuse should be considered in identifying risk factors for future abuse of prescription drugs. Pergolizzi and colleagues (2012) have shown that excessive use of gateway drugs, such as alcohol, nicotine, marijuana, and other illicit drugs, can contribute to opioid abuse. They also found a higher incidence of aberrant drug-related behaviors (including claims of having lost prescriptions, hoarding, selling prescriptions, and "doctor shopping") among those who have a familial history of drug abuse. Their research notes that first-degree relatives of opioid-dependent individuals are more likely to develop a drug-related disorder themselves (Pergolizzi et al., 2012). This biological connection may help to explain why some people have a greater propensity for addictive behaviors than other people in the same circumstances.

Access and diversion

According to the Centers for Medicare and Medicaid Services (2015), drug diversion is "the illegal distribution or abuse of prescription drugs or their use for purposes not intended by the prescriber." In other words, legitimately made and controlled prescription drugs are diverted from their lawful purpose to an unlawful use (DEA, n.d.b). Diversion is a significant contributor to the escalation of prescription drug abuse. Prescription drug diversion has important health, legal, and social implications. Examples of diversion include:

- Fraudulent prescription requests, which can be seen in "doctor shopping," claiming to have lost prescriptions, or demanding early refills (NIDA, 2018c).
- Other illegal uses or behaviors, such as taking prescription opioids to relieve anxiety symptoms or to feel the euphoric effect, using "pill mills," stealing drugs/prescriptions, and prescription forgery.

People who *doctor shop* have been known to target a varied assortment of practitioners, including physicians, dentists, and even veterinarians. Law enforcement has increased its focus on the activities of healthcare providers managing clinics suspected of being "pill mills" (DoJ, 2019; Potter, 2015). The sole purpose of these operations is to reap the profits of placing inordinate quantities of prescription drugs in the hands of those who do not require them for medical use. Additionally, the individuals working in these pill mills have access to these medications; the temptation to steal and sell or use these drugs poses a real problem. Popular prescription drugs may be stolen by

employees, not only from pharmacies but also from hospitals, senior-living facilities, veterinary clinics, and dental offices (California State Board of Pharmacy, 2013; Muha, 2017). Drug-seekers have traditionally forged prescriptions by using acetone to dissolve ink on paper prescriptions (North Carolina Board of Pharmacy, 2017). However, now that the Centers for Medicare and Medicaid Services (CMS) mandates electronic prescribing for patients with Medicare Part D plans, electronic prescriptions are more common (CMS, 2014). The major impetus behind "e-prescribing" was greater accuracy and safety. However, the new technology is also being seen as a way to prevent forgery of prescriptions for controlled substances and of tracking such prescriptions (Lucas, 2016; Myers-O'Shea, 2016).

New and less-anticipated methods of gaining prescription drug access have recently come to light. Preventing Prescription Abuse in the Workplace, a project funded by the Substance Abuse and Mental Health Services Administration (SAMHSA), has called attention to some of the less than obvious sources of illegally obtained prescription drugs (RTI International, 2018). These sources include prescription drugs stolen from homeowners during open houses and from people shopping in grocery stores. Unsuspecting homeowners may know to secure cash and checkbooks before allowing strangers into their homes, but securing prescription drugs may be a less obvious necessity (Dittmann Tracey, 2014). People who are seeking drugs do their best to blend in by dressing in businesslike attire, asking questions that make them appear interested, and displaying typical behaviors – like asking to use the bathroom. While in the bathroom unsupervised, they raid the medicine cabinet of prescription drugs. Such criminals can have very busy and productive days moving from one open house to another. Homeowners who have laborers working on projects in their homes have also reported drugs being stolen from medicine cabinets.

Another unsuspecting target is the grocery shopper who picks up a prescription at the in-store pharmacy and proceeds with grocery shopping. The burglar patiently waits for the shopper to be distracted from his or her cart and then moves in to steal the medication. Like homeowners, shoppers may be accustomed to safeguarding their wallets, but it may not occur to them that their prescription drugs are equally vulnerable targets of theft. Prevention groups have launched programs that include flyers and pamphlets aimed at customers, homeowners, and real estate agencies that suggest picking up prescriptions as the last stop when shopping and safeguarding them at home by keeping them in a secure location (see Figures 1 and 2).

Figure 1: Open House Flyer

What *Not* to Show at Your Next Open House

In 2010, 16 million Americans took prescription drugs for nonmedical purposes.* Some stole those drugs or bought them on the street from people who stole them.

An open house can be the perfect opportunity for people to steal prescription medication.

Thieves pose as homebuyers, often in pairs. One asks to use the restroom and then raids the medicine cabinet or drawers while the other distracts the Realtor.

When you list a house, advise sellers to make sure medications are properly secured. **"When you put away your valuables, put away any prescription drugs."**

*2010 National Survey on Drug Use and Health, http://oas.samhsa.gov/NSDUH/2k10NSDUH/2k10Results.htm

Figure 2: Grocery Cart Theft Flyer

Safeguard Your Prescription Drugs While Shopping

In 2010, 16 million Americans took prescription drugs for non-medical purposes.* Some stole those drugs or bought them on the street from people who stole them.

Pharmacies and grocery stores are perfect places for people to steal prescription medication.

A 52-year-old woman reported to the police that contents in her purse were stolen from her shopping cart. She had received a call on her cell phone when she walked away from her cart, leaving her purse unattended. It wasn't until she was about to leave the store that she realized several bottles of prescription medication were missing from her purse. All of her money and credit cards were left in the purse undisturbed.

Customers often place their prescription drugs in the shopping carts while they shop. Thieves will wait until the customers are distracted and take the prescription drug package out of the cart or directly from someone's purse.

Advise shoppers if they are picking up medicine from the pharmacy, to keep it out of sight while shopping or pick up their prescription last before heading out the store.

*2010 National Survey on Drug Use and Health, http://oas.samhsa.gov/NSDUH/2k10NSDUH/2k10Results.htm

Common prescribing practices

Diversion of prescription drugs cannot be fully discussed without noting some striking statistics related to access to prescription drugs. It is well documented that access to prescription drugs is quite easy for many. This situation is further exacerbated by current prescribing practices that provide patients with quantities of prescribed drugs in excess of those needed to treat their health-related issues. Little has been written linking the prescribing of CNS depressants and stimulants to prescription drug abuse (Ahmed & Virani, 2017; Lembke et al., 2018). In contrast, prescribing practices involving opioids have come under greater scrutiny as the epidemic of prescription drug abuse is more closely examined and prevention measures are put into action.

Organizations such as the NIH, NIDA, the American Dental Association (ADA), and the American Medical Association (AMA) have been watchfully surveying this topic. Between 1991 and 2009 more than 200 million opioid prescriptions were written – a staggering number that reflects a near threefold increase during that time period (NIDA, 2011a). According to the American Society of Addiction Medicine (2016), in the United States in 2012, approximately 259 million opioid prescriptions were written, enough for one bottle of pills for every U.S. adult. Some literature on this topic is focused on younger patients because they have been identified as a population at greater risk for addictive behaviors. One NIDA study that drew data from more than 35,000 U.S. pharmacies showed that in 2009 nearly 12% of all opioids prescribed were written for young patients between 10 and 29 years of age (NIDA, 2011a). Of this group, dentists were identified as the main prescribers for patients who were between 10 and 19 years of age. The frequency of prescribing practices for opioids was also examined. The findings suggest that 56% of the opioid analgesic prescriptions were offered to patients who had previously received prescriptions for pain in the past 30 days, some of which came from the same provider (Volkow et al., 2011).

A 2011 study at the University of Utah Health Sciences Center reported that more than two-thirds of patients who underwent a urological surgical procedure had leftover pain medication and more than 90% of those patients decided to keep the prescription drugs in their medicine cabinets (Bates et al., 2011). A nationwide survey conducted by the University of Pittsburgh School of Dental Medicine found that although oral surgeons reported prescribing, on average, 20 tablets of an opioid pain reliever (e.g., Vicodin or Percocet) after third molar extraction surgeries, only 8 to 12 tablets may be required to alleviate the postoperative pain associated with the procedure (Oakley et al., 2011). A study of approximately 2.7 million Medicaid patients who had undergone surgical tooth extractions between the years 2000 and 2012 found wide variations in the amount of opioids prescribed, although there did appear to have been a pattern of

more medicine than necessary being prescribed for the amount of pain that might be expected to follow the procedure (Baker et al., 2016).

A study published in 2019 found that in 2016 U.S. dentists were issuing 37 times as many prescriptions for opioids as English dentists (Mozes, 2019; Suda et al., 2019). The study also found that, although 22% of U.S. dental prescriptions were for opioids, only 0.6% of English dentists' prescriptions were for such drugs (Mozes, 2019; Suda et al., 2019).

Statistics on prescription drug access show that in 2016, more than a third of people in the United States aged 12 and older who accessed prescription pain relievers for the purposes of nonmedical use during the preceding year obtained these drugs from friends and family for free (Bose et al., 2018). Another 10.6% of the users of nonmedical pain relievers paid their friends and family for the drugs, and 4.0% stole them from the same source. In the years 2012-2013, more than 4 out of 5 of the friends and family whose prescription drugs were accessed by other individuals received their medication from only one doctor (SAMHSA, 2014b). These statistics on prescription drug access through friends and family, in concert with current overprescribing practices, shed light on the prevention tactics that will be needed to address the problem of prescription drug abuse.

In 2016, the CDC issued guidelines for prescribing opioids for chronic pain (CDC, 2016). This move came in response to the federal government's concern over the epidemic, not just of opioid abuse, but of deaths resulting from the misuse and abuse of opioids. Among the CDC's recommendations were the prescribing of nonopioid therapy, if possible, except for palliative and end-of-life care and for cancer pain. Providers were urged, even when deeming the use of opioids appropriate, to prescribe the lowest possible dose, and to closely monitor all patients (CDC, 2016). (See the Resources section of this course for a link to the 2016 CDC recommendations.)

Limitations on the dosage of opioids can be controversial, however. A law proposed for the Commonwealth of Massachusetts would have limited first-time opioid prescriptions to a 72-hour supply. Some commentators in the medical community felt that such a strict limit could impose hardship on chronic pain sufferers and interfere with the relationship between provider and patient (Miller, 2015). The law, when passed in 2016, was weaker than first proposed (Miller, 2016), yet still heralded an era of states exercising more oversight of providers' prescribing practices. Since Massachusetts passed its 2016 law, more than half of U.S. states have put limits on prescribing and dispensing opioids in cases of acute pain (Bulloch et al., 2019).

Although examining prescribing practices confirms access to certain medications, it does not necessarily imply that the drugs are being diverted or abused. It is important, however, for practitioners to be apprised of these national trends to help them make sound decisions about their own prescribing practices for their patients. This is especially true for dentists, whose area of focus often requires them to relieve their patients from pain. The next section of this course will offer suggestions to the dental team to best manage and prevent prescription drug abuse in the dental office setting.

MANAGEMENT AND PREVENTION IN THE DENTAL PRACTICE

Identification of prescription drug abusers in the dental practice

The rise in prescription drug abuse, particularly abuse of opioid pain relievers, places dental providers in a key position to assist in the identification and prevention of the misuse, abuse, and diversion of these drugs. The ADA encourages dentists to prescribe responsibly; to be aware of the abuse potential with these drugs; to recognize patients who may be seeking drugs for nonmedical purposes; and to educate their patients on the proper storage, use, and disposal of these medications (ADA, n.d.a, n.d.b, 2012, 2019). In addition, a collaborative, interprofessional approach among dental providers and other healthcare providers can assist in efforts to identify and halt this steadily rising public health problem.

Team approach

Collaborative practice agreements between pharmacists and physicians is a growing trend. A *collaborative practice agreement* is a formal partnership between a pharmacist and physician or among a group of pharmacists and physicians to allow the pharmacist(s) to manage a patient's drug therapy (Academy of Managed Care Pharmacy, 2012; CDC, 2018d). These agreements are entered into on an individual basis and clearly define the roles and responsibilities of both the physicians and pharmacists regarding patient care. Where allowed by law, such agreements can be negotiated between pharmacists and practitioners.

As of November of 2016, all but two states allowed pharmacists to enter into collaborative practice agreements (American Pharmacists Association, 2016). Some states allowed such collaborations only in an institutional setting, while the remaining states also allowed them in community settings. Such collaborative practice agreements have historically been used in nondental settings in anticoagulation therapy and for the treatment of medical conditions, including diabetes, hypertension, dyslipidemia, and asthma. Some states allow collaborative practice agreements between pharmacists and physicians only, and exclude other prescribers (American Pharmacists Association, 2015).

The complex treatment associated with managing patients with chronic pain has provided an expanded opportunity for collaborative practice agreements. Agreements between community pharmacists and pain physicians or primary care physicians are designed to better control and utilize pain medications (Strickland et al., 2007). Some potential roles of the pharmacist in such practices include:

- Counseling patients on the adverse effects of opiates.
- Monitoring OTC drug interactions and monitoring total daily acetaminophen dosage.
- Counseling patients on safe opiate storage and providing lock-boxes.
- Querying all available prescription drug-monitoring databases.
- Providing custom packaging to enable accurate pill counts.
- Providing narcotic antagonists such as intranasal naloxone to high-risk patients to treat opioid overdose.
- Helping lower-income patients obtain drugs at reduced cost.
- Being trained in drug urinalysis results to aid in spotting treatment inconsistencies.

Although such extensive agreements be-tween pharmacists and dental providers may appear to be extreme, cooperation between the two professions can be a valuable tool in preventing prescription drug abuse and diversion. The key to the success of such "informal" collaborations is the establishment of rapid and dependable communications between the dental team and local pharmacies. Local pharmacists and dental teams could establish a system to provide rapid responses to queries. Patient safety and vigilance regarding drug abuse can be enhanced if dental practices can rapidly respond to pharmacists' concerns that may be based on medical or prescription history not available to the dentist. Such queries might involve the following:

- Concerns about prescription or OTC drug interactions, including excessive use of acetaminophen-containing products.
- Pharmacy records that indicate the patient is receiving opioids from multiple sources.

- A patient history of drug abuse or addiction therapy unknown to the dentist, which might affect the prescribing of pain medications.
- Questions about quantities of medication being prescribed. In some instances, writing prescriptions for smaller quantities with a refill would allow the pharmacist to counsel the patient and help determine whether a return trip to the dental practitioner might be needed.
- Questions regarding possible alterations of prescriptions (e.g., potential changes in quantities and number of refills).
- Data derived from the prescription drug monitoring programs of a state or close neighboring states that indicate a history of doctor shopping.

This type of interprofessional communication can improve patient outcomes when collaborative practice agreements are in place between pharmacists and dental providers. Most critically, these interactions can serve to reassure the dentist that opioid prescriptions are being used as intended.

Health history

The first dentist-patient encounter at each dental visit typically involves obtaining or reviewing the patient's health history. This analysis provides an ideal opportunity to begin screening for potential drug misuse, abuse, or diversion. Yet healthcare professionals are often reluctant to probe for this information or are unaware that this initial screening can effectively take place at this first encounter. In 2005, a survey of physicians by the National Center on Addiction and Substance Abuse (CASA) at Columbia University found that only about half (53.8%) asked about prescription drug abuse when taking the health history (CASA, 2005). This may have been due, in part, to inadequate preparation of healthcare providers during training. The same CASA study found that fewer than half of the physicians surveyed received training on identifying prescription drug abuse and addiction; even fewer (19.1% to 39.2%) stated that they received training in identifying prescription drug diversion at some point in their medical school or residency programs (CASA, 2005). For dentists, the ADA and the American Dental Education Association (ADEA) have called for enhanced education regarding drug abuse and prevention during professional training (ADA, 2018a,c; ADEA, 2018).

Both providers and patients may be uncomfortable discussing the topic of drug use and abuse. Providing an opening question on a standard health history form ensures that all patients are being asked about drug use, both illicit and prescribed, and prevents patients from feeling they are being "singled out" (Ilgen, 2012). Providing a safe, private environment in which to broach and discuss the topic can also make the patient more comfortable. Familiarizing the patient with office policy that ensures the confidentiality of all personal health information can also provide reassurance to the patient.

It is important to solicit information about past and current prescription drug use, along with a history of other drug use, including alcohol and illicit drugs. Adolescents and young adults who abuse prescription drugs are more likely to report using other drugs as well (NIDA, 2018i; SAMHSA, 2019). It is important to follow up with patients who report a history of prior drug use to ascertain where they are in the recovery process because this can affect the selection of pain medication to be prescribed. In these instances, consultation with patients' physicians is necessary to safely prescribe controlled substances to these patients (ADA, 2018c). A family history of substance abuse should also be solicited because individuals with a positive family history are at an increased risk for abuse (Mayo Clinic, 2017).

Some behaviors and responses that may occur during the dental visit have been identified as potential warning signs of a possible abuse or diversion problem, particularly regarding medication for pain, a common complaint in the dental office. These patient behaviors include:

- Coming to the office at the end of the day or claiming to be going out of town (especially patients new to the practice).
- Providing convincing descriptions of pain but an ambiguous health history.
- Arriving with a radiograph supporting their claims of pain, but refusing to have a new radiograph taken.
- Being unwilling to provide the name of a primary care provider.
- Claiming to have "lost" their medication or prescription.
- Requesting a specific drug by name or claiming that certain medications "don't work."
- Putting undue pressure on the dentist to prescribe opioid medications (DEA, 1999; Girgis, 2017).

Tables 4 and 5 provide a list of these and other characteristics and behaviors that are common to the drug-seeking patient.

Table 4: Common Characteristics of the Drug Abuser

- Unusual behavior in the waiting room.
- Assertive personality, often demanding immediate action.
- Unusual appearance – extremes of either slovenliness or being overdressed.
- May show unusual knowledge of controlled substances and/or gives medical history with textbook symptoms OR gives evasive or vague answers to questions regarding medical history.
- Reluctant or unwilling to provide reference information. Usually has no regular doctor and often no health insurance.
- Will often request a specific controlled drug and is reluctant to try a different drug.
- Generally has no interest in diagnosis – fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation.
- May exaggerate medical problems and/or simulate symptoms.
- May exhibit mood disturbances, suicidal thoughts, lack of impulse control, thought disorders, and/or sexual dysfunction.
- Cutaneous signs of drug abuse: skin tracks and related scars on the neck, axilla, forearm, wrist, foot, and ankle. Such marks are usually multiple, hyperpigmented, and linear. New lesions may be inflamed. Shows signs of "pop" scars from subcutaneous injections.

Note. Adapted from "Don't Be Scammed by a Drug Abuser," by the U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control, 1999. Retrieved from https://www.deadiversion.usdoj.gov/pubs/brochures/drugabuser.htm

Table 5: Tactics Often Used by the Drug-Seeking Patient

- Must be seen right away.
- Wants an appointment toward the end of office hours.
- Calls or comes in after regular hours.
- States that he or she is traveling through town or visiting friends or relatives (not a permanent resident).
- Feigns physical problems, such as abdominal or back pain, kidney stone, or migraine headache in an effort to obtain narcotic drugs.
- Feigns psychological problems, such as anxiety, insomnia, fatigue, or depression in an effort to obtain stimulants or depressants.
- States that specific non-narcotic analgesics do not work or that he or she is allergic to them.
- Claims to be a patient of a practitioner who is currently unavailable or will not give the name of a primary or reference physician.
- States that a prescription has been lost or stolen and needs replacing.
- Deceives the practitioner, such as by requesting refills more often than originally prescribed.
- Pressures the practitioner by eliciting sympathy or guilt or by direct threats.
- Utilizes a child or an elderly person when seeking methylphenidate or pain medication.

