# Treatment of dry mouth and other non-ocular sicca symptoms in Sjögren's syndrome-I

**Last updated:** Oct 1, 2009
**Last modified:** October 1, 2009 4:54 PM

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**INTRODUCTION** — Sjögren's syndrome (SS) is a chronic multisystem inflammatory disorder, characterized by diminished lacrimal and salivary gland function. This results in the "sicca complex," a combination of dry eyes (xerophthalmia) and dry mouth (xerostomia). A variety of other disease manifestations may also be present, including systemic signs and extraglandular features.

SS occurs in a primary form not associated with other diseases and in a secondary form associated with other autoimmune rheumatic conditions, including rheumatoid arthritis and systemic lupus erythematosus.

Both local and systemic medical therapies are used in the treatment of SS [1]. These include:

- Preventive therapies and attention to other conditions, medications and environments that may exacerbate dryness complaints

- Topical therapy of dry eyes and mouth, other dry mucosal surfaces and dry skin, and the use of systemic cholinergic agents to stimulate secretions

- Systemic antiinflammatory and immunosuppressive therapies and other measures for local and systemic manifestations of SS, including extraglandular manifestations

- Treatment of fatigue and other symptoms not directly related to the inflammatory process

The treatment of dry mouth, including topical therapy and the use of systemic cholinergic agents, and topical therapies for the management of other non-ocular sicca symptoms of SS will be reviewed here. Other issues in SS, including the treatment of dry eyes and the role of systemic therapy, are discussed separately. (See "Treatment of dry eyes in Sjögren's syndrome-I" and see "Systemic therapy in Sjögren's syndrome and treatment of extraglandular manifestations".

## GENERAL APPROACH

**Overview** — The approach to management of patients with sicca symptoms is generally the same for primary or secondary SS, largely depending upon the severity of symptoms and responsiveness to therapy. (NOTE: Aus, is this OK? *Yes fine, PC*) Patients with mild SS may only require local treatment for sicca symptoms, in addition to monitoring of their condition and usual medical and dental preventive care.

Most patients will benefit from multidisciplinary care. We suggest coordination of care by a single clinician, usually a rheumatologist, in collaboration with the primary care physician and other clinicians. Patients should receive ongoing care from both an ophthalmologist and a dentist, with an interest in keratoconjunctivitis sicca and dry mouth, respectively.

Comprehensive patient education should be provided regarding SS and its management, including use of available materials from patient support groups. This is especially important for patients with SS because of the multisystem nature of the illness and the degree of self-care that is requred. There should be particular attention to self-management strategies for tear conservation and effective use of artificial tears, treatment of dry mouth symptoms and oral hygiene, and recognition of symptoms requiring medical attention.

**Approach to treatment of dry mouth** — Treatment of dry mouth due to salivary gland dysfunction aims to alleviate symptoms and prevent complications such as dental caries, periodontal disease, halitosis, salivary gland calculi, dysphagia, and oral candidiasis. Saliva has multiple functions within the oral cavity [2]. These include:

- Lubrication of the mucosa, helping to clear food residue that may lead to dental plaque and bacterial growth

- Buffering of acids that favor demineralization of teeth

- Providing antimicrobial proteins and control of bacterial and fungal populations

Replacement of salivary secretions and stimulation of existing salivary flow are major aspects of treatment [1,2].

**Basic measures —** The following measures should be used in all patients with dry mouth due to SS:

- Maintenance of good hydration by taking regular sips of water and drinking sugar-free liquids (See "Replacement of oral secretions" below)

- Avoidance of oral irritants (eg, coffee, alcohol, and nicotine)

- Avoidance of acidic drinks (eg, carbonated beverages and juices)

- Avoidance of medications that worsen oral dryness (See "Treatment of dry eyes in Sjögren's syndrome-I", section on Non-SS medications)

- Use of sugar-free stimulants of salivary flow (eg, gums and lozenges) (see "Topical stimulation of salivary flow" below)

- Meticulous oral hygiene and regular dental care (See "Prevention of dental caries" below)

**Indications for further intervention**

- In patients who do not achieve sufficient salivary excretion with topical stimulants we suggest the use of muscarinic agonists, such as pilocarpine or cevimeline. (See "Muscarinic agonists" below)

- The use of artificial saliva is suggested In patients with moderate to severe salivary dysfunction who would benefit from temporary relief of symptoms, including those who do not receive sufficient benefit from stimulants of salivary flow or water or have excessive water intake (eg, resulting in nocturia). (See "Artificial saliva" below).

