

# Xerostomia

## Etiology, recognition and treatment

JAMES GUGGENHEIMER, D.D.S.; PAUL A. MOORE, D.M.D., Ph.D., M.P.H.

**X**erostomia is defined as a subjective complaint of dry mouth that may result from a decrease in the production of saliva.<sup>1,2</sup> Xerostomia is estimated to affect millions of people in the United States.<sup>3</sup> Studies have found the condition in 17 to 29 percent of sampled populations based on self-reports or measurements of salivary flow rates.<sup>3-7</sup> Complaints of dry mouth generally are more prevalent in women.<sup>1</sup>

The presence of saliva usually is taken for granted, and it is not required for any life-sustaining functions.

**The prevalence of xerostomia and its negative effect on the patient's quality of life make it likely that the practitioner will encounter this condition on a regular basis.**

Nevertheless, its diminution or absence can cause significant morbidity and a reduction in a patient's perceptions of quality of life.<sup>2,3</sup> The primary constituents of saliva are water, proteins and electrolytes.<sup>8</sup> These components enhance taste, speech and swallowing and facilitate irrigation, lubrication and protection of the mucous membranes in the upper digestive tract.<sup>2</sup> Additional physiological functions of saliva provide antimicrobial and buffering activities that protect the teeth from dental caries.<sup>8</sup>

Hyposalivation may occur with the use of medications, as a complication of connective tissue and autoimmune diseases, with radiation therapy to the head and neck, or with a number of other conditions (Box 1).<sup>9-17</sup> Patients initially may be unaware that a reduction in salivary flow is occurring unless some of its complications, such as an increase in cervical dental caries, becomes apparent. Only after the development of symptoms—which may include soreness, burning or difficulty with swallowing—is the patient likely to seek relief from the practitioner.

**Background.** Clinicians may encounter symptoms of xerostomia, commonly called “dry mouth,” among patients who take medications, have certain connective tissue or immunological disorders or have been treated with radiation therapy. When xerostomia is the result of a reduction in salivary flow, significant oral complications can occur.

**Types of Studies Reviewed.** The authors conducted an Index Medicus-generated review of clinical and scientific reports of xerostomia in the dental and medical literature during the past 20 years. The literature pertaining to xerostomia represented the disciplines of oral medicine, pathology, pharmacology, epidemiology, gerodontology, dental oncology, immunology and rheumatology. Additional topics included the physiology of salivary function and the management of xerostomia and its complications.

**Results.** Xerostomia often develops when the amount of saliva that bathes the oral mucous membranes is reduced. However, symptoms may occur without a measurable reduction in salivary gland output. The most frequently reported cause of xerostomia is the use of xerostomic medications. A number of commonly prescribed drugs with a variety of pharmacological activities have been found to produce xerostomia as a side effect. Additionally, xerostomia often is associated with Sjögren's syndrome, a condition that involves dry mouth and dry eyes and that may be accompanied by rheumatoid arthritis or a related connective tissue disease. Xerostomia also is a frequent complication of radiation therapy.

**Conclusions and Clinical Implications.** Xerostomia is an uncomfortable condition and a common oral complaint for which patients may seek relief from dental practitioners. Complications of xerostomia include dental caries, candidiasis or difficulty with the use of dentures. The clinician needs to identify the possible cause(s) and provide the patient with appropriate treatment. Remedies for xerostomia usually are palliative but may offer some protection from the condition's more significant complications.



## BOX 1

## CAUSES OF XEROSTOMIA.

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS

## MEDICATIONS

## Primary Sjögren's Syndrome

## Secondary Sjögren's Syndrome

- Connective Tissue Disease
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Systemic sclerosis
  - Mixed connective tissue disease

## OTHER CONDITIONS

- Radiation Therapy
- Primary Biliary Cirrhosis
- Vasculitis
- Chronic Active Hepatitis
- HIV
- AIDS
- Bone Marrow Transplantation
- Graft-vs.-Host Disease
- Renal Dialysis
- Anxiety or Depression
- Diabetes, Type 1 or 2

## PATHOPHYSIOLOGY

Saliva is produced by the parotid, submandibular and sublingual glands, as well as by hundreds of minor salivary glands that are distributed throughout the mouth. Daily salivary output is estimated to be approximately one liter per day,<sup>17</sup> and flow rates can fluctuate by as much as 50 percent with diurnal rhythms.<sup>18-21</sup> Salivary flow is categorized as unstimulated, or resting, and stimulated, as occurs when an exogenous factor is acting on the secretory mechanisms.<sup>19</sup>

Both the parasympathetic and sympathetic nervous systems innervate the salivary glands. Parasympathetic stimulation induces more watery secretions, whereas the sympathetic system produces a sparser and more viscous flow.<sup>22</sup> Therefore, a sensation of dryness may occur, for example, during episodes of acute anxiety or stress, which cause changes in salivary composition owing to predominant sympathetic stimulation during such periods.

