Medications' impact on oral health

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ABSTRACT

Background. Over-the-counter and prescription drugs are used frequently, in large quantities and by many adults, particularly by those older than 65 years of age. A number of medications (prescription, over-the-counter, vitamins and minerals, herbal preparations) can affect oral health. With the population's aging, and as more drugs become available, dentists can expect to encounter medication-related oral side effects among their patients.

Types of Studies Reviewed. The author reviewed studies that ranged from case reports to randomly controlled, double-blinded studies. However, in view of the subject matter, the majority of findings are based on case reports.

Conclusions. Since many patients regularly take medications, both prescribed and nonprescribed, dentists always must take a thorough medical history so that they can be aware of medication-related problems and the impact of medications on diagnosis and treatment planning.

Clinical Implications. Dentists must be aware of the potential oral tissue complications that medications can create and develop appropriate treatment plans for their patients that consider the oral health impact of the medications they take.

In 2002, a study published in The Journal of the American Medical Association[1] reported that between January 1998 and July 1999, more than 80 percent of U.S. adults took at least one medication in the week before the survey was conducted, and 25 percent took at least five. In addition, 50 percent of U.S. adults took at least one prescription medication during any given week. The numbers are even higher for adults older than 65 years of age.[1]

Dentists must be aware of the potential oral tissue complications that medications can create.

A number of medications (prescription drugs, over-the-counter drugs, vitamins and minerals, herbal preparations) can affect oral health.[2] With the population's aging, and as more drugs become available, dentists can expect to encounter oral side effects from medication use among their patients. Since many patients regularly take prescription and nonprescription medications, dentists always should take thorough medical histories and be aware of medication-related problems and their potential effects on diagnosis and treatment planning.

This literature review groups medications into the following categories: behavior-altering agents that affect oral hygiene, agents that alter plaque composition and pH, agents that alter salivary flow and pH, agents that affect oral mucosa, agents that alter taste, agents that cause angioedema, agents that alter oral tissue pigmentation, agents that cause gingival enlargement, agents that affect hemostasis, herbal products and agents that affect alveolar bone. Although most of medications' effects on oral tissues are adverse, a few are beneficial.

BEHAVIOR-ALTERING AGENTS

Patients who take for extended periods medications that affect the central nervous system may experience behaviors that have a negative impact on oral health. For example, psychotropic drugs may cause lethargy, fatigue, and memory and motor impairment that

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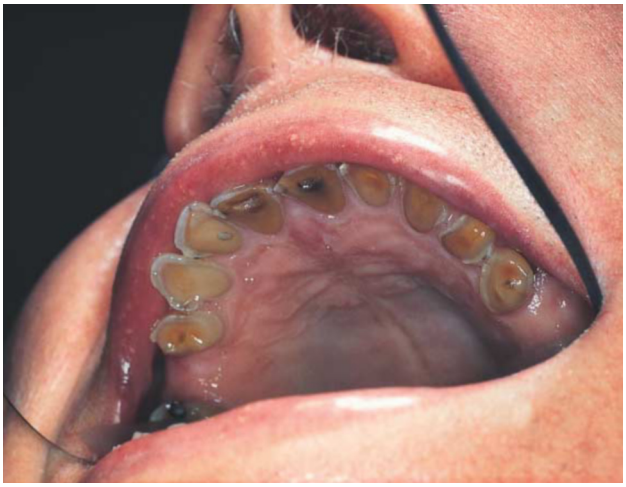

Figure 1. Tooth erosion in the maxillary arch resulting from use of chewable vitamin C tablets but which could be misdiagnosed as resulting from bulimia.