Note. Adapted from "Don't Be Scammed by a Drug Abuser," by the U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control, 1999. Retrieved from https://www.deadiversion.usdoj.gov/pubs/brochures/drugabuser.htm

Screening tools

In addition to the health history, a number of screening tools are available that specifically target drug abuse and intervention. Although most of these screening tools were developed for general physician practices, they are easily adaptable to the dental office for providers interested in incorporating approaches designed to screen for potential abuse.

Screening, brief intervention, and referral to treatment

One of the available tools, *Screening, Brief Intervention, and Referral to Treatment (SBIRT),* was originally designed as a screening tool to assess alcohol abuse in all patients presenting to an office, clinic, or emergency room for care and was found to be promising in screening for other behavioral health problems such as drug abuse. This assessment is brief (5 to 10 minutes), universal, and supported by strong evidence. Depending on the score, patients can be reinforced for healthy behavior, referred for brief intervention, or referred for more intensive intervention appropriate to the risk for abuse (SAMHSA, 2017).

NIDA-modified alcohol, smoking, and substance involvement screening test

The *NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM ASSIST)* consists of a short series of screening questions and a score that guides the identification of the level of intervention indicated (NIDA, n.d.d). A one-question version, the *NIDA Drug Use Screening Tool Quick Screen*, asks: "In the past year, how many times have you used alcohol, tobacco products, and prescription medication for nonmedical reasons, or illegal drugs?" If a positive answer is received, proceeding with NM ASSIST is recommended (NIDA, n.d.c).

Other screening tools

The *Drug Abuse Screening Test (DAST-10)* is a shortened version of the original 28-question DAST tool specific to screening for drug abuse (SAMHSA, n.d.b). The *CAGE Substance Abuse Screening Tool*, named for the four areas of questions asked (Cut down, Annoyed, Guilty, and Eye-opener) was developed in 1982 for alcohol screening and later modified as the *CAGE-AID*, or *CAGE-Adapted to Include Drugs* tool (Ewing, 1984; Johns Hopkins Medicine, n.d.). A number of other tools are also available that are targeted to screen specifically for opioid abuse in the in patients with chronic pain prior to prescribing long-term therapy.

With any of the available screening tools, thoughtful planning to identify who will conduct the screening and what will be done with positive results will make the process run more smoothly. Being aware of community resources that can assist in the referral process is also essential to follow-up for patients requiring additional treatment.

Ethical considerations

The principle of beneficence in the ADA Principles of Ethics and Code of Professional Conduct states that the "most important aspect of this obligation is the competent and timely delivery of dental care within the bounds of clinical circumstances presented by the patient, with due consideration being given to the needs, desires and values of the patient" (ADA, 2018b). When there is reasonable cause for suspicion of drug abuse, caution in prescribing drugs with high abuse potential is appropriate (Wentworth, 2008). Table 6 contains information provided by the ADA to guide dentists when treating the suspected or known drug user. It is also important to be familiar with state and federal regulatory laws for prescribing controlled substances as well as with laws regarding privacy when contemplating discussing concerns with a member of the patient's family.

Table 6: ADA Statement on Provision of Dental Treatment for Patients with Substance Use Disorders

1. Dentists are urged to be aware of each patient's substance use history and to take this into consideration when planning treatment and prescribing medications.
2. Dentists are encouraged to be knowledgeable about substance use disorders – both active and in remission – in order to safely prescribe controlled substances and other medications to patients with these disorders.
3. Dentists should draw upon their professional judgment in advising patients who are heavy drinkers to cut back, or the users of illegal drugs to stop.
4. Dentists may want to be familiar with their community's treatment resources for patients with substance use disorders and be able to make referrals when indicated.
5. Dentists are encouraged to seek consultation with the patient's physician, when the patient has a history of alcoholism or other substance use disorder.
6. Dentists are urged to be current in their knowledge of pharmacology, including content related to drugs of abuse;recognition of contraindications to the delivery of epinephrine-containing local anesthetics; safe prescribing practices for patients with substance use disorders – both active and in remission; and management of patient emergencies that may result from unforeseen drug interactions.
7. Dentists are obliged to protect patient confidentiality of substance abuse treatment information, in accordance with applicable state and federal law.

Note. American Dental Association. Adopted October 2005. Retrieved from American Dental Association. (2018). *Substance use disorders*. https://www.ada.org/en/advocacy/current-policies/substance-use-disorders. Used with permission.

Alternative prescribing practices and their efficacy

Although the risk of abuse of the prescription drugs discussed in this module needs to be considered when prescribing therapy for dental pain, it must be balanced against the need to appropriately treat patients who present to the dental office with pain. There are instances in which opioid pain relievers are indicated, and judicious use of these drugs plays a legitimate role in the practice of dental medicine. However, when the patient who presents is suspected of having an abuse problem or in situations in which pain can be adequately treated with nonopioid medications, alternative therapies are available to the healthcare provider.

Nonopioid analgesics

The pain relief potential of the nonopioid analgesics, which include the nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (APAP), is perceived by some to be inferior to "stronger" drugs such as the opioids. Yet research has shown that the nonopioid pain relievers can provide similar, if not superior, pain relief (Becker, 2010; Krebs et al., 2018; Mehlisch et al., 2010; State of Washington, 2017). The anti-inflammatory properties of the NSAIDs, in addition to their analgesic effect, make them particularly ideal for treating dental pain. There are contraindications to using either of these drugs in certain patients, reinforcing the need to obtain a comprehensive health history prior to treating dental pain. For example, patients who report a history of bleeding disorders or a condition that requires anticoagulation medications should not be treated with NSAIDs due to the risk of gastrointestinal bleeding as well as some bleeding effect from their antiplatelet activity (Becker, 2010; FDA, 2015). These patients are ideal, however, for considering acetaminophen as a potential pain reliever.

Acetaminophen is not without its own risks, however, particularly in certain populations. Because hepatotoxicity is the most adverse side effect of acetaminophen, patients with liver disease or those already taking medications with hepatotoxic potential, for example, would need to avoid or receive a decreased dosage of this medication.

Because the NSAIDs and APAP have different sites of action, studies have shown that a synergistic effect can be obtained when both medications are given together (Mehlisch et al., 2010; Merry et al., 2010; Moore & Hersh, 2013). In a 2010 randomized controlled trial, Mehlisch and colleagues compared a single-tablet combination of ibuprofen and acetaminophen to either drug alone for relieving pain in dental patients undergoing third molar extractions (Mehlisch et al., 2010). Results of the study support previous studies and suggest that this combination of analgesics is more effective than either drug administered alone in relieving moderate to severe levels of dental pain following dental surgery (Mehlisch et al., 2010). A Japanese team of dentists found that acetaminophen combined with an intravenous NSAID was as effective at relieving postsurgical pain as the NSAID combined with fentanyl, and that the recovery time of patients treated with this regimen was shorter. They concluded that acetaminophen was a good choice when opioids were contraindicated (Yoshida et al., 2018).

The effectiveness of the NSAID/APAP combination therapy can be further enhanced with patient education to take the medication "around the clock" at regular intervals to avoid the onset of pain. However, patients should be cautioned not to exceed the recommended safe daily dose of acetaminophen, in particular, due to its hepatotoxicity potential. If breakthrough pain should occur, an opioid alone can be added, or an opioid/acetaminophen combination can be given. When opioids are indicated, safe prescribing practices include limiting the quantity to that needed for a few days, and again, cautioning the patient to discontinue the use of any other acetaminophen regimen to avoid liver damage (Becker, 2010; Denisco et al., 2011; NIH, 2018b). If pain persists longer than a few days, the patient should return to the office to be reevaluated.

Additional strategies

In addition to the previously discussed analgesics, nonopioid pain management in the dental office can include administering long-acting local anesthetics before dismissing the patient, to delay the onset of pain (Denisco et al., 2011; State of Washington, 2017). As previously mentioned, oral analgesics such as the NSAID/APAP combinations should then begin immediately, before the local anesthetic effects wane. For patients undergoing dental surgical procedures, prophylactic perioperative administration of an NSAID can also help to mitigate the inflammation related to postoperative dental pain (Denisco et al., 2011).

Dental management considerations

Aside from prescribing alternatives to opioid analgesics, the dental team must consider additional sources of management to address and prevent prescription drug abuse. These sources include educating both the patient and dental team regarding the issues surrounding prescription drug abuse and ensuring that the proper resources are available to each group.

Patient education

Patients need to be informed about the perils of prescription drug abuse. They need to safeguard themselves against accidental behavior patterns that may lead to abuse. This requires that patients be honest with their physicians and other healthcare providers about the medications they are taking and that they be careful to take all medications as directed.

Most importantly, because patients provide friends and family with the greatest access to drugs for intentional abuse, patients must be knowledgeable about safe practices for storing their medications. Because the medicine cabinet is the customary location for storage, other alternatives must be explored. Using the tagline *educate before you medicate*, the National Council on Patient Information and Education (NCPIE) advises patients to safeguard all medications in a locked area or drawer. They also suggest taking an inventory of all medications every 6 months, or at least every year (NCPIE, 2008). They also guide patients to properly dispose of all unused or expired medications. To avoid future diversion, they emphasize procedures such as taking these medications out of their original containers and mixing them with unpalatable substances such as coffee grounds or kitty litter and then placing them in a nondescript container such as a sealable bag or empty can. They further remind patients that flushing medications down the sink or toilet is an acceptable manner of disposal if the accompanying patient information or the label indicates that it is appropriate to do so. They also propose that local drug "take-back" programs can serve as excellent alternatives to safely dispose of unwanted medications (NCPIE, 2008). The U.S. Food and Drug Administration advises patients to scratch all personal information off pill bottles and packaging before disposing of them (FDA, 2019a).

Patient resources

Patients who are addicted to prescription medications should seek professional assistance as soon as possible. The SAMHSA-sponsored *Behavioral Health Treatment Services Locator* is dedicated to helping patients find proper treatment centers in their area (SAMHSA, n.d.a). Patients can access assistance by calling the listed treatment referral helpline or by clicking on the substance abuse treatment services locator link. On this site, patients can access a database of more than 11,000 drug abuse/addiction treatment centers to find the center by name or by location. Also of interest may be the Frequently Asked Questions (FAQs) section that answers questions related to insurance coverage for treatment, specific drug addiction care strategies, or advice concerning finding treatment for a person who is addicted to alcohol as well as prescription pain medication (SAMHSA, n.d.a). (See the Resources section.)

Dental team education

The dental team must remain well educated on the issues that affect the dental and overall health of their patients (ADA, 2012), including prescription drug abuse. In fact, awareness of this national epidemic has led several states to mandate continuing education requirements specific to this topic.

The ADA and several other healthcare organizations have united to train practitioners in the safe and effective use of opioid medications. The Providers' Clinical Support System (PCSS) training network provides no-cost training to help healthcare professionals effectively treat chronic pain with opioids and to safely address opioid dependence. The user can easily access peer support groups, webinars, and training modules from a consortium of stakeholders, including the American Academy of Addiction Psychiatry (AAAP), the AMA, the American Osteopathic Academy of Addiction Medicine (AOAAM), the American Psychiatric Association (APA), the American Society for Pain Management Nursing (ASPMN), and the International Nurses Society on Addictions (IntNSA; PCSS, n.d.).

Dental team resources

Early planning

In order to best serve the needs of their patients, the dental team must have quick access to resources during a time of need. Because no one can predict when a patient may present and require assistance for prescription drug addiction, prior planning by the dental team is needed to ensure success. Computers at the dental office should have bookmarks to sites such as SAMHSA's Behavioral Health Treatment Services

Locator, so the dental team can expeditiously refer patients in need to local treatment centers.

Risk evaluation and mitigation strategies

Risk evaluation and mitigation strategies (REMS) are an example of a resource that can be readily accessible to the dental team. Under the direction of the Food and Drug Administration Amendments Act of 2007, the FDA has the authority to mandate drug manufacturers to provide these educational documents for patients' and providers' use whenever the benefits of a drug outweigh the risks (FDA, 2018a). The FDA website contains a list of REMS, including those for the use of extended-release (ER) and long-acting (LA) opioid medications. This list aims to reduce the risk and improve safe use of this group of drugs by providing the information needed, including patient counseling documents containing helpful "dos" and "don'ts" and doctor-prescribing directives. (See the Resources section of this course for a link to the full list.)

Prescription drug monitoring programs

The diversion of prescription drugs (such as opioids) often involves fraudulent procurement for self-use or the selling of drugs for personal gain. Access is often accomplished by the patient:

- Seeing several doctors with complaints of pain symptoms in order to get multiple prescriptions (doctor shopping).
- Filling prescriptions at several pharmacies to avoid detection (pharmacy shopping).
- Presenting to emergency rooms, outpatient clinics, and dental offices with unsubstantiated pain symptoms.
- Altering valid prescriptions (e.g., either quantities or refill authorizations).
- Producing written or electronic forgeries for presentation to pharmacies.

(Centers for Medicare and Medicaid Services, 2015; Kraman, 2004)

Some of the current methods to combat prescription drug abuse and diversion include the use of triplicate numbered prescription forms, electronic prescribing for controlled substances (in certain states), the use of tamper-resistant prescription pads (required by Medicare since October 2008), collaborative practice agreements between pharmacists and prescribers, and utilization of state-operated prescription drug monitoring programs (PDMPs; Sacco et al., 2018). Prescription drug monitoring programs are state-driven databases that collect information on controlled (scheduled) prescription drugs and allow reports to be available to certain key individuals in the prescription drug process (CDC, 2017). The goal of such programs is to provide practitioners with the most current data on a patient's controlled drug use to identify shoppers who may be abusers or diverters.

Currently, 49 states have operational PDMPs or legislated programs that are under construction (Thielking, 2017). As of late May 2019, Missouri still lacked a statewide PDMP, in spite of years of attempted legislation. However, county PDMPs do cover almost 90% of Missourians (Hauswirth, 2019; Weber, 2019). In 2017, Missouri's governor:

> *Issued an executive order to create a statewide PDMP that allows Missouri Department of Health and Senior Services to analyze and identify inappropriate prescribing, dispensing, and obtaining of controlled substances, and to address these actions by making referrals to appropriate government officials, including law enforcement and professional licensing boards. (Federation of State Medical Boards, 2018).*

Prescription drug monitoring programs vary widely across the country because each program is an independent, state-driven entity. Variability in each program centers on issues that include the following:

- Drugs Monitored: Most states, at a minimum, report Schedule II, III, and IV controlled substances to the database. Approximately 60% of states additionally monitor Schedule V drugs.
- Access to the Database: In states with a PDMP, access is available to prescribers, dispensers, law enforcement (pursuant to active investigations), and licensing boards. Pennsylvania was until recently the only state to make data available only to law enforcement officials; however, following the passage of Pennsylvania Act 191 in 2014, the Commonwealth began the process of expanding the PDMP to provide information to physicians and dispensers (Pennsylvania Department of Health, n.d.).
- Housing: States house their PDMPs within the state board of pharmacy, department of health, or other single state authority. Some states house the program at law enforcement sites such as the Office of the Attorney General.
- Frequency of Reporting: Clearly, the more recent the data available to practitioners, the more valuable it is to the clinical decision-making process. Depending on the state, data can be reported from daily to monthly. Oklahoma currently operates in real time with information going to the database at the time a prescription is filled. Such reporting is the goal of several systems, but is often limited by the expense of a real-time system.
- Interstate Data Exchange: As of 2018, 45 states had agreed to share data through the National Association of Boards of Pharmacy's PMP InterConnect program (Lockwood, 2018). The establishment of new programs or the updating of existing programs invariably includes provisions for interstate data sharing. The importance of such sharing is obvious when providers practice near borders with other states and have patients from both states.
- Required PDMP Use: The number of states requiring practitioners to access the PDMP started out small but continues to grow. Usually this requirement involves Schedule II and III drugs, under designated circumstances, such as prescribing for a new patient or prescribing more than a designated amount.
- Generation of Unsolicited Reports: The majority of states generate some form of unsolicited reports to practitioners or law enforcement indicating opioid use or prescribing out of the norm (as defined by each state). Such reports have been shown to be one of the most effective strategies to combat drug abuse and diversion.
- Funding: There are a number of funding options used by states to initiate and maintain their PDMPs. They include federal grants, pharmaceutical companies, general revenue, program user fees, third-party payer fees, court costs from prescription drug prosecutions, health professional licensing fees, and state agency grants (Clark et al., 2012; Sacco et al., 2018; National Conference of State Legislatures, 2016).

After the state of Florida instituted a PDMP and began regulating pain clinics, 80% of counties saw a decline in opioid prescriptions between the years 2010 and 2015. The number of opioid-related deaths by overdose declined as well (Bulloch & Shuman, 2018).

The impact of a PDMP in opioid prescribing and monitoring depends on the state in which a dental practitioner lives. Moreover, as new programs are introduced and others evolve, PDMP regulations change and must be monitored by practitioners. State-specific information on topics related to PDMPs is primarily available from the National Alliance for Model State Drug Laws (NAMSDL; https://namsdl.org) and the National Alliance of State Controlled Substances Authorities (NASCSA; http://www.nascsa.org).

Prevention

The first step in prevention is awareness of the problem. Educating the dental team and keeping abreast of new information and available resources related to the prescription drug crisis can provide appropriate strategies for prevention. Part of this awareness is understanding the populations most at risk for abuse: teens (particularly females), college students, the military, Native Americans, Alaska Natives, the elderly, individuals with comorbidities (coexisting physical, mental, or behavioral conditions), and patients with a previous or family history of substance abuse.

Being aware that family and friends are the most common source of prescription drug use allows the dental team to educate their patients when opioid pain relievers are prescribed. Informing patients and families of the abuse potential of these drugs and alerting them to the need for safe, locked storage of the medication can help the family recognize possible abuse and prevent diversion from the drug's intended patient and use.

When a patient presents with pain, the informed dental practitioner can consider the use of NSAIDs and APAP as first-line pain management, whether alone or in combination, when not otherwise contraindicated. Patients need to be instructed on the safe use of these medications and understand that pain that persists longer than a few days needs to be re-evaluated in the dental office. If opioids are indicated, limiting quantities to what is needed for only a few days and providing appropriate patient education will help to prevent a new abuse problem from occurring. Known or suspected drug abusers should not be prescribed opioid pain medication; consultation with their physician or pharmacist can alert other healthcare providers of the problem and set the stage for treatment referral.

Prevention of prescription drug abuse by healthcare providers will require increased professional training of dental and other healthcare professionals in the recognition and prevention of misuse, abuse, and diversion. In 2007, NIDA established Centers of Excellence (NIDA-CoEs) in collaboration with a consortium of medical schools to fill gaps in the curriculum related to illicit and prescription drug abuse and to recognize early use in order to prevent an ensuing path to addiction and abuse (Denisco et al., 2011; NIDA, 2014a). The ADA has also called on dental educators to increase their content on this subject to better prepare practitioners to participate fully in prevention efforts.