Symptoms of a lack of saliva or oral dryness may be precipitated by dehydration of the oral mucosa,<sup>18</sup> which occurs when output by the major and/or minor salivary glands decrease and the layer of saliva that covers the oral mucosa is reduced.<sup>23,24</sup>

## CAUSES

**Medications.** Xerostomia is a common and significant side effect of many commonly prescribed drugs. Establishing relative incidence rates for

xerostomia for a particular drug, however, is difficult. As with other side effects, reported rates depend on how the information is accessed (direct vs. open-ended questions), the severity of concomitant adverse reactions, over-reporting for new drug entities, the disorder being treated and the dose of the medication. Nevertheless, the risk for xerostomia increases with the number of drugs being taken.<sup>26-28</sup> Older people, therefore, are more likely to be affected. In the geriatric population, drug-induced xerostomia has been reported to contribute to difficulty with chewing and swallowing; this may result in avoidance of certain foods.<sup>29</sup> A case of a patient's inability to dissolve a sublingual nitroglycerine tablet owing to lack of saliva has been described in the literature.<sup>30</sup>

A variety of drugs that have a wide range of therapeutic activities have been reported to cause xerostomia in 10 percent or more of patients (Table).<sup>31,32</sup> Drug-induced hyposalivation also can be an extension of the drug's intended action, as seen with the parasympatholytic agents (such as atropine), or as an anticholinergic side effect with drugs such as tricyclic antidepressants.

**Sjögren's syndrome.** When xerostomia is associated with xerophthalmia, also known as "dry eyes," it may represent a chronic autoimmune condition that is recognized as Sjögren's syndrome, which affects predominantly women after the fourth decade of life.<sup>9</sup> In primary Sjögren's syndrome, the disease is limited to the eyes and salivary glands.<sup>9,10,33</sup> With secondary Sjögren's syndrome, patients also have an autoimmune or connective tissue disease (Table).<sup>1,9,10,33</sup> It is estimated that 15 percent of patients with rheumatoid arthritis, 25 percent of those with systemic sclerosis and 30 percent of those with systemic lupus erythematosus may develop Sjögren's syndrome.<sup>1</sup> Symptoms comparable with those of Sjögren's syndrome also have been reported to occur with fibromyalgia, chronic fatigue syndrome, Raynaud's phenomenon and other conditions that demonstrate the presence of autoantibodies.<sup>10</sup>

The xerostomia that is associated with primary and secondary Sjögren's syndrome has been attributed to the progressive lymphocytic infiltration that gradually destroys the secretory acini of the major and minor salivary glands.<sup>1</sup> Another explanation for the loss of glandular function may be related to an inhibition of nerve stimuli of the glands.<sup>34</sup> It has been suggested that the reduction in secretions first may affect the minor salivary