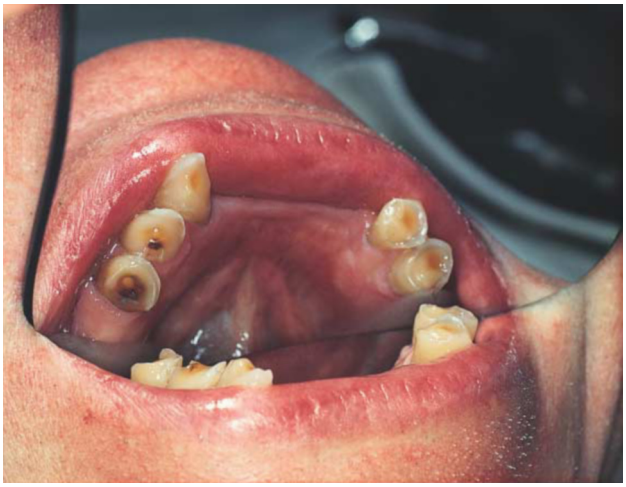

Figure 2. Tooth erosion in the mandibular arch resulting from use of chewable vitamin C tablets but which could be misdiagnosed as resulting from bruxism.

hamper a person's ability to practice good oral hygiene techniques.[3] In fact, adults taking antidepressants and antihypertensives were found to have elevated gingival and plaque index scores.[4] Centrally acting analgesics and antiepileptics also may cause these behavioral effects and have an impact on oral health. Even drugs used for cardiovascular therapy (that is, centrally acting antihypertensive and antidysrhythmic agents) can have neuropsychiatric effects, from depression and sedation to hallucinations and mania.[5]

When considering treatment plans, the dentist must understand the reason for the modification of patients' attitudes and should design oral hygiene programs based on these changes. These patients may benefit from reinforcement of toothbrushing and flossing techniques, instruction on the use of mouthrinses that are effective in reducing gingivitis and an evaluation for xerostomia (for information on evaluating patients for xerostomia, see Navazesh and colleagues[5]).

MEDICATIONS THAT ALTER PLAQUE COMPOSITION AND pH

Many medications alter plaque composition and pH in ways that are harmful to the oral cavity. Sugar sometimes is a major component of antacid tablets, antifungal agents, many liquid medications, cough drops and chewable tablets, including vitamins. In particular, children's liquid and chewable medications often are sweetened with sucrose. The high sugar content of these children's products can lead to an increased susceptibility to caries.[6]

This is especially problematic for children receiving long-term medication therapy for chronic medical problems.[7] Parents should be made aware of the potential oral health consequences of the use of sweetened medications so that they can look for unsweetened alternatives. They also can take steps to reduce the caries risk:

- providing the medication in tablet form whenever possible;
- making sure that children brush with a fluoride toothpaste or chew sugar-free gum after taking medication;
- giving medication at mealtimes instead of between meals;
- not giving medication right before bedtime;
- scheduling regular preventive care for their children.[8]

Although these steps primarily reduce the risk of developing caries, the alteration of plaque composition and retention to tooth surfaces also may have periodontal implications.

I have witnessed in my practice the dramatic oral health effect of frequent chewing of low-pH sugary tablets. A patient came to my practice with concern about the appearance of her teeth, saying that they appeared to be "disintegrating." The patient did not have health or behavioral problems that might be implicated in excessive wear to teeth such as gastroesophageal reflux, bulimia or bruxism. The patient's health history indicated that she was very health-conscious. She exercised, watched her diet and, in general, took good care of herself. As part of her health care regimen, she took two chewable 500-milligram vitamin C tablets daily. The vitamins caused the resting pH

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BOX

CATEGORIES OF DRUGS ASSOCIATED WITH XEROSTOMIA.

- Analgesics (centrally acting)
- Angiotensin-converting enzyme inhibitors
- Anorexiants
- Antacids
- Antiacne agents
- Antiallergy agents
- Antianxiety agents
- Anticholinergic/antispasmodic agents
- Anticonvulsants
- Antidepressants
- Antidiarrheal agents
- Antidysrhythmics
- Antihistamines
- Antihypertensives
- Antinausea agents
- Antiparkinsonism agents
- Antipsychotics
- Bronchodilators
- Calcium channel blockers
- Decongestants
- Diuretics
- Muscle relaxants
- Narcotic analgesics
- Nonsteroidal anti-inflammatory drugs
- Sedatives
- Smoking-cessation agents

of her mouth to be 2.0. This acidic pH, in addition to the sugar challenge, was harmful to her tooth enamel, as can be seen in Figures 1 and 2.

