OF THE CALIFORNIA DENTAL ASSOCIATION

Journal

OCTOBER 2008

PHARMACOLOGY

Peter L. Jacobsen, PhD, DDS

OF THE CALIFORNIA DENTAL ASSOCIATION
Journal
CDA Journal
Volume 36, Number 10
OCTOBER 2008

DEPARTMENTS

FEATURES

CDA JOURNAL, VOL 36, Nº10

Beyond the Tooth

ALAN L. FELSENFELD, DDS

The alignment of dentistry with medicine has become apparent in recent years. We are beginning to see and understand relationships between periodontal health and systemic ailments. Heart disease, cancer, and diabetes are conditions that have decreased incidence in patients with good periodontal health. There is some early evidence that relates poor periodontal health to dementia in some patient populations and, conversely, patients with rheumatoid arthritis are more likely to have periodontal problems.

Beyond periodontal disease, calcifications of the great vessels of the neck as an indicator of potential cerebrovascular disease can be detected on panoramic radiographs in numerous patients. Most recently, the use of saliva to diagnose serious systemic conditions has become a topic of interest. Oral health has become an indicator of systemic health for many of our patients.

The *Surgeon General's Report on Oral Health* has brought emphasis and credibility to oral-systemic relationships.[1] As research begins to show increasing levels of sophistication in using traditional dental evaluation to help diagnose and/or monitor a systemic condition, dentists may, and should, find themselves involved in internal medicine as well as classical dentistry. Are we becoming, as I was taught as a student, "physicians of the mouth"?

As we progress through dental school, we take courses in physical evaluation of patients as well as oral medicine as it relates to local manifestation of systemic diseases. Unfortunately, as we get to the later years of our education, concentration on completing requirements and doing restorative procedures for patients becomes a high priority and consideration of patient medical issues tends to diminish.

Oral health has become an indicator of systemic health for many of our patients.

To the extent that dentists incorporate medical management concerns into their practices, they become united more closely with their physician colleagues. For many of us this is not comfortable from a professional or practice management standpoint. Traditionally, dentists enjoy the autonomy of private practice as a solo practitioner. It is easy to schedule our days and emergencies are not all that common in the average practice. There is dental insurance (in reality a schedule of benefits) for many of our patients for procedures that we perform. While the reimbursement rates will vary from plan to plan it is relatively easy to know how much you will be paid for your time and efforts.

In addition, dentists have the ability to avoid being involved in third-party payer plans if they so choose. Finally, we know that most of our patients are satisfied with the level of care being given in dental offices.

The trend in medical practice has been diametrically opposed to that in dental practice. It is the rare physician who opens a solo practice. Larger groups appear to be the norm to allow for multispecialty diversity, easily attainable coverage, and other economies of scale. Most physician groups are obligated to accept Medicare as well as other insurance plans. The patient who might pay cash for a dental procedure is less likely to do so in the medical arena. Reimbursement rates for physicians have plummeted in past years. Physicians care for patients in the hospital and deal with emergency medical problems that could be counterproductive in maintaining a busy office practice. Patients tend to be frustrated with the medical system and are showing decreased satisfaction with the delivery of medical care. Dentistry is a much better alternative for bright young people entering health care professions.

Dentists are remunerated best based on procedure codes and not on cognitive skills. Medical management of dental patients does not carry with it reasonable reimbursement for the time that is required to treat our patients. As we see an increase in translational research that puts basic science discoveries into the realm of patient care, it becomes obvious there will be a greater assimilation of medical care by dentists. This may not be a comfortable concept for many of our colleagues.

We teach that the mouth is part of the body and that there is a patient beyond the tooth. The significance of this in the assessment and delivery of patient care is apparent on a daily basis as dentists are aware of the complexity of medical issues and their treatment as it relates to oral care.

CDA JOURNAL, VOL 36, Nº10

Comprehensive patient assessment and care is an integral part of dental care. As our practices mature there will be a number of patients who come to us not only for performance of procedures but for diagnostic assistance in and monitoring of systemic illnesses. Global thinking about patient care rather than a myopic approach to fixing teeth is the practice of dentistry and can be done only by dentists who are trained and function at that level. Our profession needs to continue to grow past the performance parts and into a place where we use the doctor part of our title. ■■■■

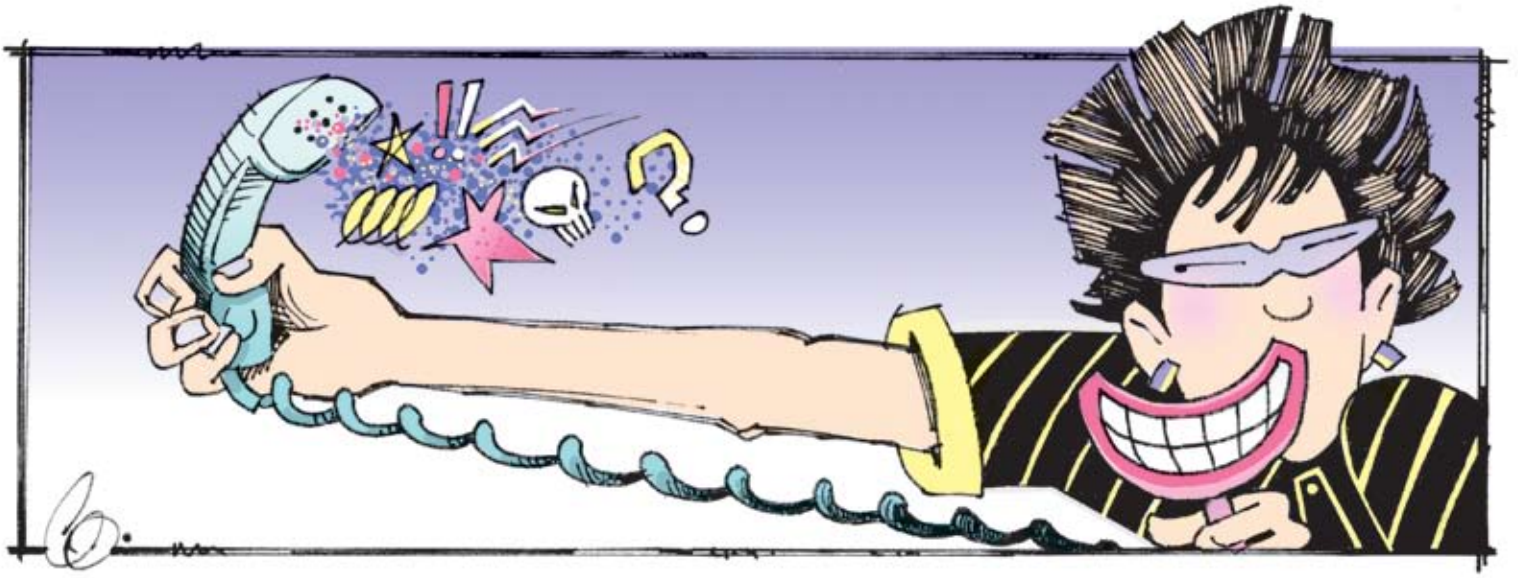
REFERENCE

1. Oral Health in America: A Report of the Surgeon General, 2000.

Address comments, letters, and questions to the editor at alan.felsenfeld@cda.org.

CDA JOURNAL, VOL 36, Nº10

Smile Yourself Sick



Responsible journalism — an oxymoron if ever there was one — has struck again!

Robert E. Horseman, DDS

ILLUSTRATION BY CHARLIE O. HAYWARD

The last time something really good happened in recent memory was when dark chocolate was discovered to be beneficial to your health and the consumption of red wine was proven to add at least a decade to your longevity.

Women immediately rushed out and consumed enough chocolate to initiate zits the size of tennis balls and reduce their wardrobe choices to muu-muus and waterproof ponchos. Both genders downed copious draughts of red wine to the point of wearing funny hats at parties and dancing on bar tops in their underwear. Then you never heard another word about it. It was like a cosmic joke played by bored reporters assigned to the Friday science health section of the paper when they'd rather cover a bikini contest in Santa Monica.

Responsible journalism — an oxymoron if there ever was one — has struck again! This time it affects the dental profession in such a significant way that all our efforts of the last 25 years may have been for naught.

What has been our goal for the last couple of decades? What have we seen as final acceptance of all our efforts? It is life, liberty and the pursuit of the Perfect Smile even if you have to hock grandma's silverware to get it. The firm belief now held by the public is that foremost in their guaranteed entitlements, even above that of their stimulus checks, should be teeth exactly like those of any number of cloned young men and women featured in the celebrity magazines. Fame based entirely on being famous, has evolved from being traditionally Hiltonesque to include an acreage of tattoos formerly the acquisition of alcohol-lubricated seamen, the wearing of clown hats regardless of the occasion and the piercing of body parts that ought not to be violated. The world can consider itself lucky that Jerry Lewis' teeth as featured in *The Nutty Professor* are not a part of the smile du jour. Not yet.

Threatening the entire dental porcelain industry, therefore, is a headline out of

CONTINUES ON 805

CDA JOURNAL, VOL 36, Nº10

DR. BOB, CONTINUED FROM 806

Frankfort, Germany, as reported by United Press International stating "Smiling can hurt your health!" It's true, says Dieter Zapf of the Johann Wolfgang Goethe University, who studied 4,000 volunteers working in a fake call center. Why 4,000 people would volunteer to take fake calls or who would be employed to make the fake calls is not quite clear, but possibly involves unlimited Heineken in large steins.

Zapf's hypothesis is this: People forced to smile and take on-the-job insults suffer more and longer-lasting stress that may harm their health. Right! And stepping in front of a Porsche 911 in top gear on the autobahn would probably do the same, but Dieter couldn't get a grant to research that.

So 2,000 of the volunteers were allowed to respond in kind to abuse on the other end of the line while the other half had to suck it up. I don't know what a German insult would sound like since we didn't study Teutonic slurs during my two years of junior college German, but maybe something like "Du bist ein dumkopf!" would produce stress in a delicate psyche wearing a forced smile. The other half who could respond vigorously with the German equivalent of "I'm rubber and you're glue … " or the classic "I know I am, but what are you?" did experience a brief increase in heart rate, but nothing compared to the bunch with the frozen Jessica Simpson smiles.

In an interview with the German health care magazine *Apotheken Umschau*, Zapf said, "Every time a person is forced to repress his true feelings there are negative consequences." He suggested that people who must keep smiling on the job should get regular breaks to let it out. At least that's what I think he said. There are no German words that translate into this English statement that contain less than 32 consonants and vowels each. If the stricken ones are not allowed time off to release their smiles before rigor sets in, I would have suggested they seek employment elsewhere, like the German DMV, IRS, or Social Security where smiling is traditionally not a job requisite.

The point is, we can't afford to have news releases like this UPI piece appearing in our press. We have too much invested in The Smile now to back off. Zapf should strive to get a real job, letting the phony calls stay in the province of der kinder with their newly acquired texting cell phones.

But how about white wine or milk chocolate? With almonds? Anybody looking into that? ■■■■

Matt Mullin

Marijuana Use Possibly Linked to Perio Disease

Like tobacco use, cannabis smoking may be associated with periodontal disease, according to a study in the *Journal of American Medical Association*.

A team, led by W. Murray Thomson, PhD, of the Dunedin School of Medicine, Dunedin, New Zealand, conducted a study to determine whether marijuana use is a factor for periodontal disease. Nine hundred and three participants who were born in Dunedin in 1972 and 1973 were assessed periodically. Cannabis use was determined at ages 18, 21, 26, and 32; dental examinations were conducted at ages 26 and 32. In June 2005, the most recent data collection when the participants reached age 32, three drug exposure groups were determined: "no exposure" (293 individuals or 32.3 percent); "some

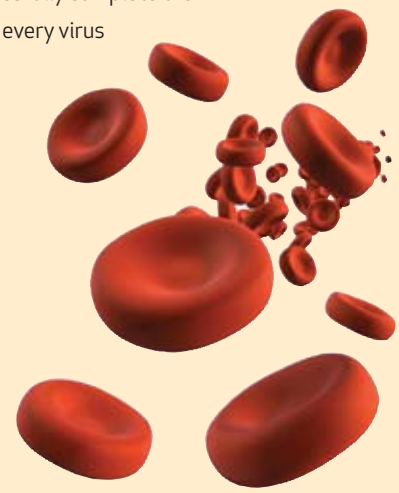
CONTINUES ON 729

Study Shows 'Cooperation' Allows HIV Replication Without Integration

A New York University College of Dentistry AIDS research team has found that weak HIV viruses piggyback onto stronger ones, raising the possibility that the human body may harbor many more HIV viruses capable of replicating and contributing to the development of AIDS than previously thought.

"We've observed a new mode of HIV replication that involves cooperative interaction between viruses," said David N. Levy, PhD, who published his findings today in BioMed Central's open access journal *Retrovirology*.

It's widely known that only about one in every 100 HIV viruses can successfully complete the process of integrating its DNA with the DNA of the human cell – a step that every virus must successfully complete before it can reproduce, according to a press release. The study by Levy's team revealed a mechanism that allows some of the other 99 percent of HIV viruses also to replicate and play a potential role in the development of AIDS.



The team said that HIV functions as a community, with those viruses that successfully integrate with the DNA in human cells rescuing the viruses that fail to integrate by providing them with the proteins they need to reproduce. What's more, the viruses that were once thought to be lost because they don't integrate may have an advantage over the others because they can skip several steps in their replication cycle and reproduce faster.

CDA JOURNAL, VOL 36, Nº10

Boost Oral Health Research Dollars, AADR Implores

Dental scientists urged Congress to increase the oral health research budget and to set aside $1 million a year to fight the early childhood caries described as "particularly common" in Native American communities.

Citing "exciting research under way and the potential to improve oral health," Marc Heft, DMD, PhD, told a House appropriations panel that additional funds for the National Institute of Dental and Craniofacial Research would advance the use of saliva-based diagnostic tests for oral and other cancers, cardiovascular diseases, and systemic conditions.

Early diagnosis and treatment also are key to "avoidance of the disfiguring surgery that may occur when malignancy is advanced and spread," Heft testified earlier this year. "NIDCR-funded research has produced a saliva test that can detect oral cancer, but further clinical studies are needed to produce and validate a diagnostic test with the accuracy required by the Food and Drug Administration.

"Imagine a world where disease can be detected at its earliest possible moment with quick, painless, and noninvasive saliva-based tests," Heft testified on behalf of the American Association for Dental Research. "Imagine getting results from a test for oral cancer or systemic diseases without a two- or three-day wait, or going to the dentist for a mineral-restoring rinse instead of getting a filling. We would not only improve Americans' quality of life but save lives and better utilize the valuable resources currently burdening our health care system."

AADR testimony also supported an American Dental Association request for $1 million a year for three years for research and clinical studies on early childhood caries.

Tooth Loss Tied to Self-esteem

With almost 20 million teeth extracted each year, numerous people are left to deal with the psychological effects of a less-than-perfect smile.

H. Asuman Kiyak, PhD, presented a course, "Enhancing the Oral Health and Quality of Life for Partially Edentulous or Fully Edentulous Patients: The Importance of Communication," during the 56th annual meeting of the Academy of General Dentistry's last July, where she discussed the post-traumatic effects a patient endures after the loss of a tooth.

"A smile serves as an individual's most powerful tool," said Laura Murcko, DMD, AGD spokeswoman. "A great smile can make a great lasting impression, boost a person's self-esteem and confidence as well as improve their overall health."

Results from a survey issued to almost 20,000 AGD members recently revealed that more than 86 percent of general dentists reported that social embarrassment is one of the major concerns related to tooth loss, with more than half of these patients avoiding social interaction for that very reason.

"The major impact of tooth loss is on the appearance and social relations component of quality of life because people cannot change their appearance with missing teeth," Kiyak said, who also noted there are ways patients can learn how to cope with the loss of a tooth. Kiyak encourages patients to:

- Weigh their options with the pros and cons for replacement teeth, or even endodontic treatment to save a "hopeless" tooth.
- Review videos or photos of others who have lost teeth and their current teeth status with removable or implant-supported dentures.
- Review testimonials of others who have undergone single, multiple, total tooth loss and replacement of these teeth with removable or implant-supported dentures, how they have coped with each stage, and how they are functioning orally, systemically, and psychologically with these dentures.

Link Unlikely Between Maternal Folate Intake and Cleft Palate

Previous studies in animals have shown positive direct results of a link between a decreased occurrence of cleft lip and/or cleft palate and the maternal intake of multivitamin supplements containing folate. In humans, however, the studies are less clear-cut. It's harder to distinguish the effects of a specific nutrient, which are generally entwined with the effects of other nutrients.

Additionally, other previous studies display design flaws such as insufficient sample size and lack of randomized sampling to have statistical significance. Studies in California and Norway reported a weak correlation in mothers who reported taking no supplements before becoming pregnant and then started taking supplements (Norway), or those who ate fortified cereal (California) during their first trimester, according to an article in *The Cleft Palate — Craniofacial Journal*. However, other studies show no change in orofacial cleft prevalence before and after the introduction of cereal fortification (Canada, Texas), or with/without use of supplements).

Cleft lip and palate are the most frequently occurring birth defects in the United States, affecting almost 7,000 children annually, or 1 in every 600 newborns.

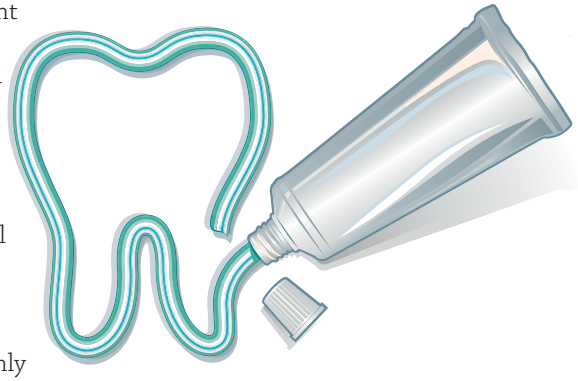
In an issue of *The Cleft Palate — Craniofacial Journal*, a new study reports that the link between periconceptional folate intake and cleft palate or cleft lip may be weaker than previously thought. Little et al. used various measures of folate status and detailed assessments of confounding factors and found no correlation between prevalence of orofacial cleft and dietary or supplemental folic acid.

New Hydrogel Systems Developed For Dentin Regeneration

More than 20 million dental restorations are placed each year in the United States alone. As such, there exists a critical need for better biologic therapeutics to restore the damaged dentin-pulp complex to its original function and form. Progress in this area, however, has been slow compared to other fields of regenerative medicine.

At the 86th General Session of the International Association for Dental Research, a team of investigators from Baylor College of Dentistry in Dallas, the University of Regensburg in Germany, and Rice University in Houston, presented its preliminary data describing the results of studies on hydrogels made of peptide amphiphiles, where a short peptide sequence is attached to a fatty acid, providing the driving force for self-assembly, according to a press release provided by the International & American Association for Dental Research.

The work takes advantage on previously untested material with new properties for the regeneration of the dentin-pulp complex. The results, researchers opined, will provide the foundation for developing multidomain peptide scaffolds as novel therapeutics for the regeneration of the dentin-pulp complex.



The researchers applied a different design concept, where the self-assembly of peptide chains is achieved without attaching a hydrophobic tail. Based on their design, the chains can include bioactive peptide sequences for cell adhesion, binding of growth factors, or other biological molecules with therapeutic potential, the authors reported. Additionally, they said multidomain peptide hydrogels represent a novel and highly versatile material offering a higher degree of control over nanofiber architecture and better chemical functionality.

The researchers said the overarching goal is to utilize these multidomain peptides as a biomimetic scaffold along with dental stem cell therapy to provide a natural 3-D environment that can control and direct the differentiation and function of dental stem cells for the targeted regeneration of the dentin-pulp complex.

CDA JOURNAL, VOL 36, Nº10

Tomography and Software Assist in Placement and Positioning of Dentures

An increasing number of edentulous patients have undergone successful implant-supported fixed restorations since the use of technology assists in identifying the best position and placement, according to a new study published in the *Journal of Oral Implantology*.

Even though various types of dentures are available as treatment, most patients want to avoid having removable prostheses because they want to experience the improved esthetics, speech, and comfort permanent dentures can offer.

In one case report, a man had been given one of three options for treatment of his maxillary and mandibular edentulism. He selected receiving implant-supported fixed-partial dentures as the best way to address his chief complaints of poor appearance and reduced function.

Dental planning software had been used to determine the best placement of the implants. Computed tomography was used to identify the best position of the dentures. Computed tomography has the ability to estimate the available bone, which is necessary to determine the implants' best position, angulation, and length. Dental planning software then used the scans obtained to fine tune the treatment plan.

Since the authors of the study carefully listened to the concerns of the patient and took the time to perform such detailed presurgical planning through computed tomography and the application of dental planning software, any issues that may have been encountered during the procedure were minimized.

To view the entire study, go to http://www.allenpress.com/pdf/orim-34-03-161-168.pdf.

I cannot give you the formula for success, but I can give you the formula for failure — which is: Try to please everybody.

HERBERT BAYARD SWOPE

UPCOMING MEETINGS

2008	
Oct. 16-19	American Dental Association 149th Annual Session, San Antonio, Texas, ada.org.
Oct. 25-29	American Public Health Association Oral Health Section's annual meeting and exposition, San Diego, www.apha.org/meetings.
Nov. 2-8	United States Dental Tennis Association Fall meeting, Palm Desert, dentaltennis.org.
Nov. 13-15	Hispanic Dental Association's 16th annual meeting, Carefree, Ariz, hdassoc.org.
2009	
May 14-17	CDA Spring Scientific Session, Anaheim, 800-CDA-SMILE (232-7645), cda.org.
Sept. 12-13	CDA Fall Scientific Session, San Francisco, 800-CDA-SMILE (232-7645), cda.org.
Oct. 1-4	American Dental Association 150th Annual Session, Honolulu, Hawaii, ada.org.
Nov. 8-14	United States Dental Tennis Association Fall meeting, Scottsdale, Ariz., dentaltennis.org.

To have an event included on this list of nonprofit association continuing education meetings, please send the information to Upcoming Meetings, CDA Journal, 1201 K St., 16th Floor, Sacramento, CA 95814 or fax the information to 916-554-5962.

Dr. Samuel D. Harris National Museum of Dentistry on the Go

The National Museum of Dentistry will offer a special preview of its "Your Spitting Image" traveling exhibition Oct. 16-18 during the ADA's Annual Session in San Antonio. The mobile exhibit will begin touring museums across the country in 2009.

The museum, which celebrated its 12th anniversary last summer, opened three new exhibitions this year: "Marvelous Mouth," the first exhibit at the museum to focus on orthodontics; the "Modern Dental Office," which features the latest dental technology available; and the new "Brush, Floss, Rinse" component to the "Your Spitting Image" exhibition that explores the connection between the body and mouth.

"We are excited that National Museum of Dentistry programs such as MouthPower Online and our traveling exhibitions are making an impact on communities nationwide," said Rosemary Fetter, executive director of the museum. "The museum fills an important role to educate the public about the importance of good oral health to overall health."

The exhibitions and programs have been making an impact on site, online, and across the country. This year, the museum's accomplishments included

- partnering with the University of Maryland Dental School and the Maryland State Dental Association to host a Give Kids a Smile event. Nearly 100 Baltimore City children came to the museum for with a hands-on exploration of the MouthPower oral health education program and free dental screenings; and
- launching a new oral health program for seniors called "Your Marvelous Mouth: The New Frontier of OralLongevity." It was created in partnership with the Elderhostel program and supports the ADA's Oral Longevity initiative to explore oral health care issues those over the age of 55 face.

MARIJUANA, CONTINUED FROM 725

exposure" (428; 47.4 percent); and "high exposure" (182; 20.2 percent). "Some exposure" was defined as an average of 1 to 40 incidents of use reported during the years assessed, and "high exposure" was considered an average of 41-plus occasions of use during those years.

Tobacco smoking has strongly been associated with periodontal disease, but there was no interaction between cannabis use and tobacco smoking in predicting the condition's occurrence.

"The study's demonstration of a strong association between cannabis use and periodontitis experience by age 32 years indicates that long-term smoking of cannabis is detrimental to the periodontal tissues and that public health measures to reduce the prevalence of cannabis smoking may have periodontal benefits for the population," wrote the authors.

Two hundred sixty-five participants (29.3 percent) at age 32 had one or more sites with 4 mm or greater periodontal combined attachment loss, and 111 participants (12.3 percent) had one or more sites with 5 mm or greater combined attachment loss. New attachment loss between the ages of 26 and 32 years in the none, some, and high cannabis exposure groups was 6.5 percent, 11.2 percent, and 23.6 percent, respectively, according to the study.

"Although definitively establishing the periodontal effects of exposure to cannabis smoke should await confirmation in other populations and settings, health promoters and dental and medical practitioners should take steps to raise awareness of the strong probability that regular cannabis users may be doing damage to the tissues that support their teeth," they said.

After controlling for tobacco use (measured in pack-years), gender, dental plaque, and irregular use of dental services were compared with those who had never smoked marijuana. Individuals in the highest exposure group for the drug had a 60 percent increased risk for having one or more sites with 4 mm or greater combined attachment loss, a 3.1 times greater risk for having one or more sites with 5 mm or greater CAL, and a 2.2 times increased risk for having new attachment loss, according to the study.

"Dental and medical practitioners should take steps to raise awareness of the strong probability that regular cannabis users may be doing damage to the tissues that support their teeth."

CDA JOURNAL, VOL 36, Nº10

Method Developed to Control Growth Rate of Replacement Tissue

University of Michigan researchers have developed a way to control the growth rate of replacement tissue and the formation of new blood vessels, solving the problems of growing replacement tissue to treat trauma and injuries.

William Giannobile, DDS, MS, DMSc, a professor at the University of Michigan School of Dentistry and College of Engineering, said the procedure could be used in bone grafts, tissue replacement, dental procedures or for diabetics or elderly patients who experience wound healing problems.

"If you have such a large defect that your body can't completely heal, this is a way to augment and dose a natural wound healing protein," said Giannobile, who coauthored the paper with Peter Ma, MS, PhD, a university professor with appointments in engineering and dentistry, and principal investigator on the National Institutes of Health project.

Researchers put platelet-derived growth factor into nanoparticles and then attached them to a lattice-like, biodegradable scaffold, according to a press release. In experiments, the growth factor recruited cells that stimulate the body's own machinery responsible for healing, said Ma, whose lab developed the scaffold and the nanoparticles. As the tissue grew, it crawled into the scaffold, which eventually dissolved.

"Growth factor is typically dumped in and releases over a period of hours," said Giannobile, who also directs the Michigan Center for Oral Health Research. "With certain wounds you might want a lot (of growth factor) in the beginning, and with others you might want a little released over a longer period of time. We've basically found a way to dial up or dial down the release rate of these growth factors."

Giannobile said the next step is to evaluate a broader range of wounds, followed by early-stage human studies.

ADA Refreshes 'OralLongevity' Web Site

The American Dental Association has spruced up its OralLongevity Web site that features improved navigation and new content that further increases awareness among older Americans to maintain good oral health for their lifetime.

The Web site, www.orallongevity.ada.org, now is arranged in three well-defined areas:

- "OralLongevity" landing page with an overview of the program objectives and information tools,
- "Resources for Dental Professionals" to raise awareness of the special oral needs of an aging population, and
- "Resources for Consumers" to empower seniors to take control of their oral health.

The Web site also offers materials to help dentists educate other health professionals, older adult patients, and caregivers about the importance of oral health. These online resources, which may be downloaded and duplicated directly, include:

- commonly asked questions and answers for patients,
- program outlines for presenting the DVD to health professionals, patients, or caregivers,
- post-test for consumers,
- sample press releases to publicize OralLongevity outreach activity, and
- clinical articles from other dental publications.

Visitors in the "Consumer Resources" section will find tips for taking care of their teeth, pointers on making the most of visiting the dentist, and a discussion of the connection between oral health and overall health. The link, "Find an ADA Member Dentist" also is located here.

CDA JOURNAL, VOL 36, Nº10

FOCUSING ON DENTAL PHARMACOLOGY

PETER L. JACOBSEN, PHD, DDS

GUEST EDITOR

Peter L. Jacobsen, PHD, DDS, is an adjunct professor at the Arthur A. Dugoni School of Dentistry, a diplomate of the American Board of Oral Medicine, and author of the *Little Dental Drug Booklet*.

Drugs. We give them and we get them.

It is my pleasure to be the guest editor of this month's *Journal of the California Dental Association* that focuses on dental pharmacology. As guest editor I primarily have the privilege and responsibility to contact some of the nation's best dental educators to tell you and me about dental pharmacology. And that is what I have done.

We are impacted each practice day by drugs, the ones we use and prescribe, and the ones that patients are taking, most of which are prescribed by their physician. Dr. Budenz has provided an informative article and update on the most common medication used in dentistry, local anesthetics. Dr. Chainani-Wu and Dr. Wu have updated us on immunosuppressant agents that we use infrequently, but are uniquely valuable in some oral soft tissue diseases. And, of course, some patients are taking immunosuppressants and the impact of these drugs on the body needs to be taken into consideration during dental treatment.

Dr. Clark has done a stunning job of broadening our awareness of pain management medication. Though it is infrequent that most of us treat chronic head and neck pain in general practice, an awareness of this group of disorders, and the broad range of medication used to treat it, is an eye-opener into the expanding scope of dentistry as a specialty within medicine.

The other side of the coin for dental pharmacology is managing patients who are taking medication unrelated to dental needs. Dr. Chavez has provided us with a framework by which to categorize pharmacological risk factors and to assist us in prioritizing management and treatment planning approaches to assure safe and successful dental outcomes. Dr. Migliorati, a national expert in the evolving science of bisphosphonate-related osteonecrosis, and his colleagues, have provided useful clinical decision-making suggestions on how to manage patients taking these drugs.