Conclusion

This course has provided an overview of the escalating problem of prescription drug abuse in the United States. The opioid drugs have been given specific attention because they are the prescription drugs most commonly abused and most relevant to the dental practitioner treating dental pain. The role of the dentist and dental healthcare team in identifying and preventing the misuse, abuse, and diversion of prescription drugs is critical for curbing this national epidemic.

More research is needed into pharmacologic alternatives, prescribing patterns of dentists and other healthcare providers, public understanding and awareness, and more effective education programs to more completely address the national problem of prescription drug abuse. The federal government has issued a call to train healthcare providers to identify early signs of an opioid use disorder among their patients (ONDCP, 2018). Dental providers and dental educators are well positioned to collaborate in research activities and to incorporate research findings into practice to promote the safe and effective use of prescription drugs and, in turn, play a significant role in addressing the prescription drug abuse epidemic plaguing the nation.

Resources

American Dental Association (ADA)
The American Dental Association's website provides information for dental professionals on the abuse of prescription drugs. It provides current ADA policies, statements, and guidelines, as well as additional resources for both the public and dental professionals.
Website: https://www.ada.org/en/advocacy/advocacy-issues/opioid-crisis

Centers for Disease Control and Prevention
CDC Guideline for Prescribing Opioids for Chronic Pain, United States, 2016
The CDC issued these recommendations in response to the epidemic of deaths from opioid overdose.
Website: https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

Commissioned Corps of the U.S. Public Health Service, Pharmacist Professional Advisory Committee
Clinical Collaborative Practice Agreements: Critical Elements in Designing a Collaborative Practice Agreement (CPA)/Clinical Protocol. This committee provides information regarding critical elements and clinical guidelines for establishing collaborative practice agreements (CPAs).
Website: https://dcp.psc.gov/osg/pharmacy/cpharm_cguide_cpa.aspx

National Coalition Against Prescription Drug Abuse (NCAPDA)
The National Coalition Against Prescription Drug Abuse (NCAPDA) is a resource created to raise awareness of the dangers caused by prescription drug abuse. The NCAPDA website targets individuals at risk for prescription drug abuse and their families and provides links to resources including community programs and drug abuse hotlines. This organization also offers downloadable educational tools for raising awareness of prescription drug abuse.
Website: https://ncapda.org

National Institute on Drug Abuse (NIDA)
The National Institute on Drug Abuse (NIDA), an arm of the National Institutes of Health (NIH), supports research to prevent and treat drug abuse and addiction. The NIDA website provides extensive information on drugs of abuse and related topics as well as links to publications and external resources. The Institute provides extensive resources for the health professional, as well as for researchers, patients and families, parents and teachers, and students and young adults.
Website: https://www.drugabuse.gov

Screening, Brief Intervention, and Referral to Treatment (SBIRT)
Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidence-based tool for community-based screening for risky health behaviors, including substance use. This and other more detailed information and resources are available through the SAMHSA-HRSA [Health Resources and Services Administration] Integrated Health Solutions website.
Website: https://www.integration.samhsa.gov/clinical-practice/sbirt

Substance Abuse and Mental Health Services Administration (SAMHSA)
The Substance Abuse and Mental Health Services Administration (SAMHSA) is a government organization that focuses on the link between behavioral health and overall health, specifically as it relates to substance abuse. The SAMHSA website provides resources for both individuals and professionals, including downloadable publications and educational resources. The Substance Abuse and Mental Health Services Administration directs individuals with concerns about treatment or who are seeking referral to treatment to various Web pages or its 24-hour referral helpline.
Website: https://www.samhsa.gov

Substance Abuse and Mental Health Services Administration (SAMHSA) Behavioral Health Treatment Services Locator
The Behavioral Health Treatment Services Locator can help with finding local treatment for substance use and mental health problems. The site protects the confidentiality of the individual seeking information.
Website: https://findtreatment.samhsa.gov

The U.S. Drug Enforcement Administration (DEA) enforces the controlled substances laws and regulations of the United States and brings to the criminal and civil justice systems those organizations and principal members of organizations involved in the growing, manufacture, and distribution of controlled substances appearing

in or destined for illicit traffic in the United States. The DEA also recommends and supports non-enforcement programs aimed at reducing the availability of illicit controlled substances on the domestic and international markets.

The DEA website contains a section on drug information, including drug fact sheets. Website: https://www.dea.gov/factsheets

U.S. Food and Drug Administration (FDA)

The FDA provides a list of Approved Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of a drug or biological product outweigh its risks.

Website: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

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PRESCRIPTION DRUG ABUSE AMONG DENTAL PATIENTS: SCOPE, PREVENTION, AND MANAGEMENT CONSIDERATIONS

Final Examination Questions

Select the best answer for each question and mark your answers on the Final Examination Answer Sheet found on page 60, or complete your test online at **EliteLearning.com/Book**

21. In an effort to oversee enforcement of all controlled substance laws, the U.S. Drug Enforcement Administration (DEA) was created in:
    a. 1973.
    b. 1970.
    c. 1963.
    d. 1953.

22. In 2017, what percentage of young adults aged 18 to 25 in the U.S. population was using a prescription psychotherapeutic drug in a manner or for a purpose other than that for which it was intended?
    a. 11%.
    b. 12%.
    c. 13%.
    d. 14%.

23. The United States makes up only 4.6% of the world's population, but uses what percentage of the global supply of opioid pain relievers?
    a. 70%.
    b. 80%.
    c. 85%.
    d. 87%.

24. Which of these commonly abused drugs is most likely to be prescribed by dentists?
    a. CNS depressants.
    b. Stimulants.
    c. Opioids.
    d. Nasal decongestants.

25. The term *prescription drug abuse* is most often synonymous in the literature with:
    a. Nonmedical use.
    b. Common misuse.
    c. Addiction.
    d. Tolerance.

26. The unintentional and incorrect use of an approved medication in a manner other than prescribed is known as:
    a. Misuse.
    b. Addiction.
    c. Tolerance.
    d. Dependence.

27. When a person who is physically dependent on a drug loses access to the drug, the expected outcome is:
    a. Withdrawal symptoms.
    b. Death.
    c. Brain injury.
    d. Stroke.

28. The need to use a higher dose of a drug to achieve the same effects previously achieved by a lower dose is known as:
    a. Physical dependence.
    b. Addiction.
    c. Tolerance.
    d. Misuse.

29. The first government attempt to regulate drugs in the United States, which was designed to prevent the manufacturing, selling, or transporting of adulterated, misbranded, poisonous, or deleterious foods, drugs, medicines, and liquors was the:
    a. Scheduled Drug Act of 1896.
    b. Uniform Controlled Substances Act of 1990.
    c. Uniform State Narcotic Drug Act of 1934.
    d. Pure Food and Drug Act of 1906.

30. Reward centers of the brain are primarily associated with the neurotransmitter:
    a. Norepinephrine.
    b. Acetylcholine.
    c. GABA.
    d. Dopamine.

31. All CNS depressants produce their pharmacological effects by interacting with which inhibitory neurotransmitter?
    a. Acetylcholine.
    b. Norepinephrine.
    c. GABA.
    d. Glutamate.

32. Which opioid is commonly delivered via skin patch?
    a. Fentanyl.
    b. Morphine.
    c. Oxycodone.
    d. Meperidine.

33. According to the report Teen Prescription Drug Abuse: An Emerging Threat, teens claim to abuse prescription painkillers because they:
    a. Like the stigma attached to these drugs.
    b. Can hide these drugs more easily than other drugs.
    c. Believe these drugs are safer to use than illicit drugs.
    d. Prefer the effects of these drugs over those of other drugs.

34. According to a 2008 study by Dr. Amelia Arria, what percentage of college students who reported a nonmedical use of stimulants also reported using alcohol?
    a. 68%.
    b. 75%.
    c. 87%.
    d. 100%.

35. According to the Department of Defense Health Related Behaviors Survey, the percentage of active duty personnel who reported misuse of prescription drugs within the last 12 months was:
    a. 4.1%.
    b. 5.3%.
    c. 6.1%.
    d. 6.3%.

36. Of the more than 80% of older patients (aged 57 to 85 years) who use at least one prescription medication on a daily basis, the percentage taking more than five medications or supplements daily is:
    a. 5%.
    b. 15%.
    c. 50%.
    d. 100%.

37. A 2009 National Institute on Drug Abuse (NIDA) study identified dentists as the main prescribers of opioids to patients between:
    a. 10 and 19 years of age.
    b. 20 and 29 years of age.
    c. 30 and 39 years of age.
    d. 40 and 49 years of age.

38. According to a nationwide survey conducted by the University of Pittsburgh School of Dental Medicine, the number of opiate pain relief tablets (e.g., Vicodin or Percocet) prescribed by oral surgeons following third molar extraction surgery averaged:
    a. 20.
    b. 22.
    c. 26.
    d. 32.

39. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (APAP) combinations:
    a. Provide more effective pain relief than prescribing either drug alone.
    b. Do not need to be taken "around the clock" at regular intervals.
    c. Should be given only after the numbing effects of the local anesthesia are gone.
    d. Can be safely used in patients with severe liver damage.

40. The safest way to dispose of an unused prescription medication is to:
    a. Donate it to someone who could use the same medication for his or her own purposes.
    b. Place it in the trash in its original labeled container.
    c. Anonymously mail it back to the manufacturer.
    d. Place it in the trash in a nondescript container with coffee grounds or kitty litter.

Course Code: DNJ05PD

Course 3: Denture Cleansing: An Essential Part of Patient Care, 4th Edition

1 CE Hour

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Faculty

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The planner who worked on this continuing education activity have disclosed that they have no significant financial or other conflicts of interest pertaining to this course book.

AGD Subject Code - 670

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INTRODUCTION

Learning objectives

After completing this course, the learner will be able to:

- Describe the diversity of microorganisms that can be found on dentures and the associated health risks.
- Discuss the relationship between yeast infestation of dentures and both oral and systemic health.
- Describe the correlation between candidal infestation of dentures and denture-induced stomatitis.
- Describe the different denture cleansing modalities, including manual brushing and effervescent cleansers.

Course overview

Most denture patients, as well as patients with removable orthodontic appliances, tend to be haphazard in practice when it comes to cleansing their dental appliances. Dental professionals and patients alike appreciate that cleansing of removable partial dentures (RPDs), complete dentures (CDs), and orthodontic appliances is essential to remove particulate matter as well as stains arising from food, beverages, and tobacco products. Ideally, cleansing ensures a fresh and odor-free mouth.

Effective denture cleansing is imperative to maintaining oral health and possibly preventing systemic diseases by removing the dental plaque biofilm and the microorganisms from the denture and other oral appliances (Rodriguez-Archilla and Garcia-Galan, 2020; Mojarad, Khalili, & Aalaei, 2017; Galvan, et al., 2021; Brown, et al., 2022; Sharma, Garg, & Kalra, 2017). In fact, there is a strong positive correlation between denture cleanliness and lower bacterial colonization of dentures, as quantified by both the total anaerobic count and total aerobic count (Brown et al., 2022).

Patients may be less concerned with the disease implications of contaminated dental appliances than with sequelae such as appearance and odor. Effective denture cleansing therefore requires both the rapid and efficient removal of debris and stains and elimination of denture plaque and any bacterial colonization. The cleansing agent, however, must not cause any damage to the denture base resin, liner materials, or orthodontic appliances, nor can it leave toxic, malodorous, or unpleasant-tasting deposits on any surface.

The two approaches most commonly used to cleanse dentures are immersion in a chemical cleaning agent and/or brushing with a toothbrush and dentifrice. Denture base materials do not resist accretion of oral bacteria and fungal organisms given the porosities in the denture acrylic base which is conducive to the development of a biofilm which promotes microbial growth (Morse et al., 2018; Cavalcanti, 2018; Rodrigues- Archilla and Garcia-Galan, 2020). Soft liners, tissue conditioners, and denture adhesives are very susceptible to microbial growth (Baygar, et al., 2018; Malhorta, et al., 2020; Sartawi, et al., 2021). These findings clearly indicate that denture hygiene is significant in terms of both oral and systemic pathology.

Dental professionals, most notably dental hygienists, play an important role in controlling denture contamination and in instructing patients in the proper care and sanitization of removable dentures and orthodontic appliances. In this course, attention is directed primarily to complete and removable partial dentures, although the discussion applies equally to all removable dental appliances and devices. This basic-level course is appropriate for all dental professionals. The course reviews the diverse colonization of microorganisms found on dentures and the associated oral and systemic health risks, the correlation between candidal infestation of dentures and denture-induced stomatitis, and the pros and cons of various denture cleansing methods.

DENTURE PLAQUE

Microorganism colonization of dentures results in the formation of deposits commonly referred to as denture plaque. The role of microorganism colonization of dentures in persistent and recurrent stomatitis has been recognized for many years (Axe, Varghese, Bosma, Kitson, & Bradshaw, 2016; Kumar, Sandhu, Kumar, & Patil, 2017; Brown, et. al.; Loewy, et al., 2018; Flores, et al., 2017). In fact, it is now well established that numerous opportunistic and pathogenic microorganisms colonize dentures and develop a diverse microbial community within the denture base itself and within the underlying mucosal tissue base (see Table 1; Sivakumar et al., 2014; Brown, et al., 2022).

Table 1: Bacteria and Fungi Found on Dentures

Gram-Positive Organisms	Gram-Positive Rods	Gram-Negative Rods	Gram-Negative Cocci	Fungi
• Staphylococcus species. • Streptococcus species.	• Arcanobacterium haemolyticum. • Actinomyces species.	• Pseudomonas species. • Enterobacter species. • Burkholderia cepacia. • Stenotrophomonas maltophilia.	• Neisseria perflava.	• Candida albicans. • Candida glabrata. • Candida paratropicalis.

Note: Based on data from O'Donnell, L. E., Robertson, D., Nile, C. J., Cross, L. J., Riggio, M., Sherriff, A., … Ramage, G. (2015). The oral microbiome of denture wearers is influenced by levels of natural dentition. *PLO ONE, 10*(9), e0137717. doi:10.1371/ journal.pone.0137717; Ribeiro, D. G., Pavarina, A. C., Dovigo, L. N., Machado, A. L., Giampaolo, E. T., & Vergani, C. E. (2012). Prevalence of Candida spp. associated with bacteria species on complete dentures. *Gerodontology, 29*(3), 203-208; and Sivakumar, I., Arunachalam, K. S., Sajjan, S., Ramaraju, A. V., Rao, B., & Kamaraj, B. (2014). Incorporation of antimicrobial macromolecules in acrylic denture base resins: A research composition and update. *Journal of Prosthodontics, 23*(4), 284-290. doi:10.1111/ jopr.12105.

Researchers have identified hundreds of bacterial species in the oral microflora (Hagenfeld et al., 2018; Nakano, Suzuki, & Kuwata, 2018; Xun, Zhang, Xu, Chen, & Chen, 2018). The literature indicates that these microorganisms can not only elicit substantial oral infections but may also induce systemic diseases (Gao, et al., 2018; Sudhakara, Gupta, Bhardwaj, & Wilson, 2018; Xun et al., 2018). Bacteria such as *Klebsiella* and Enterobacteriaceae, may play a role in denture malodor due to the production of volatile sulfur compounds (Takane, et al., 2018). A wide diversity of microorganisms is detected on removable dentures and within the oral cavity of denture wearers (Gad and Fouda, 2020; Andonissamy, et al., 2019; Takane, et al., 2018; Sivakumar et al., 2014).

Substantial contamination of dentures by microorganisms occurs within 24 hours of intraoral exposure (do Nascimento et al., 2014). The varied topography of dentures also makes some denture surfaces more prone to contamination than others. The unpolished side of dentures has pores and indentations that support microbial colonization and biofilm formation (Malhotra, et al., 2020). In addition, the porosity of the denture base material permits microbial permeation and contamination throughout the denture (Brown, et. al.; Figuerôa et al., 2018; Shinawi, 2017). High levels of *Candida* and *Staphylococcus* (including methicillin-resistant *S. aureus*) have been found on the palatal tissue surface of maxillary dentures as well (Rodriguez-Archilla, 2020). *Candida albicans* and bacterial species such as streptococcal gordonii, S. oralis and S. sanguinis combine to enhance bacterial colonization and biofilm formation which is a prerequisite to the development of denture stomatitis (Koo, et al., 2018).

The presence of bacterial species in denture plaque has an important health consequence, particularly with dependent elderly patients (Fuginami, et al., 2021). A major health problem for this population is morbidity and mortality resulting from aspiration pneumonia. Most cases of bacterial pneumonia appear to be initiated through colonization or superinfection of

the pharynx by pathogenic bacteria, followed by aspiration of pharyngeal contents. In one study of more than 100 individuals, respiratory pathogens were identified on 64.6% of the dentures examined (O'Donnell et al., 2016). Based on these findings, the researchers concluded that dentures can act as a reservoir for respiratory pathogens, thereby increasing the theoretical risk of developing aspiration pneumonia. The aspiration of microbial organisms while wearing dentures during sleep is an independent risk factor for the development of aspiration pneumonia (Takeuchi, et al., 2019). These findings clearly indicate that controlling denture plaque is important with regard to preventing aspiration pneumonia (Shinawi, 2017).

YEAST INFESTATION OF DENTURES

The components of the oral microflora in adults can be independently influenced by both patient age and the wearing of partial and/or complete dentures and their potential to cause denture stomatitis (Meira et al., 2017; Flores, 2017; Caldeira, et al., 2021). The proportions of salivary yeasts and lactobacilli increase with age and with denture use (Fujinami, et al., 2021), and fungal infections are more common among older denture wearers (Wojak, et al., 2021). In addition to age, the method of denture cleaning, the level of denture hygiene, and smoking are all factors that can favor yeast (principally *Candida albicans*) infestation of complete and partial dentures (Alzayer, Gomez, Eckert, Levon, & Gregory, 2018; Sartawi, et al., 2021; Sivakumar et al., 2014; Srivastava, et al., 2018). Patient gender does not appear to be a factor in yeast infestation. Dysphagia (difficulty in swallowing), a common disorder among the elderly population, and broad-spectrum antibiotic therapy are additional risk factors for dental and denture plaque colonization by *C. albicans* (Takeuchi, et al., 2019).

The composition of the microbial flora associated with denture stomatitis includes *Candida albicans* and other candida species with *Staphylococcus aureus* and Streptococcus mutans common bacterial inhabitants of this denture-related biofilm (Abdurahman, et al., 2020). Within the oral environment *Candida albicans* is present in 45-60% of healthy individuals with a prevalence of 60-100% in those who wear dentures (Sartawi, et al., 2021). The oral biofilm associated with dentures in which *C. albicans* exists is a complex microbial environment in which some bacteria are positively correlated with the abundance of this fungal species while other bacteria are negatively correlated with a decrease in the *C. albicans* population. A positive correlation exists between the *C. albicans* population and the bacterial genera Lactobacillus, Scardovia, and Bifdobacterium while a negative correlation is displayed between *C. albicans* and Porphyromonas, Catonella and Peptostretococcus (Fujinami, et al., 2021).

