Diagnosis and treatment of salivary gland disorders

Gwen Cohen-Brown, DDS¹/Jonathan A. Ship, DMD²

The keystone of the architecture of the oral cavity is saliva; however, it is rarely acknowledged as a vital physiologic secretion. Saliva plays three major roles in oral and systemic health. It provides host protection, assists in the initiation of food and fluid intake, and enables communication through speech. Without adequate salivary output augmented by a rich assortment of salivary proteins and electrolytes, oral and pharyngeal health declines as well as a person's quality of life. This article will provide a brief summary of the function of saliva, oral and systemic etiologies of salivary dysfunction, and methods to treat and prevent salivary disorders. Oral health care professionals can play a vital role in identifying patients at risk for developing salivary dysfunction and should provide appropriate preventive and interventional techniques that will help preserve oral health and function. (Quintessence Int 2004:35:108-123)

Key words: pathology, radiotherapy, saliva, salivary dysfunction, Sjögren's syndrome, xerostomia

ROLE OF SALIVA IN ORAL AND SYSTEMIC HEALTH

Whole saliva is an admixture of secretions from the major (parotid, submandibular, sublingual) and minor salivary glands. The minor salivary glands are located within the submucosa of the lips, cheeks, and soft and hard palate, and number between 700 and 1,000 in total. The adequate secretion of saliva is critical for preserving the health of the oral cavity and gastrointestinal system.¹ Secretion of saliva is under the control of the autonomic nervous system,² with output following a circadian rhythm,³ which controls both the quantity and type of serous versus mucinous saliva secreted.

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Saliva plays multiple roles within the oral cavity. It provides a physical barrier against local irritants, lubricates the oral mucosal soft tissues with mucins, maintains a stable intraoral pH with bicarbonate, and assists in the prevention of tooth decay and remineralization of the dental hard tissues (Table 1). Saliva contains antibacterial (eg, lysozyme), antiviral (eg, secretory leukocyte protease inhibitor), and antifungal (eg, histatins) components to help maintain the normal commensal flora.⁴ The ability of saliva to limit the growth of multiple pathogens is a major factor in sustaining both systemic and oral health.

Additional functions of saliva include aiding in digestion of fats and complex carbohydrates, assistance with food mastication and the formation of a bolus, enabling taste and swallowing, and retaining removable prosthodontic appliances. When swallowed, salivary bicarbonates help protect the esophagus by neutralizing acids associated with heartburn and hiatal hernia.⁵ Saliva physically removes the sugars and food particles that are the microbial food source. The
### TABLE 1 Salivary function and constituents

<table>
<thead>
<tr>
<th>Function</th>
<th>Representative components</th>
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<tbody>
<tr>
<td>Mucosal lubrication</td>
<td>Mucin</td>
</tr>
<tr>
<td>Mucosal repair</td>
<td>Epidermal growth factor</td>
</tr>
<tr>
<td>Food bolus formation/translocation</td>
<td>Mucin, water</td>
</tr>
<tr>
<td>Initial food processing</td>
<td>Amylase, DNase, RNase</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>sIgA, histatins, lactoperoxidase, lactoferrin, SLPI</td>
</tr>
<tr>
<td>Remineralization</td>
<td>Statherin, proline-rich proteins</td>
</tr>
<tr>
<td>Buffering</td>
<td>Bicarbonate, histatins</td>
</tr>
<tr>
<td>Mediating gustation</td>
<td>Water</td>
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SLPI = secretory leukocyte protease inhibitor.

### TABLE 2 Sequelae of salivary dysfunction

<table>
<thead>
<tr>
<th>Sequelae of salivary dysfunction</th>
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<tbody>
<tr>
<td>Dental caries</td>
</tr>
<tr>
<td>Dry lips and mouth</td>
</tr>
<tr>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Dysphagia</td>
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<tr>
<td>Gingivitis</td>
</tr>
<tr>
<td>Halitosis</td>
</tr>
<tr>
<td>Mastication problems</td>
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<tr>
<td>Mucoasitis</td>
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<tr>
<td>Oral-pharyngeal candidiasis</td>
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<tr>
<td>Poorly fitting prosthesis</td>
</tr>
<tr>
<td>Sleep difficulty</td>
</tr>
<tr>
<td>Speech difficulty</td>
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<tr>
<td>Traumatic oral lesions</td>
</tr>
</tbody>
</table>

Fig 1  Salivary dysfunction caused by antidepressant drugs, causing new and recurrent dental caries.