These authors have done the hard work so that you and I can update ourselves and our patients can thereby benefit from the knowledge we have gained.

Oh, one other thing. How can you improve your drug prescribing skills? Work with a pharmacist. See the interview between myself and Dr. Lofholm, president of the California Pharmacists Association, who have provided some interesting and informative perspective on pharmacy and dentistry.

CDA JOURNAL, VOL 36, Nº10

Selection Factors for Local Anesthetic Agents

ALAN W. BUDENZ, MS, DDS, MBA

ABSTRACT The decision to inject local anesthetic agents to achieve profound anesthesia is dependent upon many factors, particularly the depth and duration of anesthesia required, and the possible need for hemostasis. To maximize the safety of local anesthetic injections, it is necessary to weigh the risks against the benefits for each patient, for each anesthetic agent, for use of a vasoconstrictor, and for the delivery technique for the selected agent.

AUTHOR

Alan W. Budenz, MS, DDS, MBA, is a professor, Department of Anatomical Sciences and Department of Dental Practice, Arthur A. Dugoni School of Dentistry, San Francisco.

The administration of local anesthetic agents via intraoral injection is fundamental to the establishment and management of patient pain in the majority of dental procedures. Although dentists and, in most states, hygienists receive extensive training and practice in the administration of local anesthetic injections, many variables can affect the attainment of successful anesthesia in dental patients.

Clearly there are significant human variables: anatomical variations in the size, morphology and location of structures in the jaws of different individuals, and of the dental sensory nerve pathways themselves, are well recognized.[1,2] Variations in chemical sensitivity from one person to another are also significant: Any given patient will not be equally sensitive to all of the anesthetic agents available for dentistry, nor will any patient necessarily experience the same degree of anesthesia from any single anesthetic agent from one appointment to another.

Some of this variability is attributable to differences in the numbers, types, and physiologic state of anesthetic binding sites within sensory nerves.[3] This article will discuss some general properties of the anesthetic agents available in dental injection cartridges and will offer suggestions for achieving more predictable success with dental local anesthesia. **TABLE 1** lists the anesthetic agents currently available in dental injection cartridges in the United States.

CDA JOURNAL, VOL 36, Nº10

TABLE 1

Local Anesthetic Agents Available in the United States

All of the anesthetic agents currently available in a dental injection cartridge in the United States are of the amide chemical class.

- Lidocaine HCl: 2% plain or 2% with 1:50,000 or 1:100,000 epinephrine
- Mepivacaine HCl: 3% plain or 2% with 1:20,000 levonordefrin (Neo-Cobefrin)
- Prilocaine HCl: 4% plain or 4% with 1:200,000 epinephrine
- Articaine HCl: 4% with 1:100,000 or 1:200,000 epinephrine
- Bupivacaine HCl: 0.5% with 1:200,000 epinephrine

The Development of Dental Local Anesthetic Agents

Historically, the first local anesthetic agent widely used in dentistry was cocaine. The first injection of cocaine for nerve conduction blockade is attributed to noted American surgeon William Halstead in November 1884 when he performed infraorbital and inferior alveolar nerve blocks for dental procedures.[4]

Although injection of cocaine provided a major advancement in pain control, it had significant drawbacks, such as a high propensity for addiction and a short duration of action. This latter factor necessitated injection of large doses of the drug, which further increased the potential for addiction and for severe systemic toxicity.

The safety of nerve conduction blockade procedures advanced tremendously in 1905 when Alfred Einhorn and his associates synthesized an ester-based local anesthetic, named procaine.[5] As a safe and effective substitute for cocaine, the discovery of procaine, marketed under the trade name Novocain, is considered by some historians to mark the beginning of the modern era of regional anesthesia. Development of several other ester-type local anesthetics followed and these remained in wide use throughout most of the 20th century.

The next step forward occurred in 1943 when Nils Löfgren synthesized a new amide-based local anesthetic agent, derived from xylidine, and named it "lidocaine."[6] First marketed in 1948 under the trade name Xylocaine, lidocaine was more potent and less allergenic than procaine and the other ester-based anesthetics. Several other amide anesthetics have since been developed and remain in use in dentistry: mepivacaine, prilocaine, bupivacaine, and articaine. The advantages of the amide-based anesthetic agents, particularly their extremely low rate of allergenicity as compared to the ester-type anesthetics (almost nonexistent for amides versus about 1 percent of the population for the esters), led to their complete replacement of the ester-based anesthetics in dental injection cartridges.[7]

Use of Currently Available Dental Local Anesthetic Agents

The availability of a variety of local anesthetic agents enables dentists and hygienists to select an anesthetic that possesses specific properties such as time of onset and duration, hemostatic control, and degree of cardiac side effects that are appropriate for each individual patient and for each specific dental procedure. TABLE 2 briefly summarizes the properties of the anesthetic agents currently available for dental use in the United States. It should be noted that these properties, particularly duration and depth of anesthesia, are quite variable due to a number of factors and are therefore only approximations.[7]

1. Accuracy in administration of the drug
2. Anatomical variation
3. Status of the tissues at the site of drug deposition (vascularity, pH)
4. Type of injection administered (infiltration versus nerve block)
5. Individual variation in response to the drug administered

The Relation of Anesthetic Agent Selection to Injection Technique

Although technique is not everything, it is important, the technique must be matched to the anesthetic agent to achieve the desired anesthesia goals. After deciding that the outcome of a patient's dental procedure will benefit from use of a local anesthetic injection, the decision must be made between an infiltration injection technique and a block injection technique. A block injection will generally provide adequate anesthesia for approximately twice as long as an infiltration injection. However, there are some anesthetic agents for which this generality does not hold true. For example, prilocaine 4 percent HCl "plain" when administered as an infiltration injection for maxillary teeth has a pulpal anesthesia duration of only about 10 minutes, as determined by electrical stimulation studies.[9]

When injected via a block technique, this same anesthetic agent produces pulpal anesthesia from 40 to 60 minutes.[7] With the addition of a vasoconstrictor agent (prilocaine 4 percent HCl with 1:200,000 epinephrine), the pulpal anesthesia duration times of this anesthetic agent are less technique sensitive and can extend up to one hour as an infiltration injection and up to 90 minutes as a block injection.[7]

Another example is bupivacaine (0.5 percent HCl with 1:200,000 epinephrine), which is potentially the longest-acting anesthetic agent available in a dental cartridge. If administered via an

TABLE 2

Characteristics of Local Anesthetic Agents[7,8]

Local Anesthetic	Onset*	Duration of Pulpal Anesthesia**
2% Lidocaine plain	Fast: 3 to 5 minutes	Short: 5 to 10 minutes not recommended for nerve blocks
2% Lidocaine with epinephrine	Fast: 3 to 5 minutes	Moderate: 60 to 90 minutes
3% Mepivacaine plain	Fast: 3 to 5 minutes	Short: 20 to 40 minutes
2% Mepivacaine with levonordefrin	Fast: 3 to 5 minutes	Moderate: 40 to 90 minutes
4% Prilocaine plain	Fast: 3 to 5 minutes	Moderate: 10 to 60 minutes
4% Prilocaine with epinephrine	Fast: 3 to 5 minutes	Moderate: 35 to 70 minutes
4% Articaine with epinephrine	Fast: 2 to 3 minutes	Moderate: 60 to 120 minutes
0.5% Bupivacaine with epinephrine	Moderate: 6 to 10 minutes	Long: Up to 7 hours

*Time of onset: Individual variances are common. Lower number provided is average for infiltration injections; higher number is average for nerve block injections.

**Duration of pulpal anesthesia: Individual variances are common. Lower number provided is average for infiltration injections; higher number is average for nerve block injections.

infiltration injection technique in the maxilla, it has an average pulpal anesthesia duration of only 40 minutes, which is normally not as long as the duration of the same injection using lidocaine or mepivacaine.[7,10] The long duration of pulpal anesthesia with bupivacaine, up to four hours in some patients, is realized only when this agent is administered as a block injection.[10] However, it must be noted that exactly how long pulpal anesthesia will last for either type of injection with any agent is dependent upon a number of patient variables, and also upon the relative volume of anesthetic injected, the accuracy of administration of the technique used, and the presence or absence of a vasoconstrictor agent.

The Use of Vasoconstrictor Agents

The presence or absence of a vasoconstrictor has significant effects on the properties of an anesthetic agent. This is due to three main factors: (1) increased duration of anesthesia by holding the anesthetic at the local injection site longer by constriction of the local vasculature; (2) localized vasoconstriction can maintain hemostasis during dental procedures, such as root planing or surgical procedures that produce bleeding; and (3) slowed uptake of the anesthetic agent into the bloodstream, resulting in a lower concentration of anesthetic in the blood over time, which reduces the risk of systemic toxicity.[11-13]

Use of a block injection technique, which is usually given at a site some distance from the procedure site, may provide adequate pulpal and gingival anesthesia; however, it cannot provide adequate hemostasis at the procedure site; only local infiltrations close to the actual site of bleeding can effectively control bleeding.[7] Conversely, local infiltration injections may provide both local site anesthesia and hemostasis, but the duration of anesthesia is shorter and may be a less profound level of anesthesia. In order to decide which technique to use, the practitioner must consider the depth and duration of anesthesia required for the procedure and the possible need for hemostasis at the local site. For invasive root planing or surgical procedures, it may be best to use a combination of both techniques: a block injection with a vasoconstrictor-containing anesthetic for depth and duration of anesthesia, and infiltration injections with the same or a higher vasoconstrictor concentration for hemostasis.

Although the presence of a vasoconstrictor increases the duration of anesthesia, the specific concentration of the vasoconstrictor does not alter the clinical duration of anesthesia by more than a few minutes.[7,13-15] For example, lidocaine with epinephrine is available in the United States in both 1:50,000 and 1:100,000 vasoconstrictor concentrations. The 1:50,000 concentration of epinephrine will provide the best hemostasis when used as a local site infiltration injection.[7,14]

A block injection with the same 1:50,000 concentration will not provide significantly longer pulpal duration of anesthesia than a 1:100,000 concentration but is more likely to produce systemic cardiovascular side effects, such as tachycardia.[13,14] It is the author's recommendation to use the 1:50,000 concentration only for local infiltration injections and to use the lower 1:100,000 concentration for block injections. For patient safety reasons, the lowest concentration of vasoconstrictor available is generally preferable for all block injections.

Vasoconstrictor Agents

In the United States, epinephrine is the primary vasoconstrictor agent used in dental anesthetics. Levonordefrin (Neo-Cobefrin, Cook-Waite/Kodak) in a 1:20,000 concentration is used only with a 2 percent mepivacaine formulation in North America. Because levonordefrin has a reduced tachycardic effect on the heart, it is preferable to use for particularly epinephrine-sensitive patients. However, levonordefrin is contraindicated for use in all patients for whom epinephrine is contraindicated, i.e., if epinephrine should not be used because of its possible deleterious effect on the patient's medical condition,

levonordefrin should not be substituted.[16] A plain anesthetic solution without a vasoconstrictor agent should be used in the infrequent situation where use of a vasoconstrictor is medically contraindicated.

The Use of Articaine in Patients with 'Sulfur' Allergies

Articaine has become a popular dental anesthetic in the United States since its introduction in April 2000. Although classified as an amide anesthetic agent and sharing the amide characteristic of extremely low risk of allergenicity in the population, articaine is actually a hybrid of both an amide and an ester class anesthetic due to the presence of both an amide and an ester intermediate chain in its chemical composition. Biotransformation of articaine begins immediately upon its entering the bloodstream where the plasma esterase enzymes initiate the metabolic breakdown process via hydrolysis of the ester chains. Articaine metabolism is then completed in the liver by hepatic microsomal enzymes.[17]

Metabolism of all other amide anesthetic agents does not begin until they reach the liver. The more rapid metabolism of articaine suggests that articaine has a reduced risk of systemic toxicity; however, it must be remembered that articaine is available only in the higher 4 percent concentration in the United States.

Articaine is also unique in that its aromatic ring structure is a thiophene ring rather than the benzene ring characteristic of all other amide agents, a feature which significantly increases articaine's lipid solubility.[7] Contained within the thiophene ring structure of articaine is a sulfur molecule, which has led some practitioners to avoid the use of articaine in patients with sulfur and sulfa drug allergies. However, the sulfur molecule is a nonallergen, making its presence allergentically immaterial.[7,18]

Patient sulfur and sulfa drug allergies are largely caused by the sulfonamide drugs, such as bactrim and septra, or to the sodium metabisulfite used as an anti-oxidant agent to protect the vasoconstrictor in local anesthetic cartridges. To assess a patient's possible reactivity to sodium metabisulfite the dentist or hygienist should question the patient about possible food allergies.

Because foods such as dried fruits and preserved meats (pepperoni, salami) or beer and wine contain high levels of sulfites, if a patient avoids these types of food items, it is best advised to avoid all anesthetic solutions containing any form of vasoconstrictor. Unfortunately, the use of only plain anesthetics in these situations provides relatively short duration of pulpal anesthesia and may result in the need for repeated anesthetic injections.

Conclusion

The selection of a technique for administering local anesthesia injections is important to the overall goals of local anesthetic use in dental procedures: adequate anesthesia to maintain patient comfort throughout the duration of the specific procedure, maintenance of hemostasis when bleeding is anticipated, and delivery of the anesthetic agent of choice in as safe and atraumatic a manner as possible. The selection of the anesthetic agent to be used must then be matched to the chosen injection technique.

Of paramount importance throughout this decision-making process is the fact that injection of dental local anesthetic agents is an invasive procedure, and, although the agents available to the profession in dental cartridges are remarkably safe, complications may occur in any patient at any time. Selection of which local anesthetic agent(s) to use must be based on careful goal and risk versus benefit assessments for each individual patient at each individual procedure appointment. ■■■■

REFERENCES

1. Carter RB, Keen EN, The intramandibular course of the inferior alveolar nerve. *J Anat* 108(Pt 3):433-40, 1971.
2. Blanton PL, Roda RS, The anatomy of local anesthesia. *J Calif Dent Assoc* 4:55-69, 1995.
3. Hargreaves KM, Keiser K, Local anesthetic failure in endodontics: Mechanisms and management. *Endodontic Topics* 1:26-39, 2002.
4. Fink BR, History of neural blockade. In Cousins MJ, Bridenbaugh PO, eds., Neural blockade in clinical anesthesia and management of pain, second ed., JB Lippincott Co, Philadelphia, 1988.
5. Hadda SE, Procaine: Alfred Einhorn's ideal substitute for cocaine. *J Am Dent Assoc* 64:841-5, 1962.
6. Dobbs EC, A chronological history of local anesthesia in dentistry. *J Oral Ther Pharmacol* 1:546-9, 1965.
7. Malamed SF, Handbook of local anesthesia, fifth ed., Mosby, St. Louis, Mo., 2004.
8. Budenz AW, Local anesthetics in dentistry: Then and now. *J Calif Dent Assoc* 31:388-96, 2003.
9. Citanest Plain and Citanest Forte (package insert). Westborough, Mass., Astra Pharmaceutical Products, 1997.
10. Jastak JT, Yagiela JA, Donaldson D, Local anesthesia of the oral cavity, second ed., W.B. Saunders Co., Philadelphia, Pa., 1995.
11. Pallasch TJ, Vasoconstrictors and the heart. *J Calif Dent Assoc* 26(9):668-76, 1998.
12. Brown RS, Rhodus NL, Epinephrine and local anesthesia revisited. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 100(4):401-8, October 2005.
13. Milam SB, Giovannitti JA Jr., Local anesthetics in dental practice. *Dent Clin North Am* 28(3):493-508, July 1984.
14. ADA/PDR guide to dental therapeutics, fourth ed., American Dental Association and Thomson PDR, Montvale, NJ, Chapter 1:2-3, 2006.
15. Moore PA, Boynes SG, et al, The anesthetic efficacy of 4 percent articaine 1:200,000 epinephrine: Two controlled clinical trials. *J Am Dent Assoc* 137:1572-81, 2006.
16. Little JW, Miller C, et al, Dental management of the medically compromised patient, sixth ed., St. Louis, Mo., Mosby pages 568-70, 2002.
17. Malamed SF, Gagnon S, Leblanc D, Articaine hydrochloride: A study of the safety of a new amide local anesthetic. *J Am Dent Assoc* 132:177-85, 2001.
18. Hawkins M, Articaine: Truths, myths, and potentials. Academy of Dental therapeutics and stomatology (ADTS) continuing education course publication, Chesterland, Ohio, 2004.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Alan W. Budenz, MS, DDS, MBA, Arthur A. Dugoni School of Dentistry, Basic Sciences Department, 2155 Webster St., San Francisco, Calif., 94115.

CDA JOURNAL, VOL 36, Nº10

Systematic Review of the Medication List: A Resource for Risk Assessment and Dental Management

ELISA M. CHÁVEZ, DDS

ABSTRACT Polypharmacy, besides representing a risk in and of itself, points to the potential risk the underlying diseases that necessitated the drugs can present in the dental office. These diseases and medications can also present a risk to oral health. A sequence for categorizing drugs in a medication list is presented here to aid in the identification of potential risks in the dental treatment and management of patients with complex medical histories and drug regimens.

AUTHOR

Elisa M. Chávez, DDS, is an assistant professor, removable prosthodontics, Arthur A. Dugoni School of Dentistry, San Francisco.

As our population ages and people live longer, with more chronic diseases and longer medication lists, identifying potential risks for the dental patient becomes more difficult. By the year 2030, the number of Californians aged 65 and older will have increased by 130 percent from the year 2000.[1] Approximately 20 percent of people over age 65 take at least five medications, not including over-the-counter products.[2] In California, 45 percent of adults have one or more chronic conditions including diabetes, asthma, hypertension, and heart disease or rate their health as fair or poor.[3] A systematic method for breaking down a lengthy drug list that will not only help highlight medication issues, but also emphasize important considerations in caring for a medically complex population, is presented here.

Prior to administering a drug or writing a prescription, three questions should always be asked:

- Is this person allergic to this drug?
- Have they experienced an adverse drug reaction while taking it?
- Could the drug I plan to prescribe interact with any of the patient's current drug regimen?

These are basic requirements for keeping patients safe as dentists administer and prescribe drugs to them, whether they are taking many prescription drugs or none. Any patient can have an adverse drug reaction to single or multiple drugs as an expected or unexpected side effect.[4]

However, familiarity with drugs commonly used by patients with increasingly complex medical problems will help us identify potentials for problems in the dental management of these patients. These problems may arise from the use of the drug alone or by virtue of the fact they have a disease that requires management with a particular drug.

The fact that the patient is on medication suggests they have underlying disease with which dental professionals should be concerned. Some medications are prescribed in the event of an emergency. Some of the conditions for which the medications are prescribed will require laboratory evaluation to determine the risk of an adverse outcome. Some will require consultation with the patient's physician regarding alteration of their drug regimen or use in concert with other medication.

Some drugs may alter what a dentist chooses to prescribe. Some will require alteration of a dental treatment plan, treatment regimen, or plan for maintenance. In all cases, it is important to identify these potential risks when first evaluating the patient or upon review of any new diagnoses and medications with which a patient may present at any given appointment.

See **TABLE 1** for drugs that should draw the practitioner's attention.

Drugs Needed in the Event of Emergency

Any patient could have a medical emergency in the office at any time, even before they are called from the waiting room. The first drugs to look for on a medication list are those that may be necessary in an emergency, such as nitroglycerin used for angina or bronchodilators inhaled during acute exacerbation of chronic obstructive pulmonary disease.*[5,6] While it is important to stress to patients they need to bring these medications with them to each appointment, it is also necessary to keep these medications in an emergency kit. If the patient brings them to each appointment, they should place them out at each visit so time is not wasted looking through their belongings for the medication during an emergency.

TABLE 1

Four Categories and Examples of Drugs That Should Draw Attention in a Medication List

DRUGS NEEDED IN THE EVENT OF EMERGENCY

- nitroglycerin
- short-acting bronchodilators — inhalers (albuterol, pirbuterol)

DRUGS THAT HAVE THE POTENTIAL TO RESULT IN AN ADVERSE EVENT OR TELL US THE PATIENT IS AT HIGHER RISK FOR AN ADVERSE EVENT

- insulin
- anti-coagulants (warfarin [Coumadin], clopidogrel [Plavix], aspirin, NSAIDS)
- bisphosphonates (alendronate [Fosamax], ibandronate [Boniva], zoledronic acid [Zometa], clodronate [Bonefos])
- chemotherapeutics (vincristine, 5-fluorouracil, methotrexate, doxorubicin)
- immunosuppressants (prednisone, cyclosporin)
- MAO inhibitors (isocarboxazid [Marplan], phenelzine [Nardil], and tranylcypromine [Parnate])
- opioids (methadone, Fentanyl, Pentazocine)
- recreational drug use
- sedative hypnotics (diazepam [Valium], alprazolam [Xanax], alcohol)

DRUGS THAT HAVE A SPECIFIC AND POTENTIALLY SIGNIFICANT ADVERSE INTRAORAL SIDE EFFECT

- ACE inhibitors (captopril [Capoten], enalapril [Vasotec], lisinopril [Zestril])
- calcium channel blockers (amlodipine [Norvasc], felodipine [Plendil], nifedipine [Procardia, Adalat])
- cyclosporin (Sandimmune)
- phenytoin (Dilantin)
- xerostomic medications (e.g., anti-hypertensives, diuretics, antidepressants, antihistamines)
- chemotherapeutics (vincristine, 5-fluorouracil, methotrexate, doxorubicin)

OVER-THE-COUNTER AND NATURAL DRUGS THAT MAY CONTRIBUTE TO AN ADVERSE TREATMENT OUTCOME

- Aspirin
- Ibuprofen
- Feverfew
- Garlic
- Ginger
- Ginkgo biloba
- Gilberry
- St. John's wort
- Echinacea
- Ephedra (ma-huang)
- Bitter orange
- Valerian
- Kava kava
- Dong quai [5,7,8,11,12,15,16]

TABLE 2

Drugs That Have a Potential to Result in an Adverse Effect or Indicate That the Patient Is at High Risk for an Adverse Event[4,6,15,17]

Drug Groups	Example Drugs	Potential Management Problems
Anti-coagulants	Aspirin, warfarin* (Coumadin)	Excessive bleeding
Immunosuppressants	Corticosteroids* Azathioprine (Imuran)	Increase risk of bacterial and fungal infection, poor stress response
Chemotherapeutic agents	Vincristine (Oncovin) Methotrexate (Rheumatrex)	Delayed healing, mucositis, fungal infections
Sedative hypnotics*, narcotics, barbiturates	Tylenol #3, diazepam (Valium), meperidine (Demerol)	Fall risk, respiratory suppression
Hypoglycemics	Insulin*, sulfonylureas	Hypoglycemia
Bisphosphonate bone stabilizers (esp. IV bisphosphonates)	Pamidronate (Aredia) Zoledronic acid (Zometa) Alendronate (Fosamax)	Delayed bone healing, Bone necrosis
Recreational drugs	Alcohol, cocaine, heroine	Drug interactions Respiratory suppression Lver function Pain control
Opioid analgesics, anti-addictive	Methadone (Amidone)	Pain control Liver function Respiratory suppression

** Denotes drugs that are highly titrated with a narrow margin of safety*[4,15]

Drugs That have the Potential to Result in an Adverse Event or Indicate the Patient Is at Higher Risk for an Adverse Event

The second group of drugs to identify is those that may contribute to an adverse treatment outcome or adverse event in the office. Many of these drugs have a narrow margin of safety and are highly titrated (TABLE 2). One of the most recognizable in this group is insulin. Insulin itself is not generally a problem in the provision of care, but it does give some information about the patient. The first is that they are risk of developing hyper- or hypoglycemia in the office. Instructions must be clear to the patient that they follow their usual medication and diet regimen prior to treatments. An in-office finger stick blood sugar test can be useful to assess patient status prior to treatment. If they are not able to eat for some time after treatment, for instance, following multiple extractions or extensive periodontal surgery, a physician consultation should be completed to determine if this regimen should be altered on the side of mild hyperglycemia for a short period to ensure they do not become hypoglycemic during the postoperative period.

The use of insulin by a patient with type 1 or type 2 diabetes should also signal this patient may be at risk of delayed healing or even infection following treatment. As opposed to a finger stick blood test that indicates only about that patient at the date and time given, a glycosylated hemoglobin test or HbA1c is the test used to determine long-term control for the patient with diabetes. The target is generally 7 percent or less; however, this number may be altered by other conditions in older adults.[5-7] A physician consultation should be requested in order to determine their long-term control and whether or not this patient would benefit from a perioperative course of antibiotics. For patients who do not have well-controlled diabetes it is also important to inquire whether or not their kidney function may be impaired as a result of their disease, especially if they have been diagnosed with diabetes for many years. In these cases it is important to consider whether prescription dosages need to be changed as a result of impaired renal function (TABLE 3).

Anti-coagulants are drugs commonly used in the prevention of cardiac and cerebrovascular events such as myocardial infarction, atrial fibrillation, and stroke. Drugs such as aspirin, Plavix, and Coumadin are among the most commonly seen. While it is usually not necessary to alter these regimens, and, in fact, may present more of a risk than treating the patient on the drug, it is prudent to get the appropriate lab work to minimize the chance of excessive bleeding during or following a procedure.

While there are no recommended treatment modifications for patients taking clopidogrel (Plavix), there is still the potential for complications that arise as a result of anti-coagulant therapy, for

TABLE 3

Guidelines for Prescribing Commonly Used Drugs in Dentistry That Are Metabolized by the Kidney (Amoxicillin, Cephalosporin, Penicillin, Tetracycline) to Patients With Impaired Renal Function[5,7,18]

Renal Function Test	Laboratory Value	Guideline for Dental Prescribing
Glomerular filtration rate (GFR)	<10 ml/min 10-50 ml/min >50 ml/min	One dose q 24 hrs One dose q 8-12 hours One dose q 8 hours

TABLE 4

Lab Values of Concern for Patients Receiving Chemotherapeutics, Immunosuppressants or Anti-coagulants That Could Result in Impaired Healing, Risk of Infection or Excessive Bleeding Following Dental Treatment[5,7]

Test	Value of Concern	Consideration
Absolute neutrophil count (neutropenia)	Less than 500/mm3	Antibiotic prophylaxis, consult MD if concurrent with chemotherapy prior to treatment
Lymphocyte count (lymphopenia)	Less than 1,500/mm3	Patient is predisposed to fungal and viral infections
Granulocyte	Less than 2,000/mm3	Consider antibiotic prophylaxis or delay tx
Platelet count (thrombocytopenia)	Less than 50,000/mm3 Less than 10,000/mm3	Consider platelet replacement or delay until count increases Risk of life threatening spontaneous bleeding
PFA-100	Greater than 175 seconds	Consider stopping aspirin for 3 days, with MD permission
INR	Greater than 3.0	Consider consultation with MD to decrease Coumadin dosage to reach desired INR

example excessive bleeding following procedures – although rare, neutropenia, thrombocytopenia and eccymoses. A PFA-100, platelet function analyzer 100, can be requested for the patients on aspirin. A PT and INR should be requested within 48 hours prior to surgery for those patients taking Coumadin.

As a general guideline, it is safe to treat a patient with an INR of 3.5 or less if only one or two teeth are to be removed. However, the general health condition of the patient should be taken into consideration. If the patient is having extensive oral surgery, has multiple medical conditions, has other conditions which may impair coagulation, is taking other drugs that may impair coagulation, or is of an advanced age, it may be best to work at an INR of 3.0 or less, or refer the patient to an oral surgeon, and/or complete the treatment in a hospital setting in the event there is an adverse event during or following treatment.[5,7] Practitioners should use their judgment in these cases based upon their knowledge of the patient as well as knowledge about their own skills.

When a patient is on anti-coagulants, attention should be paid to surgical technique to minimize trauma and tearing of adjacent tissues. Provide sutures or primary closure where possible. The use of topical hemostatic agents such as gel foam, Surgicel or Thrombostat should also be considered.[5] Carefully review post-operative instructions with the patient or their caregiver to be sure they do not disrupt the clotting process after they have left the office. If the planned surgery is extensive and/or the patient is at risk for heavy or excessive bleeding, refer to a specialist for evaluation and treatment.

The use of oral bisphosphonates to manage patients with osteoporosis is becoming increasingly common. Many patients with breast cancer, multiple myeloma, prostate, renal, lymphatic, lung cancers, and many other cancers are receiving treatment with IV bisphosphonates. While these drugs are invaluable with regard to the management of these diseases, it has become evident that the use of these medications creates a risk of osteonecrosis following bony oral surgical procedures and sometimes from recurrent trauma such as from an ill-fitting prosthesis or even spontaneously secondary to untreated dental disease. Most practitioners will more commonly see patients taking oral bisphosphonates in their practices, which carries a much lower risk than the IV form. However, patients must be made aware of this risk prior to

TABLE 5

Guidelines for Prescribing Commonly Used Drugs in Dentistry That Are Metabolized by the Liver (Acemtaminphen, Codeine, Diazepam, Erythromycin, Ibuprofen, Ketoconazole, Lidocaine, Lorazepam, Prednisone) to Patients With Impaired Hepatic Function[5-7,18]

Liver Function Test	Normal Value	Guideline for Dental Prescribing
AST, ALT, liver transaminases	30-40 u/l	If greater than 4 times normal, do not use drugs that are toxic to or metabolized by the liver

consenting to or refusing procedures that place them at risk of osteonecrosis.[8,9]

Patients taking the IV form of the medication to treat cancer should also be carefully evaluated prior to proceeding with dental treatment since they may also be taking immunnosuppressants, placing them at risk for other adverse outcomes in the dental office.[5] A physician consultation and thorough review of relevant laboratory values should be completed prior to treating patients taking immunnosuppressants as they are at risk for poor healing and possibly excessive bleeding following treatment (TABLE 4). They may be suffering other adverse side effects of their treatment such as nausea, mucositis, or fatigue and may not be motivated to pursue or be able to tolerate general dental treatment at this time.[5,7]

Dental practitioners can aid these patients by helping them create an individualized oral hygiene/prevention regimen and careful treatment planning during this time to minimize the adverse effects of their cancer treatment on their oral health. This will not only help maintain their oral health during this time, but it can maximize their potential to complete their cancer treatment by maintaining oral comfort and nutritional intake.[5]

Some of the more commonly prescribed immunnosuppressants: glucocorticoids, cyclosporine, azathioprine (Imuran), methotrexate (Rheumatrex), and chemotheraputics such as vincristine (Oncovin) may be readily recognizable to some practitioners.[6] However, because there are so many drugs available and new drugs are constantly coming into use, it may be more efficient to review the medical history for conditions or diseases that may warrant their use, such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, organ transplant, or cancer and then carefully review the patient's medication list for the drugs used to manage these diseases.

