Contemporary Dental Pharmacology

Evidence-Based Considerations

Arthur H. Jeske
Editor

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Preface I

As in every aspect of healthcare, rapid access to important information from electronic databases is essential in the delivery of high-quality, evidence-based dental treatments. And in no discipline does information evolve more rapidly than in pharmacology. The premise that standard textbooks on pharmacology do not address the specific needs of the practicing dentist underlies the basis for the development of this concise array of chapters, developed by dental experts from around the country. Additionally, the dental practitioner must become familiar with evidence-based information about drugs prescribed for and administered to their patients, and the emphasis of this book on current, scientifically rigorous information is a step toward that essential goal in our profession.

Houston, TX, USA — Arthur H. Jeske

Preface II

Up-to-date clinical-scientific information is now an absolute requirement for the healthcare practitioner, and dental education is now undergoing a transformation that reflects this. In dental schools around the world, the profession is moving academically from a discipline based on tradition and experience to one that still requires the practitioner's psychomotor skills and judgment and the needs and preferences of the patient and which also must integrate new research findings and scientific validation of procedures, materials, and patient management.

And perhaps no other component of dental education requires more frequent scientific revision of information than pharmacology. The basic array of medications used in dentistry has changed little in the past 100 years—local anesthetics, analgesics, and antibiotics comprise the majority of drugs administered to and prescribed for dental patients. However, practitioners who graduated from dental school just 10 years ago must now revise their prescribing patterns to reflect an ever-growing list of new classes of medical drugs and new information on these drugs and the drugs they prescribe in order to be optimally effective.

There are four major objectives of this book:

1. Update the advanced dental practitioner on current, high-level scientific information regarding traditionally prescribed dental drugs.
2. Provide the advanced dental practitioner with important information on selected classes of medically prescribed drugs for cardiovascular disease (e.g., novel oral anticoagulants) and neurologic conditions, with special emphasis on incorporating this information into safe and effective patient management.
3. Identify the most important sources of information on the dental and medical drugs covered, in order to enable the advance dental practitioner to periodically assess new scientific information.
4. Summarize the state of current scientific evidence for the use of basic dental drugs, including the level(s) of evidence for their applications and the strength of recommendation taxonomies (SORT), when those are available.

This book focuses on the medications most frequently prescribed in dentistry, as well as important classes of agents which often dictate changes in both regular dental treatments and dental pharmacotherapy, such as antico-

agulant/antiplatelet agents and drugs for neurologic disorders. Rather than serve as a comprehensive pharmacology textbook, this treatise is designed to provide the practitioner with scientific evidence and assess the current evidence-based indications, contraindications, etc. for the drugs included. Finally, it is hoped that the reader will utilize the internet-based resources found in chapter "Internet Resources for Dental Pharmacology" to build upon the information presented in the book and continue to consult the scientific literature in the future management of patients.

Houston, TX, USA Arthur H. Jeske

Acknowledgment

We are indebted to Springer for undertaking this project, and the quality of the chapters reflects the expertise, clinical experience, and commitment to education of all of the contributors. My sincere thanks go to the contributors and the production personnel at Springer for making the book a reality. Finally, it is with deep affection for the dental profession that we dedicate this book to practicing dentists everywhere, who daily must work through complex treatments for their patients, and to dental educators who, through teaching evidence-based dentistry, are committed to improving overall health by improving oral health.

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About the Author

Arthur H. Jeske, D.M.D., Ph.D. is Professor, Department of General Practice and Dental Public Health and Associate Dean for Strategic Planning & Continuing Dental Education, University of Texas School of Dentistry at Houston. He earned his Ph.D. degree (pharmacology) and his D.M.D. degree at the Medical College of Georgia. Dr. Jeske is Editor-in-Chief, *Mosby's Dental Drug Reference* (8th through 12th editions) and Section Editor (Pharmacology) of the *Journal of Craniomandibular and Sleep Practice*. He has served on the American Dental Association's Council on Scientific Affairs and is a Fellow, International College of Dentists, American College of Dentists, Academy of Dentistry International, and the Pierre Fauchard Academy. Dr. Jeske holds memberships in the ADA, TDA, and GHDS, as well as Omicron Kappa Upsilon and Delta Sigma Delta, and he is recipient of the Distinguished Alumnus Award from the Medical College of Georgia School of Dentistry.

Introduction

Arthur H. Jeske

The US Food and Drug Administration Drug Approval Process

The dental profession is able to incorporate evidence-based information into the use of drugs owing to the considerable scientific data generated by the US government's Food and Drug Administration drug approval process (Watkins and Archambault 2016) as illustrated in Fig. 1.

Monographs produced as labeling information for drugs approved for the US pharmaceutical market contain detailed information about all FDA-approved agents, and .pdf versions of the entire document can be easily accessed using the following internet search term:

"fda prescribing information [drug name]"

These documents are organized in the following format:

Description. The official chemical name of the drug and its structural formula are found here, along with detailed descriptions of all of the ingredients found in all of the various dose forms of the drug. Additionally, the dose forms and their imprinted information are described. If the dose form requires additional preparation (e.g., reconstitution into a suspension), that information is also found in this section.

Clinical pharmacology. All of the pharmacokinetic information about the drug is found here (e.g., peak blood levels, maximum serum concentrations), as well as routes of metabolism and excretion. The specific actions of the drug are also found in this section (e.g., bacterial susceptibility data for antibiotics).

Indications and usage. This section lists the various conditions for which the drug has been approved for therapeutic use, including indications for its use in combination with other approved drugs. Uses not included in this list would be considered as "off label," meaning that the drug was not specifically approved by the FDA for such a use.

Contraindications. The conditions under which the drug should not be used are described in this section, such as allergy, and known diseases which may be worsened by administration of the drug.

Warnings. Serious outcomes (e.g., potentially fatal) which can occur as a result of administration of the drug are listed in this section, along with a description of the emergency measures which must be undertaken to manage the adverse outcome(s). Signs and symptoms of the development of these serious outcomes may also be included in this section.

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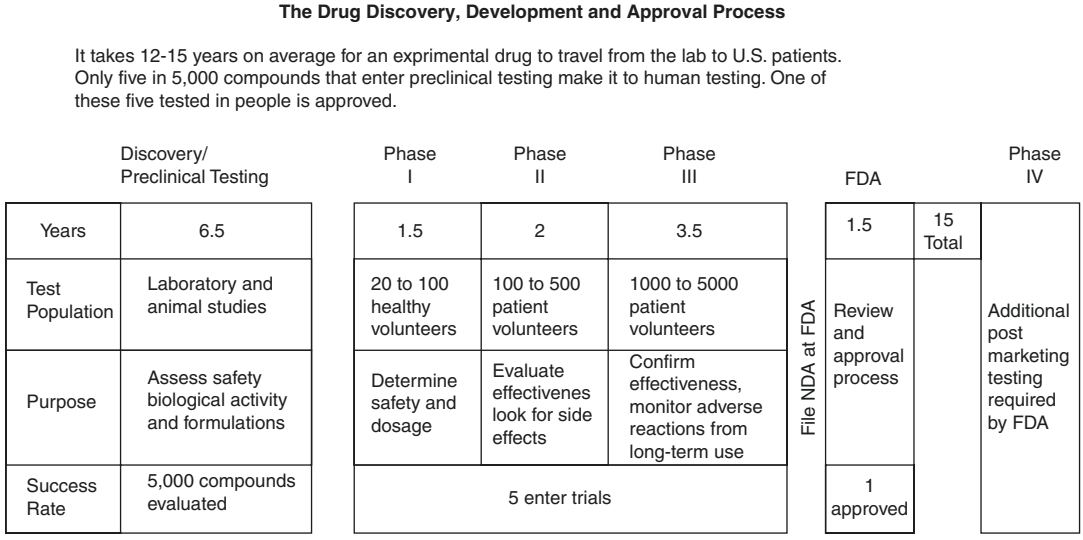

Fig. 1 Populations, purposes and success rates for compounds in the U.S. F.D.A. Drug Discovery, Development and Approval Process, with approximate times (in years) required for each phase. Reproduced with permission, Pharmaceutical Research and Manufacturers of America (PhRMA). The Complex Biopharmaceutical R&D Process. July 2018. http://phrma-docs.phrma.org/industryprofile/2018/pdfs/2018_IndustryProfile_DynamicResearchandDevEcosystem.pdf

Precautions. This section is comprised of a detailed list of preexisting conditions which may limit or preclude the use of the drug, recommendations for laboratory tests which may be indicated to monitor the development of adverse outcomes, drug interactions, drug-laboratory test interactions, possible carcinogenic and mutagenic effects of the drug, and effects of the drug on fertility. This is also where the "pregnancy category" of the drug is found. Possible adverse outcome results from the use of drug during labor and delivery and nursing are also described here, and precautions required for special populations (pediatric, geriatric) are described. Finally, "information for patients" is provided here, including dose intervals, duration of therapy, and the need for compliance with dosing instructions.

Adverse reactions. All of the possible untoward reactions to the drug are listed here, along with their incidence derived from clinical trials. These adverse reactions are organized by organ system, and special notes about adverse reactions observed when the drug is used in combination with other agents are included.

Overdosage. Instructions for managing overdose are generally provided in the first part of this section; specific outcomes from various levels of intoxication are described. Also included is information on the ability of the drug to be removed by appropriate measures, e.g., hemodialysis, and the use of antidotal (reversal agents).

Dosage and administration. Doses for adults and special populations for the drug's indication(s) are listed here, both in gross dosage units (e.g., adults 500 mg) and weight-adjusted dosage (e.g., mg/kg/day for children >3 months). Recommendations for variations in dosage are described in this section, including recommendation for patients with impaired renal and/or hepatic function, hemodialysis patients, and, if appropriate, instructions for mixing products that require reconstitution.

How supplied. This section describes all of the various dose forms and strengths of the drug, with their respective NDC code numbers, and recommendations for storage conditions.

Clinical studies. The outcomes from significant clinical studies used to develop specific dosing recommendations, combination uses, etc. are included in this section. These data are very detailed, statistical format to inform practitioners about the evidence for use of the drug for these conditions.

References. List of references for laboratory standards, special uses, etc. are found here.

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Evidence-Based Dentistry

The current definition of evidence-based dentistry, as promulgated by the American Dental Association, is:

> an approach to oral healthcare that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences.

The various types of evidence are generally presented as a pyramid, with the lowest (weakest) levels of evidence at or near the base of the pyramid and the highest (strongest) levels at the apex of the pyramid, as shown in Fig. 2.

When interpreting various types of scientific evidence, it is important to keep in mind the definitions of the various types of studies and evidence, as follows:

Meta-analysis. A statistical analysis that combines or integrates the results of multiple independent clinical trials considered by the analyst(s) "combinable" to the level of reanalyzing the original data in a single data pool, an approach also referred to as quantitative synthesis.

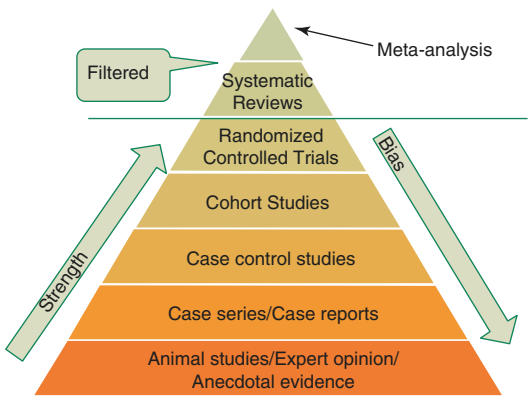

Fig. 2 Evidence pyramid showing hierarchical relationships between various levels of evidence (strongest evidence with lowest bias at apex). From (Higgins and Green 2011)

Systematic review. A review of a body of data that utilizes explicit methods to locate the relevant, primary studies applicable to a specific research question and explicit criteria to assess their quality (including risk of bias, etc.).

Randomized controlled trials (RCTs). Studies in which individual participants (subjects) are allocated to a control group and an experimental group who receive a specific intervention (treatment). The two groups are otherwise identical for any significant variables. The groups are followed (assessed) for specific therapeutic endpoints used to measure the efficacy of a given treatment when compared to the controls.

Cohort studies. In these studies, groups of people are selected on the basis of their exposure to a particular agent or condition and followed for specific outcomes at various intervals.

Case control studies. Individual patients (cases) with a specific condition are matched with controls (without the condition), and a retrospective analysis is used to evaluate difference between the two groups of cases.

Case study. A report based on a single patient (case) with a specific condition and having had a specific intervention or having been followed over a specific period of time. Multiple cases may be reported in a single publication as a short series of cases.

Expert opinion and anecdotal evidence. Evidence generated as an opinion from a thought leader or expert in a given field of study, typically based on the expert's clinical experiences in a variety of individual patient cases which were not standardized or controlled. Stronger expert opinion is based upon groups of experts achieving consensus through rigorous discussion of available case and treatment information, frequently under the auspices of a respected professional organization.

As noted above, this textbook was developed to present current or very recent, high-level scientific evidence about the use of drugs in dentistry and about specific types of medical drugs which may impact the use of dentally useful

therapies. As such, it represents a synthesis of high-level scientific evidence by experts and not opinions of experts.

Special Considerations in the Administration and Prescription of Medications in Dental Patients

There are several critical factors which the dentist must take into consideration prior to the administration or prescription of a drug. These include (Jeske 2017):

1. Use of a medical drug(s) by the patient. The use of a drug prescribed by a physician indicates the presence of a systemic medical condition that may predispose the patient to serious adverse drug-drug interactions and may limit the patient's ability to tolerate dental appointments, particularly stress. The prescribing physician(s) should be involved in the determination of the patient's ability to tolerate specific dental procedures, particularly those categorized as American Society of Anesthesiologists' physical status classification III or IV.
2. Any changes to a patient's medical drug therapy must be done by the prescribing physician, especially as this relates to drugs for serious neurologic and cardiovascular diseases, such as elevated risk of thromboembolism if antiplatelet or anticoagulant therapy is modified.
3. Vital signs and other appropriate physical assessments should be made at any dental visit in which a drug will be administered.
4. The adverse effects of medically prescribed drugs must be monitored and managed appropriately. Hyposalivation is a common example of this, and the patient and/or the patient's primary caretakers must be alerted to this consideration and should play a role in minimizing the impact of these conditions, primarily through effective oral hygiene.
5. References should be consulted to obtain detailed information about the management of patients with special needs (Wasserman 2009).

Medication-Related Osteonecrosis of the Jaw

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) updated its "Position Paper on Medication-Related Osteonecrosis of the Jaw" (MRONJ), formerly termed "bisphosphonate-related osteonecrosis of the jaw" (BRONJ) (American Association of Oral and Maxillofacial Surgeons 2014). This update expanded the list of drugs known to be associated with an increased risk for MRONJ, to include antiangiogenic drugs (e.g., denosumab, Prolia®) and corticosteroids. The updated document provides estimates of risk for MRONJ, comparisons of the risks and benefits of medications related to osteonecrosis, and guidance for clinicians on the differential diagnosis of MRONJ and prevention measures, as well as management strategies for patients with disease-stage MRONJ.

According to the AAOMS document, risk for MRONJ is increased in cancer patients who have been treated with zoledronate (Reclast®, Zometa®) and antiangiogenic monoclonal antibodies (e.g., denosumab) and tyrosine kinase inhibitors (e.g., sunitinib, Sutent®), although the incidence is lower in patients treated with the same drugs for osteoporosis.

Local risk factors for MRONJ include operative treatment (e.g., tooth extraction), anatomic features (e.g., mandibular bone supporting a complete denture), and concomitant oral disease (e.g., inflammatory dental diseases, periodontitis).

The AAOMS position paper provides additional information on genetic, demographic, and systemic factors in MRONJ and a summary of dental management strategies for patients at-risk of MRONJ, including:

- Extraction of non-restorable teeth and those with a poor prognosis prior to initiation of antiresorptive/antiangiogenic therapy
- Elimination of mucosal trauma caused by removable prostheses
- Consultation with the patient's physician(s) in order to follow patient-specific MRONJ-prevention protocols

- Maintenance of good oral hygiene and dental care
- Avoidance of dental implant placement in oncology patients receiving intravenous antiresorptive or antiangiogenic medications

For patients taking oral bisphosphonates (e.g., alendronate, Fosamax®), specific guidance for cases based on length of medication use includes:

- For individuals who have taken an oral bisphosphonate for less than 4 years and have no clinical risk factors, no alteration or delay in planned oral surgery is necessary (this includes any and all procedures common to oral and maxillofacial procedures, periodontists, and other dental providers).
- For those patients who have taken an oral bisphosphonate for less than 4 years and have also taken corticosteroids or antiangiogenic medications concomitantly, the prescribing physician should be contacted to consider discontinuation of the oral bisphosphonate ("drug holiday") for at least 2 months prior to oral surgery, if systemic conditions permit.
- For those patients who have taken an oral bisphosphonate for more than 4 years with or without any concomitant medical therapy, the prescribing physician should be contacted to consider discontinuation of the antiresorptive medication for 2 months prior to oral surgery, if systemic conditions permit.

The complete position paper should be consulted for detailed information, including information on the management of patients with established MRONJ.

Biologic Therapies

Detailed coverage of biologic therapies, such as monoclonal antibodies, is beyond the scope of this book. Monoclonal antibodies, anti-TNF agents, and other preparations are now in widespread use and account for a relatively high proportion of drug sales in the USA. While limitations on their use frequently include the need for injection, they have had a significant impact on the management of several important disorders, particularly rheumatoid arthritis and Crohn's disease. They are generally large proteins that can be manufactured via recombinant DNA methodologies. As the number of these agents increases, their impact on dental care and dental drug therapy will become clearer. At this time, the reader is provided with a current list of examples of these in Table 1 agents to call attention to the very serious diseases for which biologic therapies are indicated. The types of agents may be recognized generally by the suffixes of their official ("generic") names, e.g., "-mab" indicates "monoclonal antibody," "-ib" indicates "inhibitor," etc. (Katzung and Trevor 2015). Biologic agents can be classified as follows, based on their specific targets:

1. T-cell modulators (e.g., abatacept, Orencia®)
2. B-cell cytotoxic agents (e.g., rituximab, Rituxan®)
3. IL-1 (interleukin) blockers (e.g., anakinra, Kineret®)
4. Anti-IL-6 receptor antibody (e.g., tocilizumab, Actemra®)
5. JAK (Janus kinase) inhibitors (e.g., tofacitinib, Xeljanz®)
6. TNF (tumor necrosis factor)-alpha blockers (e.g., adalimumab, Humira®)

For dental patients taking biologic therapies, the following guidelines should be followed:

- The prescribing physician(s) should be consulted to assess the status of the patient's disease and the ability of the patient to tolerate dental procedures.
- Immunosuppression is associated with biologic therapies and may predispose the patient to a higher incidence and severity of oral and systemic infections (e.g., tuberculosis), including fungal infections.
- Because the biologic agent must be injected, injection site discomfort and acute symptoms may accompany administration (e.g., nausea, diarrhea).

Table 1 Examples of monoclonal antibodies approved for use in the USA (Jeske 2017)

Official name	Trade name	Indication(s)
Abciximab	ReoPro®	Adjunct for prevention of thromboembolism
Adalimumab	Humira®	Rheumatoid arthritis
Alemtuzumab	Campath®	Chronic lymphocytic leukemia
Basiliximab	Simulect®	Antirejection (renal transplant)
Bevacizumab	Avastin®	Metastatic colorectal and other cancers
Canakinumab	Ilaris®	Cryopyrin-associated periodic syndrome
Certolizumab	Cimzia®	Rheumatoid arthritis
Cetuximab	Erbitux®	Squamous cell carcinoma
Daclizumab	Zenapax®	Antirejection (renal transplant)
Denosumab	Prolia®	Osteoporosis (high fracture risk)
Eculizumab	Soliris®	Nocturnal hemoglobinuria
Guselkumab	Tremfya®	Plaque psoriasis
Golimumab	Simponi®	Rheumatoid arthritis
Ibritumomab	Zevalin®	Non-Hodgkin's lymphoma
Infliximab	Remicade®	Rheumatoid arthritis
Ipilimumab	Yervoy®	Unresectable metastatic melanoma
Muromonab	Orthoclone®	Antirejection (renal transplant)
Natalizumab	Tysabri®	Multiple sclerosis Crohn's disease
Ofatumumab	Arzerra®	Chronic lymphocytic leukemia
Omalizumab	Xolair®	Allergic asthma
Palivizumab	Synagis®	Respiratory syncytial virus
Panitumumab	Vectibix®	Metastatic colorectal cancer
Ranibizumab	Lucentis®	Macular degeneration
Rituximab	Rituxan®	Non-Hodgkin's lymphoma
Tocilizumab	Actemra®	Rheumatoid arthritis
Trastuzumab	Herceptin®	Breast and gastroesophageal cancers
Ustekinumab	Stelara®	Plaque psoriasis
Vedolizumab	Entyvio®	Ulcerative colitis, Crohn's disease

FDA Pregnancy and Lactation Drug Labeling

In 2015, the US Food and Drug Administration (FDA) required major changes in the labeling and information for the use of prescription drugs and biologic agents in pregnancy, including risks of exposure to pregnant and lactating females, review of the data supporting these risks, and other information to assist practitioners and patients in making informed decisions about medication use during pregnancy and lactation (U.S. Food and Drug Administration 2015). These new labeling requirements mandated that manufacturers replace the old pregnancy risk categories (A, B, C, D, and X) with the updated information within 3 years [FDA]. The various sections of the new labeling information are illustrated in Table 2.

Table 2 FDA labeling information for pregnant and lactating patients

Pregnancy
• Pregnancy exposure summary
• Risk summary
• Clinical considerations
– Disease-associated maternal and/or embryo/fetal risk
– Dose adjustments during pregnancy and postpartum
– Maternal adverse reactions
– Fetal/neonatal adverse reactions
– Labor or delivery
• Data
– Human
– Animal
Lactation
• Risk summary
• Clinical considerations
• Data
Females and males of reproductive potential
• Pregnancy testing
• Contraception
• Infertility

Additionally, the FDA now requires manufacturers to list pregnancy registry information (a pregnancy registry being an ongoing, systematic, and epidemiologic study that collects and assesses data on a mother's, fetus', or infant's adverse reactions to medications, biologic agents, and vaccines) (U.S. Food and Drug Administration n.d.).

Conclusion

Dental drug therapy typically follows and evolves from the development of new drug entities (or improvements in or new indications for existing drugs) in medicine. The FDA approval process generates a tremendous amount of information that is foundational to the evidence-based use of drugs in dental practice. When new drugs are approved, it is incumbent upon the prudent dentist to determine not only what adverse drug interactions may occur between the new medical drug and existing dental drugs but to ascertain the implications that the new drug has for the comprehensive management of the patient's dental treatment.

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Local Anesthetics

Arthur H. Jeske

Mechanism of Action and Clinical Implications

Unlike most other pharmaceuticals, local anesthetics begin their therapeutic action immediately upon application to a target tissue, usually via injection into an anatomic space adjacent to a nerve trunk (e.g., nerve block) or nerve endings (e.g., infiltration). This requirement results from the need to abolish pain impulses in small areas of the body, and the poor oral bioavailability obviates any utility of these drugs for systemic effects.

Beginning with the pioneering work of Ritchie and Greengard, which established the active form of conventional local anesthetic drugs and the influence of pH on their clinical behavior, work over the last three decades of the twentieth century has led to an understanding of the principal site of action as the voltage-gated sodium channel (Ritchie and Greengard 1966). A folding diagram of the channel is illustrated in Fig. 1.

Voltage-gated sodium channels are ubiquitous in nature and are designated by the symbol Na_v, followed by a number 1.1 through 1.9, representing isoforms found in various tissues (Alexander et al. 2017). They underlie the functioning of all electrically excitable tissues, including peripheral and central neurons and the pacemaker and conducting tissues of the heart, accounting for the typical signs and symptoms of systemic toxicity observed at elevated blood levels (see section "Local Anesthetic-Related Nerve Injury," below).

Under pathologic conditions (e.g., nerve trauma), neurons can become phenotypically altered, and there can be expression of channels which are pharmacologically characterized as "tetrodotoxin resistant," indicating extreme resistance to block, including local anesthetic block (Alexander et al. 2017; Waxman and Zamponi 2014). This is one possible explanation for the difficulty encountered by clinicians in attempting to anesthetize teeth which have been chronically infected and inflamed due to caries, trauma, etc.

Nerve block caused by local anesthetics begins to occur immediately following injection of the drug near the nerve. Following equilibration of the local anesthetic solution with the extracellular fluid, the uncharged species of the anesthetic penetrates the nerve membrane and enters the intraneuronal space. There, the anesthetic once again equilibrates into positively charged and uncharged forms, according to the Henderson-Hasselbalch equation:

$$\mathrm{pKa} = \mathrm{pH} - \log\left[\mathrm{base}\right] / \left[\mathrm{conjugate\ acid}\right]$$

When the nerve membrane is depolarized, voltage sensors alter the conformation of the

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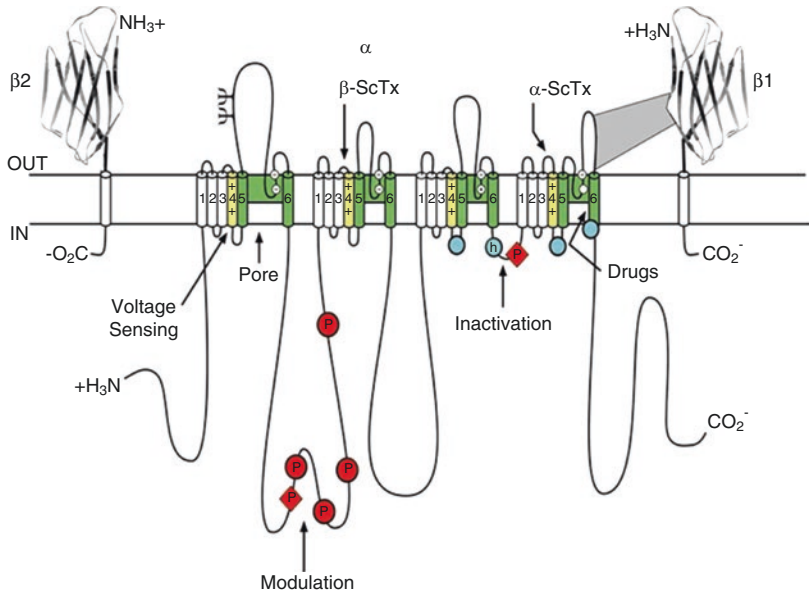

Fig. 1 Folding diagram of the mammalian voltage-gated sodium channel. The alpha subunit is comprised of four domains of six alpha-helical coiled amino acid sequences. These groups span the nerve membrane and surround and form the ion "pore." A voltage-sensing sequence of positively charged amino acids in each domain responds to changes in polarity of the adjacent nerve membrane, resulting in a transient opening, followed by inactivation (modulated by the inactivation gate) and closing of the channel during a depolarization. Local anesthetic binding occurs at the sixth transmembrane helix, at a site near the internal opening of the channel (indicated by "drugs"). Reprinted from *Neuron* Volume 26, No. 1, Catterall WA, From Ionic Currents to Molecular Mechanisms: the Structure and Function of Voltage-Gated Sodium Channels, pp. 13–25, 2000, with permission from Elsevier

channel, the sodium channels open, and local anesthetic molecules can access and bind to their active site which lies within the channel, near the inner opening, at the sixth transmembrane helices of domains 1, 3, and 4 of the channel's alpha subunit (Catterall 2012). Local anesthetic binding stabilizes the channel in the inactivated form, which cannot conduct Na+ ions. Accumulation of a sufficient number of inactivated channels prevents subsequent conduction of nerve impulses, affecting a state of nerve block, or local anesthesia.

Two additional mechanisms of local anesthetic action have been proposed, including:

1. Direct access to the anesthetic binding site from within the lipid core of the neuronal membrane. This mechanism, also known as the "hydrophobic pathway," explains the nerve-blocking actions of benzocaine, an anesthetic that only exists in an uncharged form (Catterall 2012; Lirk et al. 2014);
2. Entry of charged anesthetic molecules into the neuron via large pore vanilloid-1 (TRPV-1) channels. This pathway, also known as the "hydrophilic pathway," explains the ability of investigational fixed charge anesthetics to induce nerve blockade when these channels are activated by acute applications of capsaicin.

Local anesthetics may also act via secondary targets, including potassium and calcium channels, and G-protein-coupled and *N*-methyl-D-aspartate (NMDA) receptors (Salinas et al. 2004), although it is unlikely that these targets play a major role in the blockade of peripheral nerve fibers (Salinas et al. 2004).

Rapidly firing neurons are blocked earlier than those with lower firing rates, and smaller neurons are generally blocked before larger ones. In the case of rapidly firing neurons, the rapid opening of the voltage-gated sodium channels increases the likelihood that local anesthetic molecules can

access their binding sites within the channel, in a phenomenon known as "frequency dependence" (Drasner 2015).

Neuronal diameter and other intrinsic traits may alter the susceptibility of nerves to local anesthetic block. For example, for nerves with similar cross-sectional area, those with myelin would tend to be blocker sooner than those that lack myelin, as the myelin may serve as a "reservoir" for uncharged local anesthetic. Theoretically, larger diameter fibers are blocked later than smaller ones because the distance over which the larger fibers can passively propagate an electrical impulse is greater. Generally, the order of blockade of sensory fibers is described as (Drasner 2015):

Temperature > pain > light touch > pressure > proprioception.

Motor fibers are not blocked by dental local anesthetics unless the anesthetic is placed into close proximity to a motor nerve, e.g., cranial nerve VII, as occurs when the parotid gland is accidentally entered during mandibular block techniques, resulting in temporary facial nerve paralysis. Motor nerve block is a much more important consideration when local anesthetics are used in the setting of epidural and spinal anesthesia (Drasner 2015; Neal et al. 2018).

Physicochemical Characteristics

Injectable dental local anesthetics are relatively small molecular structures (molecular weights ranging from 234 to 321 Da). These values and their other physicochemical properties are presented in Table 1.

Relatively high lipid solubility and protein binding for bupivacaine and tetracaine are the basis for their relatively long duration of action, i.e., they possess high affinity for the proteolipid complex structure of the neuronal cell membrane. Lipid affinity is also the basis for the use of lipid emulsion for treating systemic toxicity of local anesthetics (see section "Local Anesthetic-Related Nerve Injury," below).

Chemically, conventional local anesthetics are classified as amides or esters, based upon the linkage of the aromatic (lipophilic) moiety at one end of the molecule to the intermediate, aliphatic chain. Amides are metabolized primarily via hepatic microsomal oxidation, while esters, with a relatively weak intermediate bond, are rapidly hydrolyzed by plasma cholinesterases (Salinas et al. 2004). Their relative small molecular size limits their allergenicity, although metabolic products of ester-type agents can be allergenic by token of their molecular similarity to para-amino benzoic acid (PABA). Recently, sensitization to amide local anesthetics has been noted to occur in connection with the application of large amounts of topical preparations to skin to reduce pain associated with cosmetic enhancements of the body (hair removal, etc.) (To et al. 2014).

Structure-Activity Relationships and Effect of pH and pKa

Dental local anesthetic drugs are weak bases and possess a tertiary amine terminus, which can be protonated (except for benzocaine). This highly polar group confers water solubility upon the drugs, although the positively charged form (protonated)

Table 1 Physicochemical characteristics of common local anesthetics

Drug	Lipid partition coeff.	Protein binding (%)	Mol. Wt. (Da)	Concentration in dental cartridges (%)
Articaine	17	70	321	4
Bupivacaine	346	95	288	0.5
Lidocaine	2.4	64	234	2
Mepivacaine	21	77	246	2–3
Prilocaine	25	55	220	4

Table 2 Relationship between local anesthetic pKa and fraction of unionized drug at pH 7.4

Drug	pKa	% drug uncharged
Articaine	7.8	28
Bupivacaine	8.1	15
Lidocaine	7.9	25
Mepivacaine	7.6	37
Prilocaine	7.9	24
Tetracaine	8.6	7

of the anesthetic apparently is also essential for the binding of the anesthetic to its active site in the voltage-gated sodium channel. Similarly, the aromatic ring at the opposite end of the local anesthetic molecule confers lipid solubility upon the drug, allowing it to traverse the cell membrane. Diffusion into the nerve does not occur via ion pores but through passive diffusion through the neuronal membrane by the uncharged form of the anesthetic. Thus, the higher the pKa of the anesthetic, the greater the ionization of the drug in the extracellular fluid and the lower the fraction of uncharged form (Table 2). For the long-acting agents bupivacaine and tetracaine, with relatively high pKa, their potency derives from their high lipid solubility and protein-binding affinity (Table 1), a critical factor that not only explains their higher potency, i.e., their nerve-blocking concentration, but their long duration as well (Drasner 2015).

When considering the values presented in Table 1, the reader should consider the fact that these numbers apply to plain solutions. For preparations with epinephrine, the pH of the solution is adjusted downward, and such solutions may have pH values as low as 3.3, with correspondingly greater proportions of charged versus uncharged molecules. However, once injected into body tissues, the pH quickly equilibrates to normal tissue fluid pH. This re-equilibration is not immediate, with the result that some patients may experience a burning sensation during the injection. This consideration, along with a theoretical advantage that increasing the relative proportion of anesthetic molecules in the uncharged form can accelerate the onset of the local anesthetic effect, has led to the development of buffering systems for dental local anesthetic cartridges.

The potential benefits of buffering local anesthetic solutions (to raise their pH) theoretically include faster onset and greater efficacy (owing to a larger fraction of uncharged anesthetic available to diffuse into the nerve), as well as a reduction in injection pain associated with acidic solutions. Reduced pH is also believed to play a role in the failure of local anesthetic to block nerves when their tissues of innervation are inflamed and the pH of the extracellular fluid may drop by as much as 0.5 pH units (Lirk et al. 2014).

Recent studies on the effect of bicarbonate buffering of the local anesthetic solution prior to injection have produced equivocal results. For example, Saatchi et al. (Saatchi et al. 2015) studied the effect of buffering 2% lidocaine with 1:80,000 epinephrine for the success rate of the inferior alveolar nerve block (IANB) in patients with symptomatic irreversible pulpitis. Comparing the administration of two cartridges of the non-buffered anesthetics with the same dose buffered with 0.18 mL of 8.4% sodium bicarbonate solution, the investigators achieved success rates of 62.5% for the buffered solution versus 47.5% for the non-buffered one, without achieving statistical significance. Similar outcomes were obtained in a study of the effect of 2.8 mL buffered 4% lidocaine for the IANB (versus the same protocol without buffering) that showed no significant difference for success in patients with symptomatic irreversible pulpitis (32% and 40%, respectively), nor were the ratings of pain during the injection different (Schellenberg et al. 2015).

Interestingly, one study has demonstrated that injection of sodium bicarbonate in a 2% lidocaine solution via buccal infiltration of irreversibly inflamed lower first molars followed by a conventional IANB block with 2% lidocaine with epinephrine produced significantly better success rates versus infiltration of lidocaine with distilled water (78% vs. 44%) (Saatchi et al. 2016). The mechanism by which this difference occurred may have been due simply to the additional buffered lidocaine at the tooth site, with improved diffusion from neutralization of inflamed extracellular fluid, and it is tempting to speculate that

alteration of the function of acid-sensing ion channels may also have played a role. In oral surgery, the effect of buffering 2% lidocaine with epinephrine on various clinical parameters has been investigated, including the impact on blood levels of the local anesthetic. It has been shown that the buffered preparation resulted in significantly lower blood levels after IANB, and subjects reported lower injection pain scores and shorter time to lip numbness with the buffered solution (Phero et al. 2017). Theoretically, the buffered solutions would contain smaller fractions of charged local anesthetic molecules, which are hydrophilic and would be expected to be absorbed by blood more extensively than the uncharged, less polar forms. This could become a significant factor when large amounts of local anesthetic are required for surgical procedures or for postoperative pain control, e.g., intercostal block.

Recently, a meta-analysis of the efficacy of sodium bicarbonate buffered versus non-buffered lidocaine with epinephrine for the IANB was conducted, and the outcomes of the analysis were based on 11 included studies (Guo et al. 2018). While this report found that buffering significantly decreased time of onset of anesthesia (48 s shorter) and injection pain (5-point reduction on the 0–100 VAS), there was no significant difference for anesthetic success rate or the incidence of painless injections. The investigators cautioned that the quality of evidence was low to moderate due to statistical heterogeneity and low sample sizes.

At this time, practitioners who adopt buffering as part of their IANB local anesthetic protocols for routine dental procedures can expect some reductions in onset time and injection pain but little advantage for overall pulpal anesthesia success rates. The impact of buffering on the success rates for other types of injections will require additional scientific studies.

Structural modifications to the basic local anesthetic molecule which increase lipid solubility have a marked impact on potency, protein-binding affinity, and duration of action. An example is that of bupivacaine, in which substitution of the methyl group of mepivacaine with a butyl group results in a significant increase in potency and duration of action, the latter effect owing to the increased binding affinity of the drug for the neuronal membrane. In the case of bupivacaine, two additional considerations arise from the increase proteolipid affinity—first, bupivacaine possesses an inherently higher cardiotoxicity than other local anesthetics and, second, bupivacaine can be produced in a liposomal delivery formulation, in which slow release from liposomes introduced into a surgical site produce prolonged postoperative pain relief.

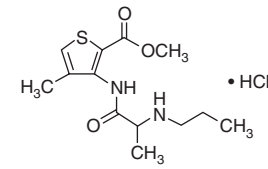

Fig. 2 Structural formula of articaine

Articaine is distinguished from other amide local anesthetics by two unique structure features—first, it possesses a sulfur-containing thiophene ring, which apparently contributes to its ability to diffuse through both soft and hard tissues more readily than other conventional local anesthetics (Fig. 2). Second, it also possesses an ester side chain, which, because it is quickly hydrolyzed by non-hepatic esterases, results in more rapid inactivation after it leaves its therapeutic site of action, contributing to a relatively short (23 min) plasma half-life.

Since the resulting hydrolysis product articainic acid is not pharmacologically active, systemic toxicity is reduced relatively rapidly, as opposed to the prototype amide lidocaine, whose initial oxidative metabolite (monoethylglycinexylidide) is an active intermediate than may prolong systemic toxicity.

Comparative Efficacy of Injectable Local Anesthetics

Beginning in 2009, there have been several systematic reviews focusing on the comparative efficacy of articaine, lidocaine, and some other local anesthetic preparations. Among the most informative, of course, are those which performed and

reported the outcomes of meta-analyses (Corbella et al. 2017; Katyal 2010; Kung et al. 2015; Paxton and Thomas 2010; St. George et al. 2018; Zhang et al. 2018). Particular interest in the comparative efficacy of articaine versus lidocaine arose from the increasingly widespread use of articaine and its availability, beginning in 1999, in the US dental marketplace.

The primary outcome measure used to compare efficacy among injectable local anesthetics is complete pulpal anesthesia, as assessed by a lack of response of test teeth to electric pulp testing or ability to perform endodontic treatment on teeth presenting with symptomatic irreversible pulpitis with no or only mild procedural discomfort. A variety of additional outcome measures have been reported, most frequently including speed of onset and duration of local anesthesia and local and systemic adverse effects. A common secondary measure is the global assessment of subjects' satisfaction with the pain control during a procedure.

For success of anesthesia, it now appears that 4% articaine with 1:100,000 epinephrine is superior to 2% lidocaine with 1:100,000 epinephrine for posterior teeth which present with symptomatic irreversible pulpitis (31% vs. 49% incidence of successful anesthesia, RR 1.60, 95% CI* 1.10–2.32) (St. George et al. 2018).

For studies of soft- and hard-tissue (e.g., tooth extraction) procedures, clear evidence favoring one particular local anesthetic is lacking (St. George et al. 2018), and variations in volume of injected anesthetic (one versus two cartridges for the inferior alveolar nerve block) did not reveal any significant differences for success between lidocaine and articaine, although in the most recent systematic review specifically of the inferior alveolar nerve block, an additional benefit of supplementary buccal infiltration was evident (Corbella et al. 2017). There is moderate quality evidence that for surgical and periodontal procedures, 2% lidocaine with 1:100,000 epinephrine was superior to 4% prilocaine plain, although comparisons for 4% prilocaine with 1:200,000 epinephrine are not available, and comparative results for surgical outcomes using 0.5% bupivacaine with 1:200,000 epinephrine versus other anesthetic agents are reported as "uncertain" (St. George et al. 2018).

Earlier systematic reviews (Katyal 2010; Kung et al. 2015) clearly demonstrated a significant contribution of greater anesthetic success for 4% articaine with 1:100,000 epinephrine for buccal infiltration compared with 2% lidocaine with 1:100,000 epinephrine to the overall estimated success rate for articaine. For example, Brandt et al. determined that the odds ratio (OR) for the overall success rate for 4% articaine versus 2% lidocaine was 2.44 (95% CI 1.59–3.76, $p < 0.0001$), while when only buccal infiltration was considered, the advantage for articaine increased to OR 3.81 (95% CI 2.71–5.3, $p < 0.00001$) (Brandt et al. 2011).