Fig 2  Salivary dysfunction caused by external beam radiotherapy in a patient who had a squamous cell carcinoma of the tongue. Patient now presents with a recurrent oral fungal infection.

remineralization process is even more effective when fluoride is present in saliva. Further, the insoluble pellicle formed by saliva on teeth limits the ability of acids to demineralize the dental hard tissues.7

**ORAL AND SYSTEMIC EFFECTS OF SALIVARY DYSFUNCTION**

Saliva plays a critical role in the maintenance of oral health, and when salivary function becomes impaired, there are multiple sequelae to oral and pharyngeal health (Table 2).1 Individuals with reduced salivary output may experience persistent dry mouth (xerostomia) and bad breath (halitosis), which can impair quality of life.8

One of the most common oral conditions that develops due to salivary dysfunction is new and recurrent dental caries (Fig 1). In the presence of persistent salivary hypofunction, the inability of the salivary system to restore oral pH and inhibit certain bacteria after food and beverage ingestion leads to an oral environment conducive to microbial colonization of caries-associated microorganisms and enamel demineralization.9-10 Salivary hypofunction-associated root surface caries is a particularly difficult condition to diagnose and treat, and therefore, identification of patients at risk will help preserve the dentition.11

Decreased salivary output leads to oral mucositis, pain, and increased susceptibility to developing microbial infections. The most prevalent infection, particularly in older persons, is candidiasis (Fig 2). This fungal infection is caused by *Candida albicans*, a commensal organism that normally resides in the oral cavity.12-13 There are five clinical manifestations of oral candidiasis: angular cheilitis of the lips; erythematous candidiasis (denture stomatitis); atrophic candidiasis; hyperplastic candidiasis; and pseudomembraneous candidiasis.

Salivary dysfunction also contributes to chewing, tasting (dysgeusia), and swallowing (dysphagia) difficulty.16-18 Changes in salivary quantity and quality have been associated with impaired use of dental prostheses, often resulting in trauma to desiccated, friable tissues and an increased rate of oral microbial infections.
TABLE 3 Classifications of intraoral salivary gland pathologies

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Etiology</th>
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<tr>
<td><strong>Infectious</strong></td>
<td></td>
</tr>
<tr>
<td>Acute sialadenitis</td>
<td>Salivary hypofunction: secondary to dehydration, debilitation, medications</td>
</tr>
<tr>
<td></td>
<td>Bacterial species: Staphylococcus aureus, Staphylococcus pyogenes, Streptococcus pneumonia, E. coli</td>
</tr>
<tr>
<td>Chronic recurrent</td>
<td>Bacterial species (see acute sialadenitis)</td>
</tr>
<tr>
<td>sialadenitis</td>
<td></td>
</tr>
<tr>
<td>Viral sialadenitis</td>
<td>Paramyxovirus, cytomegalovirus</td>
</tr>
<tr>
<td><strong>Noninfectious</strong></td>
<td></td>
</tr>
<tr>
<td>Sialectasis</td>
<td>Salivary hypofunction: secondary to dehydration and post-general anesthesia</td>
</tr>
<tr>
<td>Sialolithiasis</td>
<td>Salivary hypofunction: secondary to dehydration, debilitation, medications, metabolic disorders, poor oral hygiene</td>
</tr>
<tr>
<td>Sialadenosis</td>
<td>Malnutrition, alcoholic cirrhosis, diabetes mellitus, hyperlipidemia</td>
</tr>
<tr>
<td>Mucous cyst</td>
<td>Blockage of an excretory duct</td>
</tr>
<tr>
<td>Mucocele</td>
<td>Traumatic severance of a minor salivary gland duct, producing spillage of mucin into surrounding connective tissue</td>
</tr>
<tr>
<td><strong>Neoplastic</strong></td>
<td></td>
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<tr>
<td>Benign tumors</td>
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<tr>
<td>Pleomorphic adenoma</td>
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<tr>
<td>Monomorphic adenoma</td>
<td></td>
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<tr>
<td>Malignant tumors</td>
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<tr>
<td>Adenoid cystic carcinoma</td>
<td></td>
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<tr>
<td>Mucoepidermoid carcinoma</td>
<td></td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Malignant mixed tumor</td>
<td>*Carcinoma arising in a pleomorphic adenoma and squamous cell carcinoma.</td>
</tr>
</tbody>
</table>

Dentoalveolar and oropharyngeal infections can rapidly lead to systemic disease, particularly in a medically compromised patient. Dysgeusia, dysphagia, and difficulty chewing food secondary to salivary hypofunction can lead to changes in food and fluid selection that may compromise nutritional status. They also can precipitate oral-pharyngeal disorders, including increased susceptibility to aspiration pneumonia and colonization of the lungs with gram-negative anaerobes from the gingival sulcus.18,20

**INTRAORAL SOURCES OF SALIVARY PATHOLOGY**

Intraoral sources of salivary gland pathology can be divided into three broad classifications: infectious, noninfectious, and neoplastic (Table 3).21 Bacterial infections are more common in older persons who experience salivary hypofunction secondary to medications, head and neck radiation, systemic diseases, or dehydration.9,10 Acute parotitis was commonly seen before the antibiotic era in terminally ill and dehydrated patients and contributed to mortality by sepsis. Now, acute parotitis is observed infrequently. Chronic parotitis is not unusual, and it follows obstruction of a major salivary gland duct with subsequent bacterial colonization and infection. Signs and symptoms of bacterial salivary infections include swelling, purulence from the major salivary gland duct, and pain.22

Viral infections occur in persons of all ages, particularly in immunocompromised patients, and preferentially involve parotid glands. Mumps is caused by paramyxovirus and presents as bilateral parotid gland swellings in children. Cytomegalovirus infections tend to be mild with nonspecific findings and are observed primarily in adults.