TABLE

DRUGS ASSOCIATED WITH XEROSTOMIA.*		
CATEGORY	GENERIC NAME	TRADE NAME†
<b>Anticholinergic Agents</b>	atropine belladonna benztropine oxybutynin scopolamine trihexyphenidyl	Atrohist, Lomotil Donnatal, Respa-A.R.M. Cogentin Ditropan Transderm Scop Artane
<b>Antidepressant and Antipsychotic Agents</b> Selective serotonin-reuptake inhibitors  Tricyclic antidepressant  Heterocyclic antidepressants  Monoamine oxidase inhibitors Atypical antidepressants	citalopram fluoxetine paroxetine sertraline venlafaxine amitriptyline desipramine imipramine haloperidol mirtazapine pimozide phenelzine bupropion nefazodone olanzapine	Celexa Prozac Paxil Zoloft Effexor (generic) Norpramin Tofranil Haldol Remeron Orap Nardil Wellbutrin, Zyban Serzone Zyprexa
<b>Diuretic Agents</b>	chlorothiazide furosemide hydrochlorothiazide triamterene	Diuril Lasix HydroDiuril, Dyazide Dyrenium
<b>Antihypertensive Agents</b>	captopril clonidine clonidine/chlorthalidone enalapril guanfacine lisinopril methyldopa	Capoten Catapres Combipres Vasotec Tenex Zestril Aldomet
<b>Sedative and Anxiolytic Agents</b>	alprazolam diazepam flurazepam temazepam triazolam	Xanax Valium Dalmane Restoril Halcion
<b>Muscle Relaxant Agents</b>	cyclobenzaprine orphenadrine tizanidine	Flexeril Norflex Zanaflex
<b>Analgesic Agents</b> Central nervous system/opioids  Nonsteroidal anti-inflammatory agents	codeine meperidine methadone pentazocine propoxyphene tramadol diflunisal ibuprofen naproxen piroxicam	(generic) Demerol Dolophine Talwin Darvon Ultram Dolobid Advil, Motrin Aleve, Naprosyn Feldene
<b>Antihistamines</b>	astemizole brompheniramine chlorpheniramine diphenhydramine loratadine meclizine	Hismanal Dimetane-DX Chlor-Trimeton Benadryl, Dramamine Claritin Antivert

\* Drugs listed have been reported to have a xerostomia incidence of 10 percent or more.<sup>31,32</sup>

† For reasons of space, the name and location of each drug's manufacturer are not listed here. A complete list can be requested from the authors as hard copy or an electronic file.

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TABLE

## DRUGS ASSOCIATED WITH XEROSTOMIA.\* (Continued)

CATEGORY	GENERIC NAME	TRADE NAME
<b>Miscellaneous medications</b> Anorexiant	diethylpropion	Tenuate
Antiacne agent (retinoid)	sibutramine	Merida
Anticonvulsant	isotretinoin	Accutane
Antidysrhythmic	carbamazepine	Tegretol
Anti-incontinence agent	disopyramide	Norpace
Antiparkinsonian agent	tolterodine	Detrol
Bronchial dilator	carbidopa/levodopa	Sinemet
Ophthalmic formulation	ipratropium	Atrovent
Smoking cessation agent	brimonidine	Alphagan
	nicotine	Nicorette gum, Habitrol

\* Drugs listed have been reported to have a xerostomia incidence of 10 percent or more.<sup>31,32</sup>  
† For reasons of space, the name and location of each drug's manufacturer are not listed here. A complete list can be requested from the authors as hard copy or an electronic file.

glands, which can initiate the symptoms of xerostomia.<sup>24,25</sup>

**Radiation therapy.** Radiation therapy of the head and neck regions is employed as a primary, concomitant or adjuvant treatment modality for primary and recurrent tumors in the upper aerodigestive tract. These include squamous cell cancers of the oral cavity, oropharynx, nasopharynx and sinuses; brain tumors; melanomas; lymphomas; and sarcomas, as well as tumors that develop in the salivary glands. Ionizing radiation can injure the major and minor salivary glands; this can lead to atrophy of the secretory components and result in varying degrees of temporary or permanent xerostomia.<sup>17</sup>

**Other conditions.** Diseases with immunological abnormalities other than autoimmunity may be accompanied by Sjögren's-like manifestations or xerostomia (Box 1). Infection with HIV has been associated with arthritides, parotid gland enlargement and xerostomia.<sup>11,35,36</sup> Xerostomia has been reported in 45 to 60 percent of patients who developed chronic graft-vs.-host disease after undergoing allogeneic bone marrow transplantation.<sup>12,37</sup> Loss of saliva and a number of immunological abnormalities also have been implicated as possible complications of silicone breast implants.<sup>13</sup>

Patients undergoing hemodialysis for end-stage renal disease have developed dry mouth and reduced salivary gland function,<sup>14</sup> but these manifestations may be attributed in part to medications being used to treat coexisting conditions. Anxiety, depression or stress also may give rise to subjective symptoms of dry mouth.<sup>38,39</sup>

Patients with diabetes mellitus, particularly those who have poor glycemic control, are more

likely to complain of xerostomia and may have decreased salivary flow.<sup>15,16</sup>