As the name suggests, these drugs impair the immune system making the patient susceptible to delayed healing or infection following a procedure or refractory conditions such as periodontal disease, fungal infections, or other opportunistic infections. This may result in a need to aggressively treat recurrent or opportunistic infections and/or provide only palliative treatment until the cancer therapy is complete, assessing and reassessing laboratory values related to immune function and treating as appropriate.[5,7]

Recreational drug use can also place a patient at risk for an adverse event in the dental office. It is important to ask patients about recreational drug use during review of the medical history and medication list. The information may need to be taken into consideration as determinations are made about the use of anesthetic with vasoconstrictors or pain medication that may be prescribed.[5] Some patients may report they are on methadone to manage their drug addiction.[6] In these cases it is appropriate to consult with the patient's physician and/or pharmacist with regard to the use of pain medications. Methadone also interacts with a number of drugs that might be prescribed in dentistry, such and anti-bacterial and anti-fungal drugs.[6]

Some patients may have impaired liver function, for example those who have abused alcohol or those who have hepatitis B or C secondary to IV drug use[5] (TABLE 5). Working in conjunction with the patient's physician and/or pharmacist is important in making sure their pain is adequately addressed while also reducing the chances for an adverse outcome as a result of medication choice or dosages prescribed. Patients who are on methadone or other opioids for chronic pain conditions also will benefit from coordinated care between the dentist, physician, and pharmacist to appropriately manage oral/dental pain. The use of opioids, sedative hypnotics, narcotics and barbiturates, by prescription or otherwise, alerts the practitioner that the patient is at risk for respiratory depression and possibly falls; and this should be taken into consideration if medication for pain or sedation is to be prescribed.[5,6,15]

Antidepressants are another group of commonly prescribed medications. Most do not present a direct impact on the provision of oral health care, however the class of drugs known as MAO inhibitors can enhance the effect of vasoconstrictors such as epinephrine and levonordefrin and should be avoided.[5,6] A careful cross-check for drugs interactions should be completed prior to prescribing because these drugs also have a high potential for adverse drug interactions.[6]

Drugs That Have a Specific and Potentially Significant Adverse Intraoral Side Effect

The next group of drugs to consider is those that have specific intraoral side effects, such as gingival enlargement secondary to poor oral hygiene and use of calcium channel blockers used to treat hypertension, cyclosporine used to manage autoimmune disorders, and Dilantin used to manage seizure disorders.[6,10,11] ACE inhibitors can cause lichenoid or ery-

TABLE 6

Strategies and Considerations for Managing Patients Taking Medications That Have Intraoral Side Effects[5,7,10,11,15]

Side Effect	Drug Class	Example (Generic)	May Be Used to Treat	Strategies and Considerations
Xerostomia	Antihistamine	Claritin (loratadine)	Hay fever	Consider consultation with MD to inquire about a permanent or temporary change in medication to see if it resolves. If this is not possible, or if the patient is taking numerous drugs that impair salivary flow, provide palliative care and counsel patients about caries prevention.
	Antidepressant	Zoloft (sertraline)	Obsessive compulsive disorder	
	Calcium channel blocker	Norvasc (amlodipine)	High blood pressure	
	Diuretics	Lasix (furosemide)	High blood pressure	
Fungal infection	Antibiotics	Tetracap (tetracycline)	Periodontal disease	Emphasize good oral hygiene. Prescribe anti-fungals. Monitor for resolution and recurrence.
	Immunosuppressant	Cortan (prednisone)	Rheumatoid arthritis COPD	
Mucositis	Anti-neoplastic	Adrucil (5-fluorouracil)	Chemotheraputic for breast cancer	Provide palliative care if not already done by oncologist. Develop individualized oral hygiene routine with the patient.
Gingival hyperplasia	Anti-convulsant	Dilantin (phenytoin)	Epilepsy	In all cases, advise patients that poor oral hygiene will contribute to the problem, create an individualized oral hygiene plan.
	Calcium channel blocker	Procardia (nifedipine)	High blood pressure	
	Immunosuppressant	Sandimmune (cyclosporin)	Prevent organ transplant rejection	
Stomatitis lichenoid reactions	ACE inhibitor	Capoten (captopril)	High blood pressure	To confirm diagnosis, consult with MD to inquire about a temporary change in medication to see if it resolves. If this is not an option, consider biopsy and /or careful history of and monitoring of the lesion.
	Diuretics	Thiazide (HCTZ)	High blood pressure	
Mucosal burns	Anti-inflammatory	Ecotrin (aspirin)	Osteoarthritis	Instruct patients to swallow, not dissolve, the aspirin.

thema multiforme reactions.[6,7] And, there are a whole host of other medications that count xerostomia and diminished salivary flow as an oral side effect (TABLE 6).

Physician consultation may be required to inform the physician of the adverse effect and to inquire whether or not there is an alternative drug choice. It is important to provide the patient with strategies for minimizing or coping with these side effects, especially if there is not an alternative treatment for them. Subjects with significantly reduced salivary flow should be counseled with regard to caries prevention to limit the potentially disastrous effects of impaired salivary flow on the dentition. Salivary substitutes and stimulants may be useful for these patients, especially those with prostheses who may be experiencing discomfort or difficulty wearing them due to their impaired salivary flow.

Patients who have salivary impairment as a result of head and neck radiation or Sjögren's disease may be prescribed pilocarpine or cevimeline to stimulate salivary flow, however these drugs should be used cautiously, particularly in patients of an advanced age and/or those who are medically compromised.[5-7] They should not be used in patients with uncontrolled asthma, narrow angle glaucoma or severe hepatic impairment.[6]

Over-the-counter and Natural Drugs That may Contribute to an Adverse Treatment Outcome

There are several natural and over-the-counter medications that can play a role in adverse treatment outcomes. Valerian used for its sedative effects, often in the treatment of insomnia, can potentiate the adverse effects of sedative hypnotic or anti-anxiety medications that may be prescribed. Several other natural drugs can increase bleeding, such as St John's wort, Dong quai, Gingko biloba, garlic and ginger. Ephedra combined with anxiety and/or a vasoconstrictor can increase blood pressure and heart rate. Patients who take high

doses of aspirin or NSAIDS over-the-counter are also at risk in increased bleeding.[12-14]

Conclusion

Once a drug list is reduced to manageable segments and the potential risks identified, we can return to our original questions as we begin our treatment in the office or dismiss the patient with a prescription:

- Is the patient allergic to this drug?
- Have they had an adverse reaction to it?
- Could the drug I plan to prescribe interact with any of the drugs in the patient's current regimen?

This list of drugs and conditions that should draw the practitioner's attention is dynamic. Specific patient populations, such as pediatric, may have specific drugs or additional criteria that need to be considered.

As new drugs and treatments are developed and new side effects become evident, it will be necessary to review and add or delete items from this list as indicated by the most current information. Practitioners must use the health history and the medication list in concert, using one to make sense of the other and utilizing all the information available from reviewing each one carefully in order to manage their increasingly complex patients safely and effectively. ■■■■

REFERENCES

1. U.S. Census Bureau, population division, interim state population projections, 2005. www.census.gov/population/projections/05PyrmdCA3.pdf. Accessed July 10, 2008.
2. Frazier SC, Health outcomes and polypharmacy in elderly individuals: An integrated literature review. *J Gerontolog Nursing* 31(9):4-11, 2005.
3. Jhawar M, Wallace S, Chronic conditions of Californians: Findings from the 2003 California health interview survey: UCLA center for health policy research and the California health care foundation, 2005. www.chcf.org/documents/chronicdisease/ChronicConditionsCA05FullReport.pdf. Accessed July 10, 2008.
4. Jacobsen P, Adverse drug reactions. In: Silverman E, ed, Essentials of oral medicine. Hamilton, London, BC Decker Inc., pages 107-10, 2001.
5. Dental management of the medically compromised patient, seventh ed., Little JW, Falace DA, et al., St. Louis, Mo., Mosby Elsevier, 2008.
6. Drug information handbook for dentistry, 13th ed., Wynn RL, Meiller TF, Crossley HL, eds., Hudson, Ohio, Lexi-Comp, 2007.
7. Clinician's guide: Oral health in geriatric patients, second ed., Ship JA, ed., Ontario, Canada, BC Decker Inc., 2005.
8. American Dental Association Council on Scientific Affairs, Dental management of patients receiving oral bisphosphonate therapy. *J Am Dent Assoc* 137(8):1144-50, August 2006.
9. Ruggiero S, Marx RE, et al, Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract* 2(1):7-14, January 2006
10. Abdollahi M, Radfar M, A review of drug-induced oral reactions. *J Contemp Dent Pract* 15;4(1):10-31, February 2003.
11. Ciancio SG, Medications' impact on oral health. *J Am Dent Assoc* 135(10):1440-8; quiz 68-9, 2004.
12. Meredith MJ, Herbal nutriceuticals: a primer for dentists and dental hygienists. *J Contemp Dent Pract* 15;2(2):1-24, May 2001.
13. Ang-Lee MK, Moss J, Yuan CS, Herbal medicines and perioperative care. *JAMA* 11;286(2):208-16, 2006.
14. Miller LG, Herbal medicinals: Selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 9;158(20):2200-11, November 1998.
15. Jacobsen P, Chavez EM, Clinical management of the dental patient taking multiple drugs. *J Contemp Dent Pract* 15;6(4):144-51, 2005.
16. Williams BR, Kim J, Medication use and prescribing considerations for elderly patients. *Dent Clin North Am* 49(2):411-27, 2005.
17. Heft MW, Mariotti AJ, Geriatric pharmacology. *Dent Clinics North Am* 46(4):869 -85, xii, October 2002.
18. Principles of geriatric medicine and gerontology, fifth ed., Hazzard WR, Blass JP, et al, eds., McGraw-Hill, 2003.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Elisa M. Chávez, DDS, 2155 Webster St., San Francisco, Calif., 94115.

CDA JOURNAL, VOL 36, Nº10

Top 60 Medications Used for Orofacial Pain Treatment

GLENN CLARK, DDS, MS

ABSTRACT This article introduces the 60 top pharmacologic treatments provided for chronic orofacial pain patients. It explains that the majority of "chronic" orofacial pain patients will not find a "cure" to their pain with medications but may find a way to manage their pain. The medications in this article are the most commonly utilized "pain" medications and where it exists. This article reviews some of the current evidence supporting their use on chronic orofacial pain disorders.

AUTHOR

Glenn Clark, DDS, MS, is professor and director, Orofacial Pain and Oral Medicine Center, University of Southern California, Los Angeles.

What is chronic orofacial pain and pharmacologic treatment success? There are a multitude of review articles that describe what defines an orofacial pain diseases.[1-8] The purpose of this article is not to restate or clarify which disorders are in this group but instead introduce and briefly review the 60 top pharmacologic treatments provided for chronic orofacial pain patients. Before reviewing the relative efficacy and evidentiary basis of these 60 medications, it is appropriate to explain that the majority of chronic orofacial pain patients will not find a "cure" to their pain with medications. However, chronic pain patients can, with medications added to physical and behavioral treatment methods, find a way to manage their pain.

Some patients ask the question, "How long will I have to take these medications?" Of course, if they were being treated for diabetes or hypertension this question would be not be logical because these two diseases, like chronic pain, are not usually cured, but are instead are managed with medications. A 2005 study examined what defines treatment success from the patient's perspective.[9] Specifically, this study asked chronic pain patients (n=110) what they would consider a success on four dimensions (pain, fatigue, emotional distress, interference with daily activities). They described that the mean level of pain, fatigue, emotional distress, interference with daily activities was moderately high at their first visit to the clinic, and these patients reported they would consider their treatment "successful" if their pain scores were reduced between one-half to two-thirds.

The problem is that while patients and doctors expect and hope for this level of change, the actual long-term results for treatment of chronic orofacial pain is more modest in a large percentage of patients. The general rule with chronic pain is that the longer they have the pain, the lower the reduction in pain achieved with treatment.

Two studies actually provide follow-up data on the long-term treatment results from patients seen in a chronic Orofacial pain center. The first study reported on 109 consecutive patients seen in a chronic orofacial pain clinic.[10] This group of patients had between four to nine years of time from their first visit to the follow-up and of the 109, 85 percent responded to the questionnaire.

The bad news was only 27 percent of patients experienced total disappearance of pain and the remaining 73 percent still had ongoing pain. The second study examined the outcome of a cohort of 74 patients suffering chronic idiopathic facial pain who were first seen at a chronic pain center a minimum of nine to 19 years prior.[11] Of the 74 cases eligible for follow-up, 13 had died; 16 did not wish to participate; but the 45 remaining cases reported the following outcome: Ten out of 45 (22 percent) were free of orofacial pain at follow-up, and similar to the prior study, the remaining 78 percent reported ongoing pain.

Based on these two studies, it may be speculated that a full cessation or cure of chronic orofacial pain with treatment is between 22 and 25 percent. It almost goes without saying that the relative mix of diseases in the orofacial pain clinic population, the method of treatments and medications used, and, most importantly, the ability of the clinicians to explain and render care would greatly influence these long-term results and two studies are not enough for a definitive prediction of success. Nevertheless, the message taken from these two studies is that most chronic orofacial pain patients are managed not cured.

What Are the Top 60 Medications Used to Manage Chronic Orofacial Pain?

The 60 medications mentioned in this article were the most commonly utilized "pain" medications based on a review of 1,049 consecutive patient cases at the University of Southern California's Orofacial Pain and Oral Medicine Center[12] (**TABLE 1**). Of course, the actual number of medications being used by the previously mentioned patients produces a list longer than 60 drugs, but to make the article manageable, the author arbitrarily stopped at this number. The author then searched Medline cross-referencing the name of the drug with the words (1) pain; (2) facial pain; and (3) orofacial pain (**TABLE 1**).

TABLE 1 shows that there were many studies linking these drugs to the pain literature, but there are relatively few literature citations where these medications have been linked with orofacial pain disorders. Another example of this point is a study published in 1999 that examined the literature available for treatment of temporomandibular disorders.[13] This meta-analysis examined the literature from 1980 to 1992 and found more than 4,000 references but among these only 15 percent were clinical studies and only approximately 1 percent (N=55) were randomized controlled trials, which provided the type of evidence usually considered essential for evaluating the efficacy of a therapeutic modality. Based on this, the authors concluded it was not clear whether any of the therapies currently in use for temporomandibular disorders provided any benefit over placebo alone.

What has the Recent Literature Said About Pharmacologic Treatment of Chronic OFP?

The issue of what medications are useful for TMD/OFP and various other orofacial pain disorders has been addressed in a two review articles. The first was a 1997 paper that focused on pharmaocologic therapy for temporomandibular disorders.[14] This article reviewed NSAIDs, opioids, antidepressants, muscle relaxants, hypnotics, and anxiolytics. Regarding NSAIDs, they found little data on their use long term and quite a few reports on the potential side effects of these medications used in this fashion. The authors suggested that a short trial of an NSAID may be considered in patients with an apparent inflammatory component to their pain complaint but after two weeks, if great benefit is not achieved, they should be discontinued.

Regarding the use of opioids for pain, this review suggested that further studies are needed but this class of drugs has potential for those patients with chronic severe orofacial pain. Of course, careful patient selection to rule out drug-seeking behavior or other personality disorders; careful monitoring to individualize dose, thereby minimizing side effects and

dose escalation; and careful attention to regulatory procedures. Regarding the use of antidepressants for chronic nonmalignant orofacial pain the review concluded that tricyclic antidepressants (e.g., amitriptyline or doxepin) were potentially effective used in the lower dose range. The dose of antidepressants will usually be limited by anti-cholinergic side effects (dry mouth, constipation, blurred vision, and urinary retention) and should be adjusted in response to individual variation in analgesic response and side effects.

Regarding the use of benzodiazepines, the review was neither supportive nor opposed to their value in chronic OFP. It also suggested they should not be prescribed in large amounts and careful monitoring for dose escalation and undue dependency on these medications was warranted. This review also suggested they not be used in a patient with depression, and when used, they should be given only for a two- to four-week course, and predominately in muscle pain and trismus cases. Regarding more traditional skeletal muscle relaxants for orofacial pain-based myogenous pain and trismus, the review concluded that these medications, like the benzodiazepines, are used best only for a brief time period (e.g., two weeks) and in conjunction with physical therapy regimens.

In 2003, another systematic review of the literature was published that again assessed the pain-relieving effect and safety of pharmacologic interventions in the treatment of chronic temporomandibular disorders, including rheumatoid arthritis, atypical facial pain, and burning mouth syndrome.[15] The study reported on randomized clinical trials on adult patients with the previously mentioned diseases. They found a total of 11 studies with a total of 368 patients who met the inclusion criteria. They concluded that amitriptyline was effective in one study and benzodiazepine in two studies. The authors described one study that showed that intra-articular injection with glucocorticoid relieved the pain of rheumatoid arthritis of the TMJ, and another showed the combination of paracetamol, codeine, and doxylamine was effective in reducing chronic TMD pain.

Finally, this review found no effective pharmacologic treatment for burning mouth syndrome and interestingly only minor adverse effects were reported in these studies. The conclusions drawn from these two review articles are that there is limited data supporting a strong therapeutic benefit for most chronic orofacial pain medications. It also is critical to assess the balance between therapeutic benefit and safety for each drug for each patient.

Why Should We Be Cautious About the Current Literature?

As mentioned, there is a great paucity of studies on medications used specifically for orofacial pain management. Among those that exist, many are methodologically flawed and the population of patients with OFP studied was very heterogeneous. Patients with myogenous pain, for example, are often not distinguished in clinical trials from those who have TMJ disorders such as degenerative arthritis or displacement of the meniscus.[16,17] Observations by clinicians and case series often fail to use standardized methods for measurement of pain and dysfunction. The main evidence of a positive treatment outcome is too often the clinician's impression of improvement or the patients' failure to seek further treatment.[18,19]

Another major weakness in previous studies has been the lack of an adequate control group receiving either a placebo, a drug with known efficacy as a positive control, or no treatment. These deficiencies in study design are particularly significant given the high rate of success reported for manipulations such as placebo splints, placebo drugs, sham occlusal equilibration, a positive doctor-patient relationship, and enthusiastically presented treatment.[20-22]

An important factor that may affect the evaluation of treatment outcome to drug therapy is the fluctuating nature of orofacial pain, which may undergo remissions and exacerbations independent of treatment. The high incidence of concurrent psychological problems described in this population may also influence the onset of symptoms, reporting of pain levels, and treatment response.[23-25]

For some disorders, especially those that are not neuropathic in character, many patients eventually improve even if an initial course of therapy is not successful or if they receive no treatment at all.[26] The pharmalogic management of OFP rests on the same principles that apply to all other drugs: demonstrated efficacy for the indication (chronic orofacial pain), an acceptable side effect liability, and safety when given for prolonged periods.

If one stopped reading at this point one might conclude that few medications

TABLE 3

Time Delimited Medline Search (1997/01/01 to 2007/12/31: 10 years)

#	Drug Name	Classification	Orofacial Pain	Facial Pain	Pain
1.	Morphine	Strong opioid	31	31	6228
2.	Oxycodone	Strong opioid	1	1	430
3.	Methadone	Strong opioid	2	2	466
4.	Codeine	Medium opioid	16	17	712
5.	Hydrocodone	Medium opioid	6	7	116
6.	Tramadol	Analgesic	9	11	757
7.	Acetaminophen	Analgesic	40	40	1466
8.	Aspirin	Analgesic	17	20	1556
9.	Ibuprofen	NSAID	40	40	720
10.	Naproxen	NSAID	9	8	338
11.	Nabumetone	NSAID	1	1	27
12.	Piroxicam	NSAID	2	2	215
13.	Sodium Diclofenac	NSAID	4	5	1003
14.	Celecoxib	NSAID	14	12	458
15.	Meloxicam	NSAID	1	3	153
16.	Methylprednisolone	Steroid	14	19	1024
17.	Triamcinolone	Steroid	4	4	222
18.	Fluocinonide	Steroid	0	0	5
19.	Lidocaine	Sodium channel blocker	41	41	2595
20.	Benzocaine	Sodium channel blocker	9	9	64
21.	Carbamazepine	Strong anti-convulsant	22	31	345
22.	Oxcarbazepine	Strong anti-convulsant	0	1	55
23.	Lamotrigine	Strong anti-convulsant	4	6	172
24.	Levetiracetam	Strong anti-convulsant	0	0	33
25.	Zonisamide	Strong anti-convulsant	0	0	31
26.	Gabapentin	Mild anti-convulsant	9	10	802
27.	Pregabalin	Mild anti-convulsant	0	0	141
28.	Valproate	Migraine preventive [anti-convulsant]	1	1	130
29.	Topiramate	Migraine preventive [anti-convulsant]	2	3	115
30.	Tizanidine	Alpha adrenergic blocker	2	4	54
31.	Sumatriptan	Migraine abortive [triptan]	4	6	429
32.	Eletriptan	Migraine abortive [triptan]	0	0	74
33.	Frovatriptan	Migraine abortive [triptan]	0	0	19
34.	Rizatriptan	Migraine abortive [triptan]	0	0	128
35.	Butalbital	Barbiturate	0	0	19
36.	Dihydroergotamine	Ergotamine	1	2	61
37.	Timolol	Beta adrenergic agonist	0	0	15
38.	Propanolol	Beta adrenergic agonist	2	2	74
39.	Verapamil	Calcium channel blocker	2	2	208

TABLE 3 CONTINUED

Time Delimited Medline Search (1997/01/01 to 2007/12/31: 10 years)

40.	Amitriptyline	Tricyclic antidepressant	18	20	411
41.	Nortriptyline	Tricyclic antidepressant	3	3	64
42.	Venlafaxine	SNRI	2	2	130
43.	Duloxetine	SNRI	1	1	134
44.	Escitalopram	SSRI	0	0	47
45.	Citalopram	SSRI	0	0	57
46.	Fluoxetine	SSRI	1	1	139
47.	Metaxalone	Anti-spasmodic	0	0	4
48.	Methocarbamol	Anti-spasmodic	0	0	5
49.	Carisoprodol	Anti-spasmodic [other]	0	0	11
50.	Cyclobenzaprine	Anti-spasmodic [tricyclic]	0	0	26
51.	Botulinum Toxin	Anti-spasmodic [neurolytic]	23	24	685
52.	Baclofen	GABA-agonist	5	7	278
53.	Tiagabine	GABA reuptake inhibitor	1	1	26
54.	Diazepam	Benzodiazepine	3	3	224
55.	Clonazepam	Anti-spasmodic /Benzodiazepine	4	4	54
56.	Alprazolam	Benzodiazepine	0	0	24
57.	Indomethacin	NSAID	25	26	1012
58.	Ketamine	NMDA blocker	4	6	882
59.	Anti-virals (e.g., acyclovir)	Anti-viral: other	5	6	266
60.	Antibiotics (e.g., azithromycin)	Macrolide antibiotic	0	1	62

are proven and even fewer should be used for chronic orofacial pain. However, this is not the case and a quick visit to chronic pain centers shows that they use multiple medications. These medications are usually given in a series of titration trials to see if the patient achieves substantial benefit. Because of this, this article provides a partial description of the characteristics and possible use of the top 60 pain-related medications, and reviews some of the current evidence supporting their use for the chronic orofacial pain disorders.

Drugs No. 1-5: Opioids (Morphine, Oxycodone, Codeine, Hydrocodone, and Methadone)

The first and most important category of medications for chronic pain relief are the natural and synthetic derivatives of the opium plant, labeled opioids. These medications provide pain relief because they bind to opiate receptors in the CNS thus altering pain perception. Unfortunately, the opiate receptors produce other effects leading to physical and emotional dependency on this drug with prolonged use. Among the five opioids listed previously, the most commonly used in an outpatient orofacial pain clinic are hydrocodone and codeine drugs.

In the United States, hydrocodone, and codeine manditorily come in combination with another nonopioid analgesics when prescribed. The most common combination is with acetaminophen, aspirin, or ibuprofen. The stronger opioids (morphine, oxycodone and methadone) are prescribed as a stand-alone analgesic agents although oxycodone also can be prescribed combined with nonopioid analgesics.

There are certainly some patients who attend an orofacial pain center who are candidates for morphine, oxycodone, or methadone, especially those patients with neuropathic pain that cannot be controlled with nonopioid analgesics, anticonvulsants, and other adjunctive pain analgesics. While opioids are powerful and have a proven efficacy at reducing pain, the long-term consequence of opioids for nonmalignant pain is controversial.

One recent study examined the long-term effects of opioids on pain relief, quality of life, and functional capacity in long-term/chronic noncancer pain, and reported that while pain is certainly managed with these agents, these patients are not cured and still have substantial problems plus the additional problem that using a drug that produces a powerful physical dependency causes.[27] For

CDA JOURNAL, VOL 36, Nº10

TABLE 3

Suggested List of Steps for Opioid-based Management of Chronic Nonmalignant Orofacial Pain

1. Document the presence of pain	Document the location, quality, intensity (patient's self-report using rating scale; e.g., 0-10, or mild, moderate, severe) and temporal characteristics of the pain. The patient's self-report is the single most reliable indicator of pain.
2. Modifying factors	In addition to severity, assess the pain's effect on the patient including documenting what makes the pain better or worse (e.g., how the pain affects sleep, eating, movement, mood, and quality of life) response to prior and present analgesic medications and nonpharmacologic interventions.
3. Physical examination	Perform a complete physical exam of the head and neck region and make sure they have also had a recent physical examination by their physician.
4. Look for the etiology	If possible, determine the cause and type of the pain and institute diagnosis specific therapy if one is available.
5. Patient-doctor agreement	Discuss and establish realistic goals and limitations of pain medication therapy (e.g., quality of life improvement) with the patient appropriate for their specific pain diagnosis.
6. Pain severity dictates drug choice	Base the initial analgesic choice on the severity and type of pain. Use nonopioids for mild pain (rating 1-3/10); use opioids, often in combination with a nonopioid; for moderate (rating 4-6/10) to severe (rating 7-10/10) pain and neuropathic pain may require an antidepressant or anti-convulsant drug.
7. Establish nonopioid drug dose limit	Dose to therapeutic ceiling of nonopioid if side effects permit. There is no maximum dose or analgesic ceiling with opioids. Increase initial opioid dose until pain relief is achieved or side effects are unmanageable before changing medications. This will require several follow-up medication review visits.
8. Administer drugs P.O. (by mouth)	Avoid IM injections and IV infusions, and, if needed, they would only be administered in a hospital setting for in-patients.
9. Switch to long-acting opioids	Once an initial acceptable pain relief level is achieved switch from short-acting opioids to long-acting preparations. In addition to the long-acting opioid, an as-needed (PRN) analgesic should be available but it should be used only for breakthrough pain, and, its dose will be equivalent to a 10-20 percent increase of the 24-hour dose of the long-acting opioid.
10. Reassess, re-examine, document and adjust	With opioid therapy conduct a periodic patient reassessment and re-examination. After this exam, document and adjust the opioid dose as needed and make these visits quarterly visits (Q3M) minimum. The purpose of the visit is to make sure pain is controlled and improved quality of life goals have been met. If a patient's goal for pain control are not being met, refer patient to a chronic pain service for further work-up and treatment.
11. Start a bowel protocol	A bowel protocol of a laxative and stool softener should be started at the time opioids are initiated unless contraindicated (e.g., Senokot-S).
12. Watch for adverse opioid effects	Dependency occurs in all but addiction occurs very rarely in patients who receive opioids for pain control. Hallmarks of addiction include: a) compulsive use, b) loss of control, and c) use of opioids in spite of harm.

these reasons, the chronic use of opioids for patients with persistent orofacial pain requires careful patient selection to rule out those patients who might be exhibiting drug-seeking behavior or other personality disorders that would make opioid contraindicated.

Logically, any patient who is a candidate for opioid use must fully understand the drug dependency issues that long-term use entails. When opioids are used, the cautious clinician will perform careful perioidic monitoring of the patient while they individualize the patient's dose. A suggested list of steps is given (**TABLE 2**) that a pain-knowledgeable dentist or physician should follow when prescribing opioid medications. Only by following this process can side effects and abuse and dose escalation be minimized.

Drug No. 6: Analgesic (Tramadol)

Tramadol is a centrally acting synthetic codeine analogue that was approved by the FDA in 1995 for moderate to moderately severe pain. It is not categorized as a schedule II or III drug, and is actually currently categorized as a nonopioid analgesic so it does not have a narcotic schedule classification. For all of these reasons, tramadol is being discussed separately from the other opioids mentioned previously. Tramadol comes either alone or in combination with nonopioid analgesics such as aspirin, acetaminophen, and ibuprofen.