For virtually all studies of local anesthetics, adverse events are rare, and differences in pain on injection do not appear to be significant when comparing 4% articaine to 2% lidocaine preparations (St. George et al. 2018). The practitioner has several options for local anesthetic preparations, and, based on current scientific evidence, one practical approach is to stock both 2% lidocaine with 1:100,000 epinephrine (for blocks and maxillary buccal infiltrations), 4% articaine with epinephrine (for mandibular buccal infiltration anesthesia), and a plain solution, to be used in cases in which epinephrine is absolutely contraindicated (e.g., 3% mepivacaine plain, 4% prilocaine plain).

0.5% bupivacaine does not produce reliably long-acting anesthesia in the maxilla, and it is not recommended for use in children. Supplementary anesthetic techniques (e.g., intraosseous injections) can also be employed successfully to help overcome failures of block and/or infiltration anesthesia and to limit the total dose of anesthetic, if necessary. 2% lidocaine with 1:100,000 epinephrine and 3% mepivacaine plain are recommended for use with these techniques (Reader et al. 2017).

Local Anesthetic-Related Nerve Injury

Interest in local anesthetic-related nerve injury peaked in the 1990s, at a time when the use of 4% articaine solutions had become widespread, both

in Europe and Canada, following retrospective estimation of the incidence of paresthesias in the dental patient population versus the estimated frequency of use of various types of dental anesthetics (Haas and Lennon 1995). These concerns have persisted into the twenty-first century (Garisto et al. 2010), although limited scientific evidence now suggests that the initial assessments of neuronal toxicity may have been overestimated. In fact, a second formulation of 4% articaine (with 1:200,000 epinephrine) was subsequently approved by the US Food and Drug Administration.

It is generally accepted that local anesthetics can be neurotoxic when relatively concentrated solutions, e.g., 2–4%, are placed in close proximity to small nerves or in tissues with limited or depleted buffering capability (e.g., cerebrospinal fluid). Cauda equina syndrome is well known in medicine as a complication of spinal anesthesia (Drasner 2015). In dentistry, local anesthetic administration is among the five procedures associated with the majority of cases of nerve injury, including implant placement, endodontic treatment, bone grafting, and dentoalveolar surgery (particularly lower third molar removal) (Pogrel 2017). Mechanisms that underlie these injuries include induction of apoptosis at lower concentrations and late apoptotic or necrotic cell death at higher ones (Verlinde et al. 2016; Werdehausen et al. 2009). In a neuroblastoma cell line, all conventional local anesthetics were shown to induce apoptosis and neurotoxicity in direct relationship to the anesthetic concentration and appear to be related to the fat solubility and potency of the drug, with no significant differences between amide- and ester-type anesthetics (Werdehausen et al. 2009).

A recent literature review of local anesthetic-induced neurotoxicity identified multiple risk factors for nerve damage, including the block technique used, patient risk factors (e.g., preexisting neuropathy or neurological diseases), and surgical factors (e.g., inadvertent nerve compression). Cellular mechanisms that may be associated with neurotoxicity include effects of local anesthetics on the intrinsic caspase pathway, PI3k pathway, and MAPK pathways. For peripheral nerve blocks, this review estimated the incidence of local anesthetic-related neurological complications as less than 3% and concluded that most are "transient sensory deficits" (Verlinde et al. 2016).

In the USA, the Department of Oral and Maxillofacial Surgery at the University of California, San Francisco, has perhaps the longest-running case series of patients with iatrogenic injuries to the maxillofacial area (Pogrel and Thamby 2000). This case series now includes 324 patients whose nerve injuries could only be the result of local anesthetic injections, and the following are reported as consistent features in these cases (Pogrel 2017):

- The lingual nerve is the most frequently affected nerve (twice the rate as the inferior alveolar nerve.
- 33% of the patients experience dysesthesia as a result of the injury.
- Recovery, if it occurs, does so in 3 months and later recoveries are rare.
- Virtually all cases involved the inferior alveolar nerve block, and among permanent injuries, the vast majority involved this block injection.

There is a considerable variation in the estimates of the actual incidence of these injuries, now ranging from 1 in 6000 for temporary neural deficits with the IANB to 1 in 30,000 for permanent injuries (Pogrel and Thamby 2000).

Contrary to some expert opinion, this type of nerve damage is not associated with a specific anesthetic drug, although it does appear to predominantly affect the lingual nerve. There appears to be no established relationship to the volume of anesthetic injected, and there is no beneficial treatment known, despite unfounded suggestions that corticosteroids may improve the long-term prognosis, nor is there evidence to support a beneficial effect of vitamin and other dietary supplements. Attempts at surgical correction of dysesthesias have not been successful, and the surgery has typically not revealed macroscopic damage to the nerves.

At this time, there appears to be no known method of preventing local anesthetic-related nerve injury (Pogrel et al. 2011; Pogrel and Thamby 1999; Pogrel 2002, 2007).

The medicolegal considerations involving iatrogenic lingual nerve damage have recently been addressed (Pippi et al. 2018) and highlight the difficulties encountered when attempting to establish the etiology of the injury, i.e., differentiation of anesthetic, mechanical, chemical, and even thermal mechanisms.

It is also noteworthy that clinical tests aimed at assessing lingual nerve sensory function have low sensitivity and only moderate specificity.

Experts have concluded that the patient must be warned of the possibility of nerve injury during the informed consent process, regardless of the relatively low frequency of local anesthetic-related injury. Unfortunately, there are no good alternatives to local anesthetic injection for pain control for routine, outpatient dental procedures.

Local Anesthetic Systemic Toxicity (LAST) and Management

Local anesthetic systemic toxicity (LAST) is a serious and potentially life-threatening reaction typically associated with high doses and/or multiple injections of local anesthetics in a relatively short period of time. Occasionally, inadvertent intravenous or intraarteral injection can occur, in which case even relatively small amounts of local anesthetics may precipitate systemic toxicity. There are several mechanisms that play a role in the development of this scenario, which can result in the clinical presentation of the reaction being atypical (El-Boghdadly and Jinn Chinn 2016). The current literature suggests that LAST is relatively rare (2.0–2.8 cases per 10,000 peripheral nerve blocks) and is even less likely for infiltration anesthesia utilized in routine dental procedures (Barrington and Kluger 2013).

Factors related to the occurrence of LAST include (El-Boghdadly and Jinn Chinn 2016):

- Patient factors. In elderly patients with reduced hepatic and renal clearance of drugs, plasma protein binding and peak plasma concentration of anesthetics may differ from those seen in younger adults. Other patient conditions which may contribute to LAST include cardiac disease (which reduces blood flow to vital organs and, therefore, reduces drug clearance), liver disease (a consideration when doses are repeated or local anesthetic is continuously infused), and pregnancy (e.g., increased cardiac output beginning in the second trimester of pregnancy may increase local anesthetic absorption from injection sites and increase plasma concentrations). The well-established relationship between bupivacaine-induced LAST and pregnancy dictates extra precautions and played a role in the development of lipid emulsion therapy of LAST, described later in this section.
- Drug doses. Appropriate dosing of local anesthetics, based on patient body weight and systemic risk factors, is the single most important factor in preventing LAST. Maximum doses for common dental local anesthetics are found in Table 3 (based on manufacturer's date in FDA-approved labeling).
- Pharmacokinetics. There are only a few serious pharmacokinetic drug interactions involving amide local anesthetics (see below). In one case, some of histamine H2-receptor antagonists, e.g., cimetidine, inhibit the metabolic disposition of lidocaine by the hepatic cytochrome P450 CYP 3A4. Propranolol (Inderal®) and halogenated hydrocarbon anesthetics may reduce cardiac output and hepatic perfusion sufficiently to reduce the clearance of amide local anesthetics. In both of these cases, a careful medical history and avoidance of potentially interactive agents are warranted (Moore 1999).
- Anesthetic technique. Certain intraoral block injections, particularly the posterior superior alveolar and inferior alveolar nerve block, carry a higher probability of penetration of a blood vessel (based on likelihood of positive aspiration). Careful aspiration, slow injection, and increasing use of buccal infiltration anesthesia for routine and single-tooth dental procedures are important contributions to a reduction in LAST in the dental outpatient population.

Table 3 Maximum recommended doses (MRDs) for conventional dental local anesthetics (manufacturer's data)

Drug	Dose mg/kg	Absolute max dose (mg)[a]
Articaine	7	NA[b]
Bupivacaine	2	90
Lidocaine[c]	7	500
Mepivacaine	6.6	400
Prilocaine	8	600

[a]Dose that should not be exceeded in a single appointment
[b]The manufacturer of articaine does not specify an absolute maximum dose
[c]Applies to lidocaine preparations with epinephrine

The signs and symptoms of MAST may present in temporal variations (Lirk et al. 2014). "Instant" LAST involves rapid-onset seizures and cardiovascular depression and is usually associated with inadvertent intravascular administration of relatively high volumes of local anesthetic solution or smaller amounts injected intraarterially. "Slow" LAST typically follows overdose, rapid absorption of anesthetic by the circulation, reduced metabolism/hepatic clearance, or reduced plasma protein binding, taking up to 30 min or longer to manifest.

The classical signs and symptoms of impending LAST include sensory disturbances, following by early signs of CNS stimulation attributable to depression of central inhibitory neurons (muscle twitching and fasciculation). As plasma levels increase further, tonic-clonic seizures ensue, culminating in post-seizure depression with possible respiratory arrest. Cardiovascular parameters during LAST vary with the stage of toxicity, with increases in blood pressure during the phase of CNS excitation, and profound loss of blood pressure with severe bradycardia in the terminal stage. Exceptions to this cascade may occur, e.g., if the patient is being sedated with a benzodiazepine (which possesses anticonvulsant activity), CNS stimulation and seizures may be obtunded or not occur at all. LAST is potentially fatal, but the employment of preventive measures reduces the occurrence of cardiac arrest (El-Boghdadly and Jinn Chinn 2016).

The management of LAST involves rapid and, depending on the severity of the toxicity, aggressive rescue measures. Lipid emulsion infusion is becoming widely accepted as an interventional measure in LAST, although it does not substitute for airway management and ventilation with 100% oxygen. Intravenous infusion of lipid emulsion (e.g., 20–30% long-chain triglycerides produced from soybean oil) creates a "lipid sink" in the blood, which allows highly lipophilic local anesthetics such as bupivacaine to partition into the plasma and out of cardiac tissue, thus reducing the cardiac depression that is characteristic of this type of anesthetic. Additional mechanisms that contribute to the beneficial effects of lipid emulsion therapy of LAST-related cardiac depression include promotion of mitochondrial fatty acid metabolism and ATP synthesis and direct increases in cardiac contractility related to an increased intracellular content of calcium in myocardial cells (Fettiplace et al. 2014). Additionally, lipid emulsion can inhibit nitric oxide release and reverse cardiac sodium channel blockade (Ok et al. 2018).

A recent systematic review based on case reports has established the efficacy of intravenous lipid emulsion therapy for the management of local anesthetic-induced cardiotoxicity (Cao et al. 2015). CNS toxicity is also ameliorated by lipid emulsion therapy and has been demonstrated to be effective not only for LAST due to bupivacaine but also for lidocaine and mepivacaine. At this time, there is no evidence to confirm or refute a beneficial effect of adding epinephrine to lipid emulsion.

An example of a protocol for lipid emulsion infusion for a patient weighing 70 kg is a bolus infusion of 100 mL of Intralipid® 20% over 1 min, followed by a continuous infusion of 1000 mL per hour (Ok et al. 2018).

To summarize, the management of LAST in the dental outpatient setting would include the following (El-Boghdadly and Jinn Chinn 2016):

- **Prevention**: Appropriate local anesthetic dosing, use of less cardiotoxic anesthetics, aspiration before injection.
- **Detection**: Observe for CNS signs (agitation, confusion, seizures, mental depression, sen-

sory disturbances) and CVS signs (hypertension, tachycardia, hypotension, bradycardia, asystole).
- **Initial management**: Stop injection and dental procedure; summon help and emergency kit; open and maintain airway, ventilated with 100% oxygen; obtain vascular access (i.v. or i.o); terminate seizures (administer parenteral benzodiazepine); consider intravenous infusion of lipid emulsion if symptoms persist or recur.

The emergency use of benzodiazepines for seizure termination is described in the chapter "Basic Emergency Drugs and Non-intravenous Routes of Administration" of this book.

Beneficial and Adverse Drug Interactions Involving Local Anesthetics

Two beneficial drug-drug interactions involving dental local anesthetics include the pharmacodynamics interaction of epinephrine (a vasoconstrictor in the submucosal tissues) and most local anesthetics, which are vasodilators. By reducing local blood flow in the vicinity of the site of local anesthetic injection, the vasoconstrictor prolongs the duration of action of the anesthetic by reducing vascular uptake and "washout" (responsible for the offset and termination of the local anesthetic effect) and tends to reduce peak plasma levels of local anesthetic as the latter is more slowly absorbed.

A second beneficial interaction is the direct competitive receptor blockade of alpha adrenoceptors produced by phentolamine mesylate (e.g., OraVerse®) to reduce the time to recovery of soft-tissue sensation. The therapeutic basis for the use of phentolamine is competitive blockade of epinephrine at alpha-1 adrenoceptors (mediating vasoconstriction) and was established in a multicenter, double-blind, randomized Phase II clinical trial with 122 adult participants (Laviola et al. 2008). In the study, the participants had received one or two cartridges of dental local anesthetics with epinephrine for a dental procedure. Immediately following the procedures, a cartridge (1.8 mL) with 0.4 mg phentolamine mesylate or placebo was injected directly into the site previously used for the local anesthetic. Subjects who had received two cartridges of local anesthetics also received a second cartridge of phentolamine. Adverse events were uncommon, and the injection of the alpha-1 adrenoceptor blocker reduced the time to soft-tissue recovery by approximately 50%.

Despite this significant reduction in recovery from soft-tissue anesthesia, OraVerse® has not been widely adopted in dental practice in the USA, probably because of the additional expense and the need to perform one or two additional injections.

Adverse drug-drug interactions with local anesthetics are rare, although interactions with the vasoconstrictor component of dental local anesthetics must be considered as a second category of interaction. Interactions involving local anesthetic include summation of adverse CNS and CVS effects by the co-administration of another local anesthetic or a medically prescribed drug with local anesthetic actions (e.g., a class I anti-dysrhythmic drug). These are among the most potentially dangerous interactions and are categorized as significance rating 1/potentially life-threatening (Moore 1999).

Another life-threatening interaction is that which occurs when additive or supra-additive CNS depression as a result of co-administration of local anesthetics with sedatives and/or opioids, particularly in children with relatively low maximal allowable doses of local anesthetic (Moore 1999). An additional factor to consider in the prevention of this dangerous interaction is that the CNS-depressant effect of the sedative may mask the signs of CNS excitation seen in the early stages of LAST, a factor which delays recognition of the toxicity and effective intervention.

Interactions involving potentiation of the CVS-stimulant effects of epinephrine involve the following (Yagiela 1999):

- Cocaine
- Amphetamines
- Methylphenidate
- Tricyclic antidepressants

Monoamine oxidase inhibitors do *not* contraindicate the use of epinephrine in local anesthetic. Halogenated hydrocarbon general anesthetics and chloral hydrate sensitize the myocardium to the arrhythmogenic actions of epinephrine. Administration of epinephrine-containing local anesthetics to patients taking non-cardioselective beta-blockers (e.g., propranolol, Inderal®) can result in clinically significant bradycardia and even cardiac arrest.

The mechanism appears to be the elimination of beta-2 receptor-mediated vasodilation ordinarily produced by epinephrine, combined with alpha-adrenoceptor-mediated vasoconstriction. Increases in blood pressure resulting from the latter activate the unaffected baroreceptor reflex, causing unopposed, vagally mediated cardiac depression, since the beta-1 receptors at the heart have also been blocked by the nonselective beta-blocker (Yagiela 1999).

Less significant drug interactions are also possible, and the clinician should consult the complete prescribing information for all drugs prescribed. For elderly and medically compromised patients with systemic disease that could impact drug metabolism and/or excretion, consultation with the patient's physician is recommended.

Effect of Vasoconstrictors

In the USA, epinephrine is the most widely employed vasoconstrictor used in local anesthetic preparations in dentistry. Its actions are well known and predictable, and the dose limitations recommended in standard textbooks on local anesthetic are generally accepted as safe for adults, based on American Society of Anesthesiologists' physical status classification, as follows:

- ASA I: 0.2 mg total dose (equivalent to the amount of epinephrine contained in approximately 11 1.8 mL cartridges with a 1:100,000 concentration)
- ASA II: 0.1 mg total dose (equivalent to the amount of epinephrine contained in approximately 5.5 1.8 mL cartridges with a 1:100,000 concentration)
- ASA III: 0.04 mg total dose (equivalent to the amount of epinephrine contained in approximately two 1.8 mL cartridges with a 1:100,000 concentration)

Concentrations of epinephrine greater than 1:100,000 do not appear to confer any advantage for dental local anesthesia, either in terms of prolongation of duration of action or reduction in peak plasma levels of anesthetic.

The initial physiologic response to intravascular injection of epinephrine is tachycardia, and it has been reported that an intravascular dose of 15 μg (equivalent to 3 mL of a 1:200,000 concentration) will produce a transient increase in heart rate of ten beats or more per minute (BPM), with an approximate transient increase in systolic pressure of 15 mm Hg or more (El-Boghdadly and Jinn Chinn 2016). Felypressin, not currently available in dental local anesthetic solutions in the USA, is essentially devoid of the sympathomimetic effects seen with epinephrine, as it locally reduces blood flow via a peptidergic mechanism on venous smooth muscle, and not by activation of alpha or beta adrenoceptors.

Nasally Administered and Combination Topical Anesthetics

In the past decade, attempts to eliminate the need for injections and improve the effectiveness of topical agents have resulted in two major developments—first, an intranasal preparation to achieve dental anesthetic for maxillary teeth and supporting tissues was recently introduced (Kovanaze®). This product is a combination of a lipophilic, long-acting injectable ester local anesthetic (tetracaine 3%) with oxymetazoline 0.05%, an alpha-1 adrenoceptor agonist commonly available as a vasoconstrictor in nasal decongestants

(e.g., Afrin®). Based on the Phase II clinical trial in 45 adult subjects in need of a single maxillary tooth restorative procedure, 83% of subjects receiving the nasal spray anesthetic did not require rescue local anesthetic injection (Ciancio et al. 2013). A subsequent parallel design study comparing the tetracaine/oxymetazoline combination with a tetracaine-only and saline (placebo) spray, based on need for rescue anesthetic, determined a success rate of 84% for the combination preparation, versus 27.3% success rates for both the tetracaine-only preparation and placebo (Ciancio et al. 2016). In both studies, no serious adverse events were reported.

Initially, these studies were to have included electric pulp testing as a secondary outcome measure, but those data were not reported, and the product's FDA label indications are limited to routine periodontal and restorative and do not include endodontic procedures in maxillary premolar and anterior teeth.

Intranasal local anesthesia has several advantages, the most significant being avoidance of needle insertion, ease of administration, and ability of dental auxiliaries to administer maxillary anesthesia in licensing jurisdictions in which topical anesthetic administration is a permitted duty. There are, however, several disadvantages of the product:

- Limited types of teeth which can be effectively anesthetized (maxillary premolars, canines, and incisors)
- Limited types of procedures which can be accomplished under intranasal local anesthesia
- Significantly higher cost than injectable local anesthetics
- Significantly longer time for onset of anesthesia (up to 14 min total for the two sprays required)
- Need for refrigeration of the product
- Lack of approved indication for younger children

Intranasal anesthesia can be considered as a viable approach for routing restorative procedures and periodontal procedures when needle-phobic patients are being treated or when excessive soft-tissue anesthesia is to be avoided.

The second major development in this area is the widespread availability of combination topical anesthetics, typically produced by compounding pharmacies as extemporaneous preparations made only by prescription from a practitioner.

These "stronger" topical agents have also been diverted to non-healthcare setting by the newer cultural emphasis on cosmetic enhancements of the human body, i.e., tattoos, piercings, and hair removal. For years, 5% lidocaine ointment and 20% benzocaine have served as the mainstays of topical dental anesthesia, but reports of efficacy of combination topicals for insertion of orthodontic intraosseous anchorage devices (resembling mini implants) have also driven the increased use of combination preparations (Reznik et al. 2009). Typically, these preparations combine two topically effective local anesthetics with a vasoconstrictor (e.g., TAC Alternate Gel®, lidocaine+tetracaine+phenylephrine). While effective for obtaining soft-tissue anesthesia for routine procedures, such as SRP and pre-injection anesthesia, these combination products do not facilitate invasive dental procedures. Additionally, the combination of high percentages of local anesthetics results in doses as high as 240 mg of anesthetic per mL.

One such preparation contains lidocaine 12.5%, tetracaine 12.5%, prilocaine 3%, and phenylephrine 3%, for a total of 280 mg of local anesthetic per mL. While brief applications of small amounts of these preparations can be tolerated by adults, this quantity of local anesthetic, if swallowed or if allowed to contact large areas of skin for prolonged periods, could be disastrous in some settings, particularly small children or infants who could swallow the anesthetic.

Dentists should continue to consider emerging evidence for the use of intranasal and combination topical anesthetics for potential applications in general dentistry.

Conclusion

Conventional dental local anesthetics provide excellent pain control for routine dental procedures, and there is little financial incentive for pharmaceutical manufacturers to develop new local anesthetic drug entities for dental indications only. The safe use of these agents must be predicated on the utilization of all appropriate measures to prevent LAST, as the management of severe systemic toxicity is challenging and may require advanced techniques and agents not ordinarily available in dental offices. Dental practitioners should continue to monitor outcomes from randomized, controlled trials and systematic reviews in order to refine their selection and use of currently available local anesthetics.

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Non-opioid Analgesics

Arthur H. Jeske

Principles of Analgesic Therapy

There are several important principles that must be considered prior to prescribing an analgesic for a dental patient:

1. Analgesics are adjuncts to caries removal and surgical interventions (tooth extraction, pulpectomy, incision and drainage) and should not be used in place of these procedures in the management of acute dental pain.
2. The selection of an analgesic must be based upon the patient's medical history and current disorders and take into account the possibility of adverse events and adverse drug/drug interactions.
3. An analgesic regimen should be based upon the expected level and duration of pain, taking into consideration systemic conditions such as cardiovascular, gastrointestinal, and allergic conditions and defined clinical endpoints (reduction of pain, swelling).
4. While no longer recommended as drugs of first choice for dental pain, the opioids, particularly those marketed in combination with acetaminophen, remain important alternatives when NSAIDs are inappropriate due to allergy and other medical conditions (described below).

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Pharmacologic Characteristics of NSAID Analgesics for Acute Postoperative Dental Pain

There are several chemical classes of NSAIDs, many of which are used in various medical conditions, especially osteoarthritis. The most important class for the control of pain in dentistry is the propionic acid group, which includes ibuprofen (Advil®), naproxen (Aleve®), and ketoprofen (Orudis®). All of these agents possess analgesic, anti-inflammatory, antipyretic, and antiplatelet therapeutic actions and are ideally suited for applications in inflammatory dental conditions (acute apical periodontitis, symptomatic irreversible pulpitis). They act by inhibition of cyclooxygenase (COX-1 and COX-2), which reduces the synthesis of prostaglandins (PGs), and their analgesic action is attributable primarily to a reduction of PGE2 and F2α, which are synthesized rapidly after tissue damage and sensitize nociceptive nerve endings to a wide variety of noxious stimuli. Importantly, inhibition of PG synthesis occurs relatively early in painful inflammatory conditions, so NSAID therapy should commence as early as feasible in pain management.

A recent overview of systematic reviews provides practitioners with a wealth of high-level evidence for the comparative efficacy of various oral analgesics, based primarily on the third molar impaction surgery model of assessing acute postoperative pain (Moore et al. 2015a).

When using this reference, it is helpful to consider the Number Needed to Treat (NNT) values for the various analgesics, with values <2 being generally considered among the best for single-dose outcomes. In regard to these values, NNT refers to the number of subjects who need to receive an intervention in order to see a define beneficial effect, which in these pain trials is a reduction of pain level by at least 50%. Mathematically, NNT is defined simply as:

NNT = 1/ARR, where ARR is the absolute risk reduction (difference between active treatment and placebo).

For example, where an active (investigational) drug produces a 50% or greater reduction in pain level in 70% of the subjects and the placebo produces a 50% or great reduction in pain in 15% of the subjects, NNT is:

$$\text{NNT} = 1/0.7 - 0.15, \text{ or } 1/0.55, \text{ or } 1.8.$$

In this example, NNT would predict that the active drug would need to be given to only 1.8 individual patients (less than 2) to see the defined benefit. NNT has both advantages and disadvantages, and an advantage is that it addresses both clinical and statistical significance in an easily understood manner. However, its practical significance may vary with the significance of the disease/patient conditions, and it is only useful to compare NNT values among various interventions when the treatments are for the same condition, severity, and outcome measure (Schechtman 2002). It is also important to note that in order for a drug or drug combination to have been included in this study, outcomes must be from at least 2 randomized, controlled studies with at least 200 subjects total. The outcomes from reference (Aminoshariae et al. 2016b) are summarized in Table 1. When considering these outcomes, it is important to note that results from studies of single-dose oral analgesics used in the third molar impaction model may differ from the findings of studies done in endodontic patients. Typically, studies of relief of postoperative endodontic pain have focused on higher (e.g., 600 mg) doses of ibuprofen than those from studies highlighted in Table 1. This may be based upon the possibility that higher doses of NSAIDs provide a greater anti-inflammatory effect, in addition to their analgesic effect, or the perceived need for higher dosages may be based upon the fact that pain of endodontic origin is typically associated with a much longer duration of preoperative pain, as opposed to the pain of third molar impaction surgery, which is usually exclusively postoperative and which does not involve the prolonged period of bacterial-induced inflammation or invasive dental procedures associated with pulpal disease.

Table 1 Selected NNT values for common single-dose non-opioid oral analgesics used in dentistry, as reported in Moore et al. (2015a) (APAP denotes acetaminophen/acetyl para amino phenol)

Drug	NNT	Confidence interval 95%
Diclofenac 100 mg	1.9	1.7–2.3
Diflunisal 1000 mg	2.1	1.8–2.6
Ibuprofen 200 mg	2.9	2.7–3.2
Ibuprofen 200 mg + 100 mg caffeine	2.1	1.9–3.1
Ibuprofen 400 mg	2.5	2.4–2.6
Ibuprofen 200 mg + APAP* 500 mg	1.6	1.5–1.8
Ibuprofen 400 mg + APAP 1000 mg	1.5	1.4–1.7
Ketoprofen 100 mg	2.1	1.7–2.6
Naproxen 500–550 mg	2.7	2.3–3.3
APAP 500 mg	3.5	2.7–4.8
APAP 1000 mg	3.6	3.2–4.1

When considering the NNT values presented in Table 1, the reader should consider the fact that these numbers apply to *single* oral doses of these analgesics, with pain responses assessed over a 4- to 6-h postoperative time interval and that the subjects in the studies used in the calculations of these NNT values were *fasting.*

Acetaminophen

High-level scientific evidence from systematic reviews of acute postoperative pain in adults suggests that, based on number needed to treat

(NNT), acetaminophen administered alone is not a particularly good analgesic (Moore et al. 2015a). This has been confirmed in randomized controlled trials of post-endodontic pain as well (Elzaki et al. 2016). However, when used in combinations, acetaminophen appears to act synergistically with both NSAIDs and opioid analgesics and the combination of 200–400 mg ibuprofen plus 500–1000 mg acetaminophen (taken at the same time) results in the best NNT values in the oral surgical pain model (Moore et al. 2015a). Additionally, this combination does not result in adverse effects greater than those observed in placebo groups when used on a short-term basis (Moore et al. 2015b). However, it should also be noted that the maximum daily adult dose of acetaminophen from all sources (Rx and OTC) should not exceed 4000 mg (Jeske 2017; Moore et al. 2015a). Hepatotoxicity may occur from excessive acetaminophen intake or from interactions with chronic alcohol use. While unusual, allergy to acetaminophen can occur and would absolutely contraindicate the use of this agent.

A summary of the comparative pharmacologic characteristics of propionic acid NSAIDs, acetaminophen, and opioid analgesics is presented in Table 2.

Prescribing Considerations

1. For the management of acute postsurgical dental pain (including pain of endodontic origin), in the absence of any significant contraindications, therapy should begin with a standard dose of a combination, orally administered first-choice agents (ibuprofen with acetaminophen) (Aminoshariae et al. 2016a, b; Elzaki et al. 2016; Smith et al. 2017).
2. For optimal pain relief, the combination of 200–400 mg ibuprofen with 500–1000 mg acetaminophen has been shown to provide pain relief that is superior to virtually all acetaminophen/opioid combinations and COX-2 selective NSAIDs (Moore et al. 2015a).
3. Because peak pain associated with dental extractions appears to occur within the first 4–8 h postoperatively and then decline over the next 2–3 days, short-term administration of the ibuprofen/acetaminophen combination can be employed.
4. A need for a sedative effect, especially in the first 24 h postoperatively, may warrant the addition of an opioid analgesic in combination with the NSAID, when the patient's activities would not be affected by possible CNS depression.

Table 2 Comparative pharmacologic characteristics of nonsteroidal anti-inflammatory drugs (NSAIDs)[a], acetaminophen, and opioid analgesics available in the USA (Jeske 2017)

Characteristic	NSAIDs	Opioids	Acetaminophen	Comment
Available OTC	Yes	No	Yes	
Tolerance, dependence	No	Yes	No	Opioid tolerance and dependence are unlikely to occur with short-term use (<5 days)
CNS depression	No	Yes	No	A sedative effect of opioids may be desirable in some circumstances
Anti-inflammatory	Yes	No	No	Principal advantage of NSAIDs
Antipyretic	Yes	No	Yes	Most NSAIDs have this effect Beneficial in the presence of infection
Analgesic	Yes	Yes	Yes	NSAIDs act primarily peripherally at the site of tissue injury, while opioids act centrally (CNS). Combinations are generally superior to single-agent regimens
Antiplatelet agents (including aspirin)	Yes	No	No	Increased bleeding risk is associated with NSAIDs, primarily if taken preoperatively; the effect is reversible (unlike aspirin, which is irreversible)
GI dysfunction	Yes	Yes	No	In addition to nausea and vomiting, opioids are associated with constipation. NSAID-related GI irritation is typically seen during prolonged administration (>5 days)

[a]Propionic acid class

5. Warnings with analgesic therapy should be issued verbally and in writing on the prescription. They should include the possible development of allergic reactions, as well as GI disturbances, increased bleeding risk, and the risk of adverse interactions between acetaminophen and alcohol and acetaminophen overdose.
6. Whenever possible, analgesics should be taken on an empty stomach with a glass of water in order to hasten the dissolution of the dose form and delivery of the drug from the stomach to the small intestine.
7. To extend duration of action to >8 h, a long-acting NSAID at a higher dose (diflunisal 1000 mg) or an NSAID-acetaminophen combination at a higher dose (ibuprofen 400 mg + acetaminophen 1000 mg) can be employed.
8. Caution is advised in patients who are regularly taking NSAIDs for systemic disorders, e.g., osteoarthritis, as adding a second NSAID to their medication regimens puts them at risk for serious gastrointestinal irritation and possible ulceration, as well as nephritis and renal failure, and/or severe bleeding. In these patients, alternative analgesics (e.g., acetaminophen, opioids) should be considered and can be added to the patient's NSAID regimen if no contraindications exist.

Adverse Effects

NSAID analgesics, as prescribed in dentistry, are generally well tolerated. With the exception of allergy, most adverse effects from short-term use of NSAIDs are related to their effects on the gastrointestinal tract and platelets. NSAIDs inhibit the formation of gastroprotective PGs, and this irritant effect, combined with their antiplatelet effect, can result in ulcerations and GI bleeding. Short-term use of NSAIDs has been shown to be relatively safe when administered for dental pain (Aminoshariae et al. 2016a).

Ingestion of high doses of NSAID analgesics is associated with nephropathy, and the risk of this complication increases in elderly patients, as well as patients who are dehydrated or have preexisting renal insufficiency, heart failure, or diabetes (Kharasch 2004). It should be noted that dehydration could be present in individuals with symptomatic irreversible pulpitis who have experienced diarrhea and/or nausea and vomiting (possibly induced by self-prescribed antibiotics and/or analgesics) and who are not well nourished/hydrated due to dental pain. This is particularly problematic when patients have ingested over-the-counter NSAIDs or acetaminophen before receiving dental treatment.

Since renal blood flow and urine formation are partly regulated by physiologic PGs, blood pressure may be elevated by the ingestion of NSAIDs, and this should be considered when designing an analgesic regimen for patients with hypertension and other cardiovascular disorders.

Bleeding is associated with all NSAIDs, and increased intraoperative and postoperative bleeding must be anticipated and dealt with effectively, including the use of careful surgical technique, suturing, and other hemostatic measures (oxidized cellulose packs).

The risk of allergic and adverse respiratory reactions to NSAIDs should be evaluated through a careful medical history, especially in patients with a prior history of aspirin allergy, asthma, and reactive airway disease.

Pregnancy constitutes a contraindication to the use of NSAIDs, particularly in the first and third trimesters. Among the commonly used NSAIDs, observed differences in GI irritation only become manifest after prolonged therapy (>30 days). Typically, another drug to reduce GI irritation (e.g., misoprostol) is only prescribed during longer-term administration.

In summary, when used short term for the management of acute postoperative pain in dentistry, most NSAIDs and NSAID-acetaminophen combinations produce no greater incidence or severity of adverse effects than placebo. The evidence for

this is found in the overview of systematic reviews published by Moore et al. It should be noted, however, that this same review determined that some commonly utilized analgesics produce significantly more adverse events than placebo, and these agents include aspirin 1000 mg, diflunisal 1000 mg, all opioids, and fixed-dose combination products containing opioids (Moore et al. 2015b).

Adverse Drug Interactions

NSAID analgesics are capable of adversely interacting with other dental and medical drugs, both through pharmacodynamic and pharmacokinetic mechanisms. The most significant adverse interactions for commonly prescribed NSAID analgesics are listed in Table 3.

Corticosteroids

In some cases, anti-inflammatory corticosteroids may be beneficial in providing short-term pain relief, particularly in cases of inflammation associated with apical periodontitis, acute apical abscess, and third molar extraction. Based on recent scientific evidence, both methylprednisolone and dexamethasone can be utilized in such situations, although an injection is required (Bane et al. 2016; Chen et al. 2017). A recent systematic review determined that preoperative administration of corticosteroids (4 or 8 mg oral dexamethasone, 40 mg parenteral dexamethasone) was effective in reducing in post-endodontic pain (Aminoshariae et al. 2016b). Orally administered corticosteroids can be used to suppress inflammation, both pre- and postoperatively, and this use is commonly exploited in third molar surgery.

Table 3 Clinically significant drug interactions involving NSAID analgesics used in dentistry [modified from Ciancio (2014)][a]

Primary drug	Action	Interaction (& effect)
Alcohol	Enhanced by NSAIDs	Increased GI irritation, nausea, GI pain, bleeding
Diuretics, antihypertensive drugs	Antagonized by NSAIDs	Increased salt and water retention with increased blood pressure
Coumarins (including warfarin)	Enhanced by NSAIDs	Increased risk of bleeding
Antiplatelet agents (aspirin, clopidogrel)	Enhanced by NSAIDs	Increased risk of bleeding; increased risk of thromboembolism (ibuprofen blocks the antiplatelet effect of aspirin when the drugs are taken concurrently)
Direct oral anticoagulants (rivaroxaban, dabigatran)	Enhanced by NSAIDs	Increased risk of bleeding
Potassium-sparing diuretics	Enhanced by NSAIDs	NSAIDs may increase serum potassium levels
Potassium supplements	Enhanced by NSAIDs	NSAIDs may increase serum potassium levels
Cancer chemotherapeutic agents	Enhanced by NSAIDs	Increased risk of GI ulceration
Selective serotonin reuptake inhibitors (SSRIs)	Enhanced by NSAIDs	Increased risk of GI ulceration and bleeding
Corticosteroids	Enhanced by NSAIDs	Increase salt and water retention; increased risk of GI ulceration

[a]Less significant drug interactions are also possible—the clinician should consult the complete prescribing information for all drugs prescribed. For elderly and medically compromised patients with systemic disease that could impact drug metabolism and/or excretion, consultation with the patient's physician is recommended

The characteristics of corticosteroids are described in greater detail in the chapter "Endocrine Drugs of Significance in Dentistry."

Preemptive Analgesia

NSAIDs have been evaluated for use preemptively (preoperative administration to reduce postoperative pain). The reader is referred to an excellent update on this topic by Lieblich (2017). Typically, single-dose ibuprofen 400–600 mg, administered approximately 1 h before a procedure, is recommended, based on limited evidence, although there is limited evidence that single NSAID administration, including ibuprofen and ketorolac, is not effective for this use (Aminoshariae et al. 2016b). When used in this manner, intraoperative bleeding is increased, and the practitioner should be prepared to take additional hemostatic measures during the procedure in patients who are undergoing surgical procedures and who have received preoperative NSAID medications, and this effect has also been demonstrated in orthodontic patients following placement of bands or separators. It should be noted that evidence is lacking for a similar preemptive analgesic effect of acetaminophen when administered preoperatively.

Other strategies for preemptive analgesia include administration of long-acting local anesthetics (e.g., bupivacaine), a positive effect occurring even when used with general anesthesia for extraction of impacted third molar teeth.

Conclusion

Dentists should continue to consider emerging evidence for the use of non-opioid analgesics, especially in view of the ever-increasing problem of opioid abuse and diversion.

Dentists can now confidently prescribe an NSAID or recommend OTC (e.g., ibuprofen + acetaminophen) combinations for excellent relief of acute dental pain, based on high-level scientific evidence. This evidence is readily accessible by searching the PubMed database of the US National Library of Medicine and entering the name of a specific drug within the following search terms:

"Single dose oral _____ for acute postoperative pain in adults."

Current evidence supports the use of an NSAID (ibuprofen), in combination with acetaminophen if possible as first-choice therapy for the management of acute postoperative dental pain in adults. In children, a single NSAID is currently supported by the American Academy of Pediatric Dentistry's Guideline on Pain Management as the first-line agent in the treatment of acute mild to moderate postoperative pain (American Academy of Pediatric Dentistry 2017).

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Opioid Analgesics and Other Controlled Substances

Arthur H. Jeske

Principles of Opioid Prescribing

There are several important principles that must be considered prior to prescribing an opioid analgesic for a dental patient (American Association of Oral and Maxillofacial Surgeons 2017):

1. A nonsteroidal anti-inflammatory drug (NSAID) may be used preoperatively to reduce the severity of postoperative pain.
2. Perioperative corticosteroids can be used to reduce swelling and other discomfort after impaction surgery.
3. Long-acting local anesthetics may delay the severity and onset of postoperative pain.
4. Long-acting, extended-release opioids should not be used for acute pain.
5. Unless contraindicated, NSAIDs are first-choice analgesics for acute pain.
6. NSAIDs and acetaminophen can be used in combination to improve analgesic outcomes, although dosage must be carefully monitored.
7. Short-acting opioids may be appropriate for acute "breakthrough" pain.
8. Practitioners may be required to use prescription drug monitoring programs, and these programs can be useful to detect opioid misuse or addiction.
9. All instructions for patient analgesia and analgesic prescriptions should be carefully documented.

Pharmacologic Characteristics of Oral Opioids for Acute Postoperative Dental Pain

There are three major classes of opioids—natural opium derivatives, semisynthetic opioids, and synthetic opioid agonists. In dentistry, the most important of these is the semisynthetic class, which includes codeine, hydrocodone, and oxycodone. Synthetic agents such as fentanyl and meperidine are used primarily by the intravenous route and are not covered in this chapter. The most commonly used pharmaceutical forms of opioids for the control of pain in dentistry are combinations of the opioid component with acetaminophen (e.g., Vicodin®). All of these agents act nonselectively at mu, kappa, and delta opioid receptors and possess analgesic, antitussive, and sedative therapeutic actions but lack the beneficial anti-inflammatory and antipyretic therapeutic actions seen with the NSAIDs. The addition of acetaminophen to an opioid pain control regimen gains two specific advantages—first, the acetaminophen possesses antipyretic activity and, second, acetaminophen and opioids appear to act

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synergistically and therefore are capable of producing levels of pain relief not achievable with even higher doses of either agent taken alone.

Non-Analgesic Actions and Adverse Effects

Depending on the dose and the degree of opioid tolerance in an individual, the following non-analgesic effects are characteristic of most opioids: dizziness, somnolence, nausea, vomiting (caused by stimulation of the chemoreceptor trigger zone in the brainstem), respiratory depression (initially caused by reduction of the sensitivity of the respiratory center to carbon dioxide), miosis, constipation, cardiovascular depression, and, eventually, loss of consciousness, coma, and death (usually due to cardiorespiratory arrest). Virtually all of these actions are the result of drug binding to the mu opioid receptor, and virtually all can be reversed by the administration of sufficient doses of narcotic antagonists (e.g., naloxone).

Consideration must be given to the potential for respiratory depression in individuals who present with a compromised airway (e.g., Mallampati Class III) and those with obstructive sleep apnea (OSA). While there are many factors that determine the potential for postoperative opioid toxicity in patients with OSA, current evidence suggests a need for multimodal postoperative pain control in these individuals, including local anesthetics and non-opioid analgesics (e.g., NSAIDs) (Maund et al. 2011; American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea 2014).