### CLINICAL MANIFESTATIONS

A reduction of saliva may lead to complaints of a dry mouth, oral burning or soreness or a sensation of a loss of or altered taste. Another manifestation may be an increased need to sip or drink water when swallowing, difficulty with swallowing dry foods or an increasing aversion to dry foods.<sup>29</sup> Patients who develop Sjögren's syndrome secondary to a connective tissue disease also may complain of having dry eyes, and progressive parotid gland enlargement may become evident. These initial manifestations may precede clinically apparent alterations of the oral mucosa or any measurable reduction in salivary gland function. As the xerostomia progresses, inspection of the oral cavity may disclose an erythematous pebbled, cobblestoned or fissured tongue and atrophy of the filiform papillae (Figure 1). The oral tissues may be erythematous and appear parched. Palpation of the oral mucosa may result in the finger's adhering to the mucosal surfaces instead of readily sliding over the tissues. Application of a dry cotton swab at the parotid and submandibular duct orifices followed by external palpation of the glands may reveal delayed or inapparent salivary flow from the ducts.

Dental-related findings include evidence of an increased tendency to develop cervical caries and denture discomfort accompanied by loss of retention.<sup>40,41</sup>

Lack of saliva increases susceptibility to infection of the oral cavity and oropharynx by the opportunistic fungus *Candida albicans*, or thrush.<sup>42</sup> Manifestations of oral infection with

Candida include erythema of the oral mucosa; white, curdlike patches that adhere to the mucosal surfaces; and inflamed fissures at the corners of the mouth, a condition called cheilitis.<sup>43</sup>

## DIAGNOSIS

Because of the wide range of flow rates that fall within the normal physiological range,<sup>18-20</sup> it may be difficult to substantiate salivary gland hypofunction in patients who complain of xerostomia. In addition, patients initially may not have a measurable reduction in salivary flow. It has been estimated that a 50 percent reduction in salivary secretion needs to occur before the xerostomia becomes apparent.<sup>19</sup> Asking several questions of the patient regarding symptoms may help confirm salivary gland hypofunction. An affirmative response to at least one of the five following questions about symptoms has been shown to correlate with a decrease in saliva: "Does your mouth usually feel dry? Does your mouth feel dry when eating a meal? Do you have difficulty swallowing dry foods? Do you sip liquids to aid in swallowing dry foods? Is the amount of saliva in your mouth too little most of the time, or don't you notice it?"<sup>44-46</sup>

A number of supplemental tests are available that can be used to confirm the subjective manifestations of xerostomia. Salivary output can be measured, and a collected amount of less than 0.12 to 0.16 milliliters per minute (unstimulated) has been suggested to be the criterion for hypofunction.<sup>21</sup> Imaging modalities, including sialography and scintigraphy, also have been used to examine salivary gland function.<sup>47</sup> Regardless of whether these tests provide definitive results, a patient's report of xerostomia nevertheless may indicate the need for palliative therapy to provide symptomatic relief.

Criteria for the clinical, laboratory and histopathologic manifestations that are consistent with a diagnosis of Sjögren's syndrome recently were revised.<sup>33</sup> Patients who have manifestations of Sjögren's syndrome secondary to rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis may demonstrate a number of clinical abnormalities that are associated with these



**Figure 1. The tongue of a patient with xerostomia showing atrophy of the filiform papillae and the pebbled appearance.**

diseases.<sup>48,49</sup> Clinical laboratory abnormalities may disclose anemia, leukopenia, an increased erythrocyte sedimentation rate and the presence of rheumatoid factor or autoantibodies.<sup>50</sup> A biopsy from the lower lip may reveal focal lymphocytic infiltrates in the minor salivary glands.<sup>33</sup>

## COMPLICATIONS

Saliva consists primarily of water (99 percent) plus a number of proteins and electrolytes.<sup>8</sup> The fluid component contributes to irrigation of the oral cavity and dilution of oral contents. Among the proteins, several mucins assist with the lubrication of the mucosal surfaces.<sup>8</sup> Other proteins may inhibit the growth of microorganisms.<sup>8</sup> The electrolytes contribute to the buffering capacity of saliva and may enhance remineralization of tooth enamel.<sup>8</sup>

The initial reduction in salivary flow may cause only symptoms of a loss of oral moistness and lubrication which, if unpleasant, may lead the patient to seek relief from a health care provider. After further reduction in saliva, however, and as its physiological functions become increasingly impaired, clinical abnormalities may become apparent.