Noninfectious (reactive) causes of salivary pathology are most commonly due to obstruction of a salivary gland excretory duct and can be divided into acute and chronic conditions. Acute sialadenitis usually results from an immediate, partial, or complete ductal obstruction (ie, sialolithiasis), whereas chronic recurrent sialadenitis occurs as a result of prior infection and/or ductal scarring.23

Mucoceles are the most common reactive lesion of the mandibular lip and are caused by local trauma (Fig 3). When a minor salivary gland duct is severed, mucin leaks into the surrounding connective tissue, resulting in a smooth surfaced painless nodule in the submucosal tissues. Mucous cysts (mucoceles) of the sublingual gland, and less frequently the submandibular gland, are referred to as ranulas. They present as
either unilateral circumscribed lesions (subsequent to ductal obstruction and cystic dilatation) or plunging lesions (following extravasation of saliva herniating through the tissues of the floor of the mouth and the mylohyoid muscle). Both types of ranulas require surgical excision and possible marsupialization of the cyst.

The vast majority of calculi (sialoliths, stones) develops in the submandibular duct system (Fig 4) and is caused by calcification of mucous plugs and cellular debris typically as a result of dehydration and glandular inactivity. Sialoliths occur infrequently in the parotid duct system and are considered rare in the sublingual gland and minor salivary glands.

Most salivary gland tumors are benign, arising from epithelial tissues; however, neoplasms may originate from any adjacent tissue or structure (adipose, nerves, blood vessels, lymph nodes, lymphatics). The preponderance of benign salivary gland neoplasms occurs within the parotid gland, with the majority (80%) being pleomorphic adenomas. Malignant salivary gland tumor incidence increases with age, and these tumors are more common in the submandibular and sublingual glands, compared to the parotid gland. When epithelial neoplasms arise in the submandibular or sublingual glands, only 50% are benign. Pleomorphic adenomas tend to be unilateral and most commonly present as an asymptomatic mass in the tail of the parotid gland. They are slow growing, well delineated, and encapsulated.

Mucoepidermoid carcinoma is the most common malignant salivary gland tumor, followed by adenoid cystic carcinoma (cylindroma), acinic cell carcinoma, adenocarcinoma, squamous cell carcinoma, and carcinoma arising in a pleomorphic adenoma. The most commonly affected intraoral site is the palate followed by the maxillary lip. Adenoid cystic carcinomas are aggressive tumors that undergo perineural invasion. These tumors have good 10-year survival rates, but long-term mortality is likely. Signs and symptoms of a malignant salivary gland tumor include a swelling with facial nerve paralysis, pain, or facial paresis.

**TABLE 4  Systemic and exogenous sources of salivary dysfunction**

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Exogenous</th>
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<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Head and neck radiotherapy</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Medications</td>
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<tr>
<td>HIV/AIDS</td>
<td>Chemotherapy</td>
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<tr>
<td>Lupus</td>
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<td>Parkinson's disease</td>
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<td>Rheumatoid arthritis</td>
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<td>Sarcoidosis</td>
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<td>Sjögren's syndrome</td>
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<tr>
<td>Stroke</td>
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**SYSTEMIC SOURCES OF SALIVARY PATHOLOGY**

Many older adults experience salivary gland dysfunction and complain of a dry mouth (xerostomia). While it was previously thought that salivary function declined with greater age, it is now accepted that output from major salivary glands does not undergo clinically significant decrements in healthy individuals. It is likely that numerous medical conditions and their treatments (medications, head and neck radiation, chemotherapy) contribute significantly to salivary gland dysfunction in the elderly (Table 4).

The most common cause of salivary disorders is prescription and nonprescription medications. For example, 80% of the most commonly prescribed medications...
in 1992 were reported to cause xerostomia with over 400 medications causing a side effect of salivary gland dysfunction. The intake of prescription medications increases with age, with more than 60% to 78% of people over the age of 65 years taking at least one prescription medication. With the increased intake of prescription and nonprescription medications, many of which cause salivary gland dysfunction, the prevalence of medication-induced xerostomia is greater among the elderly.

The most common types of medications causing salivary dysfunction have anticholinergic effects (Fig 5), which will inhibit the movement of fluid from serum, through salivary acinar cells, into the ductal system and ultimately into the mouth. These medications include tricyclic antidepressants, sedatives and tranquilizers, antihistamines, antihypertensives, cytotoxic agents, anti-Parkinson and anti-seizure drugs. Chemotherapy for cancer treatment has also been associated with salivary disorders. Fortunately, these changes appear to occur only during and immediately after treatment, and salivary function returns to prechemotherapy levels in most patients after completion of therapy. Finally, radioactive iodine (1-131) used in the management of thyroid gland cancers may cause parotid but not submandibular dysfunction in a dose-dependent fashion.