Comparative Efficacy of Opioids

High-level scientific evidence from systematic reviews of acute postoperative pain in adults suggests that, based on number needed to treat (NNT) that single opioids and opioid-acetaminophen combinations are generally equivalent to single NSAIDs but are inferior to pain relief outcomes associated with some NSAIDs and the combination of ibuprofen and acetaminophen (Moore et al. 2015). These outcomes are particularly relevant to acute postoperative dental pain, as the majority of the randomized controlled trials that comprise these systematic reviews and meta-analyses were conducted using the third-molar impaction surgery pain model. A summary of the comparative efficacy of various analgesics based on number-needed-to-treat values for single doses of various opioids and opioid combination products suggests that oxycodone, in combination of higher doses of acetaminophen, appears to be worth of consideration when an NSAID cannot be used for acute postoperative dental pain (Table 1).

Some caution must be observed when interpreting the NNT values shown in Table 1.

NNT is a relative measure of the reduction of pain level following a single dose of an analgesic and does not quantify the subjective relief of pain that may be produced by drugs with significant CNS depressant effects, such as opioids. While a given opioid analgesic's NNT (as reported above) may be less favorable, i.e., higher than a non-opioid's, this value alone does not predict the entire pain-relieving effect, which varies with the opioid's alteration of the central

Table 1 Number-needed-to-treat (NNT) values for opioid and opioid-acetaminophen combination analgesics vs. placebo, based on overview of systematic reviews and meta-analyses (Gaskell et al. 2009; Moore et al. 2015)

Drug	NNT	Confidence interval 95%
Oxycodone 5 mg + APAP 325 mg	5.5	na
Oxycodone 10 mg + APAP 650 mg	2.7	2.4–3.1
Oxycodone 10 mg + APAP 1000 mg	1.8	1.6–2.2
Oxycodone 15 mg	4.6	2.9–11
Codeine 30 mg + APAP 300 mg	6.9	4.8–12
Codeine 60 mg + APAP 600–650 mg	3.9	2.9–4.5
Codeine 60 mg + APAP 800–1000 mg	2.2	1.8–2.9
Codeine 60 mg	12	8.4–18

APAP acetaminophen/acetyl para amino phenol

processing of pain stimuli and the interpretation of the pain. This same phenomenon also makes the quantitative study of opioid analgesia, based on VAS instruments and other tests, more challenging.

Of interest for practitioners in the United States is the absence of systematic reviews and meta-analyses for pain relief outcomes using hydrocodone and hydrocodone-acetaminophen combinations. This is likely due to the fact that hydrocodone has been banned or is unavailable in many other countries for some time. It is possible to glean some moderate-quality evidence for the combination of hydrocodone and acetaminophen from a limited number of clinical trials. For example, in a comparison of celecoxib 400 mg with hydrocodone and hydrocodone-acetaminophen in outpatient orthopedic patients, hydrocodone compared favorably to placebo and performed equally well with celecoxib over the first 8 h postoperatively but was inferior to celecoxib at subsequent test intervals, and the hydrocodone products produced a significantly higher incidence of adverse effects. Similarly, international studies of hydromorphone (Dilaudid®) are not available in systematic reviews, and this agent, therefore, is not recommended as evidence-based pain control in dentistry.

Prescribing Considerations

1. For acute postoperative pain, only short-term administration of the analgesic should be needed.
2. A need for a sedative effect, especially in the first 24 h postoperatively, may warrant the use of an opioid analgesic in combination with acetaminophen or an NSAID, when the patient's activities would not be affected by possible CNS depression and when no other contraindications exist.
3. Warnings with opioid analgesic therapy should be issued verbally and in writing on the prescription. They should include the prohibition of alcohol intake during opioid treatment, as well as possible interactions with other CNS depressant drugs, development of allergic reactions, as well as possible nausea and vomiting. The adverse interactions between acetaminophen and alcohol underscore the need for warning the patient about alcohol ingestion.
4. Pregnancy constitutes a contraindication to the use of NSAIDs, particularly in the first and third trimesters. Among the commonly used NSAIDs, observed differences in GI irritation only become manifest after prolonged therapy (>30 days). Typically, another drug to reduce GI irritation (e.g., misoprostol) is only prescribed during longer-term administration.
5. Scientific evidence to support the selection of hydrocodone over another opioid, e.g., oxycodone, is lacking. While there are a limited number of systematic reviews and meta-analyses for oxycodone, this type of evidence has not been available for hydrocodone, partly because the drug is not available in many countries other than the United States. For this reason, and because oxycodone responses appear to be less susceptible to CYP-related pharmacogenetic variations, the author recommends the use of immediate-release forms of oxycodone as an evidence-based opioid analgesic to be used in combination with acetaminophen for the management of acute postoperative pain in adults.
6. Systemic diseases must be taken into consideration when prescribing opioids. Liver disease can compromise the metabolic disposition of opioids, as well as first-pass elimination during the initial absorption of orally administered opioids. In such cases, the dose should be reduced and the dosage interval increased to reduce the potential for toxicity. In patients with kidney disease, opioids with active metabolites (e.g., codeine, meperidine, and morphine) should be avoided, as these metabolites are ordinarily excreted in the urine (Wie 2017).
7. When prescribing oxycodone, the prescription should note that an immediate-release form, not an extended-release one (e.g., Oxycontin®), is to be issued to the patient.

An example of an evidence-based prescription for an opioid for short-term management of acute postoperative pain in an otherwise healthy adult without contraindications is illustrated in Fig. 1. It should be noted that the rationale for the use of this combination is based upon data from the overview analysis of systematic reviews by Moore et al. (2015) and is designed to provide effective reduction in pain level and to take advantage of the synergistic actions of opioids combined with acetaminophen and the prolongation of effect at the relatively higher dose of each component.

The prescription illustrated here limits the total daily exposure of the patient to 3000 mg (3 doses of 1000 mg over 24 h), and it limits the total amount of opioid dispensed to less than 10 tablets. If a longer duration of pain control is needed, the number of opioid dosage units can be increased proportionately.

Rx

Oxycodone 5 mg immediate-release tabs

Dispense 6 (six) tabs

Sig: Take 2 (two) tabs with 1,000 mg acetaminophen every 8 hours for acute dental pain.

Warnings: Do not drive or operate machinery while taking. Do not drink alcohol or use other CNS depressants while taking. May be habit forming.

Fig. 1 Sample prescription for acute postoperative dental pain using an opioid in combination with over-the-counter acetaminophen

Adverse Drug Interactions, Opioid Pharmacogenetics

Opioid analgesics are capable of adversely interacting with other dental and medical drugs, both through pharmacodynamic and pharmacokinetic mechanisms (Haas 1999). The most significant adverse interactions for commonly prescribed opioids are found in Table 2.

Less significant drug interactions are also possible—the clinician should consult the complete prescribing information for all drugs prescribed. For elderly and medically compromised patients with systemic disease that could impact drug metabolism and/or excretion, consultation with the patient's physician is recommended (Haas 1999).

Among the commonly prescribed opioids, three are prodrugs, i.e., they are metabolically converted from an inactive/less active parent form into an active metabolite. These agents include codeine (metabolized to morphine), hydrocodone (metabolized to hydromorphone), and tramadol (metabolized to the active M-1 opioid structure). All of these reactions depend on the activity of the cytochrome P450 isoform CYP 2D6. Figure 2 illustrates the oxidation of hydrocodone by this enzyme.

Variations in patient responses to these agents is based upon 4 levels of CYP 2D6 activities, and patients can be classified as either poor metabolizers, intermediate metabolizers, extensive metabolizers, or ultrarapid metabolizers (Bernard et al. 2006). Based on the relative rates of this enzymatic drug activation reaction, ultrarapid metabo-

Table 2 Clinically significant drug interactions involving opioid analgesics (Haas 1999)

Primary drug	Significance rating	Interaction and effect
Alcohol	2/moderate	Increased CNS depression, dizziness, somnolence
Antihistamines	2/moderate	Increased salt and water retention with increased blood pressure
MAO inhibitors	1/severe	Increased risk of seizures (meperidine)
Selective serotonin reuptake inhibitors	2/moderate	Increased CNS depression; possible reduced analgesic action (hydrocodone)
Sedative/hypnotic drugs	1/severe	Increased CNS depression, risk of cardiorespiratory depression/arrest
Muscle relaxants	1/severe	

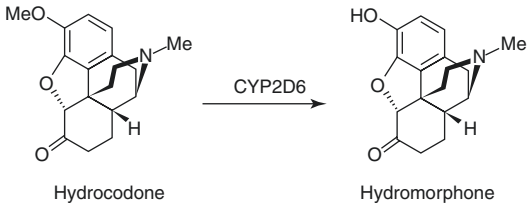

Fig. 2 Oxidative demethylation of hydrocodone to hydromorphone by the action of CYP2D6 enzyme

lizers would be expected to exhibit exaggerated analgesic responses, as well as exaggerated adverse effects. Stauble et al. (2014) demonstrated that pain relief from the administration of hydrocodone in female patients following Caesarean section was correlated with plasma concentrations of the hydromorphone metabolite, not the parent molecule hydrocodone, establishing hydrocodone as a prodrug, i.e., a drug which must be metabolically converted to an active metabolite to achieve a therapeutic effect. The incidence of the variations among these CYP 2D6 phenotypes is described and in the study of Stauble et al.

The distribution of CYP 2D6 among females in the study was 60% extensive metabolizers, 30% intermediate metabolizers, 3% poor metabolizers, and 7% ultrarapid metabolizers, and this is typical of the distribution for the general population of the United States (Bernard et al. 2006; Stauble et al. 2014).

At present, because of the limited availability of pharmacogenetic testing (primarily associated with testing costs), dentists are not able to base opioid selection on phenotype.

Sedative/Hypnotics

In the past 20 years, both the efficacy and the safety of benzodiazepines for routine sedation of dental outpatients have been unequivocally established. While there are many benzodiazepines on the market, their principal clinical differences derive primarily from differences in pharmacokinetics and their propensity to induce sleep versus relief of anxiety, i.e., their usefulness as hypnotics for the management of insomnia or antianxiety actions with less impact on consciousness. At this time in the United States, the benzodiazepines most commonly used in the dental setting include:

- Diazepam (e.g., Valium®)
- Lorazepam (e.g., Ativan®)
- Midazolam (e.g., Versed®)
- Triazolam (e.g., Halcion®)

There are very few randomized controlled trials of these drugs for dental outpatient sedation, and none carry an FDA-approved label indication specifically for dental sedation. However, this "off-label" use has become accepted over time through case studies and retrospective safety analyses (Dionne et al. 2006; Ehrich et al. 1997).

The clinical pharmacologic properties of these representative sedative/hypnotics are found in Table 3.

Unlike diazepam and lorazepam, midazolam and triazolam have a rapid onset, even when used orally, and are subject to a high first-pass effect due to rapid inactivation of approximately 25% of the absorbed dose by hepatic cytochrome P450 enzymes (Becker 2011). It should be noted that administration of the oral dose form sublingually effectively bypasses initial hepatic degradation and results in higher peak plasma levels with intensified sedative actions (Becker 2011).

The safety and efficacy of benzodiazepines and related drugs (e.g., zolpidem) for sedation of anxious dental patients has been validated over the past two decades. Following the introduction of triazolam (Halcion®) on the US market in 1982 for the short-term management of insomnia, the

Table 3 Pharmacologic properties of selected benzodiazepine sedative/hypnotic agents

Drug	Adult dose	Plasma half-life (h)	Duration of action
Diazepam	5–15 mg	20–70	2–3 h
Lorazepam	2–4 mg	10–20	8–12 h
Midazolam[a]	0.25–0.5 mg/kg	1–5	30–45 min
Triazolam	0.125–0.5 mg	1–5	6–8 h

[a]Approved in the United States for oral use only in patients under the age of 18

dental profession began to use it for preoperative sedation of dental outpatients, recognizing that its short duration of action and absence of active metabolites were favorable when compared with longer-acting benzodiazepines with active metabolites, such as diazepam. In 1997, its comparative safety and efficacy with diazepam in patients with documented anxiety undergoing endodontic treatment were studied (Ehrich et al. 1997). Oral doses of 0.25 mg triazolam were found to be more effective than and equally safe with orally administered 5 mg diazepam and without a prolonged recovery period. Subsequently, the Dental Organization for Conscious Sedation (DOCS) protocols were promulgated, with the recommendation that patient responses to the initial sedative doses be carefully monitored prior to administration of an additional dose of sedative (Gordon et al. 2007).

The most significant adverse drug interactions involving benzodiazepines involve excessive CNS depression with possible cardiorespiratory depression when they are co-administered with other CNS depressants, particularly opioids, alcohol, and barbiturates. Additionally, serious pharmacokinetic interactions may occur, particularly for benzodiazepines with high oral bioavailability and, therefore, high susceptibility to agents which reduce the "first-pass" effect (hepatic extraction of the drug as it passes from the gastrointestinal tract to the circulation) (e.g., midazolam and triazolam). Of particular note in dentistry are the effects of macrolide antibiotics and azole-type antifungal drugs. According to the manufacturer's data for oral midazolam, erythromycin, administered at doses of 500 mg three times daily, increases the C_{max} of oral midazolam by approximately 170%, while once-daily doses of ketoconazole increase the C_{max} by over 300%. Increases in area under the curve (AUC) for these same interactions were 281–341% and 1490%, respectively. Obviously, the doses of midazolam administered to patients taking these antibiotics and antifungal agents would need to be significantly reduced to avoid excessive sedation. The emergency antidote for benzodiazepine overdose, flumazenil, is described in greater detail in chapter "Basic Emergency Drugs and Non-intravenous Routes of Administration".

All benzodiazepines commonly used for dental outpatient sedation are Schedule IV controlled substances in the United States and may produce tolerance and dependence when used for prolonged periods. The short-term administration of these drugs for dental outpatient sedation is not associated with tolerance or dependence. One of these agents—alprazolam (Xanax®)—is currently among those drugs being marketed in large quantities through illicit channels, even in "counterfeit" forms. Benzodiazepines are now frequently implicated in cases of drug overdose deaths (Lembke et al. 2018).

Carisoprodol

Carisoprodol (e.g., Soma®) is now classified by the US Drug Enforcement Administration as a Schedule IV controlled substance. It is included here because it may be diverted to illicit channels and co-abused with other addictive substances, including opioids and/or benzodiazepines. Carisoprodol is a centrally acting skeletal muscle relaxant whose precise mechanism of action is unknown. It is indicated as an adjunct to rest, physical therapy, analgesics, and other measures for the relief of discomfort of acute, painful musculoskeletal conditions. Adverse effects include a high incidence of somnolence and occasional tachycardia, facial flush, dizziness, headache, light-headedness, dermatitis, nausea, abdominal cramps, and dyspnea. Carisoprodol also possesses properties of physical and psychological dependence, and its frequent co-abuse with opioids and benzodiazepines as part of this "Holy Trinity" of co-abused drugs led to its being classified by US Drug Enforcement administration as a Schedule IV controlled substance in 2012 (Horsfall and Sprague 2017).

Carisoprodol interacts with benzodiazepines in the brain to produce a synergistic increased in dopamine in the nucleus accumbens with respiratory depression, increasing the likelihood of respiratory arrest when co-ingested with opioids (Horsfall and Sprague 2017). This reclassification reportedly has resulted in fewer cases of carisoprodol overdose in some states (Sun et al.

2017). These characteristics distinguish the drug from other types of commonly prescribed skeletal muscle relaxants, which are not currently classified as controlled substances.

Withdrawal from sustained abuse of carisoprodol results in a severe syndrome resembling neuroleptic malignant syndrome (Paul et al. 2016). Management of carisoprodol withdrawal may require more extreme pharmacologic measures than simply administering an i.v. benzodiazepine, including the infusions of high doses of propofol, fentanyl, ketamine, quetiapine, and haloperidol (Vo et al. 2017).

Prescription Monitoring Programs

Currently, there are many states in the United States which have now implemented prescription drug monitoring programs designed to continuously assess the prescribing patterns for controlled substances among healthcare providers, including veterinarians, in their jurisdictions. Frequently operated by state boards of pharmacy, these programs use electronic databases to track all prescriptions for controlled substances issued in their jurisdictions and can be used by state regulatory boards and law enforcement agencies to identify inappropriate patters of prescribing. Examples of such inappropriate patterns could include:

- One patient receiving prescriptions for a controlled substance from multiple practitioners within the same time period
- Multiple patients with the same address receiving prescriptions for controlled substances
- Prescriptions for controlled substances that are not within the scope of practice of a particular type of practitioner (e.g., an amphetamine prescription issued by a dental provider)

Data on controlled substance prescriptions issued by dentists over a 2-year period in a US state (South Carolina) were analyzed and published in 2016 (McCauley et al. 2016). That study determined that 653,650 prescriptions were issued by dentists, and, significantly, 113,818 patients had received multiple opioid prescriptions within a 30-day period. These data can be used to inform the dental profession about the extent to which prescribing controlled substances is problematic in a given geographic area, and prescription monitoring programs have the capability to issue alerts on certain patients who appear to be engaging in "doctor shopping," drug diversion, and drug abuse. A survey of members of the US National Dental Practice-Based Research Network found that higher levels of opioid prescribing were associated with less consistent implementation of the use of prescription drug monitoring programs (McCauley et al. 2018).

Conclusion

Dentists should continue to consider emerging evidence for the use of non-opioid analgesics, especially in view of the ever-increasing problem of opioid abuse and diversion.

While NSAIDs or NSAID-acetaminophen combinations provide excellent relief of acute dental pain, they cannot be used in a significant number of patients who have contraindications (e.g., gastrointestinal or renal disease), and opioids remain the mainstay of therapy in this population, preferably when used in combination with acetaminophen for acute postoperative dental pain in adults. In children, the traditional use of codeine in combination with acetaminophen is now questionable, based on the possibility that children who are ultrarapid metabolizers for CYP 2D6 may experience cardiorespiratory arrest when this drug is used.

Practitioners who carefully consider the CNS depressant properties of opioid analgesics can safely and effectively prescribe a single, immediate-release opioid with an effective dose of an over-the-counter NSAID or acetaminophen with confidence, based upon robust scientific evidence. Minimizing the amount of opioid dispensed to the patient and utilization of prescription monitoring programs when available can help reduce abuse and diversion of prescription opioids.

At present, single benzodiazepines remain drugs of choice for routine sedation of dental

outpatients, based on known efficacy and safety, and relatively low risk of abuse when prescribed in very small quantities. However, the practitioner must now consider the increasing prevalence of drug overdose reactions involving benzodiazepines when prescribing them.

Carisoprodol has few indications in dentistry, and, based on its recent classification as a Schedule IV controlled substance, the dentist should carefully consider the possibility of abuse and diversion associated with it.

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Antibiotics and Antibiotic Prophylaxis

Arthur H. Jeske

Introduction and Principles

Antibiotics play an important role in the management of odontogenic infections (primarily as adjuncts to surgical procedures) and for the prevention of systemic infections arising from bacteremias associated with dental procedures in patients at risk for serious systemic infective complications (e.g., infective endocarditis). However, dental professionals must be vigilant in the use of these drugs to avoid their overuse and help address the serious issue of increasing antibiotic resistance (Antibiotic Resistance Threats in the United States 2013). Since the approval of phenoxymethyl penicillin (penicillin V) by the Food and Drug Administration in 1956, dental infections in outpatients have been managed successfully with a penicillin or another oral narrow-spectrum antibiotic, which is effective against infections caused by susceptible gram-positive and anaerobic bacteria. Currently, only a few, selected classes of antibiotics are indicated for the dental management of oral infections, including penicillins, cephalosporins, lincosamides, and macrolides (American Association of Endodontists 2012; American Academy of Pediatric Dentistry 2014; Flynn 2011). Recently, three recent publications have summarized the frequency of various antibiotic prescriptions written in the USA (Germak et al. 2017; Roberts et al. 2017) and internationally (Segura-Egea et al. 2017). The outcomes of these survey-based studies indicate that virtually all of the antibiotics considered to be appropriate for the management of odontogenic infections at the end of the twentieth century remain antibiotics of choice in contemporary dental practice. An exception to this generalization from the international survey outcomes is the continued presence of erythromycin as an antibiotic of choice (Segura-Egea et al. 2017).

In the USA, the unfavorable characteristics of erythromycin base and other erythromycin salts, including poor pharmacokinetics, irritancy in the gastrointestinal tract, and rapid development of bacterial resistance, are documented sufficiently so that its use in this country has largely been abandoned.

Tetracyclines, metronidazole, and macrolides may be used in the management of periodontitis, particularly refractory cases, where sub-antimicrobial doses of tetracyclines and macrolides appear to be beneficial (Haffajee et al. 2003; Hirsch et al. 2012). This chapter is focused on commonly used oral antibiotics, with an emphasis on high-level scientific evidence. The reader is referred to other sources for information on antiviral and antifungal agents.

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There are several important principles that must be understood prior to prescribing an antibiotic for a dental patient:

1. Antibiotics are adjuncts to debridement and/or surgical interventions (tooth extraction, pulpectomy, incision and drainage) and should not be used in place of these procedures in the management of infections.
2. Antibiotics are not effective against viruses or fungal organisms. Their successful use depends on an accurate diagnosis, which should confirm a bacterial etiology.
3. An antibiotic regimen should be based upon the signs and symptoms of the bacterial disease. The patient's responses to an antibiotic should be monitored using defined clinical endpoints (reduction of swelling, reduction of body temperature).
4. Prophylactic use of antibiotics in dentistry is limited (see Prescribing Considerations). The practitioner must be familiar with the current scientific evidence for this use, as well as current guidelines established by dental and medical professional organizations.
5. Some antibiotics may carry a high risk of allergic reactions and should be used only after careful consideration of the patient's medical and dental history.
6. There are relatively few randomized, controlled clinical trials of antibiotics in dentistry and, therefore, relatively few systematic reviews and meta-analyses on which to base therapeutic decisions.
7. The prescription of antibiotics is not appropriate as an interim measure when symptoms warrant immediate physical examination of the patient, particularly in children (Cherry et al. 2012).

Antibiotics Commonly Used in Dentistry

Penicillins: There are many forms of penicillin, the most common being phenoxymethyl penicillin (penicillin VK), a beta lactam penicillin. Aminopenicillins have an extended spectrum, which includes some gram-negative organisms that are not typically involved in odontogenic infections. Amoxicillin is now the most widely prescribed drug in this class, owing primarily to its pharmacokinetic traits. Because penicillins act by inhibition of bacterial cell wall synthesis, they have little systemic toxicity in mammals (mammalian cells lack a "cell wall"). However, penicillins carry a relatively higher risk of allergy than other dental antibiotics. Penicillin was formerly recommended as the antibiotic of first choice for routine dental infections, and while amoxicillin has largely replaced it in the USA, its use remains appropriate and, in some cases, very favorable owing to its wide availability and low cost.

Cephalosporins: Since the development of cephalexin, considered a first-generation agent in the USA, there are now four generations of cephalosporins. Each later generation was synthesized to provide a broader spectrum of activity. While cephalosporins are indicated for antibiotic prophylaxis in selected patients, they are generally not preferred as routine agents in cases of odontogenic infections. They are included among alternative agents for antibiotic prophylaxis because of their effectiveness against gram-positive cocci.

In patients with allergy to penicillin, first-generation cephalosporins (e.g., cephalexin, Keflex®) carry a relatively low rate of cross-sensitivity of approximately 1%, but this can vary considerably for other generations of these agents (Campagna et al. 2012). In cases in which a cephalosporin is appropriate for the management of an odontogenic infection, an agent from the second-generation cephamycin subgroup should be selected, as this group possesses greater antibacterial efficacy against gram-negative anaerobes than other groups of cephalosporins (Molavi 1991). Agents in this subgroup include cefoxitin, cefotetan, and cefmetazole. Cephalosporins are bactericidal and possess a mechanism of action similar to that of the penicillins, i.e., inhibition of bacterial cell wall synthesis by blocking the transpeptidation reaction.

Lincosamides: Clindamycin is a lincosamide that is very effective against anaerobic and mixed aerobic-anaerobic infections. It possesses favorable pharmacokinetics and has become a widely used alternative for dental infections in cases of penicillin allergy. Lincosamides were initially implicated as a major causative agent for pseudomembranous colitis. It now appears that they have a risk for this complication similar to that of the cephalosporins and aminopenicillins. Lincosamides may be bactericidal in some bacterial species, particularly at higher dosages, and their mechanism of action involves inhibition of bacterial protein synthesis by binding to the same 50s ribosomal subunit as erythromycin.

Macrolides: Erythromycin, clarithromycin, and azithromycin are members of this group and may be bacteriostatic or bactericidal, at higher concentrations. Macrolides inhibit protein synthesis by binding to the 50s ribosomal RNA. Macrolides possess less favorable characteristics for use in dentistry than the other antibiotic classes. Macrolides also bind to cytochrome P450 hepatic enzymes and can result in numerous seriously toxic drug interactions. Macrolides (azithromycin) are associated with cardiac arrhythmias, and erythromycin may also stimulate uncomfortable contractions of GI smooth muscle because of its similarity to a locally released GI pro-motility hormone, motilin. Except for use as alternatives for infective endocarditis prophylaxis, they are not preferred as first-choice or penicillin-alternative drugs for routine odontogenic infections. For the management of odontogenic infections with agents from this class, erythromycin base and its various salts are not recommended, and azithromycin, based on its favorable pharmacokinetics, is the preferred representative for dental use of this class of antibiotic.

Nitroimidazoles: Metronidazole was originally marketed for use in the treatment of protozoan infections that also has proven bactericidal activity against anaerobes. Because many oral infections (acute periodontal infections) are predominantly anaerobic in nature, metronidazole may be useful alone or in combination with amoxicillin. It has proven to be very effective when tested in vitro against periodontal pathogenic organisms. Because metronidazole is effective only against anaerobic organisms, its recommended role is as an adjunct to be used with a penicillin when a suboptimal clinical response to the penicillin occurs (Bali et al. 2015).

Tetracyclines: Tetracyclines, including doxycycline, are broad-spectrum, bacteriostatic agents which inhibit bacterial protein synthesis by binding to the 30s ribosomal subunit. They chelate calcium ions and thus have a propensity

Table 1 Classification and characteristics of common dental antibiotics for oral administration

Antibiotic	Class	Mechanism of action	Common adult oral dosage[a]	Special considerations
Penicillin VK	Beta lactam penicillin	Bactericidal	500 mg q 6 h	Absorption impaired by food
Amoxicillin	Aminopenicillin	Bactericidal	500 mg q 8 h	Absorption not impaired by food, available with beta lactamase inhibitor
Cephalexin	Cephalosporin	Bactericidal	2 g 30 min-1 h before procedure	Risk of cross-allergy with penicillins is low; alternative agent for prophylaxis
Clindamycin	Lincosamide	Bactericidal	300 mg q 6 h	Excellent alternative in cases of penicillin allergy
Azithromycin	Macrolide	Bacteriostatic	500 mg day 1, then 250 mg 1 q day	Once daily dosing; alternative agent for prophylaxis
Clarithromycin	Macrolide	Bacteriostatic	500 mg q 12 h	Alternative agent for prophylaxis
Metronidazole	Nitroimidazole	Bactericidal	500 mg q 8 h	Disulfiram-like reactions with alcohol; effective against anaerobes only
Doxycline	Tetracycline	Bacteriostatic	20 mg q 12 h prior to meals	Adjunct for periodontal therapy; available in local delivery forms

[a]See American Academy of Pediatric Dentistry (2014) for information regarding pediatric dosages

to cause fluorescent tooth staining through incorporation into the enamel of developing teeth, and even into remineralizing enamel of teeth that have already erupted (McKenna et al. 1999). While not typically indicated for routine odontogenic infections, tetracyclines at sub-antimicrobial doses modulate matrix metalloproteinases (collagenases) involved in the breakdown of extracellular structures and inflammation. They are used in selected cases of periodontitis refractory to conventional therapy procedures. Some patients may develop photosensitivity to these drugs, which can be severe (Jeske 2017).

The specific names and other characteristics of dentally useful antibiotics are shown in Table 1 (Jeske 2017).

Prescribing Considerations

1. Following the diagnosis of a bacterial infection and removal of the infected tissue (i.e., drainage or extraction or root canal therapy), the dental provider can begin antibiotic therapy with a standard dose of an orally administered first-choice agent (such as amoxicillin 500 mg) or an alternative agent. It is appropriate to initiate antibiotic therapy on an empirical basis (without obtaining culture and sensitivity testing). Culture and sensitivity testing requires additional time and may or may not identify specific etiologic pathogens. Culture and sensitivity testing should be considered if initial therapy is not effective.
2. The typical course of antibiotic therapy for dental infections runs for 5–7 days, unless symptoms persist. The patient should be monitored closely at the beginning of antibiotic therapy. Noticeable improvement should be expected within 24–48 h.
3. Because of reduced absorption in the presence of food, penicillin V should be prescribed 1 h before meals or 2 h after meals.
4. Penicillins do not appear to be effective for the management of symptomatic irreversible pulpitis (Keenan et al. 2005). Guidelines for the selection and use of antibiotics in adults for endodontic infections have been published by the American Association of Endodontists (American Academy of Pediatric Dentistry 2014).
5. The American Academy of Pediatric Dentistry has promulgated guidelines for antibiotic use in children (American Academy of Pediatric Dentistry 2014). Note that antibiotic dosages must be adjusted for the child's body weight. Generally, the same antibiotics routinely used for odontogenic infections in adults are also the preferred agents in the pediatric patient population.
6. Warnings with antibiotic therapy should be issued verbally and in writing on the prescription. They should include the possible development of allergic reactions and diarrhea and other GI disturbances. It is recommended that refills not be authorized for antibiotic prescriptions so that unnecessary, prolonged exposure of the patient to the drug is avoided, minimizing the risk of adverse effects, as well as development of antibiotic-resistant bacterial strains.

Antibiotic Prophylaxis

While there is little scientific evidence to support the use of prophylactic antibiotics to prevent postoperative complications, guidance from professional resources suggests its continued use in patients at highest risk of developing complications from infective endocarditis (Thornhill et al. 2018). Most regimens involve a single, preoperative dose of a bactericidal agent with activity against *Streptococcus viridans*. There is limited evidence showing that a second dose will not enhance outcomes (Lopes et al. 2011). There is also limited evidence that antibiotic prophylaxis reduces complications following implant placement and no strong evidence supporting use to prevent complications of third-molar surgery (Esposito et al. 2013; Lodi et al. 2012). Antibiotic prophylaxis prior to dental treatment in patients with total joint arthroplasty (artificial joint) is controversial, and professional guidance now emphasizes good oral hygiene to prevent infective complications in these patients. At this time, there is insufficient scientific evidence on which to base the practice (American Academy of Orthopedic Surgeons and American Dental Association 2012).

However, when in doubt, the dentist is obligated to consult with the patient's physician(s) to determine the need for antibiotic prophylaxis and the appropriateness of the recommended regimen. Recently, a secular trend analysis of the incidence of infective endocarditis in a country in which antibiotic prophylaxis for patients at risk of infective endocarditis had been abandoned suggests that the abandonment of the practice may have contributed to a rise in cases of infective endocarditis. Further, it appears that this increase affected patients previously deemed not having conditions that put them at high risk for developing infective endocarditis (Dayer et al. 2015).

At this time, recent expert analyses of the practice of antibiotic prophylaxis to prevent infective endocarditis have been published with important major conclusions. Dayer et al. (2018) concluded that while antibiotic prophylaxis to prevent infective endocarditis produces a "marginal gain," the benefits of the prophylaxis outweigh the risks, especially in patients at high risk for endocarditis and even for those at moderate risk. This group further suggested that when all evidence is considered, the possibility that antibiotic prophylaxis has some small impact cannot be discounted. Finally, these authors indicated that antibiotic prophylaxis involves very little expense and the dosing regimens currently recommended minimize the risk of development of antibiotic resistance.

In a related publication, Thornhill et al. (2018) suggest that patients previously classified as "moderate risk" for infective endocarditis might also be considered as high risk and that current guidelines for stratifying the risks of infective endocarditis related to dental procedures may require re-evaluation. This appears to have been confirmed indirectly in a recent report of an outbreak of bacterial endocarditis in a US oral surgery practice (Ross et al. 2018). In this report on 15 patients who developed infective endocarditis and who underwent oral surgical procedures, 10 had predisposing cardiovascular conditions, and of these, 5 had mitral valve prolapse, a condition for which current guidelines no longer recommend prophylactic antibiotic (Wilson et al. 2007).

Adverse Effects

Antibiotics, as prescribed in dentistry, are generally well tolerated. With the exception of allergy, most adverse effects from antibiotics are related to their effects on the gastrointestinal tract. Virtually all antibiotics may irritate the stomach or stimulate contractions of gastrointestinal smooth muscle, resulting in nausea, vomiting, and cramping. They may also disrupt the normal flora, resulting in diarrhea or leading to antibiotic-associated colitis and a potentially life-threatening overgrowth of *C. difficile*.

Symptoms with most cases of antibiotic-associated diarrhea dissipate when the antibiotic is discontinued. It is imperative that patients be cautioned against the use of antidiarrheal drugs and/or probiotics in place of medical diagnosis and management of this rare, but serious, complication. The development of any sign or symptom of an allergic reaction (rash, itching, and/or hives) requires that the antibiotic agent be discontinued immediately and the patient be evaluated medically (Beacher et al. 2015).

Penicillins are typically associated with a rate of allergy that is relatively higher than for other classes of antibiotics. These reactions may range from delayed-onset, mild forms (e.g., rash) to immediate-onset type I anaphylaxis.

Adverse Drug Interactions

Antibiotics are capable of adversely interacting with other dental and medical drugs, both through pharmacodynamic and pharmacokinetic mechanisms. The most significant adverse pharmacodynamic interaction for commonly prescribed antibiotics is the mutual antagonism that occurs when a bactericidal agent (penicillins, cephalosporins) is co-administered with a bacteriostatic agent (tetracycline). The recent scientific evidence does not support an adverse interaction between oral contraceptives and antibiotics used in dentistry (Taylor and Pemberton 2012).

Conversely, if drugs with similar mechanisms of action are administered together, a beneficial

Table 2 Clinically significant drug interactions involving antibiotics used in dentistry—[modified from Ciancio (2011)]

Primary drug	Action	Interaction (and effect)
Alcohol	Metabolism decreased by	Metronidazole (severe nausea, vomiting)
Benzodiazepines	Enhanced by	*Erythromycin*, *clarithromycin* (increased CNS depression)
Carbamazepine	Enhanced by	*Erythromycin*, *clarithromycin* (increase carbamazepine toxicity
Coumarins (including warfarin)	Enhanced by	*Erythromycin*, *clarithromycin*, *metronidazole*, penicillins, tetracyclines (increased risk of bleeding)
Digoxin	Enhanced by	*Erythromycin*, *clarithromycin* (increased toxicity of digoxin, including cardiac arrhythmias
Lidocaine	Enhanced by	*Erythromycin*, *clarithromycin* (increased toxicity of lidocaine, CNS depression)
Penicillins	Antagonized by	Probenecid, salicylates, coumarin, diphenylhydantoin, griseofulvin (reduced efficacy against infection)
Statins	Enhanced by	*Erythromycin*, *clarithromycin* (increased statin toxicity, e.g., rhabdomyolysis)
Tetracyclines	Antagonized by	Antacids, iron (reduced absorption of tetracyclines)
Tetracyclines	Antagonizes	Penicillin (reduced efficacy against infection)
Theophylline	Potentiated by	Erythromycin, clarithromycin (increase toxicity of theophylline, possible cardiac arrhythmias)

synergism may result. Combinations of antibiotics are not generally recommended in dentistry. However, the addition of *metronidazole* to a penicillin regimen may improve outcomes because of the selective action of metronidazole on strictly anaerobic organisms. Among the antibiotics discussed here, macrolides are the most likely to produce pharmacokinetic drug interactions. Serious adverse interactions of the various classes of dental antibiotics are listed in Table 2 (Ciancio 2011).

Less significant drug interactions are also possible—the clinician is urged to consult the complete prescribing information for all drugs prescribed.

For medically compromised patients with systemic disease that could affect drug metabolism and/or excretion, consultation with the patient's physician is recommended.

Antibiotics for Periodontitis

Both systemic and locally applied antibiotics have been investigated for the management of periodontal diseases, focused primarily on refractory periodontitis (periodontitis that responds poorly to conventional therapy).

A recent systematic review of this subject indicates that the scientific evidence for systemic antibiotics in the treatment of refractory periodontitis does not support this indication, nor does it show that systemic antibiotics add an incremental benefit to conventional treatment along (e.g., mechanical debridement) (Santos et al. 2016). Until there are more studies with less heterogeneity and with parallel design, the use of systemic antibiotics for periodontal therapy remains controversial.

Conclusion

Antibiotics continue to play an important, albeit adjunctive, role in the management of routine odontogenic infections. They are safe and effective when prescribed at recommended doses and based on the patient's presenting signs, symptoms, and coexisting medical conditions. The number of patients who are candidates for antibiotic prophylaxis is relatively small, and prophylactic use should be guided by the current recommendations of professional organizations, as based on scientific studies. Dentists should continue to consider emerging evidence for the use of low-dosage antibiotics in cases of refractory

periodontitis and other inflammatory diseases. At present, the topic of dental antibiotics can be summarized as follows:

1. Penicillins and aminopenicillins (e.g., amoxicillin) remain drugs of first choice for the management of routine odontogenic infections.
2. Alternative antibiotics to be used in cases in which penicillins are contraindicated include clindamycin, azithromycin, metronidazole, and moxifloxacin.
3. Antibiotic resistance is problematic in medicine but is still of limited significance in the treatment of odontogenic infections in dental outpatients.
4. Based upon the consensus of experts, antibiotic prophylaxis remains indicated in limited groups of patients with specific, high-risk conditions for cardiac and prosthetic joint infections.
5. At the present time, there is no compelling scientific evidence that mandates changes in current guidelines for the use of antibiotics in dentistry.
6. New findings from retrospective case studies and secular trend analyses of populations may disrupt current practices of antibiotic prophylaxis to prevent infective endocarditis, and the practitioner is urged to regularly monitor the guidelines for antibiotic prophylaxis promulgated by professional medical and dental organizations.

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Pharmacologic Management of Patients with Drug-Related Coagulopathies

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Understanding Clinical Hemostasis: The Key to Patient Management

Understanding and applying clinical knowledge of hemostasis is essential in managing patients undergoing dental procedures who are on "blood thinners." This requires the clinician to make the distinction between the function of antiplatelet and anticoagulant medications. Patients utilize these medications for primary or secondary prevention of thromboembolic complications of vascular disease (Palareti and Cosmi 2009). The clinical implications and management will vary accordingly, and a portion of these patients will be on a combination of multiple antiplatelet or antiplatelet and anticoagulants.

The prevalence of antiplatelet and anticoagulant use is increasing due to an aging population and increased survival of cardiovascular or cerebrovascular insults. As a result, clinicians will regularly encounter this population of patients in their practices. This chapter will focus on patients who are using these medications for acquired medical problems and not on patients who utilize these medicines for congenital coagulopathies, diseased-induced states (e.g., pregnancy, cancer, severe trauma or burns, etc.), or effects of medications that are procoagulant (e.g., birth control). The authors intend to provide the clinician with an understanding of the physiology of clotting and associated medication therapies and, more importantly, evidence-based principles and recommendations on how to manage patients on "blood thinners." We will provide an overview of the elements involved in clotting in response to vascular injury, especially due to dental procedures, which will further aid the clinician in making evidence-based clinical judgments when treating this patient population.

Clinical Hemostasis

Hemostasis is a multifactorial and dynamic process. After vessel injury, there is an immediate vasoconstriction phase to decrease the flow of blood, lasting approximately 20 min (Mingarro-de-León et al. 2014). Injury to the vessel wall also leads to exposure of subendothelial collagen and the progression into the platelet phase of hemostasis.

Prior to understanding platelet function after vessel wall injury, the clinician should recognize that the uninjured, vascular endothelium inhibits platelet function, and this prevents a thrombotic event. When a vessel wall is disrupted, as with surgical intervention, there is a series of events that lead to hemostasis. This series of events is described in Fig. 1.