**Dental caries.** A major complication of xerostomia is the promotion of dental caries (Figure 2). This process is accelerated owing to a reduction in oral irrigation and an inability to clear foods from the oral cavity rapidly, particularly if



**Figure 2. A patient with xerostomia who had rampant cervical caries involving the mandibular incisors.**

they contain sugar or acids. In addition, salivary proteins and electrolytes that inhibit cariogenic microorganisms and buffer oral acids, respectively, are diminished. The development of rampant caries, particularly at the cervical area, has been observed within a few weeks after radiation therapy to the head and neck.<sup>8</sup> Although loss of taste does not appear to be a major complaint among patients with xerostomia, the increasing sensation of dryness or difficulty with chewing and swallowing may result in the consumption of softer, more cariogenic foods. Frequently, patients also will resort to excessive consumption of sugar-containing confections or beverages in an attempt to stimulate salivary flow and keep the mouth moist.

**Candidiasis.** Reduction of saliva predisposes patients to an overgrowth of the fungus *C. albicans*.<sup>42</sup> This may be augmented by the use of dentures, by smoking and by the presence of diabetes.<sup>51</sup> The risk of developing candidiasis also increases if the patient has Sjögren's syndrome with a connective tissue disease that is being treated with corticosteroids or other immunosuppressants.

## MANAGEMENT

The general approach to treating patients with hyposalivation and xerostomia is directed at palliative treatment for the relief of symptoms and prevention of oral complications.

If the patient's xerostomia is caused by the side effect of a drug, the dentist can recommend an alternative medication, but this course may not be beneficial if the alternate drug has a mode of action similar to that of the original drug.<sup>31</sup> Modification of the dosage regimen is another strategy that may increase salivary flow.<sup>31</sup> The practice of carrying and sipping bottled water throughout the day, which has become popular, also may offer relief for affected patients. When at home, the patient can hold ice chips in his or her mouth to provide moisture and possibly alleviate symptoms.

A number of over-the-counter products that can function as saliva substitutes have been developed specifically for patients with xerostomia. Available in a variety of formulations—including rinses, aerosols, chewing gum and dentifrices (Box 2)—these products also may promote salivary gland secretions.<sup>52</sup> Commercial mouth rinses that contain alcohol may desiccate the oral mucosa, and patients with xerostomia should avoid using them.

Cholinergic agents stimulate acetylcholine receptors of the major salivary glands. The use of parasympathomimetic drugs such as pilocarpine hydrochloride can stimulate salivary gland secretions and has been shown to be effective for patients with Sjögren's syndrome and for those who have had irradiation therapy or bone marrow transplantation.<sup>37,53-55</sup> Another cholinergic agent, cevimeline hydrochloride, recently was approved for use in patients with Sjögren's syndrome.<sup>56</sup> Patients using parasympathomimetic drugs, however, may experience a number of unpleasant side effects that may limit the efficacy of these medications.<sup>53</sup>

When conventional medical interventions do not provide satisfactory relief, or for patients with xerostomia who prefer alternative medical therapies, acupuncture may be beneficial.<sup>57-59</sup>

Patients who develop candidiasis secondary to xerostomia can be treated with oral or systemic antifungal drugs. Increasing oral moisture also may reduce the prevalence of this opportunistic infection.<sup>52</sup>

A number of therapeutic interventions are

available for the control and prevention of dental caries. These primarily consist of rigorous attention to personal oral hygiene, strict adherence to a noncariogenic diet, placement of sealants and the application of topical fluorides. The latter may be useful if an increased incidence of coronal caries, root caries or both becomes apparent, even when fluoridated community water is available. This strategy may be effective for both prevention of caries and possible reversal of decalcification. Supplements that contain sodium fluoride, acidulated phosphate fluoride or sodium monofluorophosphate are available for professional application as well as for home use.<sup>60,61</sup> These products can be applied in a variety of vehicles, including gels, rinses, lozenges and chewable tablets.<sup>62</sup> Interest now is focused on the use of varnishes that provide prolonged exposure to fluoride.<sup>63,64</sup> This approach may prove to be useful for the prevention of caries associated with xerostomia.