Several medical conditions are associated with salivary dysfunction, the most common being Sjögren's syndrome (Fig 6). Sjögren's syndrome is primarily a disease of women (it may be as prevalent as 1 out of every 2,500 females), with a typical onset during the fourth or fifth decade of life. Clinically, Sjögren's syndrome presents in either primary or secondary forms. Primary Sjögren's syndrome is characterized by xerostomia and xerophthalmia (dry eyes) which are the result of a progressive loss of salivary and lacrimal function. Secondary Sjögren's syndrome includes involvement of one or both of these exocrine sites in the presence of another connective tissue disease such as rheumatoid arthritis, systemic sclerosis, or systemic lupus erythematosus. Lymphocytic infiltrates of salivary glands increase as the inflammatory disease progresses, ultimately producing acinar gland degeneration, necrosis, atrophy, and complete destruction of the salivary gland parenchyma.

Other autoimmune conditions associated with Sjögren's have salivary dysfunction, including rheumatoid arthritis, scleroderma, and lupus. HIV-infected individuals and those with AIDS frequently experience salivary dysfunction from lymphocytic destruction of the glands and as a sequela of medications. Diabetes may cause changes in salivary secretions, and associations have been made between poor glycemic control, peripheral neuropathies, and salivary dysfunction. Alzheimer's disease, Parkinson's disease, strokes, and cystic fibrosis will also inhibit salivary secretions.

**EXOGENOUS SOURCES OF SALIVARY PATHOLOGY**

The primary exogenous source of salivary pathology is head and neck radiotherapy. It is a common treatment modality for head and neck cancers and has long been associated with severe and permanent complications including salivary gland dysfunction and xerostomia. In many studies, xerostomia has been found to be the most common late side effect of irradiation for head and neck malignancies and a major cause of decreased quality of life.

External beam radiation has an immediate and permanent affect on salivary gland tissue. The loss of salivary gland function after radiation therapy is dependent on the dose and field of the radiation. Dosages as low as 2 Gy can cause alterations in salivary secretions, and total salivary dosages greater than 26 Gy will cause...
permanent salivary destruction. Since typical therapeutic dosages exceed 60 Gy for head and neck tumors, salivary dysfunction is a common result of head and neck radiotherapy. Apoptosis, or programmed cell death, appears to be the primary mechanism whereby radiation induces salivary gland cellular death.

**TREATMENT OF SALIVARY DYSFUNCTION**

Treatment for salivary dysfunction begins with appropriate diagnosis, including a careful review of the patient’s history and physical findings. Frequent dental evaluations are critical with a focus on preventing the myriad of oral disorders that develop due to salivary hypofunction. Several questionnaires, specifically designed for assessing the subjective complaint of a dry mouth (xerostomia), and verified scientifically, may be helpful in clinical practice. Once a diagnosis has been established, treatment is designed based upon the etiopathogenesis of the disorder and the prognosis. For example, if the etiology is medication-induced salivary dysfunction, then drug substitution or modification can ameliorate some symptoms of dry mouth. If the prognosis for restoration of normal salivation is poor, such as with head and neck radiotherapy for oral cancers, then use of salivary replacements and stimulants may help.

For all patients with xerostomia and salivary dysfunction, maintenance of proper oral hygiene and hydration (water is the drink of choice) are helpful. Several habits, such as smoking, mouth breathing, and consumption of caffeine-containing beverages, have been shown to increase the risk of xerostomia. Limiting or stopping these practices should lessen the severity of dry mouth symptoms. Daily topical fluoride use and antimicrobial mouthrinses help prevent caries in patients with reduced salivary flow. Sugar-free chewing gum, candies, and mints can stimulate remaining salivary secretions. In the absence of remaining salivary tissue, artificial saliva and lubricants may ameliorate some xerostomic symptoms. These products tend to diminish the sensation of oral dryness and improve oral functioning. Preference of products depends on effect duration, lubrication, taste, delivery system, and cost; many patients nevertheless primarily use water. Several products available without a prescription include Biotene (Laclede) (mouthwash, toothpaste, and chewing gum), Salivart (an aerosol artificial spray) (Xenex), Fre dendent (Wrigley) (a low-tack, sugar-free chewing gum), and Oralbalance oral lubricant (Laclede). Over the last decade there has been some interest in using acupuncture techniques to enhance saliva flow. There is data suggesting that acupuncture therapy can maintain an improvement in stimulated saliva up to 6 months after the completion of radiotherapy. Although this treatment modality is not commonly utilized, it presents a treatment option for patients who respond well to muscarinic agonists (eg, pilocarpine, cevimeline) yet have difficulty taking these medications due to secondary side effects.