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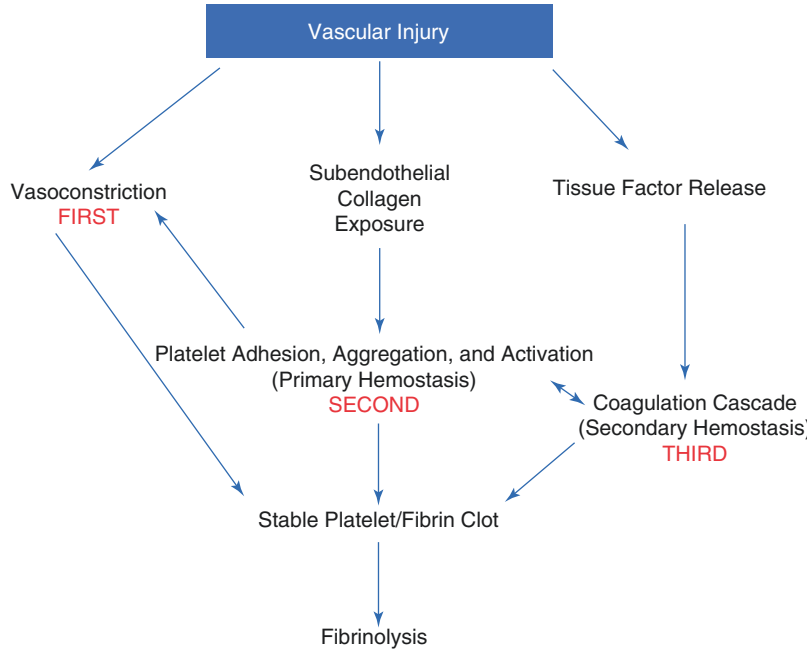

Fig. 1 Hemostatic response to vascular injury

Platelet Phase

The fundamental cell responsible for production of platelets is the megakaryocyte, which is derived from hematopoietic stem cell precursors. The megakaryocyte produces and releases platelets and is primarily regulated by the enzyme thrombopoietin (TPO), which is principally produced in the liver, with some contribution from the kidney and bone marrow. The circulating platelet has a life span of 7–10 days with approximately 33% of platelets being stored in the spleen (Wilson et al. 2015). Normal platelet count is 150,000–450,000/uL, and a significant decrease in platelets may also represent risks associated with postoperative bleeding (Branehög et al. 1975).

Once circulating platelets are no longer inhibited to binding to the vessel wall, promotion of adhesion of platelets to the exposed collagen occurs. This is initially mediated by exposed von Willebrand factor (VWF), which is naturally bound to the subendothelial collagen and released upon injury (note: additional VWF is also released by subsequent platelet activation) (Wilson et al. 2015). This helps form a platelet plug that improves hemostasis (Mingarro-de-León et al. 2014). Aggregation of the platelet plug is then assisted by the activation of platelet glycoprotein (Gp) IIb/IIIa (αIIbβ3) receptor that facilitates binding of VWF and fibrinogen to these receptors (Yip et al. 2005). Figure 2 provides greater detail of the platelet cascade and the factors involved in obtaining a platelet plug. It is important to note that circulating endogenous thrombin, adenosine phosphate (ADP), epinephrine, and thromboxane A2 are important in platelet activation and clot formation (Howard et al. 2013). Inhibition of these select proteins has important clinical consequences on the formation of the platelet plug.

Coagulation Phase

Following the platelet phase is the coagulation phase (Fig. 3). Binding of coagulation factor X to receptors on the platelet surface occurs and accelerates conversion to factor Xa, which is critical in converting prothrombin to thrombin. Thrombin then acts to convert the soluble fibrinogen clot to a strong insoluble fibrin plug (Mingarro-de-León et al. 2014).

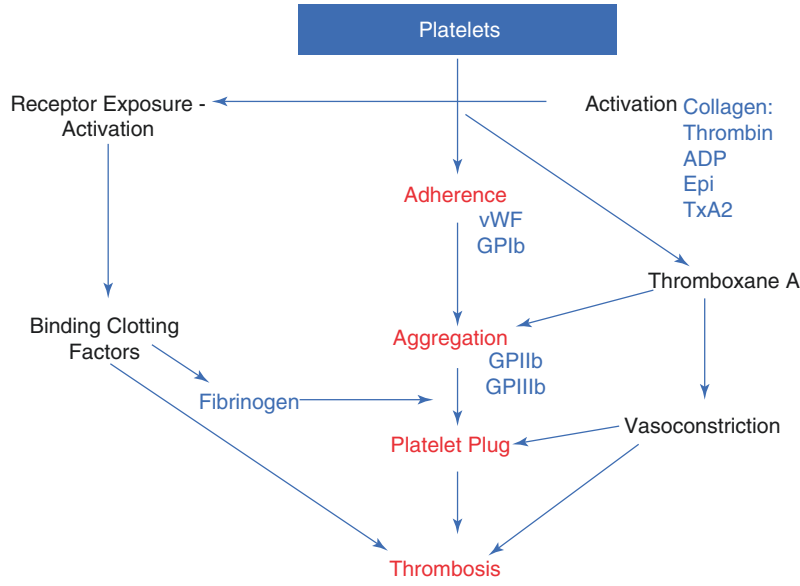

Fig. 2 Platelet phase of hemostasis

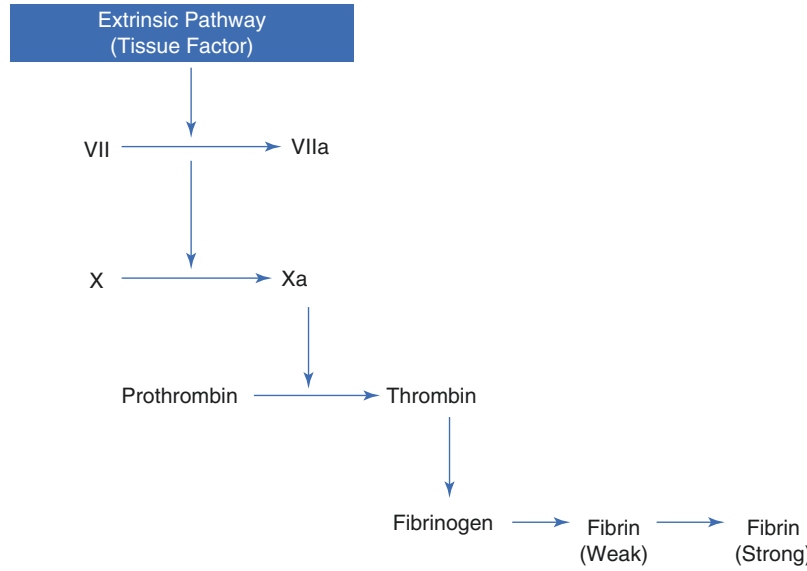

Fig. 3 Coagulation phase of hemostasis

The coagulation phase terminates when the damaged vessel wall is repaired and/or the clot is stable. The clot then undergoes fibrinolysis, which is facilitated by the conversion of prekallikrein to kallikrein by factor XII. Kallikrein then converts inactive plasminogen to active plasmin which then lysis the fibrin plug (Mingarro-de-León et al. 2014).

Antiplatelet therapy targets the initial stages of clotting formation by disrupting platelet aggregation and formation of a platelet plug as described earlier in the chapter. Anticoagulation therapies target the latter stages of clot formation by inhibiting the function of clotting factors and disrupting the coagulation cascade (Bagot and Arya 2008).

Knowing the physiology of hemostasis, the dental clinician can better co-manage the use of blood thinners with the physician and plan how to approach providing dental care to patients on these medications.

When treating patients taking antiplatelet medications, the clinician should anticipate the likelihood for prolonged intra- and/or immediately postoperative bleeding. With patients on anticoagulants, however, the clinician should anticipate relatively normal intra- or immediately postoperative hemostasis but with the potential for bleeding problems or complications hours later when the coagulation cascade occurs.

Antiplatelet Therapy

Indications for Antiplatelet Therapies

The understanding of antiplatelet and anticoagulant therapies is directly tied to the underlying pathophysiology of thrombosis. In the 1850s, Virchow described three phenomena that increased the likelihood of thrombosis. These concepts have been further refined over the past decades but are summarized as follows:

- Interrupted blood flow (stasis)
- Irritation of vessel lining (endothelial or vessel wall injury)
- Blood coagulation (hypercoagulopathy) (Bagot and Arya 2008)

Antiplatelet therapy is widely used to reduce the risk of myocardial infarction and in the treatment of patients with high-risk atherosclerotic vascular disease, acute coronary syndrome, and arterial/venous thrombosis. It is also utilized in patients with a history of prior percutaneous coronary interventions, coronary bypass surgery, atrial fibrillation, and stroke (Dinkova et al. 2013).

Table 1 illustrates these morbidities and how they contribute to an increased likelihood of thrombosis.

Assessing Platelet Function

Platelet Function Tests

Historically, bleeding time (BT) has been used to determine platelet functionality. It was initially described in vivo by Duke in 1910. BT was regarded as the most useful screening tool of platelet function until the early 1990s. However, overwhelming literature suggests that prolonged BT does not translate into increased blood loss from surgery. Many studies have shown that a low dose of acetylsalicylic acid (aspirin) has an effect on bleeding time but has no clinical significance (Dinkova et al. 2013).

Other available platelet function tests can be subdivided into platelet adherence, aggregation, or activation studies. These studies are best utilized for special patient populations, such as in individuals with congenital platelet disorders (e.g., light transmission aggregometry [LTA]) or in trauma (e.g., thromboelastogram [TEG]).

Antiplatelet Medications

Multiple mediators precipitate platelet aggregation and adhesion. Antiplatelet medications have been developed to individually target these mediators to achieve their desired effects. Examples of these medications are outlined in Table 2.

COX Inhibitors: Aspirin

Acetylsalicylic acid was initially synthesized in the 1850s by acetylation of salicylic acid. Methods to synthesize acetylsalicylic were further refined over the next few decades. In 1899, scientists at Bayer had named it as “aspirin” and began large-scale distribution (Dinkova et al. 2013).

Aspirin irreversibly binds with platelets to inhibit aggregation by acetylation of serine residues of the COX enzymes, which renders the platelet nonfunctional for the duration of its life span. In turn, the generation of thromboxane A2, which is a catalyst of platelet aggregation, is decreased. This inactivation of COX lasts for up to 10 days (i.e., the entire life of the platelet) (Malmquist 2011).

There are no significant differences in COX enzyme inhibition between doses of 81 or 325 mg. The differences are limited to anti-inflammatory and antipyretic activities that are outside the scope of this chapter (Dinkova et al. 2013).

Table 1 Antiplatelet morbidities and how they contribute to risk of thrombosis (Dinkova et al. 2013)

Pathophysiology	Phenomena contributing to thrombosis	Adverse outcome
Atherosclerotic vascular disease/acute coronary syndrome/myocardial infarction	Vessel wall injury (due to atheromatous plaques deposited within the tunica intima) Interrupted blood flow (due to formation of atheroma in coronary arteries which disrupts laminar blood flow)	Myocardial infarction and its sequelae such as rupture of the myocardium
Venous thrombosis	Interrupted blood flow (due to stasis, immobilization, peripheral vascular disease, etc.) Vessel wall injury (due to trauma, surgery, etc.)	Superficial or deep vein thrombosis, which may lead to an embolism such as a pulmonary embolism
Arterial thrombosis	Interrupted blood flow (due to stasis, aneurysm, vessel wall dissection, etc.) Vessel wall injury (due to aneurysm, vessel wall dissection, etc.)	Arterial thrombosis which can lead to an arterial embolus
Percutaneous coronary intervention (i.e., angioplasty and coronary stents)	Vessel wall injury (sclerosis of intravascular walls requiring widening of vessel diameter or placement of an indwelling intravascular stent) Interrupted blood flow (turbulent blood flow in the presence of stents)	Thrombosis of coronary vasculature, myocardial ischemia, myocardial infarction
Coronary bypass surgery	Interrupted blood flow (via surgical placement of a shunt to bypass a coronary artery blockage)	Thrombosis of bypass graft
Atrial fibrillation	Interrupted blood flow (inadequate atrial contraction leading to turbulent blood flow which potentiates thrombosis)	Stroke (ischemic)
Transient ischemic activity (TIA)/stroke (ischemic)	Interrupted blood flow (due to thrombus formation in cerebral arteries or emboli from proximal arteries)	Cerebral ischemia and possible cerebral infarction

Table 2 Classes of antiplatelet medications (Dinkova et al. 2013)

COX inhibitors	Inhibitors of ADP-mediated activation of P2Y12 receptors	Prostaglandin analogues	Phosphodiesterase inhibitor	Fibrinogen receptor antagonist
Acetylsalicylic acid (aspirin)*	Clopidogrel (Plavix)*	Alprostadil	Dipyridamole	Abciximab
	Prasugrel (Effient)*	Iloprost		Tirofiban
	Ticagrelor (Brilinta)*			
	Ticlopidine (Ticlid)*			

*Most commonly used agents for antiplatelet therapy

Clopidogrel/Ticagrelor/Prasugrel/Ticlopidine

Clopidogrel is an antiplatelet agent belonging to the thienopyridine family. Clopidogrel blocks the P2Y12 receptor on the platelet cell membranes, inhibiting the ADP-induced platelet aggregation. It is a prodrug and needs to be metabolized to its active metabolite by several hepatic cytochrome P450 isoenzymes.

Clopidogrel is indicated for monotherapy for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischemic stroke, or peripheral arterial disease. It is also used in conjunction with aspirin in patients suffering from acute coronary syndrome (ACS) for non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a percutaneous

coronary intervention (PCI) with stent placement and ST segment elevation following acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

Platelet inhibition by clopidogrel is both dose- and time-dependent, and patients are usually given a loading dose of 300–600 mg and then maintained on 75 mg/day.

The duration of clopidogrel therapy varies according to the indication (Dinkova et al. 2013):

- Myocardial infarction—from a few days to less than 35 days
- Ischemic stroke—from 7 days to less than 6 months
- Following the insertion of a bare metal stent (BMS)—4–12 weeks
- Following the insertion of a drug-eluting stent (DES)—6–12 months

Ticagrelor is a new direct inhibitor of the platelet P2Y12 receptor and therefore does not require metabolic activation. Unlike thienopyridines, ticagrelor binds reversibly to the P2Y12 receptor and at a site that is independent of ADP. However, it still results in suppression of ADP-induced platelet activation by temporarily "locking" the receptor in an inactive state until it dissociates. Ticagrelor has significantly faster onset and offset of antiplatelet activity compared with clopidogrel in subjects with stable coronary artery disease or acute coronary syndromes. Ticagrelor is indicated for the prevention of thrombotic events in patients with acute coronary syndrome or myocardial infarction with ST elevation. The drug is combined with acetylsalicylic acid unless the latter is contraindicated (Dinkova et al. 2013).

Prasugrel is the newest member of the thienopyridine family and also irreversibly binds to P2Y12 receptor with a rapid onset and stronger inhibitory effect compared with clopidogrel. It is licensed for use with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome (Dinkova et al. 2013).

Ticlopidine is an ADP receptor blocker, preventing the binding of fibrinogen to platelet glycoprotein. It is indicated for use as a SAPT in patients who cannot tolerate aspirin or with aspirin in DAPT (Dinkova et al. 2013).

Management of Patients on Single and Dual Antiplatelet Therapy

Antiplatelet therapies are used to manage a multitude of medical conditions. Single antiplatelet therapy (SAPT) is commonly used to manage cerebrovascular accidents (CVA), cerebrovascular disease, coronary artery bypass grafts (CABG), and percutaneous coronary intervention (PCI) or as a final treatment modality after a period of dual antiplatelet therapy (DAPT). Dual antiplatelet therapy is typically used for patients who have had a recent cardiac stent placed due to coronary artery disease. Though many patients often transition to SAPT after a period of time, there will be a subset of high-risk patients that will maintain long-term DAPT. It is also important for the dental clinician to confirm the type of stent and date of placement (patients are given a medical card after stent placement that specifies the type of stent inserted). Patients with bare metal stents are normally maintained on DAPT for a minimum of 1 month and usually maintained on a single antiplatelet therapy after that. Patients with drug-eluting stents are normally maintained on dual antiplatelet therapy for a minimum of 12 months and then usually maintained on a single antiplatelet therapy afterward (Singh et al. 2013). It is important that DAPT remain uninterrupted in these time frames to prevent thromboses and associated morbidity (Grines et al. 2007).

Providing safe and predictable care to the dental patient who is on antiplatelet therapy can be confusing and in many instances without evidence-based direction. Many variables must be taken into account when making treatment decisions for these patients. These include the patient's overall state of health, the risk of bleeding from the planned surgical procedure, as well as the risks associated with cessation of any antiplatelet medications. The dental clinician

should always consult the appropriate managing physician, whether it is a primary care provider (PCP) or specialist (ADA 2018). When discussing the patient's care with the medical clinician, it is imperative to review the extent of the surgery and anticipated bleeding and determine a risk assessment on whether to treat the patient from a medical standpoint. After review of the literature, the authors' goal is to provide the dental clinician with evidenced-based data that will help him/her discuss the decision on the management of the patient's antiplatelet medications, whether SAPT or DAPT, with the managing physician.

When determining the course as it relates to antiplatelet therapy and dental surgery, the clinician must consider that discontinuing therapy increases the risk of systemic morbidities. Prior studies have shown that discontinuing antiplatelet therapy for surgical intervention provides significantly increased systemic risks versus the risk of bleeding and complications of bleeding if antiplatelet therapy is maintained. Maulez et al., in a case-controlled study, looked at 309 patients who were diagnosed with an ischemic stroke or transient ischemic attack (TIA) undergoing long-term aspirin therapy before their event and 309 patients with an ischemic stroke (IS) and TIA who did not have aspirin therapy 6 months prior to their event (Maulaz et al. 2005). The results showed that aspirin interruption increased the risk of an IS/TIA by 3.4-fold with a 95% confidence interval (CI). Risks were even greater for patients with a prior diagnosis of coronary heart disease (Maulaz et al. 2005). When contemplating the cessation of aspirin or SAPT for dental procedures, the risk of an ischemic event and associated morbidities must be compared to the risk of hemorrhage from the surgical intervention. The risk of cessation of antiplatelet therapy is only one component in making treatment decisions for this patient population. The clinician must also have valid data to determine if patients who remain on antiplatelet therapy have a risk of significant bleeding after dental surgical procedures.

Traditionally, the dental clinician requests that the managing physician hold antiplatelet therapy prior to dental surgical procedures. We now know that cessation of antiplatelet therapy can have significant systemic consequences. In addition, many studies have shown that maintaining antiplatelet therapy has no significant increased morbidity associated with postoperative bleeding. Napeñas et al. in 2013 published data from a literature review of 15 articles and found that there was no clinically significant increase in the risk of postoperative bleeding on patients either on SAPT or DAPT that underwent invasive dental procedures (Napeñas et al. 2013).

In 2015, Dezsi et al. compared postoperative bleeding in patients undergoing dental extractions who were on SAPT or DAPT. Patients were observed in office until stable clot formation was noted. Those on SAPT took up to 60 min to form a stable clot, whereas DAPT patients took as long as 130 min. However, clinical outcomes were no different in either group and no morbidity was recorded. The authors concluded that dental extractions could be safely performed while maintaining single or dual antiplatelet therapy (Dézsi et al. 2015). These studies provide clear evidence that the risk of maintaining antiplatelet therapy for invasive dental procedures is low and the systemic risks of discontinuing therapy are high. Treatment decisions must therefore take into account the dental clinician's professional comfort level with hemostasis control, the complexity and invasiveness of the procedure, and the baseline risk of bleeding especially with a patient on antiplatelet therapy. For complex dental surgery, it may be prudent for the dental clinician to stage procedures to decrease the associated risk of bleeding complications.

Cardona-Tortajada et al. monitored 155 patients on varied SAPT who underwent dental extractions. Twenty-six patients had minor bleeding complications that were controlled by local hemostatic measures, and one patient had severe bleeding and required an emergency room visit. The antiplatelet drug had no influence on postoperative bleeding, yet the number of teeth extracted was statistically relevant to postoperative bleeding

complications. Cardona-Tortajada et al. advised not to extract more than three teeth at a time and that these should either be adjacent or correlative and not in different parts of the dental arch (Cardona-Tortajada et al. 2009). These recommendations seem to make sense, as more extensive and invasive surgeries have an inherent increased risk of bleeding as a baseline, which will only be amplified for the patient on antiplatelet therapy.

In summary, the data presented clearly shows that cessation of antiplatelet therapy, whether SAPT or DAPT, has a greater risk to systemic morbidity than the risk of bleeding from dental surgery while these therapies are maintained. Other important factors for the clinician to consider when making treatment decisions include patient medical comorbidities, patient medications, invasiveness and extent of the procedure, dentist's comfort level with hemostasis and care of the medically complex patient, as well as patient's ability to recognize postoperative bleeding issues and having access to after-hours care. Patients on antiplatelet therapy may have an increased risk of postoperative bleeding, yet this bleeding is usually well controlled with local hemostatic measures and without associated morbidity. Additionally, in more invasive and extensive surgeries, the clinician should stage the procedure to decrease the risk of significant post-op bleeding.

Anticoagulation Therapy

Indications for Anticoagulation Therapies

The dental clinician should be aware of the general indications for the use of anticoagulants, which include atrial fibrillation, venous thromboembolisms, and presence of a mechanical heart valve (Guyatt et al. 2012a, b). Unlike antiplatelet therapies, the efficacy of anticoagulant therapies has been traditionally monitored (we will discuss the changing paradigm in the novel anticoagulants section). The severity of the disease state usually dictates more aggressive anticoagulation (usually monitored by the patient's international normalized ratio (INR)). Table 3 summarizes the indications for anticoagulant therapies.

In these scenarios, the clinician is placed in a dilemma. Unplanned cessation of anticoagulant therapy can have devastating effects, such as fatal mechanical heart valve (MHV) thrombosis in 15% of patients, embolic stroke leading to death or major disability in 70% of patients, and with venous thromboembolism a case-fatality rate of approximately 5–9%. On the other hand, continuing anticoagulant therapy results in major bleeding risk of 2–4%, of which there is a case-fatality rate of 8–10% (Spyropoulos and Douketis 2012).

Table 3 Suggested risk stratification for perioperative thromboembolism (Spyropoulos and Douketis 2012)

Risk category	MHV	Atrial fibrillation	Venous thromboembolism
High (>10%/year risk of ATE or 10%/month risk of VTE)	Any mechanical mitral valve	$CHADS_2$ score 5 or 6	Recent (<3 months) VTE
	Caged-ball or tilting disc valve in mitral/aortic position	Recent (<3 months) stroke or TIA	Severe thrombophilia
			Deficiency of protein C, protein S, or antithrombin
	Recent (<6 months) stroke or TIA	Rheumatic disease	Antiphospholipid antibodies
			Multiple thrombophilias
Intermediate (4–10%/year risk of ATE or 4–10%/month risk of VTE)	Bilateral AVR with major risk factors for stroke	$CHADS_2$ score 3 or 4	VTE within past 3–12 months
			Recurrent VTE
			Non-severe thrombophilia
			Active cancer
Low (<4%/year risk of ATE or <2%/month risk of VTE)	Bilateral AVR with major risk factors for stroke	$CHADS_2$ score 0–2 (and no prior stroke or TIA)	VTE > 12 months ago

TIA transient ischemic attack, *AVR* aortic valve replacement, *ATE* atrial thromboembolism, *VTE* venous thromboembolism, *MHV* mechanical heart valve

Because of the more severe clinical consequences of thrombosis over major bleeding, a strategy that incurs 3–10 more cases of major bleeds to prevent one case of thrombosis or stroke would, in theory, be clinically acceptable. This is based on the devastating consequences of a stroke as compared with a bleed that in the majority of cases can be surgically controlled.

Assessing Coagulation Function

We will briefly review concepts that aid the clinician in managing anticoagulated patients undergoing dental surgical procedures.

Prothrombin Time (PT)/International Normalized Ratio (INR)

The INR was developed to incorporate the international sensitivity index (ISI) values and attempt to make prothrombin time (PT) results uniformly useable. The working reference has been calibrated against internationally accepted standard reference preparations that have an ISI value of 1.0. The ISI value is the exponent in the formula and is therefore critical for calculation of the INR:

$$\text{INR} = \left(\text{patient PT} / \text{mean normal PT}\right)^{\text{ISI}}$$

Consequently, small errors in the ISI assignment may affect the calculated INR substantially. An otherwise healthy patient who is not anticoagulated will have an INR value of 1 (Al-Mubarak et al. 2007).

Partial Thromboplastin Time (PTT)

Partial thromboplastin time (PTT) has been described as measuring the overall speed of a clot formation, correlating with the activity of the intrinsic clotting cascade. PTT must be interpreted with caution as it doesn't reflect the in vivo hemostatic response and the interaction between the vessel wall, platelets, fibrinogen, and circulating coagulation factors (World Health Organization 1999).

Anticoagulation Medications: Warfarin

Current oral anticoagulant practice dates back almost 75 years to when vitamin K antagonists were discovered as a result of investigations into the cause of hemorrhagic disease in cattle. Characterized by a decrease in prothrombin levels, this disorder was caused by ingestion of hay containing spoiled sweet clover. Hydroxycoumarin, a lactone, which was isolated from bacterial contaminants in the hay, interferes with vitamin K metabolism, thereby causing a syndrome similar to vitamin K deficiency. This paved the way for discovering a more potent variant of coumarins, namely, warfarin, for use as a rodenticide. Warfarin is derived from WARF—for Wisconsin Alumni Research Foundation and—arin for its connection to coumarin (Link 1959).

Warfarin interferes with the synthesis of the vitamin K-dependent clotting factors, which include prothrombin (factor II) and factors VII, IX, and X. The synthesis of the vitamin K-dependent anticoagulant proteins, proteins C and S, is also reduced by warfarin.

Mechanism of Action

All of the vitamin K-dependent clotting factors possess glutamic acid residues at their N-termini. A posttranslational modification adds a carboxyl group to the γ-carbon of these residues to generate γ-carboxyglutamic acid.

Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby blocking the γ-carboxylation process. This results in the synthesis of vitamin K-dependent clotting proteins that are only partially γ-carboxylated.

Warfarin acts as an anticoagulant because these partially γ-carboxylated proteins have been reduced or absent biologic activity. The onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts.

The antithrombotic effect of warfarin depends on a reduction in the functional levels of factor X and prothrombin, clotting factors that have half-lives of 24 h and 72 h, respectively (FDA n.d.-a).

Pharmacology

Warfarin is a racemic mixture of R and S isomers and is rapidly and almost completely absorbed from the gastrointestinal tract. Racemic warfarin has a plasma half-life of 36–42 h, and more than 97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active (Wilson et al. 2015).

Variability of anticoagulation with warfarin in between individuals is significantly depending on the expression of group of cytochrome P-450-2C9 (CYP2C9) enzymes, which is responsible for oxidative metabolism (metabolic clearance) of the more active S-enantiomer, and the vitamin K epoxide reductase enzyme (VKORC1) which reduces the vitamin K, the cofactor necessary for gamma-carboxylation of vitamin K-dependent clotting factors. This can predispose to overdosage conditions and a higher risk of bleeding.

In 2007, the FDA issued a black box warning that updated the product label of warfarin by advising physicians to consider CYP2C9 and VKORC1 genetic tests to improve their initial estimate of warfarin dose (FDA n.d.-a).

Interactions with Other Commonly Used Medications

The fundamental mechanisms of interaction between warfarin and antibiotics are twofold:

1. Antimicrobial agents disrupt gastrointestinal flora that synthesize vitamin K (Onysko et al. 2016).
2. Antimicrobials inhibit cytochrome p450 (CYP450) enzymes (primarily CYP2C9 and 3A4), which are responsible for the metabolism of warfarin. The antibiotics most likely to interfere with warfarin are TMP/SMX (trimethoprim and sulfamethoxazole), ciprofloxacin, levofloxacin, metronidazole, fluconazole, azithromycin, and clarithromycin. Low-risk agents include clindamycin, cephalexin, and penicillin G. A 2008 study investigated the anticoagulation effects of a 10–20% preemptive warfarin dose reduction vs no dosing change in patients taking TMP/SMX or levofloxacin. The investigators found that the preemptive warfarin dose reduction (intervention) significantly decreased the number of supratherapeutic INR values above 4 when compared to controls (2 of 8 vs 8 of 9) (Onysko et al. 2016). There is no consensus in the dental literature to support adjusting warfarin dosing in the presence of trimethoprim/sulfamethoxazole (Bactrim®) or metronidazole (Flagyl®) in the pre- or postoperative setting, but the clinician should be aware of increased risk of bleeding if the patient has been recently prescribed antibiotics, especially TMP/SMX or metronidazole (Onysko et al. 2016).

Anticoagulation Medications: Heparin

Heparin is a proteoglycan that functions as a cofactor of the naturally occurring anticoagulant antithrombin. Because the half-life of heparin is short (60 min), the therapeutic levels are maintained by intravenous bolus injections followed by monitored infusion. The therapeutic range is monitored by prolongation of the partial thromboplastin time (PTT). There are several different types of heparin, notable is low-molecular-weight heparin (LMWH) with a longer half-life and can be delivered subcutaneous once or twice a day in contrast to unfractionated heparin (FDA n.d.-b).

Patients who have been on long-term therapy with heparin do not require laboratory monitoring; however, when monitoring is required (such as intraoral bony surgery), an anti-Xa assay is used because the PTT is not predictably prolonged (Malmquist 2011).

Complications associated with heparin are limited, the most notable being heparin-induced thrombocytopenia (HIT). HIT is a rare, life-threatening complication of heparin due to an autoimmune response toward platelet factor 4 and heparin complex that results in thrombocytopenia and arterial and venous thrombosis. The most common manifestations are bleeding and drop of platelet count. It is typically treated with immediate cessation of heparin and the use of an alternative, non-heparin-based anticoagulant (Greinacher et al. 2017).

Novel Oral Anticoagulants (NOAC)

The novel oral anticoagulants (NOAC) are a new class of drugs that act to attenuate coagulation by targeting a specific factor in the coagulation pathway. Due to the new nature of these drugs, the nomenclature in the literature is somewhat varied and without absolute consensus. In 2015 Barnes et al. published a discussion of the various terms and recommendations on nomenclature for these new drugs for the International Society on Thrombosis and Hemostasis Subcommittee on the Control of Anticoagulation. The varied nomenclatures discussed by Barnes et al. were novel oral anticoagulants (NOAC), target-specific oral anticoagulants (TSOAC), and direct-acting oral anticoagulants (DOAC) (Barnes et al. 2015). The subcommittee recognized that the oldest and most commonly used term was novel oral anticoagulants (NOAC). Yet they also recommend that the classification term for these drugs be transitioned to direct-acting oral anticoagulants (DOAC) as this better describes their mechanism of action (Barnes et al. 2015). For the purpose of this chapter, and to limit confusion in terminology, the term novel oral anticoagulants (NOAC) will be used.

NOAC either prevent the generation of thrombin (factor IIa) or directly inhibit thrombin. The drugs that indirectly inhibit thrombin formation do so by targeting factor Xa. Inhibition of factor Xa interferes with the formation of the fibrin clot by blocking the conversion of fibrinogen to fibrin. Even more recent agents act by directly inhibiting thrombin in the clotting cascade, inactivating thrombin, and inhibiting thrombogenesis (Thean and Alberghini 2016).

The most commonly used NOAC include dabigatran, rivaroxaban, and apixaban and are noted in Table 4 (Thean and Alberghini 2016).

Reversal Agents for Anticoagulants

Fresh frozen plasma (FFP) is the most commonly used method in North America for rapidly reversing warfarin. The usual dose of FFP for anticoagulant reversal is 15 mL/kg of body weight. When urgent reversal of a therapeutic (rather than supratherapeutic) INR is required, a lower dose of 5–8 mL/kg may be appropriate. FFP rarely completely corrects the INR without the use of Vitamin K, irrespective of the FFP dose or the INR value. Risks of FFP include failure to completely reverse coagulopathy, immune-mediated thrombocytopenia, and anaphylactoid reactions to name a few (Joseph et al. 2014; Frontera et al. 2014).

These limitations have led to recommendations that prothrombin complex concentrates (PCCs) be used in place of FFP for the treatment of anticoagulant-associated coagulation factor deficiencies. PCCs reverse coagulopathy laboratory markers from warfarin over coagulation more rapidly and effectively than FFP (Joseph et al. 2014; Frontera et al. 2014).

There are two different PCCs available, the 3-factor and the 4-factor concentrates. Both contain factors II, IX, and X, yet the 4-factor concentrate also contains factor VII. The 4-factor concentrate, in theory, should be more effective at correcting INR due to factor VII inclusion. The recommended dose of prothrombin complex concentrate (PCC) for reversal of anticoagulation ranges from 25 to 100 U/kg depending on the product used (Joseph et al. 2014; Frontera et al. 2014).

Irrespective of the blood product administered to reverse warfarin anticoagulation, the patient should also receive intravenous vitamin K at a dose of 2.5–5 mg administered over 30 min; otherwise, the INR is unlikely to completely correct, and a "rebound coagulopathy" may develop after

Table 4 Most commonly used novel oral anticoagulants (Thean and Alberghini 2016)

Brand name	Generic name	Target factor	Indications	Clearance
Pradaxa®	Dabigatran	IIa	Atrial fibrillation	Renal
Xarelto®	Rivaroxaban	Xa	DVT, atrial fibrillation	Renal, GI tract
Eliquis®	Apixaban	Xa	Atrial fibrillation	Renal, GI tract

the transfused factors are cleared. Intravenous administration of vitamin K has a small risk of severe anaphylactoid reaction and should only be given by slow intravenous infusion (over 20–30 min), and oral vitamin K should be used whenever possible. Because more rapid reversal is achieved with intravenous administration, it is preferred in cases when urgent reversal is required, such as life-threatening bleeding or reversal of coumarin effect in a patient diagnosed with acute HIT (Crowther and Warkentin 2008).

Preparation, delivery, and administration of FFP, PCC, and IV Vitamin K do not make them a practical method of reversal of a bleeding patient using anticoagulants in the typical office setting.

Specific Reversal Agents for NOAC

Ligand-specific and small molecule reversal agents have been more recently utilized, and long-term outcomes are still currently under investigation. These agents are likely to be primarily used in life-threatening bleeding and emergent surgery (Abed et al. 2017). In addition, these agents may allow the safer implementation of uninterrupted or minimally interrupted NOAC protocols for elective surgery.

Idarucizumab (Praxbind) is a monoclonal antibody that acts as a noncompetitive irreversible inhibitor of unbound and thrombin-bound dabigatran and its active metabolites. The compound has a high affinity, and it is a specific inhibitor of dabigatran action. The agent has a rapid onset mechanism of action and has been demonstrated to be safe and efficacious with a simple dosing regimen. Laboratory evidence of reversal is observed within minutes. Idarucizumab has been approved by the FDA in 2015 and is widely incorporated into protocols for use in acute bleeding or emergent surgery (Dalal et al. 2016; Andresen et al. 2018).

Andexanet alfa (AndexXa) is a recombinant modified human factor Xa decoy protein. It binds with high affinity to factor Xa inhibitors within 2 min of IV administration, thereby neutralizing the direct and indirect effects of factor Xa. A bolus dose is followed by an infusion with restoration of thrombotic activity being reflected by the change in thrombin generation and quantitative anti-FXa activity. Andexanet alfa reverses the anticoagulant effects of small molecule anti-FXa agents (rivaroxaban, apixaban, and edoxaban) as well as low-molecular-weight heparin and fondaparinux (the latter two being indirect FXa inhibitors). This was approved by the FDA in May 2018 (Dalal et al. 2016; Andresen et al. 2018).

Management of Patients on Warfarin Therapy

The risk of thrombosis and determining the continuation of anticoagulation during surgical intervention always plays a role in treatment decisions. The ninth edition of the ACCP (American College of Chest Physicians) Antithrombotic Therapy and Prevention of Thrombosis Guidelines recommend initially stratifying patients based on their risk of thrombosis (low, intermediate, or high) (Guyatt et al. 2012a; Spyropoulos and Douketis 2012). Subsequently the clinician should assess the complexity of the planned procedure. In patients who have a high risk of thrombosis, regardless of the complexity of the case, they should undergo an anticoagulation bridging protocol to minimize the duration of not being anticoagulated. Data has shown heparin bridging therapy will reduce the postoperative VTE risk by approximately two thirds. On the opposite end of the spectrum, in patients with a low risk of thrombosis, regardless of the complexity of the case, bridging is not typically indicated, and a strategy that considers stopping anticoagulation prior to surgery can be utilized. It is in the intermediate-risk patients where clinical judgment and experience of the clinician dictates what approach to bridging is warranted. It would be prudent to not bridge in cases where significant bleeding is predicted and therefore consider cessation of anticoagulation prior to surgery in concert with the supervising managing physician. In cases with a low risk of bleeding such as most dental surgical procedures, it would be in the patient's overall best interest to continue anticoagulation by either continuing the patient's typical regimen or utilizing bridging protocols.

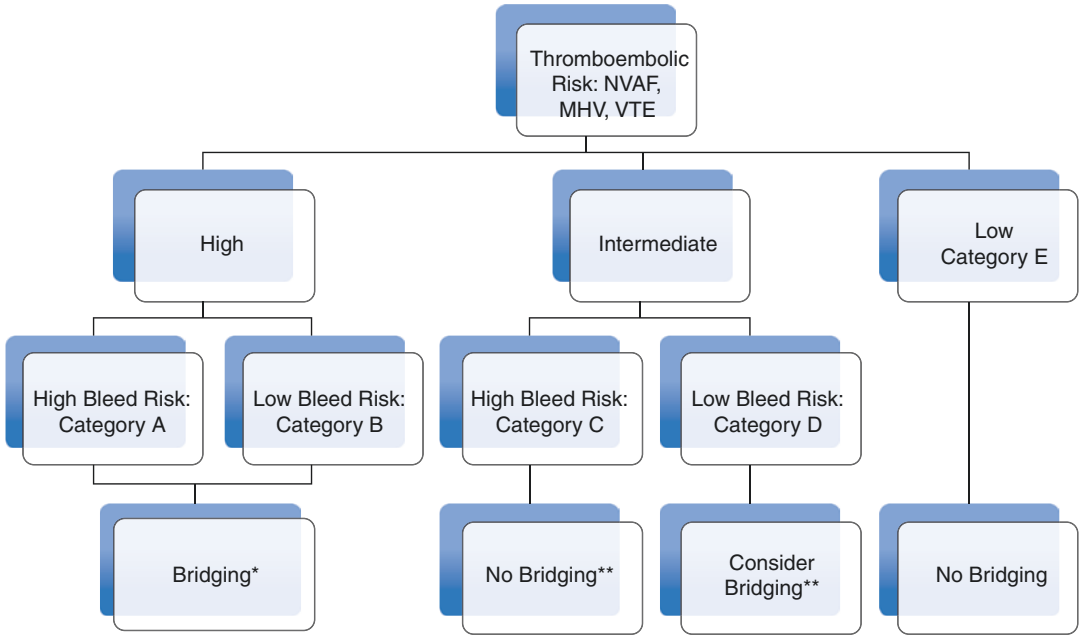

Fig. 4 Suggested periprocedural heparin bridging strategies for patients on chronic VKA therapy based on patient thromboembolic and procedural bleed risk (Spyropoulos and Douketis 2012) (reprinted with permission)

The flowchart noted in Fig. 4 provides a useful guide to help the clinician with the decision process (Spyropoulos and Douketis 2012).

In scenarios where bridging is warranted, the managing physician will guide the dental clinician with a strategy that includes timing of cessation of the patient's regimen and initiation of the bridging treatment (Spyropoulos and Douketis 2012). Many bridging protocols have been proposed, one such example that a physician may utilize is illustrated in Table 5.

Spyropoulos cited a recent systematic review of 7169 patients undergoing periprocedural bridging therapy and found a thromboembolism rate of 0.9% (95% CI, 0.0–3.4%) and a major bleeding rate of 4.3% (95% CI, 2.4–6.2%) primarily when LMWH bridging was used (Spyropoulos and Douketis 2012). The authors' professional approach to mitigating bleeding risks in these patients is based on the determined risk of postoperative bleeding, accounting for the extent of the surgery and the assessment of systemic bleeding risks. The patient treated in an outpatient setting who is at lower risk of a bleeding event may require a same-day follow-up call and post-op day 1 follow-up appointment or call. Yet for a patient with a concern for higher risk of a bleeding event, the prudent clinician may choose to observe the patient for a period of time in-office after the procedure, followed by post-op calls, or an inpatient observation status when deemed needed.

In patients who are at intermediate to high risk of thrombosis, an alternative strategy to bridging may be to not interrupt their anticoagulation therapy. Wahl showed a 0.95% incidence of severe thrombosis when warfarin was discontinued for tooth extractions, most of which led to patient death (Wahl 1998). Akopov conducted a retrospective analysis of 197 patients presenting over a 12-month period with nonfatal cardioembolic cerebral infarction, 14 (7.1%) of these patients suffered infarcts related to the discontinuation of warfarin therapy for procedures (Akopov et al. 2005).