Even health-conscious parents do not hesitate to give cough drops to their children. Some cough drops are vitamin C–enhanced—making them, in effect, a sugar delivery system with an acid pH. Although parents may be more cautious about giving their children candy, cough drops containing vitamin C may create a more serious challenge in the oral cavity than candy may.

Over-the-counter, or OTC, medications and liquid preparations are used daily by some adults as well. These readily fermentable carbohydrates in thick liquid preparations, lozenges and troches may alter the plaque pH significantly, cause root-surface caries in older patients[9] and have an effect on the metabolism of periodontal pathogens. For a review of the role of sugar in the caries process, see the article by Touger-Decker and van Loveren.[10]

Elderly patients may have other risk factors for developing caries, so it is important to develop a treatment plan that addresses their high-risk status. Among the strategies the treatment plan could include are the use of antibacterial agents; the use of high-fluoride dentifrices; the use of supplementary low-dose, high-frequency fluoride rinses; patient education; and shorter recall intervals.[11]

AGENTS THAT AFFECT SALIVARY FLOW AND pH

Xerostomia, commonly known as "dry mouth," is a side effect of approximately 400 medications[12] (Box). Some of the more common groups of medications that cause xerostomia are cardiovascular medications (antihypertensives, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers); antidepressants; sedatives; centrally acting analgesics; antiparkinsonism medications; antiallergy medications; and antacids.[13] When evaluating patients with xerostomia, dentists must consider whether the xerostomia is drug-induced or the result of a health condition. For example, xerostomia also is seen in patients with Sjögren's syndrome, endocrine disorders, nutritional deficiencies, stress or depression, as well as in patients who have undergone radiation therapy or chemotherapy. Clinicians also need to recognize the possibility that complaints associated with perceived salivary dysfunction may be psychogenic.[14] In each case, the dentist needs to understand the cause of the xerostomia to recommend appropriate treatment.

Xerostomia is a concern for dental professionals because saliva plays a major role in protecting both the soft and the hard tissues in the mouth.[15] Oral candidiasis is one of the major side effects of drugs that dry the mouth.[16] In such cases, oral candidiasis may be low-grade and, therefore, lacking in the obvious clinical "cottage cheese" appearance. Rather, the tissues can appear erythematous, especially at the more acute stages of the infection.

Patients with xerostomia also suffer from an increase in the incidence of coronal and root-surface caries,[17,18] as well as excess plaque formation and all of its associated problems. In a study that evaluated the effect of antihypertensives on the oral cavity,[19] two groups of patients were matched for age; sex; number of decayed, missing and filled teeth; and oral hygiene status. Bone loss was similar for both groups; however, the group taking antihypertensives had xerostomia and 60 percent more root-surface caries than did the control group. It can be expected that root-surface caries will be one of the major problems with which dentists will be challenged as the pop-

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TABLE 1

MEDICATIONS THAT CAN CAUSE LICHENOID OR ERYTHEMATOUS LESIONS.

GENERIC NAME	BRAND NAME (MANUFACTURER)*
Antibiotic: Clindamycin	Cleocin (Pfizer, New York)
Barbiturates: Phenobarbital Secobarbital	 Nembutal (Abbott, North Chicago, Ill.), Seconal (Ranbaxy Pharmaceuticals, Princeton, N.J.)
Captopril	Capoten (Mylan Pharmaceuticals, Morgantown, W.Va.)
Carbamazepine	Tegretol (Novartis, Parsippany, N.Y.)
Chlorpropamide	Diabinese (Pfizer)
Diflunisal	Dolobid (Merck, West Point, Pa.)
Flurbiprofen	Ansaid (Pfizer)
Furosemide	Lasix (Aventis Pharmaceuticals, Bridgewater, N.J.)
Ibuprofen	Advil (Wyeth Consumer Healthcare, Madison, N.J.), Motrin (McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, Pa.), Nuprin (Bristol-Myers Squibb, Princeton, N.J.)
Methyldopa	Aldomet (Apotex, Weston, Ontario, Canada)
Phenylbutazone	Cotylbutazone (C.O. Truxton, Bellmawr, N.J.)
Phenytoin	Dilantin (Parke Davis, New York)
Sulfonamides	Azulfidine (Pfizer), Gantanol (Roche, Nutley, N.J.), Gantrisin (Roche)

* Brand names given are examples only. More brand names may be available.

ulation ages and uses more medications that cause xerostomia and its associated problems.[20(p505)] In addition to being at risk of developing caries, patients wearing dentures may have severe denture retention problems as a consequence of decreased salivary flow.