Candidal growth occurs with polymethyl methacrylate (PMMA) denture bases (Gad, Al-Thobity, Shahin, Alsaqer, & Ali, 2017; Petrović, Bonvin, Hofmann, & Ebersold, 2018) and with dentures carrying resilient liners. Glazing of the denture fitting surface or surface sealing of resilient liners does appear to reduce both bacterial and yeast colonization however such coatings can influence the adaptation of the denture to the tissue surface and compromise retention (Tsuji, et al., 2016; Gad and Fouda, 2020; Hirasawa, et al., 2018). The application of sulfobetaine or hydrophilic monomers on the tissue-bearing surface of a denture creates a surface which has significantly less *C. albicans* than non-coated denture surfaces (Gad and Fouda, 2020; Sivakumar et al., 2014). In contrast, Kang, Lee, Hong, Kim, and Kwon (2013) reported greater Candida adhesion with hydrophilic surfaces. Denture adhesives, however, do not appear to affect denture microbiota (Darwish, et al., 2021). It should be noted here that there is greater adherence of *C. albicans* (and *S. mutans*) to tissue conditioners and soft liners than to conventional acrylic denture base resin (Singh, et al., 2018; Baygar et al., 2018; Malhotra, et al., 2020). *C. albicans* readily penetrates denture soft lining materials (Baygar, et al., 2018 Malhorta, et al., 2020). Researchers continue to experiment with composites and coatings to discourage the adhesion of microorganisms (Gad et al., 2017; Huang, Jing, Zhuo, Meng, & Wang, 2017; Petrović et al., 2018).

The presence of *C. albicans* on dentures or the oral mucosa, as discussed in the next section, is typically associated with denture stomatitis (Galvin, et al., 2021; Hayran, Sarikaya, Aydin, & Tekin, 2018; Morse et al., 2018; Ohshima, Ikawa, Kitano, & Maeda, 2018). However, other studies found that the proliferation of *Candida albicans* was not an important risk factor in the development of denture stomatitis (Cankovic, et al., 2017). It has been found, for example, that asymptomatic denture wearers may have a significantly higher prevalence of Candida but no stomatitis (Huang et al., 2017; Rodrigues-Archilla and Garcia-Galan, 2020).

DENTURE-INDUCED STOMATITIS

The etiology of denture-induced stomatitis is multifactorial and includes ill-fitting dentures, continuous wear of dentures, poor oral hygiene, and microbial infection (Barua, Basavanna, & Varghese, 2017; Malhotra, et al., 2020; Loewy, et. al., 2018). However, evidence suggests that denture plaque, a combination of yeasts and microorganisms, is probably a major etiological factor (Glick, 2019; Lowey, et al., 2018). In fact, *C. albicans* represents only part of the total cultivable flora in denture stomatitis patients (Fujinami, et al., 2021; Abdurahman, et al., 2020; Shi et al., 2016). Nevertheless, the significance of yeast proliferation on dentures and denture plaque cannot be overlooked, and it clearly contributes to denture stomatitis. Furthermore, research suggests that plaque formation is a multistep process that involves initial adherence of *C. albicans*, progressing to colonization, thin biofilm formation, development of a multilayer, and finally denture plaque deposits (Koo, et al., 2018; Morse et al., 2019). This process is thought to be facilitated by salivary and serum pellicles (Heller et al., 2016; Malhotra, et al., 2020) . *C. albicans* forms biofilms on a wide variety of medical devices and prostheses and serve as a scaffolding for microbial aggregation and proliferation (Abdurahman, et al., 2020).

Denture-induced stomatitis occurs frequently with rates as high as 70% in denture wearers (Anwander, Rosentritt, Schneider-Feyrer, & Hahnel, 2017; Garaicoa et al., 2016; Gardizani, Pinke, de Lima, & Lara, 2017; Loewy, et.al., 2018]. Regardless of the actual prevalence, denture-induced stomatitis presents a problem for denture wearers, particularly older patients. Denture-induced stomatitis occurs more often in women than men an increases in prevalence with aging among both genders. (Malhotra, et al., 2020).The authors suggested that the reasons for this may be related to hormonal changes in older women and various aging-related changes in health and hygienic habits.

Although not directly related to denture-induced stomatitis, bacterial infestation of dentures also leads to denture malodor. Certain bacteria isolated from oral and denture microflora, such as Klebsiella and Enterobacteriaceae, are thought to be involved in denture malodor (Takane et al., 2018) although other studies suggest that oral malodor is mainly a result of the presence of volatile sulfur compounds (Bicak, 2018;; (Ye, et al., 2020; Suzuki et al., 2018). This is an important consideration because, among older adults wearing complete dentures, there is a considerable increase in the prevalence of periodontopathic bacteria, some of which produce volatile sulfur compounds (Andjelkovic et al., 2017).

CLEANSING METHODS FOR DENTURES

The importance of oral (and denture) hygiene for denture wearers is essential and it is imperative that dental clinicians emphasize this to their patients and review the protocols by which these prostheses are cleaned and maintained. It should not be assumed that these denture patients understand the importance of denture hygiene and the optimal means by which these prostheses are cleaned. (Galvan, et al., 2021; Cavalcanti, 2018). Effective cleansing of dentures is imperative to avoid or at least control denture-induced stomatitis and denture odor with the quality of the cleaning more important than the actual method(s) used (Martins and Gontijo, 2017). The strong association between yeast (especially *C. albicans*) proliferation on dentures and denture stomatitis has resulted in much of the literature on denture cleansing being devoted to preventing or removing fungal attachment to denture base materials (Anwander et al., 2017; Cierech et al., 2018; Gad et al., 2017; Herman et al., 2017).

Oral candidiasis, for example, may be treated with topical antifungal agents such as nystatin and amphotericin B or with systemic medications such as fluconazole, and the treatment is typically effective, at least initially (Centers for Disease Control and Infection, 2017; Gad and Fouda, 2020; Martins and Gontijo, 2017). However, such medication can produce side effects in some patients, and when therapy is stopped, the condition can recur (Sá et al., 2018; Glick, 2019). There have also been attempts to incorporate antifungal agents within tissue conditioners to inhibit mycelial growth as an alternative treatment of denture stomatitis Carvacrol is an essential oil that is contained in plants such as oregano and thyme. Its inclusion in soft denture lining materials has demonstrated antimicrobial activity against oral pathogens such as *C. albicans* which is among the etiologic factors in the development of denture stomatitis (Baygar, et al., 2018). Denture adhesives can contain substances such as sodium tetra borate, hexachlorophene and sodium borate plus ethanol which can exert antimicrobial activity against *Candida albicans* and can aid in the treatment of denture stomatitis (Lamfon, 2021). A recent study found that denture adhesive might actually inhibit innate antimicrobial activity but that the inclusion of antifungal agents in the adhesives might help to prevent or treat Candida infections (Bates, Garaicoa, Fischer, & Brogden, 2017).

With advances in nanotechnology, some researchers have also been investigating the incorporation of silver nanoparticles into acrylic resins as these silver nanoparticles are biocompatible and have a strong antimicrobial effect against a wide range of bacteria, viruses and fungi (Gad and Fouda, 2020). Other researchers have examined the use of rechargeable anticandidal denture material. One study reported that disks loaded with miconazole demonstrated anticandidal activity for up to 30 days in saliva (Malakhov et al., 2016). These disks can also be charged with chlorhexidine (Malakhov et al., 2016).

Ingredients such as peroxides, hypochlorite, acids and enzymes are the active ingredients in many of the commercially available denture cleaners (Karthikeyan, et al., 2018). The use of solutions of 0.5% sodium hypochlorite, 0.2% digluconate chlorhexidine and alkaline peroxide solutions are among the best cleaning agents for the reduction of the total microbial counts on the surfaces of dentures (Lamfon, 2021).

The two principal approaches used to cleanse dentures are (a) toothbrushing with dentifrice and (b) immersion cleaning, with the most popular method of cleaning among complete and partial denture wearers reported to be brushing (Loewy, 2018; Papadiochu and Polyzois, 2018; Lamfon, 2021). Although cleaning dentures by brushing may be popular, it is not particularly effective in ensuring the long-term removal of microorganisms from denture surfaces and is limited to accessible areas (Lamfon, 2021; Papadiochu and Polyzois, 2018). In addition to poor removal of harbored microorganisms, brushing can cause other problems such as abrasive damage, particularly with soft lining materials (Axe et al., 2016; Kiesow, Sarembe, Pizzey, Axe, & Bradshaw, 2016; Galvan, et al., 2021). Dentifrices and even low-abrasivity denture pastes will cause surface roughening and grooving of denture bases, with the type of paste cleaner, the brush characteristics, and the denture material affecting the observed surface abrasion (Kiesow et al., 2016; Loewy, et al., 2018). The surface abrasion and consequent grooving and surface roughening from brushing with pastes will result in a greater tendency toward staining and plaque formation (Shinawi, 2017; (Kurniawan, et al., 2019). Although it has been suggested that household cleaning powders and cleansers containing hypochlorites are effective stain removers, hypochlorites are known to be damaging to acrylic resins, as well as metal alloys (Badaró et al., 2017; Galvan, et al., 2021; Lamfon, 2021). Repeated soaking of a denture in a 0.5% hypochlorite solution has also been reported to lighten the pink pigment of denture acrylic and residual traces of hypochlorite left on the denture can cause mucosal irritation (Gad and Fouda, 2020; Galvan, et al., 2021).

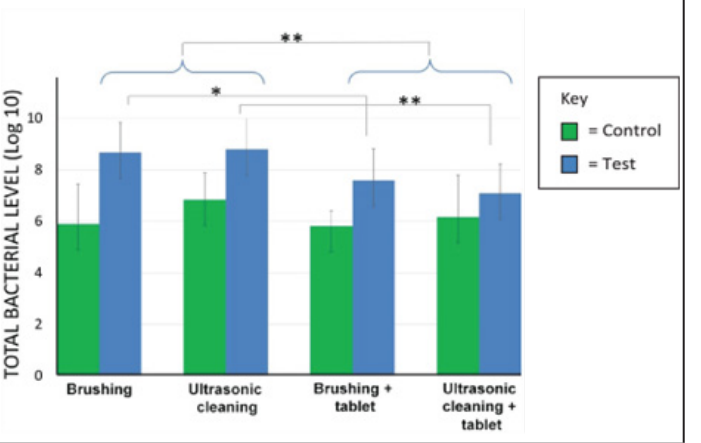
Toothbrushes themselves, even those with stiff bristles, have a negligible abrasive effect when used with water, but abrasion can occur if an dentifrices which contain abrasives such as calcium carbonate or silica calcium carbonite are used (Shinawi, 2017; Ramadhan, 2018). Bristles sustain damage over time from repeated use which increases their abrasiveness on surfaces. The bristles will harbor the microorganisms which they remove from the denture surface so the cleansing and disinfection of the bristles is necessary to prevent microbial re-inoculation of the denture surfaces (de Arruda, et al., 2021). The surface grooves created by brushing with abrasive pastes will render the denture surface, and especially resilient liner surfaces, more susceptible to stain buildup and facilitate plaque accumulation (Axe et al., 2016; Shinawi, 2017; Mahboub et al., 2017).

A further consideration, at least for geriatric and arthritic patients, is that manual or mechanical brushing of dentures requires a certain degree of manual dexterity and visual acuity and can make cleaning difficult (Lamfon, 2021; Hoben, Poss, Norton, & Estabrooks, 2016; Khan, Dhaded, & Joshi, 2016; Kartthikeyan, et al., 2018; Yuzugullu, Acar, Cetinsahin, & Celik, 2016). In addition, many patients simply do not know how best to clean their dentures (Axe et al., 2016). Careful observation of the brushing technique of denture wearers indicates that cleansing is primarily directed toward the teeth and cameo surfaces, with far less attention being given to the highly important intaglio surfaces (Duyck et al., 2016).

It has been suggested that greater denture cleaning efficiency is possible when both an immersion cleanser and brushing are used (Brown, et al., 2022; Duyck et al., 2016;; Salinas, 2017; Loewy, et al., 2018). Other researchers have suggested that the combined use of ultrasonic agitation (Duyck et al., 2016) microwave radiation and ultraviolet radiation (Polychronakis, Polyzois, Lagouvardos, Andreopoulos, & Ngo, 2018;]; Galvan, et al., 2021; Loewy et al., 2018). with effervescent cleansers is very effective in removing adherent denture plaque. Figure 1 shows a comparison of brushing and ultrasonic cleaning, both with and without use of a cleansing tablet. In both cases, reduced numbers of colony- forming units (CFUs) are seen with the combination approach. It is worth noting, however, that little is known of the effects of ultrasonic agitation on denture base materials, and before this measure is recommended for routine use, particularly for dentures carrying soft (resilient) liners or tissue conditioners, the possible cavitation effects of simultaneous exposure to ultrasonic vibrations and the effervescent action of denture cleansers should be studied. Studies to date have produced contradictory results with ultrasonic agitation (Galvan, et al., 2021).

Whether microwave-assisted denture cleansing can be recommended is even more contentious in view of the heating effect associated with microwave radiation. Microwave irradiation for 3 minutes at 650 W once a week for 14 days was as effective at disinfecting dentures contaminated with different bacteria and Candida as 0.2% chlorhexidine, 0.02% sodium hypochlorite and the use of topical nystatin (Sousa, et al., 2020). This method did not affect the structure or stability of the dentures (Jaiswal, et al., 2108). However, the use of 650 W of microwave irradiation for 6 minutes caused detrimental effects to the physical and mechanical properties of the acrylic resin of the denture (Mojarad, et al., 2017). Microwave irradiation of a denture immersed in denture cleanser for 2-3 minutes at 450 W resulted in disinfection with no viable candida cells left (Jaiswal, et al.,). Yet controversy exists about the effectiveness of microwave irradiation and its potential to cause deformation of the acrylic resin and to alter the color of the acrylic (Galvan, et al., 2021). The use of microwave irradiation for the disinfection of a denture must be used with caution and under controlled circumstances. The power of microwaves will vary and the actual cleanliness of a microwave oven that is used for culinary purposes are issues to consider before this technique is used. The immersion of a denture with microbial contamination in water during microwave irradiation inactivates microorganisms as this protocol will cause the coagulation of the principal proteins of microorganisms (Mojarad, et al., 2017).

Figure 1: Total Bacterial Levels Recovered from Dentures after Cleaning



*p < 0.05; **p < 0.01

Note. Adapted from Duyck, J., Vandamme, K., Krausch-Hofmann, S., Boon, L., De Keersmaecker, K., Jalon, E., & Teughels, W. (2016). Impact of denture cleaning method and overnight storage condition on denture biofilm mass and composition: A cross-over randomized clinical trial. *PLOS ONE, 11*(1), 1-16. doi:10.1371/journal.pone.0145837.

EFFERVESCENT CLEANSERS

Overall, the literature indicates that sanitizing prostheses with immersion denture cleansers is one of the most effective and convenient methods for plaque control, particularly for soft denture lining materials as brushing can damage and roughen the surface of a soft denture line (Salcetti, 2022; Hayran et al., 2018; Mahboub, et al., 2017). This is an important consideration because, as noted earlier, tissue conditioners and soft liners promote or at least support *C. albicans* and other fungal growth and/or colonization in vivo and in vitro (Jadhav, Shetty, Malhotra, et al., 2020; Baygar, et al., 2017;Kumar, Kumar, Natarajan, & Sreenivasan, 2018; Singh, et al., 2018). This colonization leads to penetration of *C. albicans* within soft lining materials (Krishnamurthi & Hallikerimath, 2016; Singh, et al., 2018; Malhotra, et al., 2020).

Denture stomatitis is a common disorder among denture wearers and the actual prevalence varies among studies yet the early prevention of denture plaque accretion is important to decrease its role in the development of this inflammatory condition (Sartawi, et al., 2021). The literature, however, is somewhat conflicting with regard to the efficacy of immersion (effervescent) cleansers in removing denture plaque and microorganisms such as *C. albicans*. Some studies show a moderate reduction of *C. albicans* while others show no difference or even an increase of *C. albicans* after immersion in a commercial chemical dental cleanser (Han, et al., 2020). This is likely the result of the almost continuous change in available products and product formulation of commercial denture cleansers.

The storage medium of a denture overnight can also influence the *C. albicans* population in a denture. One study found that dry storage is an option for the reduction of the *C. albicans* population while storage in only water without a cleansing tablet may promote *Candida albicans* colonization. Dry storage did not cause any significant change in the dimensions of the denture (Verhaeghe, et al., 2019). The routine use of denture cleaners can alter the color, gloss and hardness of the acrylic resins of dentures surface roughness of the acrylic (Ayaz and Ustun, 2020).

Oxidizing cleansers containing perborate, persulfate, peroxides and similar oxidants are useful for cleaning dentures (Karthikeyan, et al., 2018; Lamfon, 2021) and have been shown to reduce total microorganisms and total streptococci (Gad and Fouda, 2020; de Arruda, et al., 2021). These cleansers do not always effectively reduce *C. albicans* populations (Lamfon, 2021). It was hypothesized that this may be because *C. albicans* is located deeper and therefore somewhat protected by streptococci, which are on a more superficial layer.

Notwithstanding the benefit of immersion cleansers compared with denture pastes, immersion cleansers, when used alone, may not be completely effective for the control of heavy plaque. The combination of brushing the denture after which an immersion cleaner is used is more effective in the removal of plaque and microorganisms than by the reliance of the effervescence of an immersion cleanser alone (Galvan, et al., 2021). Enzymes such as β-1,3-glucanase which are contained in some denture cleansers decrease the amount *C. albicans* by the exertion of a hydrolytic against these fungal organisms and can be more effective than some denture cleansers (Indrawati, et al., 2016). A symbiotic relationship exists between *C. albicans* and some streptococcal bacteria. *C. albicans* promotes bacterial colonization and biofilm formation with an increased virulence of this combined bacterial and fungal microbial community (Koo, et al., 2018). As noted earlier, this could be the result of streptococci being present on more superficial layers of biofilm, ultimately protecting the *C. albicans* that is present on a deeper level with the physical coadhesion of these microbes significantly enhanced in the presence of sucrose (Abdurahman, 2020). The effectiveness of enzyme- containing cleansers may be due to their ability to destroy intercellular adhesion resulting in fungicidal activity and the ability to remove yeasts.

Though a combination of immersion cleansers and brushing removes the greatest amount of plaque, it follows from these considerations that immersion cleansers are more suitable for cleaning dentures than abrasive pastes, particularly for those carrying resilient liners and tissue conditioners. Denture cleansers can cause a color change in the denture base resin, roughen the tissue surface of a denture and can reduce the flexural strength of a denture (Gad and Fouda, 2020). Alkaline peroxide-based solutions can change the color of dental resins and can result in the loss of the surface gloss due to the release of oxygen and can cause adverse effects to the physical properties of the denture if used incorrectly (Ayaz and Ustun, 2020). Interestingly, it has been suggested that dentures fabricated from light-activated resins may be the materials of choice for patients

prone to denture stomatitis, as they have shown less overall degradation from candidal treatment modalities (von Fraunhofer, 2013).

The use of immersion cleansers may present some associated risks of damage to chairside-applied soft liners for dentures; these problems arise from the chemical action of immersion cleansers and the nature of the liner materials (Mahboub et al., 2017). It has been suggested that oxygenation in strong alkaline solution can decrease the tensile strength and increase the hardness of the soft reline material (Mahboub, et al., 2017; Baygar, et al., 2017); while researchers have this immersion technique does not.

It is important that patients using effervescent immersion cleansers understand how to properly use the tablets specifically that these cleansers are not intended for internal use. Older patients, in particular, may have difficulty reading the instructions and warnings on the cleansers.