Maintaining warfarin anticoagulation in the perioperative setting requires the clinician to keep a few principles in mind:

Table 5 Anticoagulation bridging protocols (Spyropoulos and Douketis 2012) (reprinted with permission)

Periprocedural anticoagulation and bridging protocol	
Day	Intervention
Preprocedural intervention	
−7 to −10	Assess for perioperative bridging anticoagulation; classify patients as undergoing high-bleeding risk or low-bleeding risk procedure; check baseline labs (Hgb, platelet count, creatinine, INR)
−7	Stop aspirin (or other antiplatelet drugs)
−5 or −6	Stop warfarin
−3	Start LMWH at therapeutic or intermediate dose[a]
−1	Last preprocedural dose of LMWH administered no less than 24 h before start of surgery at half the total daily dose; assess INR before the procedure; proceed with surgery if INR < 1.5; if INR > 1.5 and < 1.8, consider low-dose oral vitamin K reversal (1–2.5 mg)
Day of procedural intervention	
0 or +1	Resume maintenance dose of warfarin on evening of or morning after procedure[b]
Postprocedural intervention	
+1	Low-bleeding risk: restart LMWH at previous dose; resume warfarin therapy
	High-bleeding risk: no LMWH administration; resume warfarin therapy
+2 or +3	Low-bleeding risk: LMWH administration continued
	High-bleeding risk: restart LMWH at previous dose
+4	Low-bleeding risk: INR testing (discontinue LMWH if INR > 1.9)
	High-bleeding risk: INR testing (discontinue LMWH if INR > 1.9)
+7 to +10	Low-bleeding risk: INR testing
	High-bleeding risk: INR testing

[a]LMWH regimens include enoxaparin 1.5 mg/kg once daily or 1.0 mg/kg twice daily subcutaneously, dalteparin 200 IU/kg once daily or 100 IU/kg twice daily subcutaneously, and tinzaparin 175 IU/kg once daily subcutaneously. Intermediate-dose LMWH (i.e., nadroparin 2850–5700 U twice daily subcutaneously; enoxaparin 40 mg twice daily subcutaneously) has been less studied in this setting

[b]Loading doses (i.e., two times the daily maintenance dose) of warfarin have also been used

- Patients who are anticoagulated are at an inherent increased risk of a bleeding event.
- Patients who are not in a therapeutic range are at increased risk of thrombosis.
- Patients who are at supratherapeutic levels have an even greater risk of significant post-surgical bleeding.

The question then lies in patients who are kept on warfarin therapy. Are there INR ranges that are safe from a dental surgical standpoint to treat with minimal risk of a significant postoperative bleeding while maintaining the thrombosis prevention benefits of anticoagulation? Morimoto et al. in a 2011 prospective study performed 433 extractions on 382 patients with a postoperative hemorrhage rate of 3.9%. Greater than 90% of the cases with postoperative bleeding occurred within 6 days of extraction, and 60% had an INR of 3.0 or greater. Bleeding events in patients with an INR of 2.0–3.0 were twofold lower compared with patients with an INR greater than 3.0. The study also noted that surgical factors that increased the risk of bleeding included acute inflammation and the need for surgical extraction (Morimoto et al. 2011). Weltman et al. performed a systematic review in 2015 of the management of patients undergoing dental extractions who were also receiving warfarin therapy. The authors' findings determined that patients whose INR was 3.0 or less can safely continue their warfarin regimen prior to dental extraction procedures, without significant risk of bleeding. The study did also show that gelatin sponge packing did improve post-op bleeding in this patient population (Weltman et al. 2015).

The clinician must recognize that most medical diagnoses treated with warfarin require a therapeutic INR range between 2.0 and 3.0 (e.g., atrial fibrillation, DVT w/ or w/o PE) with mechanical heart valve patients requiring higher INR ranges of 2.5–3.5. As the data reaffirms, patients with INR ranges of 3.0 or less can be safely treated with minimal risk of a significant postoperative bleed. Accounting for the fact that most indications for warfarin therapy call for a therapeutic INR ranges of 3 or lower, patients can be safely treated while minimizing the risk of thrombosis. Patients that present with supratherapeutic INR ranges (3 or greater) should be deferred by the dental clinician for optimization by their physician. It is critical to remember that

PT/INR lab testing should be performed on the same day of treatment to ensure an accurate preoperative INR.

If the patient is deemed at low risk of thromboembolic event (as described earlier in this section), withdrawal of warfarin without bridging is typically accomplished 2–7 days preoperatively. The variability of the withholding period depends on other systemic factors, including advanced age, systolic heart failure, and liver function.

In order to assist the dental clinician in determining the safety of dental treatment for patients receiving warfarin, we have slightly modified a table originally published by Herman et al. in 1997 as noted in Table 6 (Herman et al. 1997). The recommendations have been adapted from the original recommendations to align with the more current data that we have presented. Clinical judgment and each patient's unique history and treatment needs should be considered when following these recommendations.

Regardless of the choice between stopping warfarin with or without bridging, anticoagulation can be restarted the evening of the procedure if there is minimal concern for bleeding at the conclusion of the procedure. With bridging, the parenteral anticoagulant can be discontinued when the INR is within the therapeutic range.

Table 6 The warfarin patient-outpatient dental procedure safety recommendations (Herman et al. 1997)

Dental procedure	Suboptimal INR range		Normal INR range			Out of range
	<1.5	1.5–<2.0	2.0–<2.5	2.5–3.0	>3.0–3.5	>3.5
				Mechanical prosthetic heart valve		
			Atrial fibrillation, venous thrombosis, pulmonary embolism			
Examination, radiographs, impressions, orthodontics						
Simple restorative dentistry, supragingival prophylaxis						
Complex restorative dentistry, scaling and root planing, endodontics					Probably safe with local measures[a]	
Simple extraction, biopsy			Local measures[a]	Probably safe with local measures[a]		
Multiple extractions, single surgical extraction (including bony impaction)			Local measures[a]	Probably safe with local measures[a]		
Single dental implant placement, gingivectomy, minor periodontal flap procedure		Local measures[a]	Probably safe with local measures[a]			
Full-arch or full-mouth extractions	Local measures[a]	Probably safe with local measures[a]				
Extraction of multiple bony impactions, placement of multiple dental implants, extensive flap surgery	Probably safe with local measures[a]					

[a]Increased need for the use of local measures such as sutures, Gelfoam®, SURGICEL®, topical thrombin, and tranexamic acid

Management of Patients on Novel Oral Anticoagulants (NOAC)

Treating patients on novel oral anticoagulants (NOACs) presents additional challenges for the dental clinician. These novel therapies have been introduced relatively recently for patient use, and as such treating patients on these medications in a surgical setting is limited. With increasing indications of use and market penetration, the number of patients on these drugs will continue to grow. Soon after the FDA approval of the first NOACs, Pradaxa® in 2010 and Xarelto® in 2011, Firrolo and Hupp in 2012 published a clinical manuscript addressing the use of NOACs and implications for the management of the dental patient (Firriolo and Hupp 2012). At the time, the authors concluded that the clinical data present to make sound judgment on the management of these therapies and dental extractions was lacking and that clinical studies were needed. The authors reinforced discussing options, risks, and management with the patient's physician. They concluded as a precaution that in cases where it is deemed necessary to stop NOAC for surgery (i.e., risk of major bleeding), the medication should be stopped at least 24 h prior to procedure. They also concluded that it should be restarted only after the risk of bleeding has become minimal, within the first 24–48 h. In 2014, Elad et al. attempted to better clarify directive care for this population by performing a review of 18 randomized clinical trials (Elad et al. 2016). Elad et al. took into account factors such as risk of procedural bleeding, issues of reversing and monitoring these agents, risk of thromboembolism as proposed by the ACCP (Guyatt et al. 2012a), as well as patient comorbidities. From this review, they concluded that there are four possible options when treating this patient population:

1. Continue NOAC.
2. Perform procedure as late in the day as possible.
3. Discontinue use 24 h prior to treatment.
4. Discontinue use 48 h prior to treatment.

Their final recommendation was that patients on NOAC would most likely benefit from options 1 or 2 (Elad et al. 2016). Elad et al. developed a suggested treatment algorithm as noted in Fig. 5.

Elad et al. also cautioned the dental clinician in caring for these patients, stating that until there is greater evidence about the bleeding risk in patients on NOACs, referral to a hospital-based dental clinic or an oral and maxillofacial surgeon should be considered.

A dental narrative published in the *Australian Dental Journal* in 2015 by Thean and Alberghini (2016) reaffirms those recommendations provided

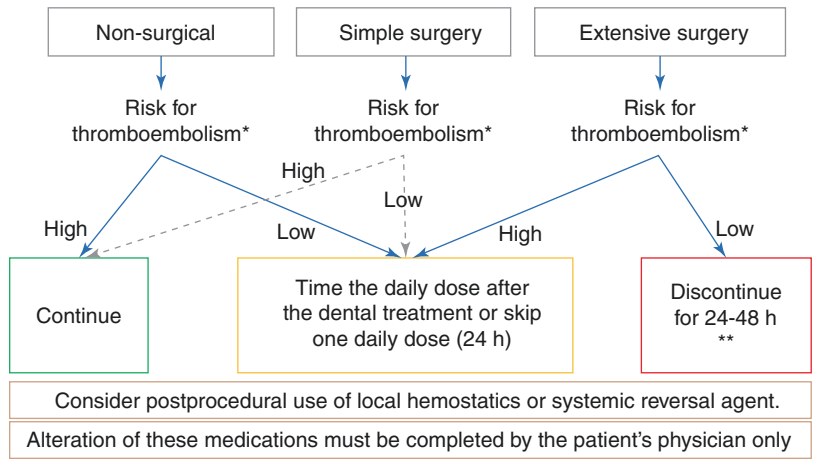

Fig. 5 Suggested algorithm for management approach prior to dental intervention (Elad et al. 2016) (reprinted with permission)

Table 7 Preoperative oral anticoagulant cessation recommendations (Spyropoulos and Douketis 2012) (reprinted with permission)

Preoperative interruption of new oral anticoagulants: a suggested management approach			
Drug (dose)[a]	Patient renal function	Low-bleeding risk surgery[b] (two or three drug half-lives between last dose and surgery)	High-bleeding risk surgery[c] (four or five drug half-lives between last dose and surgery)
Dabigatran (150 mg twice daily)			
$t_{1/2}$ = 14–17 h	Normal or mild impairment (CrCl >50 mL/min)	Last dose: 2 days before surgery (skip two doses)	Last dose: 3 days before surgery (skip four doses)
$t_{1/2}$ = 16–18 h	Moderate impairment (CrCl 30–50 mL/min)	Last dose: 3 days before surgery (skip four doses)	Last dose: 4–5 days before surgery (skip six to eight doses)
Rivaroxaban (20 mg once daily)			
$t_{1/2}$ = 8–9 h	Normal or mild impairment (CrCl >50 mL/min)	Last dose: 2 days before surgery (skip one dose)	Last dose: 3 days before surgery (skip two doses)
$t_{1/2}$ = 9 h	Moderate impairment (CrCl 30–50 mL/min)	Last dose: 2 days before surgery (skip one dose)	Last dose: 3 days before surgery (skip two doses)
$t_{1/2}$ = 9–10 h	Severe impairment[d] (CrCl 15–29.9 mL/min)	Last dose: 3 days before surgery (skip two doses)	Last dose: 4 days before surgery (skip three doses)
Apixaban (5 mg twice daily)			
$t_{1/2}$ = 7–8 h	Normal or mild impairment (CrCl >50 mL/min)	Last dose: 2 days before surgery (skip two doses)	Last dose: 3 days before surgery (skip four doses)
$t_{1/2}$ = 17–18 h	Moderate impairment (CrCl 30–50 mL/min)	Last dose: 3 days before surgery (skip four doses)	Last dose: 4 days before surgery (skip six doses)

[a]Estimated $t_{1/2}$ based on renal clearance
[b]Aiming for mild to moderate residual anticoagulant effect at surgery (<12–25%)
[c]Aiming for no or minimal residual anticoagulant effect (<3–6%) at surgery
[d]Patients receiving rivaroxaban, 15 mg once daily

by Elad et al. (2016). Thean and Alberghini reinforced that the dental clinician must direct care under the guidance of the patient's physician, and not unilaterally withhold anticoagulation therapy for dental treatment. They recommended NOAC can be continued and bleeding controlled with local measures for procedures with low risk of bleeding, such as simple single extractions. These local measures included the use of Gelfoam® or SURGICEL® packing, mechanical pressure, suturing, and/or tranexamic acid mouthwash. For high-risk procedures, such as multiple extractions or surgical extractions, they also recommend the dental clinician refer to an oral and maxillofacial surgeon for care. For patients undergoing more extensive surgery, cessation of NOAC may be indicated (Thean and Alberghini 2016).

In 2012, Spyropoulos discussed the possible need for 2–3 days of a low-dose LMWH bridging regimen (e.g., enoxaparin 40 mg once daily) in postoperative patients who are unable to take oral medications (Spyropoulos and Douketis 2012). For patients undergoing cessation of NOAC therapy, Spyropoulos recommends cessation time periods based on renal clearance and surgical risk of bleeding. He defines simple dental extractions as low risk of bleeding (a 2-day risk of major bleed of 0–2%) and multiple tooth extractions as a high risk for bleeding (2-day risk of major bleed 2–4%). Based on the patient's renal function and the risk of procedural bleeding, he then provides preoperative drug cessation recommendations as summarized in Table 7 (Spyropoulos and Douketis 2012).

In summary, the dental clinician must review the anticoagulated patient's overall health and the risk for developing a thrombosis, determine the potential for major postoperative bleeding, utilize the guidance of the patient's managing physician to direct anticoagulation management, and plan for intraoperative and postoperative contingencies in the consultation appointment. In instances where additional resources are required to safely carry out the surgical plan, the clinician should consider referral to a hospital-based provider or an oral and maxillofacial surgeon.

Local Hemostatic Agents

What we have discussed so far are all preparations in anticipation for the planned surgical procedure. In any of the abovementioned scenarios (bridging, continuation of oral anticoagulant, or cessation of anticoagulation), the patient may continue to have more than expected intraoperative bleeding. Fortunately, there are agents available as discussed below that can help control the intraoperative oozing. It should be noted that none of these measures substitute the first response to any persistent bleeding, which is to apply firm pressure either manually or with the patient biting on folded gauze for at least 10 min.

Gelfoam®

Gelfoam® is a water-insoluble, porous, pliable product prepared from purified porcine skin capable of absorbing up to 45 times its weight of whole. It may be cut without fraying and is able to absorb and hold within its interstices, many times its weight of blood and other fluids. It is theorized that Gelfoam® promotes coagulation both by surface area hemostasis and by providing a mechanical framework for coagulation. When used, it must be applied with moderate pressure to the site of bleeding. It should not be used in locations with a risk of infection (i.e., surgical extraction of an infected tooth), and it typically resorbs within 6 weeks (Achneck et al. 2010).

SURGICEL®

Another adjunct that can be used for capillary, venous, and small arterial bleeds is SURGICEL®, which is an oxidized regenerated cellulose agent. Due to the low pH level, it has acidic properties and achieves hemostasis via denaturation of blood proteins, mechanical activation of the clotting cascade, and local vasoconstriction. Another distinguishing factor is the antibacterial properties of SURGICEL®. It should be used in caution in areas where there is potential of nerve exposure (i.e., inferior alveolar nerve, mental nerve, etc.) due to its acidic nature. Invariably, SURGICEL® should be retrieved after hemostasis is achieved unless its removal poses a significant risk of rebleeding. This is to prevent complications such as a giant cell type of reaction at the surgical site (Achneck et al. 2010).

Morimoto et al. reported 87 cases receiving antiplatelet drugs. Teeth were extracted without reducing antiplatelet therapy, oxidized cellulose was applied, and suturing was performed for local hemostasis. They also concluded that sufficient hemostasis can be obtained in most cases of tooth extraction, and appropriate local hemostatic methods can be successful when postoperative hemorrhage occurs (Morimoto et al. 2008).

Fibrin Glue

Fibrin glue is effective as a hemostatic agent as it mimics the final pathway of coagulation cascade where fibrinogen is converted into fibrin under the action of thrombin, factor XIII, fibronectin, and ionized calcium (Brewer and Correa 2006). It is comprised of two components: thrombin (principally human) and fibrinogen (normally plasma derived) (Achneck et al. 2010). Fibrin glue is effective in managing bleeding in patients with high risk of prolonged and excessive bleeding after surgery. Traditionally it has been used to manage bleeding in cardiovascular, hepatic, and splenic surgeries. It also has proven itself as a useful tool in the armamentarium for treating the dental surgery patient who is at high risk for bleeding during or after surgery (Mankad and Codispoti 2001). Fibrin glue contains human or animal components, leading to hesitation of use in certain patients (Achneck et al. 2010).

Tranexamic Acid (TXA) and ε-Aminocaproic Acid (Amicar®)

Tranexamic acid (TXA) and ε-aminocaproic acid (Amicar®) are antifibrinolytic agents that block the proteolytic site of plasmin and inhibit plasminogen activator incorporation into the nascent fibrin clot. A 4.8% of TXA solution has been

proven to be effective in reducing bleeding complications (Dinkova et al. 2013). This solution may be difficult to obtain from a pharmacy unless prior arrangements have been made. A recommended regimen is to hold 10 mL in the mouth for 2 min, 30 min preprocedure, and then repeat every 2 h for 6–10 doses as needed (Carter and Goss 2003).

Carter et al. demonstrated that a 2-day course of 4.8% TXA is as efficacious as a 5-day course in controlling hemostasis postdental extractions in patients anticoagulated with warfarin (Carter and Goss 2003).

Topical Thrombin

Thrombin forms the foundation of a fibrin clot by promoting the conversion of fibrinogen to fibrin. Thrombin is commonly derived from bovine sources, yet bovine thrombin has been known to cause a significant immune response in some patients. As such, new formulations derived from human plasma or recombinant human sources are available and are being formulated (Achneck et al. 2010). The application of thrombin in controlling hemostasis during dental surgery can be performed by applying thrombin directly to the surgical site, yet it is best utilized by combining thrombin synergistically with a second hemostatic agent, such as Gelfoam®, as a carrier. This combination can then be packed into the surgical site for hemostatic control.

Conclusion

The data presented in this chapter demonstrates that in most clinical cases the decision can be made to maintain antiplatelet or anticoagulation therapy for routine dental treatment, including "simple" extractions. This is especially true for patients who are at high medical risk of a thromboembolic event and/or patients requiring minor dental surgical procedures.

Intraoperative hemostatic measures would benefit any patient who is on one or more blood thinners, irrespective of the treatment algorithm chosen. However, it is most critical in the patient who maintains his/her blood thinner therapy during his/her operative course. Malmquist provided a list of key hemostatic measures that should be considered that include (Malmquist 2011):

1. Avoid flap procedures.
2. Limit surgical trauma, e.g., limiting the number of teeth extracted or the sectioning of teeth.
3. Curette associated socket granulation tissue.
4. Obtain primary closure when a flap has been elevated.
5. Use non-resorbable sutures to control the tension on the flap, and eliminate the possibility of premature breakdown of the suture material.
6. Use topical hemostatic materials in the surgical site to reduce bleeding.
7. Use electrocautery or laser to reduce bleeding.
8. Apply an appropriately placed pressure dressing for a sufficient period of time.
9. Use topical rinses, such as tranexamic acid, to inhibit fibrinolysis.
10. Provide treatment early in the day, allowing for observation for bleeding throughout the day.

Given the prevalence of patients on anticoagulation therapy presenting for oral surgical procedures, the clinician will be required to make clinical decisions to optimize the patient's outcomes (i.e., minimizing the risk of thrombosis and postoperative bleeding). These decisions include assessing the need to continue anticoagulation, assessing the likelihood of major bleeding with the planned surgical procedure, intraoperative hemostasis strategies, and an appropriate postoperative surveillance.

Patient care for these patients on blood thinners should always be co-managed under the guide of the treating physician and include the consideration of:

- The physiology and sequence of hemostasis
- The clinical indications for the use of these medications and the risks associated with the

continued use or cessation of these agents when treating this patient population
- When can patients be maintained on these therapies
- If stopping antiplatelet and/or anticoagulation therapy is decided
- What are the increased systemic risks as they are weighed to the benefits of decreasing bleeding risks

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Pharmacologic Management of Patients with Neurologic Disorders

Miriam R. Robbins

Introduction

Psychiatric and neurologic diseases are common in the general population and therefore are commonly encountered in dental patients. Such diseases may vary in severity and consequences, but treatment of these chronic conditions generally involves long-term use of multiple pharmacologic agents. Because of the similarity in the underlying pathophysiology of the diseases presented, there is overlap between the medications used. For example, anticonvulsant medications are also used to treat mood disorders. The majority of patients with Parkinson's disease (PD) and Alzheimer's disease (AD) will exhibit neuropsychiatric symptoms including depression, anxiety, agitation, apathy, and psychosis at some time during the course of disease. The focus of this chapter is to summarize potential drug interactions of clinical importance to the oral healthcare provider, based on a review of the most current evidence-based literature available with an emphasis on systematic reviews (Table 1). Although the information presented on various medications used to treat these disorders is presented here, it is intended to highlight the undesirable interactions of these drugs with drugs commonly prescribed by dentists. Comprehensive information on the pharmacodynamics and pharmacokinetic of these psychotropic and neurologic drugs can be accessed elsewhere.

Psychiatric Disorders

Psychiatric diseases are common in the United States. One in five US adults lives with a mental illness (44.7 million or 18.5% in 2017). Mental health surveys carried out in the United States suggest that during any 1-year period, approximately 26% of the population will have a mental disorder, and almost 50% of all people will have mental illness sometime during their lifetime (Nimh.nih.gov 2018a). 1.1% of adults in the United States live with schizophrenia (Nimh.nih.gov 2018b). 2.6% of adults in the United States live with bipolar disorder (Nimh.nih.gov 2018c). 6.9% of adults in the United States—16 million—had at least one major depressive episode in the past year (Nimh.nih.gov 2018d), and 18.1% of adults in the United States experienced an anxiety disorder such as generalized anxiety, post-traumatic stress disorder, obsessive-compulsive disorder, and phobias (Nimh.nih.gov 2018e). Psychiatric disorders have high rates of co-occurrence with patients exhibiting more than one type of symptom (e.g., depression and anxiety frequently occur together).

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Table 1 Dental drug interactions

Dental drugs	Interacting drug(s)	Details of interaction	Recommendations	Key references
Aspirin and NSAIDs	Lithium	NSAIDs inhibit renal clearance of lithium, potentially resulting in lithium toxicity within 5–10 days	Best to use diflunisal Limit use of NSAIDs to 2–3 days Decrease dose of lithium	Bauer and Mitchner (2004), Hashimoto et al. (2002), Alda (2015)
	SSRIs (fluoxetine, sertraline, paroxetine) SRI (duloxetine) Donepezil Galantamine Rivastigmine	Increased risk of bleeding (especially GI) due to interference with platelet function	Limit use to 2–3 days. Avoid in patients with history of GI bleeding or bleeding diathesis	Serebruany (2006), Anglin et al. (2014), Mansour et al. (2006), Loke et al. (2008)
	Divalproex sodium Valproic acid	Synergistic effect on bleeding with aspirin	Avoid	Vasudev et al. (2010), Abdallah (2014), Manu et al. (2016)
Acetaminophen	Carbamazepine Phenytoin	Increased potential hepatotoxicity of acetaminophen and decrease its pharmacologic effects	Avoid concurrent use max daily dose of acetaminophen <2 g	Patsalos and Perucca (2003), Perucca (2006)
	Lamotrigine	Reduction in therapeutic levels of lamotrigine	Limit use to 2–3 days	Patsalos and Perucca (2003)
Tramadol	Bupropion MAOIs SSRIs TCAs	Increased seizures and/or serotonin syndrome	Avoid	Sansone and Sansone (2009)
	Pramipexole	Increased CNS and/or respiratory depression	Monitor	
	MAOIs	Hypertension and autonomic reactions	Avoid	
Codeine Hydrocodone Oxycodone	SSRIs (fluoxetine, sertraline, paroxetine) Bupropion Haloperidol	Decreased efficacy of pain medication due to delayed metabolism (CYP2P6 inhibitors) of prodrug to active morphine derivative	Alternative pain medications	Becker (2008), Friedlander and Norman (2002)
	Antipsychotics Benzodiazepines TCAs	Increased central CNS depression	Reduce dose of narcotics, alternate pain medications	
Doxycycline Metronidazole Tetracycline	Lithium	Increased lithium levels; risk of toxicity	Avoid	Hashimoto et al. (2002), Alda (2015)
Metronidazole	Antipsychotics Carbamazepine Phenobarbital Phenytoin Primidon	Decreased seizure threshold	Use with caution, reduce dose	Kennedy et al. (2013), Ozeki et al. (2010), Patsalos and Perucca (2003), Perucca (2006)

Table 1 (continued)

Dental drugs	Interacting drug(s)	Details of interaction	Recommendations	Key references
Macrolides Erythromycin Clarithromycin	Benzodiazepines (except lorazepam) Carbamazepine Phenobarbital Phenytoin Valproate	Inhibition of AED/psychotropic drug metabolism leading to increased CNS depression (CYP450 inhibition)	Avoid or monitor AED/psychotropic drug levels	Gubbins and Heldenbrand (2010), Patsalos and Perucca (2003), Perucca (2006)
	Valproate	Increased valproate concentration (CYP3A4 inhibition)	Avoid	Vasudev et al. (2010), Abdallah (2014)
	Fluoxetine Haloperidol Pramipexole Quetiapine Sertindole Venlafaxine Zotepine	QT prolongation	Avoid	Kennedy et al. (2013), Ozeki et al. (2010)
	Donepezil Galantamine	Decreased hepatic metabolism of cholinesterase inhibitors increasing cholinergic activity	Monitor, consult with physician if extended course is anticipated	Defilippi and Crismon (2003), Bentué-Ferrer et al. (2003)
Doxycycline	Carbamazepine Phenobarbital Phenytoin	Decreased doxycycline half-life by 50%	Use alternate antibiotic	Perucca (2006)
Fluconazole Ketaconazole Itraconazole	Carbamazepine Clonazepam Phenobarbital Phenytoin Quetiapine Benzodiazepines	Inhibition by antifungal of metabolism of drug (CYP450) inhibition) potentiating psychotropic effects and possibly toxic serum levels	Avoid or monitor AE/psychotropic drug levels	Kennedy et al. (2013), Gubbins and Heldenbrand (2010), Perucca (2006)
	Donepezil Galantamine	Decreased hepatic metabolism of cholinesterase inhibitors increasing cholinergic activity	Monitor, consult with physician if extended course is anticipated	Defilippi and Crismon (2003)
Local anesthetics with epinephrine	Older generation antipsychotics (haloperidol and chlorpromazine). Not seen with newer atypical antipsychotics	Blockage of α_1-receptors can cause orthostatic hypotension that rarely can be worsened by the β_2-receptor stimulation by epinephrine	Monitor vital signs during and after administration. Limit to 2 carpules of 1:100,000 epinephrine or less. Aspirate to avoid intravascular injection. Avoid use of epinephrine impregnated retraction cord. Avoid levonordefrin use with TCAs	Friedlander and Marder (2002)
	COMT inhibitors Entacapone Tolcaone	Delayed metabolism of both epinephrine and levonordefrin possibly potentiating cardiovascular effects		Malamed (2014), Balakrishnan and Ebenezer (2013)
	TCAs	Possible potentiation of the sympathetic effects of epinephrine or levonordefrin (more prevalent with levonordefrin)		Yagiela (1999), Brown and Rhodus (2005), Moodley (2017), Malamed (2014), Saraghi et al. (2017)

Additionally, patients may have medical comorbidities, either as direct effect of the underlying pathophysiology or as a side effect of chronic and/or debilitating disease. More than 50% of patients with substance abuse disorders have a co-occurring mental illness (Substance Abuse and Mental Health Services Administration 2015). Psychiatric disorders are frequently associated with decreased rates of compliance with medical and dental treatment.

A mainstay of treatment for psychiatric disorders is psychotropic medications. Patient responses are variable, so the use of combination therapy is common. Patients may be on several different medications depending on their underlying symptoms, and there is crossover between the medications and disorders. Psychotropic medications may have short- and long-term adverse effects and frequently have drug interactions with clinical implications for medical and dental providers. Common types of medications include antidepressants, mood stabilizers, antipsychotics, and antianxiety drugs (Box 1).

Antidepressants

While the exact mechanism is not known, it is hypothesized that antidepressants drugs work by inhibiting the uptake of serotonin and/or norepinephrine in the synapse. Millions of patients take antidepressant medications in the United States for the treatment of depression but also to treat anxiety, panic disorders, post-traumatic stress disorder, obsessive-compulsive disorder, and seasonal affective disorder. Some antidepressants are prescribed off-label to treat problems such as chronic pain, insomnia, ADHD, menstrual symptoms, migraines, and tobacco cessation (Fishbain 2000; Salerno et al. 2002).

Antidepressant classes are named depending on their effect on reuptake or enzyme inhibition. Commonly prescribed antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and bupropion. Tricyclic antidepressants (TCAs), tetracyclics, and monoamine oxidase inhibitors (MAOIs) are older classes of antidepressants that are used less frequently because of higher incidence of side effects (including xerostomia, orthostatic hypotension, and cardiac toxicities) and more adverse drug interactions. Today, TCAs are more commonly used in the management of chronic pain and insomnia due to their ability to elevate synaptic norepinephrine concentrations and sedative properties (Finnerup et al. 2015; Catalani et al. 2014).

MAOIs were the first group of drugs used to treat depression but are currently only used to treat patient resistant to other pharmacologic therapies. MAOIs act by inhibiting the activity of presynaptic monoamine oxidase (MAO; MAO-A and MAO-B), leading to increased epinephrine, norepinephrine, serotonin, and dopamine concentrations in the neuronal cytoplasm (Becker 2008) leading to downregulation of postsynaptic receptors (Bhat and Preethishree 2015). They fell out of favor because of serious dietary and drug restrictions that were needed to avoid life-threatening hypertensive episodes. These included dietary restrictions of any foods containing tyramine and any other drugs with an effect of serotonin uptake (Rabkin et al. 1984).

Tricyclic antidepressants gained popularity in the 1960s as the major antidepressant medication in the United States. In addition to limiting the reuptake of neurotransmitters, TCAs have alpha-1 antagonist, anticholinergic, and antihistamine properties (Baldessarini 2006). Anticholinergic side effects include xerostomia, urinary retention, and constipation, while the alpha-1 blockade causes orthostatic hypotension. Metabolism occurs in the liver, via the cytochrome P450 pathway. Notable central nervous system effects of TCAs include sedation and a reduction in the seizure threshold. Cardiovascular effects of TCAs include tachycardia and changes in cardiac conduction possibly leading in some cases to cardiac arrhythmias and causing widening of the QRS complex and QT prolongation. TCAs display analgesic properties at doses significantly lower than those used to treat depression and are considered a first-line drug in the treatment of neuropathic pain, fibromyalgia, back pain, and chronic headaches (Fennema et al. 2017).

Selective serotonin reuptake inhibitors (SSRI) inhibit the neuronal uptake of serotonin

Box 1 Psychiatric Medications

ANTIDEPRESSANTS			
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram (Celexa®) Escitalopram, (Lexapro®) Fluoxetine (Prozac®) Fluvoxamine (Luvox®) Paroxetine (Paxil®) Sertraline (Zoloft®)	**Mood Stabilizers**	Carbamazepine (Tegretol®) Divalproex (Depakote®) Gabapentin (Neurontin®) Lamotrigine (Lamictal®) Lithium (Eskalith®, Lithonate®) Oxcarbazepine (Trileptal®) Topiramate (Topamax®) Valproic acid (Depakene®, Epival®)
Tricyclics	Amitriptyline (Elavil®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Doxepin (Sinequan®) Imipramine (Tofranil®) Nortriptyline (Pamelor®) Protriptyline (Vivactil®) Trimipramine (Surmontil®)	**Antipsychotics**	**Typical (first generation)** Chlorpromazine (Thorazine®) Flupenthixol (Fluanxol®) Fluphenazine (Modecate®) Haloperidol (Haldol®) Loxapine (Loxapac®) Mesoridazine (Serentil®) Pericyazine (Neuleptil®) Perphenazine (Trilafon®) Pimozide (Orap®) Pipotiazine (Piportil®) Prochlorperazine (Stemetil®) Thioridazine (Mellaril®) Thiothixene (Navane®) Trifluoperazine (Stelazine®) Zuclopenthixol (Clopixol®)
Monoamine oxidase inhibitors (MAOIs)	Phenelzine (Nardil®) Tranylcypromine (Parnate®)		
Serotonin norepinephrine reuptake inhibitor (SNRI)	Venlafaxine (Effexor®) Duloxetine (Cymbalta®)		**Atypical (second generation)** Aripiprazole (Abilify®) Clozapine (Clozaril®) Lurasidone (Latuda®) Olanzapine (Zyprexa®) Quetiapine (Seroquel®) Risperidone (Risperdal®)
Serotonin-2 antagonist/ reuptake inhibitor (SARI)	Trazodone (Desyrel®)	**Anxiolytics**	**Benzodiazepines** Alprazolam (Xanax®) Bromazepam (Lexotanil®) Chlordiazepoxide (Librium®) Clonazepam (Klonopin®) Clorazepate (Tranxene®) Diazepam (Valium®) Flurazepam (Dalmane®) Lorazepam (Ativan®) Nitrazepam (Mogadon®) Oxazepam (Serax®) Temazepam (Restoril®) Triazolam (Halcion®)
Norepinephrine dopamine reuptake inhibitor (NDRI)	Bupropion (Wellbutrin®, Zyban®)		**Non-benzodiazepine** Buspirone (BuSpar®) Hydroxyzine (Vistaril®) Meprobamate (Miltown®) Pregabalin (Lyrica®) Propranolol (Inderal®)

and generally have the least side effects of all classes of antidepressants. They are used to treat mild to moderate depression, obsessive-compulsive disorder, panic disorder, social phobias, and post-traumatic stress disorder. With the exception of paroxetine, SSRIs have relatively minimal anticholinergic properties or sedative effects. Unlike TCAs, SSRIs do not affect the seizure threshold or cardiac conduction. Common side effects include nausea, diarrhea, headache, jitteriness and agitation, and insomnia. SSRIs (especially fluoxetine, paroxetine, and sertraline) are also potentially associated with an increase in sleep bruxism, although the exact etiology is currently unknown (Garrett and Hawley 2018).

Other atypical antidepressants include the SNRIs represented by venlafaxine and duloxetine. They resemble the tricyclic antidepressants in action and have similar side effects including sedations, nausea, insomnia, xerostomia, and constipation. They can cause elevations and heart rate and blood pressure because of norepinephrine uptake inhibition. They are also commonly used in the treatment of chronic neuropathic pain including diabetic neuropathy, fibromyalgia, and postherpetic neuralgia (Finnerup et al. 2015).

Dental Pharmacology Implications for Patients Medicated with Antidepressants

Potential drugs interactions of dental concern may occur between antidepressants and sedatives, narcotic analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and epinepherine/levonordefin. Antidepressants have significant sedative properties, and caution should be taken when prescribing any other medication with sedative side effects. Antidepressants that elevate serotonin levels can precipitate seizures or serotonin syndrome if used in conjunction with other medications that increase serotonin levels. Serotonin syndrome is a potentially fatal consequence of excessive central nervous system serotonergic activity characterized by hyperreflexia, muscle rigidity and tremors, agitation, and confusion (Sansone and Sansone 2009). Additional symptoms can include diaphoresis, tachycardia, hyperthermia, hypertension, visual hallucinations, and coma. Dental drugs of concern include opioid analgesics (especially meperidine) and anesthetic agents including fentanyl, tramadol, and erythromycin and should be avoided in patients taking serotonergic drugs.

SSRIs and SNRIs increase the risk of bleeding through the reduction of platelet levels of serotonin that can cause decreased platelet aggregation and clot formation (Serebruany 2006). Patients taking SSRIs (especially fluoxetine, paroxetine, and sertraline) have an increased risk of upper gastrointestinal (GI) bleeding, and this risk may be synergistically increased by concurrent use of NSAIDs (Anglin et al. 2014). Additionally, paroxetine, sertraline, and fluvoxamine inhibit the enzymes needed to metabolize NSAIDs including ibuprofen, naproxen, diclofenac, and celecoxib, further increasing the risk of significant bleeding (Mansour et al. 2006; Loke et al. 2008).

The SSRI antidepressants also can inhibit several of the cytochrome P450 enzymes produced in the liver, impacting the biotransformation and clearance of other drugs. Inhibition occurs to the greatest degree with paroxetine and with varying intensity with fluoxetine. Of clinical relevance is the inhibition of CYP2D6, which is responsible for metabolizing codeine, hydrocodone, and oxycodone from a prodrug to an active morphine metabolite. Patients medicated with these SSRIs may not experience the expected analgesic effect from codeine or its derivatives (Becker 2008; Friedlander and Norman 2002).

A long-held and commonly believed drug interaction is between MAOIs and local anesthetics with vasoconstrictors. It was believed that inhibition of MAO could potentiate the activity of epinephrine by delaying its oxidation, leading to increased and potentially harmful cardiovascular reactions. Restriction on using local anesthetic with epinephrine or levonordefrin is frequently listed as a contraindication with MAOIs. However, review of the literature shows an absence of case reports to support this claim. More recent reviews show no credible evidence of a significant interaction between MAOIs and epinephrine or levonordefrin (Yagiela 1999; Brown and Rhodus 2005), and this has been supported by human and animal studies and clinical experience.

A similar contraindication for the use of epinephrine and levonordefrin has been proposed for TCAs. Animal models show significant interaction between TCAs and adrenergic vasoconstrictors (Yagiela 1999) including increases in systolic blood pressure. However, there are no case reports in the English literature that translate into clinically adverse events at the doses of local anesthetic used during most dental procedures, especially with epinephrine (Moodley 2017; Malamed 2014; Saraghi et al. 2017). Despite this, most anesthesia texts and pharmacology sites continue to suggest limiting the use of local anesthetics with epinephrine to 0.05 mg and avoiding the use of anesthesia with levonordefrin all together. Additional human research is needed to determine if therapeutic doses of local anesthetic with vasoconstrictors are related to negative cardiovascular outcomes in patient taking TCAs.

Mood Stabilizers

Traditionally, mood stabilizers were primarily antimanic agents, but more recently, the definition has been expanded to include agents with efficacy in treating acute symptoms of manic and depressive symptoms as well as in preventing these symptoms in bipolar disorder (Bauer and Mitchner 2004). Lithium is the only psychotropic agent that is truly a mood stabilizer, and it is considered the first-line drug for the treatment of bipolar disorder. While the mechanism of action is not completely understood, it is thought to somehow stabilize neuronal membranes, thereby reducing their rate of discharge and neurotransmitter turnover (Hashimoto et al. 2002; Alda 2015). It is excreted solely by the kidneys and has a number of side effects including cardiac dysrhythmias, GI disturbances, and tremors. It has a very narrow therapeutic ratio and a high risk of toxicity, necessitating strict adherence to a daily dosing schedule and careful monitoring of serum lithium levels. Early signs of lithium toxicity included nausea, vomiting, lethargy or drowsiness, slurred speech, and muscle weakness which quickly progress to ataxia, dysrhythmias, seizures, renal failure, and coma if serum levels are not lowered. In addition to lithium, the atypical antipsychotic olanzapine is also use to treat bipolar depression in patients who have refractory disease or are unable to tolerate lithium's side effects.

Several anticonvulsant medications have also proven useful in managing bipolar affective disorders in addition to seizure disorders. It is thought that they work by stabilizing the neuronal membranes and helping to suppressing the spread of impulses to neighboring neuron pathways. Commonly used anticonvulsants include carbamazepine, topiramate, lamotrigine, gabapentin, and valproate (both as divalproex and valproic acid) (Melvin et al. 2008).

Dental Pharmacology Implications for Patients Medicated with Lithium and Anticonvulsants

NSAIDs and metronidazole are two dental drugs that can cause lithium toxicity by reducing renal clearance in a short period of time. Likewise, tetracycline and doxycycline can raise lithium levels through an unknown mechanism causing the potential of toxicity. Macrolides such as erythromycin and clarithromycin can lead to increased serum levels of carbamazepine and divalproex/valproic acid leading to toxicity. Alternative antibiotics and pain medications are recommended.

Valproate (divalproex and valproic acid) can cause thrombocytopenia, abnormal platelet function, and changes in coagulation factor levels, leading to an increased risk of bleeding (Vasudev et al. 2010; Abdallah 2014). NSAIDs and aspirin should be avoided in patients taking these drugs. Carbamazepine can also cause blood dyscrasias, including anemia, leukopenia, and agranulocytosis, and so patients taking this drug are usually carefully monitored via frequent CBCs (complete blood counts) (Manu et al. 2016).

Antipsychotics

Antipsychotics are psychotropic drugs used to treat psychotic symptoms such as delusions and hallucinations seen in schizophrenia, mania, delusional disorder, and psychotic depression. They are also frequently used in patients with Alzheimer's

disease who have acute agitation. They are generally classified as typical (first generation) or atypical (second generation). They work as antagonists at dopamine receptors in various parts of the brain. Blockage of the D_2 receptors in the limbic system produces the antipsychotic result, but most of these drugs lack specificity for this receptor. Interaction with other dopamine receptors as well as other receptor systems, including histaminic, muscarinic, serotonergic, and α-(including histaminic, muscarinic, serotonergic and alpha-adrenergic receptors) receptors, produces many side effects (Miyamoto et al. 2012). These include extrapyramidal symptoms such as akathisia and tardive dyskinesia (more prevalent with typical antipsychotics), sedation, weight gain, xerostomia, orthostatic hypotension, cognitive impairment, prolactin effects, and cardiac changes including QT interval prolongation (Kennedy et al. 2013). Development of extrapyramidal symptoms with the typical antipsychotic medications is often treated by the addition of anticholinergic drugs, nonselective beta-blockers, or benzodiazepines.