Fluorides also are used for the management of dental caries in patients whose xerostomia has resulted from radiation therapy to the head and neck. The comprehensive care of these patients has been reviewed extensively in a number of publications.<sup>17,65,66</sup>

Patients with complete dentures who experience xerostomia are more likely to develop other complications, including pain from denture irritation and loss of retention.<sup>31,41</sup> The greater risk of developing candidiasis in edentulous patients may contribute to their discomfort. Soft denture liners or incorporation of metal in the palate of the maxillary denture have been shown to be beneficial treatment options for some patients.<sup>67,68</sup>

## BOX 2

### MANAGEMENT OF HYPOSALIVATION AND XEROSTOMIA.

#### PALLIATIVE RECOMMENDATIONS

- Avoid the use of alcoholic beverages and mouth rinses. Mouth rinses containing alcohol may desiccate the oral mucosa and worsen xerostomic symptoms.
- Use a humidifier at night.
- Use salivary flow stimulants such as
  - sugarless chewing gum;
  - Biotène Dry Mouth Gum (Laclede, Rancho Dominguez, Calif.);
  - XyliFresh (Leaf, Espoo, Finland);
  - sugarless hard candies;
  - Salix Lozenges (Scandinavian Naturals, Perkasio, Pa.).

**Authors' note:** Any commercial sugarless gum and lozenge can provide symptom relief. The specific products listed also may contain xylitol, lactoperoxidase and/or glucose oxidase.

#### SALIVA SUBSTITUTES/ORAL LUBRICANTS

These over-the-counter agents are formulated as solutions, sprays or gels. Formulations have multiple contents including carboxymethyl- or hydroxymethylcellulose, electrolytes and flavoring. Most salivary substitutes provide relief for only a limited time. They are most useful when used immediately before bedtime or speaking. There are few data to indicate superiority of any of the products; selection therefore should be based on availability and personal preference.

- Moi-Stir (Kingswood Laboratories, Indianapolis)
- MouthKote (Parnell Pharmaceuticals, Larkspur, Calif.)
- ORALbalance (Laclede)
- Salivart (Xenex Laboratories, Coquitlam, British Columbia, Canada)
- Xero-Lube (Colgate Oral Pharmaceuticals, Canton, Mass.)

#### CHOLINERGIC DRUGS

Cholinergic drugs may alter cardiac conduction, and their use should be avoided in patients who have significant heart disease. These parasympathomimetic stimulating agents are contraindicated for patients who have uncontrolled asthma, narrow-angle glaucoma and acute iritis. Visual impairment has been noted, particularly in an environment with reduced lighting.), 30 mg three times per day

- Cevimeline (Evovac, Daiichi Pharmaceutical Co., Montvale, N.J.)
- Pilocarpine (Salagen, MGI Pharma, Minneapolis), 5–10 milligrams, three or four times per day

## CONCLUSIONS

Xerostomia is a condition of dry mouth that is experienced by many patients. The prevalence of this complaint and its negative effect on the patient's quality of life make it likely that the practitioner will encounter this condition on a regular basis. Xerostomia results from the loss of saliva that may develop as a side effect from the use of medications, as a manifestation of Sjögren's syndrome secondary to a number of connective tissue diseases or as a complication of radiation therapy. Treatment is primarily palliative, with emphasis on the use of saliva substitutes. Some patients may benefit from pharmacological stimulation of the salivary glands. The predominant complications that result from reduced saliva are dental caries, which requires compre-

## hensive dental management and candidiasis, which can be treated with antifungal agents. ■

Dr. Guggenheimer is a professor, Department of Oral Medicine and Pathology, School of Dental Medicine, G-137 Salk, University of Pittsburgh, 3501 Terrace St., Pittsburgh, Pa. 15261, e-mail "guggen@pitt.edu". Address reprint requests to Dr. Guggenheimer.

Dr. Moore is a professor, Department of Dental Public Health, School of Dental Medicine, University of Pittsburgh.

Additional information about xerostomia and a number of support services are available from the Sjögren's Syndrome Foundation Inc., 8120 Woodmont Ave., Bethesda, Md. 20814, 1-800-475-6473, "www.sjogrens.org"; and from the National Oral Health Information Clearing House, 1 NOHIC Way, Bethesda, Md. 20892-3500, 1-301-402-7364, "www.nohic.nidcr.nih.gov".

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