Conclusion

Proper denture cleansing is imperative to maintaining oral health and preventing systemic disease, and it is important that dental health professionals carefully review denture care and best practices with their patients. The literature indicates that effervescent cleansers are an effective and convenient means of cleaning dentures, posing minimal risk of damage to acrylic denture bases. They present a markedly lower risk of causing damage to resilient liners and tissue conditioners than other cleaning methods, such as brushing with denture pastes or dentifrices. However, some studies do report color changes associated with the routine use of denture cleansers.

In addition, although the efficacy of effervescent cleansers toward microorganisms has been confirmed by numerous studies, the unassisted action of the cleansers may be insufficient for heavy plaque deposits. In such cases, brushing of the denture after use of a cleanser might be useful. There are also suggestions in the literature that the resistance of denture plaque to the action of effervescent cleansers may result from the presence of *C. albicans* within the deposits. Effective removal of *C. albicans* and other fungal deposits from dentures presents a challenge to effervescent cleansers over short immersion times. The literature, however, does indicate that the incorporation of enzymes in the cleanser formulation facilitates their action against yeast deposits.

By following these guidelines, significant disinfection benefit can be achieved, with negligible potential for adverse effects either for patients or for their dental appliances.

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DENTURE CLEANSING: AN ESSENTIAL PART OF PATIENT CARE, 4TH EDITION

Final Examination Questions

Select the best answer for each question and mark your answers on the Final Examination Answer Sheet found on pages 60, or complete your test online at **EliteLearning.com/Book**

41. Substantial contamination of dentures by microorganisms occurs within how many hours of intraoral exposure?
    a. 12.
    b. 24.
    c. 48.
    d. 72.

42. Which bacterial species has been associated with the production of volatile sulfur compounds?
    a. Staphylococcus aureus.
    b. Klebsiella.
    c. Streptococcus oralis.
    d. Streptococcus sanguinis.

43. The presence of bacterial species in denture plaque can have important health consequences, including risk for:
    a. Meningitis.
    b. Tuberculosis.
    c. Rheumatic fever.
    d. Aspiration pneumonia.

44. In addition to age, the method of denture cleaning, the level of denture hygiene, and smoking are all factors that can favor yeast infestation of complete and partial dentures, the primary yeast being:
    a. Candida albicans.
    b. Candida gattii.
    c. Candida rugosa.
    d. Candida neoformans.

45. Glazing of the denture fitting surface or surface sealing of resilient liners has been shown to:
    a. Improve patient comfort.
    b. Eliminate the need for daily cleansing.
    c. Reduce both bacterial and yeast colonization.
    d. Prevent bleaching effects caused by effervescent cleansers.

46. The factor that is the least contributory to the development of denture-induced stomatitis is:
    a. Continuous use of the denture(s).
    b. Regular cleaning of the denture(s).
    c. Ill-fitting denture(s).
    d. Microbial infection.

47. The probable major etiological factor involved in denture-induced stomatitis is:
    a. Patient age.
    b. Denture plaque.
    c. Prior oral surgery.
    d. History of diabetes.

48. Research suggests that plaque formation is a multistep process that involves the initial adherence of:
    a. Gram-positive rods and cocci.
    b. Gram-negative rods and cocci.
    c. Candida albicans.
    d. Streptococcus mutans.

49. The prevalence of denture-induced stomatitis in patients with removable dentures is estimated to be as high as:
    a. 10%.
    b. 30%.
    c. 50%.
    d. 70%.

50. Denture-induced stomatitis is more prevalent in:
    a. Women and the elderly.
    b. Patients with chronic respiratory disease.
    c. Men and those who consume a vegan diet.
    d. Those who have worn dentures for less than 2 years.

51. A microbicidal effect on oral strains of Candida has been reported with the use of denture adhesive that contains:
    a. Broad-spectrum antibiotics.
    b. Hexachlorophene.
    c. Magnesium.
    d. Valcyclovir.

52. The most popular method of denture cleansing is:
    a. Soaking in water.
    b. Use of effervescent cleansers.
    c. Brushing with a dentifrice.
    d. Microwave irradiation.

53. In the long term, cleaning of dentures by brushing with a dentifrice to remove microorganisms is:
    a. The recommended method.
    b. Not particularly effective.
    c. As effective as soaking.
    d. Recommended only for older adults.

54. Although it has been suggested that household cleaning powders and cleansers containing hypochlorites are effective stain removers, hypochlorites are known to:
    a. Be damaging to acrylic resins.
    b. Result in smoothening of the denture surface.
    c. Be ineffective against gram-negative bacteria.
    d. Cause allergic reactions in a high percentage of the population.

55. Ultrasonic agitation as a method of cleansing dentures is currently not recommended for routine use because:
    a. It does not remove dead microorganisms.
    b. It requires expensive equipment that most older adults cannot afford.
    c. Little is known of the effects of ultrasonic agitation on denture base materials.
    d. Studies have shown that it is an ineffective means of removing microorganisms.

56. A concern regarding microwave-assisted denture cleansing is that:
    a. It requires a long processing time.
    b. It is incompatible with immersion cleansing.
    c. Residual heat can cause injury to the oral mucosa.
    d. The power and cleanliness of microwave ovens can vary.

57. The presence of streptococci in the superficial layer of the oral biofilm make yeasts such as Candida albicans:
    a. Greater resistance to chemical agents.
    b. Equal resistance to chemical agents.
    c. Slightly reduced resistance to chemical agents.
    d. Significantly reduced resistance to chemical agents

58. The effectiveness of enzyme-containing cleansers may result from their ability to destroy intercellular adhesion resulting in:
    a. Sterilization.
    b. Fungicidal activity.
    c. Spore formation.
    d. Virucidal activity.

59. It has been suggested that the denture base material of choice for patients prone to denture stomatitis is:
    a. Light-activated resins.
    b. Autopolymerizing resins.
    c. Unpolymerized resins.
    d. Soft lining material.

60. It has been suggested that strong alkaline solution is primarily damaging to soft liners as a result of:
    a. Low pH.
    b. Combustion.
    c. Oxygenation.
    d. Decomposition.

Course Code: DNJ01DC

Chapter 4: Three Drug Classes: Antibiotics, Analgesics, and Local Anesthetics Mod III: Anesthetics, 3rd Edition

2 CE Hours

Release Date: May 9, 2022 **Expiration Date**: April 12, 2025

Faculty

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Mark Donaldson has disclosed that she has no significant financial or other conflicts of interest pertaining to this course.

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AGD Subject Code - 134

How to receive credit

- Read the entire course online or in print.
- Depending on your state requirements you will be asked to complete:
  - A mandatory test (a passing score of 75 percent is required). Test questions link content to learning objectives as a method to enhance individualized learning and material retention.
- Provide required personal information and payment information.
- Complete the mandatory Course Evaluation.
- Print your Certificate of Completion.

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Learning objectives

After completing this course, the learner will be able to:

- Describe the evolution and pharmacology of local anesthetics.
- Explain the types of local anesthetics used in dentistry.
- Explain the vasoconstrictors present in local anesthetics.
- Identify the signs and symptoms of local anesthetic toxicity and the maximum recommended doses.
- Identify the appropriate local anesthetics for special populations.

Course overview

Upon completing this intermediate-level course, the learner will be able to discuss the differences among local anesthetics typically administered by oral healthcare professionals. The course will also fill gaps in knowledge concerning the selection, timing, and dosage of appropriate anesthetics for certain special populations requiring advanced consideration. The principles

learned will be directly applicable to the appropriate selection of local anesthetics for the cardiac, pregnant, and breast-feeding patient, as well as to the recognition and best and safest treatment of patients with a significant allergic history.

INTRODUCTION

According to the Index Medicus, since publishing the second edition of this module in 2018, there have been 764 publications on, "local anesthetic and dentistry," circulated in the peer-reviewed literature (https://www.ncbi.nlm.nih.gov/pubmed). This updated 2021 edition incorporates the findings of these latest research papers as well as current guidelines from regulatory and professional authorities, while continuing to emphasize the founding principles of appropriate local anesthetic selection and administration.

Oral healthcare professionals (OHCPs) are routinely involved with the selection and administration of local anesthetics to address patient comfort during dental procedures. Patient comfort as it relates to orofacial pain has both physiological and psychological components. Unfortunately, an experience of discomfort related to dentistry can lead patients to avoid or postpone treatment, making these patients more difficult to treat and less likely to comply with future appointments or oral healthcare treatment planning. Local anesthetics administered preoperatively help mitigate pain and improve patient comfort as well as clinical outcomes, making them an integral part of dental practice. The variety of local anesthetics available, whether combined with a vasoconstrictor or as a plain solution, offer unique pharmacological properties that allow the practitioner to tailor therapy to the individual and match the best drug to the specific patient and clinical situation.

Most dental pain or discomfort is acute in nature and typically accompanied by tissue injury or inflammation. Although this pain can resolve spontaneously once the underlying cause (e.g., inflamed pulp, carious lesion, or abscessed gingiva) is definitively treated, a pharmacological approach to pain management is considered the standard of care. Local anesthetics administered prior to a dental procedure help minimize pain and improve patient comfort to allow the procedure to go forward. Excellent intraoperative pain control with the appropriate selection and dose of local anesthesia will set both the OHCP and patient up for success, especially when combined with excellent postoperative analgesic medication selection.

Designed for dentists, dental hygienists, and dental assistants, this course will review the pharmacology of local anesthetic agents and update the participant on current guidelines and therapeutic choices in order to optimize prescribing practices. Since the goal of local anesthetic therapy is to ensure selection of the right drug at the right time and at the right dose, for the right patient and the right procedure, the information presented in this course should be considered essential knowledge for all OHCPs, both seasoned and newly credentialed.

Upon completing this intermediate-level course, the learner will be able to discuss the differences among local anesthetics typically administered by oral healthcare professionals. The course will also fill gaps in knowledge concerning the selection, timing, and dosage of appropriate anesthetics for certain special populations requiring advanced consideration. The principles learned will be directly applicable to the appropriate selection of local anesthetics for the cardiac, pregnant, and breast-feeding patient, as well as to the recognition and best and safest treatment of patients with a significant allergic history.

HISTORICAL PERSPECTIVE

Cocaine

The people of Peru have long depended on the leaves of the coca plant to relieve fatigue, hunger, and altitude sickness, as well as to lift the spirits, especially during long nights tending their flocks in the high mountains. Scientific interest in the psychotropic properties of this naturally occurring herbal medication led the German chemist Albert Friedrich Emil Niemann to isolate the active ingredient, cocaine (its nomenclature being derived from *coca* and the alkaloid suffix *-ine*) and publish his findings in 1860. It would be another 20 years before Basil von Anrep would publish the results of his studies investigating the clinical application of cocaine in humans. He recommended cocaine as a surgical anesthetic, although it is the ophthalmologist Carl Koller who is usually credited with empirically demonstrating, in 1884, the benefits of cocaine use in medicine as a topical adjunct in ocular surgery (Grzybowski, 2008). This usage continues today, usually as a 4% topical solution for both ocular and nasal surgeries (Saif, Farboud, Delfosse, Pope, & Adke, 2016; MacNeil et al., 2020).

During the 1880s, the famous surgeon William Halsted was among those who demonstrated the local anesthetic potential of cocaine in nerve block anesthesia (Lathan, 2010), at around the same time that James Leonard Corning discovered the drug's usefulness in peridural anesthesia (Loosely, 2009). Augustus Karl Gustav Bier used cocaine for spinal anesthesia in 1898 (Calthorpe, 2008). While the general acceptance of cocaine to support medical and dental procedures was widely appreciated at the turn of the century, cocaine's potential for adverse reactions and abuse led to the investigation and discovery of much safer and non-addicting local anesthetics.

Procaine

The German chemist Alfred Einhorn is credited with first synthesizing procaine in 1905 (Sneader, 2005). He patented the drug under the name Novocain (from the Latin *novo-* [meaning new] and *-caine*, the common suffix for alkaloid anesthetics). Novocain was found to be safe and effective when compared to cocaine, although its anesthetic effects were weaker and some patients demonstrated a strong allergic reaction, most likely due to procaine's amino ester group (Tetzlaff, n.d.). Regardless, Novocain quickly became the standard local anesthesia, and even today, many patients refer to local anesthesia generically as "novocaine," even though procaine is no longer used.

PHARMACOLOGY OF LOCAL ANESTHETICS

Mechanism of action

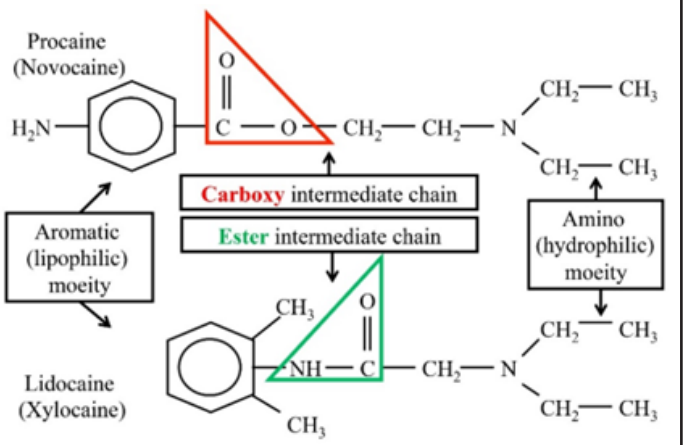
All local anesthetics block the sensation of pain by interfering with the propagation of peripheral nerve impulses. They do not significantly alter the resting membrane potential of the nerve, but they do impair dynamic responses to nerve stimulation, thereby inhibiting both the generation and conduction of action potentials.

Although an inactive nerve membrane is relatively impermeable to sodium ions, when the nerve is stimulated, sodium conductance increases, causing the nerve to become less electronegative compared to the outside environment. Sufficient neuronal stimulation pushes depolarization over a threshold that leads to a nerve impulse being propagated down the nerve and on to the next. The action potential is very transient, and the sodium ion channels close rapidly in response to an outward flow of potassium ions. Local anesthetics interact directly with neuronal sodium channels, preventing the gating mechanism that underlies the opening of sodium channels, and thereby inhibiting nerve conduction.

Pharmacodynamics

Pharmacodynamics focuses specifically on the relationship between drug concentration at the site of action and the resulting effect; it further includes the time course and intensity of therapeutic and adverse effects. The typical local anesthetic molecular structure can be divided into three parts: an aromatic group, an intermediate chain, and a secondary or tertiary amino terminus. The overall pharmacodynamic activity of the local anesthetic is determined by the combination of these three components. The aromatic portion of the molecule confers lipophilic properties, while the amino group determines the water solubility. The intermediate chain provides for the appropriate spatial separation between the lipophilic and hydrophilic ends and typically contains either an ester or amide moiety that helps to catalogue the local anesthetic's class. Figure 1 presents the structure of procaine (Novocain) in the ester class and lidocaine (Xylocaine) in the amide class.

Figure 1: Local Anesthetic Structure and Classes



This classification is important because there are significant differences in metabolism and allergenicity between these two classes of local anesthetics. The ester class of local anesthetics is metabolized in the blood and is used in dentistry solely for topical administration. The ester class includes:

- Benzocaine (Dermoplast, Orajel, Anbesol, Orabase).
- Cocaine.
- Dyclonine (Dyclone).
- Procaine (Novocain, Mericaine).
- Tetracaine (Pontocaine, Viractin, Dermocaine).

The amide class of local anesthetics is metabolized in the liver and includes:

- Articaine (Septocaine, Zorcaine).
- Bupivacaine (Marcaine).
- Etidocaine (Duranest).
- Lidocaine (Xylocaine).
- Mepivacaine (Carbocaine, Polocaine).
- Prilocaine (Citanest).

Pharmacologically, the local anesthetics can be further categorized as low potency agents with a short duration of action (procaine), local anesthetics of intermediate potency and duration of action (lidocaine, prilocaine and mepivacaine), and agents of high potency and long duration (tetracaine, etidocaine and bupivacaine). The blood levels of these agents are dependent on their rate of absorption, tissue redistribution, metabolism, and excretion (i.e., each drug's unique pharmacokinetic profile). It is their unique pharmacodynamic profile (i.e., lipid solubility, pKa, protein binding, and vasodilator activity) that determines each local anesthetic's potency and onset and duration of activity.

Lipid solubility

Lipid solubility significantly affects the activity of local anesthetics. Alterations of any portion of the local anesthetic molecule can significantly influence a drug's action. For example, the addition of a chlorine atom to the ortho position of the aromatic ring of procaine creates chloroprocaine, a more lipophilic local anesthetic with four times the potency but only half the toxicity of procaine. Agents with lower lipid solubility are generally marketed at higher concentrations (Table 1).

Table 1: Relationships Between Lipid Solubility and Clinically Effective Local Anesthetic Concentration

	Medication	Lipid Solubility
Articaine	40	4
Bupivacaine	560	0.5
Etidocaine	1,853	1.5
Lidocaine	110	2
Mepivacaine	42	2-3
Prilocaine	55	4
Procaine	80	2

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Phar Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Local Anesthetics: Pharmacology and Toxic 54(4), pp. 587-599; and "Legal Considerations," by D. J. Orr, II, 2021, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (7th ed.), Elsevier Mosby, p. 412.

pKa

At physiological pH of 7.4, all local anesthetic molecules exist in two states: a free base (uncharged) that readily penetrates tissues and lipid-rich membranes and a cation (positively charged species) that is unable to cross membranes. The pKa of a molecule is the pH at which the proportion of these two species is 50:50. Since all local anesthetics are weak bases, their pKa range is between 7.7 and 8.9. In other words, they prefer to be in balance at a more basic pH, above 7.4. Since physiological pH is less than the pKa of all local anesthetics (i.e., the physiological pH is more acidic), when introduced to the body, all local anesthetics exist primarily in the cationic, positively charged form and are unable to cross membranes. Differences in pKa among local anesthetics result in differences in their onset time (Table 2). As can be seen, the closer the pKa is to tissue pH (7.4), the faster the onset of the local anesthetic. This is particularly important when there is an infection present. When an infection is present, the pH of the tissue drops and it becomes more acidic. Therefore, choosing local anesthetics with the lowest pKa in these situations would be pharmacologically prudent.

Table 2: Relationships Among pKa, Ionization, and Local Anesthesia Onset at pH 7.4

Medication	pKa	% Cationic	% Free Base	Onset Time (min)
Articaine	7.8	71	29	2-4
Bupivacaine	8.1	83	17	5-8
Etidocaine	7.9	76	24	2-4
Lidocaine	7.8	71	29	2-4
Mepivacaine	7.7	67	33	2-4
Prilocaine	7.8	71	29	2-4
Procaine	8.9	90	10	5-8
Tetracaine	8.4	87	13	2-4

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Phar Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Local Anesthetics: Pharmacology and Toxic 54(4), pp. 587-599; and "Legal Considerations," by D. J. Orr, II, 2021, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (7th ed.), Elsevier Mosby, p. 412.

Protein binding

Increased protein binding allows local anesthetic molecules to be more firmly attached to proteins at receptor sites. The general rule is that increased protein binding leads to a longer duration of action (Table 3). Although this may be true in general, it is important to remember that duration of action of local anesthesia is dependent on other factors as well: affinity for the nerve membrane, type of injection, the presence or absence of a vasoconstrictor, and whether the goal is pulpal versus soft tissue anesthesia (Table 4).