Dental Pharmacology Implications for Patients Medicated with Antipsychotics

Antipsychotic medications may potentiate other central nervous system depressants such as narcotic analgesics. Caution should be used when prescribing to prevent orthostatic hypotension and respiratory depression (Friedlander and Marder 2002). Blockage of α1-receptors by the typical antipsychotics can cause orthostatic hypotension that theoretically could be worsened by the β2-receptor stimulation by epinephrine. Local anesthetic with epinephrine should be limited to no more than 0.05 mg of epinephrine in patients taking older antipsychotics like haloperidol and chlorpromazine. The macrolide antibiotics clarithromycin and erythromycin should be used cautiously in some of the newer atypical antipsychotics (like quetiapine) because of competing metabolism leading to increased serum levels of the antipsychotic. This can lead to QT interval prolongation and cardiac arrhythmias (Kennedy et al. 2013; Ozeki et al. 2010).

Benzodiazepines

Benzodiazepines are most commonly used to treat anxiety and are the drug of choice for generalized anxiety disorder. They are often used in combination with other antidepressants to treat panic disorders and other anxiety states. They work by indirectly enhancing γ-aminobutyric acid (GABA) neurotransmission and receptor sensitivity. Side effects include depressed respiration and cardiovascular tone, sedation, fatigue, and dependence (Kyrios 2014).

Dental Pharmacology Implications for Patients Medicated with Anxiolytics

Drug tolerance and dependence are of concern. Benzodiazepines have a wide therapeutic index, and therefore most dental drug interactions are unlikely to produce significant toxicity (Griffin III et al. 2013). Exceptions include macrolide antibiotics erythromycin and clarithromycin and the azole antifungals (fluconazole, ketoconazole, and itraconazole) that compete for the same hepatic cytochrome P450 enzyme needed to metabolize all benzodiazepines (except lorazepam). Co-administration can cause elevated serum levels and prolonged action, especially with triazolam and midazolam (Gubbins and Heldenbrand 2010). Additionally, caution should be used with other drugs that have the potential to enhance CNS and respiratory depression.

Parkinson's Disease

Parkinson's disease is a progressive neurological condition believed to be the result of both genetic and environmental factors. It is due to a loss of dopaminergic neurons in the substantia nigra region of the brain. It is estimated that more than 1.5 million people in the United States have Parkinson's disease (Tysnes and Storstein 2017). This number does not account for the thousands of cases that go undetected. Men are one and a half times more likely to have Parkinson's than

women (Anon 2018). Parkinson's disease ranks among most common late-life neurodegenerative diseases (after Alzheimer's disease) and affects approximately 1.5–2.0% of people aged 60 years and older (Nussbaum and Ellis 2003; Wirdefeldt et al. 2011; Pringsheim et al. 2014).

Clinical manifestations of Parkinson's disease include rigidity and bradykinesia accompanied by a resting tremor. Additionally, neuropsychiatric symptoms including cognitive impairment, depression, anxiety, hallucinations, and psychosis are common (Aarsland et al. 1999, 2009; Miyasaki et al. 2006).

Pharmacologic treatment of Parkinson's disease can be divided into symptomatic and neuroprotective (disease modifying) therapy aimed at controlling symptoms and maintaining functional independence. Treatment protocols aimed at controlling symptoms focus on increasing dopamine availability and preventing its breakdown by inhibiting acetylcholine. This is usually done via levodopa or levodopa/carbidopa alone or with the addition of catechol-O-methyltransferase (COMT) inhibitors. Although levodopa is the most effective medication available for treating the motor symptoms of Parkinson's disease, other neuroprotective medications such as monoamine oxidase type B inhibitors (MAO-BIs), amantadine, anticholinergics, β-blockers, or dopamine agonists may be initiated first to avoid levodopa-related motor complications (Connolly and Lang 2014). Neuropsychiatric symptoms are treated using SSRIs as the first drugs of choice, but tricyclic antidepressants, SNRIs, and antipsychotics may all be used depending on severity of the symptoms and patient's response to drugs (Menza et al. 2009; Bomasang-Layno et al. 2015; Suchowersky et al. 2006; Chen 2012) (Box 2). Common side effects of medications used to treat Parkinson's

Box 2 Pharmacologic Treatment of Parkinson's Disease (Suchowersky et al. 2006; Chen 2012)

Tremor control	**Cholinesterase inhibitors**
Amantadine (Symmetrel®)	Rivastigmine (Exelon®)
Trihexyphenidyl (Artane®)	Donepezil (Aricept®)
Benztropine (Cogentin®)	Galantamine (Razadyne®)
Propranolol (nonselective beta-blocker)	Tacrine (Cognex®)
Dopamine precursor	***N*-methyl-D-aspartate antagonist**
Levodopa/carbidopa	Memantine (Namenda®)
Sinemet®	Memantine and donepezil (Namzaric®)
Parcopa®	
Stalevo®	
Rytary®	
Dopamine agonists	**Antidepressants**
Pramipexole (Mirapex®)	Citalopram (Celexa®)
Ropinirole (Requip®)	Fluoxetine (Prozac®)
Apomorphine (Apokyn®)	Paroxetine (Paxil®)
Rotigotine (Neupro®)	Sertraline (Zoloft®)
Bromocriptine (Parlodel®)	Trazodone (Desyrel®)
MAO-B inhibitor	**Anxiolytics**
Selegiline (Eldepryl®)	Lorazepam (Ativan®)
Rasagiline (Azilect®)	Oxazepam (Serax®)
Safinamide (Xadago®)	Alprazolam (Xanax®)
Zydis selegiline HCL (Zelapar®)	Buspirone (BuSpar®)
COMT inhibitors	**Antipsychotics**
Entacapone (Comtan®)	Aripiprazole (Abilify®)
Tolcaone (Tasmar®)	Clozapine (Clozaril®)
Anticholinergics	Olanzapine (Zyprexa®)
Trihexyphenidyl (Artane®)	Quetiapine (Seroquel®)
Benztropine (Cogentin®)	Risperidone (Risperdal®)
	Ziprasidone (Geodon®)

disease include orthostatic hypotension, xerostomia, and bruxism.

Dental Pharmacology Implications for Patients Medicated for Parkinson's Disease

Potential drug interactions of concern include COMT inhibitors and local anesthetics with vasopressors. These drugs reversibly block catechol-O-methyltransferase inhibiting the inactivation of exogenously administered epinephrine and levonordefrin contained in a local anesthetic solution. Tachycardia, hypertension, and arrhythmias have been reported. Vasoconstrictors should be used with caution. Vital signs should be monitored during and after administration of the first carpules, and the total dose should be limited to 2 or less carpules of 1:100,000 (0.034 mg) of epinephrine. Care should be taken to aspirate to prevent intravascular injection (Malamed 2014; Balakrishnan and Ebenezer 2013). Retraction cord impregnated with epinephrine should not be used. Most antiparkinsonian drugs aimed at increasing the amount of dopamine present cause CNS depression, and therefore any additional sedative could have additive effect (Friedlander et al. 2009). Other drug reactions with the psychotropic drugs used in Parkinson's are covered previously.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition that accounts for 80% of all cases of dementia in the United States (Alz.org 2018). AD is characterized by a progressive and irreversible deterioration in cognitive abilities including memory and abstract thought and functionality that impairs activities of daily living ultimately leading to death. The exact etiology of AD is not known, but it is believed to be multifactorial, involving several genetic, environmental, and biologic risk factors. The formation of cerebral plaques composed of intracellular neurofibrillary tangles of tau proteins and extracellular amyloidal protein deposits is a key pathologic finding. These plaques lead to neuroinflammation that results in the progressive damage and destruction of cortical neurons (Selkoe and Schenk 2003; Walsh and Selkoe 2004; Kumar and Singh 2015). An estimated 5.7 million Americans are living with Alzheimer's dementia in 2018 including an estimated 5.5 million people age 65 and older and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's. Alzheimer's disease is the sixth leading cause of death in the United States and the fifth leading cause of death among those aged 65 and older (Alzheimer's Association 2018).

The rate of progression of the cognitive changes of AD is variable from patient to patient, but on average, a person with AD lives 4–8 years after diagnosis. Symptoms often predate a formal diagnosis by several years. Diagnosis is made on the basis of a history of pattern of symptoms over time including a clinical history of progressive dementia and the exclusion of other causes. Along with cognitive changes seen in AD, psychiatric and behavioral symptoms are common in patients with AD and contribute substantially to the morbidity of the illness. During the early stages, patients may experience personality changes such as irritability, depression, and anxiety. In the later stages, symptoms such as apathy, psychomotor impairment, and psychosis become more prevalent. Delusions or hallucinations appear in 30–50% of AD patients, and as high as 80% of patients exhibit agitated or aggressive behavior (Ropacki and Jeste 2005; Lopez et al. 2001).

Pharmacologic treatment of AD is aimed at modulating the decline of cognitive, functional, and behavioral symptoms by increasing the concentration of neurotransmitters in the brain (Box 3) (Kumar and Singh 2015; Casey 2015; Orgeta et al. 2017). None of the current pharmacologic treatments available alter the progressive pathophysiology of the disease or stop the damage and destructions of neurons but rather are considered to be symptomatic therapies. There are five FDA-approved drugs for the treatment of AD: three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), one *N*-methyl-D-

Box 3 Pharmacologic Management of Alzheimer's Disease (Casey 2015; Orgeta et al. 2017)

First-line medications	
Cholinesterase inhibitors	Donepezil (Aricept®) Galantamine (Razadyne®) Rivastigmine (Exelon®)
***N*-methyl-D-aspartate receptor Antagonists**	Memantine (Namenda®)
Combination	Memantine and donepezil (Namzaric®)
Adjunctive medications	
Antidepressants	Citalopram (Celexa®) Fluoxetine (Prozac®) Paroxetine (Paxil®) Sertraline (Zoloft®) Trazodone (Desyrel®) Venlafaxine (Effexor®)
Anxiolytics/hypnotics	Lorazepam (Ativan®) Alprazolam (Xanax®) Zolpidem (Ambien®) Triazolam (Halcion®)
Antipsychotics	Aripiprazole (Abilify®) Clozapine (Clozaril®) Haloperidol (Haldol®) Quetiapine (Seroquel®)
Mood stabilizers	Carbamazepine (Tegretol®) Divalproex sodium (Depakote®) Lamotrigine (Lamictal®) Levetiracetam (Keppra®)

aspartate (NMDA) antagonist (memantine), and one combination drug (memantine combined with donepezil). Early- to moderate-stage AD is treated using the cholinesterase inhibitors, which prevent the breakdown of acetylcholine and can delay worsening of symptoms and improved cognitive function for 1–5 years for about 50% of the patients that take them (Han et al. 2017). Common side effects include GI distress (nausea, vomiting, and diarrhea) as well as dizziness and fatigue (Noetzli and Eap 2013). Memantine either alone or with donepezil is used in more advanced disease and may delay worsening of symptoms by modulating the glutamate-induced overactivation of the NMDA receptor that contributes to neuronal damage and death (Kishi et al. 2017).

As AD progresses, behavioral symptoms and mood disorders often necessitate the initiation of psychotropic medications to modify these effects. These include all of the major groups of psychiatric medications including antidepressants (tricyclic, SSRI, and SNRI) for depression and apathy; anxiolytics for anxiety, restlessness, verbally disruptive behavior, and resistance; antipsychotic medications for hallucinations, delusions, aggression, agitation, hostility, and uncooperativeness; mood stabilizers for agitation; and sleeping aids for AD-associated sleep disturbances (Sink et al. 2005; Gauthier et al. 2010). While atypical antipsychotics are generally the first drugs of choice, they have been associated with increased mortality in patients with dementia and behavioral symptoms, and their effectiveness is low with no significant difference from placebo. Risperidone and olanzapine in particular have been linked to an elevated risk of cerebrovascular adverse events (Mulsant et al. 2005; Giron et al. 2001; Olin et al. 2002; Schneider et al. 2006; Wang et al. 2015). These drugs all cause some degree of xerostomia, which can increase the rate of caries and periodontal disease. The use of antipsychotic medications (especially the first-generation neuroleptics)

increases the risk of development of extrapyramidal symptoms that can lead to involuntary jaw movements making it difficult for the patient to eat, speak, and tolerate a removable prosthesis if needed.

Dental Pharmacology Implications for Patients with Alzheimer's Disease

Increased potential for adverse drug interactions may occur with the AD patient on multiple medications.

Care should be taken before prescribing antimicrobials, analgesics, and anxiolytics. Co-administration of galantamine with macrolide antibiotics or azole antifungals may decrease the metabolism of the cholinesterase inhibitors leading to both peripheral and central hypercholinergic effects, such as agitation, excitation, bradycardia, and loss of consciousness (Defilippi and Crismon 2003; Bentué-Ferrer et al. 2003). Many of the potential drug interactions of concern relate to the psychiatric drugs used to treat the behavioral aspect of AD and are covered earlier in the chapter (Pasqualetti et al. 2015).

Seizure Disorders

A seizure is the result of spontaneous excessive electric discharge of cerebral neurons that results in alteration in level of consciousness, motor activity, sensory changes, and behavioral abnormalities. Approximately 10% of Americans will experience a seizure in their lifetime. An isolated seizure can be due to many things including a high fever, drug or alcohol withdrawal, or a metabolic imbalance and is not classified as epilepsy.

Epilepsy refers to a group of common neurologic disorders characterized by chronic and recurrent paroxysmal seizure activity (at least two unprovoked episodes of unknown etiology) (Epilepsy Foundation 2018). It is the fourth most common neurologic disorder in the United States. In 2015, the Centers for Disease Control and Prevention estimated that 1.2% of the total US population (~3.4 million people) had active epilepsy (Zack and Kobau 2017). Incidence is highest among young children (<2 years of age) and the elderly (>70 years of age). There are over 30 different types of seizures and over 60 different types of epilepsy. Each is defined by such factors as cause, seizure type, age of onset, and clinical manifestations. There is frequent overlap of signs and symptoms, sometimes making the final diagnosis of the type of epilepsy difficult. Many patients have more than one type of seizure, and the features of each type of seizures may change over time (Robbins 2009).

The International League Against Epilepsy developed an international classification of epileptic seizures based on clinical and electroencephalographic features in 1981 which was revised in 2017 (Fisher et al. 2017). Seizures are divided into focal (previously partial) or generalized depending if one or both hemispheres of the brain are involved. Subcategories include motor or non-motor onset (for both) and retained or impaired awareness for focal seizures. Antiepileptic drugs (AEDs) are the mainstay of treatment (Box 4) (Glauser et al. 2016; Schmidt and Schachter 2014). They work by suppressing seizure occurrence but do not correct the underlying pathologic process that produces the seizures in the first place. Therefore, patients with epilepsy frequently need lifelong treatment. There are many available AEDs, some of which are used as monotherapy and others that are used in combination with other medications. They are categorized as first, second, and third generation based on when they were introduced for use. The majority of the older first generation AEDs are metabolized by the liver. These first-generation medications (carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid) are still commonly used but have a higher rate of undesirable dose-dependent side effects, including cognitive and sedating effects. Carbamazepine, ethosuximide, phenobarbital, phenytoin, and primidone are potent inducers (valproic acid is an inhibitor) of drug-metabolizing hepatic enzymes leading to clinically important adverse drug interactions.

Box 4 Antiepileptic (AED) Drugs (Glauser et al. 2016; Schmidt and Schachter 2014)

Narrow-spectrum AEDs (focal seizures)

- Carbamazepine (Tegretol®)
- Felbamate (Felbatol®)
- Gabapentin (Neurontin®)
- Lacosamide (Vimpat®)
- Oxcarbazepine (Trileptal®)
- Phenobarbital (Luminal®)
- Phenytoin (Dilantin®)
- Pregabalin (Lyrica®)
- Primidone (Mysoline®)
- Tiagabine (Gabitril®)
- Vigabatrin (Sabril®)

Broad-spectrum AEDs (focal and generalized seizures)

- Clonazepam (Klonopin®)
- Divalproex (Depakote®)
- Ethosuximide (Zarontin®)
- Lamotrigine (Lamictal®)
- Levetiracetam (Keppra®)
- Rufinamide (Bonze®)
- Topiramate (Topamax®)
- Valproic acid (Depakene®)
- Zonisamide (Zonegran®)

Compared to first-generation AEDs, the newer or second-generation agents generally have wider therapeutic ranges and fewer serious adverse effects (Löscher et al. 2013; Zhuo et al. 2017). Since fewer of these AEDs are metabolized by the liver, protein binding and drug interactions are not as problematic as some of the older medications (Chen et al. 2018).

The second-generation agents are also prescribed "off-label" "for non-seizure disorders, such as chronic neuropathic pain (including migraine), fibromyalgia, and trigeminal neuralgia. When used to treat pain, these agents may be referred to 'analgesics'." Their actions and use are significantly different from opiates or nonsteroidal anti-inflammatory drugs. Carbamazepine, gabapentin, lamotrigine, topiramate, and valproate are used as mood stabilizers in the treatment of bipolar disorder (Melvin et al. 2008). Anticonvulsants have been evaluated in some disorders of impulse control, such as impulsive aggressiveness (Brodie et al. 2016).

Dental Pharmacology Implications for Patients Taking AEDs

Anticonvulsants may increase hepatic microsomal enzyme activity, which can reduce the blood concentration of other drugs metabolized by the same enzyme system. Carbamazepine, phenytoin, primidone, and phenobarbital are particularly strong hepatic enzyme inducers leading to reduced serum concentrations of the coadministered drug and reduced pharmacologic effect. Affected drugs of clinical importance in dentistry include antibiotics (doxycycline, metronidazole), benzodiazepines (alprazolam, clobazam, clonazepam, diazepam, and midazolam), and steroids (dexamethasone and prednisone) (Patsalos and Perucca 2003). Clarithromycin, erythromycin fluconazole, ketoconazole, and metronidazole all inhibit the metabolism of carbamazepine, leading to potentially toxic level (Perucca 2006). Miconazole and fluconazole can substantially increase plasma concentrations of phenytoin. Valproate (divalproex and valproic acid) can cause thrombocytopenia, abnormal platelet function, and changes in coagulation factor levels, leading to an increased risk of bleeding (Vasudev et al. 2010; Abdallah 2014). NSAIDs and aspirin should be avoided in patients taking these drugs.

Conclusion

Neurologic and psychiatric illnesses are estimated to affect as many as 1.5 billion people worldwide. This number is expected to increase as the population ages—a number that is expected to grow as life expectancy increases (Gooch et al. 2017). Treatment of these chronic conditions involves long-term use of multiple pharmacologic agents, raising the concern of side effects and possible drug interactions with medications used during the delivery of dental care. With the

continued introduction of new therapeutic classes of drugs for these conditions, the potential for adverse drug interactions will continue to grow. Appropriate preoperative assessment of dental patients should always include obtaining a thorough medical history that includes a current complete list of medications. It is incumbent on the oral healthcare practitioner that an analysis of possible drug interactions be done prior to the administration or prescription of any drugs used during the provision of dental care.

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Endocrine Drugs of Significance in Dentistry

Arthur H. Jeske

Adrenocorticosteroids

Adrenal Supplementation for Medical Treatment of Adrenal Deficiency

Prolonged medical therapy with corticosteroids is a common intervention for a wide variety of diseases and conditions, including autoimmune diseases (e.g., lupus erythematosus, allergic reactions), eye and gastrointestinal diseases, musculoskeletal conditions, neurologic disorders, organ transplantation, and, of course, replacement of corticosteroids associated with adrenal cortical disorders, such as autoimmune Addison's disease. Natural adrenocorticosteroids are classified as glucocorticoids (with effects on intermediary metabolism and immunity, e.g., cortisol), mineralocorticoids (having salt-retentive functions, e.g., aldosterone), and androgenic/estrogenic hormones (Katzung and Trevor 2015).

Glucocorticoids have significant suppressive effects on inflammatory processes, by affecting the numbers, distribution, and functions of leukocytes and by reducing cytokines and chemokines. They also inhibit macrophage activity and antigen-presenting cells and block phospholipase A_2 with concomitant reduction of prostaglandin synthesis (Katzung and Trevor 2015).

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In dentistry, corticosteroids with anti-inflammatory activity are used in a variety of inflammatory conditions (e.g., pulpitis) and to control postoperative morbidity (e.g., oral surgery). Among the most frequently used and studied agents are dexamethasone (e.g., Decadron®), methylprednisolone, and prednisolone.

In endodontics, evidence from several recent systematic reviews suggests that steroids appear to be effective in cases of irreversible pulpitis (Aminoshariae et al. 2016; Nogueira et al. 2018) and, depending on the type and dose of agent, can be effective for management of postoperative pain of endodontic origin (Shamszadeh et al. 2018). Among betamethasone, dexamethasone, prednisolone, and methylprednisolone, prednisolone appeared to produce significantly greater pain reduction at 6 h, possibly associated with its more rapid diffusion into cells, where nuclear DNA transcription is affected by these agents (Shamszadeh et al. 2018). Anti-inflammatory corticosteroids available in the USA and their dosages are summarized in Table 1.

The perioperative use of corticosteroids in oral surgery is well-documented, with demonstrated effectiveness for the reduction of swelling and trismus, although outcomes for pain reduction are equivocal (Arora et al. 2018; Varvara et al. 2017). Administration of the corticosteroid achieves greater effectiveness when the parenteral, rather than other, route is utilized, and by administration of the corticosteroid prior to the surgical procedure

Table 1 Summary of anti-inflammatory corticosteroids

Agent	Anti-inflammatory activity[a]	Equivalent dose (mg)[b]
Hydrocortisone	1	20
Cortisone	0.8	25
Prednisone	4	5
Prednisolone	5	5
Methylprednisolone	5	4
Betamethasone	25–40	0.6
Dexamethasone	30	0.75

[a]Relative to hydrocortisone
[b]Dose equivalent to hydrocortisone

(Herrera-Briones et al. 2013), preoperative administration is likely more successful because of the relatively slow onset of action of these agents, associated with their principal action in altering gene transcription. With regard to dose of synthetic corticosteroids, a recent prospective randomized clinical study demonstrated that there was no difference between 4 and 8 mg doses of dexamethasone in the suppression of postoperative edema following third-molar surgery, although the same study was unable to detect a significant analgesic action of the drug (Arora et al. 2018).

Currently, the American Association of Oral and Maxillofacial Surgeons recommends consideration of the use of a perioperative corticosteroid (dexamethasone) to limit swelling and decrease postoperative discomfort after third-molar extractions as part of its white paper recommendations on opioid prescribing and acute and postoperative pain management (American Association of Oral and Maxillofacial Surgeons 2017), without specification of dosage.

Management of Patients At-Risk of Acute Adrenal Insufficiency

It is generally held that corticosteroid therapy lasting longer than 2 weeks can result in adrenal cortical suppression due to negative feedback of the supplemental hormone on the secretory cells of the adrenal cortex. It is important to note that this suppression is also associated inhalational use of corticosteroids for chronic asthma. Symptoms associated with acute adrenal insufficiency may occur during stressful dental procedures, and while rare, they can be life-threatening. This condition is classified as primary adrenal insufficiency (e.g., destruction or atrophy of the adrenal gland), secondary adrenal insufficiency (e.g., pituitary disorders), Cushing syndrome (e.g., long-term corticosteroid use as anti-rejection therapy in organ transplantation), and adrenal crisis. Adrenal crisis is of great concern when managing patients undergoing stressful or prolonged procedures, such as quadrant surgeries. Clinically, adrenal crisis is due to inadequate secretion of endogenous corticosteroids during stress and involves several organ systems, including the GI tract (cramping, nausea, vomiting), with hypotension, weakness, fatigue, headache, cyanosis, dehydration, and muscle and joint pain. The underlying biochemical changes include hyponatremia, eosinophilia, hypoglycemia, and azotemia. Therapy must be immediate and aggressive and usually involves administration of fluids and electrolytes and infusion of high doses of hydrocortisone (Miller et al. 2001). Risk factors for the development of adrenal crisis include adrenal insufficiency, pain, infection, invasive procedure, general anesthesia, and poor health status at the time of the procedure. Fortunately, this condition occurs only rarely, with an estimated risk of less than one case per 650,000 with adrenal insufficiency. This is based on a recent systematic review that identified six documented case reports over a 66-year period (Khalaf et al. 2013).

In spite of the low incidence of adrenal crisis in patients with adrenal insufficiency who are undergoing dental procedures, recommendations for perioperative corticosteroid supplementation persist, despite findings that routine dental procedures done under local anesthesia are very unlikely to precipitate adrenal crisis (Miller et al. 2001). Dental outcomes notwithstanding, the incidence of clinically significant adrenal insufficiency appears to be significantly higher in surgical intensive care unit populations. In one prospective study of patients seen for trauma, general surgery, urology, and gynecologic oncology over a 9-month period, the overall rate of adrenal insufficiency was 0.66% (Barquist and Kirton 1997). On this basis, recommendations

Table 2 Corticosteroid supplementation for various types of dental procedure risk category in patients with adrenal insufficiency (Miller et al. 2001)

Corticosteroid supplementation for types of dental procedures by risk category in patients with adrenal insufficiency
Negligible risk
Nonsurgical dental procedures
Supplementation regimen: none required
Mild risk
Minor oral surgery (limited number of simple extractions, biopsies)
Supplementation regimen: 25 mg hydrocortisone equivalent day of procedure
Moderate-to-major risk
Major oral surgery (multiple extractions, quadrant periodontal surgery, impaction surgery, general anesthesia, procedures >1 h)
Supplementation regimen: 50–100 mg hydrocortisone equivalent day of procedure and for at least 1 day postoperatively

for supplementation have been based upon stratified risks, as presented in Table 2.

Oral Contraceptives, Estrogen/Progestogens

Oral contraceptive drugs are among the most widely prescribed pharmaceutical products throughout the world. Recent estimates based on a large-scale cohort in the UK indicate that 16.2% of women aged 12–49 years used a combination of oral contraceptive and an additional 5.6% used a progestogen-only birth control pill (Cea-Soriano et al. 2014). In the USA, based on estimates from 2018, prescriptions for estrogens, ethinyl estradiol, and various contraceptive combination products typically represent several preparations among the most widely drugs.

For many years, the relationship between the use of estrogens and periodontal disease and postsurgical complications (e.g., acute alveolar osteitis) has been known and studied in dentistry (Almeida et al. 2016). Additionally, the increased risk of pregnancy in female dental patients taking oral contraceptives caused by antibiotic therapy has raised medicolegal concerns in the dental profession.

Antibiotic/Oral Contraceptive Interaction

There are three potential mechanisms by which the effectiveness of oral contraceptives may be reduced by antibiotics (Taylor and Pemberton 2012):

1. Diarrhea and vomiting. Both vomiting and persistent diarrhea result in reduce absorption of combined oral contraceptives (e.g., progestogen with ethinyl estradiol) and progestogen-only formulations. In such cases, it is recommended that if vomiting occurs within 2 h of taking the medication, another dose should be taken immediately, and in the case of diarrhea, additional contraceptive measures should be used until recover is complete.
2. Enzymatic induction by antibiotics. Rifamycin-type antibiotics (e.g., rifampicin, rifabutin) can induce hepatic microsomal oxidase enzymes which breakdown ethinyl estradiol, and the resultant decrease in circulating ethinyl estradiol levels reduces its contraceptive effect. While this interaction has been scientifically documented to result in alterations to estrogen pharmacokinetics, no studies to date have evaluated actual pregnancy risks associated with the alteration of blood levels of oral contraceptive (Simmons et al. 2018a).
3. Disruption of gastrointestinal flora associated with antibiotics. Ethinyl estradiol also undergoes enterohepatic cycling necessary for the activation by gut bacteria of the hormone prior to it being reabsorbed, although progestogens do not undergo this recycling. Therefore, concerns have been raised about non-rifamycin-type antibiotics, including common dentally prescribed agents such as penicillins, and their potential to reduce the effectiveness of oral contraceptives containing ethinyl estradiol. However, a recent systematic review with 29 included studies indicated that evidence derived from clinical and pharmacokinetic studies does not support the existence of drug interactions between hormonal contraception and non-rifamycin antibiotics (Simmons et al. 2018b). Concurrently, another individual

study of the impact of dicloxacillin on pregnancy risk among 364 Danish females taking oral contraceptives and using dicloxacillin prior to conception determined an odds ratio for unintended pregnancy of 1.18 (95% CI 0.84–1.65), although the risk was slightly higher for users of progestogen-only contraceptives (OR 1.83, 95% CI 0.63–5.34) (Pottegard et al. 2018). Interestingly, virtually all authors of publications related to this subject advise caution and the recommendation for supplementary contraceptive measures for some or all conditions in which females are exposed to antibiotics while taking oral contraceptive agents (Taylor and Pemberton 2012).

Oral Contraceptives and Periodontal Disease

Oral contraceptive use has for quite some time been associated with gingival inflammation (Heasman and Hughes 2014), apparently beginning in the early era of oral contraception in which estrogen dosages were relatively high. However, the most recent studies demonstrate that in the era of "modern" low-dose oral contraceptive formulations, these drugs do not place patients at an increased risk for gingivitis or periodontitis (Preshaw 2000).

Oral Contraceptives and Risk of Postoperative Localized Alveolitis

The increased risk for localized alveolitis in users of oral contraceptive drugs has been well-documented and known to be positively associated with the dose of estrogen in the contraceptive. It is also documented that the risk for this post-extraction complication can be reduced in users of oral contraceptives if tooth extraction is performed during the 23rd through 28th day of the pill cycle (Catellani et al. 1980). Recently, a meta-analysis has provided more robust statistical estimates of the likelihood of alveolar osteitis in oral contraceptive users (Bienek and Filliben 2016). In this review that included 29 studies, it was found that among females, oral contraceptive use nearly doubled the rate of alveolar osteitis (13.9% among users, 7.5% among nonusers). Additionally, this study demonstrated a greater risk generally for females than males, and the vast majority of the studies reviewed determined that smokers had a significantly higher risk of complication. Therefore, the current scientific evidence suggests a need for additional vigilance in monitoring patients for the development of localized alveolitis following tooth extraction if they take oral contraceptives.

Thyroid and Antithyroid Agents

The appropriate dental management of patients with thyroid disease rests upon understanding the physiological effects of the disease, recognition of the signs and symptoms that represent inadequate control of the disease, and safely using dental therapeutic agents, with an emphasis on avoiding adverse drug interactions and side effects. Worldwide, the prevalence of overt hyperthyroidism in countries with sufficient iodine supplementation ranges from 0.2 to 1.3% (Taylor et al. 2018). In the USA, based on the 2002 National Health and Nutrition Examination Survey (NHANES III), overhyperthyroidism occurred in 0.5% of the population, with 0.7% having subclinical hyperthyroidism, and there is a significantly higher incidence in females than males (2.7% vs. 0.23%) (Taylor et al. 2018).

There are three major classes of agents used to manage thyroid disease in outpatients (Table 3) (Katzung and Trevor 2015). The major concerns for the dental management of patients with thyroid disease center on the assessment of the stability of the patient's disease, compliance of the patient with thyroid supplementation (in cases of hypothyroidism), physical assessment of the patient at the time of the dental procedure (e.g., vital signs), recognition of the signs and symptoms of hypo- and hyperthyroidism, and planning for potential emergencies that might be expected in patients with thyroid disease. One of the major

Table 3 Major classes of drugs used in the treatment of thyroid disease

Drug class	Indication	Toxicity(ies)
Thyroid preparations (levothyroxine, liothyronine)	Hypothyroidism	Symptoms of thyroid excess (text)
Antithyroid preparations (methimazole, propylthiouracil)	Hyperthyroidism	GI distress, rash, agranulocytosis, hepatitis, hypothyroidism
Beta blockers (propranolol)	Hyperthyroidism	Asthma, AV block, hypotension, bradycardia

concerns has been related to the potential interaction between thyroid supplementation and vasoconstrictors used in local anesthetics.

In dental patients, in addition to the patient's medical history, hypothyroidism is associated with hypotension, tachycardia, lethargy, cold intolerance, myxedema, reduced respiratory rate, and weight gain. Significantly, hypothyroidism may also put the patient at increased risk of seizures (Garber et al. 2012). Hyperthyroidism is associated with heat intolerance, tachycardia, palpitations, nervousness, proptosis, tremor, warm skin, and weight loss.

The most recent guidelines for the management of patients with thyroid disease suggest that it be done in three phases—pretreatment, intraoperative, and posttreatment (Pinto and Glick 2002). Prior to dental treatment, the type of thyroid disease should be determined, as well as the possible presence of comorbid conditions, such as cardiovascular disease. In any case in which thyroid disease is suspected but untreated, elective dental therapy should be postponed until medical evaluation and stabilization has been completed. It is recommended that medical control of the disease be determined by obtaining baseline thyroid-stimulating hormone levels and complete blood counts. The type of medication(s) used to treat the disease should also be determined and potential adverse drug interactions evaluated. Baseline vital signs must be assessed prior to undertaking dental treatment.

During treatment, vital signs should be regularly monitored, and appointment duration is limited to the patient's tolerance. Local anesthetics with epinephrine are not contraindicated when medical therapy has resulted in a normal (euthyroid) state (Johnson et al. 1995). However, one review article suggests that summation of the cardiovascular effects of epinephrine with those of excessive blood levels of thyroid hormone can occur, and the interaction was rated as category 4 (major or minor, with "possible," not established, documentation) (Yagiela 1999). Current drug literature databases (drugs.com; see chapter "Internet Resources for Dental Pharmacology") rate the interactions as "moderate," with a need for monitoring for signs and symptoms of adverse effects. A recent case report suggests that rapid intervention in suspected cases of thyroid storm can result in uneventful recovery, although medical assistance should be summoned (Lee et al. 2016).

Following treatment, caution should be exercised in regard to the increased sensitivity of the hypothyroid patient to central nervous system depression, e.g., with opioid analgesics. In hyperthyroid patients, precautions should be taken in regard to the use of NSAID analgesics or aspirin, due to the possible presence of cardiovascular disease and the reduced binding of thyroxin (T_4) to T_4-binding globulin, resulting in increased levels of free thyroxin and possible thyrotoxicosis (Yagiela 1999).

Conclusion

The pharmacological management of dental patients with endocrine disorders varies with the severity of the disease and the type(s) of medications and/or hormonal supplements prescribed by physicians managing the endocrine disease. In patients with endocrine disorders, a careful medical history and consultation with patients' physicians are necessary to not only safely administer and prescribe dental drugs but to assess the patient's physical status, ability to tolerate dental procedures, and anticipate emergencies that might arise in conjunction with dental treatment.

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Pharmacologic Management of Oral Mucosal Inflammatory and Ulcerative Diseases

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Oral Mucosal Inflammatory and Ulcerative Diseases of Infectious Origin

Herpes Simplex Virus Type 1 (HSV-1) Infections

Description

Primary herpetic gingivostomatitis usually arises in children and young adults. Primary infection may be mild or asymptomatic; however, clinical features can present in up to 30% of patients. Infection is almost always associated with HSV-1 although primary orofacial HSV-2 infection has been reported in some older patients due to sexual practices.

Clinical Features

Primary HSV Infection

- There is a wide range of signs and symptoms including myalgia or malaise followed in 1–3 days by mucocutaneous vesicular eruptions of the lips, tongue, hard and soft palates, buccal mucosa, and gingiva. The blisters quickly breakdown to form painful shallow ulcers surfaced by a yellow to gray pseudomembrane with a red halo. The ulcers generally heal within 2 weeks without scarring. Other clinical findings may include lymphadenopathy, headache, coated tongue and malodor, loss of appetite, and hypersalivation.
- Differential diagnoses of primary HSV include herpetiform recurrent aphthous ulcerations, necrotizing ulcerative gingivitis, infectious mononucleosis, erythema multiforme minor, Coxsackie virus, and varicella-zoster virus infection.

Recurrent HSV Infection

- Reactivation of the latent HSV can be triggered by many causes or may be spontaneous. Reported trigger factors include fever, invasive dental procedures, UV light, emotional stress, fatigue, immunosuppression, and trauma.
- Recurrent HSV in immunocompetent individuals typically occurs on the lips and keratinized oral mucosa such as hard palate and attached gingiva. The lesions begin as red macules which form vesicles which are highly infectious. The vesicles break forming scabs or ulcers. In the oral cavity, due to masticatory forces, vesicles may not be seen. In addition, rather than a single ulcer, small crops of shallow ulcers can occur, chiefly on the palate. The ulcers generally heal within 2 weeks.

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Chronic (Recrudescent) Herpetic Ulcers

- Associated with immunosuppression, including solid organ and bone marrow transplants, AIDS, and long-term immunosuppressive drug therapy. Unlike recurrent HSV-1 intraoral lesions in immunocompetent individuals, chronic HSV lesions can present on both keratinized and nonkeratinized mucosa and hence may be difficult to distinguish from other oral mucosal disorders including recurrent aphthous ulcers. The lesions can last for prolong periods of time and may appear as crateriform ulcers or can exhibit a distinct linear ulceration. The ulcers may be red or have a pseudomembranous cover (Table 1).

Diagnosis

- Usually diagnosis of primary and recurrent HSV infection is based on the clinical history and patient presentation. When the presentation is atypical (i.e., chronic herpetic ulcers), confirmatory laboratory testing is required.
- A Papanicolaou (Pap) test or Tzanck test can show virally altered epithelial cells obtained from the lesion. However, false negatives can occur as the test reportedly detects <60% of infections.
- Detection of viral DNA of HSV by polymerase chain reaction (PCR) is more sensitive than tissue culture and is not contingent upon the presence of viable virus.
- Serological testing of HSV is not always accurate and may give both false negatives and false positives, particularly in type-specific antibody tests for HSV-1 and HSV-2.

Therapeutic Guidelines

- Primary HSV-1 infection is a self-limiting condition in an immunocompetent individual and needs only symptomatic treatment. It is important to ensure adequate hydration and nutrition. Other topical therapies include ice, lip balms, and over-the-counter topical anesthetic preparations.
- In immunocompetent individuals, therapy may be of limited benefit for primary HSV-1 infection. Systemic antiviral therapy has proven beneficial if the drug is started within 48 h of onset (Table 2).
- Prophylactic antiviral therapy in immunosuppressive patients at high risk for chronic HSV is usually administered (Table 2). Sunscreen, especially to the lips, may help in preventing recurrent HSV infection.

Table 1 Differential diagnoses for oral inflammatory and ulcerative diseases based on clinical presentation and etiology

	Etiology		
Type	Infectious	Immunologic	Other
Primary			
Acute	Primary herpesvirus infection	Erythema multiforme	Traumatic ulcers
Chronic	Mucositis: candidiasis Ulcer: cytomegalovirus infection Deep fungal infections: histoplasmosis and blastomycosis	None	Oral squamous cell carcinoma, necrotizing sialometaplasia, ulcerations with sequestration
Recurrent			
Acute	Recurrent herpes simplex virus and herpes zoster virus infection	Recurrent aphthous stomatitis (RAS) Herpes-associated erythema multiforme	None
Chronic	Chronic HSV	Lichen planus, mucous membrane pemphigoid, pemphigus vulgaris drug-mediated oral reaction	None

Table 2 Commonly prescribed pharmacologic therapy for primary and recurrent oral HSV infection

Disease status	Acyclovir	Valacyclovir	Famciclovir
Immunocompetent patient			
Primary HSV infection	200 mg 5× day for 10 days	1000 mg BID for 10 days	250 mg TID for 10 days
Recurrent HSV infection	200 mg 5× day for 5 days	500 mg BID for 3 days	125 mg BID for 5 days
HSV-prophylaxis/suppression[a]	400 mg BID	500 mg QD	250 mg BID
Immunocompromised patient			
Primary HSV infection	400 mg 5× day for 10 days	N/A	N/A
Recurrent HSV infection	400 mg TID for 7–10 days	500 mg BID for 7 days	500 mg BID for 7 days
HSV-prophylaxis/suppression[a]	400 mg BID	500 mg BID	500 mg BID

Note: Use all systemic HSV medications with caution when prescribing to patients with impaired renal function and hepatic disease. For use in prepubescent children use acyclovir

[a]Off-label use for suppressive antiviral therapy for recurrent erythema multiforme

- Both topical (acyclovir 5% ointment and penciclovir 1% cream) and systemic antiviral therapies (acyclovir, famciclovir, and valacyclovir) are approved for treating primary and recurrent oral HSV infections (Table 2).

Oral Candidiasis and Associated Oral Lesions

Description

Oral candidiasis, a fungal infection, is the most common opportunistic infection affecting the oral cavity. *Candida albicans* (*C. albicans*) is a commensal organism and is part of the normal oral flora, found in at least 35% of healthy, asymptomatic mouths. The organism becomes a pathogen when the immune system is compromised or mucosal barriers are disrupted causing disease. Local predisposing factors include removable dentures, xerostomia, and local immunosuppression such as topical steroid or antibiotic use. Systemic predisposing factors include diabetes mellitus, HIV infection, B12 or iron deficiency anemia, and medications such as corticosteroids, broad spectrum antibiotics, and chemotherapy. Most oral infections are caused by *C. albicans*, but other species have been isolated including *C. tropicalis*, *C. glabrata*, and *C. krusei*. *C. albicans* is a dimorphic organism and can grow as a yeast or in hyphal form, which can colonize the superficial layers of the oral epithelium.

Clinical Features

Oral candidiasis has numerous clinical presentations, and the patient may have more than one presentation at the same time.