Xerostomia is a major problem in this country today, and its incidence and side effects will continue to increase. Topical and systemic treatments will become more significant in helping the growing population of xerostomic patients.

The following World Wide Web sites offer more information on xerostomia and salivary gland hypofunction:

- Dry Mouth.info ("www.drymouth.info/consumer/default.asp");
- National Institute of Dental and Craniofacial Research (see the index at "www.nidcr.nih.gov/HealthInformation/OralHealthInformationIndex/SalivaAndSalivaryGlandDisorders.htm");
- National Oral Health Information Clearinghouse publication on dry mouth ("www.nohic.nidcr.nih.gov/pubs/drymouth/dmouth.htm");
- Sjögren's Syndrome Foundation ("www.sjogrens.org");
- University of Manitoba Wisdom Tooth Home Page: Dry Mouth ("www.umanitoba.ca/outreach/wisdomtooth/drymouth.htm").

AGENTS THAT AFFECT ORAL MUCOSA

Some medications predispose patients to erythema multiforme or lichenoid lesions. Erythema multiforme appears as symmetrical mucocutaneous lesions. Lichenoid lesions typically appear as white striations (Wickham's striae) on the buccal mucosa and lateral borders of the tongue.[21] These conditions sometimes present as multiple aphthous ulcers. When medication-associated, they usually have an onset from days to weeks after the patient begins taking the offending drug, and they resolve when the patient discontinues use of the drug.

The pathogenesis of lichenoid lesions and erythema multiforme is not well-understood.[21] The drugs most commonly associated with these conditions are listed in Table 1. As can be seen from the table, they include drugs used to treat various medical problems.

Treatment involves consulting with the patient's physician to discontinue use of the drug. In cases in which the condition results in swelling

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TABLE 2

MEDICATIONS THAT CAN CAUSE DYSGEUSIA.

DRUG CATEGORY	GENERIC NAME	BRAND NAME (MANUFACTURER)*
β-adrenergic Blocking Agents	Atenolol Metoprolol	Tenormin (AstraZeneca, Wilmington, Del.), Lopressor (Novartis, Parsippany, N.J.)
Carbonic Anhydrase Inhibitor	Acetazolamide	Diamox (Wyeth, Madison, N.J.)
Cardiovascular Agent	Diltiazem	Cardizem (Marion Merrell Dow, Kansas City, Mo.), Dilacor (Watson, Corona, Calif.), Tiazac (Forest, New York)
Central Nervous System Stimulant	Dextroamphetamine	Dexedrine (GlaxoSmithKline, Research Triangle Park, N.C.)
Nonsteroidal Anti-inflammatory Drugs	Phenylbutazone	Cotylbutazone (C.O. Truxton, Bellmawr, N.J.)
Respiratory Inhalants	Cromolyn	Intal (Fisons, Ipswich, Suffolk, England), Nasalcrom (Pfizer, New York), Opticrom (Fisons)
Smoking-Cessation	Nicotine skin patches	Habitrol (Basel, Summit, N.J.)

* Brand names given are examples only. More brand names may be available.

or ulceration, use of topical corticosteroids is recommended. Topical anesthetic ointments also can be used to treat pain.