Eating and swallowing problems secondary to salivary hypofunction can impair intake of fiber-rich foods, restricting some adults to a primarily soft and carbohydrate diet. Accordingly, patients must be counseled on a well-balanced, nutritionally adequate diet and the importance of limiting sugar intake, particularly between meals. Problems with swallowing may be treated with oral moisturizers and lubricants and careful use of fluids during eating. At night, bedside humidifiers can provide some assistance for patients experiencing significant nocturnal oral dryness.

The treatment of lesions and tumors associated with the salivary glands starts with an appropriate diagnosis. Incisional or excisional biopsies and histopathologic evaluation are critically important. Salivary gland swellings also can be evaluated with a variety of imaging techniques. Sialograms can identify changes in the salivary gland architecture and are performed with radio-opaque iodine and extraoral radiographs (lateral cephalograms, panographs, etc). Radioactive isotope scintiscans (eg, T99 pertechnetate) can provide a qualitative functional assessment of the major salivary glands. Magnetic resonance imaging (MRI) and computed tomography (CT) scans will help rule out salivary gland tumors and other pathoses associated with the craniofacial region that may adversely affect salivation. The treatment of lesions and tumors associated with the salivary glands varies significantly between the different tumors and is dependent upon size and grade of the lesion as well as the histologic classification. Salivary gland neoplasms comprise about 1% of all head and neck tumors. The average annual age-adjusted incidence rate per 100,000 persons was reported as 4.7 for benign tumors and 0.9 for malignant tumors.

Treatment for benign and malignant tumors is surgery with the possibility of postoperative radiotherapy. Benign tumors of salivary gland origin (pleomorphic adenoma, monomorphic adenoma) require careful excision since they are encapsulated, and residual tissue after surgery can increase the risk of tumor recurrence. For example, 1.6% of pleomorphic adenomas recur following surgical excision. Recurrent lesions are frequently multinodular, and treatment is determined by the extent of the disease, prior therapy, and amount of recurrence. Malignant degeneration is uncommon (carcinoma arising in a pleomorphic adenoma) and most often arises in tumors that have been present for at least 25 years, or tumors that have had multiple recurrences and multiple failed therapies.
Salivary gland tumors that recur require more extensive treatment, including wider surgical margins and postsurgical radiotherapy. Malignant salivary tumors require complete excision and removal of regional lymph nodes at risk for tumor spread. A full course of external beam radiotherapy is used as an adjuvant 3 to 4 weeks after surgery. Malignant salivary gland neoplasms approach 60% 5-year survival with several exceptions. Adenoid cystic carcinomas have good 5-year survival rates (79%), but extremely poor 10-year (46%), 15-year (54%), and 20-year survival rates (25%) due to late metastasis through perineural spread. Low-grade mucoepidermoid carcinomas have excellent cure rates with surgery alone, but moderate or high-grade tumors are considered more aggressive with very poor survival rates.

Postsurgical radiotherapy provides greater survival chances for most squamous cell cancers with lymphatic involvement but is associated with a host of adverse short-term and permanent complications. These include xerostomia and salivary gland dysfunction, oral mucosal ulcerations, oral microbial infections, dysphagia, dysgeusia, new and recurrent dental caries, impaired retention of removal prostheses, and increased risk of developing osteoradionecrosis. Chemotherapy is a recent treatment modality for salivary gland cancers and has not been shown to definitively increase the odds of cancer survival. No currently available chemotherapeutic agent or combination regimen has produced consistent results. Presently, chemotherapy is indicated only for pain relief in symptomatic patients who have either recurrent cancers or nonresectable tumors. Treatment of medication-associated salivary gland dysfunction requires consultation with the patient’s physicians. The first step is to decrease the number of medications a person is taking that cause salivary hypofunction. When the administration of xerostomia-associated drugs is inevitable, substitution with similar acting medications with fewer xerostomic side effects is preferred. Some classes of medications provide better opportunities for substitution (eg, antihypertensives; change a diuretic to an angiotensin-converting enzyme inhibitor). If drug substitution is not possible, there are other strategies for altering pharmaceutical regimens in order to avoid xerostomia. Salivary output is lowest during night-time, and anticholinergic drugs taken before bedtime will produce even greater inhibitions during these hours. If these medications can be taken during the daytime, patients can manage better the xerostomic effects and avoid awakening at night due to severe xerostomia. Another strategy, if applicable, is to divide drug administration into several dosages, which will minimize unwanted side effects from a large single dose.