Pseudomembranous Candidiasis

- It is the most readily recognized form of oral candidiasis that presents with white/yellow curd-like adherent plaques that can be removed with scraping. The underlying mucosa is erythematous. This form of candidiasis can occur anywhere in the oral cavity although the tongue, buccal vestibule, and oropharynx are typically infected. Patients may complain of an altered taste and may have mild pain.
- Pseudomembranous candidiasis may occur as localized infection in the soft palate in asthmatic patients using inhaled corticosteroids. Oral candidiasis associated with inhaled corticosteroid use is seen more commonly in patients using high-potency corticosteroid fluticasone than those treated with low potent beclomethasone.

Atrophic (Erythematous) Candidiasis

- Presents as diffuse erythema lacking any of the white curd-like pseudomembranes. Acute erythematous candidiasis results from persistent pseudomembranous candidiasis.
- Palate and dorsal tongue are the most common sites for chronic atrophic candidiasis. It commonly presents as generalized diffuse erythema with depapillation (atrophic glossitis) of the dorsal surface of the tongue. Typically,

the dorsal tongue appears red and atrophic or bald with loss of the filiform papillae. Affected patients frequently complain of chronic tongue soreness and burning sensation, particularly when eating spicy foods.

- Chronic erythematous candidiasis is the most common type of candidal infection seen in the elderly and in individuals wearing removable complete or partial dentures with acrylic denture base, commonly known as denture stomatitis.

Denture Stomatitis

- Presents as erythema under a full or partial acrylic denture and is caused by poor denture hygiene. The maxillary alveolus and hard palate are most commonly affected sites. Denture stomatitis can be mistaken for a contact allergy as the erythema corresponds to the denture margins. Most commonly seen in 24-h denture wearers. Chronic irritation from poor-fitting dentures and failure to remove the dentures while sleeping are the main causes for the development of chronic candidal infection.
- Candidal adherence to the acrylic denture bases occurs directly to the poorly fitting dentures with roughened surfaces, and pre-existing bacterial plaque leads to the formation of candidal biofilm. Formation of the candidal biofilms in denture bases promotes transition from blastospores to hyphae, increasing their virulence and infectivity. Hence, poorly fitting dentures acting as reservoirs for candidal organisms contribute to recurrence of this form of candidiasis in denture wearers.

Median Rhomboid Glossitis

- Presents as a central area of erythema along the midline dorsal tongue with atrophic papillae. Steroid inhalers, smoking, and poor oral hygiene are predisposing factors. Occasionally, a similar lesion can be observed on the palate where the affected tongue comes in contact.
- Median rhomboid glossitis may be asymptomatic, or patients may comp\lain of altered taste or discomfort when eating spicy or acidic foods.

Angular Cheilitis

- Presents as erythematous fissured areas at the corners of the mouth and is a mixed fungal and bacterial infection. Predisposing factors include loss of vertical dimension, whereby the mucosa of the upper and lower lips overlap, creating a constant warm and moist environment promoting infection.
- Although angular cheilitis can occur alone, it is often seen with intraoral candidiasis, usually the atrophic form including denture stomatitis. Patients complain of discomfort particularly when opening the mouth. Circumoral type of erythematous candidiasis, involving entire upper and lower lips and perioral skin, is seen in patients who habitually lick their lips or frequently use petroleum-based lip balms for dry lip.

Chronic Hyperplastic Candidiasis

- Presents as isolated thick white plaques that do not wipe off. Clinically it can be confused with oral leukoplakia. It frequently occurs in individuals without any local or systemic predisposing factors, involving the retrocommissural area or lateral surface of the tongue.
- Hyperplastic candidiasis mimicking leukoplakia would resolve completely after a course of antifungal treatment. In contrast, conventional leukoplakia with dysplasia (premalignant lesion) which frequently have secondary candidal infection/colonization will not resolve with a course of antifungal treatment.

Diagnosis

- Most forms of oral candidiasis can be diagnosed based on the clinical findings, along with detailed medical and dental history. If the patients have had a recent history of antibiotic or steroid use, or if the presentation is an area of bright erythema underneath a denture, the diagnosis is often straightforward.
- Chronic hyperplastic candidiasis can mimic oral leukoplakia and may require biopsy to confirm the infectious nature of the clinical findings. Oral exfoliative cytology can confirm the presence of candidal hyphae and yeast forms.

- Fungal cultures can also be used, but this is rarely done except in individuals who are resistant to standard therapy. A culture can identify the exact species of *Candida* and their drug sensitivity.

Therapeutic Guidelines

- Determining the predisposing factor(s) causing oral candidiasis is the important first step, as even with appropriate antifungal medication recurrent candidiasis can be an ongoing problem.
- Patients with complete and removable partial dentures should remove the dentures while sleeping. Frequent denture disinfection is recommended to prevent the recurrence of denture stomatitis. This can be accomplished by soaking the denture overnight in chlorhexidine, which has fungal static properties.
- Alternative methods for disinfecting acrylic denture bases include soaking the denture in sodium hypochlorite (1%) for 10 min or subjecting the dentures for microwave irradiation (800 W) immersed in water for 6 min.
- Candidiasis in patients with xerostomia benefit from a multipronged approach as hyposalivation can have many causes. The most common cause is drug-induced xerostomia, but radiation to the head and neck and Sjögren syndrome are also associated with xerostomia. Patients should be encouraged to maintain good oral hygiene, proper hydration, and frequent rinsing to keep the mouth moist. Over-the-counter saliva substitutes may be helpful, and in some cases, pilocarpine or cevimeline, which stimulate salivary flow, can be prescribed.
- Patients with oral candidiasis secondary to steroid inhalers should be educated on the importance of rinsing the mouth thoroughly after inhaler use or using inhalers with spacer devices.
- Patients need to be reminded to remove their dentures when using the topical treatment as the medication will not reach the affected area. In addition, denture wearers can line the inside of the denture with either nystatin or clotrimazole cream daily as an appropriate antifungal treatment for the denture.
- Topical nystatin, ketoconazole, and clotrimazole creams are also useful for angular cheilitis (Table 3). If there is a significant inflammatory component, topical antifungal-corticosteroid combination therapy with either clotrimazole-betamethasone cream or nystatin-triamcinolone cream can be used as the steroid will quickly reduce the inflammation.
- Topical or systemic antifungal therapies are usually the first line of treatment in oropharyngeal candidiasis which are listed in Table 3. Nystatin oral suspension or pastilles and clotrimazole troches used as topical therapy are usually effective in resolving the oral candidiasis. The patient needs to be reminded not to rinse, drink, or eat for at least 30 min after using the topical antifungal medications to prevent the drug from being diluted or washed away. Topical miconazole, a mucoadhesive tablet sold under the brand name of Oravig, is applied to the maxillary vestibule near the canine fossa once a day.
- Systemic medications for oral candidiasis include fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole, and echinocandins; however fluconazole is the first-line systemic treatment (Table 3).
- Fluconazole is effective in oropharyngeal candidiasis and in patients who have failed topical antifungal treatment. Fluconazole is used to treat candidiasis in patients with immunosuppression from HIV infection, cancer therapy, solid organ and marrow transplant, as well as autoimmune disease. Fluconazole can also be used as a preventive agent in this population who are susceptible to recurrent infections. It is important to be aware of drug interactions before prescribing fluconazole, including warfarin, statins, phenytoin, proton pump inhibitors, and sulfonylureas. Fluconazole should be used with caution in patients who have impaired liver function.
- Posaconazole is recommended as prophylaxis for invasive candidiasis in severely immunocompromised and allogenic hematopoietic stem cells transplant (aHSCT) patients. Posaconazole is the treatment of choice for

Table 3 Commonly prescribed pharmacologic therapy for oropharyngeal candidiasis and angular cheilitis

Disease	Nystatin	Clotrimazole	Fluconazole	Posaconazole[a]
Oropharyngeal candidiasis	Oral suspension; 100,000 units/mL 1tsp, 4× daily for 2 weeks, hold for 3 min, expectorate, no food/ liquid/rinsing for 30 min[b]	Troches, 10 mg 5× day for 2 weeks, NPO 30 min[b]	Tablet, 100 mg, BID on day 1, then 100 mg/day for 13 days[c]	Oral suspension; 40 mg/mL 100 mg (2.5 mL) PO BID on day 1, then 100 mg PO QD for 13 days
Angular cheilitis	Cream; 100,000 units/g; apply topically 4× day for 2 weeks	Clotrimazole and betamethasone dipropionate; 1%/0.05% apply topically 4× day for 2 weeks	N/A	N/A

[a]Prophylaxis for invasive candidiasis in severely immunocompromised and allogeneic hematopoietic stem cells transplant (aHSCT) patients and treatment for oropharyngeal candidiasis refractory to fluconazole
[b]*Note: If the patients wear dentures, these must be removed before rinsing*
[c]*Note: Be aware of possible drug interactions with warfarin, statins, oral hypoglycemic agents; may need a 4-week course in selected cases*

oropharyngeal candidiasis refractory to fluconazole (Table 3).

Immune-Mediated Oral Mucosal Inflammatory and Ulcerative Diseases

Recurrent Aphthous Stomatitis

Description

Recurrent aphthous stomatitis (RAS) commonly known as aphthous ulcers or canker sores is a self-limiting, chronic oral mucosal disease that presents as solitary single or multiple painful ulcers. RAS is the most frequent form of recurrent solitary oral ulcers affecting approximately 20% of the general population with a slight female predilection. Most RAS patients are healthy young (age range 10–19 years) individuals without any underlying systemic immune deregulation.

Clinical Findings

Recurrent Aphthous Stomatitis (RAS)

- RAS is usually preceded by prodromal symptoms of burning or tingling for up to 48 h before lesion onset. The ulcers generally occur on nonkeratinized mucosa and appear as an ulcer with a white-yellow pseudomembranous covering surrounded by an erythematous halo.
- RAS is classified into three forms based on size, site, duration, and the tendency to heal with scarring; minor (MiRAS), major (MaRAS), and herpetiform (HeRAS) types.
- Minor RAS (MiRAS) is the most common type seen in 80% of RAS patients. The MiRAS ulcers are usually less than 1 cm in diameter and heal within 2 weeks.
- Major RAS (MaRAS) are rare and more severe form of RAS presenting as continuously recurring ulcers measuring more than 1 cm in diameter with a healing time exceeding 2–3 weeks. These ulcers tend to heal with scaring and have predilection to lips and posterior portion of the oral cavity (soft palate and oropharyngeal fauces).
- Herpetiform RAS (HeRAS) is the least common form of RAS that appear as numerous small ulcers (2–3 mm in diameter) that can affect multiple intraoral sites. HeRAS tends to occur at a later age (>20 years) than other clinical types which is more common in females than males.

Behçet's Syndrome

- Behcet's syndrome is a rare systemic vasculitis characterized by oral and genital ulcers and ocular lesions, including uveitis. Vascular manifestations include venous thrombosis in up to 30% of cases.

- Arthritis and/or arthralgia is frequently the presenting feature most commonly of the knees and ankles along with other systemic manifestations. The cause is unknown but is believed to be due to an autoimmune process triggered by an environmental or infectious agent in a genetically predisposed patient. HLA-B51 on chromosome 6p is the most strongly associated risk factor for Behçet's syndrome.
- Patients presenting with constant recurrence of >3 major aphthous ulcer are diagnosed as "complex aphthosis" which is considered to be a "forme fruste" (attenuated manifestation) of Behcet's syndrome.

Periodic Fever Adenitis Pharyngitis Aphthous Ulcer (PFAPA) Syndrome

- PFAPA is a recurrent fever syndrome characterized by episodes of fever lasting between 3 and 6 days, associated with at least one additional clinical finding: aphthous stomatitis, cervical adenitis, and pharyngitis. PFAPA regularly recurs every 3–8 weeks. The age of onset varies but usually presents in children and adolescents.

Drug-Induced Aphthous-Like Oral Ulcers

- In rare instances, older patients without a history of RAS develop ulcers after starting taking a new drug. Antianginal drug nicorandil is the most frequently cited drug to cause aphthous-like ulcerations.
- The angiotensin-converting enzyme (ACE) inhibitor captopril and the ACE II antagonist losartan may also cause aphthous-like oral ulcers.
- Other systemic drugs implicated in oral ulcers include a number of nonsteroidal anti-inflammatory drugs (i.e., diclofenac, naproxen, flurbiprofen, piroxicam, and rofecoxib), proton pump inhibitor esomeprazole (Nexium), and immunosuppressive drugs (i.e., sirolimus, everolimus, methotrexate).

Diagnosis

- In most cases, RAS can be diagnosed based on the history and clinical presentation. There is no specific laboratory test for diagnosing RAS. However, it is important to differentiate oral ulcers due to local factors, infections, autoimmunity/hypersensitivity, and malignancy. Microscopic features of RAS ulcers are non-specific and may appear similar to a traumatic ulcer. If the ulcers appear atypical, then a biopsy is recommended to exclude ulcers of infectious origin or malignancy.
- HeRAS can clinically be confused with intraoral HSV-1 infection. Unlike HeRAS which arises in nonkeratinized mucosa, HSV-1 ulcers in an immunocompetent patient occur on keratinized mucosa.
- The diagnosis of Behçet's syndrome is by clinical presentation and exclusion of other diagnoses. There is no specific laboratory tests exist for Behçet's syndrome. The International Study Group guidelines for diagnosing BD include frequent recurrence of oral aphthosis (mandatory criteria), associated with at least two other criteria among a list of genital, cutaneous, and ocular manifestations (i.e., genital ulcers, erythema nodosum, uveitis).
- There is no specific test that exists for the diagnosis of PFAPA and diagnosis may be delayed. Response to corticosteroid therapy is often used to confirm diagnosis. Testing to rule out cyclic neutropenia or one of the monogenic fever syndromes can be ordered.
- Identifying and discontinuing the offending medication with resolution of ulcers without recurrence is the diagnostic criteria for drug-induced aphthous-like oral ulcers. Unlike recurrent aphthous ulcers, when the medication is withdrawn, the ulcers regress and do not recur.

Therapeutic Guidelines

- Although there is no permanent cure for RAS, recurrence of oral ulcers becomes less frequent and may even resolve completely with advancing age.
- Patients should be advised to avoid trauma that can arise with braces, dental appliances, and malposed dentition. Patients should be encouraged to use a soft-bristled toothbrush and toothpaste without the detergent sodium

lauryl sulfate (SLS). Some patients will report an association with certain foods such as nuts, chocolate, fruits, and vegetables, as well as ingredients in some toothpastes, gums, and hard candies. The culprit is different for different patients, and keeping a food diary may help to isolate a specific item with an outbreak of aphthous ulcers.

- For drug-induced aphthous-like ulcer, the offending medication should be discontinued, but treatment of the ulcer is similar to aphthous ulcers.
- Drug treatment for RAS is generally based on the severity of disease, the impact on the patient's quality of life, accompanying systemic medical conditions, and potential adverse side effects of the therapeutic agent. In evaluating the treatment efficacy of drug therapy for RAS, it is important to realize that aphthous ulcers heal spontaneously and that the frequency of recurrence, lesion duration, and degree of pain perception vary among patients. This makes it difficult to critically evaluate treatment regimens that claim a reduction in frequency of recurrence, pain, or time to healing. Furthermore, many treatment reports are little more than case studies without adequate controls, and thus are of questionable validity.
- Categories of aphthous ulcer medications include over-the-counter topical pain preparations, antimicrobial agents, topical and intralesional glucocorticoids, systemic glucocorticoids, and systemic immunosuppressive agents (Table 4). In addition, physical manipulation by surgery or cauterizing agents has been attempted.
- Use of antimicrobial oral rinses (i.e., chlorohexidine), topical analgesics, topical occlusive pastes, and topical corticosteroid remains the first line of treatment for minor RAS.
- Over-the-counter drugs such as Zilactin-B® adhesive gel (contains 10% benzocaine) and Orabase-B® paste (contains 20% benzocaine) provide protective coatings with topical anesthetics. For symptomatic relief, apply either of these drugs topically to the ulcers 4× day until resolution of the ulcers. Topical application of amlexanox (Aphthasol), which is an anti-allergic and anti-inflammatory drug, reduces pain and accelerates ulcer healing. This topical drug 5% amlexanox is recommended for patients who develop MiRAS infrequently but have a low tolerance to pain.
- In North America, topical, intralesional, and systemic glucocorticoids are the most commonly prescribed therapy for RAS depending on the frequency of the recurrence, type, and number of ulcers (Table 4).
- Corticosteroid-sparing therapies for severe major RAS also known as complex aphthosis and major RAS associated with Behcet's syn-

Table 4 Commonly prescribed pharmacologic therapy for recurrent aphthous stomatitis (RAS)

Disease	Topical corticosteroid	Intralesional corticosteroid injection	Systemic corticosteroid	Pentoxifylline
Minor RAS	Clobetasol propionate or fluocinonide 0.05% gel/cream BID-TID	N/A	N/A	N/A
Major RAS <3 ulcers Less frequent	[a]Clobetasol propionate 0.05% gel 4–5× day for 2 weeks	N/A	N/A	N/A
Complex aphthosis and major RAS of Behcet's syndrome	[a]Dexamethasone oral solution, 0.05 mg/5 mL 4× daily for 10 days; hold for 3 min, expectorate, no food/liquid or rinsing for 30 min	Triamcinolone acetonide 40 mg/mL (Kenalog-40); 0.4 mg/cm^2	[a]Prednisolone 1.0 mg/kg or 0.16 mg/kg dexamethasone oral solution with a rapid taper for 2–3 weeks	400 mg, TID for 3–6 months for maintenance to prevent or reduce recurrences

[a]Prescribe chlorhexidine oral rinse or fluconazole for antifungal prophylaxis

drome include immunosuppressive drugs such as thalidomide, azathioprine, cyclophosphamide, methotrexate, and cyclosporine A (Table 4). Severe cases of corticosteroid-refractory cases of major RAS can be treated also with the anti-TNF-α drugs such as pentoxifylline, infliximab, etanercept, and adalimumab and anti-interleukin 1 drug anakinra. These drugs should be reserved for dermatologist, internists, and rheumatologists because of the serious adverse effects associated with these drugs.

Erythema Multiforme

Description

Erythema multiforme (EM) is an acute, self-limiting immune-mediated mucocutaneous disease presenting with distinct cutaneous targetoid lesions with or without oral, ocular, and genital mucosal lesions. EM is considered a cell-mediated type IV hypersensitivity reaction triggered by certain infections or drugs.

Clinical Findings

- Erythema multiforme is more common among younger males, and it is rare in young children (<3 years) and older adults (>50 years).
- EM typically presents with an abrupt onset of cutaneous eruptions and mucosal ulcerations without any prodromal symptoms. Based on the increasing severity, EM is subdivided into three clinical types: (1) EM-minor, less severe form, with localized cutaneous lesions with minimal or no mucosal involvement; (2) EM-major, severe form with generalized cutaneous lesions with mucosal involvement; and (3) Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), most severe form; mucosal lesions are similar to EM-major with different types of cutaneous lesions.
- Infectious agents are the most common cause for precipitating EM in children and young adults, whereas EM in adults is triggered by medications and environmental chemicals. EM-minor is most commonly triggered by herpes simplex virus (HSV; types 1 and 2). Mycoplasma species are the second most common infectious agents implicated in precipitating EM.
- Drugs are the most common cause for triggering EM-major, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The common drugs implicated in precipitating EM are anticonvulsants, antibiotics, and nonsteroidal anti-inflammatory drugs.
- Almost 50% of EM cases are idiopathic, occurring without any known triggers. Subclinical HSV infection is considered the most likely trigger for idiopathic EM. Frequent occurrence of EM (>6 episodes per year) is linked in most cases to HSV infections, which is known as recurrent herpes-associated EM (HAEM).
- The "target" or "iris" lesions are the hallmark of EM and appear as fixed, symmetrical, round lesions with concentric rings and central duskiness, especially on the palms. Skin lesions present as itchy dull-red, purpuric macules or urticarial plaque that may progress to vesicle or bulla. The Nikolsky sign is negative in the affected skin or mucosa. Oral mucosal lesions present as painful diffuse erythema, with or without hemorrhagic ulcers.
- The oral mucosal involvement in Stevens-Johnson syndrome is more severe and more extensive than that of EM-major. Oral ulcers of EM-major commonly present as solitary ulcers closely resembling aphthous ulcers.

Diagnosis

- EM is diagnosed on the clinical findings, and there is no specific laboratory test for diagnosing erythema multiforme. Laboratory testing and cultures may be indicated in recurrent cases of EM to identify the microbial pathogen precipitating the EM.
- Biopsy of non-ulcerated mucosa is indicated to confirm the diagnosis of erythema multiforme and to rule out any other immunologically mediated mucocutaneous disease.

Therapeutic Guidelines

- Erythema multiforme has an uncomplicated clinical course in most patients, except in patients with an immunocompromised status

who are at risk for developing secondary bacterial infections of the skin or the mucosa. The most important step in the treatment of patients with EM is identifying and eliminating the causative drug(s) or agent.

- Antimicrobial (chlorhexidine 0.12%) and local anesthetic oral rinses are recommended to reduce the pain and prevent secondary infection of the oral ulcerations.
- Severe cases of erythema multiforme major, SJS, and TEN require hospitalization in a burn unit for managing complications such as impaired oral fluid intake, dehydration, and secondary infection.
- There is no consensus on the use of systemic corticosteroid for treating SJS and TEN patients. Use of systemic corticosteroid in SJS and TEN patients with widespread skin sloughing (>10% of total body surface) is associated with higher fatality rates due to increased risk for infection and sepsis.
- Should systemic corticosteroid therapy be indicated to SJS and TEN patients, it should be started early in the disease course with 2–2.5 mg/kg/daily IV methylprednisolone in divided doses followed by rapid tapering until the new blister formations cease. Corticosteroid-sparing treatments for SJS and TEN patients include cyclosporine (5 mg/kg/daily) and IV immunoglobulins.
- Severity of oral mucosal involvement in EM may vary significantly. Patients with severe oral mucosal ulcerations may need a short course of prednisolone (40–60/day) tapered over 2–3 weeks. Patients with minor oral ulcerations and erosions can be managed with a high-potency topical corticosteroid gel (i.e., clobetasol 0.05%) or topical corticosteroid oral rinse (dexamethasone oral solution, 0.5 mg/5 mL). Therapeutic dose and duration are similar to the ones used for treating major RAS (see Table 4).
- The standard of care for patients with HSV-associated recurrent EM and idiopathic recurrent EM is antiviral prophylaxis with acyclovir (400 mg PO, BID) or valacyclovir (500 mg PO, BID) or famciclovir (250 mg PO, BID) for more than 6 months (see Table 2).
- Recurrent EM unresponsive to antiviral prophylaxis may need to be treated with systemic immune-modulating drugs such as azathioprine, dapsone, mycophenolate mofetil, and cyclosporine. However, the effectiveness of these drugs in controlling the recurrence of EM has not been validated in well-controlled clinical trials. Moreover, these drugs are associated with significant side effects and hence should be used cautiously.

Oral Lichen Planus and Lichenoid Oral Mucositis

Description

Lichen planus (LP) is a relatively common immunologically mediated mucocutaneous inflammatory and ulcerative disease affecting approximately 2% of the adult population. Although LP is suspected to be an autoimmune disease, the target antigen is unknown. LP affects the skin, nails, hair, and mucosal surface lined by stratified squamous epithelium but does not involve the internal organs. The prevalence of oral LP is higher in patients with chronic hepatitis C virus (HCV) infections, and hence, oral LP is considered as one of the extrahepatic manifestations of chronic HCV.

Clinical Findings

- Mucosal LP most commonly involves the oral cavity (oral LP) and in rare instances may affect the oropharynx, esophagus, and vulvovaginal mucosa.
- Oral LP usually develops in adults over the age of 40 with a strong female predilection. The following intraoral sites are, in descending order, the most common sites of involvement for LP: gingiva, buccal mucosa, tongue, lips, and palate.
- Oral LP has several clinical types that include reticular, erosive/ulcerative, and plaque-like variants. The reticular variant is the most common clinical type of oral LP and presents as lacy white keratotic striae and patches. These lesions exhibit symmetrical distributions involving bilateral buccal mucosa, lateral and

ventral surface of the tongue, and lips. On the dorsal tongue, LP often appears as a thick hyperkeratotic plaque resembling leukoplakia. Both reticular and plaque variants of LP are asymptomatic and are usually detected as an incidental finding during a routine oral examination.

- Erosive LP presents as painful, diffuse erosive, and ulcerative areas of erythema with white striae and patches at the periphery. Erosive LP frequently affects the gingiva presenting as desquamative gingivitis. Chronic irritation or trauma exacerbates oral lesions of lichen planus, which is known as an isomorphic response or Koebner's phenomenon. Lichen planus involving the gingiva (desquamative gingivitis) tends to be more active in areas with fixed prosthesis (i.e., crown, bridges, and dental implants) compared to natural teeth.

Diagnosis

- The clinical differential diagnoses for oral LP include a lichenoid reaction to medications, contact hypersensitivity reaction to local allergens (i.e., cinnamon flavoring) or amalgam, discoid lupus erythematosus, and chronic graft-versus-host disease (cGVHD).
- The most common group of drugs implicated in triggering lichenoid drug reactions are:
  - Antihypertensive and antiarrhythmic agents (i.e., hydrochlorothiazide, beta blockers, angiotensin-converting enzyme inhibitors, quinidine)
  - Anticonvulsants (i.e., carbamazepine)
  - Antimalarial agents
  - Nonsteroidal anti-inflammatory drugs
  - Drugs used in the treatment of arthritis and gout (i.e., sulfathiazine, allopurinol, penicillamine, gold)
  - Therapeutic monoclonal antibodies used for treating malignancies and chronic immune-mediated inflammatory diseases
- A diagnosis of lichen planus is made on the basis of the typical clinical appearance and an incisional biopsy of the representative and non-ulcerated lesion. An incisional biopsy for routine histopathology and direct immunofluorescence testing is necessary to distinguish oral LP from oral epithelial dysplasia, lupus erythematosus, and mucous membrane pemphigoid.
- Clinicopathologic correlation is necessary to distinguish idiopathic oral LP from lichenoid mucositis triggered by medications, amalgam, local allergens (i.e., cinnamon), chronic GVHD, and chronic hepatitis C infections.
- Oral precancers with epithelial dysplasia and proliferative verrucous leukoplakias may present with a dense band of lymphocytic infiltrate at the epithelial-connective tissue interface (interface mucositis) closely mimicking lichen planus resulting in misdiagnosis as lichen planus.

Therapeutic Guidelines

- The treatment of patients with oral LP must be individualized based on the severity of symptoms, extent of the oral lesions, and response to treatment (Table 5). Patients presenting with asymptomatic reticular or plaque variants of oral LP do not need any drug therapy. Because of the possible risk of malignant transformation in long-standing oral LP, patients with both symptomatic and asymptomatic oral LP should undergo regular periodic follow-up and biopsy of any suspicious lesions.
- Although no curative treatments are currently available for treating oral LP, topical or systemic immunomodulating drugs are used to control symptomatic oral lesions with inflammation, atrophy and erosion as well as to aid healing of the ulcerated lesions.
- If lichenoid drug reaction is suspected, changing the offending medication results in the resolution of the lesions. Lichenoid contact hypersensitivity reaction to amalgam would resolve when the amalgam restoration is replaced with composite. If cinnamon-induced contact lichenoid hypersensitivity reaction is suspected, patients should be advised to discontinue the use of cinnamon-flavored oral hygiene products, foods, and chewing gums. Elimination of chronic mucosal trauma and dry mouth would also help in preventing exacerbation of oral LP.

Table 5 Commonly prescribed pharmacologic therapy for oral lichen planus (OLP)

Disease	Topical corticosteroid	Intralesional corticosteroid injection	Systemic corticosteroid	Tacrolimus	Others
Erosive OLP – mild and localized	[a]Fluocinonide or clobetasol propionate gel 0.05%; 3–4 times/day for 3–4 weeks +	N/A	N/A	[b]Tacrolimus ointment; 0.1%, 3 × 4 times/day for 2–3 weeks	N/A
[c]Gingivitis-associated with OLP	[a]Clobetasol propionate gel 0.05%; 2–3 times/day using medication carrier tray for 2–3 weeks	N/A	N/A	**b**Tacrolimus ointment; 0.1%, 2–3 times/day for 2 weeks using medication carrier tray	[c]Doxycycline 100 mg, QD for 2–6 months
Erosive OLP – moderate and widespread	[a]Dexamethasone oral solution, 0.5 mg/5 mL 4× daily for 2–3 weeks swish and spit	N/A	N/A	[b]Tacrolimus aqueous oral rinse; 1 mg/1 L of water; rinse for 2 min and spit; 4×daily for 3 weeks	N/A
Severe erosive ulcerative OLP	N/A	Localized: triamcinolone acetonide 40 mg/mL (Kenalog-40); 0.1–0.2 mL/cm^2	[a]Widespread: prednisolone 1.0 mg/Kg or 0.16 mg/Kg dexamethasone oral solution with slow tapering for 3–6 weeks	N/A	[b]Hydroxychloroquine (Plaquenil) 200–400 mg/day for 1–6 months

[a]Prescribe chlorhexidine oral rinse or fluconazole for antifungal prophylaxis

[b]Off-label use

[c]*For managing gingivitis associated with lichen planus, doxycycline (anti-collagenolytic effect) is used for the initial 2–6 months of treatment, and then topical steroids are used for maintenance. Important: Remember that doxycycline may decrease the effectiveness of birth control pills, so those patients will need supplemental birth control. Also, remember to warn about possible photosensitivity*

- Patients diagnosed with oral LP may need to be screened for chronic hepatitis C infection. Treatment of chronic hepatitis C infection using "direct-acting" antiviral medications is reported to cure the associated oral LP lesions.
- Corticosteroid remains the first line of therapy for oral LP. Localized and less severe oral LP lesions are best managed by the use of a high-potency topical corticosteroid gel or oral solutions (Table 5).
- Lichen planus involving the gingiva (desquamative gingivitis) is best managed using a topical high-potency corticosteroid applied using medication carrier trays. Use of a medication carrier tray to apply corticosteroid topically to the affected gingiva not only improves the local absorption of the medication but also prevents the drug dissolving in the saliva and being swallowed.
- Severe generalized erosive and ulcerative oral LP may need to be treated with systemic corticosteroid therapy with either prednisolone or dexamethasone oral solution (Table 5). The dosage and duration of the treatment vary depending on the severity and the extent of the lesions. Intralesional injection of triamcinolone acetonide suspension is the preferred choice of treatment for severe localized ulcerative lesions of oral LP, minimizing the adverse effects associated with systemic corticosteroid treatment (Table 5).
- Prophylactic antifungal treatment should be coadministered with topical or systemic corticosteroid treatment for oral LP to prevent the development of candidiasis secondary to corticosteroid treatment (Table 5).
- Patients with oral LP who are unresponsive to corticosteroid therapy or develop severe adverse effects can be treated with other topical and systemic immunomodulating drugs, such as cyclosporine, tacrolimus, mycophenolate, methotrexate, hydroxychloroquine (Plaquenil), rituximab, and apremilast (Table 5). Unfortunately, larger randomized clinical trials to support the effectiveness of most of these treatments are lacking, and many treatments are recommended based on anecdotal evidence. Most of these medications are associated with severe adverse effects related to liver toxicity and immunosuppression and should be used under close medical supervision.
- In a number of cases, oral LP may undergo spontaneous remission or may remain inactive for years with occasional flare-up resulting in symptomatic lesions. Flare-up of oral LP is associated with a long list of triggers, the most important being stress and anxiety.

Mucous Membrane Pemphigoid

Description

Mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid, is a chronic autoimmune disease characterized by development of painful vesiculobullous lesions predominantly involving the mucosa. MMP is a humoral autoimmune disorder in which affected patients have autoantibodies directed against specific adhesion molecules localized within the hemidesmosomes of the basal keratinocytes and in the lamina lucida of the basement membrane. The true incidence of MMP is unknown, but it is a rare disease compared to oral lichen planus and cutaneous bullous pemphigoid.

Clinical Findings

- MMP is more common among women with a female to male ratio of 2:1 and frequently affects the elderly population (age range, 60–80 years).
- MMP may involve all mucosal sites surfaced by stratified squamous epithelium but rarely affects the skin. Oral (90% of cases) and ocular mucosa (65% of the cases) are the most commonly affected sites. MMP involving the genital, esophageal, nasopharyngeal, and laryngeal mucosal surfaces are less frequent.
- MMP patients with lesions limited to oral mucosa have a better prognosis compared to patients with MMP involving other mucosal surfaces. The disease severity and extent of the involvement is highly variable from mild cases with gingival lesions only (low risk) to severe cases with ocular, genital, and esopha-

geal mucosa (high risk) with increased morbidity and poor prognosis.
- Oral mucosal lesions of MMP initially present as blisters and bullae which are short-lived and rapidly break into painful ulcers.
- The most common oral manifestation of MMP is desquamative gingivitis, which presents as swollen bright red attached gingiva with focally denuded and ulcerated areas extending into the unattached gingival mucosa. More than 85% of patients with MMP have gingival involvement. In contrast, only 25% of patients with oral lichen planus and 18% of patients with pemphigus vulgaris have gingival involvement.
- The palate represents the second most common site affected by MMP, and the affected area appears as localized erythema with superficial chronic ulcers covered by necrotic pseudomembrane. These ulcers may heal with scars, and scarring of the ocular lesions may lead to blindness.

Diagnosis

- Clinical, histo-, and immunopathologic studies are necessary for diagnosing MMP and distinguishing from other autoimmune mucocutaneous diseases such as lichen planus, pemphigus vulgaris, and erythema multiforme.
- An incisional biopsy of the affected and nonulcerated mucosa should be taken for routine histopathologic and direct immunofluorescence testing. Microscopically, MMP exhibits a subepithelial split with a chronic inflammatory cell infiltrate with a few neutrophils and eosinophils.
- The direct immunofluorescence studies are positive for a linear deposition of IgG, C3, and occasionally IgA along the basement membrane zone. Indirect immunofluorescence testing for the detection of circulating autoantibodies is not indicated for MMP because the titer of these autoantibodies is low in MMP patients and does not correlate with the disease activity.

Therapeutic Guidelines

- Patients diagnosed with MMP involving the oral mucosa should be advised to consult an ophthalmologist to rule out conjunctival involvement. MMP patients experiencing soreness, pain, and ulcerations of genital mucosa or other anatomical sites should be referred to the appropriate specialist for further evaluation, assessment, and/or treatment.
- Similar to other immunologically mediated mucocutaneous diseases affecting the oral mucosa, topical, and systemic corticosteroids remain the mainstay of MMP therapy. For choosing the appropriate therapy, MMP patients are subdivided into "low risk" and "high risk" based on the severity and the extent of the disease involvement.
- Low-risk MMP patients with limited oral mucosal and gingival involvement are typically managed by moderate to high-potency topical corticosteroids (Table 6).
- Desquamative gingival lesions associated with MMP are managed more effectively with topical corticosteroid gels applied using the medication carrier trays. Low-risk MMP patients with diffuse oral ulcerations who are not responding adequately for topical corticosteroid treatment are treated with a low dose of systemic corticosteroid therapy with antifungal prophylaxis (Table 6). Alternatively, localized oral ulcerative MMP can be treated with an intralesional injection of triamcinolone acetonide.
- High-risk MMP patients with severe disease are treated with a combination systemic corticosteroid and cyclophosphamide.
- Corticosteroid-sparing treatments are necessary in low-risk MMP patients to reduce corticosteroid-related adverse effects, especially in patients with diabetes mellitus.
- Treatment with a combination of tetracycline or doxicycline and nicotinamide is effective, safe, and well-tolerated in low-risk MMP patients with mild oral disease.
- Corticosteroid-sparing agents used in the treatment of high-risk MMP patients include dapsone, azathioprine, mycophenolate mofetil, rituximab, and intravenous immunoglobulin (IVIg).
- There is insufficient evidence to determine optimal therapies for MMP and the advan-

Table 6 Commonly prescribed pharmacologic therapy for mucous membrane pemphigoid (MMP)

[a]Gingivitis associated with MMP	Low-risk MMP with mild to moderate oral ulcerations	High-risk MMP with severe oral ulcerations, ocular, and other mucosal involvement
[b]Clobetasol propionate gel 0.05%; 2–3 times/day using medication carrier tray for 2–3 weeks	[b]Mild disease with widespread: dexamethasone oral solution, 0.05 mg/5 mL 4× daily for 2–3 weeks swish and spit	Prednisone (0.5 mg−1.5 mg/kg/day with slow tapering for 3–6 months) + cyclophosphamide (1–2 mg/kg/day for 1-year)
[c]Doxycycline 100 mg, QD for 2–6 months	Localized chronic and painful ulcers: triamcinolone acetonide 40 mg/mL (Kenalog-40); 0.1–0.2 mL/cm^2; can be repeated every 4–8 weeks	Prednisone (0.5 mg−1.5 mg/kg/day with slow tapering for 3–6 months) + azathioprine (1–2 mg/kg/day for 1-year)
	Moderate disease with widespread: prednisolone 1.0 mg/kg or 0.16 mg/kg dexamethasone oral solution (0.16 mg/kg) with slow tapering for 3–6 weeks	
	Mild disease with widespread: steroid-sparing Rx, [c]tetracycline (1–2 g/d) + nicotinamide (2–2.5 g/day) 1–2 months	
	Moderate disease with widespread: steroid-sparing Rx Dapsone, start with 25 mg/day and increase daily dose by 25 mg every 2 weeks to 75–100 mg/day	

[a]*For managing gingivitis associated with MMP doxycycline (anti-collagenolytic effect) is used for the initial 2–6 months of treatment and then topical steroids are used for maintenance. Important: Remember that doxycycline may decrease the effectiveness of birth control pills, so those patients will need supplemental birth control. Also, remember to warn about possible photosensitivity*

[b]Prescribe chlorhexidine oral rinse or fluconazole for antifungal prophylaxis

[c]Off-label use

tages of using corticosteroid-sparing therapies over systemic corticosteroid monotherapy.

Pemphigus Vulgaris

Description

Pemphigus vulgaris (PV) is an extremely debilitating, potentially life-threatening, chronic vesiculobullous disease of the skin and mucous membrane. It is a humorally mediated autoimmune disorder caused by circulating antibodies against desmosomal proteins, desmogleins 1 and 3, resulting in acantholysis and intraepithelial blistering. In rare instances, PV can be induced by certain drugs such as penicillamine and angiotensin-converting enzyme inhibitors. Paraneoplastic pemphigus is a rare disorder that clinically and microscopically may mimic pemphigus but occurs in association with an underlying malignancy, most often a leukemia or lymphoma. Paraneoplastic pemphigus is mediated by autoantibodies against envoplakin.

Clinical Findings

- PV is a rare vesiculobullous and ulcerative disorder affecting the oral mucosa with an estimated incidence of 1–10 people per million worldwide.
- Although PV mainly afflicts adults between the ages of 40 and 60 years, it may be seen in children and young adults. PV does not have a gender predilection. PV is more common among persons of Jewish, Mediterranean, and Asian descent.
- The oral cavity is the primary and initial site of disease manifestation in the majority of PV patients; skin lesions do not appear until months

or even years later. The bullous lesions of the skin remain localized at early stages and become widespread after 6–12 months if left untreated. PV may also affect the anogenital mucosa, nasopharynx, pharynx, and esophagus.

- Oral lesions of PV develop as vesicles or small bullae that burst rapidly leaving painful erosions and ulcers. Established PV lesions may resemble major aphthous ulcers or large superficial ulcers surfaced by a necrotic pseudomembrane with erythematous and irregular outlines.
- The most common intraoral sites affected by PV in descending order are soft palate, hard palate, buccal mucosa, ventral tongue, and floor of the mouth. Gingival involvement by PV (desquamative gingivitis associated with PV) is less frequent (15–20%) compared to mucous membrane pemphigoid and lichen planus.

Diagnosis

- Clinical, histopathological, and direct and indirect immunofluorescence examinations are necessary to diagnose PV and distinguish it from other immune-mediated mucocutaneous diseases. Gentle rubbing of perilesional mucosa leads to the stripping of the epithelial surface known as a positive Nikolsky sign.
- Microscopically, PV is characterized by suprabasilar clefting with intraepithelial acantholysis resulting in free-floating Tzanck cells. Underlying lamina propria typically exhibits mild chronic inflammation with occasional eosinophils. Direct immunofluorescence examination reveals intercellular IgG and C3 positivity. Indirect immunofluorescence testing is positive for circulating autoantibodies that bind to the intracellular junction of stratified squamous epithelium of the normal esophagus.
- Immunoblotting studies and indirect immunofluorescence testing using rat bladder transitional epithelium as substrate are necessary to distinguish PV from paraneoplastic pemphigus.

Therapeutic Guidelines

- Treatment with a high-dose of corticosteroid alone or in combination with other systemic immunosuppressive drugs is the standard of care for PV. Patients with PV should be under the care of a dermatologist with expertise in managing patients with PV. Patients diagnosed with PV should be treated immediately with prednisolone (1 mg per kg per day) irrespective of extent and severity of the disease (Table 7).