- Patients with dental caries or very low salivary production should be seen by a dentist with an interest in dry mouth dentistry to determine if remineralizing mouth washes, special toothpastes, fluoride applications or other measures are required. (See "Prevention of dental caries" below).

- Physicians should maintain a high level of suspicion for oral candidiasis, especially in patients with mouth pain, burning, increased sensitivity, diffuse or patchy mucosal erythema, or white mucosal patches, so that treatment can be promptly instituted (See "Oral candidiasis" below).

TOPICAL STIMULATION OF SALIVARY FLOW — Salivary flow should be stimulated In patients with residual salivary function by sucking on sugarless candies, gum, and lozenges. Particular care must be taken not to increase the risk of dental caries. For example, sugar-free lozenges contain significantly less sugar than "low sugar" mints. A clear advantage of one product over another has not been rigorously shown, and a variety of products should be tried to determine which is most acceptable and effective in a given patient. Examples include:

- Sugar-free hard candies or lozenges (eg, Salive).

- Sugar-free chewing gums, containing various sweeteners such as aspartame, saccharin, and sorbitol.

- Xylitol-containing gum or candy (eg, Xylichew, Spry, TheraGum), which may also reduce the cariogenicity of the oral bacterial [2].

- Citrus flavored sugarless tablets (eg, Salivasure), which may also contain malic acid, normally found in fruits such as apples or pears, and which stimulates salivary flow.

- Maltose lozenges, which may reduce symptoms of oral dryness, as shown in an observational study [3].

- Dried fruit slices such as peaches or nectarines, which stimulate flow in many patients.

## MUSCARINIC AGONISTS

**Indications and use** — Use of a systemic sialogogue (administered orally) is indicated in patients with more than very mild salivary dysfunction, who do not achieve sufficient salivary excretion with topical stimulants such as those described above. There are two such agents, the muscarinic agonists pilocarpine and cevimeline, which are currently approved by the US Food and Drug Administration for treatment of dry mouth [4]. These medications increase salivary flow and improve symptoms of dry mouth.

Pilocarpine and cevimeline are most effective in patients with greater residual excretory capacity [1]. Their use may sometimes be limited by poor tolerance, largely due to cholinergic side effects including sweating.

Choice of medication is determined by individual factors which may affect patient preference, including cost, convenience, clinical response, and tolerance of adverse effects.

Some patients do not respond sufficiently well to the muscarinic agonists to justify continued use, especially when cholinergic side effects are present. Responses to these agents, however, may be gradual. In patients whose symptoms do not appear to improve upon trial of pilocarpine or cevimeline, we suggest a trial of at least three months duration if the medication is tolerated. NOTE: au, is this OK? *Yes fine PC*

**Precautions and adverse effects** — These medications are contraindicated in patients with the following conditions:

- Pregnancy
- History of uncontrolled asthma
- Acute iritis
- Narrow angle glaucoma
- Severe hepatic impairment

The following warnings should be considered:

- Patients with unstable cardiovascular disease may have difficulty compensating for transient changes in hemodynamics or cardiac rhythm induced by pilocarpine.

- Patients with controlled asthma, chronic bronchitis, and chronic

obstructive lung disease may experience Increased airway resistance and bronchial secretions.

- Patients with cholelithiasis, biliary tract disease, and nephrolithiasis are at risk of adverse effects of gallbladder, biliary tract or ureteral smooth muscle contraction, respectively.

- Patients with moderate hepatic impairment require dose adjustment of pilocarpine. The initial frequency of dosing should be twice daily in this setting.

