Aetiology and management of xerostomia and salivary gland hypofunction

Dry mouth can be disabling for the patient and challenging for the clinician to manage. Xerostomia is the subjective perception of oral dryness whereas salivary hypofunction is an objectively measured decrease in whole saliva production. Management includes saliva substitutes and stimulants which may only give partial symptom relief.

Saliva is important in maintaining oral health. It contains mineral ions (calcium and phosphate) which remineralise teeth to protect against dental caries (*Figure 1*) and dentine hypersensitivity, and it also provides lubrication which allows discomfort-free eating and speech (Rogers and Atkin, 2012). Patients who present with 'dry mouth' may be categorized into those with perceived oral dryness and those with actual reduction in or absence of saliva. Dry mouth or xerostomia is defined as less than 1.5 ml unstimulated salivary flow in 15 minutes (Navazesh and Kumar, 2008). There are numerous causes of xerostomia and management should focus on ruling out pathology such as Sjögren's syndrome which increase lymphoma risk in longstanding disease (Risselada et al, 2013). It is difficult to accurately describe the epidemiology of xerostomia and salivary hypofunction as there are often multi-factorial issues. It has recently been estimated that the incidence of xerostomia in non-smokers is 13% and in smokers is 37%, whereas the incidence of salivary hypofunction in non-smokers is 8% and in smokers is 43% (Dyasanoor and Saddu, 2014). Xerostomia can increase with age.

Treatment includes saliva stimulants and substitutes prescribed for frequent use to alleviate the symptoms caused by dryness or prescription of medication which stimulates residual saliva flow, usually in the form of pilocarpine, a cholinergic agent. Referral to specialist care such as the oral medicine department should be considered when diagnosis is uncertain and simple measures such as maintaining an adequate fluid intake and reducing intake of beverages promoting diuresis, including caffeine and alcohol, has failed.

The oral effects of dry mouth are numerous (*Table 1*). The social implications for patients can be significant secondary to these symptoms. As none of the saliva substitutes produce lasting lubrication, it can also be difficult to find time to use them frequently enough to gain meaningful benefit. The impact of dry mouth on quality of life can be profound.

The aetiology of dry mouth

Frequently a complex aetiological picture contributes to an individual perceiving xerostomia (*Table 2*). Advancing age, polypharmacy, co-existing medical comorbidities, psychological issues and lifestyle choices such as smoking, alcohol and recreational drug use contribute to the often multifactorial aetiology. With the population living

Figure 1. Dental caries in a xerostomic patient.

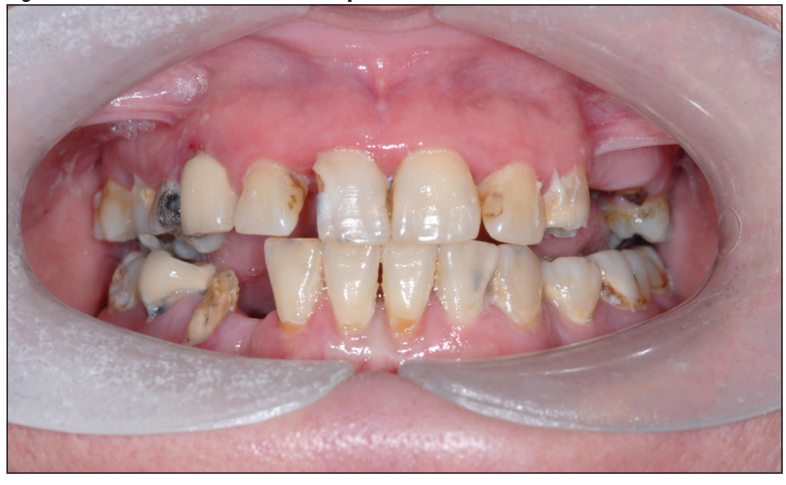

Table 1. Oral effects of dry mouth

Dental caries (*Figure 1*)
Dysgeusia (altered taste perception)
Dysarthria
Burning mouth
Dysphagia
Odynophagia (painful swallow)
Speech difficulties
Foul taste in mouth
Halitosis
Superinfection or predisposition to fungal and bacterial oral infections (*Figure 2*)
Difficulty in tolerating dentures and/or development of traumatic ulceration

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longer and chronic diseases requiring numerous medications, polypharmacy is an issue all clinicians must face daily in practice (Moore and Guggenheimer, 2008) (*Table 3*).