Even though it is classified by the FDA

as a nonopioid analgesic this drug does bind to the mu-opioid receptor in the central nervous system. It also acts like a tricyclic antidepressant agent causing inhibition of serotonin and norepinephrine at the synaptic cleft.[28,29] The effects of these actions (mu-opioid binding and serotonin-norepinephrine reuptake inhibition) both produce inhibition of the ascending pain signals and can activate the descending pain inhibitory pathway.

Tramadol's opioid affinity and activity are also substantially less than those of morphine. Due to tramadol's (albeit weak) opioid activity, there have been questions about potential abuse. A proactive surveillance program revealed that the vast preponderance of patients who abuse tramadol have a previous record of substance abuse.[30]

Drugs No. 7-8: Analgesics (Aspirin, Acetaminophen)

The World Health Organization recommends nonopioid analgesics for the initial treatment of pain. The three most common analgesics that do not have opioid receptor-binding action are aspirin, acetaminophen, and the nonsteroidal anti-inflammatory drugs. Generally, the WHO analgesic ladder is designed for acute pain management, and, unfortunately, this organization does not modify their recommendations for chronic pain. This is a problem since while aspirin (acetylsalicylic acid) is an important analgesic for acute pain, it does not appear appropriate for chronic pain use because of the known gastropathic-inducing side effects (gastric irritation and nausea). The same concern (induced gastropathic disease) also exists for NSAIDs.

Nevertheless, aspirin is widely available and used for pain since it is an over-the-counter product. The primary mechanism of action of the aspirin is

that it inhibits prostaglandin synthesis and acts on the hypothalamus to reduce fever. When nociceptive fibers are being stimulated by an endogenous inflammatory reaction in the peripheral injury site, prostaglandin is a critical component of the inflammatory cascade of events. For this reason inflammatory pain is effectively blocked by aspirin. A review article on aspirin as a postoperative analgesic suggests it is effective but has substantial side effects, even in short-term use.[31]

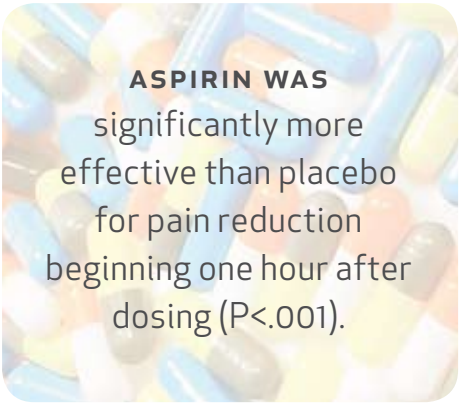
This meta-analysis examined 72 studies where aspirin was compared to other analgesic agents or placebo agents. These studies included in total more than 6,550 subjects divided between those getting placebo and those getting active agents. These studies were all short term because the primary use of aspirin is for postoperative pain. Aspirin was found to be significantly superior to placebo with single oral doses of 600/650 mg, 1,000 mg and 1,200 mg. Of course, aspirin is used by patients with chronic pain and especially by patients with episodic pain due to headache, sometimes resulting in benefit and sometimes with harm.

One study examined the efficacy and tolerability of aspirin versus placebo for the acute treatment of a single acute attack of migraine.[32] This prospective, randomized, double-blind, parallel-group, placebo-controlled study evaluated the efficacy of a single, 1,000 mg dose of aspirin for the treatment of acute moderate to severe migraine, with or without aura. Again, this study examined only the short-term efficacy of aspirin looking at headache pain response at two hours.

Of 485 subjects with migraine attacks enrolled, 201 used aspirin and 200 used placebo. The two-hour headache response rate was 52 percent with aspirin versus 34 percent with placebo (P<.001).

Aspirin was significantly more effective than placebo for pain reduction beginning one hour after dosing (P<.001) and continuing throughout the six-hour evaluation period. This study demonstrated that aspirin used in this fashion was safe and effective for treatment of acute migraine in appropriately selected patients.

In addition to aspirin, acetaminophen is another over-the-counter nonopioid analgesic used by pain patients. Like aspirin, this drug is an important analgesic for acute pain, and, if used at levels that are nontoxic, can be used for chronic pain use. While this drug does not cause gastropathy as a side effect, the major concern with acetaminophen is that it is not uncommon for patients to inadvertently take more than maximum daily dose (4,000 mg/day) and produce a liver toxicity that causes rapid irreversible liver damage, which can be fatal.[33] The primary mechanism of action of acetaminophen is that it inhibits prostaglandin in the central nervous system and peripherally blocks pain impulse generation, and it acts on the hypothalamus to reduce fever.[34]



A recent meta-analysis examined this drug assessing 46 clinical studies that compared acetaminophen to placebo.[35] These studies in total included 2,530 subjects who received acetaminophen, and 1,594 who received placebo and its analgesic benefit above and beyond a placebo is well established. Both aspirin, and, to a much greater extent, acetaminophen and its European equivalent, paracetamol, are used as headache abortive agents, and depending on the frequency of the headache, this can mean daily use of these drugs. A recent study examined the effectiveness of nonprescription combination of acetaminophen, aspirin, and caffeine at alleviating migraine headache pain.[36]

The study was a triple-double-blind, randomized, parallel-group, single-dose, placebo-controlled experiment that included migrainers with moderate or severe headache pain. The study enrolled 1,357 patients, and 1,250 took study medication and 1,220 were included in the efficacy-evaluable data set. The results showed that significantly greater reductions in migraine headache pain intensity occurred one to six hours after dose in patients taking the acetaminophen, aspirin, and a caffeine combination than in those taking a placebo. Pain intensity was reduced to mild or none two hours after dose in 59.3 percent of the 602 drug-treated patients, compared with 32.8 percent of the 618 placebo-treated patients (P< .001). In addition the obvious efficacy, this drug combination also has an excellent safety profile and is well tolerated.

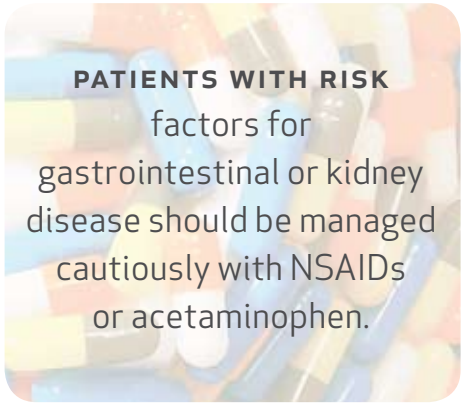
Unfortunately, because it has a good effect for episodic headaches, over-the-counter analgesic sometimes are overused and this can lead to a disorder called medication overuse headache. The basic concept behind this is that analgesic use can cause central sensitization of the trigeminal and somatic nociceptive systems, and these changes are thought to be occurring in the cerebral supraspinal structures.[37]

Drugs No. 9-15: NSAIDs (Ibuprofen, Naproxen, Nabumetone, Piroxicam, Sodium Diclofenac, Celecoxib, Meloxicam)

In this category, five commonly used nonspecific cyclooxygenase (COX) inhibiting nonsteroidal anti-inflammatory drugs for arthritis pain (ibuprofen, naproxen, nabumetone, piroxicam, and sodium diclofenac) and two cyclooxygenase-2 specific inhibiting medications (celecoxib, meloxicam) are included. Like aspirin, these drugs are used for acute pain and for phasic arthritic pain. The primary mechanism of action of the all of the NSAIDs reviewed herein is that they inhibit prostaglandin synthesis by decreasing the activity of the cyclooxygenase enzyme. The main drawback for the five nonspecific COX inhibiting NSAIDs when used on a continuous basis is that they cause gastropathy (gastric irritation and nausea).[38]

Retrospective studies have established an association between increased risk of upper gastrointestinal bleeding and ingestion of aspirin or NSAIDs.[39-41] This side effect is less likely with the two COX-2 inhibitors, but they have the added side effect of an increased risk of cardiac damage.[42] Nevertheless, NSAIDs are used widely for both headache and arthritic pain since two of them (ibuprofen and naproxen) are available as an over-the-counter product. Considering the adverse effects of long-term NSAIDs, and the lack of clinical evidence demonstrating a therapeutic effect for these nonopioid analgesics in the symptomatic treatment of myalgia or fibromyalgia, this must be weighed against the potential for serious toxicity with chronic use in for myogenous-based disease.

A short trial of an NSAID may be considered in patients with an apparent TMJ inflammatory component to their pain complaint but a lack of therapeutic effect after a seven- to 10-day trial or the development of any gastrointestinal symptoms should prompt discontinuation of the NSAID. Patients with risk factors for gastrointestinal or kidney disease should be managed cautiously with NSAIDs or acetaminophen and should not take these drugs for prolonged periods of time. For those patients with gastritis the possibility exists for them to use a topic NSAID, and a recent study examined the efficacy and tolerability of a topical ketoprofen patch in the treatment of uncomplicated ankle sprain.[43]



Of course it would be nice if such data were available for TMJ strain, unfortunately such data is not available. Nevertheless, for ankle strain, a randomized, double-blind, placebo-controlled, multicenter, two-week trial was performed on 163 subjects. Pain levels were the primary outcome measure and it was found that the ketoprofen patch was better than a placebo. Specifically, ketoprofen demonstrated a greater reduction in pain after seven days than those assigned to a placebo. Adverse events, mostly local skin reactions, occurred in 30.9 percent of the ketoprofen group and in 24.4 percent of the placebo group.

The issue of safety of COX-2 selective NSAIDs such as celecoxib or meloxicam has received great attention in recent years. A recent review examined the clinical effectiveness of several COX-2 selective NSAIDs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis.[44] This review included only randomized controlled trials and they concluded that although the COX-2 selective NSAIDs as a class of medications offered protection against serious GI events, the amount of evidence for this protective effect varied considerably across individual drugs.

The relative cardiovascular safety also varied substantially between COX-2 selective NSAIDs. An increased risk of MI compared to nonselective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient years. There is no study that has examined meloxicam for TMJ-related arthritis or pain but a 2004 study on TMD did examine the relative efficacy of celecoxib versus naproxen and a placebo in a randomized controlled clinical trial.[45]

This study included 68 subjects with painful TMJs secondary to disc-displacement with reduction. The results showed that naproxen significantly reduced the symptoms of painful temporomandibular joint disc-displacement with reduction as determined by most efficacy measures, and also showed a significant improvement in pain intensity during the study. Celecoxib and naproxen were equally well tolerated, with similar number of reported adverse effects. In conclusion, the final choice to use a COX-2 selective NSAID or a nonselective NSAID is left up to the practitioner who will weigh the benefit of the medication with the risk of an adverse event.

Drugs No. 16-18: Corticosteroids (Methylprednisolone, Triamcinolone, Fluocinonide)

Three commonly used corticosteroids are methylprednisolone, triamcinolone, and fluocinonide. The first agent is often given systemically or via injection for acute pain and inflammation.[46] The second agent is also available for systemic use, but it is more commonly used as an intracapsular injections for joint pain or for topical application to for skin reactions where inflammation is present.

These agents are powerful anti-inflammatory agents, and, like aspirin, are used for acute pain and even sometimes for chronic pain, but they are not specifically FDA-approved for pain. They are approved for a wide variety of inflammatory diseases including autoimmune disease (e.g., erosive lichen planus, pemphigus, graft versus host disease, rheumatoid arthritis). Like aspirin and NSAIDs these agents when used continuously will cause gastropathy (gastric irritation and nausea) as well as many other major side effects. Both methylprednisolone and triamcinolone are generally used short term either as a system dose for inflammatory disease or as an injectable agent for arthritic pain.

Only occasionally will these agents be used chronically and then in generally lower doses. The primary mechanism of action of these two agents is to decrease inflammation by suppression of migration of leukocytes and reversal of increased capillary permeability. By producing a general suppression of the immune system, inflammatory-related pain is effectively blocked.

The third corticosteroid in this category is fluocinonide and in a recent double-blind clinical trial examined the efficacy of topical steroids for treatment of chronic oral vesiculoerosive disease.[47] This study conducted a double-blind clinical trial comparing two potent topical corticosteroids (clobetasol propionate and fluocinonide ointment in orabase) as treatments for controlling oral vesiculoerosive diseases. Sixty patients were included (43 women and 17 men) and final data were available for 55. The study duration was 28 days and outcomes included pain, erythema, atrophy, and size of lesion. The results showed that both medications had a beneficial effect in the control of symptoms and signs of oral vesiculoerosive diseases with minimal side effects although candidiasis was observed in 13 patients at the end of treatment in this population. The authors suggested that concurrent treatment with anti-fungal therapy might be indicated in some cases.

Drugs No. 19-20: Local Anesthetic/Sodium Channel Blockers (Lidocaine, Benzocaine)

The anesthetics lidocaine and benzocaine are both membrane stabilizing agents that work by blocking voltage-gated Na+ channels.[48] Local anesthetic agents have been shown to effectively treat neuropathic pain in animal models.[48] Clinically, neuropathic pain states respond transiently to intravenous infusion of lidocaine, but unfortunately the effect is only present during the infusion. There are two clinically available cutaneous local anesthetic preparations: (1) EMLA cream (AstraZeneca, Wayne, Penn.), which is a eutectic mixture of the local anesthetics lidocaine and prilocaine, and (2) Lidoderm, which is a 5 percent lidocaine patch (Endo Labs, Chadds Ford, Penn.).[49] Although EMLA is useful for venipuncture and cutaneous biopsy, it has not found a role in chronic pain management.[50]

In contrast, the topical 5 percent lidocaine patch may be useful in management of peripheral neuropathic pain conditions. An open-label trial showed that the patch gave moderate or better pain relief in 81 percent of a small group of patients with cutaneous refractory neuropathic pain states.[51] Controlled studies are ongoing, but the Lidoderm patch has been approved by the FDA for treatment of postherpetic neuralgia. The dose is one patch to the affected area every 12 hours, and serum levels are insignificant. In general lidocaine and even benzocaine are safe to use topically, but there is a risk of methemoglobinemia.[52]

Drugs No. 21-25: Anti-convulsants (Carbamazepine, Oxcarbazepine, Lamotrigine, Levetiracetam, Zonisamide)

In this category are five anti-epileptic drugs, AED, also called anti-convulsants that are known to depress abnormal neuronal discharges and raise the threshold for the propagation of neural impulses. AEDs have been found to have therapeutic efficacy in all neuropathic pain including orofacial neuropathic pain states. The most frequently used is carbamazepine, which is the AED of choice for treating trigeminal neuralgia for many years.[53] These agents do not have an FDA narcotic schedule classification

but are dangerous nonetheless. These five agents reviewed here (carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, zonisamide) are approved for control of epileptic seizures and carbamazepine is approved for trigeminal neuralgia as well.

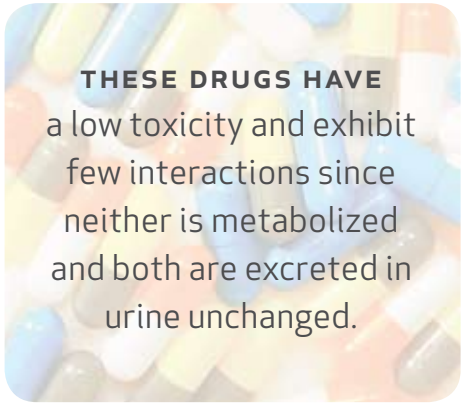
Carbamazepine and oxcarbazepine are the mainstay of trigeminal neuralgia therapy. While it is not specifically approved for trigeminal neuralgia, oxcarbazepine is a ketocarbamazepine and its metabolite is the active agent. This metabolite has many of the therapeutic properties of carbamazepine while avoiding some of its toxicities. The primary mechanism of action of carbamazepine and oxcarbazepine is based on their ability to block voltage-gated Na+ channels and modulating voltage-activated Ca++ currents as well.

Since this disease is stimulation-triggered pain when the nerves are suppressed, the pain is completely stopped. Unfortunately, carbamazepine is a self-inducing drug, which means it acts to stimulate the liver enzymes that metabolize it to work faster. The end result is that after several weeks of continuous use, the drug level in the blood drops as it is metabolized much faster so the dose must be increased.

The substantial advantage of oxcarbazepine is that it is not a self-inducer so once dose is established it is more stable. Since there are known adverse effects on liver function the starting dose is 200 mg b.i.d. and the patient is titrated upward to the effective dose ranges from 400 to 1,000 mg/day. The most common side effects are drowsiness, diplopia, and unsteadiness. Aplastic anemia occurs in 1:200,000, reversible leukopenia and thrombocytopenia are more common. Published reports have shown efficacy in trigeminal neuralgia.[54] For oxcarbazepine, the starting dose is 300 mg at bedtime, with weekly increases of 300 to 600 mg/day up to a maximum of 1,200 to 2,400 mg/day.

Drugs No. 26-27: Anti-convulsants (Gabapentin, Pregabalin)

The two anti-convulsants discussed here are gabapentin and pregabalin. These two drugs are separate and distinct from the previously mentioned anti-convulsants since they have much less risk of adverse events when used in pain patients. Gabapentin has been in use since 1994 and pregabalin was approved in 2005. Both have been used frequently for suppression of neuropathic pain.



These agents do not have an FDA narcotic schedule classification and are approved for control of epileptic seizures. Pregabalin is also approved for diabetic peripheral neuropathy. These drugs have a low toxicity and exhibit few interactions since neither is metabolized and both are excreted in urine unchanged. Caution must be used in any patient with compromised renal function. Moreover, because gabapentin is not approved for neuropathic pain it is used off-label. The mechanism of action of gabapentin is uncertain but most likely acts similarly to pregabalin, which is known to affect a central voltage-dependent L-type Ca++ channel.

Unfortunately, neither drugs can stop neuronal activity, only suppress it, so efficacy of these agents for pain is limited. The most common side effects of gabapentin and pregabalin are drowsiness, somnolence, nausea, and fatigue. The common adverse side effects are usually self-limiting and subside after a couple of weeks allowing gradual dose escalation. The usual starting dose for gabapentin is 100 to 300 mg per day taken at bedtime. The dose is gradually increased to 1,200 mg/day and is taken over 10 to 15 days in a divided dose schedule. Some patients may require 3,600 mg/day for a clinical effect. The starting dose for pregabalin is 150 mg/d and maximum dose is 300 mg/d. After the initial titration and adjustment period, these drugs can be switched from before sleep to dosing on a three times a day schedule.

Drugs No. 28-30: Chronic Daily Headache Preventives (Valproic Acid, Topiramate, Tizanidine)

This category includes three medications that are used as headache preventive agents. The first two are anti-convulsants and the third is an alpha-adrenergic agonist. The first is valproic acid and it is in the anti-convulsant category and it has been shown to be effective in prophylaxis of migraine headache.[55]

Valproic acid blocks voltage-gated Na+ channels as carbamazepine and phenytoin do, but also increases levels of aminobutyric acid (GABA) by decreasing its degradation. Side effects include nausea, vomiting, sedation, ataxia, rash, alopecia, and appetite stimulation. Forty percent of patients experience elevated transaminase levels, and 1 in 50,000 develop hepatic failure. The second drug in this group is topiramate, which was approved for use in 1997 and it has shown promise for cluster headache and diabetic neuropathy.[56]

Topiramate is a unique monosaccharide compound structurally unlike other AEDs. It potentiates GABA responses, significantly increasing central nervous

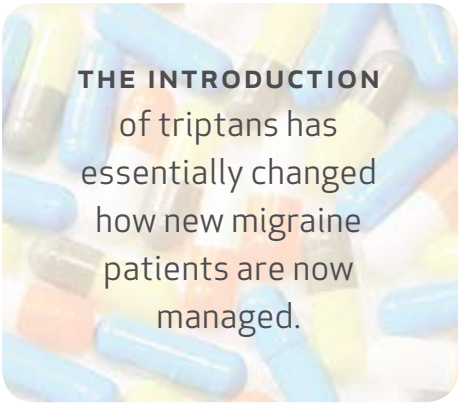
system GABA levels, and also blocks the AMPA kainate excitatory receptor. Topiramate is also a weak carbonic anhydrase inhibitor. The effective dose range is 200 to 400 mg/day b.i.d. The dose is 25 mg b.i.d. and is increased 50 mg/week up to the dose range. Side effects include unusual central nervous system effects such as abnormal delusional and psychotic thinking. Occasionally, patients develop renal stones. These side effects are rare, occurring in <2 percent to 3 percent of patients, but are troubling to those patients.

Finally, the third drug in this section is tizanidine, an alpha-adrenergic agonist has both a peripheral and a central mechanism of action in migraine headache. A recent review examined the relative value of various medications, including tizanidine for preventative treatment when dealing with patients who have chronic migraine or tension-type headaches.[57] The individual results for the other two drugs (baclofen and botulinum toxin) are discussed later in this article. This article was based on a literature review of clinical drug trials. The author concluded that the literature supported the use of tizanidine as a preventive treatment of chronic daily headache was better than placebo therapy. The author noted that it is often used in combination with a long-acting NSAID to aid in the treatment of medication rebound headache.

Drugs No. 31-34: Migraine Abortives (Sumatriptan, Eletriptan, Frovatriptan, Rizatriptan)

The triptan medications have been described as a miracle drugs for episodic migraine sufferers. Unfortunately, they are moderately expensive and don't always work or the patient may not be able to tolerate the medications side effects. The introduction of triptans has essentially changed how new migraine patients are now managed. For example, one study compared pharmacoepidemiology of headache treatment in two different groups. One group were patients (n=612) who were attending a headache center for their first visit and another group were more chronic headache patients (n=620) attending a headache specialty center for a follow-up treatment assessment.[58]

Most of these headache patients suffered from migraine. The 49.4 percent of the first visit headache group patients were taking drugs prescribed by a doctor and 41.5 percent were taking over-the-counter analgesics, but 9.1 percent were not taking any drug. For the recall headache patients, 81.3 percent were taking prescription drugs; 15.8 percent took over-the counter analgesics; and 2.9 percent did not take any drugs. Triptans were being used by only 9.1 percent of the first-time visit group whereas 31.8 percent of the recall chronic headache patients were using triptans. Amitriptyline was the drug most commonly used for prophylaxis.



Drugs No. 35-36: Miscellaneous Migraine Medications (Butalbital, Dihydroergotamine)

This section is focused on two older medications that have been, and still are, commonly used for recurrent episodic and chronic headaches. The first is butalbital, the main agent in a combination drug that usually contains acetaminophen, caffeine, and butalbital. Butalbital is categorized as a analgesic but acts as a bartiturate, and, as such, has many of the adverse events and dependency complications associated with this class of drug. A recent study examined the amount of health resources utilized by patients who repeatedly use emergency department services for headache care.[59]

Specifically the study involved a retrospective review of urgent care/emergency department charts, clinic charts, and pharmacy rosters for patients who made three or more visits for a headache to an urgent care/emergency department (UC/ED) facility over a six-month study period. The study included data on 54 subjects who were classified as "repeaters." This number represented more than 10 percent of the 518 patients who visited the UC/ED for primary headache complaints. This group of 54 repeating patients produced more than 502 visits (50 percent of total visits) during the study period. Pharmacy rosters showed use of narcotics in 41 of these patients and butalbital products were used in 27 patients. The authors concluded these two medications — opioids and butalbital — did not seem to provide a successful approach to the recurrent migraine or tension-type headache problems, and it is possible the medications themselves were contributing to the repeated visit pattern.

In agreement with the above study are two reports that discuss the problems of using opioids and barbiturates for headache management. The first is a study that examined the national trends of prescription medication use for headache.[60] The study involved secondary analysis of data obtained during the 2000 Medical Expenditure Panel Survey, a representative survey of the U.S. noninstitutionalized

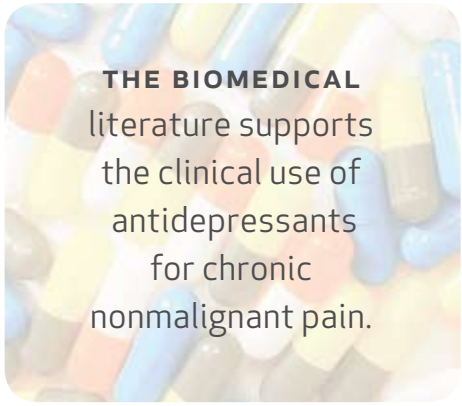
population. These authors reported that 46 percent of patients reported using at least one medication for the treatment of headache and migraine-specific abortive medication (i.e., selective serotonin receptor agonists and ergotamine derivatives) were the most frequently (36 percent) used medications. Opiate analgesics and butalbital-containing products also experienced extensive prescribing reported by 22 percent and 17 percent of survey respondents, respectively.

The second is a review of the literature on the topic of butalbital-containing drugs for migraine.[61] This study described a qualitative systematic literature search and reported that between 14 percent and 36 percent of diagnosed migraineurs are prescribed butalbital-containing products, often as initial therapy in spite of the fact that the only identified controlled trial of these drugs for migraine treatment showed that butalbital-containing products were inferior to butorphanol (an opioid). The article discussed a consortium of U.S. headache specialists' published guidelines and it discouraged administration of butalbital-containing products for migraine due to serious dependency issues with this medication.

Finally, in a recent single center open-label pilot study, the efficacy of dihydroergotamine (DHE 45) for migraine headaches with allodynia was examined.[62] This drug is occasionally used for severe migraines when a patient is nonresponsive to a triptan medication rather than giving the patient an opioid to control the pain. The study involved nine patients who were treated on two occasions for episodic migraine with allodynia using the drug dihydroergotamine 1.0 mg administered via a intramuscular injection. The authors concluded that whether they took the dihydroergotamine early or late in the attack, most patients (>55 percent) had headache relief within two hours, and at least 44 percent of patients achieved headache-free status by eight hours postdose. The authors suggested a large, placebo-controlled trial of dihydroergotamine in allodynic patients was now warranted.

Drugs No. 37-39: Miscellaneous Headache Preventatives (Propranolol, Timolol, Verapamil)

Beta-adrenergic receptor blockers and calcium channel blockers have been used for many years to help prevent chronic and frequent migraines. A recent open label study examined the efficacy of combining a beta-blocker plus topiramate in migraine patients previously resistant to the two medications in monotherapy.[63] Those patients who had not responded to a beta-blocker and topiramate received a combined treatment; 58 patients completed the study. Of these 33 (57 percent) met criteria for chronic migraine/medication overuse headache; 18 (31 percent) for migraine without aura; and 7 (12 percent) for migraine with aura. The results showed 10 patients (17 percent) discontinued due to adverse events but 36 of the other 48 patients who tolerated the combination showed a >50 percent reduction in frequency of headache. The authors concluded that the combination of beta-blocker plus topiramate showed a benefit in around 60 percent of patients who had not previously responded to monotherapy. Adverse events led to discontinuation in one out of six patients.



Regarding calcium channel blockers such as verapamil, this class of drug has been used for migraine and cluster headache prophylaxis. A report by the European Federation of Neurologic Societies task force recently examined the available literature on treatment of the trigeminal autonomic cephalgias.[64] The headaches included in this review included cluster headache, paroxysmal hemicrania, and short-acting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome. They concluded that the literature supported the use of oxygen (100 percent) with a flow of at least 7 l/min over 15 minutes and 6 mg subcutaneous sumatriptan for the acute treatment of cluster. Prophylaxis of cluster was best performed with verapamil at a daily dose of at least 240 mg (maximum dose depends on efficacy or tolerability).

Finally, they noted that while the quality of the studies were lower, the use of corticosteroids (100 mg methylprednisone or an equivalent corticosteroid given orally or at up to 500 mg IV per day over five days then tapering down) was another method of managing a cluster headache.

Drugs No. 40-41: Tricyclic Antidepressants (Amitriptyline, Nortriptyline)

Often described as adjunctive pain medications are the tricyclic antidepressant (TCA) drugs and they have been used for more than 30 years for the management of pain from a wide variety of conditions, including chronic orofacial pain.[65] The biomedical literature supports the clinical use of antidepressants for chronic nonmalignant pain

when other treatments have failed or if depression accompanies the pain.

Tricyclic antidepressants with both serotinergic and noradrenergic effects (e.g., amitriptyline, nortriptyline) appear to be most effective. There are multiple tricyclic medications that are useful alternatives to amitriptyline, and have some differences in the side effect profiles and the half-lives. For example, desipramine, the least anti-cholinergic and sedative of the TCAs, showed pain relief after three weeks, independent of mood alterations in a placebo-controlled randomized clinical trials of 26 patients with postherpetic neuralgia.[66] Nortriptyline, the active metabolite of amitriptyline, is also popular, maybe because it seems to be better tolerated than amitriptylline. The starting dose is 10 mg at bedtime and increased after three to five days to 20 mg at bedtime and then carefully titrated.

A recent study compared whether selective serotonin reuptake inhibitor (SSRI) antidepressants were associated with an increased or decreased risk of cardiovascular adverse events (AEs).[67] The study examined the published literature and it defined serious AEs as death due to a cardiovascular cause, heart failure, stroke, transient ischemic attack, and myocardial infarction. Nonserious adverse events were defined as palpitations, chest pain, angina, arrhythmia, hypertension, hypotension-syncope, and unspecified cardiovascular or neurologic events.

Adverse event rates were calculated in four medication groups: (1) SSRIs; (2) tricyclic antidepressants (TCAs); (3) other active therapies but not an SSRI or TCA; and (4) placebo. The authors reported that they were unable to detect differences in odds between SSRI and placebo for both serious or nonserious AEs. There were more nonserious AEs for TCAs versus SSRIs.