Table 3: Relationships Between Protein Binding Characteristics and Local Anesthetic Duration of Action

	Approximate Protein Binding (%)	Duration of Action (minutes)
Articaine	95	60-220
Bupivacaine	95	40-440
Etidocaine	94	30-470
Lidocaine	65	60-190
Mepivacaine	75	25-165
Prilocaine	55	40-220
Procaine	6	14-45

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Phar Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Local Anesthetics: Pharmacology and Toxic 54(4), pp. 587-599; and "Legal Considerations," by D. J. Orr, II, 2021, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (7th ed.), Elsevier Mosby, p. 412.

Table 4: Average Duration of Local Anesthesia After Intraoral Injection (Minutes)

Medication	Maxillary Infiltration		Inferior Alveolar Block	
	Pulpal	Soft Tissue	Pulpal	Soft Tissue
4% Articaine with 1:100,000 or 1:200,000 epinephrine	60	170	90	220
0.5% Bupivacaine with 1:200,000 epinephrine	40	340	240	440
1.5% Etidocaine with 1:200,000 epinephrine	30	280	240	470
2% Lidocaine with 1:50,000 or 1:100,000 epinephrine	60	170	85	190
3% Mepivacaine	25	90	40	165
4% Prilocaine	20	105	55	190

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Phar Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Local Anesthetics: Pharmacology and Toxic 54(4), pp. 587-599; and "Legal Considerations," by D. J. Orr, II, 2021, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (7th ed.), Elsevier Mosby, p. 412.

Vasodilator activity

With the exception of cocaine, all local anesthetics are vasodilators. Vasodilation is the direct result of relaxation of peripheral arteriolar smooth muscle fibers. The greater the vasodilator activity of a local anesthetic, the faster the drug is absorbed and therefore the shorter the duration of action. A vasoconstrictor such as epinephrine or levonordefrin is often added to the local anesthetic solution to counteract this vasodilation, which in turn will increase the drug's duration of action.

To summarize the structure-activity relationship among local anesthetics:

- The **aromatic portion** is responsible for lipophilicity of the local anesthetic (i.e., the lipid/water distribution). Lipophilicity is the major determinant of potency for local anesthetics, and the general rule is that higher lipid solubility equates to higher potency. As a result, agents with lower lipid solubility are generally marketed at higher concentrations. The aromatic portion also determines the protein binding, or affinity of the molecule to bind to proteins. Increased protein binding allows anesthetic molecules to attach more firmly to proteins at receptor sites. The general rule is that increased protein binding equates to a longer duration of action.
- The **amine portion** is usually a secondary or tertiary amine and is associated with water solubility of the compounds, but is not necessary for local anesthetic activity. However, compounds lacking the amine portion are insoluble in water and useful only topically.
- The **intermediate chain** connects the aromatic and amine portions via an ester or amide linkage. The type of linkage is important in determining which class of local anesthetics the drug belongs to and therefore the route of metabolism and the allergic potential of the compounds.

Table 5 exhibits the general differences in pharmacodynamic properties among the "plain" local anesthetics (without vasoconstrictors).

Table 5: Pharmacodynamic Differences Among Commonly Used Local Anesthetics

Medication	Potency	Duration of Action	Onset of Action
Articaine	Moderate	Moderate	Fast
Bupivacaine	High	High	Moderate
Etidocaine	High	High	Fast
Lidocaine	Moderate	Moderate	Fast
Mepivacaine	Moderate	Moderate	Fast
Prilocaine	Moderate	Moderate	Fast
Procaine	Low	Short	Moderate
Tetracaine	High	High	Moderate

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Phar Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Local Anesthetics: Pharmacology and Toxic 54(4), pp. 587-599; and "Legal Considerations," by D. J. Orr, II, 2021, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (7th ed.), Elsevier Mosby, p. 412.

Pharmacokinetics

Pharmacokinetics focuses specifically on the absorption of drugs, the distribution to their site of action within the body, their metabolism, and finally their excretion. In the case of local anesthetics, absorption of the parenteral formulations – following routes of administration such as intravenous, intramuscular, and subcutaneous, in which absorption bypasses the gastrointestinal tract – represents few challenges because the medications are being injected directly into the target area. In contrast, when some local anesthetics are administered topically, their absorption depends on local characteristics such as mucosal keratinization, adipose, fascia, and layers of musculature, as well as blood flow to the area. Distribution also represents few challenges as the medication tends to be deposited directly at the targeted area whether injected or applied topically. Metabolism and excretion, however, depend much more on the drug's molecular structure as previously described, and these differences will be highlighted in the following subsections.

The half-life (t1/2) of the various local anesthetics ranges from 90 minutes for common agents such as lidocaine to nearly 300 minutes for bupivacaine. Half-life is the time it takes the body to eliminate half the amount of local anesthetic injected. An understanding of half-life is essential in helping practitioners avoid exceeding the maximum recommended limits of local anesthetic administration during lengthy procedures, since accumulation of these medicines beyond their maximum recommended limits is possible with medication readministration at a rate that may be faster than the drug's half-life.

TYPES OF LOCAL ANESTHETICS

Lidocaine

Lidocaine is often considered the prototype of the amide class of local anesthetics. It was first produced and marketed by the Swedish drug manufacturer Astra in 1948 (Gordh, Gordh, & Lindqvist, 2010; Singh, 2012), and it continues to be one of the most widely used and versatile local anesthetics (Goodchild & Donaldson, 2018b). It is several times more potent than procaine and has a faster onset of action, a longer duration of action, and a reduced allergenicity profile. Two-percent lidocaine hydrochloride combined with 1:100,000 epinephrine may be considered the gold standard for routine dental use, although it is also available as a plain solution or with the more concentrated 1:50,000 epinephrine for vasoconstriction. The drug has an elimination half-life of about 96 minutes.

Mepivacaine

Mepivacaine was originally introduced in 1957 (Singh, 2012) as an intermediate-duration amide local anesthetic. It has pharmacologic properties similar to lidocaine such as a rapid onset of action (usually within 2 to 4 minutes), although its duration of action may be slightly longer (1 to 2.5 hours in the mandible and 2.5 to 5.5 hours in the maxilla). Available preparations are either a 3% mepivacaine plain solution or a 2% mepivacaine solution in combination with 1:20,000 levonordefrin as the vasoconstrictor. The drug has an elimination half-life of about 114 minutes.

In dentistry, local anesthetic toxicity occurs more frequently in children and most often with the use of mepivacaine (Moore & Hersh, 2010; El- Boghdadly & Chin, 2016). Plain mepivacaine is often preferred in pediatric dentistry for its shorter duration of activity, but it can lead to higher systemic blood levels, which have a slow clearance rate. Even with the addition of the vasoconstrictor levonordefrin, blood levels are not reduced as they are with lidocaine with epinephrine, and mepivacaine (especially 3% mepivacaine without a vasoconstrictor) has been associated with the most reported fatalities due to excessive dosing (Hersh, Helpin, & Evans, 1991; Moore, 1992; El-Boghdadly & Chin, 2016). Regardless, given its low pKa, mepivacaine may have some distinct advantages over other local anesthetics when used for infiltration in infected and inflamed tissues.

Prilocaine

Prilocaine is also an intermediate-duration amide local anesthetic, with a pharmacologic profile similar to that of lidocaine. The primary differences between prilocaine and lidocaine are that prilocaine has an increased volume

of distribution and a lack of vasodilation, which reduces prilocaine's toxicity. However, it does have the propensity to cause methemoglobinemia, secondary to metabolism of the aromatic ring to O-toluidine. Methemoglobinemia is a condition in which excessive methemoglobin levels reduce the amount of hemoglobin available for oxygen transport to the tissue, resulting in reduced blood oxygenation. The clinical symptoms include dark blood and greyness or cyanosis of the lips, mucous membranes, and nail beds. The development of methemoglobinemia is usually seen only when exceeding the maximum recommended dose of prilocaine (8 mg/kg or more), and it does not typically cause significant sequelae in healthy patients. The IV administration of methylene blue (1 to 2 mg/kg) is the usual treatment. Prilocaine is available as a 4% plain solution or with 1:200,000 epinephrine for vasoconstriction. The drug has an elimination half-life of about 96 minutes.

Etidocaine

Etidocaine is a long-acting amide local anesthetic originally introduced in 1972 (Agasti, 2011) by Astra. Its pharmacokinetic properties are characterized by an onset of action similar to that of lidocaine (2 to 4 minutes) and a duration of action (up to 470 minutes) comparable to that of bupivacaine, which will be discussed in the next section. Etidocaine is more lipophilic than lidocaine, which contributes to its higher potency, rapid onset of action, and a prolonged duration of local anesthesia. Etidocaine is primarily used as a 1.5% solution with 1:200,000 epinephrine for vasoconstriction. Etidocaine products were removed from the United States market in 2001, not for reasons of safety or effectiveness (Kux, 2012), but because the small market share made the product unprofitable for the manufacturer.

Bupivacaine

Introduced in 1963 (Gadsden, n.d.), bupivacaine has been one of the most commonly used amide local anesthetics (Moore, Nahouraii, Zovko, & Wisniewski, 2006). Bupivacaine is a long-acting agent capable of producing sustained anesthesia and analgesia that can be prolonged even further by the addition of epinephrine. The molecular structure of bupivacaine is identical to mepivacaine except for a four-carbon substitution of the one carbon group at the amino moiety of the molecule. The addition of this butyl group to mepivacaine increases the lipophilic nature and protein binding properties of the drug, such that the effective concentration of bupivacaine for most dental procedures is just 0.5%. Although bupivacaine provides effective local anesthesia, its long duration of action makes it most useful for postoperative pain management. Clinical trials have shown that bupivacaine, having a high pKa of 8.1, and therefore a slightly longer onset time of 5 to 8 minutes, combined with a shorter intraoperative local anesthetic such as lidocaine, results in sustained local anesthesia in patients, when injected close to the end of the dental appointment. Onset time and local anesthetic profundity are additionally optimized when preparations of bupivacaine include epinephrine, such that the duration of action can last for up to 440 minutes, beyond the completion of the dental procedure (Laskin, Wallace, & DeLeo, 1977; Trieger & Gillen, 1979; Moore & Dunsky, 1983; Becker & Reed, 2012).

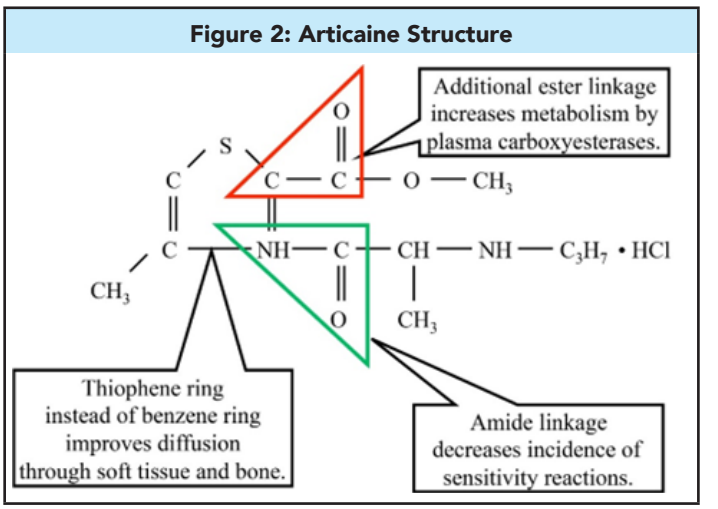
With its high lipid solubility, bupivacaine is substantially more cardiotoxic than lidocaine. The cardiotoxicity of bupivacaine is cumulative and considerably greater than would be expected from its local anesthetic potency alone. Part of the cardiotoxicity of bupivacaine can be mediated centrally, as studies have shown that direct injection of bupivacaine into the medulla produces malignant ventricular arrhythmias. Because of its toxicity profile, cumulative doses of bupivacaine beyond 90 mg should be avoided. Bupivacaine is employed most commonly as a 0.5% solution with 1:200,000 epinephrine for vasoconstriction. The drug has an elimination half-life of about 210 minutes.

Articaine

Articaine is the newest local anesthetic in North America, first introduced in Canada in 1982 but not in the United States until 2000. It has gained much of the market share in North America, while the use of other agents has remained fairly constant (Snoeck, 2012; Malamed, 2021). Articaine's popularity results in part from its ability to diffuse into bone better than other local anesthetics. This makes it an ideal agent for cases when there is difficulty achieving profound anesthesia with mandibular blocks. Articaine has an onset and duration of action similar to lidocaine but, given its unique chemical structure that includes carboxyl group ester linkage, articaine is metabolized very quickly (Figure 2).

Articaine is metabolized rapidly into articainic acid by plasma carboxylesterases with a plasma half-life of 20 minutes (Oertel, Rahn, & Kirch, 1997). Because less than 10% of articaine is metabolized by cytochrome P450 isoenzymes, it is relatively resistant to pharmacokinetic drug interactions (U.S. Food and Drug Administration, 1998). The drug is available as a 4% solution with either 1:100,000 or 1:200,000 epinephrine for vasoconstriction. It has been suggested that this higher drug concentration of articaine is responsible for an increased number of patients with prolonged paresthesias compared to other local anesthetics. However, scientifically sound research and data fail to support this claim (Toma et al., 2015; Hopman, Baart & Brand, 2017). Additionally, a clear causal relationship between anesthetic agent and neurological complications like paresthesia cannot be confirmed from the literature (Yapp, Hopcraft, & Parashos, 2011; Hopman, Baart & Brand, 2017). Based on the clinical research to date, procedural trauma appears to be a valid alternative explanation for these reported neurological complications. The act of administering local anesthetics via nerve blocks can cause damage to the nerves in the region, regardless of which solution is used.

Figure 2: Articaine Structure



Liposomal bupivacaine

More recently there has been an increased interest in a new product utilizing liposomal bupivacaine (Exparel®) as a possible therapy to offer very long-acting local anesthesia (up to 96 hours, while helping to reduce reliance on prescribing opioids for post-operative pain management (Lexicomp, 2021). Unfortunately, there are some significant patient safety issues associated with the liposomal formulation of bupivacaine beyond the exorbitant cost (over $200 per injection), compared to commercially

available bupivacaine in dental cartridges. The most recent published systematic review and meta-analysis on this subject concurs that, "The overall evidence level was low [for the safety of local liposomal bupivacaine infiltration], which means that further research is likely to significantly alter confidence levels in the effect, as well as potentially changing the estimated value" (Zhang, Yang, & Zhang, 2017). A Cochrane review published later that same year had very similar conclusions (Hamilton et al., 2017). The following year Goodchild and Donaldson answered the question, "Does liposomal bupivacaine fulfill an unmet need in dentistry?" with an emphatic "no" based on current evidence (Goodchild & Donaldson, 2018a).

VASOCONSTRICTORS

The addition of a vasoconstrictor to a local anesthetic delays the drug's vascular absorption and increases the duration of drug contact with nerve tissues. The overall effect is prolongation of the blockade by as much as 50% and a decrease in the systemic absorption of local anesthetic, which improves the overall safety. Dental treatment with insufficient vasoconstriction within the local anesthetic formulation can result in less than adequate pain control and increased levels of endogenous catecholamines, which can add to the patient's discomfort and anxiety. Ineffective pain control increases patient health outcomes risk because a rise in endogenous catecholamines increases blood pressure and can have other cardiotoxic effects. Vasoconstriction may be more important for infiltration injections in vascular sites compared to mandibular blocks, as the presence of a vasoconstrictor can also help to provide local hemostasis (decreased bleeding). For example, on a clinical note, if a patient presents with postoperative bleeding from an extraction site, administering local anesthetic with a vasoconstrictor often stops the bleeding without the need for any other intervention.

Epinephrine

Epinephrine is the most common vasoconstrictor and is combined with local anesthetics in formulations of 1:50,000, 1:100,000, and 1:200,000. Concentrations above 1:200,000 do not offer any additional advantage in prolonging the local anesthetic effect or in reducing blood concentrations of the local anesthetic. Higher concentrations also do not provide a faster onset or longer duration of action following inferior alveolar nerve block or in reducing blood concentrations of the local anesthetic (Dagher, Yared, & Machtou, 1997; Scott, Jebson, Braid, Ortengren, & Frisch, 1972; Tófoli, Ramacciato, de Oliveira, Volpato, & Ranali, 2003). However, greater concentrations (e.g., 1:100,000 and 1:50,000) may be used to provide better hemostasis at the surgical site, when this effect is desired. Epinephrine causes vasoconstriction by stimulating alpha-1 receptors in mucous membranes. It also stimulates beta-1 receptors in the heart (increasing heart rate, strength of contraction, and myocardial oxygen consumption) and the beta-2 receptors, resulting in vasodilation of blood vessels in the skeletal muscle. Drug interactions with epinephrine tend to be the result of use with drugs that affect these same receptors. These drugs include non-selective beta-blockers such as propranolol (Inderal) and metoprolol (Toprol), tricyclic antidepressants such as amitriptyline (Elavil) and desipramine (Norpramin), general anesthetics, and cocaine.

levonordefrin

Levonordefrin is the second most common vasoconstrictor used in dental cartridges. It is combined with local anesthetics as a 1:20,000 solution, which is equivalent to 1:100,000 epinephrine in terms of alpha receptor activity (vasoconstriction). It is the vasoconstrictor present in 2% mepivacaine. Following infiltration, levonordefrin and epinephrine have similar efficacy in constricting submucosal vessels, and their effects on local hemorrhage and anesthetic absorption are equivalent. Structurally, levonordefrin resembles norepinephrine and therefore lacks beta-2 receptor activity (resulting in less vasodilation of blood vessels in the skeletal muscle). Whereas epinephrine can increase heart rate and systolic pressure but lower diastolic pressure based on beta-2 stimulation, levonordefrin increases systolic, diastolic, and mean arterial pressures, which triggers a reflex slowing of heart rate (Westfall & Westfall, 2011). Because of this property, levonordefrin has been suggested as an alternative to epinephrine-containing local anesthetics when treating patients with cardiovascular heart disease. However, this drug does exert an undesirable influence on blood pressure.

The maximum recommended doses for vasoconstrictors are shown in Table 6.

Table 6: Maximum Recommended Dosages of Vasoconstrictors

	Concentration		Maximum Recommended Dosage		
	mg/mL	Parts per Thousand	mg	mL	Number of Carpules
Epinephrine	0.02	1:50,000*	0.2	10	5
	0.01	1:100,000	0.2	20	11
	0.005	1:200,000	0.2	40	11†
Levonordefrin	0.05	1:20,000	1.0	20	11

* 1:50,000 should be reserved for local hemostasis.
† Maximum number of carpules is limited by the local anesthetic.

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Pharmacological Considerations," by D. E. Becker and K. L. Reed, 2012, Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Preventing Local Anesthesia Toxicity," by P. A. Moore, 1992, Journal of the American Dental Association, 123(9), pp. 60-64; "Local Anesthetics: Pharmacology and Toxicity," by P. A. Moore and E. V. Hersh, 2010, Dental Clinics of North America, 54(4), pp. 587-599; "Legal Considerations," by D. J. Orr, II, 2013, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (6th ed.), Elsevier Mosby, p. 350; and "Adrenergic Agonists and Antagonists," by T. Westfall and D. P. Westfall, 2011, in L. L. Brunton, B. A. Chabner, & B. C. Knollmann (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics (12th ed.), McGraw-Hill, pp. 277-334.