AGENTS THAT ALTER TASTE

Taste alteration (dysgeusia) has been associated with some medications, with taste changes ranging from bitter to metallic. Although the mechanism of this effect is unclear, there is some evidence that medications alter taste by affecting trace metal ions, which interact with cell membrane pores (for a review of the subject, see Ackerman and Kasbekar[22]). Drugs sometimes prescribed by dentists that fall into this category are metronidazole, baclofen and chlorhexidine. Dysgeusia also is associated with a number of other drugs administered for medical conditions (Table 2).[22]

AGENTS THAT CAUSE ANGIOEDEMA

Angioedema is a nonpitting edema usually limited to the skin and the mucous membranes of the face and upper respiratory tract. Angioedema may be the result of drug-induced hypersensitivity reactions and can be life-threatening when the mucosal and submucosal tissues of the upper respiratory tract are involved.

Angiotensin-converting enzyme, or ACE, inhibitors (Table 3), angiotensin receptor blockers (Table 3) and nonsteroidal anti-inflammatory drugs, or NSAIDs, have been associated with angioedema,[23] possibly involving bradykinin-induced vasodilation that results in an increase in vascular permeability. This condition most often develops soon after drug use is initiated,[24] but also can follow prolonged use of the drug.[25]

Angioedema also may be triggered by dental materials.[26] Some clinicians might mistakenly think patients taking these drugs have a periodontal or endodontic abscess that is causing facial swelling. However, if the swelling is not dentally related, stopping use of the medication will result in reversal of the edema within hours (depending on the half-life of the drug).

ACE inhibitors also can cause dysgeusia, lichenoid lesions and mucositis. Therefore, dentists should be aware of these possible side effects affecting the oral cavity.

AGENTS THAT ALTER ORAL TISSUE PIGMENTATION

Some medications can cause discoloration of the oral tissues, mimicking Kaposi's sarcoma, lead pigmentation or amalgam tattooing. For example, the tetracycline agent minocycline, which commonly is used to treat acne, can cause an area of black pigmentation in the gingival tissue and underlying alveolar bone. Minocycline has an affinity for bone, which can cause the extraction socket of a patient using this medication to appear black or gray. In addition, minocycline may result in a black-to-gray discoloration of permanently erupted teeth.[27]

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AGENTS THAT CAUSE GINGIVAL ENLARGEMENT

A number of medications may cause gingival enlargement. Phenytoin (Dilantin, Pfizer, New York) was the first drug reported to produce this effect, with the incidence ranging between 3 and 62 percent.[28] Although the occurrence of gingival enlargement with phenytoin is clear, its mechanism of action is not. A number of investigations have suggested a causal relationship between inflammation and gingival enlargement, with the implication made that this enlargement could be minimized or prevented if gingival inflammation were eliminated.[29] It is possible that if patients are placed on a strict program of oral hygiene within 10 days of initiation of therapy with medications promoting gingival enlargement, the occurrence can be minimized.[30,31]

TABLE 3

ANGIOEDEMA–ASSOCIATED DRUGS.

GENERIC NAME	BRAND NAME (MANUFACTURER)*
Angiotensin-Converting Enzyme Inhibitors	
Benazepril	Lotensin (Novartis, Parsippany, N.Y.)
Captopril	Capoten (Mylan Pharmaceuticals, Morgantown, W.Va.)
Enalapril	Vasotec (Merck Human Health, West Point, Pa.)
Fosinopril	Monopril (Bristol-Myers Squibb, Princeton, N.J.)
Lisinopril	Zestril (AstraZeneca, Wilmington, Del.)
Moexipril	Univasc (Schwarz Pharma AG, Monheim, Germany)
Perindopril	Aceon (Solvay Pharmaceuticals, Marietta, Ga.)
Quinapril	Accupril (Parke-Davis, New York)
Ramipril	Altace (King Pharmaceuticals, Bristol, Tenn.)
Trandolapril	Mavik (Abbott, North Chicago, Ill.)
Angiotensin II Inhibitors	
Candesartan	Atacand (AstraZeneca)
Eprosartan	Tevetan (Biovail, Mississauga, Ontario, Canada)
Irbesartan	Avapro (Bristol-Myers Squibb)
Losartan	Cozaar (Merck Human Health)
Telmisartan	Micardis (Boehringer Ingelheim, Ridgefield, Conn.)
Valsartan	Diovan (Novartis)

* Brand names given are examples only. More brand names may be available.