Drugs No. 42-43: Serotonin-Norepinephrine Reuptake Inhibitor: Duloxetine, Venlafaxine

Duloxetine and the similar but earlier drug venlafaxine have been used for both chronic muscle pain and for neuropathic pain. There are two studies that examine duloxetine efficacy for fibromyalgia.[68,69] Both enrolled patients with fibromyalgia using ACR (American College of Rheumatology) criteria, and with at least moderate pain, and had sensible exclusions. One was exclusively and one predominantly in women. In the 532 randomized women, 38 percent had at least 50 percent improvement in pain over 12 weeks with 60 mg duloxetine (once or twice a day) compared with 21 percent with placebo. There were improvements in quality of life, and more adverse events with duloxetine, especially nausea and dry mouth.

Drugs No. 44-46: Selective Serotonin Reuptake Inhibitor (Escitalopram, Citalopram, Fluoxetine)

Clinically, it is well known that chronic pain induces depression, anxiety, and a reduced quality of life. Several animal studies have proven that experimental neuropathic pain induces anxiety with changes in opioidergic function in the central nervous system.[70] In a follow-up study, the anxiolytic-like effects of several types of antidepressants were examined on a chronic neuropathic pain-like state.[71] The study used a sciatic nerve-ligated mouse model with demonstrated thermal hyperalgesia and tactile allodynia. It then administered the tricyclic antidepressant (TCA) imipramine, the serotonin noradrenaline reuptake inhibitor (SNRI) milnacipran, and the selective serotonin reuptake inhibitor (SSRI) paroxetine and showed a reduction in anxiety behavior of the mouse after the medication.

These antidepressants also produced a significant reduction in thermal hyperalgesia and tactile allodynia. The authors concluded that serotonergic antidepressants were effective for treating anxiety associated with chronic neuropathic pain.

Another study compared the use pattern of an SSRI (paroxetine or citalopram) versus a anti-convulsant medication (gabapentin) on 101 painful diabetic neuropathy patients.[72] The authors reported that over a six-month study period, the patients receiving SSRIs reported greater satisfaction and fewer concerns of the side effects with their treatment ($P<0.05$) compared with the patients taking gabapentin. There was statistically significant better mood in the SSRI group, but overall, 43.5 and 40.5 percent of those taking SSRIs and gabapenin, respectively, noticed no effect of the medication on their pain. The authors concluded that the lack of negative effects on quality of life, the better compliance, and the comparable efficiency of SSRIs on patient mood suggests that these drugs may be considered as an alternative to gabapentin in painful diabetic neuropathy.

Drugs No. 47-49: Muscle Relaxants (Caridisprodol, Metaxalone, Methocarbamol)

Muscle relaxants or anti-spasmodics are often used as adjuvants for patients with chronic musculoceletal pain but the

clinical evidence for their long-term use in true chronic pain states is weak. Two agents that are commonly for short-term masticatory muscle spasm and pain are clonazepam and caridisprodol. These two agents are thought to reduce skeletal muscle tone because of their anxiolytic effects.

Clonazepam is a benzodiazepine-type medication and is used for the treatment of certain types of seizures. It is also used in painful conditions, including myoclonus and muscle spasms.

Clonazepam acts by enhancing the GABA-induced increase in chloride conductance. Side effects include sedation, lethargy, ataxia, and dizziness.

Caridisprodol is one of the oldest drugs of this class and most likely acts centrally to depress polysynaptic reflexes.[73] It was first evaluated for chronic orofacial pain in a study published in 1960.[74]

Finally, because some of these drugs may have an addictive potential, the daily dosage and duration of treatment requires a careful open doctor-patient discussion and agreement. The clinician should consider the alternative nonpharmacological treatment options, such as physiotherapy (with myofascial release techniques), massage, relaxation/biofeedback techniques, or acupuncture. There is insufficient evidence to assist clinicians in a rational approach to the use of muscle relaxants as analgetic and anti-spastic treatments.

Overall, the scientific literature does not provide unequivocal support for either the use of benzodiazepines or their condemnation on the basis of lack of efficacy or potential toxicity. Like all drugs, they should only be used in patients whose symptoms are suggestive of potential efficacy and should not be prescribed in large amounts that would permit dose escalation without professional supervision or the development of dependence with long-term therapy.

For patients whose pain appears to be of musculoskeletal origin, they may benefit from a two- to four-week course of a benzodiazepine, possibly in combination with an NSAID. A lack of efficacy or the onset of sedative side effects or depressive symptoms should be an indication to reduce the dose or discontinue the benzodiazepine. If difficulties in sleep onset or duration are the primary complaint, consideration should be given to the use of a benzodiazepine indicated for hypnosis (triazolam) to minimize drug effects during the day. Patients who appear to have depressive symptoms before therapy should be referred to a psychiatrist for consultation and possible antidepressant therapy rather than being prescribed a benzodiazepine with putative antidepressant properties.

In any event, therapy with a benzodiazepine should not be extended beyond a few weeks, because the natural course of myofascial pain combined with conservative therapy will likely result in a lowering of symptomology to acceptable levels that would not justify the risks of pharmacologic intervention. Patients for whom such a therapeutic course fails should be re-evaluated for additional physical medicine and behavioral therapy rather than "managed" with long-term benzodiazepine treatment.

Drug No. 50: Anti-spasmodic (Cyclobenzaprine)

An anti-spasmodic drug that has less abuse potential than clonazepam and caridisprodol is cyclobenzaprine. This drug is used and is thought to be partially effective for some chronic musculoskeletal disorders.[75] For example, cyclobenzaprine has been found to be superior to placebo for pain in the cervical and lumbar regions associated with skeletal muscle spasms and reduces electromyographic signs of muscle spasm.[76,77] Although it has not been directly assessed for TMD, these findings are suggestive of efficacy for muscle relaxation in the orofacial region.

There appears to be a discrepancy between the common clinical use of skeletal muscle relaxants and the results of controlled clinical trials evaluating their efficacy in comparison with placebo. It is also not clear whether they are specific for muscle relaxation or produce nonspecific central nervous system depression, thereby reducing muscle tone. Little supporting evidence exists for their efficacy in chronic orofacial pain of myogenic origin, nor is it clear if they provide an additive effect with exercises or splint therapy aimed at muscle relaxation.

Given this modest scientific support, clinicians should probably limit the use of skeletal muscle relaxants to a brief trial in conjunction with physical therapy regimens. Further studies are needed to document efficacy for chronic orofacial pain in comparison with an active placebo with sedative properties to help differentiate nonspecific sedative properties from muscle relaxation. Five randomized trials were included in a meta-analysis, but neither trials nor review appear to be of a particularly high standard.[78]

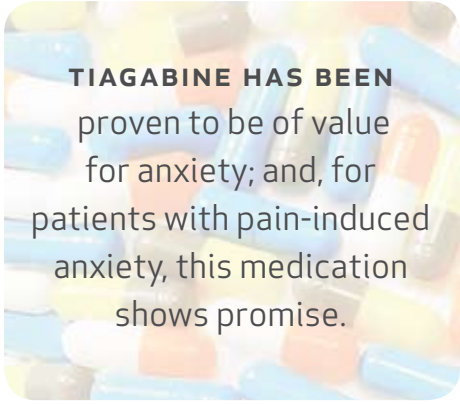
Drug No. 51: Anti-spasmodic (Botulinum Toxin-A)

Botulinum toxins are potent neurotoxins produced by *Clostridium botulinum* that can block acetylcholine release at the neuromuscular junction. *C. botulinum* was first identified as a causative agent in food poisoning in 1895 and by the 1920s, isolation of a relatively crude form of toxin had occurred. A crystallized form of the "A" subtype, BTA, became available and stimulated scientific interest. The FDA-approved botulinum toxin-A for the treatment of strabismus in 1989.[79] With appropriate dosing, the injected muscles motor function is only partially blocked. These effects occurs within a few days to two weeks after injection and they last from six weeks to six months, but the typical duration is two to three months.[80]

During the peak effect, histologic studies showed evidence of atrophy, but fiber size and function return to normal, even after multiple cycles of injection and recovery.[81] Botulinum toxin-A was approved by the FDA for use in painful orofacial and craniocervical muscle hyperactivity syndromes, including cervical dystonia (torticollis) and hemifacial spasm.[82] The recommended treatment interval between injections is at least three months and numerous studies confirmed that injecting multiple sites within a muscle improves spasticity relief and decreases side effects.

Most recently it has been shown helpful for chronic migraine problems that do not respond to medications, but this is an off-label usage of this medication. There is much ongoing research on the efficacy of and indications for these injections for other conditions including nonspastic neuropathy and even trigeminal neuralgia.[83]

At this time, evidence suggests these injections are best used for conditions where a clear-cut muscle spasticity is present and the literature on botulinum toxin-A for nonspastic pain disorders has been unconvincing. Finally, a 2003 review of the literature by Freitag examined preventive treatments used for dealing with patients with chronic migraine or tension-type headaches. One of the agents he reviewed was botulinum toxin injections. He concluded that this agent has some efficacy for medication-resistant chronic migraine sufferers, but this is not so for chronic tension-type headache patients. Fortunately, there are relatively few significant adverse events seen with the use of botulinum toxin-A in headache treatment.



Drugs No. 52-53: GABAergic Drugs (Baclofen, Tiagabine)

Drugs that target GABA-A and B receptors are proven to suppress motor activity and also play a role in pain suppression. Baclofen is a GABA agonist and tiagabine is a selective GABA reuptake inhibitor. Regarding baclofen, a 2003 review of the literature by Freitag examined this agent as a preventive treatment for dealing with chronic migraine or tension-type headache patients. He reported that while there has been very limited research on the use of baclofen for CDH prevention, this agent does act centrally via GABA(A) receptors, in migraine and cluster headache, and therefore has potential. The two open trials conducted to date both suggest and support the use of baclofen for the preventive treatment of headache. Obviously the data is not conclusive yet.

Regarding tiagabine, this drug is both an anxiolytic and an anti-convulsant GABA reuptake inhibitor commonly used as an add-on treatment of refractory partial seizures. This drug has been reported to have some value in the suppression of bruxism in severe cases.[84] Specifically, a case report described that in four of the five cases, tiagabine was able to effectively suppress nocturnal bruxism, trismus, and consequent morning pain in the teeth, masticatory musculature, jaw, and temporomandibular joint areas. Tiagabine has a benign adverse-effect profile, is easily tolerated, and retains effectiveness over time. Bed partners of these patients report that grinding noises have stopped; therefore, the tiagabine effect is probably not simply anti-nociceptive, but motor suppressive. The doses used to suppress nocturnal bruxism at bedtime (4-8 mg) are lower than those used to treat seizures.

Clearly additional data is needed on this drug used in this way. Tiagabine has been proven to be of value for anxiety; and, for patients with pain-induced anxiety, this medication shows promise. A recent study examined the efficacy and tolerability of tiagabine in 266 adults with generalized anxiety disorder over an eight-week period.[85] The study was a randomized, double-blind, multicenter, placebo-controlled study, and doses ranged from 4 to 16 mg/day. The results showed that tiagabine reduced symptoms of GAD but it was not much better than placebo agents. Overall, tiagabine was generally well tolerated and not associated with changes in sexual functioning or depressive status.

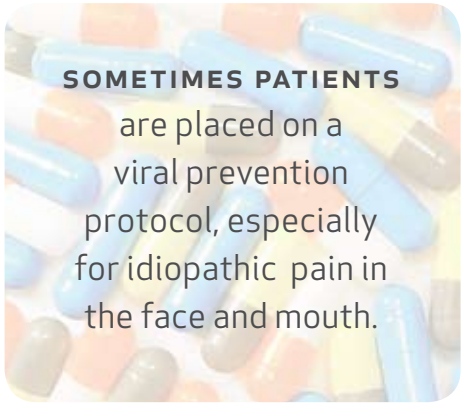
Drugs No. 54-56: Benzodiazepine Drugs (Diazepam, Clonazepam, Alprazolam)

A recent study reported on a randomized blinded controlled trial of the effect of topical clonazepam on burning mouth pain.[86] The study included 48 patients, of whom 41 completed the study. The 14-day long protocol had the patients suck a tablet of 1 mg of either clonazepam or a placebo three times a day. They were told to hold the dissolved medication/saliva mix near the pain sites in the mouth without swallowing for three minutes and then to spit. The clonazepam treatment was shown to reduce pain significantly versus the placebo and the blood level of the clonazepam was negligible. A 1997 study examined the clinical efficacy, the side effects of ibuprofen and diazepam on chronic myogenous facial pain in a double-blind, randomized, controlled clinical trial.[87] The study included 39 subjects (35 women, four men) with daily or near-daily orofacial pain of at least three months' duration and tenderness to palpation of masticatory muscles.

The treatment groups included placebo, diazepam, ibuprofen, or a combination of diazepam and ibuprofen. Pain, mood, muscle tenderness, maximal interincisal opening were measured following two-week baseline and four-week treatment periods. The authors reported that pain was significantly decreased in the diazepam and diazepam plus ibuprofen groups, but not for the ibuprofen or placebo groups. Analysis of variance showed a significant drug effect for diazepam, but not for ibuprofen, indicating that pain relief was attributable to diazepam. This study supported the efficacy of diazepam in the short-term management of chronic orofacial muscle pain.

Drug No. 57: Episodic Headache Abortive (Indomethacin)

There are a group of headaches (e.g., hemicranial continua, paroxysmal hemicranias and short-lasting unilateral neuralgiform headaches) that have been shown to be very responsive to a specific NSAID medication (indomethacin).[88] One study examined the use of indomethacin on three cases of hemicranias continua and found the intramuscular injection of 50 mg of this medication relieved pain and thus served as a diagnostic test for these headaches.[89] Another study reported on two cases of hemicranias continua masquerading as a TM disorder.[90] The report described that indomethacin could help differentiate this headache from a TMJ problem.



Drug No. 58: NMDA Blocking Drug (Ketamine)

A recent study reported on the use of ketamine infusion for the treatment of complex regional pain syndrome (CRPS).[91] Ketamine's mechanism of action is that it is a N-methyl-D-aspartate (NMDA) receptor blocking agent. The study specifically looked at pain reduction in CRPS patients using an open label, prospective, pain journal evaluation of a 10-day infusion of intravenous ketamine. Patients made journal entries each day prior to the infusion of 40-80 mg of ketamine. The reported data showed that there was a significant reduction in pain intensity from initiation of infusion (Day One) to the 10th day, with a significant reduction in the percentage of patients experiencing pain by Day 10 as well as a reduction in the level of their "worst" pain.

The side effects of ketamine, when used for chronic pain, was reported on by a recent study.[92] This study described and evaluated the side effects of this drug based on 32 patients with diabetic polyneuropathy and with postherpetic neuralgia. They found that substantial sedation and dizziness were observed in 15.6 percent and 44 percent of patients after the initial infusion and in 19 percent and 22 percent of patients in the course of the subsequent oral therapy, respectively.

Interestingly, during the observed three-month treatment period, five patients (15.6 percent) withdrew from the treatment due to a failure of therapy and four patients (12.5 percent) due to untolerated side effects (dizziness, sedation, loss of appetite, nausea, and vomiting). One study examined the efficacy of ketamine when used in the management of orofacial pain.[93]

The specific problem being treated with ketamine was atypical odontalgia, AO, and the study included 10 AO patients and 10 matched healthy controls. Treatment involved intravenous infusion of ketamine or a mu-opioid agonist fentanyl on spontaneous AO pain. Outcomes included the effect of the medications on their chronic pain and for both the AO and the control patients, intraoral pain was evoked by topical application of capsaicin. The study was performed in a randomized, placebo-controlled, cross-over manner.

The results showed that both drugs failed to produce an analgesic effect on spontaneous AO pain, but fentanyl effectively reduced capsaicin-evoked pain. Finally, a 1995 and a follow-up 2001 study examined the effect of ketamine intramuscular injection test dose followed by oral ketamine for three nights on the neuropathic orofacial pain patients.[94,95] The study reported there was reduction in pain after the intramuscular injection. The authors noted a positive correlation between a long pain history and lack of analgesic effect in these cases.

Drug No. 59: Anti-virals (Acyclovir and Others)

Anti-viral drugs (e.g., acyclovir) are used mostly for acute viral disease with clear-cut clinical manifestations. However, sometimes patients are placed on a viral prevention protocol, especially for idiopathic pain in the face and mouth. The efficacy of anti-viral agents used in this fashion is not established by the literature and recently the use of anti-viral medications for a condition such as Bell's palsy has been questioned.[96] A recent double-blind placebo-controlled study on 551 patients with Bell's palsy concluded that early treatment with prednisolone significantly improved the chances of complete recovery at three and nine months, but there was no evidence of a benefit of acyclovir given alone or an additional benefit of acyclovir in combination with prednisolone.

These findings are remarkable since another recent paper with a smaller data set of Bell's palsy case (n=221) reported that valacyclovir was helpful.[97] Specifically, the study involved a prospective randomized placebo-controlled design and they concluded that the combination of valacyclovir and prednisolone therapy was more effective in treating Bell's palsy than the conventional prednisolone-only therapy. Overall, there is no evidence basis for using anti-viral agents (acyclovir or valacyclovir) for the suppression of chronic pain.

Drug No. 60: Anti-bacterial Drugs (e.g., Azithromycin and Others)

Many physicians and dentists use antibiotics as a standard aspect of their postoperative protocol after a tonsillectomy or oral surgery. One recent study actually examined if antibiotics were of value for reducing pain postoperatively after tonsillectomy.[98] Specifically, this study review all randomized controlled trials to see if any consistent effect existed for antibiotics versus placebo. Based on their review of nine trials that met the eligibility criteria, the authors concluded there was no consistent or significant reduction in pain as a result of antibiotic usage postoperatively. The authors also concluded that antibiotics used postoperatively also were not associated with a reduction in significant secondary hemorrhage rates, although they did appear to reduce fever.

A KNOWLEDGEABLE orofacial pain practitioner must also understand the pros and cons of at least 60 drugs used in monotherapy and in combination.

If the problem was inappropriate antibiotic used after surgery as a preventive for infection, then the answer is to use to fewer, if any, antibiotics under these conditions. However, the problem is also antibiotic use for chronic pain of unknown origin. This problem is compounded by the fact that certain antibiotics do suppress pain. In fact, there is growing evidence that a specific class of antibiotics (macrolides, e.g., azithromycin) exert their beneficial effect not only by inhibiting or killing bacterial pathogens but also by down-regulating proinflammatory mechanisms. Three recent articles described the immunomodulatory properties of macrolide antibiotics in chronic rhinosinusitis.[99-101] Specifically, these articles described how macrolides antibiotics' inhibition of proinflammatory cytokines such as interleukin-8. This effect is probably secondary to inhibition of the activation of transcription factor NF-kappaB. As a result, there is an attenuation of neutrophilic inflammation and then pain takes place.

Caution must be used when using macrolides because macrolide-resistant bacterial strains might be developed, although, to date, they have not been of clinical importance. Of course, not all antibiotics are immunomodulatory and others that provide pain relief might work because of a strong placebo effect. At present, it is does not seem logical or appropriate to recommend antibiotic therapy for chronic orofacial pain, at least until more information about the pain suppression effect is known and the possible risk of bacterial resistance is elucidated.

Conclusions: Pharmacotherapeutic Management of Orofacial Pain Disorders

There are a many very painful diseases that cause chronic orofacial pain. Some involve acute inflammation, chronic inflammation, neurovascular, neurogenic and neuropathic pain, and myogenic pain. These disorders are treated with many physical and behav-

ioral, and even surgical, methods. The review provided herein demonstrates that a knowledgeable orofacial pain practitioner must also understand the pros and cons of at least 60 drugs used in monotherapy and in combination.

Some of the drugs in this article are being used on-label and some are clearly off-label. Dentists who treat these patients with off-label medications must fully understand the literature and evidence supporting any drug they use. This article showed there is a paucity of well-controlled studies of these 60 medications used specifically for chronic orofacial pain in the relevant patient population and used for periods of administration that approximate their use clinically. This paucity does not mean that these medications cannot be used, only that they must be used with caution, with reasonable concern and full knowledge of the existing literature.

For example, assuming there is a reliable differential diagnosis, pain with a neuropathic or an atypical neurogenic component would logically be managed with a trial with a tricyclic antidepressants, sodium channel blockers, and, possibly, even anti-convulsants. Pain of musculoskeletal origin is probably best managed by physical medicine procedures using tricyclics and SNRIs as supplements. Patients with manifestations of psychosocial dysfunction may not benefit from drug therapy aimed at pain and should be considered as candidates for physical medicine modalities and behavioral methods and SSRI medications.

For patients on whom other therapeutic modalities have failed, or for whom a specific treatment is not readily apparent, such as patients for whom the non-narcotic analgesic medications and physical and behavioral medicine procedures have not worked adequately, might be eligible for a trial with opioids. What is evident is that a wide variety of adjuvant analgesic and anti-convulsant drugs show efficacy in the treatment of chronic painful conditions. Recently, a European pain task force evaluated the existing published evidence about the pharmacological treatment of neuropathic pain.[102]

Only pharmacologic treatments feasible in an outpatient setting were evaluated, and they used the effect of these agents on pain symptoms/signs, quality of life, and other disease comorbidities as outcomes. They reported that most of the randomized controlled trials included patients with postherpetic neuralgia (PHN) and painful polyneuropathies (PPN) mainly caused by diabetes.

Using these diseases, the task force concluded that the data provides high level of evidence for the efficacy of tricyclic antidepressants, gabapentin, pregabalin, and opioids, with a large number of class I trials, followed by topical lidocaine (in PHN), and the newer antidepressants venlafaxine and duloxetine (in PPN). The biggest problem is that the previously mentioned recommendations apply only to PHN and DN, and, if used on other similar but untested conditions, like atypical odontalgia and burning mouth syndrome, it is not clear if the efficacy will carry over to these disorders.

For this reason, using medications such as these requires caution. Given the complex nature of chronic orofacial pain, a multidimensional treatment approach, including nonpharmacological methods, is advocated, avoiding use of several adjuvant medications prone to side effects.

Furthermore, periodic trials of decreasing dosages and eliminating chronic medications should be considered. However, the targeted and limited use of adjuvant analgesic treatments for defined pain syndromes provides a valuable addition toward relief of pain. ■■■■

REFERENCES

1. Benoliel R, Eliav E, Neuropathic orofacial pain. *Oral Maxillofac Surg Clin North Am* 20(2):237-54, May 2008.
2. Clark GT, Ram S, Orofacial pain and neurosensory disorders and dysfunction in cancer patients. *Dent Clin North Am* 52(1):183-202, ix-x, January 2008.
3. Graff-Radford SB, Temporomandibular disorders and other causes of facial pain. *Curr Pain Headache Rep* 11(1):75-81, February 2007.
4. Clark GT, Classification, causation and treatment of masticatory myogenous pain and dysfunction. *Oral Maxillofac Surg Clin North Am* 20(2):145-57, May 2008.
5. Clark GT, Persistent orodental pain, atypical odontalgia, and phantom tooth pain: When are they neuropathic disorders? *J Calif Dent Assoc* 34(8):599-609, August 2006.
6. Suarez P, Clark GT, Burning mouth syndrome: An update on diagnosis and treatment methods. *J Calif Dent Assoc* 34(8):611-22, August 2006.
7. Ram S, Kumar SK, Clark GT, Using oral medications, infusions and injections for differential diagnosis of orofacial pain. *J Calif Dent Assoc* 34(8):645-54, August 2006.
8. Clark GT, Minakuchi H, Lotaif AC, Orofacial pain and sensory disorders in the elderly. *Dent Clin North Am* 49(2):343-62, April 2005.
9. Robinson ME, Brown JL, et al, Multidimensional success criteria and expectations for treatment of chronic pain: the patient perspective. *Pain Med* 6(5):336-45, September-October 2005.
10. Wolf E, Nilner M, et al, Long-term follow-up by means of a questionnaire of 109 patients with long-lasting orofacial pain. *Swed Dent J* 26(3):125-34, 2002.
11. Allerbring M, Haegerstam G, Chronic idiopathic orofacial pain. A long-term follow-up study. *Acta Odontol Scand* 62(2):66-9, April 2004.
12. Suarez P, Clark GT, Oral conditions of 1,049 patients referred to a university-based oral medicine and orofacial pain center. *Spec Care Dentist* 27(5):191-5, September-October 2007.
13. Antczak-Bouckoms AA, Epidemiology of research for temporomandibular disorders. *J Orofac Pain* 9(3):226-34, Summer 1995.
14. Dionne RA, Pharmacologic treatments for temporomandibular disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 83(1):134-42, January 1997.
15. List T, Axelsson S, Leijon G, Pharmacologic interventions in the treatment of temporomandibular disorders, atypical facial pain, and burning mouth syndrome. A qualitative systematic review. *J Orofac Pain* 17(4):301-10, Fall 2003.
16. Fassbender HG, Pathology of rheumatic diseases. Springer-Vertag, New York, 303-14, 1975.
17. Goss AN, Speculand DB, Hallet E, Diagnosis of temporomandibular joint pain in patients seen at a pain clinic. *J Oral Maxillofacial Surg* 43:110-4, 1985.
18. Greene CS, The fallacies of clinical success in dentistry. *J Oral Med* 31:52-5, 1976.
19. Okeson JP, Moody DM, et al, Evaluation of occlusal splint therapy and relaxation procedures in patients with temporomandibular disorders. *J Am Dent Assoc* 107:420-4, 1983.
20. Greene CS, Laskin DM, Splint therapy for the myofascial pain-dysfunction (MPD) syndrome: A comparative study. *J Am Dent Assoc* 84:624-8, 1972.
21. Laskin DM, Greene CS, Influence of the doctor-patient relationship on placebo therapy for patients with myofascial pain