Treating xerostomia with medications that enhance salivation is another therapeutic option, particularly in the relatively healthy person for whom polypharmacy may not be a critical concern. Secretagogues such as pilocarpine can increase secretions and diminish xerostomia complaints in patients with sufficiently remaining exocrine tissue. Pilocarpine is typically given in a dosage of 5 mg orally three times a day and before bedtime. When taken approximately 30 minutes before mealtime, patients may benefit from the increased salivation in eating their meal. The total daily dose should not exceed 30 mg. Adverse effects include increased perspiration, greater bowel and bladder motility, and feeling hot and flushed. Patients with a history of bronchospasm, severe chronic obstructive pulmonary disease, congestive heart disease, and angle closure glaucoma should not take pilocarpine. A new secretogogue, cevimeline, has recently been approved by the Food and Drug Administration (FDA) for the treatment of dry mouth in Sjögren’s syndrome in a dosage of 30 mg orally three times daily. Like pilocarpine, it is a muscarinic agonist that increases production of saliva. Pilocarpine is a nonselective muscarinic agonist, whereas cevimeline reportedly has a higher affinity for M1 and M3 muscarinic receptor subtypes. Since M2 and M4 receptors are located on cardiac and lung tissues, cevimeline can enhance salivary secretions while minimizing adverse effects on pulmonary and cardiac function. Patients with uncontrolled asthma, significant cardiac disease, and angle closure glaucoma should not take cevimeline.

Head and neck radiotherapy causes significant and permanent salivary hypofunction and xerostomia, and therefore requires a lifetime of supportive care. Techniques are available to assist in diminishing salivary disorders that develop during radiotherapy. Salivary-sparing radiotherapy techniques can deliver high radiotherapy dosages to tumors and regional lymph nodes considered at risk for tumor spread, while limiting dosages to contralateral salivary glands. Using three-dimensional treatment planning techniques, salivary function from spared glands is able to return to pre-RT flow rates 6 to 12 months postradiotherapy with an improvement in xerostomia-associated quality of life. Further, tumor recurrence in the regions of spared radiotherapy has not been reported.

Another technique available during radiotherapy is the concomitant use of several medications that may increase salivation and provide cytoprotection. Amifostine (a broad-spectrum cyto- and radio-protectant) may provide cytoprotection against myelotoxicity, nephrotoxicity, mucositis, and xerostomia associated with various chemotherapy and radiation modalities. Pilocarpine, a muscarinic agonist, can improve symptoms of xerostomia when given during radiotherapy.
and after the completion of radiotherapy. Cevimeline hydrochloride, another muscarinic agonist, may be useful as a more specific muscarinic agonist.

Pilocarpine and cevimeline are also effective for stimulating saliva in patients who have systemic diseases that have been associated with salivary dysfunction (eg, Sjögren's syndrome, HIV, diabetes). In the late-stage Sjögren's patient, where all fluid-producing acinar cells have been replaced by connective tissue, pharmacologic agents will not be helpful. However, in the early stages of Sjögren's and in other diseases where remaining acinar tissues are viable, pharmacologic stimulants are helpful despite their side effects (eg, increased perspiration, greater bowel and bladder motility, and feeling hot and flushed). Importantly, it is critical to have careful coordination of drug prescribing between dental and medical health care providers in order to avoid polyparmacy complications.

The secondary effects of salivary hypofunction on oral hard and soft tissues also require appropriate diagnosis and treatment. Desiccated oral mucosal tissues are more susceptible to ulcerations and traumatic lesions. Soft tissue management includes maintaining mucosal integrity to avoid local (ie, candidal infections) or systemic infections from oral microflora. Dry mouth–induced oral lesions are susceptible to developing secondary infections by microbial flora that normally inhabit the oral cavity as well as by exogenous organisms. Prompt treatment of oral infections with the appropriate antibiotic is required, and occasional use of antimicrobial mouthrinses (eg, chlorhexidine 0.12%) is helpful.

Oral candidiasis is the most frequent oral infection secondary to dry mouth, and is most commonly treated with topical antifungal agents. Oral rinses, ointments, pastilles, and troches are effective for most forms of oral candidiasis (Table 5), and systemic antifungal therapy (eg, ketoconazole, fluconazole) should be reserved for refractory disease and immunocompromised patients. Dentures may harbor fungal infections and thus require treatment. Patients must be instructed to perform daily hygiene of the appliance, and to keep the prosthesis out of the mouth for extended periods and while sleeping. Prostheses can be soaked for 30 minutes in solutions containing benzoic acid, 0.12% chlorhexidine, or 1% sodium hypochlorite and then thoroughly rinsed. A few drops of nystatin oral suspension or a thin film of nystatin ointment (eg, chlorhexidine 0.12%) is helpful.

Oral candidiasis is the most frequent oral infection.
practitioners is critical for patients who have systemic diseases and/or who are being treated with medications, surgery, radiotherapy that have been associated with salivary dysfunction. Further, the patient with complaints of xerostomia or objective findings of salivary pathoses requires referral to the appropriate health care provider for diagnosis, management, and follow-up.