STRATEGIES TO IMPROVE LOCAL ANESTHESIA

Warming or cooling

Some researchers recommend warming local anesthetic solutions to decrease injection pain, while others believe it offers no benefits (Davidson & Boom, 1992). Suggested mechanisms of action for this phenomenon include: increased solubility of the solution; nociceptor stimulation, based on the belief that cold is more painful than warm; and changes of the pKa to create a more basic form of the anesthetic to decrease latency (Finsen, 2017; Martin, Jones & Wynn, 1996).

Recently, Gumus and Aydinbelge conducted a double-blind, split-mouth clinical study comparing the pain perception of room temperature (21°C) versus warmed (37°C) articaine in children aged 5-8 years (Gumus & Aydinbelge, 2020). One hundred subjects received a maxillary buccal infiltration and the results showed a statistically significant reduction in pain perception and heart rate when the warmed local anesthetic was used. Practitioners can use low-tech methods for warming a dental local anesthetic cartridge before injection - placing in in a cup of warm water or holding it in the hand for a few minutes to warm it via body heat. Cartridge warming devices can also be used to achieve a recommended temperature of 37 to 43°C for the warmed cartridge contents (Aravena, Barrientos, Troncoso, Coronado, & Sotelo-Hitschfeld, 2018; Lundbom, et al., 2017).

Although research on cooling local anesthetics is scarce and less compelling, a study by Dabarakis et al examined the effect of temperature on the onset and duration of pulpal anesthesia using 3% mepivacaine (Dabarakis, Tsirlis, Parisis & Tsoukalas, 2006). Following injection of mepivacaine at room temperature (20°C) or cooled (4°C), there was no statical difference in the onset of anesthesia among the subjects but the cooled anesthetic showed a statistically significant increase in duration (29% increase). Measurement of injection pain was not an outcome of the study, however the authors stated, "the majority of our subjects mentioned experiencing more pain during the cold injection."

Vibration and distraction

Melzack and Wall described Gate Control Theory in 1965 as a pain-modulating system in which a neural "pain gate" present in the spinal cord can open and close, thereby modulating the perception of pain (Melzack & Wall, 1965). Some nerve fibers in the body transmit pain (e.g., Type A delta and Type C dorsal root fibers), while others can transmit touch or pressure (e.g., Type A beta fibers). In situations where both painful and pressure stimuli are felt, the dual transmissions of sensations race to the brain to be interpreted, each by different nerve tracks. According to the Gate Control Theory if a non-painful stimulus reaches the brain first, neural gates will close and the non-painful stimulus will override the painful stimulus thereby decreasing the perception of pain.

The smaller, unmyelinated Type A delta and Type C nerve fibers which transmit pain sensations are susceptible to nerve block via local anesthetics. Larger, myelinated Type A beta fibers transmit touch, temperature, and pressure sensations, and these impulses are transmitted faster than unmyelinated nerve fibers. Type A beta fibers can be stimulated by wiggling the patient's cheek during local anesthetic administration or when using a vibrating device. Literature on the use of vibrating devices to improve patient comfort during local anesthesia administration is generally positive but is equivocal (Nanitsos, Vartuli, Forte, Dennison & Peck, 2009; Nasehi, Bhardwaj, Kamath, Gadicheria & Pentapati, 2015; Shaefer, Lee & Anderson, 2017).

Three examples of vibrating devices are: a vibrating device that snaps on to the barrel of an existing metal syringe (VibraJect® Injection Comfort System, https://www.physicsforceps.com/vibraJect-comfort-solution); a cordless, and a rechargeable handheld wand featuring tips that vibrate (DentalVibe®. https://www.dentalvibe.com/); and transcutaneous electronic nerve stimulation (TENS) units which pass a high-frequency, low-voltage, electric current between two electrodes to activate the Type A beta fibers, sending signals to the brain that block or scramble normal pain signals.

A study by Ching et al, compared pain rating scale measurements in a split-mouth study in 36 adolescent patients aged 10 to 17 (Ching, Finkelman & Loo, 2014). Each patient received two infiltration injections, one of the injections involved the use of a vibrating device and immediately after the amount of discomfort was rated from 0 to 10 using the Wong-Baker FACES Pain Rating Scale. The median difference between pain felt by the two groups was two, with 17 of the patients reporting zero pain on injection, compared to only 3 by the control group. The authors concluded that most subjects (83%) reported significantly less pain than in the control group. This study supports the earlier work of Nanitsos where it was concluded that, "applied vibration decreases pain associated with a local anesthetic injection," however, in this study the vibration stimulus was applied extra orally by the patient during the time of the injection (Nanitsos, Vartuli, Forte, Dennison & Peck, 2009).

A study by Shaefer used the Symptom Severity Index (SSI) including a Visual Analog Scale (VAS) to not only evaluate pain, but to inquire about the experience of the injection with the practitioner using a vibrating device (Shaefer, Lee & Anderson, 2017). In 60 subjects receiving a IANB injection there was a significant difference in both SSI scores (intensity of discomfort, unpleasantness, and how easy it was to endure the injection) and VAS. The authors concluded the vibrating device, "reduced pain from dental anesthesia when used with injections that are routinely difficult for patients to tolerate," such as the inferior alveolar nerve block.

Buffering

Alkalinization of dental local anesthetics or buffering to raise the pH of these acidic solutions is a well-documented technique that results in clinical benefits such as decreased injection pain, reduced onset time, and the need for less overall volume of local anesthesia (Cepeda et al., 2015; Goodchild & Donaldson, 2016; Kattan, Lee, Hersh & Karabucak, 2019; Goodchild & Donaldson, 2019). The pH range of commercially available local anesthetic solutions containing a vasoconstrictor such as epinephrine is between 3 and 5, and this low pH may contribute to injection-site pain and slow onset (Whitcomb, Drum, Reader, Nusstein & Beck, 2010). To mitigate the adverse effects of these acidic local anesthetic solutions, the addition of 8.4% sodium bicarbonate to alkalinize or buffer these solutions closer to physiologic pH has been extensively studied in dentistry and medicine (McKay, Morris & Mushlin, 1987; Stewart, Chinn, Cole & Klein, 1990; Capogna, Celleno, Laudano & Giunta, 1995; Curatolo, et al. 1998; Cepeda et al., 2015; Kattan, Lee, Hersh & Karabucak, 2019).

Buffering or alkalinization of these solutions drives the stoichiometric relationship toward more uncharged local anesthetic molecules in situ. As these molecules are lipid soluble, they readily cross lipid membranes, resulting in faster, more profound, and more effective local anesthesia clinically. The results of a recent systematic analysis showed that buffered local anesthetics are more effective than nonbuffered local anesthetics when used for mandibular or maxillary anesthesia in pulpally involved teeth, and that buffered local anesthetics have 2.29 times greater likelihood of achieving successful anesthesia (Kattan, Lee, Hersh & Karabucak, 2019).

On the horizon, FDA approval is being sought for new buffered local anesthetics which promise to overcome the current barrier to adoption of buffered local anesthetics, which is admixture at

chairside. If these products are supplied in a standard 1.7 mL dental cartridges, and at a cost more comparable to current non-buffered drugs, they could represent the next generation and new standard for local anesthetics in dentistry. In addition, removal of sodium chloride from the formulation will significantly reduce the current hypertonicity of buffered mixtures (approximately 217 mOsm/L), which will further contribute to patient comfort. Perhaps most importantly, the possibility of local toxicity or sterility breaches due to current "chairside compounding" techniques will be completely eliminated. This is significant, as 8.4% sodium bicarbonate has an osmolality of 2,000 mOsm/L, and chairside compounding adds additional failure points in the sterility chain (Senewiratne, Woodall & Can, 2021).

LOCAL ANESTHETIC TOXICITY

Local anesthetics are relatively safe. However, repeated injections or even a single inadvertent intravascular injection can result in high systemic absorption, which could lead to toxicity. This is the primary reason that clinicians should aspirate prior to every injection. The signs and symptoms of local anesthetic toxicity are mainly neurologic in nature. Initially the patient may appear sedated or lightheaded, with slurred speech. These symptoms are very similar to the symptoms seen in the patient who develops hypoglycemia while in the dental chair, and this differential diagnosis must be immediately ruled out or treated based on the patient's medical history. Some patients can go on to develop diplopia (double vision), muscle twitching, or other sensory disturbances such as disorientation. At higher blood levels, local anesthetic toxicity can result in tremors, respiratory depression, and even tonic-clonic seizures. In severe cases, the local anesthetic overdose can result in respiratory or cardiovascular collapse or even coma. The maximum recommended doses for local anesthetics are shown in Table 7.

Table 7: Maximum Recommended Dosages for Local Anesthetics

Local Anesthetic	Maximum Dose	Number of Carpules: Adults	Number of Carpules: 50-lb Child
Lidocaine with 1:100,000 epinephrine (2%-36 mg)	3.3 mg/lb (500 mg)	13.8	4.6
Lidocaine with 1:50,000 epinephrine	3.3 mg/lb (500 mg)	5.5	NR*
Lidocaine without epinephrine	2.0 mg/lb (300 mg)	8.3	2.8
Mepivacaine (3% – 54 mg)	2.6 mg/lb (400 mg)	7.4	2.5
Mepivacaine (2% with 1:20,000 levonordefrin)	2.6 mg/lb (400 mg)	11.1	3.7
Prilocaine plain (4% – 72 mg)	4.0 mg/lb (600 mg)	8.3	2.8
Prilocaine with 1:200,000 epinephrine		8.3	2.8
Bupivacaine (0.5%)	0.6 mg/lb (90 mg)	10.0	NR
Articaine (4% – 72 mg)	3.3 mg/lb (500 mg)	6.9	2.3
Lidocaine with 1:100,000 epinephrine (2% – 36 mg)	3.3 mg/lb (500 mg)	13.8	4.6
Lidocaine with 1:50,000 epinephrine	3.3 mg/lb (500 mg)	5.5	NR
Lidocaine without epinephrine	2.0 mg/lb (300 mg)	8.3	2.8

*NR: Not recorded.

Note. Adapted from "The ADA/PDR Guide to Dental Therapeutics" (5th ed.), by the American Dental Association and the Physicians' Desk Reference, 2009, PDR Network, pp. 11-13; "Local Anesthetics: Review of Pharmacological Considerations," by D. E. Becker and K. L. Reed, 2012, Anesthesia Progress, 59(2), pp. 90-102; "An Update on Local Anesthetics in Dentistry," by D. A. Haas, 2002, Journal of the Canadian Dental Association, 68(9), pp. 546-551; "Management of Pregnant Patient in Dentistry," by S. Kurien, V. S. Kattimani, R. R. Sriram, S. K. Sriram, V. K. P. Rao, A. Bhupathi, … N. Patil, Journal of International Oral Health, 5(1), 88-97; "Preventing Local Anesthesia Toxicity," by P. A. Moore, (1992), Journal of the American Dental Association, 123(9), 60-64; "Local Anesthetics: Pharmacology and Toxicity," by P. A. Moore and E. V. Hersh, 2010, Dental Clinics of North America, 54(4), pp. 587-599; and "Legal Considerations," by D. J. Orr, II, 2013, in S. F. Malamed (Ed.), Handbook of Local Anesthesia (6th ed.), Elsevier Mosby, p. 350.

On May 23, 2018, the U.S. Food and Drug Administration issued a safety announcement warning consumers not to use teething products containing benzocaine in infants and children younger than 2 years (U.S. Food and Drug Administration, 2018). While this is a completely separate topic from the injectable local anesthetic formulations being discussed in this module, the importance of this warning bears mention. The announcement updates previous reports of benzocaine's association with methemoglobinemia, and warns that benzocaine-containing products should not be used to treat infants and children younger than 2 years because they carry serious risks and provide little to no benefit for treating sore gums in infants due to teething. There have been more than 400 cases of benzocaine-associated methemoglobinemia reported to FDA since 1971, with 119 cases being reported just in the last 10 years.

SPECIAL POPULATIONS

Cardiac patients

Although local anesthetics themselves are relatively safe, solutions containing a vasoconstrictor may be considered less safe in cardiac patients (Guimaraes, et al., 2021). The current recommendations in clinical practice when managing high risk patients with cardiovascular disease include aspiration prior to injection; appropriate monitoring; behavioral modification such as lowering and raising the dental chair more gradually; and appropriate prescribing for dental treatment, such as prophylactic and restorative approaches rather than surgical intervention, if possible (Becker & Reed, 2012). The use of reasonable amounts of local anesthetic with minimally effective concentrations of epinephrine (not levonordefrin) is also recommended, although the 1:50,000 concentration of epinephrine should typically be avoided and practitioners should

be aware of the maximum recommended doses of both the local anesthetic and vasoconstrictors shown in Tables 6 and 7. In most cases, limiting the total amount of epinephrine to 0.04 mg (the equivalent of two cartridges of 2% lidocaine with 1:100,000 epinephrine or 4 cartridges of 4% articaine with 1:200,000 epinephrine) may be considered best practice in this population (Santos-Paul, Neves, Neves, & Ramires, 2015; Guimaraes, et al., 2021).

The dental patient who is pregnant or breast-feeding

The pregnant dental patient presents two significant challenges to the dental professional. First, although most dental procedures are elective and can be postponed until after the pregnancy is over, dental treatment for a pregnant woman who has oral pain, advanced disease, or infection present should not be delayed. Second, not all women of childbearing age know that they may be pregnant, and when selecting, prescribing, or administering a medication for any woman of childbearing age, the clinician always should consider the possibility of the patient being pregnant or conceiving while she still is receiving the medication. The aim when administering medication to a pregnant patient is to balance the risks of the drug's potential adverse effects (usually on the fetus) with the benefit (usually to the mother) of treating the disease (Donaldson & Goodchild, 2012; U.S. Department of Health and Human Services [HHS], 2011).

To reflect the dangers associated with the use of drugs in pregnancy, the U.S. Food and Drug Administration (FDA) has traditionally classified drugs on the basis of the level of risk they pose to the fetus (Table 8; HHS, 2011). Accordingly, drugs in categories A and B are considered safe for use in pregnancy, whereas drugs in category C may be used only if the benefits outweigh the risks. Use of drugs in category D should be avoided except in certain exceptional circumstances, and use of category X drugs in pregnant women is strictly prohibited. Although the FDA is phasing out the lettered system, many drugs will continue to show the letters on their labels for the next few years (American Society of Health- System Pharmacists, 2015; FDA, 2014).

Table 8: U.S. Food and Drug Administration Pregnancy Risk Factor Definitions

Category	Definition
A	The results of controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either the results of animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women. OR the results of animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of risk in later trimesters.
C	Either the results of studies in animals have revealed adverse effects (teratogenic, embryocidal or other) on the fetus and there are no controlled studies in women. OR results of studies in women and animals are not available; drug should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits of use in pregnant women may be acceptable despite the risk (for example, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Results of studies in animals or humans have demonstrated fetal abnormalities or evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit; use of the drug is contraindicated in women who are or may become pregnant.

Note. Adapted from "Content and Format Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," by the U.S. Food and Drug Administration, 2014. Retrieve and-format-of-labeling-forhuman-prescription-drug-and-biological-products-requirements-for; "Drug Safety and Availability," by the U.S. Food and Drug Administration, 2015a. Retrieved from http://www.fda.gov/Drugs/Dr Requirements for Over-the-Counter Drugs," by the U.S. Food and Drug Administration, 2015b. Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.80; "Pregnancy, Lactation, Products-Content and Format Draft Guidance for Industry," by the U.S. Food and Drug Administration, 2020. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnancy-lactat

All local anesthetics can cross the placental barrier, primarily through passive diffusion. However, lidocaine with epinephrine and prilocaine may be considered the safest local anesthetics in this patient population because they are listed in the FDA's traditional letter classification as pregnancy category B; there are no contraindications to their careful use in pregnant patients. Even above the maximum recommended dose, neither lidocaine nor prilocaine has shown evidence of fetal harm (California Dental Association Foundation; American College of Obstetricians and Gynecologists, District IX, 2010; Cengiz, 2007; Donaldson & Goodchild, 2012; Hilgers, Douglass, & Mathieu, 2003). Both of these local anesthetics are also considered compatible with breast-feeding according to the American Academy of Pediatrics (2001).

Human case reports have shown fetal bradycardia to be a complication of administering bupivacaine and mepivacaine, while studies in rabbits have shown bupivacaine to be embryocidal at five times the maximum recommended daily dose. One study found decreased survival in newborn rats when administered bupivacaine at nine times the maximum recommended daily dose. It may be considered a best practice to avoid the use of long-acting local anesthetics in this special population, to minimize the risk of fetal exposure and toxicity given the risk of increased free drug concentrations in pregnant women (Donaldson & Goodchild, 2012; Hilgers, et al., 2003).

Articaine, bupivacaine, and mepivacaine may be considered less safe in pregnant patients compared to lidocaine and prilocaine, as they are all listed in the FDA's traditional classification system as pregnancy category C. Although this class of drugs is generally considered compatible with breast-feeding according to the American Academy of Pediatrics (AAP; 2001), articaine remains the one exception and should be avoided.

As mentioned previously, lidocaine with epinephrine is considered the safest local anesthetic in treating pregnant or breast-feeding patients (Cengiz, 2007; Donaldson & Goodchild, 2012; Fayans, Stuart, Carsten, Ly, & Kim, 2010). Vasoconstrictors are often combined with local anesthetics to impede systemic absorption, increase the efficacy, and prolong the duration of these agents. In pregnant mothers there may be a concern that the alpha-adrenergic effects of epinephrine may decrease uterine blood flow, while its beta-adrenergic activity may decrease uterine activity and prolong labor (Donaldson & Goodchild, 2012; Hood, Dewan, & James, 1986). However, concentrations of vasoconstrictors in local anesthetics are in very small amounts – 1:100,000 (0.01 mg/mL) or 1:200,000 (0.005 mg/mL) of epinephrine or 1:20,000 (0.05 mg/mL) of levonordefrin – and a cumulative dose of up to 0.1 mg can be administered safely to pregnant patients. This amount equates to 5 cartridges of a local anesthetic containing 1:100,000 epinephrine, or 10 cartridges containing 1:200,000 epinephrine. OHCPs are reminded that careful technique is paramount to avoid an accidental intravascular injection (Donaldson & Goodchild, 2012). In spite of the general lack of studies concerning the use of epinephrine during human lactation, the drug's short half-life means that it is not contraindicated for use during breast- feeding and it is unlikely that epinephrine distributes into breast milk (Donaldson & Goodchild, 2012; Gunatilake & Patil, n.d.; Hale, 2010).

The other vasoconstrictor in dental local anesthetic cartridges, levonordefrin, is supplied as a 1:20,000 concentration, which is equipotent to 1:100,000 epinephrine. (Epinephrine is five times as potent as levonordefrin; Robertson, Taylor, & Gage, 1984.) Unlike epinephrine, levonordefrin disproportionately affects the alpha-adrenergic system and retains less vasopressor activity (75% alpha-adrenergic versus 25% beta-adrenergic effects; Lawaty, Drum, Reader, & Nusstein, 2010). In medicine, this property has shown levonordefrin to incite less cardiac and central nervous system stimulation, although this has not been the same experience in dentistry given the much lower concentrations used (Guglielmo, Reader, Nist, Beck, & Weaver, 1999). The use of levonordefrin cannot be recommended because, as is the case with epinephrine, there is no FDA pregnancy risk classification for this drug. Even so, some scholars suggest that levonordefrin is safe for women during pregnancy and lactation (Donaldson & Goodchild 2012; Fayans et al., 2010; Hilgers et al., 2003).