dysfunction (MPD) syndrome. *J Am Dent Assoc* 85:892-4, 1972.
22. Goodman P, Greene CS, Laskin DM, Response of patients with myofascial pain-dysfunction syndrome to mock equilibration. *J Aria Dent Assoc* 92:755-8, 1976.
23. Moody PM, Kemper JT, et al, Recent life changes and myofascial pain syndromes. *J Prosthet Dent* 48:328-30, 1982.
24. Greene CS, Oleson RE, Laskin DM, Psychosocial factors in the etiology, progression, and treatment of MPD syndrome. *J Am Dent Assoc* 105:443-8, 1983.
25. Speculand B, Goss AN, et al, Temporomandibular joint dysfunction: Pain and illness behavior. *Pain* 17:139-50, 1983.
26. Greene CS, Laskin DM, Long-term evaluation of conservative treatment for myofascial pain-dysfunction syndrome. *J Am Dent Assoc* 89:1365-8, 1974.
27. Eriksen J, Sjogren P, et al, Critical issues on opioids in chronic noncancer pain: An epidemiological study. *Pain* 125(1-2-):172-9, November 2006; e-pub July 13, 2006.
28. Gibson TP, Pharmacokinetics, efficacy, and safety of analgesia with a focus on Tramadol HCl. *Am J Med* 101(suppl 1A):47–53, 1996.
29. Dalgin PH, Use of tramadol in chronic pain. *Clinical Geriatrics* 5:51–69, 1997.
30. Cicero TJ, Adams EH, et al, A postmarketing surveillance program to monitor Ultram (tramadol HCl) abuse in the United States. *Drug Alcohol Depend* 57:7–22, 1999.
31. Edwards JE, Oldman AD, et al, Oral aspirin in postoperative pain: A quantitative systematic review. *Pain* 81(3):289-97, June 1999.
32. Lipton RB, Goldstein J, et al, Aspirin is efficacious for the treatment of acute migraine. *Headache* 45(4):283-92, April 2005.
33. Raffa R, Pharmacological aspects of successful long-term analgesia. *Clin Rheumatol* 25(Suppl 1):S9-15, 2006; e-pub June 2, 2006.
34. Bigal ME, Rapoport AM, et al, Transformed migraine and medication overuse in a tertiary headache centre — clinical characteristics and treatment outcomes. *Cephalalgia* 24(6):483-90, June 2004.
35. Gray A, Kehlet H, et al, Predicting postoperative analgesia outcomes: NNT league tables or procedure-specific evidence? *Br J Anaesth* 94(6):710-4, June 2005; e-pub April 15, 2005.
36. Lipton RB, Stewart WF, et al, Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 55(2):210-7, February 1998.
37. Ayzenberg I, Obermann M, et al, Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures. *Cephalalgia* 26(9):1106-14, September 2006.
38. Goldstein JL, Challenges in managing NSAID-associated gastrointestinal tract injury. *Digestion* 69 Suppl 1:25-33, 2004.
39. Holvoet J, Terriere L, et al, Relation of upper gastrointestinal bleeding to nonsteroidal anti-inflammatory drugs and aspirin: A case control study. *Gut* 32:730-4, July 1991.
40. Laporte J-R, Came X, et al, Upper gastrointestinal bleeding in relation to previous use of analgesics and nonsteroidal anti-inflammatory drugs. *Lancet* 337:85-9, 1991.
41. Kaufman DW, Kelly JP, et al, Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 53:485-94, 1993.
42. Leone S, Ottani A, Bertolini A, Dual-acting anti-inflammatory drugs. *Curr Top Med Chem* 7(3):265-75, 2007.
43. Gregory AJ, Topical ketoprofen patch for ankle sprain. *Clin J Sport Med* 17(2):170-4, March 2007.
44. Chen YF, Jobanputra P, et al, Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib) for osteoarthritis and rheumatoid arthritis: A systematic review and economic evaluation. *Health Technol Assess* 12(11):1-178, April 2008.
45. Ta LE, Dionne RA, Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: A randomized placebo-controlled comparison of celecoxib to naproxen. *Pain* 111(1-2):13-21, September 2004.
46. Ernberg M, Hedenberg-Magnusson B, et al, Short-term effect of glucocorticoid injection into the superficial masseter muscle of patients with chronic myalgia: A comparison between fibromyalgia and localized myalgia. *J Orofac Pain* 11(3):249-57, Summer 1997.
47. Lozada-Nur F, Miranda C, Maliksi R, Double-blind clinical trial of 0.05 percent clobetasol propionate (corrected from proprionate) ointment in orabase and 0.05 percent fluocinonide ointment in orabase in the treatment of patients with oral vesiculoerosive diseases. *Oral Surg Oral Med Oral Pathol* 77(6):598-604, June 1994.
48. Jett MF, McGuirk J, et al, The effects of mexilitine, desipramine, and fluoxitine in rat models involving central sensitization. *Pain* 69:161-72, 1997.
49. Argoff CE, New analgesics for neuropathic pain: The lidocaine patch. *Clin J Pain* 16(suppl 2):S62-6, 2000.
50. Fassoulaki A, Sarantopoulos C, et al, EMLA reduces acute and chronic pain after breast surgery for cancer. *Reg Anesth Pain Med* 25:350-5, 2000.
51. Devers A, Galer BS, Topical lidocaine patch relieves a variety of neuropathic pain conditions: An open-label study. *Clin J Pain* 16:205-8, 2000.
52. Moos DD, Cuddeford JD, Methemoglobinemia and benzocaine. *Gastroenterol Nurs* 30(5):342-5, September-October 2007.
53. Nicol CF, A four-year double-blind study of tegretol in facial pain. *Headache* 9:54-7, 1969.
54. Remillard G, Oxcarbezepine in the treatment of trigeminal neuralgia. *Epilepsia* 35(suppl 3):S28-9, 1994.
55. Ghose K, Niven B, Prophylactic sodium valproate therapy in patients with drug-resistant migraine. *Methods Find Exp Clin Pharmacol* 20:353-9, 1998.
56. Perucc E, Bialer M, The clinical pharmacokinetics of the newer anti-epileptic drugs. Focus on topiramate, zonisamaide, and tiagibine. *Clin Pharmcokine* 31:29-46, 2000.
57. Freitag FG, Preventive treatment for migraine and tension-type headaches: Do drugs having effects on muscle spasm and tone have a role? *CNS Drugs* 17(6):373-81, 2003.
58. Ferrari A, Pasciullo G, et al, Headache treatment before and after the consultation of a specialized centre: A pharmacoepidemiology study. *Cephalalgia* 24(5):356-62, May 2004.
59. Maizels M. Health resource utilization of the emergency department headache "repeater." *Headache* 42(8):747-53, September 2002.
60. Devine JW, Farley JF, Hadsall RS, Patterns and predictors of prescription medication use in the management of headache: Findings from the 2000 Medical Expenditure Panel Survey. *Headache* 45(9):1171-80, October 2005.
61. Wenzel RG, Sarvis CA, Do butalbital-containing products have a role in the management of migraine? *Pharmacotherapy* 22(8):1029-35, August 2002.
62. Silberstein SD, Young WB, et al, Dihydroergotamine for early and late treatment of migraine with cutaneous allodynia: an open-label pilot trial. *Headache* 47(6):878-85, June 2007.
63. Pascual J, Rivas MT, Leira R, Testing the combination beta-blocker plus topiramate in refractory migraine. *Acta Neurol Scand* 115(2):81-3, February 2007.
64. May A, Leone M, et al, EFNS Task Force. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 13(10):1066-77, October 2006.
65. Magni G, The use of antidepressants in the treatment of chronic pain. *Drugs* 42:730-8, 1991.
66. Kishore-Kumar R, Max MB, Schafer SC, et al, Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 47:305–312, 1990.
67. Swenson JR, Doucette S, Fergusson D. Adverse cardiovascular events in antidepressant trials involving high-risk patients: a systematic review of randomized trials. *Can J Psychiatry* 51(14):923-9, December 2006.
68. Arnold LM, Lu Y, et al, A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum* 50: 2974-2984, 2004.
69. Arnold LM, Rosen A, et al, A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 119: 5-15, 2005.
70. Narita M, Kaneko C, et al, Chronic pain induces anxiety with concomitant changes in opioidergic function in the amygdala. *Neuropsychopharmacology* 31(4):739-50, April 2006.
71. Matsuzawa-Yanagida K, Narita M, et al, Usefulness of Antidepressants for Improving the Neuropathic Pain-Like State and Pain-Induced Anxiety through Actions at Different Brain Sites. *Neuropsychopharmacology* 33(8):1952-65, July 2008.
72. Giannopoulos S, Kosmidou M, et al, Patient compliance with SSRIs and gabapentin in painful diabetic neuropathy. *Clin J Pain* 23(3):267-9, March-April 2007.
73. Elenbaas JK. Centrally acting oral skeletal muscle relaxants. *Am J Hosp Pharm* 37:1313-23, 1980.
74. Margolin S. Pharmacologic demonstration in man of increased thresholds to tooth pain following carisoprodol and other analgesics. *Proc Soc Exp Biol Med* 105:531-3, December 1960.
75. Brown BR, Womble J, Cyclobenzaprine in intractable pain syndromes with muscle spasm. *JAMA* 240:1151-2, 1978.
76. Basmajian JV, Cyclobenzaprine hydrochloride effect on skeletal muscle spasm in the lumbar region and neck: Two double-blind controlled clinical and laboratory studies. *Arch Phys Med Rehabil* 59:58-63, 1978.
77. Bennett RM, Gatter RA, et al, A comparison of cyclobenzaprine and placebo in the management of fibrositis. A double-blind controlled study. *Arthritis Rheum* 31:1535–1542, 1988.
78. Tofferi JK, Jackson JL, et al, Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. *Arthritis Rheum* 51: 9-13, February 2004.
79. Clark GT, Stiles A, et al, A critical review of the use of botulinum toxin in orofacial pain disorders. *Dent Clin North Am* 51(1):245-61, January 2007.
80. Jankovic J, Hallet J, eds. Therapy with Botulinum Toxin. New York: Marcel Dekker, Inc., 1:15, 1994.
81. Brown MC, Hopkins WG, Keynes RJ, Comparison of effects of denervation and botulinum toxin paralysis on muscle properties in mice. *J Physiol* 327:29–37, 1982.
82. Raj PP, Botulinum toxin in the treatment of pain associated with musckuloskeletal hyperactivity. *Curr Rev Pain* 1:403–416, 1997.
83. Piovesan EJ, Teive HG, et al, An open study of botulinum-A toxin treatment of trigeminal neuralgia. *Neurology*

65(8):1306-8, Oct 25, 2005.
84. Kast RE. Tiagabine may reduce bruxism and associated temporomandibular joint pain. *Anesth Prog* 52(3):102-4, Fall 2005.
85. Pollack MH, Roy-Byrne PP, et al, The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 66(11):1401-8, November 2005.
86. Gremeau-Richard C, Woda A, et al, Topical clonazepam in stomatodynia: A randomised placebo-controlled study. *Pain* 108(1-2):51-7, March 2004.
87. Singer E, Dionne R, A controlled evaluation of ibuprofen and diazepam for chronic orofacial muscle pain. *J Orofac Pain* 11(2):139-46, Spring 1997.
88. Cohen AS, Matharu MS, Goadsby PJ, Trigeminal autonomic cephalalgias: Current and future treatments. *Headache* 47(6):969-80, June 2007.
89. Baldacci F, Nuti A, et al, INDOTEST in atypical hemicrania continua. *Cephalalgia* 28(3):300-1, March 2008.
90. Taub D, Stiles A, Tucke AG, Hemicrania continua presenting as temporomandibular joint pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 105(2):e35-7, February 2008.
91. Goldberg ME, Domsky R, et al, Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. *Pain Physician* 8(2):175-9, April 2005.
92. Cvrcek P, Side effects of ketamine in the long-term treatment of neuropathic pain. *Pain Med* 9(2):253-7, March 2008.
93. Baad-Hansen L, Juhl GI, et al, Differential effect of intravenous S-ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain. *Pain* 129(1-2):46-54, May 2007, e-pub Nov. 7, 2006.
94. Mathisen LC, Skjelbred P, et al, Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. *Pain* 61(2):215-20, May 1995.
95. Rabben T, Øye I, Interindividual differences in the analgesic response to ketamine in chronic orofacial pain. *Eur J Pain* 5(3):233-40, 2001.
96. Sullivan FM, Swan IR, et al, Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 357(16):1598-607, Oct. 18, 2007.
97. Hato N, Yamada H, et al, Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. *Otol Neurotol* 28(3):408-13, April 2007.
98. Dhiwakar M, Clement W, Supriya M, McKerrow W. Antibiotics to reduce post-tonsillectomy morbidity. *Cochrane Database Syst Rev* 16;(2):CD005607, April 2008.
99. Cervin A, Wallwork B, Macrolide therapy of chronic rhinosinusitis. *Rhinology* 45(4):259-67, December 2007.
100. Amsden GW, Anti-inflammatory effects of macrolides--an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimicrob Chemother* 55(1):10-21, January 2005, e-pub Dec. 8, 2004.
101. Tamaoki J, Kadota J, Takizawa H, Clinical implications of the immunomodulatory effects of macrolides. *Am J Med* 117(Suppl 9A):5S-11S, Nov. 8, 2004.
102. Attal N, Cruccu G, et al, EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 13(11):1153-69, November 2006.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT
Glenn Clark, DDS, MS, Orofacial Pain and Oral Medicine Center, University of Southern California, Los Angeles, Calif., 90089.

CDA JOURNAL, VOL 36, Nº10

Dental Management of Patients With a History of Bisphosphonate Therapy: Clinical Dilemma

CESAR A. MIGLIORATI, DDS, MS, PHD; CHIU-JEN HSU, DDS; SONIA CHOPRA, DDS; AND STEVEN S. KALTMAN, DMD, MD

ABSTRACT Bisphosphonate osteonecrosis, BON, was recently described in the literature. Lack of scientific evidence explaining the pathophysiologic mechanisms involved in the development of this oral complication has generated uncertainties about proper management of patients treated with a bisphosphonate. This manuscript discusses the dental management of two breast cancer patients treated with intravenous bisphosphonates as part of their cancer management and who developed oral disease. Clinical management decisions will be presented as well as the treatment outcomes.

AUTHORS

Cesar A. Migliorati, DDS, MS, PHD, is a professor, oral medicine, at Nova Southeastern University, College of Dental Medicine, in Fort Lauderdale, Fla.

Chiu-Jen Hsu, DDS, is an assistant professor, prosthodontics, at Nova Southeastern University, College of Dental Medicine, in Fort Lauderdale, Fla.

Sonia Chopra, DDS, is with Nova Southeastern University, College of Dental Medicine, in Fort Lauderdale, Fla.

Steven S. Kaltman, DMD, MD, is with Nova Southeastern University, College of Dental Medicine, in Fort Lauderdale, Fla.

Bisphosphonate osteonecrosis, BON, was first reported in 2003.[1,2] Since the first reports, it became evident that most of the cases develop in cancer patients receiving intravenous bisphosphonates.[3-5] A number of publications including case series, white papers, and guidelines addressed management strategies with the objective of guiding the dental clinician on the proper management of patients with this oral complication.[5-9] However, due to the lack of a universally accept treatment protocol, dentists are uncertain on how to best manage a patient with this oral complication.

BON is defined as the unexpected appearance of necrotic bone anywhere in the oral cavity of a patient taking a bisphosphonate who has no history of radiation therapy to the head and neck. The necrotic area persists for six to eight weeks despite the provision of standard care.[6] Patients usually complain of pain and have active infection with pus at the area of necrosis. This definition is representative of cases where necrotic bone is found during the intraoral examination. However, there may be patients who fit the profile previously described but who do not have visible exposed bone in the mouth.[10]

Because of the awareness the reports of BON have generated in the dental and

medical communities, it is not uncommon that a patient on bisphosphonate therapy who has signs and symptoms of oral disease, even without the presence of visible intraoral necrotic bone, will be given a possible diagnosis of BON. Once BON is suspected, the dentist may be reluctant to provide routine dental care to the patient involved. The authors have recently received a number of referrals of patients in this situation who have been denied care by dental colleagues.

Following is the presentation of two of these cases and a discussion on the management decisions during the treatment of both patients.

Case No. 1

Antonia S., an 84-year-old woman, was referred to the oral medicine clinic at NSU College of Dental Medicine in Fort Lauderdale, Fla., for evaluation of an oral infection. The patient complained of severe pain and swelling of the upper anterior jaw that was present for several weeks. The patient was being treated by her dentist who was trying to control dental deterioration by grinding the patient's teeth down to the gingival level to avoid extraction and with the use of antibiotics.

In a recent dental consultation, the patient had tooth No. 5 extracted. The patient could not recall the exact date of the extraction but reported that the healing was delayed. She had to be treated with antibiotics and topical mouthrinses until healing, with closure of the alveolar socket eventually occurring. Prior to the referral, the dentist told the patient that her medical and dental problems were too complex and that he could not continue treating her. The patient was then referred to the NSU oral medicine clinic.

The patient's medical history was significant for breast cancer diagnosed 11 years ago. Antonia had been treated with bilateral mastectomies, several cycles of chemotherapy, and radiation. She later developed several areas of skeletal metastasis and severe pain. Recently, she had her left leg irradiated due to intense pain and a fracture due to extensive metastasis. Two months prior to her visit to NSU, the patient experienced intense pain. At that time, she was submitted to surgery for a complete hip replacement. The patient was receiving only hormonal therapy and no other cancer treatment modality.

The medical history was also significant for well-controlled diabetes and hypertension. Because of the skeletal metastasis the patient had been treated with zoledronic acid 4 mg IV infusions every three to four weeks for the past three years. Due to the delayed healing episode after the extraction of tooth No. 5, her medical oncologist discontinued the use of zoledronic acid prior to the initial visit to NSU.

The clinical examination revealed minor swelling of the buccal plate of tooth No. 6 and the extraction area distal to No. 6. The anterior right maxilla was painful upon palpation and teeth Nos. 6 and 7 were sensitive to percussion and palpation. Purulence could be expressed from the sulcus around No. 6; however, no visible necrotic bone could be found during the clinical examination (FIGURE 1A). Panoramic and periapical radiographs revealed radiolucency and evidence of bone loss around the root of tooth No. 6 as well as a vertical defect with an irregular contour on the distal surface at the alveolar crest. A localization radiograph showed a gutta-percha point that was introduced through the sulcus, distal of No. 6 and localized at the extraction site of tooth No. 6 (FIGURES 1B-C). Vitality pulp testing confirmed a necrotic pulp for No. 6 and positive for No. 7 and the contralateral teeth.

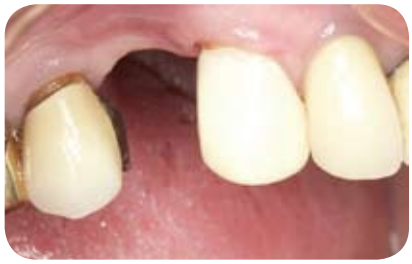


FIGURE 1A. Breast cancer patient complaining of pain on the anterior right maxilla. Clinical and radiographic findings. Note absence of clinically exposed necrotic bone.

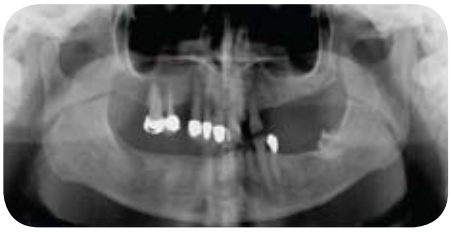


FIGURE 1B. Panoramic radiograph reveals radiolucency at the anterior right maxilla. Observe residual roots of teeth that had been ground down to the gingival level by the previous dentist to avoid extraction.

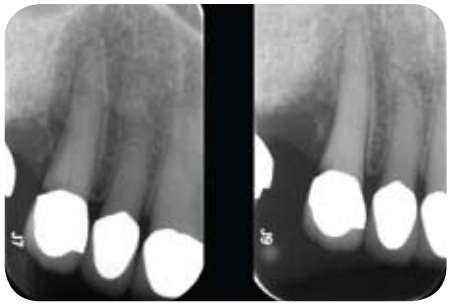


FIGURE 1C. The periapical radiographs show with more detail the involved areas around tooth No. 6.

FIGURE 1D. Localization of the osseous defect with a gutta-percha point ending directly at the extraction site of tooth No. 5.

Could a Diagnosis of BON Be Made at This Point?

The patient's clinical presentation did not fit in the classical definition of BON due to the absence of clinically visible necrotic bone. However, the history of long-

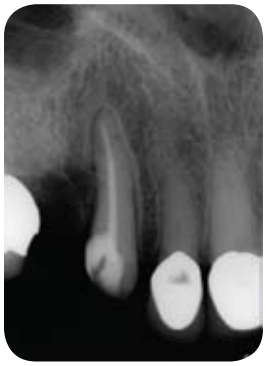


FIGURE 2. Final radiograph after endodontic therapy. Observe sclerosis at the lamina around tooth No. 6. This may be an early sign of BON.

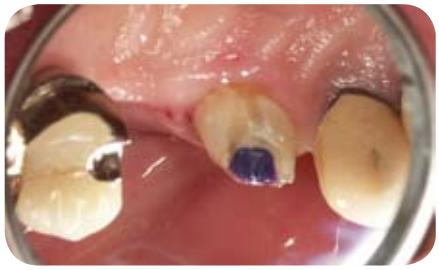


FIGURE 3A. Clinical view of tooth No. 6 after crown preparation. Note absence of any necrotic bone exposure in the area.

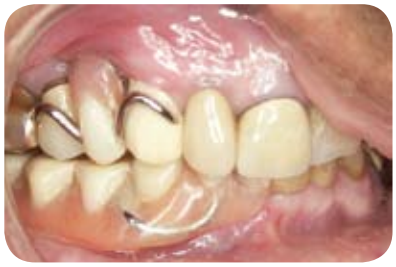


FIGURE 3B. Buccal view of the temporary crown and the removable partial bridge. No evidence of exposed necrotic bone.

term IV bisphosphonate therapy (three years of zoledronic acid), the patient's advanced age, history of recent extraction, presence of active infection in the area, no response to antibiotic therapy, and delayed healing, allowed the authors to suspect BON without visible exposed necrotic bone. The presence of diabetes in her medical history could also be considered an additional predisposing factor. Radiographically, the authors found a track leading to the area of extraction, a radiolucency around the root of tooth No. 6, and evidence of sclerosis periradicular at the lamina dura area. This has been considered an early sign of BON (**FIGURE 1D**).

With the Working Diagnosis of BON, What Would be the Best Way to Manage the Patient?

The first concern in spite of the possible diagnosis of BON was to treat the acute symptoms to alleviate pain. After a brief discussion with the patient's medical oncologist for confirmation of current medical status, the patient was given a course of 500 mg amoxicillin q.i.d., and chlorhexidine mouthrinses b.i.d. In addition, the patient was given oral hygiene instructions and was told not to use the removable partial denture to minimize trauma to the area.

What was the Treatment Plan Proposed in This Case?

A consultation with the patient's medical oncologist confirmed an advanced stage of breast cancer (stage 4: Tumor had spread beyond the breast and internal mammary lymphnodes, lymphnodes above the collar bone, lung, liver bones, and brain) when no curative therapy could be offered to the patient. At this point, maintaining the patient's quality of life was the most important objective. The oncologist also revealed no desire to start zoledronic acid infusions again.

A consultation with an oral and maxillofacial surgeon discarded the extraction of the involved tooth, especially considering the working diagnosis of BON. The patient was informed about the nature of her dental disease and the possibility of BON, related to the use of a bisphosphonate. She was told that the authors would not do any invasive therapy at that point. She had a consultation with an endodontist and a prostodonthist to evaluate continuation of dental care after the resolution of the acute phase. The patient was offered to have endodontic treatment and a temporary crown of No. 6, and adjustment of the existing maxillary partial bridge. She agreed with the proposed treatment plan and signed an informed consent. She received endodontic treatment of No. 6 while on amoxicillin (**FIGURE 2**).

The use of antibiotic therapy throughout the endodontic treatment was elected based on the recent hip replacement and the presence of active infection. The patient responded well to endodontic therapy and became pain-free. However, a persistent purulent secretion continued to drain from the periodontal sulcus. She was seen by the prosthodontist who constructed a temporary acrylic crown on No. 6 and adjusted it to fit the existing partial bridge (**FIGURES 3A-B**). The patient was placed on follow-up visits every month. She was instructed to continue taking amoxicillin 500 mg q.i.d. and to clean the area around tooth No. 6 with the help of a cotton swab and chlorhexidine. In subsequent follow-up visits, it was observed that the clinical lesions had improved considerably and that only minimal amounts of pus could be expressed after palpation of the area. The patient is now considering the possibility of having further routine dental care for restoration of the remaining teeth. She remains pain-free after several months of periodic follow-up.

The working diagnosis for this patient continues to be BON second to the use of zoledronic acid, without evidence of intraoral exposed necrotic bone.

Case No. 2

Annette S., a 70-year-old woman, came to the NSU oral medicine clinic in June 2007 complaining of severe pain and swelling of the anterior right maxilla. Pain was present for months. After being denied dental treatment by several colleagues, Annette was told that the only place she could find help was at the authors' clinic. The medical history review was significant for breast cancer (stage 4), for which she was currently under treatment. She had a history of thyroid cancer treated with radioactive iodine. Annette was a former smoker and now had chronic obstructive pulmonary disease. She was dependent on oxygen and used an oxygen dispenser most of the day. Annette had

active gout and rheumatoid arthritis that caused pain and discomfort while walking.

She was recently diagnosed with myasthenia gravis that affected mostly the eye muscles but was under control. Because of metastatic breast cancer to the skeleton, the patient was treated with pamidronate and zoledronic acid IV infusions daily for a total of six years. Following a discussion with the medical oncologist in August 2006, she had discontinued the use of bisphosphonates, due to the development of oral signs and symptoms. Because of active skeletal metastasis, the medical oncologist was waiting for the resolution of the oral problems to restart the use of IV bisphosphonates. The oral examination revealed deteriorating oral health. Annette had pain and swelling of the anterior right maxilla. No visible necrotic exposed bone could be seen (**FIGURE 4A**).

In the past week, the pain became almost unbearable to her. She presented with several areas of decay under the crowns of an existing maxillary bridge despite the fact that she was brushing and flossing twice daily, and rinsing with peroxide. Her desire was to have all maxillary teeth extracted and a new maxillary full denture. A panoramic radiograph confirmed the poor dental health revealing a failing fixed bridge (**FIGURE 4B**). There was radioluncency around the roots of teeth Nos. 6 and 7, as well as a failing implant in the left maxilla, confirming that the best treatment plan for the patient at this point would probably be the extraction of all maxillary teeth, the removal of the dental implant, and a full maxillary denture.

At this point, the patient revealed that she had no financial means to afford any dental therapy. Additionally, her husband was also under therapy for gastric cancer and that she was responsible for taking care of him. At this point, the first question that comes to mind is: Is this a case of BON?

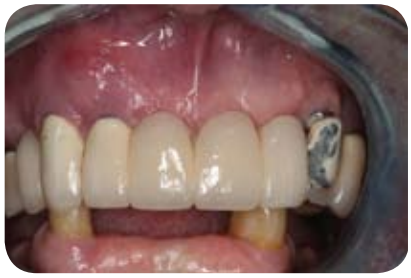


FIGURE 4A. Breast cancer patient referred to the clinic for evaluation and treatment of infection in the anterior maxilla. Note swelling and redness at the apical area of teeth Nos. 6 and 7. Areas were painful upon palpation and percussion.

FIGURE 4B. Panoramic radiograph shows a suspicious area around the root of No. 6. Observe extensive decay, bone loss and a failing dental implant.

Once again, despite the history of long-term use of IV bisphosphonates for six years, the clinical presentation in this case does not fit the classical definition of BON due to the absence of visible exposed necrotic bone. Therefore, the authors could not be certain of a definitive diagnosis for the oral disease. In the differential diagnosis, one should include the possibility of BON without exposed necrotic bone or just a routine dental infection.

How to Manage the Acute Oral Cavity Symptoms in View of This Patient's History of Long-term IV Bisphosphonate Therapy?

The authors chose to be conservative at first to see how the patient would respond to routine antibiotic therapy and no invasive procedures. Annette was prescribed penicillin V-K 500 mg to take q.i.d. and was given a chlorhexidine mouth rinse to use b.i.d. She received oral hygiene instructions, was asked to avoid the use of the removable partial to prevent further trauma, and was asked to return to the clinic in a week. In the meantime, the authors presented the case to an oral and maxillofacial surgeon for evaluation and management decision. In the discussion with the surgeon, the authors agreed that full maxillary extraction was the only viable treatment in view of the deterioration of oral health, the patient's medical history, and the financial constraints. Although the patient had advanced cancer and many other medical complications, having all maxillary teeth extracted and a new full maxillary denture constructed would have an immediate impact on the patient's quality of life, nutrition, and would be financially feasible.

Other treatment alternatives like endodontic therapy, new implants and crown and bridge, would require many visits to the dental office, a very high cost that could not be afforded by the patient, and a questionable investment based on the short life expectancy for this patient. In addition, having all teeth extracted and a full maxillary denture was the initial desire of the patient.

Although the radical treatment could result in the exposure of necrotic bone and confirm the diagnosis of BON, the authors felt that the proposed treatment was the best option for the patient. The treatment plan was discussed with the medical oncologist, who informed the authors that the patient was in an advanced stage of breast cancer and that only palliative therapy and maintenance of quality of life were being considered. Additionally, the medical oncologist said her complex medical history was under control and should not prevent the authors from providing her with radical treatment.

On the following visit the patient felt much better and the swelling had improved. She claimed the pain was gone and that she had been able to eat. At this time, the authors had the oral surgeon explain to the patient the need for full maxillary extraction. The authors discussed

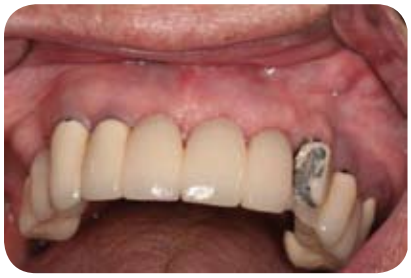


FIGURE 5A. Note the outcome of the various steps of therapy. Patient at the day of surgery. Observe the great improvement of the infection at the area of teeth Nos. 6 and 7.

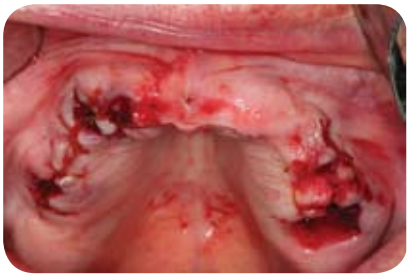


FIGURE 5B. View immediately after extraction of all remaining maxillary teeth and the dental implant. Note normal bleeding.

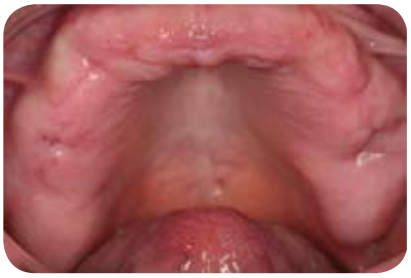


FIGURE 5C. Final healing several weeks postextraction. Note that the tissues are normal and there is no evidence of osteonecrosis.

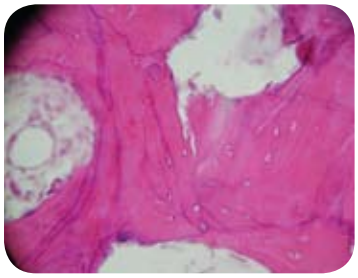


FIGURE 6. H and E section demonstrating the presence of vital bone. This was observed in all bone samples collected at the time of surgery. *(Courtesy Dr. Ines Velez)*

FIGURE 7A. Final view of the patient wearing a full maxillary denture.

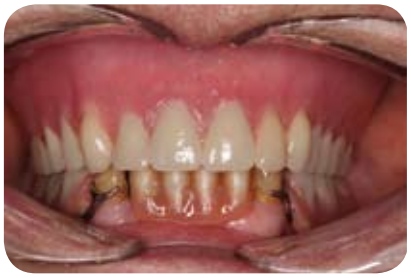


FIGURE 7B. No complications have been observed several months after the delivery of the denture.

with her the risks involved with surgery and that it was believed this was the best treatment for her. After she signed an informed consent, she was instructed about the need for continuing on antibiotic therapy and maintaining good oral hygiene. The authors continued to follow the patient for a few more weeks to observe the progress of the clinical infection.

At the time of the August 2007 surgery, the patient was completely asymptomatic and the clinical findings presented considerable improvement (**FIGURE 5A**). At this time, the patient was informed that the dental treatment was going to be made almost completely free of charge, as a didactic case, and that she had to pay only for the prosthodontic laboratory fees. The surgical procedure went well and no major complications or bleeding developed (**FIGURE 5B**).

During surgery, bone samples for histopathology were obtained. At the time of surgery, the authors requested a consultation with a prosthodontist who agreed to build a maxillary full denture and to adjust to fit the existing mandibular removable bridge. The postoperatory visit was done a week later. The patient did not have any complaints and was still taking penicillin. Healing was progressing well and no evident dehiscence or exposed bone could be seen (**FIGURE 5C**). The pathology report confirmed vital bone and inflammation (**FIGURE 6**). One month later the oral tissues had healed and the prosthodontic work was initiated. The dentures were delivered September 2007 (**FIGURES 7A-B**) and no signs of osteonecrosis could be found.

The patient continues periodic follow-up and is maintaining good oral health. Occasional denture adjustments have been made to avoid trauma to the soft tissues. The final diagnosis was that of periapical abscess of tooth No. 6.