**CONCLUSION**

This article reviews the most common causes and treatments of salivary disorders. Oral and systemic conditions, medications, and head and neck radiotherapy are the etiologic agents of salivary dysfunction, which ultimately lead to a host of oral and pharyngeal disorders including dental caries, oral microbial infections, impaired speech/swallowing/extracigaret tobacco retention, and oral pain. Gustatory and masticatory stimulants as well as muscarinic/cholinergic drugs are useful for increasing salivary output in a patient with residual salivary function. The patient with little or no remaining salivary tissue has few treatment options, other than the frequent use of salivary substitutes and nonsugared beverages. All patients with salivary dysfunction must adhere to regular recall visits to their dental professionals so that they can monitor their condition and implement early treatment and preventive techniques in order to help preserve oral health.

**REFERENCES**


Pilocarpine is a parasympathetic drug extracted from the Pilocarpus plant and exerts a broad spectrum of pharmacologic activities, with a predominately muscarinic-cholinergic action. It has been shown to stimulate lacrimal, salivary, gastric, intestinal, respiratory, and pancreatic secretions. Pregnancy risk factor C.

### XEROSTOMIA: RX PILOCARPINE HYDROCHLORIDE

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
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<tbody>
<tr>
<td>1. Indications</td>
<td>Treatment of xerostomia.</td>
</tr>
<tr>
<td>2. Contraindications</td>
<td>Hypersensitivity to the drug or any of its components.</td>
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<tr>
<td></td>
<td>Pilocarpine is contraindicated in patients with uncontrolled asthma or severe hepatic impairment.</td>
</tr>
<tr>
<td>4. Drug interactions</td>
<td>Increased myopia with sympathomimetic amines.</td>
</tr>
<tr>
<td>5. Administration (route and dosage)</td>
<td>Dosage form: 5 mg tablets.</td>
</tr>
<tr>
<td></td>
<td>Oral: Initially give 2.5 to 5.0 mg, three times daily; may be titrated up to 30 mg per day at variable dosage intervals.</td>
</tr>
<tr>
<td>6. Monitored efficacy and toxicity</td>
<td>Improved salivary flow, which is not necessarily accompanied by subjective improvement.</td>
</tr>
<tr>
<td></td>
<td>Peak effect may require up to 4 weeks to become evident.</td>
</tr>
<tr>
<td></td>
<td>Secondary indications of efficacy may be diminished mucositis, candidiasis, and dysphagia.</td>
</tr>
<tr>
<td></td>
<td>The patient should be examined every 6 to 8 weeks to assess efficacy, determine adverse reactions, and adjust dosage regimen.</td>
</tr>
<tr>
<td></td>
<td>Common adverse reactions include blurred vision, miosis, headache, diaphoresis, and polyuria.</td>
</tr>
<tr>
<td></td>
<td>Symptoms of overdose include bronchospasm, bradycardia, involuntary urination, vomiting, hypotension, and tremors.</td>
</tr>
<tr>
<td></td>
<td>Atropine, 0.5 to 1.0 mg, administered intravenously or intramuscularly, is the treatment of choice for toxic muscarinic symptoms.</td>
</tr>
<tr>
<td></td>
<td>Epinephrine, .01 to 1.0 mg, 1:10,000, administered subcutaneously, may be helpful in reversing severe cardiovascular of pulmonary sequelae.</td>
</tr>
<tr>
<td>7. Length of treatment</td>
<td>Indefinite, as long as salivary flow is adequate and no serious side effects are noted.</td>
</tr>
<tr>
<td>8. Cessation of treatment</td>
<td>May be discontinued without tapering.</td>
</tr>
<tr>
<td>9. Instructions to the patient</td>
<td>May impair adaptation to dark; therefore, use with caution while driving at night or performing hazardous tasks in poor illumination.</td>
</tr>
<tr>
<td></td>
<td>Promptly report any adverse drug effect and inform all health care professionals that you are taking pilocarpine.</td>
</tr>
</tbody>
</table>

For additional information, please review the manufacturer’s recommendations.
XEROSTOMIA: R\textsubscript{x} CEVIMELINE HYDROCHLORIDE

Cevimeline hydrochloride is an acetylcholine derivative that has been approved by the US Food and Drug Administration for the treatment of xerostomia caused by Sjögren's syndrome. Presumably it could also be used to treat radiation- and drug-induced xerostomia. It has a high affinity for muscarinic-cholinergic receptors located on lacrimal and salivary gland cells and a much lower affinity for cardiac parasympathetic receptors. Pregnancy risk factor C.

