Contemporary Dental Pharmacology

Evidence-Based Considerations

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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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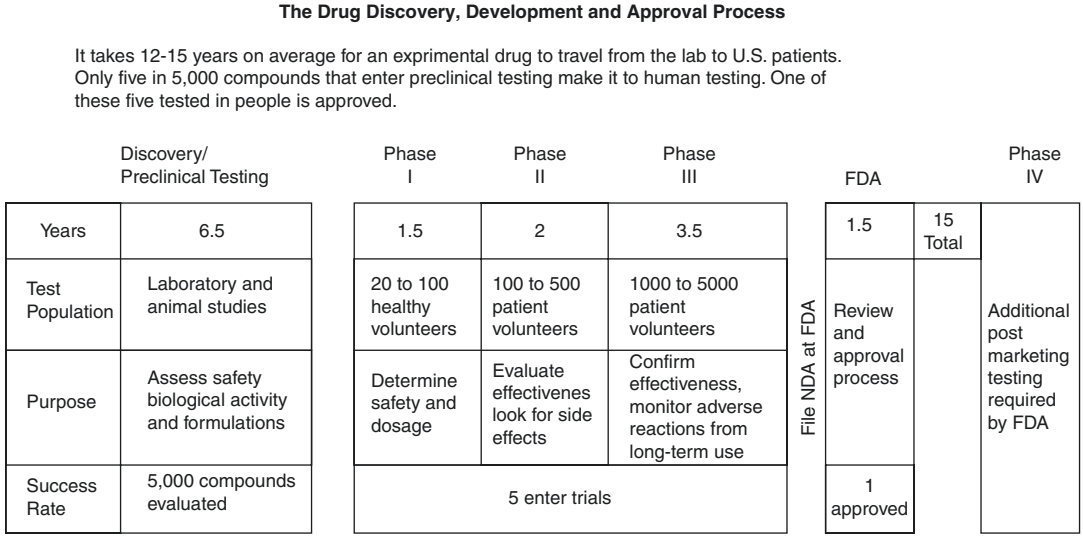

Fig. 1 Populations, purposes and success rates for compounds in the U.S. F.D.A. Drug Discovery, Development and Approval Process, with approximate times (in years) required for each phase. Reproduced with permission, Pharmaceutical Research and Manufacturers of America (PhRMA). The Complex Biopharmaceutical 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.

Trademark/copyright date information.

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.

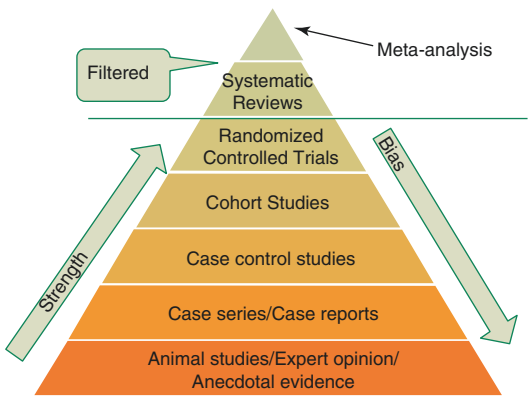

Fig. 2 Evidence pyramid showing hierarchical relationships between various levels of evidence (strongest evidence with lowest bias at apex). From (Higgins and Green 2011)

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).