Discussion

The authors presented two patients with stage 4 breast cancer who had been treated with IV bisphosphonate for prolonged periods and who developed oral disease during their therapy. Because of the medical history and the use of IV bisphosphonates, both had been denied dental care, despite the presence of severe pain and infection. Neither patients presented the classical intraoral findings of BON, exposed necrotic bone, associated with the oral disease. Therefore, even assuming there was a potential for BON in both cases, despite years of experience managing these individuals, the authors could not make a definitive diagnosis at the time the patients came to the clinic for consultation.

The authors understand that dental colleagues may not feel equipped or comfortable to provide dental care to patients with such history. The goal of this case presentation is to inform the dental practitioner how the authors treated the patients. In both cases the initial management procedure was to address the acute oral disease. If there is pain and evidence of infection, conservative therapy with systemic antibiotics and topical measures are usually enough to control symptoms.

A review of the medical history of these individuals is important. The use of IV bisphosphonates has been associated with about 10 percent incidence of BON. Therefore, there are about 90 percent of patients who use the same medication and who do not develop BON. The longer the time on bisphosphonate therapy, the higher the risk for BON.[5,9]

In the presented cases, the patient with three years' history of therapy developed BON. The other patient had six years' history of IV bisphosphonate use and was treated surgically. She healed well without complications and did not develop BON. The reader should keep in mind that neither of the cases presented here represented classical cases of BON where exposed necrotic bone that does not heal and is progressive. Therefore, the authors did not have a final diagnosis for the dental disease when first seeing the patients. It is possible the patient in case No. 1 was an example of the type of clinical situation faced by dental colleagues prior to the discovery of BON. During the diagnostic phase and management of this patient, the authors became certain that there was necrotic bone in the area of tooth No. 5. The lack of good response to the endodontic therapy of tooth No. 6 and the persistence of infection and purulent secretion confirmed the impression that we were dealing with a BON case. A less-experienced clinician would probably have performed an apical surgery or extracted No. 6, exposing the necrotic bone to the oral cavity.

It is also important to notice that in both cases, there was not a definitive diagnosis. Nevertheless, the patients were treated based on what was felt to be the best treatment for each of the cases. In presenting the treatment plan to the patients, it was discussed the risk for BON based on the medical history and a signed informed consent was obtained. The management decision for each patient involved the participation of a multiprofessional team of dental experts and the medical oncologists. It is believed this is fundamental in the management of patients who have been medicated with a bisphosphonate drug.

As risk factors for BON become more evident from prospective controlled studies, and as more is learned about the pathophysiology of this complication, new guidelines based on science will become available. This should make dental professionals more secure to provide care to these patients. In the meantime, using good clinical judgment and keeping in mind that all patients deserve to be cared for, should guide the clinician in the management of patients on bisphosphonate therapy. ■■■■

REFERENCES

1. Marx R, Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg* 61(9):1115-7, 2003.
2. Migliorati C, Bisphosphanates and oral cavity avascular bone necrosis. *J Clin Oncol* 21(22):4253-4, 2003.
3. Migliorati C, Schubert, M, et al, Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: An emerging oral complication of supportive cancer therapy. *Cancer* 104(1):83-93, 2005.
4. Ruggiero S, Mehrotra B, et al, Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 62(5):527-34, 2004.
5. Woo S, Hellstein J, Kalmar J, Narrative (corrected) review: Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 144(10):753-61, 2006.
6. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 65(3):369-76, 2007.
7. Khosla S, Burr D, et al, Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22(10):1479-91, October 2007.
8. Mavrokokki T, Cheng, A, et al, Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg* 65(3):415-23, 2007.
9. Migliorati C, Casiglia J, et al, Managing the care of patients with bisphosphonate-associated osteonecrosis: An American Academy of Oral Medicine position paper. *J Am Dent Assoc* 136(12):1658-68, 2005.
10. Migliorati C, Siegel M, Elting L, Bisphosphonate-associated osteonecrosis: A long-term complication of bisphosphonate treatment. *Lancet Oncol* 7(6):508-14, 2006.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Cesar A. Migliorati, DDS, MS, PhD, NSU College of Dental Medicine, 3200 S. University Drive, Fort Lauderdale, Fla., 33328.

CDA JOURNAL, VOL 36, Nº10

Immunosuppressants

NITA CHAINANI-WU, DMD, MS, PHD, AND TIMOTHY C. WU, DMD, MS

ABSTRACT This paper provides a brief introduction to some of the common immunosuppressants used in oral medicine, the prevention and treatment of oral adverse effects of immunosuppressants, and considerations for dental treatment in patients taking immunosuppressants.

AUTHORS

Nita Chainani-Wu, DMD, MS, PHD, is a health sciences assistant clinical professor, Orofacial Sciences Department, University of California, San Francisco; a research associate and project director at the Preventive Medicine Research Institute, Sausalito Calif.; and in private practice, oral medicine in Sunnyvale, Calif.

Timothy C. Wu, DMD, MS, is in private practice, periodontics, in Sunnyvale, Calif.

We live in a world where it appears that "we" and "the environment" are clearly separated. On closer inspection, that separation is not all that clear. Are the microorganisms we call "normal flora" that populate our bodies part of us or the environment? We carry on and within our bodies more bacteria than cells. And this is when we apparently are in perfect health. When does the food ingested go from being a part of the environment to a part of our "self"?

The immune system has the seemingly impossible task of distinguishing our "self" from "nonself." The most obvious "nonself" entities include pathogenic microorganisms that are not part of the normal flora. The immune surveillance also helps keep the amount and proportion of normal flora in check. Most of the time it does these things very well. And of course, we want our immune system to keep doing that very well. A good immune system is the foundation of good health.

However, sometimes our immune system seems to stop recognizing some part/parts of our body as "self" and starts attacking these tissues. This can result in a spectrum of conditions broadly called autoimmune diseases. When this happens, a suppression of the immune system can help control these autoimmune diseases. Some of the well-known autoimmune diseases include rheumatoid arthritis, lupus erythematosus, multiple sclerosis, and Hashimoto's disease.

Also, in some individuals the immune system can react strongly against substances that don't have much potential to otherwise be harmful such as dust mites, peanuts, pollen, and many others. This strong immune reaction can be very harmful — even life threatening — and this can be in response to benign substances that most other people can tolerate without any harmful effects.

The management of such allergic reactions (including allergy-induced asthmatic reactions) may include the use of immunosuppressive medica-

CDA JOURNAL, VOL 36, Nº10

TABLE 1

Systemic Immunosuppressant Medications Used in the Treatment of Oral Diseases

Name of Medication	Indications in Oral Diseases	Common Adverse Effects
Glucocorticosteroids[1] e.g., prednisone	Pemphigus vulgaris, mucous membrane pemphigoid, oral lichen planus, erythema multiforme, lichenoid drug reactions, major aphthous ulcerations, Behçets syndrome.	Short-term use (<3 weeks): insomnia, mood changes, fluid retention, weight gain, hyperglycemia. Long-term use: osteoporosis, hypertension, hyperglycemia, gastrointestinal disturbances, delayed healing, increased risk of infections, aseptic necrosis, cataracts, psychiatric problems, suppression of the hypothalamus-pituitary-adrenal axis.
Azathioprine[2]	Used as a steroid-sparing agent in combination with systemic glucocorticosteroids for long-term use in chronic conditions like pemphigus vulgaris, mucous membrane pemphigoid, lichen planus, or recurrent major aphthous ulcerations.	Bone marrow suppression especially in individuals with low expression of TPMT (thiopurine methyl transferase); hepatotoxicity, gastrointestinal disturbances, increased risk of hematological malignancies and infections.
Mycophenolate mofetil[3]	Used as a steroid-sparing agent in combination with systemic glucocorticosteroids for long-term use in chronic conditions like pemphigus vulgaris, mucous membrane pemphigoid, lichen planus, or recurrent major aphthous ulcerations.	Gastrointestinal disturbances, bone marrow suppression, genito-urinary effects, increased risk of infections.
Cyclophosphamide[4]	Wegener's granulomatosis, usually in combination with prednisone for induction of remission.	Bone marrow suppression, increased risk of infections and malignancies, mucositis, renal toxicity, gastrointestinal disturbances, hepatotoxicity, urinary system effects and respiratory system effects.
Methotrexate[4,5]	Wegener's granulomatosis, usually in combination with prednisone for maintenance of remission. In less severe cases it may be used for induction of remission instead of cyclophosphamide.	Hepatotoxicity, mucositis, bone marrow suppression, increased risk of infections and malignancies.

tions, along with avoidance of the allergens, depending on the severity and the chronicity of the conditions.

The other situation when suppression of the immune system is desirable is when a person receives an organ or hematopoeitic cell transplant. The immune system's normal function of attacking nonself results in an attack on the transplanted tissue and a subsequent rejection.

Therefore, in case of autoimmune diseases and organ and hematopoeitic cell transplantation, immune suppression is desirable. Transplant patients are routinely on immunosuppressant medications, and individuals with allergies and autoimmune diseases may be on immunosuppressants depending on the chronicity and severity of their conditions.

This paper provides a brief introduction to some of the common immunosuppressants used in oral medicine, the prevention and treatment of oral adverse effects of immunosuppressants and considerations for dental treatment in patients on immunosuppressants.

Common Immunosuppressants Used in Oral Medicine

A number of autoimmune inflammatory conditions affect the oral mucosa, and depending on the severity and chronicity of these conditions, the use of immunosuppressant medications may be indicated.

Due to the possibility of adverse effects with use of these medications, especially in those with underlying medical conditions, the benefits versus the risks should be carefully considered before use and only those clinicians with training and experience in use of these medications should prescribe them. When dealing with systemic conditions that affect the oral cavity (e.g., pemphigus vulgaris, Wegener's granulomatosis) and with patients with serious or complex medical conditions, it is appropriate to involve the patient's physician(s) in a team approach for management of the patient.

TABLE 2

Use of Immunosuppressants for Treatment of Some of the More Common Oral Mucosal Conditions

Diseases Affecting the Oral Mucosa	Treatment Options Using Immunosuppressive Medications
Aphthous ulcers	Patients with frequent, multiple or major aphthous ulcerations may benefit from treatment with glucocorticosteroids. Topical preparations such as fluocinonide 0.05% or clobetasol 0.05% ointment mixed in equal parts with orabase B, applied to the affected areas at the first symptom of an impending ulceration may cut down healing time significantly, and may be all that is required for most patients with this condition. Intralesional steroids such as betamethasone for large painful ulcerations can be helpful to hasten healing. For severe flares with multiple ulcerations, systemic corticosteroids can be used, prednisone 40 mg to 60 mg daily for up to a week is usually sufficient. However, for very frequent recurrences of severe flares a more customized treatment plan may be required with consideration of longer term treatment with prednisone along with a steroid-sparing immunosuppressive agent.
Oral lichen planus, mucous membrane pemphigoid	These diseases maybe well-maintained with topical glucocorticosteroids, such as fluocinonide 0.05% or clobetasol 0.05% ointment mixed in equal parts with orabase B, and/or a mouthrinse such as elixir of dexamethasone 0.5 mg/5 ml. For initial control of symptoms and for occasional flare-ups a short course of prednisone 40 mg to 60 mg daily for about 1 week can be helpful (FIGURES 1A–B). In more severe disease, a longer course of prednisone in combination with a steroid-sparing immunosuppressive agent such as azathioprine or mycophenolate mofetil may be necessary.
Oral erythema multiforme	In many cases oral erythema multiforme responds dramatically to systemic glucocorticosteroids and a short course of prednisone 40 mg to 60 mg daily for about 1 week can result in significant improvement or complete resolution. For very frequent recurrences or a chronic presentation a longer course of immunosuppressants can be considered or in cases of herpes-associated erythema multiforme prophylactic anti-virals can be used.
Hypersensitivity reactions	These are treated by discontinuation of the agent triggering the hypersensitivity reaction. Topical or systemic glucocorticosteroids can be used to hasten resolution of symptoms if necessary.
Pemphigus vulgaris	Long-term immunosuppression is generally required for treatment of pemphigus vulgaris. Relatively high starting doses of prednisone (60 mg to 80 mg daily) may be needed, along with a steroid-sparing immunosuppressive agent such as azathioprine (50 mg to 100 mg daily) or mycofenolate mofetil (2 g to 3 g daily). In case of very severe disease higher initial doses may be needed. Taper of the medications is done slowly and is based on clinical response. Close monitoring is needed especially until the disease process and medications are stabilized. The topical steroid pastes and mouthrinse mentioned above can also be used for control of oral lesions in addition to the systemic medications if necessary.
Wegener's granulomatosis	For induction of remission, cyclophosphamide in combination with gluocorticosteroids is used. In less severe cases methotrexate can be used instead of cyclophosphamide. For maintenance therapy methotrexate or azathioprine alone or usually in combination with glucocorticosteroids are used. In the case of isolated upper respiratory tract involvement cotrimoxazole is a treatment option. Doses vary significantly based upon disease severity.[4]

The systemic immunosuppressant medications commonly used in oral medicine, common indications, and common adverse effects are summarized in TABLES 1 AND 2. Periodic tests including, complete blood counts and liver function tests are necessary to monitor for these adverse effects.[2-4] For long-term glucocorticosteroid use, baseline tuberculin testing as well as baseline and periodic tests of bone mineral density (DEXA scans), blood pressure monitoring, blood glucose monitoring and periodic eye exams are recommended.[1]

Topical preparations of immunosuppressant medications including glucocorticosteroids, cyclosporine and tacrolimus are also used for treatment of oral inflammatory conditions in order to avoid the side effects associated with systemic use.

Oral Adverse Effects of Immunosuppressants Medications

Some oral adverse effects are commonly seen with certain immunosuppressants.

Cyclosporin-induced gingival hyperplasia is a well-known adverse effect of this medication, which is commonly used post-transplantation.[6-8] It can be prevented with good oral hygiene and plaque control.[9,10] Treatment includes scaling and surgical

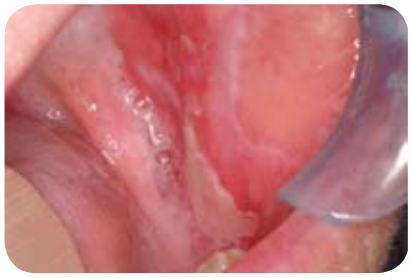


FIGURE 1A. Oral lichen planus before treatment with prednisone (60 mg per day for one week).

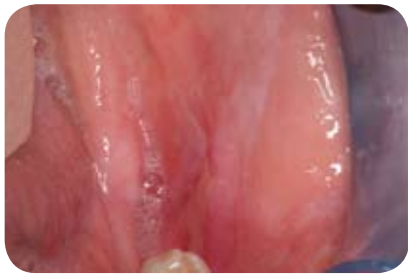


FIGURE 1B. Oral lichen planus after treatment with prednisone (60 mg per day for one week).

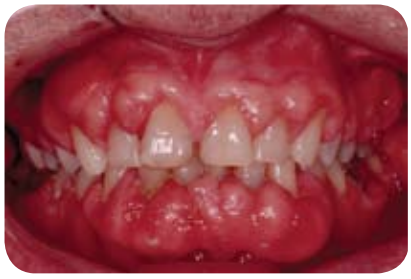


FIGURE 2A. Cycloporin-induced gingival hyperplasia before surgical periodontal treatment.

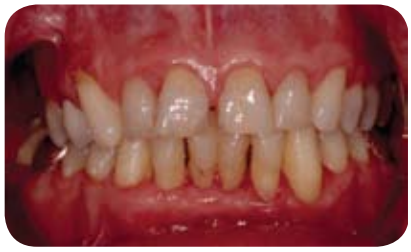


FIGURE 2B. Cycloporin-induced gingival hyperplasia after surgical periodontal treatment.

excision if necessary[11-13] (**FIGURES 2A–B**).

Use of topical and inhalation glucocorticosteroids can predispose to development of oral candidiasis.[14] This can be prevented by applying topical steroids only on the affected areas on the oral mucosa in the smallest amount necessary, and after use of inhalation steroids rinsing out the mouth with water or a mouthrinse. Oral candidiasis is treated with topical anti-fungals (e.g., nystatin, clotrimazole) or systemic anti-fungals (e.g., fluconazole, ketoconazole).

Methotrexate used both for treatment of malignancies and in lower doses for rheumatoid arthritis, psoriasis and other conditions commonly causes oral ulcerations.[15] This can be prevented and/or treated by use of supplemental folic acid or folinic acid. However, in severe cases of methotrexate-induced oral ulcerations, decreasing the dose or discontinuation of the medication may be necessary.

Cyclophosphamide is used in cancer chemotherapy and also in some autoimmune or inflammatory conditions. Oral ulcers and loss of taste are common side effects of this medication, which generally resolve after completion of treatment.[4]

Considerations for Dental Treatment of Patients on Immunosuppressive Medications

The underlying reasons for immunosuppressive treatment are very diverse, and patients taking these medications range from being in relatively good health to being seriously ill.

Cancer chemotherapeutic agents also have the side effect of immunosuppression and patients undergoing chemotherapy for malignancies are immunosuppressed to varying degrees depending on the treatment protocol.

The medical history of patients on immunosuppressive medications, including the underlying medical problems, as well as dose and duration of immunosuppressive therapy is very important in evaluating possible risks during dental treatment.

Depending on these factors, the patient's susceptibility to infections and bleeding, and the ability to tolerate stress and medications may vary. The need for pre- or perioperative medications such as antibiotics or glucocorticosteroid supplementation, and the need for laboratory evaluations also vary based on these factors as well as on the extent of the planned dental surgical procedures.

For routine minor dental procedures, perioperative glucocorticosteroid supplementation is not recommended for patients with current or recent use of glucocorticosteroids. The usual daily dose of glucocorticosteroid should be taken prior to (within two hours before) the dental procedure, which, preferably, should be scheduled in the morning. However, for extensive dental procedures and for surgical procedures, perioperative glucocorticosteroid supplementation is recommended for patients with current or recent corticosteroid use. The details on glucocorticosteroid supplementation are beyond the scope of this paper, however relevant published recommendations are included in the bibliography.[16-21]

A consultation with the patient's physician(s) may be necessary to get a clear understanding of the patient's medical history and current treatment, as well as suggestions on how to medically compensate for dental procedures that may have an adverse medical impact, particularly in those patients who require extensive dental surgical procedures. Such consultations can also be helpful in making decisions on the appropriate perioperative, short-term or long-term medications for patients with complex medical histories and/or multiple medication use.

Adjustment of the usual dosage of commonly prescribed medications in dentistry may be needed in some patients, particularly those with a relative contraindication to the drug, and/or compromised renal or hepatic function. The patient's physician(s) can calculate the adjusted dose for the patient based on current renal and/or hepatic function or other relevant parameters. Periodic laboratory tests may also be necessary during the time of administration of the

drug, and the dentist and physician can work together to monitor the therapeutic effects of the drug and any adverse effects requiring modification of the dosage.

In case of interaction of necessary medications with the patient's current medication(s), in some situations the patient's physician may be able to incorporate the needed medications; this may involve a temporary or a longer-term change in the patient's other medications, if appropriate. ■■■■

REFERENCES

1. Jackson S, Gilchrist H, et al, Update on the dermatologic use of systemic glucocorticosteroids. *Dermatologic Therapy* 20(4):187-205, 2007.
2. Wise M, Calle JP, Azathioprine: A guide for the management of dermatology patients *Dermatologic Therapy* 20(4):206-15, 2007.
3. Zwerner J, Fiorentino D, Mycophenolate mofetil. *Dermatologic Therapy* 20(4):229-38, 2007.
4. White ES, Lynch JP, Pharmacologic therapy for Wegener's granulomatosis. *Drugs* 66(9):1209-28, 2006.
5. Bangert CA, Costner MI, Methotrexate in dermatology. *Dermatologic Therapy* 20(4):216-28, 2007.
6. Rateitschak-Plüss EM, Hefti A, et al, Initial observation that cyclosporin-A induces gingival enlargement in man. *J Clin Periodontol* 10:237-46, 1983.
7. Tyldesley WR, Rotter E, Gingival hyperplasia induced by cyclosporin-A. *Br Dent J* 157:305-9, 1984.
8. Seymour RA, Jacobs DJ, Cyclosporin and the gingival tissues. *J Clin Periodontol* 19:1-11, 1992.
9. McGaw T, Lam S, Coates J, Cyclosporin-induced gingival overgrowth: Correlation with dental plaque scores, gingivitis scores, and cyclosporin levels in serum and saliva. *Oral Surg Oral Med Oral Pathol* 64:293-297, 1987.
10. Seymour RA, Smith DG, The effect of a plaque control program on the incidence and severity of cyclosporin-induced gingival changes. *J Clin Periodontol* 18:107-10, 1991.
11. Kantarci A, Cebeci I, et al, Clinical effects of periodontal therapy on the severity of cyclosporin A-induced gingival hyperplasia. *J Periodontol* 70:587-93, 1999.
12. Pernu HE, Pernu LM, Knuuttila ML, Effect of periodontal treatment on gingival overgrowth among cyclosporine A-treated renal transplant recipients. *J Periodontol* 64:1098-100, 1993.
13. Mavrogiannis M, Ellis JS, et al, The efficacy of three different surgical techniques in the management of drug-induced gingival overgrowth *J Clin Periodontol* 33:677-82, 2006.
14. Chainani-Wu N, Silverman S Jr, et al, Oral lichen planus: Patient profile, disease progression and treatment responses. *J Am Dental Assoc* 132:901-9, 2001.
15. Kalantzis A, Marshman Z, et al, Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 100:52-62, 2005.
16. Gibson N, Ferguson J, Steroid cover for dental patients on long-term steroid medication: Proposed clinical guidelines based upon a critical review of the literature. *Br Dent J* 197(11):681-5, 2004.
17. Little J, Falace D, et al, Dental management of the medically compromised patient, sixth ed. Copyright 2002, Mosby, Inc.
18. Coursin D, Wood K, Corticosteroid supplementation for adrenal insufficiency. *JAMA* 287(2): 236-40, 2002.
19. Miller C, Little J, Falace D, Supplemental corticosteroids for dental patients with adrenal insufficiency, reconsideration of the problem. *J Am Dent Assoc* 132:1570-9, 2001.
20. DeRossi S, Glick M, Lupus erythematosus: considerations for dentistry. *J Am Dent Assoc* 129:330-9, 1998.
21. Salem M, Tainsh R, et al, Perioperative glucocorticoid coverage, a reassessment 42 years after emergence of a problem. *Ann Surg* 219(4):416-25, 1994.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Nita Chainani-Wu, DMD, MS, PhD, 693 East Remington Drive, Suite B, Sunnyvale, Calif., 94087.

CDA JOURNAL, VOL 36, Nº10

Dentist/Pharmacist Relations: Professional Responsibility, Scope of Practice, and Rational Prescription Writing

DEBRA BELT

ABSTRACT Earlier this year, CDA engaged the California Pharmacists Association in discussion about the relationship between dentists and pharmacists and the most efficient ways to handle prescriptions. Professionals agree that the situation where a pharmacist fails to fill a dentist-written prescription does not occur frequently. However, when it does occur, all parties — the dentist, the pharmacist and the patient — are challenged. This discussion led to the following interview.

AUTHOR

Debra Belt is managing editor of *CDA Update*.

INTERVIEWEES

Peter L. Jacobsen, PHD, DDS, for 25 years directed the oral medicine clinic at University of the Pacific Arthur A. Dugoni School of Dentistry and is currently an adjunct professor in the Department of Pathology and Medicine. He serves as vice chair of the ADA Council on Scientific Affairs and is a diplomate of the American Board of Oral Medicine. He is the author of the "Little Dental Drug Booklet," a succinct guide to dental therapeutics and over-the-counter dental products. He has a private practice in San Francisco.

Paul W. Lofholm, PHARMD, FACA, FACVP, is a clinical professor of pharmacy at University of California, San Francisco, and an adjunct clinical professor of pharmacy at University of the Pacific. He is president of the California Pharmacists Association and his appointments include vice president of clinical affairs for the American College of Apothecaries. His published writings include the chapter on Rational Prescribing and Prescription Writing in "Basic and Clinical Pharmacology" 10th edition edited by Bertram G. Katzung, MD, PhD. Dr. Lofholm is the owner of Ross Valley Pharmacy in Larkspur and Golden Gate Pharmacy in San Rafael.

Let's begin with talking about the shared interest of both professions to ensure appropriate care for patients.

Q How do patients benefit from a shared responsibility in properly prescribing and dispensing drugs? Is there a system of checks and balances in play?

DR. LOFHOLM: In terms of benefits to patients, the health care system has always had a system of checks and balances. The prescriber, in this case the dentist, has the responsibility to make the diagnosis, establish the therapeutic goals, and select the appropriate therapy for that purpose. This may or may not generate a prescription. Health care providers don't always prescribe drugs; other kinds of therapy could be education or referral, surgery, or other such things.

Then the prescription is given to the pharmacist either directly from the dental office or from the patient, and the pharmacist's responsibility is to verify and validate the prescription given whatever clinical data is available. Is it the right patient? Is it the right drug? Is it the right dose?

The pharmacist has equal responsibility with the prescriber in terms of what the patient ultimately gets. The pharmacist is the last person on the health care team to make sure that the patient is getting what is intended.

Historically, pharmacists compounded prescriptions. In doing so, they prevented obvious overdoses because of decimal errors or therapeutic incompatibilities. We've taken that secondary role as oversight, if you will, and as the last checkpoint. Our job is to in-

Drs. Paul W. Lofholm (left) and Peter L. Jacobsen. (*Photographs by Charr Crail*)

terpret what the dentist prescribes, to validate the order to extent that we can, and to properly label, counsel, and advise the patient on how to use the medication.

DR. JACOBSEN: On the dentists' side of things, we do have the responsibility, as previously mentioned, to make the diagnosis and when necessary write the appropriate prescription. We depend greatly on the pharmacist — I like to think not to interpret the prescription because it should be clearly written — but certainly as counselor to the patient and dentist about safety, drug interactions, and things we may not be aware of because, as you know, dentistry and medicine, and pharmacy are getting incredibly complex these days. Dentists and physicians depend on pharmacists for their special knowledge not only in understanding and dispensing drugs, but also in advising the patient and the dentist relative to the safety, complications, or potential problems.

DR. LOFHOLM: In that regard, a pharmacist should have a complete drug history and balance off the new prescription against that drug history. Likewise, the dentist has a responsibility to do a drug history as well. Drug interactions are particularly important, and any questions about this are essential communication points for dentists and pharmacists.

Q What do dentists need to understand about the responsibilities, obligations, and laws governing the profession of pharmacy?

DR. LOFHOLM: Let's start very general. Health professionals are licensed to prescribe medications. If you consider a broad approach, they can prescribe anything, provided it is within their scope of practice, including training, to use the drug. I don't have a problem with dentists prescribing a drug as long as they understand what they are doing. The classic issue from an ethical point of view is a dentist who prescribes birth control pills for his dental assistant. Is that appropriate? I think you get where I am coming from.

Dentists usually write prescriptions to be filled only once. Acute pain and antibiotics are typically what's used. We're not used to seeing dentists write prescriptions for chronic disease. However, I do have a dental pain expert in my community, and I would expect her to prescribe medication for chronic pain such as TMJ; but this not a typical situation. When I see a prescription from a dentist, it's usually a single fill for an acute episode. Once we enter the chronic therapy arena, we have a monitoring piece that we need to look at.

So, the pharmacist would generally ask the question: Is the patient being monitored or not? As long as there is an understanding that there is an ongoing relationship, I personally don't have a problem with a dentist prescribing whatever. If there is a dentist prescribing a drug for an indication that is not in the package insert, the official FDA labeling, then it is incumbent upon the prescriber to be able to justify his or her actions. This does not mean that what they did was wrong, but if there is a question of liability, the burden of proof is upon the prescriber and secondarily upon the pharmacist. Why did the prescriber do this and why did the pharmacist dispense it? These are the questions that would be asked. But we have plenty of literature that says people do things "off label" and that could be a gray area.

Because I'm not used to filling prescriptions for dentists on a chronic basis, that might raise red flag. If a prescription comes to my desk, and I have a question, I would do one of two things. If I do not know the dentist, I would make a judgment that it should or should not be filled, given the equal responsibility question. Or, I could telephone the dentist and ask: 'What are you trying to accomplish with this prescription?'

What we need to establish is whether the prescription is safe and appropriate for the patient or not, hence the inquiry. That's really where we are coming from.

DR. JACOBSEN: I agree with what you describe. I understand there are two questions that come up regularly. One is about legibility, and of course prescriptions should be legible and accurate. I think dentists understand and appreciate any communication about this. The key thing is scope of practice. Even dentists have a difficult time keeping up with scope of practice in dentistry. As you defined, scope of practice not only involves what's taught in dental school, but also what is learned through experience, as well as additional training. I would think it is a challenge for a pharmacist to keep up on scope of practice for dentists as well as pharmacists and physicians.

How does a pharmacist define scope of practice?

DR. LOFHOLM: Generally, the law reflects on dentists working on the oral cavity, oral pathology, and diagnosis. Having said that, what is the relationship between the mouth and the rest of the body? As you know, there are plenty of issues to deal with, from systemic infection to heart disease. So, a pharmacist would not have a problem with mouth-related issues. Beyond that, they may challenge it. That's where we have to understand the groundwork.

If you want to treat pain, one question is: "Where is the pain?" If it's related to the mouth, that's not a problem. If it's related to the knee, that could be a problem. That's the kind of issue we're looking at. Say an ophthalmologist prescribes prednisone to a patient to treat iritis, and three weeks later the patient dies due to the systemic effects of the prednisone. So, those are the kinds of questions we at least ask about. Again, depending on the thoroughness and clinical experience of the prescriber, it may or may not be a problem.