<table>
<thead>
<tr>
<th>1. Indications</th>
<th>• To stimulate salivary flow in patients with salivary gland dysfunction secondary to drug-induced xerostomia.</th>
</tr>
</thead>
</table>
| 2. Contraindications | • Cevimeline is contraindicated in patients with known hypersensitivity to acetylcholine.  
  • Cevimeline is contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, or iritis.  
  • Cevimeline should be used with caution in patients with cardiovascular disease, urinary tract obstruction, or Parkinson's disease. |
| 3. Drug interactions | • Cevimeline has additive effects in slowing cardiac conduction in patients taking a beta-blocker.  
  • Cevimeline antagonizes the effects of antimuscarinic drugs such as atropine or scopolamine. |
| 4. Administration (route and dosage) | • Oral.  
  • 30.0 mg, three times daily. |
| 5. Monitored efficacy and toxicity | • The endpoint for therapeutic efficacy is increased salivary flow, which is not necessarily accompanied by symptomatic improvement.  
  • Secondary indicators of efficacy, when applicable, include diminished oral mucositis and candidiasis, and decreased dysphagia.  
  • The patient should be examined every 6 to 8 weeks to assess parameters of efficacy as well as evidence of adverse drug effects.  
  • Common adverse effects include sweating, nausea, rhinitis, diarrhea, and visual disturbances (especially at night); the dosage can be titrated downward and/or the dosage interval can be increased.  
  • Symptoms of overdose may include bronchospasm, bradycardia, involuntary urination, vomiting, hypotension, and tremors:  
    • Atropine, 0.5 to 1.0 mg, administered intravenously or intramuscularly, is the treatment of choice for toxicity manifesting as significant muscarinic symptoms.  
    • Epinephrine, 0.1 to 1.0 mg, administered subcutaneously, may be useful in reversing severe cardiovascular or pulmonary sequelae. |
| 6. Length of treatment | • Cevimeline may be continued indefinitely as long as the salivary flow continues to be stimulated and the patient experiences no serious drug effects. |
| 7. Cessation of treatment | • Cevimeline may be withdrawn immediately and completely without adverse effects. |
| 8. Instructions to the patient | • Use caution while driving at night or performing hazardous tasks in poor illumination because the drug may affect adaptation to the dark. Promptly report any adverse drug effect and inform all health care professionals that you are taking acetylcholine.  
  For additional information, please review the manufacturer's recommendations. |
Nystatin is a polyene antifungal agent effective against Candida species. It binds to the sterol component of fungal cell membrane causing increased membrane permeability and leakage of cellular contents. It is poorly absorbed from the skin, mucous membranes, or gastrointestinal tract. Pregnancy risk factor B for topical administration. Pregnancy risk factor C for oral administration.

1. **Indications**
   - Treatment of oral candidiasis.

2. **Contraindications**
   - Hypersensitivity to the drug or any of its components.

3. **Warnings/precautions**
   - None noted.

4. **Drug interactions**
   - None noted.

5. **Administration (route and dosage)**
   - Dosage forms: oral suspension 100,000 units/mL; lozenge 200,000 units.
   - Suspension: rinse with 5 mL for 2 minutes four times daily and swallow.
   - Lozenge: let one lozenge dissolve in mouth five times a day. Do not chew.

6. **Monitored efficacy and toxicity**
   - Assess patient weekly for evidence of reduced candidiasis.
   - Medication should be continued for a week after disappearance of clinical signs of candidiasis.
   - Common adverse reactions include mild gastrointestinal disturbances, such as vomiting, nausea, diarrhea, and stomach ache.

7. **Length of treatment**
   - As dictated by clinical circumstances. If no improvement is noted within 2 weeks, another agent should be considered.

8. **Cessation of treatment**
   - May be discontinued without tapering.

9. **Instructions to the patient**
   - Use as directed.
   - Disinfect all removable prostheses with a commercially available antifungal denture soaking solution.
   - Advise health care providers if you cannot adequately dissolve the lozenge.

For additional information, please review the manufacturer's recommendations.
**ORAL CANDIDIASIS: R<sub>x</sub> CLOTRIMAZOLE**

Clotrimazole is an imidazole antifungal agent effective against Candida species. It binds to the phospholipid component of fungal cell membrane causing increased permeability and loss of cellular contents. Pregnancy risk factor B for topical administration. Pregnancy risk factor C for oral administration.

1. **Indications**
   - Treatment of oral candidiasis.

2. **Contraindications**
   - Hypersensitivity to the drug or any of its components.

3. **Warnings/precautions**
   - None.

4. **Drug interactions**
   - Inhibits CYP2A6, 2C8/9, 2E1, and 3A4.

5. **Administration (route and dosage)**
   - Dosage form: troche 10 mg.
   - Troche: let one troche dissolve in mouth five times a day.

6. **Monitored efficacy and toxicity**
   - Assess patient weekly for evidence of reduced candidiasis.
   - Medication should be continued for 1 week after resolution of clinical candidiasis.
   - Common adverse reactions include mild gastrointestinal disturbances, such as nausea and vomiting.

7. **Length of treatment**
   - As may be dictated by clinical circumstances.
   - If no improvement is noted within 2 weeks, another agent should be considered.

8. **Cessation of treatment**
   - May be discontinued without tapering.

9. **Instructions to the patient**
   - Use as directed.
   - Disinfect all removable prostheses with a commercially available antifungal denture soaking solution.
   - Advise health care providers if you cannot adequately dissolve the troche.

*For additional information, please review the manufacturer’s recommendations.*