It has been reported that phenytoin has the ability to stimulate bone cell proliferation and differentiation and may mature osteoblastic activities to stimulate bone formation.[32] If so, this may explain the authors' clinical impression of minimal bone loss in patients with phenytoin-induced gingival hyperplasia. This effect also may explain an early report in which a patient receiving phenytoin therapy experienced an unusual phenomenon in orthodontic tooth movement: with no special rapid movement planned, the teeth moved in half the usual time, with no adverse effects on bone or shortening of the roots.[33] In this case, phenytoin may have facilitated bone remodeling. It is possible that although phenytoin produces an increased risk of developing gingival enlargement and its associated gingivitis, it may result in a decreased risk of experiencing the bone loss found in periodontitis.

Gingival enlargement also has been associated with a number of calcium channel blockers, including nifedipine, verapamil, diltiazem, amlodepine and, to a lesser extent, isradipine. A study conducted in England with 911 participants found that nifedipine caused gingival enlargement in 6.3 percent of patients, which was a higher percentage than that for either diltiazem or amlodepine.[34] Examples of this enlargement are shown in Figures 3 and 4.

A proposed mechanism of action of gingival enlargement involves inflammatory factors within the gingival tissue. It has been shown histologically that tissue from a patient treated with nifedipine resembled tissue with an inflammatory-type hyperplasia similar to that described for phenytoin, in which numerous inflammatory cells replaced collagen in connective tissue.[35] This research supported the concept that alteration of the intracellular calcium level in gingival cells by nifedipine, in combination

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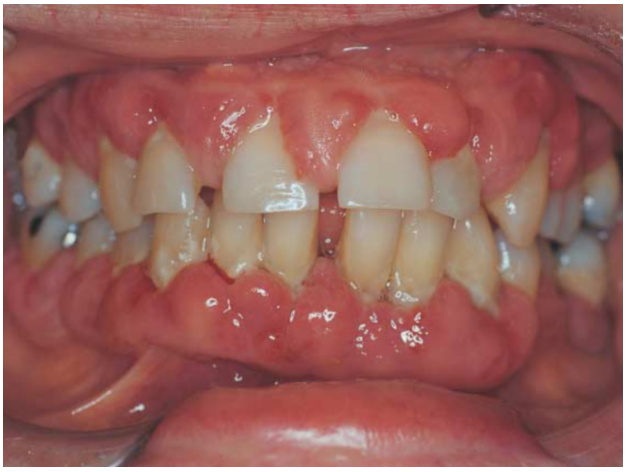

Figure 3. Severe gingival enlargement associated with two years' use of a calcium channel blocker.

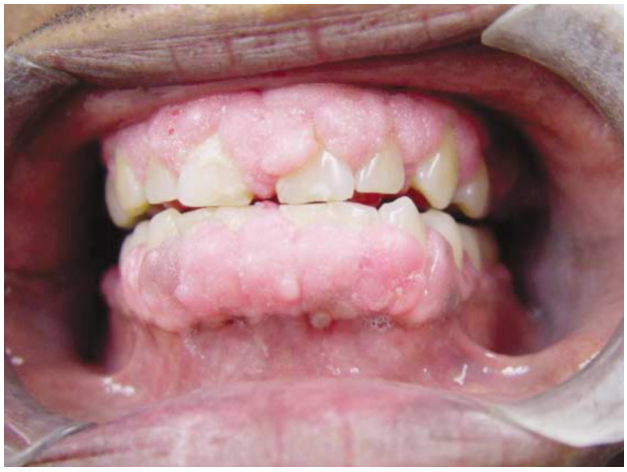

Figure 4. Severe gingival enlargement associated with cyclosporine therapy.

with appropriate local inflammatory factors, is important in eliciting gingival enlargement.