To summarize, the scope of practice for dentists in a typical setting involves treating the oral cavity. It generally does not involve treating systemic diseases or conditions. It is typically a one-time prescription and hence not a chronic-use situation. If the medication does become chronic, a monitoring plan should be in place to access the efficacy and toxicity and should be documented in the patient's chart. This falls with a more medical model and an ongoing chronic-treatment model.

DR. JACOBSEN: To further clarify the pharmacist's role in deciding scope of practice for dentists, as you explained, the pharmacist looks for education and experience to make that definition. That seems reasonable. If it feels like it's out of the scope of practice per the law, the pharmacist will call the dentist and it's incumbent upon the dentist to educate the pharmacist about specific training and background. This is something within the realm of dentistry, which has to do head and neck pain. So this is purely a communication and education issue for everybody.

DR. LOFHOLM: The main issue we need to get across is the communication side.

There may be things I may suggest therapeutically that you have not thought of before. There may be issues you're trying to treat that I have not considered before. As we get into the specialties — it's one thing to talk about the tooth — but for example, what about dry mouth? Is it a systemic cause? It is a local cause? Is it secondary to radiation or secondary to other disease? Because we're close to University of the Pacific and UCSF dental school, we receive prescriptions that are atypical. But these specialists are trying to meet special therapeutic dental needs.

DR. JACOBSEN: I like what you are saying about communication and mutual growth and education as the appropriate way to ensure that things continue smoothly for the safety and benefit of the patient.

Drug interactions are particularly important, and any questions about this are essential communication points for dentists and pharmacists.

Q Can you discuss the scope and obligation of pharmacists in suspected drug diversion?

DR. LOFHOLM: Controlled substances are defined in the law because they have potential for abuse and misuse. The pharmacist's responsibility is to establish a legitimate medical or dental need for the use of these substances. It is illegal to treat an addict. We have some pretty elaborate patient activity. For instance, the patient who brings X-rays to a dentist and says, "See how bad my teeth are, I need Vicodin." The pharmacist has the responsibility to establish that there is a bona fide dentist-patient relationship. I have the responsibility to verify it is a legitimate prescription, including asking for patient identification at the time of dispensing.

Just because a dentist writes a prescription does not mean that I will automatically fill it. Another way to look at the whole question is to ask: Is there any reason why I should not dispense this prescription? There are about 20 reasons why I wouldn't. Diversion is an issue that we are alert to and sensitive about.

There was a case in Fresno where a pharmacist was adjacent to an oral surgeon and the pharmacy's dispensing of controlled substances was high. Is that legitimate? Of course it is. There is not a problem with this situation as long as you understand it. On the other hand, there was a situation in San Francisco where a guy would pick up street people and take them to a physician 20 miles away in San Leandro who would write prescriptions for money. The prescriptions were filled in two pharmacies back in San Francisco. The individuals involved would be given money to buy the drugs, which they would turn over as soon as they walked out of the pharmacy. Then they would receive their payment, which typically was a bottle of wine. These drugs were

ending up in the streets of Seattle and Philadelphia with San Francisco pharmacy names on them. People who want to abuse drugs will go to extremes. Dentists might be hit by these same kinds of individuals. We have to be on guard, frankly.

DR. JACOBSEN: The responsibility of pharmacists has to be emphasized. This is an opportunity for dentists who don't want to be hit upon by these drug-seeking individuals. If something does not seem right, you need to call the pharmacist and say something doesn't seem to fit here. With specific patients, pharmacists can check their records for patterns of abuse.

DR. LOFHOLM: Typically if such a patient is going to work a pharmacist, he would come into the pharmacy with a questionable prescription at 5 p.m. on a Friday after the dentist has shut his door and gone home.

People who want to abuse drugs will go to extremes. Dentists might be hit by these same kinds of individuals.

Q Can you please comment on the broadening scope of dental medicine and give some specific examples of drugs that are appropriate in dental medicine?

DR. JACOBSEN: As Dr. Lofholm said, the most common prescriptions dentists write are for classic antibiotics and pain medications, and they are for short-term use. There are other oral problems that dentists are now trained to treat in dental school as well as the problems they are learning to treat in continuing education and advanced training programs, including oral soft tissue diseases — lichen planus, pemphigoid, and other vesicular bullous diseases — which respond to corticosteroids. Those kinds of prescriptions are appropriate for a dentist to write, but since these are often chronic medications, pharmacists may feel they need additional documentation that these medications are being prescribed appropriately.

The other area where dentists are getting involved, and where training does occur, is in chronic head and neck pain. This is beyond a bad toothache and includes trigeminal neuralgia, atypical migraine, and a variety of head and neck pain a dentist didn't learn about in dental school. Advanced training programs in oral medicine, oral surgery, or periodontics include education about diagnosis and management of such problems. Medications used to treat these problems are things such as Neurontin and antidepressants. These clearly have never been in the scope of practice for dentists in the past, but now are appropriate, depending on the dentist's training.

So, once again, communication is crucial. Once a pharmacist understands the purpose — that this is head and neck area pain — and that the dentist has made the appropriate diagnosis, conducted the appropriate tests, understands the appropriate pharmacologic management, and has in place a way to monitor the chronic use of these drugs, then that's communication and that's education. That's where proper prescribing for the benefit of the patient takes place.

DR. LOFHOLM: The way to facilitate this would be to include in the directions the purpose for the drug that you are treating pain, for example. That would clarify many issues. Antidepressants, for example, can be used for a variety of reasons including depression, but can also affect neuropathic pain.

We are moving in a direction to have the purpose of the medication as part of the directions for use. That would likely solve more than 50 percent of the problems encountered.

DR. JACOBSEN: That's simple and a great idea that dentists may not be aware of.

Regarding off label use, I prescribe Lidex ointment for oral lesions, so it is an intraoral use, but the package says for extraoral use only. I have to explain this to patients. This is a recognized off-label use. Is there a simple way to communicate this to the pharmacist?

DR. LOFHOLM: Putting the use in the directions would be fine. Are you using compounded products, such as Orabase compounded with Lidex?

DR. JACOBSEN: I've given up on requesting compounded medications.

DR. LOFHOLM: Compounded medications can be a secondary problem. Most pharmacies do not compound. I happen to, but most do not. So that's another issue.

If you wanted to get a compounded prescription filled, find a pharmacist who is willing and capable of doing that. As you hand the prescription to the patient, inform him as to where he can get it filled in your locale. That makes it easier for the patient. There are drugs that are sometimes in short supply, are not stocked, or the pharmacist does not have the technique to do what you need. Calling the pharmacist ahead of time to check on availability is helpful and can save everybody time.

But as for prescribing Lidex, if you put in the sig "Apply two times a day for oral lesion." That makes it clear what you have in mind.

DR. JACOBSEN: Usually that will raise a red flag since it's not FDA-approved for oral use.

DR. LOFHOLM: I understand. Here's what's going to happen beyond that. The pharmacist is required to consult with the patient either in writing or orally about how to use the medication. I'm not saying it's done all the time. If they are handed a sheet of paper that says Lidex for topical use — unless it is edited to say it is going to be used in the mouth — that' a problem. It will create doubt in the patient's mind and affect their willingness to use the prescription. The pharmacist can help overcome this problem.

Q What drugs truly fall outside of the scope of dentistry and should not be prescribed?

DR. JACOBSEN: As Dr. Lofholm pointed out earlier, birth control pills. Some dentists unfortunately think it is innocuous enough, since it's not a drug of abuse. So they will prescribe such things as birth control pills, or for that matter even medicine for sinusitis when there is no oral component or complaint. Once again, dentists think it is innocuous because it is not a controlled substance.

What dentists have to understand is that pharmacists have a legal obligation and an ethical obligation to fill only within the scope of training. Even though dentists may be trying to help whomever they are prescribing for — by decreasing medicine costs for example — it's not legal.

What dentists have to understand is that pharmacists have a legal obligation and an ethical obligation to fill only within the scope of training.

DR. LOFHOLM: What I would say is treatment of systemic disease that is not related to the oral cavity. Let's say diabetes. We would recommend that a diabetic patient see a periodontist often. The question is, what about managing the diabetes? It is unlikely to be done by a dentist. Of course with training dentists could — they are no different than other health professionals — they understand the disease process. My bias is, is the patient getting the care he or she needs? If I am satisfied that is happening, then I don't have a problem.

DR. JACOBSEN: Another situation where dentists can overstretch their training is when they are writing a prescription for a medication that is legally within their training but the medication is being used for another part of the body. For instance, a patient with a bad hip getting 100 Vicodin from his dentist even when a physician has already legitimately prescribed the medication because of ongoing pain. The dentist can just be trying to help by saving the patient money by not having to go back to the physician. It may be based on good intentions but it is inappropriate prescribing.

Another example is fungal infections for mucosal surfaces other than the oral cavity. Again, it's inappropriate for dentists to prescribe, even though they can legally prescribe anti-fungal medications.

It is better to disappoint someone early on by not writing an inappropriate prescription rather than disappointing the state dental board later.

One other area where the scope of practice is being challenged is smoking cessation. This is in purview and training of dentists, and they are encouraged to prescribe medications such as Chantix and Zyban in appropriate situations. However, some pharmacists find it uncomfortable to fill these prescriptions. In several states this very situation has been taken all the way to the state medical board for a decision. In all situations when the physician and pharmacist have been adequately informed and educated, dentists have been allowed to write such prescriptions. It seems to be a matter of education.

Q What prescription drugs fall within what could be considered a gray area in relation to dental practice?

DR. JACOBSEN: As far as gray areas, for dentists who are trained in smoking cessation, Chantix is not a gray area. But for other dentists, it is considered a gray area; they don't feel comfortable prescribing it. For many pharmacists, it would be a gray area. I think this is a good current example.

Other instance that could be considered a gray area is prescribing Zoloft for the management of chronic pain or Neurontin for neurological pain. As mentioned before, these are drugs that can be used by dentists, with appropriate training, to treat chronic head and neck pain.

DR. LOFHOLM: The Chantix red flag now is suicidal behavior, which implies that you need to do some psychiatric evaluation before you prescribe the drug. Chantix affects dopamine. Patients who have high dopamine levels may be schizophrenic versus patients with low dopamine levels who have Parkinsonism. So, the issue is that if you prescribe the drug and the patient has a mental health condition, the disease could be exacerbated by using the drug. The problem is that 85 percent of schizophrenics smoke. So a dentist doing a history at the chair and trying to sort this out could say this is a good drug to use. But he has to evaluate the risk.

Whenever we prescribe drugs, we are looking at the benefit versus the risk.

Is it better to have people not smoke? Of course the answer is yes, but I think the problem is that the drugs we give for schizophrenia cause people to want to overcome their dopamine problem. They want to get back to the high they had before and this becomes a pharmacological dilemma. So, from that standpoint, pharmacists may be a little gun-shy to have a dentist prescribe Chantix. Frankly, the drug is not doing very well. It is an interesting concept. You can stop smoking completely if you have psychological weapons do so. Or we can give you substitution therapy using things such as patches or gum, or you can use this new agent. The new agent works 40 percent of the time. It has some efficacy but it also has some risk. Before prescribing or dispensing, we will look at the benefits versus the risks.

Q Please comment on the broadening scope of pharmacy and professional responsibilities.

DR. LOFHOLM: Pharmacists have expanded their scope. For instance, we give immunizations now and manage, under protocol, patients in hypertension or diabetes. Pharmacists can alter the dosage or strength in terms of appropriate use of medications. We can order lab tests in respect to monitoring drug therapy. We are also in the area of medication management. If you look at the RVS code or CPT code, psychiatry manages medications and pharmacists also fall into that same category. If a dentist prescribes Vicodin, it's my responsibility to refill when appropriate — not too early or not too late — for that drug, and in no case after six months. So that's a given and it's universal. The question is could I prescribe Vicodin? We now have midlevel practitioners who actually prescribe controlled substances. Peter Koo, a pharmacy professor and pain-management specialist at UCSF, started this. He manages all the postneurosurgical patients at the university. So pharmacists also get involved in that situation.

Is it likely that a protocol could be developed between a dentist and pharmacist? Possibly. I don't know that I have thought about this before. Take chlorhexidine, for example. Should every patient get chlorhexidine? Should you and I enter into an agreement that under certain circumstances these patients may have it? There is no reason why pharmacists and dentists could not develop a collaborative agreement.

If a dentist prescribes Vicodin, it's my responsibility to refill when appropriate — not too early or not too late — for that drug, and in no case after six months.

Pharmacists also, de facto, may prescribe prophylactic antibiotics because the dentist is not aware of what to do in a certain situation — if a patient can't take penicillin for example. Or, say, I'm across the hall from a cardiologist and I see a lot of patients with hardware and a patient comes to me and says I have to go to the dentist tomorrow and I'm supposed to take an antibiotic. Will you take care of it? I, in essence, prescribe it although I ultimately consult with the dentist or the cardiologist. So we're facilitating the appropriate use of drugs.

DR. JACOBSEN: There is the use of the term "expanding scope of practice." It could be better couched that all health care providers are looking to better serve the medical, dental, and pharmaceutical needs of patients in a knowledgeable, efficient, and economic way. I think we will see more of this blending to optimize the time and the skills and responsibilities of the different specialties of health care. The term "expanding scope of practice" sometimes has a threatening connotation. The intention is that everyone is looking for better ways to serve the health needs of the public.

DR. LOFHOLM: If we look at it from what we teach pharmacy students, which is: Given the diagnosis, what is the appropriate therapy? So patients understand it, understand the prognosis, and can select the appropriate therapy. This doesn't mean they do it, but ultimately in making this validation, they bless it or authorize it.

Q What things (indicators, situations) cause a pharmacist to not fill a prescription?

DR. LOFHOLM: The issue of not filling prescriptions comes down to whether the drug is appropriate for the patient or not. I might ask a patient: What did the dentist tell you about this prescription? Often what we see is a prescriber issuing a piece of paper to get filled. So the question is: Was there communication about this prescription? Now, this does not mean the dentist did not think about it but perhaps just didn't communicate it to the patient. What we are trying to figure out is what happened during this encounter.

If this prescription came from University of the Pacific dental center as opposed to my neighborhood dentist, there is an implied cutting edge. The question becomes: What about this? Is this something he heard at a seminar last weekend? And this is

OK. We then just need to verify what is known about this mediation and if there has been consideration about specifics such as what other drugs the patient is taking.

So, if you are conservative you don't do anything. If you are liberal, you ask questions and, ideally, you ask appropriate questions to resolve the issue. That's where we are coming from.

DR. JACOBSEN: Communication is crucial between the pharmacist and the dentist, but it starts with dentists communicating effectively with their patients and making sure they understand why they are getting the medication. That is just good dental practice.

DR. LOFHOLM: A good reference is the chapter on "Rational Prescription Writing" that is in the *Basic and Clinical Pharmacology*, 10th edition. It goes through the thought process that a prescriber should use.

Q What guidelines do pharmacists use to make their decision to fill or not fill a prescription?

DR. LOFHOLM: Is there any reason why I should not fill this prescription? That is the basic question.

As a rule, a pharmacist will have a higher index of suspicion if a dentist prescribes any medication not associated with the oral cavity until they are satisfied that the prescriber has necessary knowledge. Again, because of the responsibility question: Why did you dispense the medication if you knew the dentist was treating a toenail infection and not an oral cavity infection?

To be fair, because dentists are not prescribing drugs as often as physicians, the pharmacist may spend more time looking at a prescription if it is out of the ordinary. I have no problem with an antibiotic or a narcotic, but once we go off into other areas, then the question is whether the patient is being served. As long as we establish that, it's not a problem.

Q Are pharmacists required to contact dentists if there is a question about the prescription?

DR. LOFHOLM: They are not required to contact dentists. They may look at prescription and say, "I can't fill it" or "I won't fill it."

Most of the time, if I know the patient and have no clue who the dentist is, I will call and say, "Tell me what you are you trying to accomplish here."

Communication is crucial between the pharmacist and the dentist, but it starts with dentists communicating effectively with their patients.

On the other hand, the number of prescriptions filled by pharmacists this decade will double. We're going from 3 billion to 6 billion prescriptions per year. So pharmacies are busy places.

Also, it's my experience that problems are not likely to be therapeutic. The problem is likely to be insurance coverage. When I submit online, my Drug Enforcement Administration number goes in and ultimately my National Prescribers Identification number. If I am not "on the list," the submission will get rejected. So, the issue may be if a prescription is presented to me, and I put in the dentist's number and it gets rejected, I'm not likely to call him or her and say the insurance company won't honor this. Now, I can manipulate the situation, depending upon how well I know the patient. I can ask who the primary physician is and have him or her be the prescriber and let the dentist know.

DR. JACOBSEN: As you said, prescriptions are going to double. There are times when dentists don't know about an NPI number. One area of not getting a response from a pharmacist could be a purely technical aspect of dentists not registering properly. Dentists need to keep up on this.

I would like to pin down a detail. Dentists have the perception that it's legally required for pharmacists get in touch with them if they do not fill a prescription. You're saying that is not so?

DR. LOFHOLM: It's an ethical question, but not a legal question. From a practical standpoint, I'm processing papers across my desk. Some will go through and some will not, for various reasons, one of which may be the problem with a particular drug. Remember, if I am a good businessperson, I will try to figure out who this guy is. And by the way, if you ever have a patient in Marin County, call me. So there may be other reasons to establish this relationship.

The questions that you raise in terms of gray areas, I don't think I've seen for a long time anything in the pharmacy literature about this. We talk about it in terms of physicians and podiatrists a little bit, but I don't think we've seen any literature in terms of dentists. It's an important area to look at. We may need to support your prescribing practices in a scientific way, if we can, especially concerning drugs that are not traditionally prescribed by dentists.

If you look at barriers to getting prescriptions filled, there are many. What we are trying to do is break down these barriers.

Q How can dentists professionally communicate with pharmacists about the drugs they can prescribe?

DR. LOFHOLM: We talked about putting in the sig, the directions for use, including the purpose. Some prescribers don't what to hang their hat on making a diagnosis and that's OK. At least if we get at the purpose, we can do that. We can go so far as to say "If there are any questions about this prescription, call me." This could be done, but we don't see this very often. If a prescription is unusual, that's what I would suggest.

If a case ends up in court, the pharmacist will be asked: 'Did you communicate with this person? Did you establish that this was legitimate?'

Q Are there any proactive measures dentists can take to help ensure that their prescriptions are filled?

DR. JACOBSEN: Make sure the sig is adequately descriptive.

DR. LOFHOLM: If you want to prescribe something that is generally not available, difficult to prepare, or unusual, then you might want to set up a network of pharmacies to handle those situations. It may be necessary to establish places where your prescriptions can be filled, in order to minimize the barriers for the patient.

If you are into exotics, a patient can spend a long time, including days, trying to find a drug. Ultimately, it would be good to try to facilitate getting your order carried out.

My objective is to analyze the order, and if it's appropriate, get it to the patient.

Q Is there anything about this issue you would like to add?

DR. JACOBSEN: Dentists and hygienists may have over-the-counter products they recommend to patients. In this situation, it's valuable to find a local pharmacy that is comfortable stocking the products and know that you'll refer patients there. This helps eliminate a barrier to patients getting what they need.

DR. LOFHOLM: We should at least touch upon that some dentists dispense medications. I think we should reference the rules of dispensing. An endodontist may put tetracycline in an envelope and give it to the patient. This is not appropriate packaging. It's not child proof or resistant to the environment, etc.

Questions Pharmacists Consider Before Dispensing a Medication:

- What are the benefits versus the risks of the medication?
- Is the prescription safe and appropriate for the patient?
- Is there any reason why I should not dispense this medication?
- Is the patient being monitored?
- What is the prescriber trying to accomplish with this prescription?'
- Was there communication with the patient about this prescription?
- Has there been consideration about other drugs the patient is taking?

Tips for Writing Prescriptions

- Make sure the signature is adequately descriptive. Include in the directions the purpose for the drug, especially if it is an "off-label" use.
- Communicate effectively with patients to ensure they understand why they are receiving the medication.
- If prescribing a medication that could be considered unusual, write a note to have the pharmacist call if there are any questions.
- If prescribing medications that are difficult to prepare or unusual, set up a network of pharmacies to handle those situations.

Requirements for Prescriber Dispensing

A dentist may dispense drugs to his or her patients at his or her place of practice if all of the following conditions are met:

- Drugs were not furnished to the dentist by a nurse or physician attendant
- Drugs are necessary for the dentist's treatment of the patient
- Dentist does not keep a pharmacy or other retail operation to furnish drugs
- Fulfills all labeling, recordkeeping, and packaging requirements, including the use of childproof containers
- Dentist does not use a dispensing device, unless the dentist personally owns the device and its contents
- Prior to dispensing, the dentist must offer to give a written prescription to the patient that the patient may elect to have filled by the prescriber or by any pharmacy
- Dentist provides patient with written disclosure that the patient has a choice between obtaining the prescription from the dispensing prescriber or obtaining the prescription at a pharmacy of the patient's choice
- Drugs dispensed by a dentist must be properly labeled with the prescriber's name, patient's name, drug name, date of issue, dosage, quantity, directions for use, expiration date, physical description of the drug, and, if requested by the patient, the condition for which the drug is dispensed. False or misleading information may not be included on a prescription label.
- Drugs to be dispensed must be stored in a secure area, which means a locked storage area within the dentist's office. The keys to the locked storage area shall be available only to staff authorized by the dentist.
- A record or log of drug acquisition and disposition must be maintained by the dentist. Records must be preserved for three years.
- A prescription is not necessary in the sale of controlled substances at retail in pharmacies or wholesale by pharmacies, wholesalers or manufacturers, to dentists and other licensed prescribers.
- A dentist with a current Drug Enforcement Agency registration may dispense to a patient under his or her care a Schedule II controlled substance in an amount not to exceed a 72-hour supply in accordance with normal use.
- For each Schedule II-, Schedule III-, or Schedule IV-controlled substance dispensed by a dentist, the dentist must record the patient's name, address, telephone number, gender, and date of birth; the prescriber's license category (dentist) and license number, DEA registration number, the National Drug Code number of the controlled substance dispensed; quality of controlled substance dispensed; ICD-9 (diagnosis code) if available; number of refills ordered; whether drug was dispensed as a refill or as a first issue; and date of prescription. This information must be reported to the state Bureau of Narcotics Enforcement CURES Program. The reporting requirement does not apply to the administration of the controlled substance. It also does not apply to the dispensing of Schedule IV controlled substance in a quantity limited to an amount adequate to treat for 48 hours or less. Reporting the dispensing of Schedule II- and Schedule III-controlled substances must be done monthly unless a controlled substance is dispensed in a quantity to treat the patient for more the 48 hours, then dispensing must be reported weekly.

Samples

A dentist may furnish to a patient, at no charge, a limited quantity of drug samples if furnished in the package provided by the manufacturer. This transaction should be recorded in the patient record.

Resources

Bureau of Narcotics Enforcement CURES Program

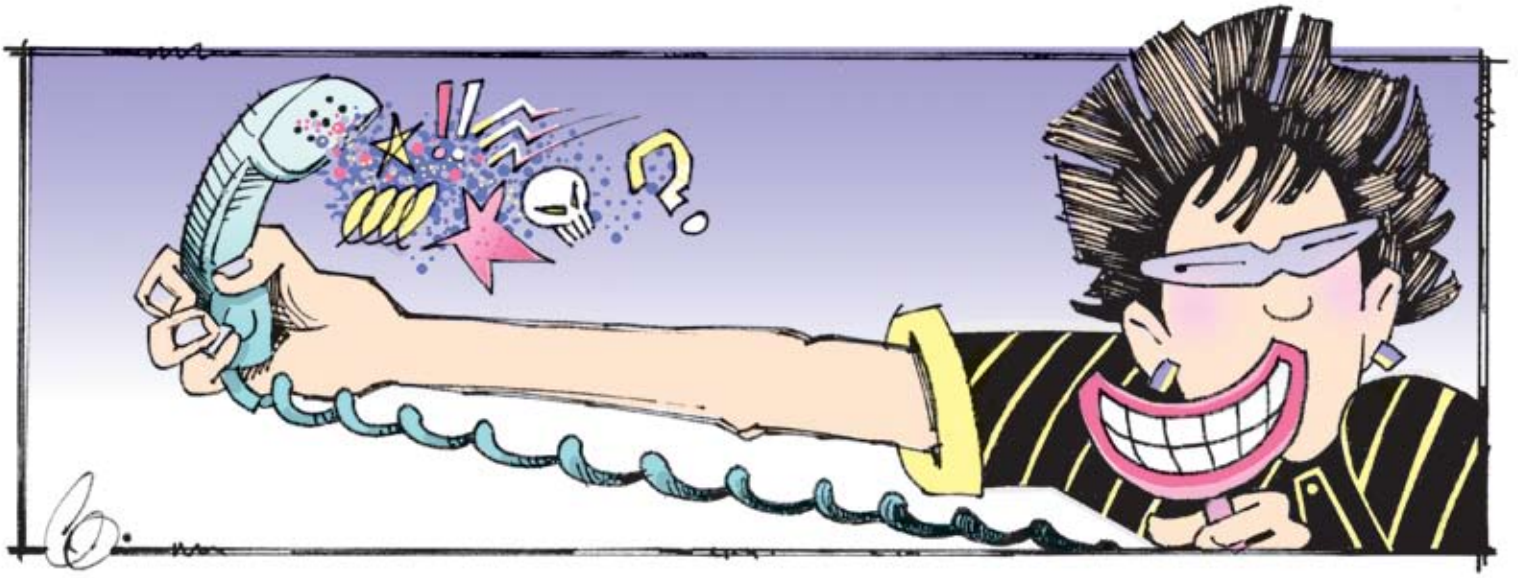
Business & Professions Code Sections 4076, 4077(b) , 4078, 4170(a), 4171, 4172

Health & Safety Code Sections 11158, 11190-11191, 11250-11251

California Code of Regulations Title 16 Section 1356.3

CDA JOURNAL, VOL 36, Nº10

Smile Yourself Sick



Responsible journalism — an oxymoron if ever there was one — has struck again!

Robert E. Horseman, DDS

ILLUSTRATION BY CHARLIE O. HAYWARD

The last time something really good happened in recent memory was when dark chocolate was discovered to be beneficial to your health and the consumption of red wine was proven to add at least a decade to your longevity.

Women immediately rushed out and consumed enough chocolate to initiate zits the size of tennis balls and reduce their wardrobe choices to muu-muus and waterproof ponchos. Both genders downed copious draughts of red wine to the point of wearing funny hats at parties and dancing on bar tops in their underwear. Then you never heard another word about it. It was like a cosmic joke played by bored reporters assigned to the Friday science health section of the paper when they'd rather cover a bikini contest in Santa Monica.

Responsible journalism — an oxymoron if there ever was one — has struck again! This time it affects the dental profession in such a significant way that all our efforts of the last 25 years may have been for naught.

What has been our goal for the last couple of decades? What have we seen as final acceptance of all our efforts? It is life, liberty and the pursuit of the Perfect Smile even if you have to hock grandma's silverware to get it. The firm belief now held by the public is that foremost in their guaranteed entitlements, even above that of their stimulus checks, should be teeth exactly like those of any number of cloned young men and women featured in the celebrity magazines. Fame based entirely on being famous, has evolved from being traditionally Hiltonesque to include an acreage of tattoos formerly the acquisition of alcohol-lubricated seamen, the wearing of clown hats regardless of the occasion and the piercing of body parts that ought not to be violated. The world can consider itself lucky that Jerry Lewis' teeth as featured in *The Nutty Professor* are not a part of the smile du jour. Not yet.

Threatening the entire dental porcelain industry, therefore, is a headline out of

CONTINUES ON 805

CDA JOURNAL, VOL 36, Nº10

DR. BOB, CONTINUED FROM 806

Frankfort, Germany, as reported by United Press International stating "Smiling can hurt your health!" It's true, says Dieter Zapf of the Johann Wolfgang Goethe University, who studied 4,000 volunteers working in a fake call center. Why 4,000 people would volunteer to take fake calls or who would be employed to make the fake calls is not quite clear, but possibly involves unlimited Heineken in large steins.

Zapf's hypothesis is this: People forced to smile and take on-the-job insults suffer more and longer-lasting stress that may harm their health. Right! And stepping in front of a Porsche 911 in top gear on the autobahn would probably do the same, but Dieter couldn't get a grant to research that.

So 2,000 of the volunteers were allowed to respond in kind to abuse on the other end of the line while the other half had to suck it up. I don't know what a German insult would sound like since we didn't study Teutonic slurs during my two years of junior college German, but maybe something like "Du bist ein dumkopf!" would produce stress in a delicate psyche wearing a forced smile. The other half who could respond vigorously with the German equivalent of "I'm rubber and you're glue … " or the classic "I know I am, but what are you?" did experience a brief increase in heart rate, but nothing compared to the bunch with the frozen Jessica Simpson smiles.

In an interview with the German health care magazine *Apotheken Umschau*, Zapf said, "Every time a person is forced to repress his true feelings there are negative consequences." He suggested that people who must keep smiling on the job should get regular breaks to let it out. At least that's what I think he said. There are no German words that translate into this English statement that contain less than 32 consonants and vowels each. If the stricken ones are not allowed time off to release their smiles before rigor sets in, I would have suggested they seek employment elsewhere, like the German DMV, IRS, or Social Security where smiling is traditionally not a job requisite.

The point is, we can't afford to have news releases like this UPI piece appearing in our press. We have too much invested in The Smile now to back off. Zapf should strive to get a real job, letting the phony calls stay in the province of der kinder with their newly acquired texting cell phones.

But how about white wine or milk chocolate? With almonds? Anybody looking into that? ■■■■