- Patients should be cautioned about driving at night or performing hazardous activities in reduced lighting because they may experience decreased visual acuity (particularly at night and in patients with central lens changes) and impaired depth perception.

Pilocarpine — Pilocarpine, a muscarinic agonist that stimulates predominantly muscarinic M3 receptors, can significantly increase aqueous secretions in patients with residual salivary gland function [5,6]. The usual dose is 5 mg three or four times/day. It is most effective when taken four times/day because of its short duration of action. We suggest that patients try to take the medication four times daily if they do not receive adequate symptomatic relief with tree times daily dosing. Side effects, including sweating, abdominal pain, flushing, or increased urination, may limit its use. In some patients with unacceptable levels of side effects at the full dose, a reduced dose of 2.5 to 3.75 mg three times daily may still provide benefit [2].

The longest reported study of pilocarpine in SS evaluated 20 patients taking 10 to 30 mg/day for one year; six patients complained of sweating and four of abdominal cramps [7]. None of the patients chose to discontinue taking pilocarpine because of these side effects. The subjective benefit in oral comfort did not correlate closely with objective changes in salivary flow.

In addition to effects upon xerostomia, pilocarpine may improve symptoms of ocular dryness, although without any objective change in tear production [8]. (See "Treatment of dry eyes in Sjögren's syndrome-I").

Cevimeline — Cevimeline, an effective sialogogue, is a derivative of acetylcholine with a higher affinity for muscarinic M1 and M3 receptors on the lacrimal and salivary epithelium than for receptors on cardiac tissue [9]. Doses of 30 or 60 mg three times daily alleviate the symptoms of dry mouth, dry eyes, and stimulate salivary flow. The 30 mg dose is nearly as effective as the higher dose and is better tolerated [10]. We suggest dosing at 30 mg three times/day.

When initiating therapy, we suggest gradually increasing the dose and taking it about 30 minutes before meals. Initially, some patients experience dyspepsia, which can be minimized by use of a proton pump inhibitor while initiating therapy and taking it with food. Major side effects of cevimeline include excessive sweating, nausea, rhinitis, diarrhea, and visual disturbances. Use of lower doses in patients with poor tolerance of the full dose have been reported, but are obtained by dissolving the desired fraction of a 30 mg capsule's contents in water to take it at a reduced dose or to use it in a "rinse-and-spit" regimen to minimize systemic absorption [2]. These alternate forms of administration have not been approved by the US Food and Drug Administration.

In randomized trials, cevimeline significantly increases salivary flow and patient oral "quality of life" [10-14]. As an example, the efficacy of cevimeline was illustrated in a study that randomly assigned 197 patients with either primary or secondary SS to cevimeline or placebo [11]. The following were observed:

- Patients' global assessments of dryness were improved significantly more often by cevimeline 30 mg three times daily than by thrice daily doses of 15 mg or placebo (65, 32, and 35 percent, respectively).

- The most common adverse events seen more often with the drug (30 or 15 mg TID) than placebo were nausea (21 and 12 versus 7 percent), increased sweating (18 and 5 versus 1 percent) and diarrhea (16 and 14 versus 7 percent).

- Withdrawl from the study for adverse events was more common in patients on cevimeline (30 or 15 mg TID) compared with placebo (16.1 and 13.8 versus 4.3 percent, respectively).

- Serious adverse events were seen in <3 percent of patients and were

not more common with cevimeline.

Major side effects of cevimeline include excessive sweating, nausea, rhinitis, diarrhea, and visual disturbances.

In addition to increasing saliva flow, cevimeline induced changes in the protein content of saliva, including the release of aquaporin 5 (AQP5), a membrane pore protein which functions as a water channel, together with lipid rafts, amylase, mucin, and lysozyme [12,15]. Changes in saliva AQP5 levels after cevimeline administration occurred simultaneously with changes in saliva flow rates. AQP5 may have a role in both salivary and lacrimal glands and in the brain as a regulator of water transport after cholinergic stimulation [16-21].