Table 9 summarizes the recommendations for local anesthetic and vasoconstrictor use in dental patients who are either pregnant or lactating (Donaldson & Goodchild, 2012). In the case of combination products (such as lidocaine with epinephrine), the safety with respect to either pregnancy or breast-feeding is dependent on the highest risk moiety (AAP, 2001).

Table 9: Key Medication Considerations During Pregnancy and Breastfeeding

Medication	FDA Risk Category	Safe During Pregnancy?	Safe During Breastfeeding?
Articaine	C	Use with caution	Use with caution
Bupivacaine	C	Use with caution	Yes
Lidocaine Plain	B	Yes	Yes
Lidocaine (with epinephrine)	B	Yes	Yes
Mepivacaine Plain	C	Use with caution	Yes
Mepivacaine (with levonordefrin)	C	Use with caution	Yes
Prilocaine	B	Yes	Yes

Note. Adapted from "Pregnancy, Breast-Feeding and Drugs Used in Dentistry," by M. Donaldson and J. H. Goodchild, 2012, Journal of the American Dental Association, 143(8), pp. 858-871.

In 2015 the FDA replaced the former pregnancy risk letter categories on prescription and biological drug labeling with new information to make them more meaningful to both patients and healthcare providers (Brucker & King, 2017). The old five-letter system left patients and providers ill- informed and resulted in false assumptions about the actual meaning of the letters. The new labeling system allows better patient-specific counseling and informed decision making for pregnant women seeking medication therapies. While the new labeling improves the old format, it still does not provide a definitive "yes" or "no" answer in most cases. Also, the Pregnancy and Lactation Labeling Final Rule (PLLR) went into effect on June 30, 2015 yet the timelines for implementing this new information on drug labels (also known as the *package insert*) is still variable. Clinical interpretation is still required on a case-by-case basis, and for this reason most practitioners continue to rely on the traditional five-letter system.

The A, B, C, D and X risk categories, in use since 1979, are now replaced with narrative sections and subsections as shown in Table 10 (U.S. Food and Drug Administration, 2016).

Allergy status

Although adverse reactions to local anesthetics are relatively common, most such events are not true allergic reactions. The two distinct types of allergic reactions to local anesthetics are allergic contact dermatitis with delayed swelling at the site of administration and urticaria (hives) with anaphylaxis. The former type of reaction is well established, while the latter is rare, with the data limited to case reports. However uncommon – their estimated prevalence is much less than 1% in the general population – allergic reactions to local anesthetics can occur (Batinac, Sotošek Tokmadžić, Peharda, & Brajac, 2013; Volcheck & Mertes, 2014; Chan, 2016; Bina, Hersh, Hilario, Alvarez, & McLaughlin, 2018). In general, the ester class of local anesthetics (mainly used as topicals in dentistry) pose a greater potential for true allergic reactions than the amide class (used in solutions).

Although nonallergic reactions to local anesthetics are more common than true allergic reactions, these "pseudoallergic reactions" can mimic true allergic reactions and include vasovagal syncope, sympathetic stimulation, psychomotor or anxiety-related reactions, and systemic toxic effects related to the pharmacologic properties of these agents. Clinical manifestations of nonallergic reactions can resemble aspects of allergic reactions and include palpitations, dyspnea, hypotension, lightheadedness, and syncope – signs and symptoms that can be seen in both allergic and nonallergic reactions. However, development in a patient of wheezing, pruritus, urticaria, or angioedema strongly suggests a true allergy.

Table 10: U.S. Food and Drug Administration Information That is in the Pregnancy and Lactation Labeling Rule (PLLR) Section			
General Information	**Risks**	**Clinical Considerations**	**Background Data**
Pregnancy			
Inclusion of statement on background risk. Contact information about scientifically acceptable pregnancy registries.	• Fetal Risk Summary: Information from all relevant sources. • Risk conclusion regarding developmental abnormalities in humans and other relevant risks: whether likely drug increases risk or not. • If increased risk identified by human data, a narrative will be included. • If data demonstrate drug is not systemically absorbed, a statement is included that maternal use is not expected to result in fetal exposure. • When drug is systematically absorbed, statements of risk are divided based on type of data, human or animal, with findings from human studies presented first.	• Statement on inadvertent exposure in early pregnancy or notation no data is available. • Description of any known risk to woman or fetus from the untreated disease. • Dosing adjustments during pregnancy. • Maternal adverse effects of drug unique or increased during pregnancy. • Effects of dose, timing, and duration of treatment with drug during pregnancy. • Potential neonatal complications and interventions needed. • If drug potentially used during intrapartum, even if not an FDA-approved indication, information will be included about effects on woman, fetus, or newborn; duration of labor and birth; risk of complications including need for interventions and long-term potential effects on the child.	• Include study type, dose, duration, timing, and results including fetal abnormalities or other adverse effects. • Human data is presented first, including positive and negative effects, number of subjects, and study duration. • Animal study includes species involved and recalculation of doses into human dose equivalents.
Lactation			
General information is not mandated in rule.	• Risk Summary: Information from all relevant sources is included and identified. • Statement that drug is compatible with breastfeeding if no effect on quality of milk, quantity of milk; if nondetectable in milk; or no adverse effects found with child. • As applicable, a summary of the drug and effect on milk production, presence in milk, and effects on child will be included.	• Label will provide the following information, when available: ○ Strategies to minimize exposure to the child, including topical drugs to nipple; information about potential drug effects that could be useful to caregivers, such as monitoring for adverse effects, how to respond when they occur; and information about adjustments of maternal doses.	• Overview of the data that are the basis of Risk Summary and Clinical Considerations. • Human data to be presented first.
Females and Males of Reproductive Potential			
	• Risks are not specially noted as part of Females and Males of Reproductive Potential, but the following address when it must be included and imply risks: ○ When pregnancy testing and/or contraception are required or recommended before, during, or after drug therapy and/or ○ When there are human and/or animal data that suggest drug-associated fertility effects.	• Clinical considerations are not specifically noted as part of Females and Males of Reproductive. • Potential, but the following list content of potential clinical importance must be included, in order: ○ Pregnancy testing. ○ Contraception. ○ Infertility.	

Note. U.S. Food and Drug Administration (2016). Pregnancy and lactation labeling final rule [online]. Retrieved from: https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol4/xml/CFR-2016-title21-vol4-sec201-57.xml.

Typically, a clinical history consistent with a delayed cutaneous reaction to a local anesthetic, combined with a positive patch test result, is sufficient to diagnose a local anesthetic allergy. Patch testing is a means of diagnosing hypersensitivity reactions by controlled exposure of a small area of skin to the suspected allergen (Fonacier, 2015). The patient should not have applied topical glucocorticoids to the tested skin for at least one week, and should not have taken systemic glucocorticoids for at least one to two weeks prior to testing. Some local anesthetics may contain sulfites (bisulfite or metabisulfite) as stabilizers or preservatives when a vasoconstrictor is added. A few case reports have described local reactions attributed to sulfite sensitivity in patients (Dooms-Goossens, de Alam, Degreef, & Kochuyt, 1989; Henderson, 2011; Schwartz & Sher, 1985). One case described a woman who developed severe edema of the face and neck after receiving a local anesthetic for dentistry, with a positive patch test to both metabisulfite and the local anesthetic (Dooms-Goossens et al., 1989).

Patients with suspected allergic reactions to local anesthetics should be evaluated because most patients can tolerate other local anesthetic agents (Grzanka, Wasilewska, Śliwczyńska, & Misiołek, 2016). Case reports show evidence of cross-reactivity among the group of amide-type local anesthetics – bupivacaine, lidocaine, and mepivacaine – and a lack of cross-reactivity between the ester-type and amide-type groups of local anesthetics (Calderon et al., 2013; Cuesta-Herranz et al., 1997; Warrington & McPhillips, 1997; Bina, Hersh, Hilario, Alvarez, & McLaughlin, 2018). This evidence should be considered when choosing other local anesthetics to test as possible treatment alternatives. It is often recommended that the clinician choose one or more alternatives from the other local anesthetic group as an alternative agent for patch testing.

Skin testing and challenge is typically reserved for patients with a history of symptoms that could have been either nonallergic (such as syncope or hypotension) or a true IgE-mediated allergic reaction (Table 11). Skin testing and challenge are performed to determine what alternative local anesthetics the patient may tolerate.

If the local anesthetic associated with the reaction is known to be an ester, a potential alternative local anesthetic from the amide group is tested or, if the culprit drug is an amide, an alternative amide-type local anesthetic should be tested (Schatz, 1992). If the local anesthetic associated with the reaction is unknown, lidocaine should be chosen, since it is commonly available and since there are cases of tolerance of lidocaine even in patients who reported previous reactions to lidocaine (Barer & McAllen, 1982). Local anesthetics without vasoconstrictors should be used for skin testing because the vasoconstrictor may mask a positive test (Ravindranathan, 1975). Finally, for patients with a documented amide local anesthesia allergy in whom ester local anesthesia is also contraindicated, diphenhydramine with epinephrine may be a safe and somewhat effective alternative. Limiting injection volumes to less than 5 mL of 1% diphenhydramine with 1:100,000 epinephrine may limit facial swelling and drowsiness (Bina, Hersh, Hilario, Alvarez, & McLaughlin, 2018).

Table 11: Skin Testing Protocol for Patients with a Possible Local Anesthetic Allergy

Step	Route	Volume (mL)	Dilution*
1	Puncture	--	Undiluted
2	Intradermal	0.02 cc	1:100

Patch (epicutaneous) testing is performed initially, with appropriate positive (histamine) and negative (diluent) controls. Results are assessed at 20 minutes. A positive result consists of a wheal 3 mm greater than the ne injecting 0.02 mL of a 1:100 dilution of the local anesthetic in question.

* The concentration of the local anesthetic (usually 1 to 2 percent) to be used for the procedure.

Note. Adapted from "Local and General Anesthetics Immediate Hypersensitivity Reactions," by G. W. Volcheck and G. W. Mertes, 2014, Allergy Clinics of North America, 34(3), pp. 525-546.

Conclusion

The development of local anesthetics has been of great importance in the history of dental practice. These agents have improved overall patient satisfaction with oral health care by reducing intraoperative pain, postoperative pain, and anxiety, and by improving the overall comfort of the oral healthcare team as well.

The slightly varying clinical characteristics of these highly effective agents, which are based on their structures, lead to different pharmacokinetic and pharmacodynamic profiles. Dentists should avoid relying on a single local anesthetic for all of their patients. They should try all of the commercially available local anesthetics and carefully consider the pharmacologic properties of each and learn how to take advantage of those properties in various clinical situations. For example, in the presence of an infection, it may be best to consider using mepivacaine because of its low pKa value. Another clinical example involves using articaine, with its ability to diffuse into bone, in cases of difficulty in achieving profound anesthesia with mandibular blocks. Matching the right drug at the right dose for the right patient and the right procedure is more of the art than the science of dentistry. However, when employed properly, even in some of the highest risk patient populations (e.g., cardiac, pregnant, or breast-feeding patients), these agents are not only inherently safe, but provide for overall safer dentistry.

Resources

Helpful websites and literature to enhance further learning:

- **http://www.globalrph.com/local-anesthetics.htm**
  This website covers the general pharmacology of individual local anesthetics, and includes calculators for dosing and drug interaction information.
- **http://www.colgate.com/en/us/oc/oral-health/procedures/**anesthesia/article/local-anesthesia
  There are a number of modules available in this vendor-sponsored website to include both patient and practitioner resources as they relate to local anesthesia.
- **http://multimedia.3m.com/mws/media/597398O/loc-compendium-brochure-ebu.pdf?fn=LOC_Comp_Brochure_EBU.pdf**
  This compendium provides a scientific overview of both material handling and technologies for the interested reader. Aspects such as neuronal structures, chemistry, and pharmacology of local anesthetics and of vasoconstrictors are highlighted, along with dental anesthetic techniques and clinical aspects such as posology/dosage, adverse effects, and precautions concerning use.
- **www.SafeFetus.com**
  SafeFetus.com is a website set up for pregnant mothers and their physicians and pharmacists in order to protect the baby, whether during pregnancy or during lactation, from any harmful effects of medication (whether prescribed or over-the-counter). The site also provides information on maternal exposures, whether to physical agents, infectious agents, or diseases, and ways they may affect the unborn child. The site is maintained by a fully qualified team of physicians and pharmacists who work continually to update the information, adding new drugs that are emerging in the markets, with the aim of producing a fully comprehensive worldwide database. All information is presented in an unbiased manner and is extracted from well-documented and respectable sources.

- **The University of Toronto Hospital for Sick Children: MotheRisk Program**
  The MotheRisk Program ("Treating the mother – Protecting the unborn") at the Hospital for Sick Children is affiliated with the University of Toronto and provides up-to-date information for mothers and professionals in regard to issues around medications, pregnancy, and lactation. MotheRisk counselors talk to hundreds of women and their healthcare providers each day, providing guidance, support, and peace of mind, as well as supporting research in this field.
  Website: http://www.motherisk.org

In addition to electronic resources, the reader is also directed to more traditional textbooks that focus specifically on orofacial pain, diagnosis, and treatment:

- G. Fischer, 2018, *Local Anesthesia in Dentistry, With Special Reference to the Mucous and Conductive Methods: A Concise Guide for Dentists, Surgeons and Students*. London, UK: Franklin Classics (ISBN: 978-0-342-02547-3).
- S. F. Malamed, 2019, *Handbook of Local Anesthesia*, 7th Edition. St. Louis, MO: Elsevier Mosby (ISBN: 978-0-323-58207-0).
- Johns Hopkins Hospital, K. Kleinman, l. McDaniel, & M. Molloy, 2021, *The Harriet Lane Handbook*, 22nd Edition, (ISBN: 978-0-323-67407-2)
- G. G. Briggs, C. V. Towers, & A. B. Forinash, 2021. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* (12th ed.). Philadelphia, PA: Lippincott Williams & Wilkins (ISBN: 978-1-975-16237-5).

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THREE DRUG CLASSES: ANTIBIOTICS, ANALGESICS, AND LOCAL ANESTHETICS MOD III: ANESTHETICS, 3RD EDITION

Final Examination Questions

Select the best answer for each question and mark your answers on the Final Examination Answer Sheet found on page 60, or complete your test online at **EliteLearning.com/Book**

61. What was the name of the first synthetic form of local anesthesia?
    a. Benzocaine.
    b. Procaine.
    c. Prilocaine.
    d. Articaine.

62. Which channels do local anesthetics block to inhibit nerve conduction?
    a. Sodium.
    b. Chloride.
    c. Magnesium.
    d. Potassium.

63. Which of the following local anesthetics used topically in dentistry is a member of the ester class?
    a. Benzocaine.
    b. Editocaine.
    c. Prilocaine.
    d. Articaine.

64. Which of the following is considered the prototype of the amide class of local anesthetics?
    a. Lidocaine.
    b. Mepivacaine.
    c. Bupivacaine.
    d. Prilocaine.

65. Which local anesthetic has a propensity to cause methemoglobinemia?
    a. Lidocaine.
    b. Mepivacaine.
    c. Bupivacaine.
    d. Prilocaine.

66. Although the use of most local anesthetics has remained fairly constant, one local anesthetic that was introduced in the United States in 2000 and that has since gained much of the market share is:
    a. Lidocaine.
    b. Mepivacaine.
    c. Bupivacaine.
    d. Articaine.

67. The vasoconstrictor epinephrine is available in local anesthetics in formulations of 1:50,000, 1:100,000 and:
    a. 1:150,000.
    b. 1:200,000.
    c. 1:250,000.
    d. 1:300,000.

68. Which of the following statements is true regarding the vasoconstrictor present in 2% mepivacaine?
    a. It contains 1:50,000 epinephrine.
    b. It contains 1:100,000 epinephrine.
    c. It contains 1:20,000 levonordefrin.
    d. It contains no vasoconstrictor.

69. An easy way for dental professionals to minimize local anesthetic toxicity is to:
    a. Perform injections via blocks rather than with infiltrations.
    b. Use local anesthesia only when absolutely necessary.
    c. Aspirate prior to every injection.
    d. Minimize the use of vasoconstrictors.

70. According to the U.S. Food and Drug Administration, which of the following local anesthetics is a category B drug and therefore safe to administer to patients who are pregnant or breast-feeding?
    a. Lidocaine.
    b. Mepivacaine.
    c. Bupivacaine.
    d. Articaine.

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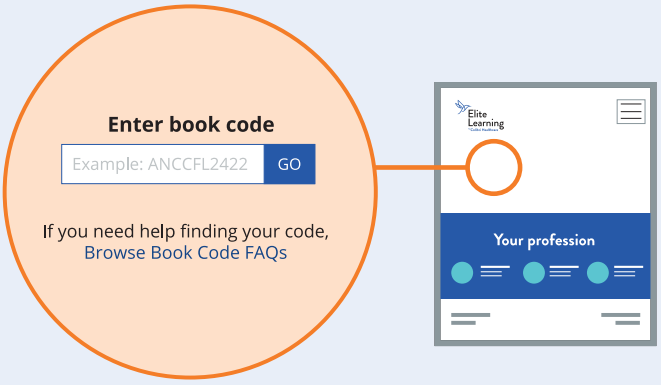

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1	○	○	○	○	16	○	○	○	○	31	○	○	○	○	46	○	○	○	○	61	○	○	○	○
2	○	○	○	○	17	○	○	○	○	32	○	○	○	○	47	○	○	○	○	62	○	○	○	○
3	○	○	○	○	18	○	○	○	○	33	○	○	○	○	48	○	○	○	○	63	○	○	○	○
4	○	○	○	○	19	○	○	○	○	34	○	○	○	○	49	○	○	○	○	64	○	○	○	○
5	○	○	○	○	20	○	○	○	○	35	○	○	○	○	50	○	○	○	○	65	○	○	○	○
6	○	○	○	○	21	○	○	○	○	36	○	○	○	○	51	○	○	○	○	66	○	○	○	○
7	○	○	○	○	22	○	○	○	○	37	○	○	○	○	52	○	○	○	○	67	○	○	○	○
8	○	○	○	○	23	○	○	○	○	38	○	○	○	○	53	○	○	○	○	68	○	○	○	○
9	○	○	○	○	24	○	○	○	○	39	○	○	○	○	54	○	○	○	○	69	○	○	○	○
10	○	○	○	○	25	○	○	○	○	40	○	○	○	○	55	○	○	○	○	70	○	○	○	○
11	○	○	○	○	26	○	○	○	○	41	○	○	○	○	56	○	○	○	○					
12	○	○	○	○	27	○	○	○	○	42	○	○	○	○	57	○	○	○	○					
13	○	○	○	○	28	○	○	○	○	43	○	○	○	○	58	○	○	○	○					
14	○	○	○	○	29	○	○	○	○	44	○	○	○	○	59	○	○	○	○					
15	○	○	○	○	30	○	○	○	○	45	○	○	○	○	60	○	○	○	○					

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