It also has been shown that in patients unable to discontinue nifedipine use, gingival enlargement did not recur after gingivectomy when thorough plaque control was carried out—again supporting earlier reported findings of the role of inflammation and plaque.[36]

Gingival enlargement also has been reported with cyclosporine, with an incidence of approximately 25 percent in patients with multiple sclerosis.[37] There are a number of similarities between the clinical and histopathologic changes seen in cyclosporine- and phenytoin-induced gingival enlargement. Also, both drugs are known to have an effect on the immune system, including the induction of lymphoid hyperplasias and lymphomas.[38] For these patients, meticulous plaque control as a preventive procedure may be of value, as it is for phenytoin-treated patients.[39,40]

AGENTS THAT AFFECT HEMOSTASIS

Abnormal hemostasis is seen with drugs that interfere with platelet function or that decrease coagulation by depressing prothrombin synthesis in the liver. Herbal agents are included in this category. These patients do not necessarily need to stop receiving anticoagulation therapy, but dentists should have a plan for the assessment of such patients. The following steps have been proposed for such a plan:[41]

- identify the reason for the anticoagulation therapy;
- consider the potential risk versus the benefit of altering the drug's regimen;
- know the laboratory tests used to assess anticoagulation levels;
- know the local methods of obtaining hemostasis both intraoperatively and postoperatively;
- consult with the patient's physician.

Abnormal hemostasis is seen not only in patients taking anticoagulants and antithrombic agents but also in patients taking NSAIDs, ginger, gingko biloba and garlic. Additionally, in patients taking warfarin, an increased anticoagulant effect can occur with coadministration of dong quai, danshen and papaya.[42]

HERBAL PRODUCTS

Approximately 25 percent of our population routinely uses herbal products and other dietary supplements.[43] Many of these agents may have adverse effects on oral tissues,[42] as listed in Table 4.

AGENTS THAT AFFECT ALVEOLAR BONE

Long-term use of corticosteroids such as methylprednisolone and prednisone may result in osteoporosis, which is seen mainly in long bones but also can occur in alveolar bone.[44] Similarly, ambulatory patients taking enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital, carbamazepine and primidone have been documented as having lower bone mineral density than those taking non–enzyme-inducing drugs such as valproic acid, lamotrigine, clonazepam, gabapentin, topiramate and ethosuximide.[45]

In contrast, tetracyclines—especially doxycycline—now are known to inhibit pathologically excessive, host-derived matrix metalloproteinase activity associated with periodontal and other diseases. The discovery of the anticollagenolytic

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properties of the tetracyclines was made using an animal model of both pathologically excessive collagenase activity in gingival tissues and periodontal breakdown.[46,47] Treating germ-free and pathogen-reduced rats, inoculated with *Porphyromonas gingivalis*, with a nonantibiotic dose of a tetracycline or chemically modified nonantimicrobial tetracycline significantly inhibited periodontal bone loss.[48]

TABLE 4

SIDE EFFECTS OF HERBAL AGENTS.

HERB	ADVERSE EFFECTS
Ephedra	Hypertension, fast heart rate, anxiety, psychosis, palpitations, stroke
Garlic	Increased bleeding
Gingko Biloba	Immunosuppression, decreased wound healing, liver toxicity
Ginseng	Increased bleeding, elevated blood pressure
Kava	Enhanced effect of sedatives
St. John's Wort	Increased metabolism of other drugs, photosensitivity
Valerian Root	Enhanced effect of sedatives

Inhibition of periodontal bone loss also has been reported in long-term clinical studies.[49] This effect of a subantimicrobial-dose doxycycline has been developed to treat periodontitis and is marketed as Periostat (CollaGenex Pharmaceuticals, Newtown, Pa.).

Antibiotics also have been shown to be of value in arresting bone loss in special types of periodontal disease, such as generalized aggressive periodontitis, localized aggressive periodontitis and refractory periodontitis, with the mechanism of action related to the drugs' antimicrobial effects.[50]

NSAIDs may reduce bone loss in both animal and human models.[51] Epidemiologic studies of the periodontium of patients receiving NSAIDs on a long-term basis for arthritis suggested that they had less alveolar bone loss than a similar population not receiving these medications.[52] The mechanism of action of these agents appears to be related to their effect on prostaglandins.

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CONCLUSION

Since many patients regularly take prescription and nonprescription medications, dentists always must take thorough medical histories and be aware of medication-related problems and their effects on diagnosis and treatment planning. This article identifies and describes drugs that may affect oral health. ■

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