## OTHER AGENTS

- **Hydroxychloroquine** — Use of hydroxychloroquine and other systemic antiinflammatory and immunosuppressive agents that may be of benefit for patients with xerostomia is discussed separately. (See "Systemic therapy in Sjögren's syndrome and treatment of extraglandular manifestations").

- **Cholinergic agonists** — Bethanechol and pyridostigmine are cholinergic agents that are approved in the US for use in urinary retention and myasthenia gravis, respectively, but not for SS. They have mixed muscarinic and nicotinic activity and are used much less often for SS because of greater adverse effects compared with pilocarpine and cevimeline [1].

- **Topical interferon alpha** — Oral interferon alpha was promising in early studies [22,23]. However, results were less encouraging in a subsequent 24 week trial in 497 patients randomized to receive either interferon alpha lozenges (150 IU three times a day) or placebo. Primary efficacy measures were not significantly improved over placebo responses. Unstimulated salivary flow rates were significantly improved in those who received oral interferon (0.76 versus 0.58 gram/5 minutes). A role for the maltose content of the placebo lozenges used contributing to the unexpectedly high placebo response has been proposed but is unproven. Further studies will be needed before this medication is available.

**REPLACEMENT OF ORAL SECRETIONS** — Various solutions can be used to replace oral secretions ranging from water to forms of artificial saliva containing a unique mix of multiple components in each preparation, such carboxymethylcellulose, polyethylene glycol, sorbitol, and electrolytes. Several different products should be tried if a particular substitute is not acceptable, as patient preferences vary and products differ in viscosity and other characteristics [24].

**Water** — For replacement of oral secretions most simply, we suggest frequent sips of water. The water does not have to be swallowed, but can be rinsed around the mouth and expectorated. Although water provides temporary moisture, it does not provide the lubricating properties that are characteristic of the mucin/water mixtures that constitute normal saliva.

Too frequent sipping of water may reduce the mucus film in the mouth and increase symptoms. If water consumption is excessive, especially in the evening, nocturia can occur, resulting in sleep disturbance that may worsen fatigue, cognitive difficulties, and pain that some patients experience.

**Artificial saliva** — We suggest a trial of artificial saliva for patients requiring temporary relief of dry mouth symptoms who do not receive sufficient benefit from stimulants of salivary flow or water. A number of artificial saliva preparations that provide more viscosity and lubrication than water are available. These products can help relieve symptoms temporarily in patients with moderate to severe salivary dysfunction [1,2]. They may be most useful prior to sleep or when waking at night with dry mouth symptoms, during telephone conversations, social and workplace interactions, and in patients with dentures. The efficacy of most of these preparations has not been subjected to critical analysis and they should only be tried after an adequate trial of simple water.

Many artificial salivas are dispensed as sprays, but liquids, including mouthwashes, lozenges or pastilles are available. NOTE: Au's, in which patients do you recommend which preparations? Are there different clinical characteristics that determine which you would use first, second, etc? Thanks*: Lozenges or pastilles are generally easiest for patients to use and more convenient as*

*can be carried around. Mouthwashes difficult as need to spit out. Sprays helpful but some patients find sensation in mouth unpleasant. Bottom line is, try several things and see what patient finds works best for them PC* Sprays may be more difficult to use for patients with arthritis. The product should be applied to the inner lips, buccal mucosa, and hard palate.

Commonly used sprays include Salivart and Mouth Kote. If painful gums are a problem, a gel such as Oral Balance can be helpful. Numoisyn is a product available as a liquid and throat lozenge that contains a linseed oil extract which can reduce dry mouth symptoms [25].

Several different products should be tried if a particular substitute is not acceptable, as products differ in viscosity and other characteristics, and patient characteristics and preferences vary [24]. An illustrative selection of products available in the United States and the United Kingdom are listed (~~show table 1A-1B~~).

The remainder of this topic review is discussed separately. (See "Treatment of dry mouth and other non-ocular sicca symptoms in Sjögren's syndrome-II").

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