Table 7 Commonly prescribed pharmacologic therapy for pemphigus vulgaris (PV)

[a]Gingivitis-associated pemphigus vulgaris	PV-limited to oral mucosa	Severe PV with cutaneous and oral mucosal involvement
[b]Clobetasol propionate gel 0.05%; 2–3 times/day using medication carrier tray for 2–3 weeks	Prednisolone 1.0 mg/kg or 0.16 mg/kg Dexamethasone oral solution with slow tapering for 3–6 weeks	[b]Prednisone (2.0 mg −2.5 mg/kg/day with slow tapering for 3–6 months) + mycophenolate mofetil (500 mg^{-2} g/day)
[c]Doxycycline 100 mg, QD for 2–6 months	Localized chronic and painful ulcers: triamcinolone acetonide 40 mg/ml (Kenalog-40); 0.1–0.2 mL/cm^2; can be repeated every 4–8 weeks	[b]Prednisone (2.0–2.5 mg/kg/day with slow tapering for 3–6 months) + azathioprine (2–3 mg/kg/day for 1 year)
	Steroid-sparing Rx Mycophenolate mofetil, 500–1500 mg; 4–8 weeks	

[a]*For managing gingivitis associated with pemphigus vulgaris, doxycycline (anti-collagenolytic effect) is used for the initial 2–6 months of treatment, and then topical steroids are used for maintenance. Important: Remember that doxycycline may decrease the effectiveness of birth control pills, so those patients will need supplemental birth control. Also, remember to warn about possible photosensitivity*

[b]Prescribe chlorhexidine oral rinse or fluconazole for antifungal prophylaxis

[c]Off-label use

- Other immunosuppressive drugs that can be used in combination with corticosteroids to treat more severe and refractory cases of PV include azathioprine, cyclophosphamide, methotrexate, mycophenolate, and rituximab (Table 7). This treatment should be continued until the cessation of new bulla formation and oral mucosa and skin surfaces are negative for Nikolsky sign. Subsequently, the dosage can be reduced to half and continued until all of the lesions are resolved.
- PV patients may need to be on a minimum effective maintenance low-dose corticosteroid as a long-term management strategy. PV patients undergoing treatment with systemic corticosteroids and other immunosuppressive drugs are at high risk for developing oral candidiasis, and concurrent treatment with antifungal medication is critical (Table 7).
- Other immunosuppressive and immunomodulating drugs currently used in the treatment of PV with refractory systemic corticosteroid include cyclophosphamide, dapsone, methotrexate, intravenous immunoglobulin, rituximab, and infliximab.
- Therapeutic plasma exchange (plasmapheresis), immunoadsorption for rapid removal of circulating autoantibodies against Dsg1 and Dsg3, and extracorporeal photochemotherapy are used as adjuvant therapies for selected cases of PV that are refractory conventional drug treatments.

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Basic Emergency Drugs and Non-intravenous Routes of Administration

Arthur H. Jeske

Emergency drugs in the dental outpatient setting are considered to be adjunctive to physical measures, e.g., airway opening and oxygenation. As such, the array of drugs listed here is a basic list, and many of these agents can be obtained through purchase of emergency kits. Before purchasing such kits, the dentist should consider the following:

1. No single kit meets the requirements of all dental offices, especially in regard to reversal ("antidotal") agents.
2. Emergency drugs go out of date at different intervals, and expiration dates must be monitored accordingly.
3. Dose forms must be compatible with the abilities of the dental teams to use various routes of administration. This can be problematic when drugs indicated for intravenous use only are administered by non-vascular routes, which reduces efficacy and prolongs onset.
4. The training of the dentist(s) and staff members, requirements of the practice's licensing jurisdiction, and the types of patients in the practice and the sedation modalities employed in the practice (Rosenberg 2010).

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Antihistamines

Antihistamines are appropriate for mild, delayed-onset allergic reactions, as are corticosteroids. They lack important actions necessary to alleviate the rapid pathophysiologic effects of Type 1 (anaphylactic) allergic reactions. In anaphylaxis, antihistamines, corticosteroids, and beta agonists are secondary treatments (LoVerde et al. 2018). Outcomes from the administration of oral or intramuscular antihistamines include sedation and anticholinergic actions, which must be considered prior to discharge and in the follow-up care of the patient.

Antiplatelet Drugs (Aspirin, Clopidogrel)

According to the American Heart Association's Advanced Cardiac Life Support protocols, an antiplatelet drug is an important component of the first intervention in cases of acute coronary syndrome (American Heart Association 2016). Current, high-quality scientific evidence supports the beneficial actions of orally administered aspirin in patients with acute coronary syndrome, while other agents historically indicated in this emergency condition (morphine, oxygen, nitrates) are supported only by limited evidence and may actually result in less favorable post-event outcomes (McCarthy et al. 2017). A recent

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systematic review also highlighted the potential application of a clinical decision tool to optimize the use of antiplatelet agents in cases of acute coronary syndrome (Reynard and Body 2017). Non-steroidal anti-inflammatory drugs should not be used in place of aspirin or clopidogrel for an antiplatelet action in cardiac-related emergency situations (American Heart Association 2016).

Antiseizure Agents

In the dental office setting, benzodiazepines are recommended as being both safe and effective for the management of status epilepticus prior to hospital admission. Typically, midazolam or lorazepam is recommended for terminating the potentially life-threatening seizures of status epilepticus. Outcomes from the RAMPART study of interventions for this serious emergency, based on a total sample of 800 patients, indicated that intramuscular administration of 10 mg midazolam in adults (5 mg in children <40 kg) was equivalent to the administration of 4 mg of lorazepam administered intravenously in adults (2 mg in children <40 kg) and that the overall interval until seizure termination (including both the time actual drug administration and the onset of action of the drug) was essentially the same in both the i.m. and i.v. drug groups (Silbergeit et al. 2013). A recent systematic review of various routes of administration of midazolam and diazepam for status epilepticus has confirmed that non-intravenous midazolam is as effective and safe as intravenous or rectal diazepam in terminating early status epilepticus in children and probably also in adults (Brigo et al. 2015). Other drugs evaluated for this indication include lorazepam, phenobarbital, phenytoin, and paraldehyde (Appleton et al. 2008).

Atropine

Like many of the drugs described in this chapter, atropine is available in preloaded syringes. While atropine is not typically included in commercially available drug kits, it is an important agent for the management of acute bradycardia, as may occur in local anesthetic overdose reactions. Clinically significant bradycardia is defined as a heart rate lower than 60 bpm in awake individuals and nonathletes (American Heart Association 2016; Barstow and McDivitt 2017). When bradycardia occurs acutely, atropine is the drug of choice for its management (Deal 2013). Available in prefilled syringes, the typical dose for management of bradycardia in an adult is 0.4 mg intramuscularly, and an aggregate dose of 2 mg will produce total loss of vagal control of the heart, which must be considered when repeat doses are administered. Atropine autoinjectors (e.g., AtroPen®) are available with several concentrations of atropine, from 0.25 to 2 mg per administration.

Beta Adrenergic Agonists

The principal indication for beta agonists (e.g., isoproterenol, albuterol) is the management of acute bronchial constriction. These agents are typically available in dental emergency drug kits in inhalational dose forms, which can accurately meter the dosage. Importantly, beta agonists are powerful cardiac stimulants and may cause excessive cardiac workload when improperly administered. In the management of acute bronchial constriction, albuterol is typically administered by inhalation, using a propellant-driven aerosol liquid. The dose is commonly 90 mcg per actuation of the inhaler device. Adverse effects of albuterol can be serious and include cardiac stimulation, due to activation of cardiac beta receptors. It is important to note that corticosteroid-based inhalers used by asthmatic outpatients are not rescue inhalers, due to the long onset of action of the corticosteroid. A recent systematic review has confirmed that inhaled, short-acting beta-2 adrenergic agonists such as albuterol remain the mainstay of treatment for acute asthma and that the metered-dose inhaler delivers improved lung function as the nebulizer or intravenous administration (Green 2011).

Corticosteroids

Glucocorticoids are typically stocked in dental office emergency kits for the management of anaphylaxis. While they are regularly used in the medical management of asthma and as adjuncts to epinephrine and antihistamines in cases of anaphylaxis, their therapeutic benefit and adverse effects in anaphylaxis have not been scientifically validated (Choo et al. 2012). Their therapeutic effect appears to be optimal when administered intravenously, likely due to the relatively slow onset of action when administered by other routes. Typically, a corticosteroid with a high ratio of anti-inflammatory to salt-retaining activity is preferred, such as dexamethasone, administered intravenously or intraosseously.

Epinephrine

Despite lack of validation from randomized and quasi-randomized controlled clinical trials (Sheikh et al. 2008), epinephrine remains the drug of first choice for the management of Type 1 allergic reactions, i.e., anaphylaxis (American Heart Association 2016). Its benefits derive from direct agonist effects at beta-2 adrenoceptors that mediate bronchial dilation, as well as cardiac stimulation mediated by beta-1 adrenoceptors and alpha-1-mediated vasoconstriction (American Heart Association 2016). The optimal route of administration in non-hospital settings is intramuscular, usually at a dose 0.3 mg for adults. Epinephrine is widely available in prefilled autoinjectors but can be obtained in ampuls and vials. Recent reviews suggest that autoinjectors are associated with accidental injection of thumbs and insufficient needle lengths in obese patients, while syringe-administered epinephrine is associated with inadvertent subcutaneous or i.v. administration, as well as dosing errors (Chime et al. 2017). The adult dose is 0.3 mg administered intramuscularly, and the pediatric dose is 0.15 mg, also i.m. These doses are accurately metered by autoinjector devices, if the devices are used properly.

Glucagon

Like glucose, glucagon is used to manage acute hypoglycemia, but unlike glucose, it requires parenteral administration and may be indicated when the patient lapses into an unconsciousness as a result of hypoglycemia and can no longer safely be given oral glucose. According to a recent systematic review (Villani et al. 2017), 1 mg glucagon administered intramuscularly can be effective for the emergency management of hypoglycemia in the unresponsive adult (Vaccine Administration n.d.). Glucagon is available as a lyophilized solid and must be solubilized using the manufacturer-provided diluting solution. It is important to note that the efficacy of glucagon is dependent on the presence of glycogen in the patient's liver, where glucagon stimulates its breakdown to glucose. There are few adverse effects of glucagon when administered in a single dose for the management of acute hypoglycemia. However, glucagon is best reserved for use when intravenous glucose is not available or cannot be given (see next section "Glucose").

Glucose

In the past, table sugar and sweet beverages (e.g., cola, orange juice) were considered "frontline" sources of glucose for diabetic patients experiencing acute hypoglycemia. However, the sugars found in substances like cake icing (sucrose) are more complex than the simple sugar glucose molecule. Nevertheless, mild hypoglycemia appears to be manageable with carbohydrate-containing foods and beverages (Evert 2014). A study of hypoglycemic children with Type 1 diabetes found that sucrose derived from candy is equally effective with glucose tablets for elevating blood glucose, while fruit-derived fructose was less effective than either glucose or sucrose (Husband et al. 2010). A recent systematic review found that high-quality scientific evidence for the management of hypoglycemia is lacking, and, therefore, recommendations for various treatments are, therefore, limited (Villani et al. 2017). However, there is consensus that 15–20 g of oral

sucrose or glucose (i.e., fast-acting carbohydrates) should be used in conscious patients with glucose levels less than 70 mg/dL, and those with blood glucose levels less than 50 mg/dL should eat 30 g of fast-acting carbohydrates, and this dose can be repeated in 10–15 min, as indicated (Cornelius 2017). The recommended treatment for unresponsive patients is 10% glucose administered intravenously or 1 mg of glucagon administered intramuscularly. Both 50 mL of dextrose 50% or 500 mL of dextrose 5% will elevate blood glucose levels approximately 75–125 mg/dL (Cornelius 2017).

Nitrates

Nitrates, such as nitroglycerin, were considered frontline agents for combination drug therapy (MONA) in cases of acute coronary syndrome by virtue of reducing peripheral vascular resistance with corresponding decreases in cardiac workload and myocardial oxygen demand (American Heart Association 2016). It should not be administered if systolic blood pressure is less than 90 mmHg or if there is marked bradycardia or tachycardia (McCarthy et al. 2017). Because nitroglycerin appears to possess an analgesic action, it is important to note that relief of chest pain after the administration of nitroglycerin is not diagnostic of acute coronary syndrome. The victim is given one sublingual tablet or one spray dose every 3–5 min as appropriate and indicated, up to a total of three administrations. Recently published scientific evidence suggests that the benefits of nitrate administration in acute coronary syndrome may be only marginal, although its use in acute coronary syndrome continues (McCarthy et al. 2017).

Oxygen

In many emergencies in which airway compromise or other respiratory embarrassment may occur (e.g., overdose of CNS depressant drugs with depression of the respiratory center), oxygen is considered an important first-choice agent when combined with ventilation in cases involving significant hypoxemia (PaO2 < 94%). However, recent evidence has called into question the standard practice of administering high-flow oxygen in acute coronary syndrome. In such cases, oxygen would be indicated only in hypoxic patients with an O_2 saturation less than 90% (McCarthy et al. 2017). Concerns about the use of high-flow oxygen therapy in normoxic patients with acute coronary syndrome include reduction of cardiac output and left ventricular perfusion, increased coronary vascular resistance, and the potential development of reactive oxygen radicals which can cause cardiac dysrhythmias (McCarthy et al. 2017).

Reversal (Antidotal) Drugs

Naloxone

Naloxone (e.g., Narcan®) is a nonselective opioid receptor antagonist that is now being marketed in multiple preparations as a result of the current opioid overdose crisis in the USA. Naloxone is characterized clinically by a relatively short duration and the complete reversal of all actions of opioids in patients, including pain control, and may precipitate severe withdrawal in individuals who are addicted to opioids. Naloxone is typically administered parenterally, either i.m. or i.v., with the i.v. route producing the most reliable actions with the fastest onset of action. In nonhospital settings, naloxone is typically used by first responders by the intramuscular route, with a prefilled autoinjector (e.g., Evzio®) at a dose of 0.4 mg. However, recent case reports suggest that individuals who have acutely overdosed with fentanyl or fentanyl analogs may require much higher, repeated doses as high as 4 mg (Tomassoni et al. 2017). Naloxone can be administered by the nasal route, although there is less scientific documentation for this route. A recent systematic review of the effect of the route of administration of naloxone in cases of out-of-hospital opioid overdose found that a higher concentration intranasal dose of naloxone (2 mg/mL) appears to have efficacy equivalent to that of intramuscular naloxone with a comparable rate of adverse events (e.g., agitation) (Chou et al. 2017). The intranasal route of administration can be accom-

Fig. 1 Commercially available naloxone nasal spray preparation, with atomization device. Image courtesy of Adapt Pharma, Inc.

plished with a commercially available preparation, illustrated in Fig. 1.

Flumazenil

Flumazenil (e.g., Romazicon®) is a nonselective benzodiazepine receptor antagonist which, like naloxone, lacks inherent efficacy at these receptors (pure antagonist). Also like naloxone, it has a relatively short duration and the potential to induce severe withdrawal in individuals who have taken benzodiazepines long term, including seizures, and may precipitate seizure activity in patients with epilepsy. Recently, the need for adherence to the FDA's label indication, "for intravenous use only" has been emphasized (Weaver 2011). Typically, a 1 to 3 mg i.v. dose should be safe and effective when administered in cases of benzodiazepine-induced unconsciousness and apnea. Importantly, the short duration (20–45 min) of a single dose of flumazenil can result in recurrence of benzodiazepine-induced CNS depression, which can also be significant if the flumazenil has been administered to simply reawaken the patient to reduce recovery time. The actual dose of flumazenil required for emergency management will vary directly with the total dose of benzodiazepine that has been administered to the patient for sedation. Small doses (e.g., 0.2 mg) have been incorrectly recommended by the sublingual or intramuscular route, as both this dose and these routes of administration are unlikely to achieve therapeutic concentrations in time to prevent serious, permanent injury to the patient (Weaver 2011).

Vascular Access/Intraosseous Administration

Developed initially by the US military forces for vascular administration of drugs and fluids under battlefield conditions, intraosseous drug administration is now a mainstream route that is routinely employed by emergency medical technicians and is included in the American Heart Association's Advanced Cardiac Life Support guidance for several management protocols, which cite the following advantages of this route of administration (American Heart Association 2016):

- Access can be established in all age groups.
- Access can often be achieved in 30–60 s.
- Preferred over endotracheal route.
- May be easier to establish than the endotracheal route in cardiac arrest.
- Any ACLS drug that is administered intravenously can be given IO.

Intraosseous infusion can be accomplished at two sites in both adult and pediatric patients (tibial and humeral sites only). The driver is illustrated in Fig. 2, and a schematic drawing of the indwelling needle and tubing connection to the needle and the syringe is seen in Fig. 3. The noncollapsible marrow venous plexus in the proximal head of the tibia, as well as the humerus, allows rapid administration and vascular uptake of medications delivered, including crystalloids, colloids, and even blood (Leidel et al. 2009). However, because the humerus provides more rapid delivery to the heart, it may be preferred for specific cardiovascular emergencies.

Caution must be exercised in performing intraosseous emergency medications in conscious patients, as the pressure from the drug infusion can elicit temporary, sharp pain. While a small amount of a plain lidocaine solution can be administered prior to administration of the actual interventional drug, the single administration of

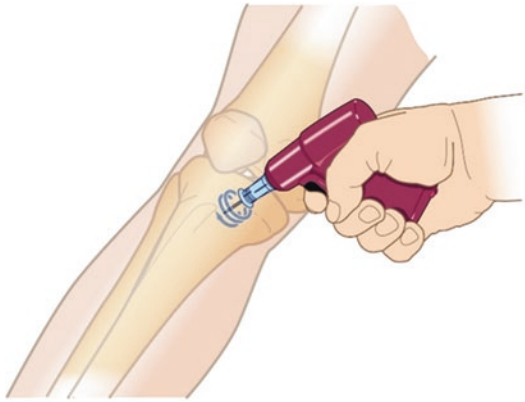

Fig. 2 Intraosseous driver insertion in proximal head of the tibia (Image courtesy of Teleflex, Inc.)

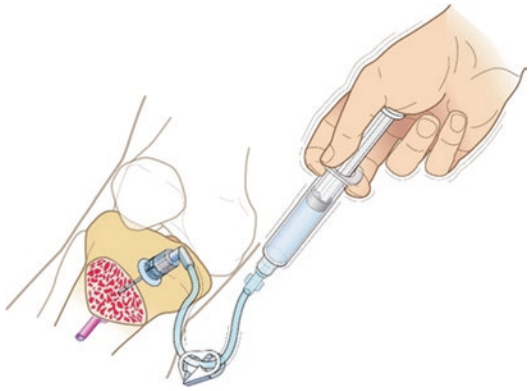

Fig. 3 Intraosseous injection technique at proximal head of the tibia, syringe-to-cannula-indwelling needle in place (Image courtesy of Teleflex, Inc.)

an urgently required emergency drug in the emergent prehospital setting (e.g., a reversal agent) could be significantly delayed if this step is taken.

Intranasal (Inhalational) Administration

The intranasal route of drug administration has been used in medicine for decades, including uses in over-the-counter preparations and prescription drugs for respiratory diseases (e.g., asthma). Recently, there has been a resurgence in interest in this route of administration for emergency drugs, including naloxone for opioid overdoses (Corrigan et al. 2015). Based on currently available studies, the advantages of this route include the following:

- Needles not required, less painful
- Rapid drug delivery
- Pharmacokinetics more favorable than i.m. in obese and elderly patients
- Minimizes risk of needlestick injuries and spread of blood-borne diseases

There are, however, several limitations to this technique, including:

- Limited volume of medication (<1 mL)
- Limited data/evidence for safety and efficacy
- Costs greater than those of i.v.
- Contraindicated in cases of nasal trauma or recent use of nasal vasoconstrictors
- Less reliable than i.v. or i.o. routes
- Patient acceptance (palatability) variable
- May cause nasal mucosal irritation

At this time, two emergency drugs commonly stocked in dental offices—midazolam and naloxone—may be effectively used by the intranasal route, for the management of seizures and opioid overdose, respectively, when the preferred intravenous route is unavailable or impractical (Rech et al. 2017). The armamentarium for intranasal drug administration includes a conventional syringe and a special medication atomization device that is attached to the syringe after the medication is drawn up and which provides a seal when inserted into the nasal orifice (Fig. 4).

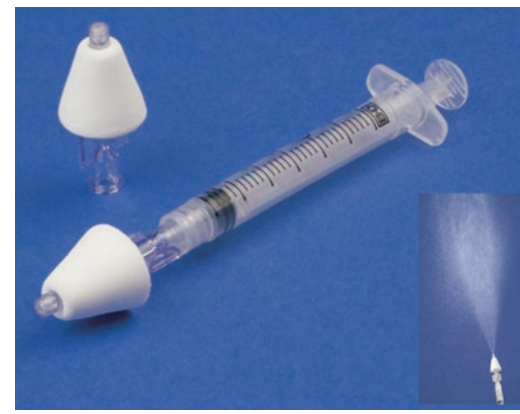

Fig. 4 Medication atomization device (MAD), showing nasal cone attached to conventional Luer-lock disposable syringe. Image courtesy of Teleflex, Inc.

Other drugs that have been documented to be effective when administered intranasally include fentanyl, sufentanil, ketamine, hydromorphone, flumazenil, and glucagon (Corrigan et al. 2015).

Intramuscular Administration

Perhaps the simplest parenteral route of drug administration, i.m. injection is reliable and relatively safe and is used with autoinjectors for bystander treatments of anaphylaxis and opioid overdoses. Recent scientific evidence from studies in children and adolescent patients has confirmed that the intramuscular administration of midazolam with a commercial autoinjector device is as effective as rectally or intravenously administered diazepam for the acute management of seizures (Mula 2017). However, the proper armamentarium may include filter needles (for drugs drawn from ampuls) and may require various gauges and needle lengths, depending on the age/size of the target muscle (Vaccine Administration n.d.) (Table 1).

Table 1 Current evidence-based doses and routes of administration recommended for basic emergency drugs in adults without contraindications[a]

Drug	Dose	Route(s)
Albuterol (bronchodilator)	90 mcg	Inhalation
Antihistamine (diphenhydramine)	50–100 mg	i.m.
Antiplatelet drug (clopidogrel)	300 mg	Oral
Antiplatelet drug (non-enteric-coated aspirin)	160–325 mg	Oral, chewed
Antiseizure drug (lorazepam)	4 mg	i.v.
Antiseizure drug (midazolam)	10 mg	i.m., intranasal
Atropine	0.4 mg	i.m.
Corticosteroid (dexamethasone)		i.m. or i.v.
Epinephrine	0.3 mg	i.m.
Flumazenil		i.v., i.o., intranasal
Glucagon	1 mg	i.m.
Glucose	15–20 g	Oral
Naloxone	0.4 mg	i.m.
Nitroglycerin	0.4 mg	Sublingual
Oxygen 100% (high-flow, non-rebreathing bag-valve-mask)	15 lpm	Inhalation

[a]Initial dose only; readministration should be based on recurrence of emergent symptoms, physiologic status of the patient, etc.

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Internet Resources for Dental Pharmacology

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The list of Internet-based resources for information on dental pharmacology is not intended to be comprehensive, and the site URLs and their content may change without notice. They are included here because they meet three criteria:

1. They are publicly accessible at no cost.
2. They are based strictly on scientific or US government-vetted information.
3. In most cases, they contain summaries that can easily be understood and communicated to members of the healthcare team and patients.

The reader should note that some for-profit (.com) sites are included, but they offer useful, no-cost features of importance to dental pharmacology. Neither the author nor Springer Publishing has any financial interest in these sites.

American Academy of Oral Medicine

http://www.aaom.com

Perhaps the best tool available at this website is the access to the authoritative journal, *Oral Surgery*, *Oral Medicine*, *Oral Pathology*, and *Oral Radiology*. This can be accessed using the top tool button labeled "Publications and News" and then accessing "OOOO Journal." Past issues of this journal are archived and can be easily searched within the site using the search feature.

American Academy of Pediatric Dentistry

http://www.aapd.org

The AAPD publishes an extensive list of clinical guidelines at its Internet site, and most of these documents are regularly revised, ideally on their every 3-year cycle. Those AAPD Guidelines with particular relevance to dental pharmacology can be found under the categories "Oral Health Policies and Recommendations," "Recommendations," "Clinical Practice Guidelines," and "Best Practices" and include:

1. Use of local anesthesia for pediatric dental patients
2. Use of nitrous oxide for pediatric dental patients
3. Use of antibiotic therapy for pediatric dental patients
4. Antibiotic prophylaxis for dental patients at risk for infection
5. Useful medications for oral conditions

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American Heart Association

Of greatest importance at this website is a variety of patient and practitioner resources for the management of patients with cardiovascular diseases that increase the risk of serious systemic and cardiovascular device infections. While there is a great deal of information at this site, many of its features are written in plain English for the lay person, and it can easily be searched using the simple alphabetical search tool at the top of the web page.

The most relevant documents available from the AHA site can be found under the following terms:

1. Infective endocarditis (include guidelines for antibiotic prophylaxis for dental patients and a downloadable "wallet card" for patients, in both English and Spanish)
2. Cardiac Medications At-a-Glance (includes an overview of all categories of cardiovascular drugs, with explanations of their mechanisms of action, indications, etc.)

American Academy of Periodontology

http://www.perio.org

This site contains several features with relevance to dental pharmacology. At the website, select "Publications" from the top toolbar and then "AAP Clinical and Scientific Papers." At this page, the dentist can select "Position Papers" for information on the following topics:

1. Drug-associated gingival enlargement
2. Systemic antibiotics in periodontics
3. Tobacco use and the periodontal patient

Also at this page, by selecting "Academy Statements," the following relevant papers may be accessed:

1. Periostat® as an adjunct to scaling and root planing
2. Use of moderate sedation by periodontists

American Association of Endodontists

https://www.aae.org

No dental specialty utilizes antibiotics, anti-inflammatory drugs, analgesics, and local anesthetics to a greater extent in the outpatient setting than endodontics. The authoritative US resource for guidelines in this area is the American Association of Endodontists (AAE), which regularly publishes its *Colleagues for Excellence* information newsletter, and all issues of this publication are archived at the AAE website.

Searches at this site related to dental pharmacology would begin at the "For Professionals" tool. The dentist can then select "Publications & Research" to access the *Journal of Endodontics* archives and the *ENDODONTICS: Colleagues for Excellence* publications. This is the current location for the document, "Use and Abuse of Antibiotics."

Selection of the tab "Clinical Resources" followed by "Guidelines and Position Statements" allows access to two other useful documents related to antibiotic use:

1. *AAE guidance on the use of systemic antibiotics in endodontics*
2. *AAE guidance on antibiotic prophylaxis for patients at risk of systemic disease*

American Association of Oral and Maxillofacial Surgeons

https://www.aaoms.org

Two very significant publications reside at this website. The first is the AAOMS' *Position Paper on Medication-Related Osteonecrosis of the Jaw* and the other *White Paper on Opioid Prescribing* which are perhaps the most significant resources for the general dentist. The paper on MRONJ is addressed in this book in chapter "Introduction", and the latter publication on opioid prescribing is described in greater detail in chapter "Opioid Analgesics and Other Controlled Substances".

American Dental Association (ADA) Center for Evidence-Based Dentistry

https://www.ebd.ada.org/

This site contains clinical guidelines and critical summaries of systematic reviews developed under the auspices of the ADA's Center for Evidence-Based Dentistry. The critical summaries are brief (two-page), expert evaluations of the outcomes of systematic reviews. The site is organized under the following topic areas, with specific content in parentheses:

- Evidence (browse evidence database, guidelines, critical summaries, plain language summaries, systematic reviews)
- Education (courses in EBD, tutorials, ADA science podcasts)
- Resources (links to databases and PubMed clinical queries)

The clinical guidelines feature of this website represents the strongest evidence for various dental interventions, materials, and procedures, as they are based on outcomes from multiple systematic reviews and are vetted by ADA expertise, including the ADA Council on Scientific Affairs and ADA Division of Science.

Cochrane Library

https://www.cochrane.org

Widely regarded as the world's most authoritative library of systematic reviews, the Cochrane Library, established in 1941, only accepts reviews based on randomized controlled trials (RCTs) (Fig. 1). In spite of this high standard, the healthcare professional can access thousands of systematic reviews of medical and dental interventions. The site features a "Browse by Topic" search tool, under which

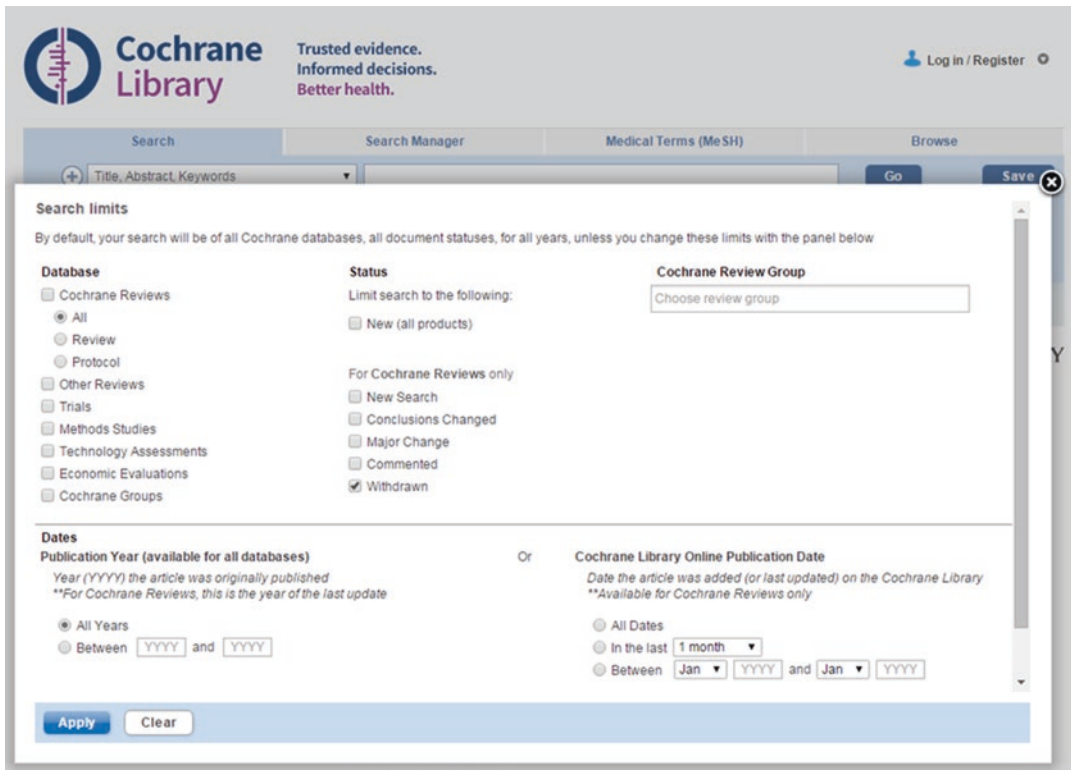

Fig. 1 Cochrane Library homepage

two topics particularly suited to this textbook can be found:

1. Pain and anesthesia
2. Dentistry and oral health

Under this item (2), the reader can access a number of dentally relevant reviews, for example, "Pharmacological interventions for preventing dry mouth and salivary gland dysfunction following radiotherapy." After selecting a review of interest, the dentist can select the abstract, which briefly describes the background for the systematic review, the objectives, the search methods, the selection criteria (used for identifying those studies which were included and excluded), the methods used to collect and analyze data, the main results of the systematic review, the authors' conclusions, and an easy-to-interpret "Plain language summary." Finally, a search tool allows the reader to access the entire systematic review ("Get access to the full text of the systematic review"). Throughout this book, the reader can see the use of Cochrane systematic reviews (e.g., in chapter "Non-opioid Analgesics").

Drug Enforcement Administration (USA)

https://www.dea.gov/

This site is primarily concerned with legal, regulatory, and administrative information related to controlled substances for the USA. For practitioners who prescribe controlled substances, there are several very helpful tools and documents that reside here. Examples include the following major headings, with selected resources following:

Drug Info

1. Drug fact sheets
2. Drug scheduling
3. Controlled Substances Act

Resource Center

1. Drug disposal
2. How do I… (this feature addresses commonly asked questions, including how to change registration address, etc.)

The reader is cautioned that this agency and its web-based information are only applicable to jurisdictions within the USA and US-related locations within DEA jurisdiction. Also, the ordering, administration, and prescription of controlled substances in the USA are also regulated by applicable state law and rules and regulations of dental and medical licensing boards.

Drugs.com

https://www.drugs.com

This commercial website is very useful and efficient when information on adverse drug interactions is needed. At the top of the website, the toolbar contains an "Interactions Checker." The practitioner enters a series of drug names and then clicks "Check for Interactions." The software does not limit the number of drugs which can be entered in this feature. The information is provided both in plain English and professional format and includes a severity rating in regard to specific interactions, as well as advice of management of interactions. Like other websites of this nature, it also contains package insert information on prescription drugs, as well as links to a variety of apps and important patient-oriented descriptions of common diseases through links to the *Harvard Health Guides* and *Mayo Clinic Disease References*. The site also has an "advanced search feature," a phonetic search feature and drug information downloadable in Spanish.

In a "Q&A" section, questions about various drugs can be posted and responded to, and there is a list of support groups for patients with various serious systemic diseases.

Additional important features of this website include:

- Master list of drugs A–Z
- Drugs by condition
- Drugs by class
- Drug comparisons
- Generic drugs
- OTC drugs
- International drugs
- Natural products
- Veterinary products
- Drug side effects
- Dosage guides
- Drugs in pregnancy
- Breastfeeding warnings
- Pricing and coupon availability
- Inactive ingredients

Finally, there is a "Pro Edition" tool with an A–Z professional drug list, FDA prescribing data, AHFS Drug Information Monographs, A–Z drug facts, natural products, Stedman's Medical Dictionary, a list of current medical conferences, and a comprehensive list of international pharma companies.

This website is one of several Internet-based drug information services, which also include commercial healthcare and pharmaceutical advertising, and is described here as an example of such sites, rather than as an endorsement by the author.

Food and Drug Administration (USA)

https://www.fda.gov/

As the official informational website of the US Food and Drug Administration, this site is very likely the most information-intensive one of all those included in this chapter. For the busy dental practitioner, it can be somewhat challenging to navigate. The recommended starting point is the tool button "Drugs" at the top of the first page. Second, the tab "Find Information about a Drug" opens a wide variety of resources, and particularly useful are links to "Consumer-friendly Information" and the link "Drugs@FDA," which leads to the full label information for all FDA-approved drugs, including approval history. Another potentially useful tab is "Orange Book Search," which provides access to therapeutic equivalencies of different brands of a particular medication.

National Library of Medicine/ PubMed

https://www.ncbi.nlm.nih.gov/pubmed/

Among the most powerful scientific search engines ever developed, the US National Library of Medicine's PubMed database is relatively easy to use and allows customization of search criteria to make literature searches very efficient. A complete description of the operation of this website is beyond the scope of this textbook. However, the reader is advised to take advantage of several features of this website:

1. On the first page of the site, under the "Using PubMed," "PubMed Tutorials" can be accessed to become more familiar with the use of the site.
2. On the first page of the site, under the "PubMed Tools" category, a "Clinical Queries" feature can be activated to help guide a very specific search of relevant articles.
3. On the first page of the site, under "More Resources," the "MeSH" tool can be activated (Medical Subject Headings), to help make searches by subject more efficient.

After a specific abstract has been located by entering a search term in the top search field, a list of "Similar Articles" appears to the right of the main search outcome screen, and the availability of free, complete texts of articles is noted in the upper right of the screen, as well as just below the abstract, and these allow downloads of the article in pdf format at no cost. Both of these features are illustrated in Fig. 2.

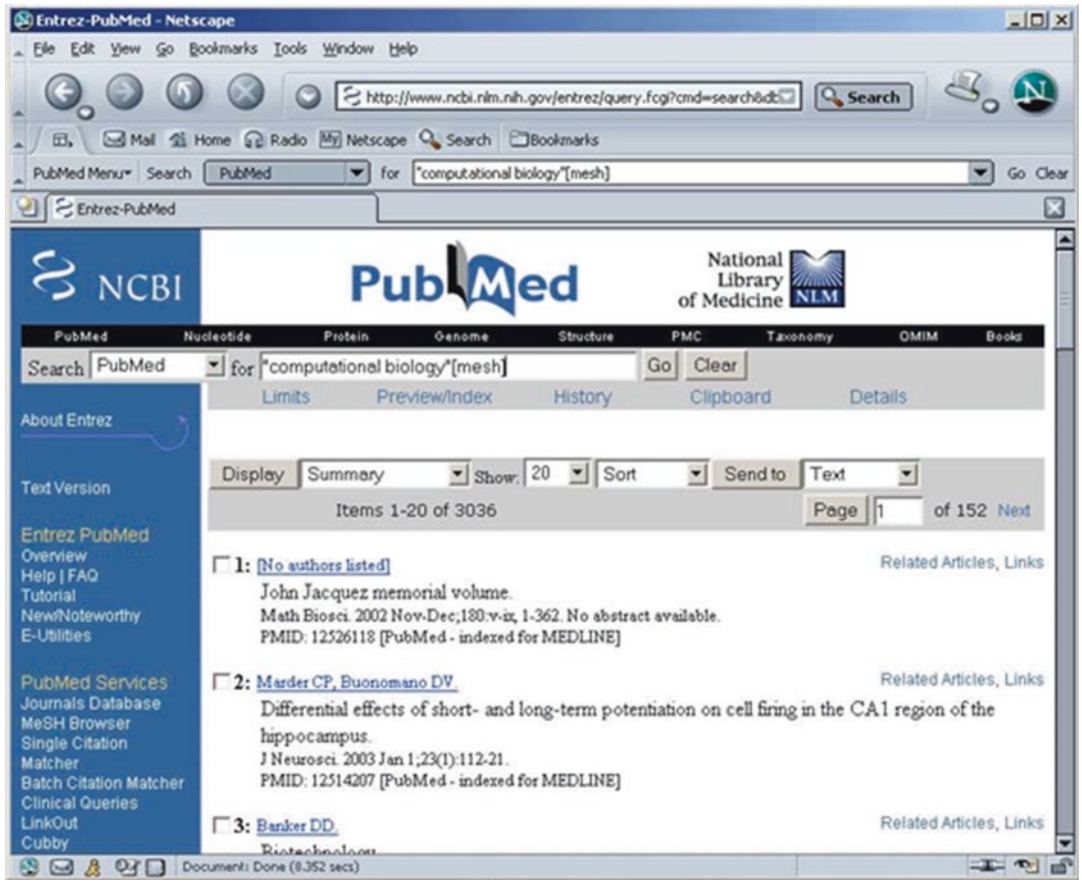

Fig. 2 NLM PubMed homepage

University of Washington

https://www.dental.washington.edu/dept-oral-med/special-needs/patients-with-special-needs/

While not comprehensive for all disease entities, this site contains descriptions of appropriate dental and medical considerations and treatment modifications required for the management of many patients with special needs. Once at the homepage, the tool "Additional Guidance" can be selected, which then leads to "Special Needs Fact Sheets." At this page, there are four categories of information designed for "parent/caregiver," "children," "adults," and "medical." While this site does not comprehensively cover all serious systemic conditions, it addresses many of the more common ones which carry serious implications for possible modifications in dental management and dental drug therapy.

Evaluation of Randomized Controlled Trials and Systematic Reviews

There is a wealth of literature related to various methodologies used for the evaluation of the validity of systematic reviews and randomized controlled trials. Perhaps the simplest and most reliable for systematic reviews is the AMSTAR tool (Assessment of Multiple Systematic Reviews), which has been published in an updated, refined format as AMSTAR 2 (Shea et al. 2017). The AMSTAR instrument is based on a simple list of 11 items, each of which is categorized into a standardized set of four possible

responses, "yes," "no," "can't answer," and "not applicable," and a summary score is determined as the sum of all of the "yes" responses. Recently, the AMSTAR instrument and a modified form of it were critically evaluated, and it was determined that AMSTAR is simple, reliable, and valid, although additional research is needed for systematic reviews of mixed study designs, such as diagnostic accuracy test studies, studies of disease etiologies, and studies of prognoses (Pieper et al. 2015).

With regard to the reporting of randomized trials, an instrument termed "CONSORT" is now widely accepted as a standard reporting format and is acknowledged routinely in many journals in which the CONSORT-compliant studies are published (Begg et al. 1996; Moher et al. 2001). Practitioners should familiarize themselves with the fundamental evaluations provided in these publications prior to making changes in patient care based on published literature.

Conclusion

There are many reliable, scientifically vetted Internet resources to obtain a variety of information related to dental pharmacology. Most are free of cost and commercial interests and, if used efficiently, can significantly augment the dental practitioner's access to reliable and, perhaps most importantly, up-to-date information. At this transitional time in the dental profession, i.e., moving from practice based largely on historical uses of drugs and the application of medical drug information to off-label dental prescribing scenarios to evidence-based dental practice, the practitioner must carefully assess both the qualitative and quantitative attributes of scientific literature and filter it based on the various levels of scientific evidence. While it is often tempting to adopt a procedure, material, or drug to dental practice based solely on the recommendation of an "expert" speaker (level 6 evidence), such decisions must be weighed carefully against the availability—or lack thereof—of higher levels of scientific evidence from randomized controlled trials (RCTs) and systematic reviews (level 1 scientific evidence). Caveat emptor.

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