Clinical features of xerostomia

An individual with a truly dry mouth may be identified by him/her carrying bottled water. He/she may require frequent sips to enable him/her to speak in comfort. Clinical examination may reveal evidence of salivary hypofunction including dental caries (*Figure 1*), diffusely enlarged salivary glands, intra-oral candidosis (Williams and Lewis, 2011) which can be acute, chronic or acute-on-chronic (*Figure 2*) and angular cheilitis (*Figure 3*). Examination may be difficult as the dental mirror sticks to the dry oral mucosae which may appear shiny, tight and desiccated. The tongue may take on a lobulated or fissured appearance (*Figure 4*) and the gingivae may lose their characteristic stippling and become shiny. Dental caries may be rampant and characteristically affects the necks of the teeth ('cervical caries') (*Figure 1*) and periodontal health may be impacted upon by the inability to clear food debris and plaque build up through by usual cleansing action by saliva. The oral cavity may display minimal, frothy saliva and the usual pooling of saliva in the floor of the mouth may be absent. It may not be possible to milk any saliva from the major salivary gland ducts on bimanual palpation. Paradoxically, those with anxiety-related xerostomia may be normal in the above regards during the consultation as they do not exhibit hypofunction; many have normal salivary flow.

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Figure 2. Oral candidosis affecting the palate in a xerostomic patient.

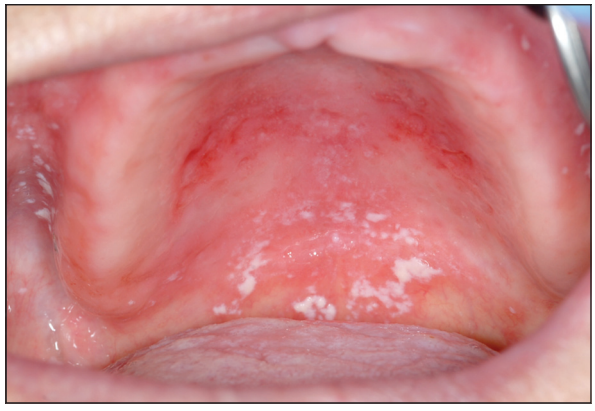

Figure 3. Angular cheilitis in a xerostomic patient.

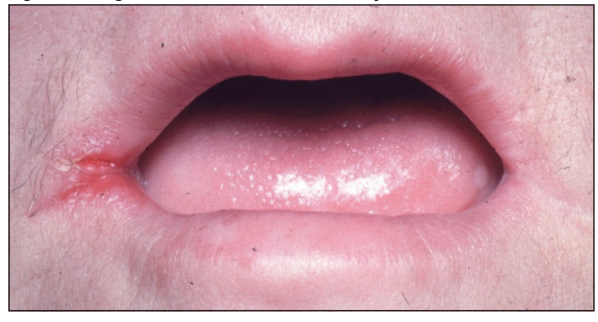

Table 2. The aetiology of dry mouth

Iatrogenic	Drugs (*Table 3*)
	Radiotherapy to the salivary glands
	Cytotoxic therapy
	Smoking
	Smokeless tobacco use (e.g. paan, khat)
	Alcohol
	Recreational drug use (e.g. amphetamines, cocaine, cannabis)
Organic disease	Sjögren's syndrome
	Diabetes mellitus
	Graft *vs* host disease
	HIV infection
	Hepatitis C infection
	Thyroid disease
	Sarcoidosis
	Amyloidosis
	Aberrant iron storage (haemochromatosis, thalassaemia)
	Mumps (transient)
Functional causes	Dehydration or inadequate daily intake of fluid
	Persistent diarrhoea and/or vomiting
Psychogenic causes	Anxiety
	Depression
	Habitual mouth breathing

Table 3. Drugs that may cause dry mouth

Antimuscarinics including treatment for urinary incontinence and increased frequency, e.g. oxybutynin, solifenacin, trospium chloride
Tricyclic antidepressants, e.g. amitriptyline, dosulepin, lofepramine
Proton pump inhibitors, e.g. omeprazole, lansoprazole
Antihistamines
Antiemetics (including both antihistamines and phenothiazines)
Antipsychotics, e.g. quetiapine, risperidone, clozapine
Sympathomimetics, e.g. dopamine, adrenaline
Highly active antiretroviral therapy (HAART) (antivirals used in the treatment of HIV infection)
Drugs used to treat Parkinson's disease, e.g. pramipexole, ropinirole
B2 agonists, e.g. salbutamol, formoterol, ipratropium
Older antihypertensives, e.g. clonidine
Appetite suppressants (legally prescribed amphetamines)
'Cold cures' bought over the counter including ephedrine or pseudoephedrine

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Investigation of dry mouth

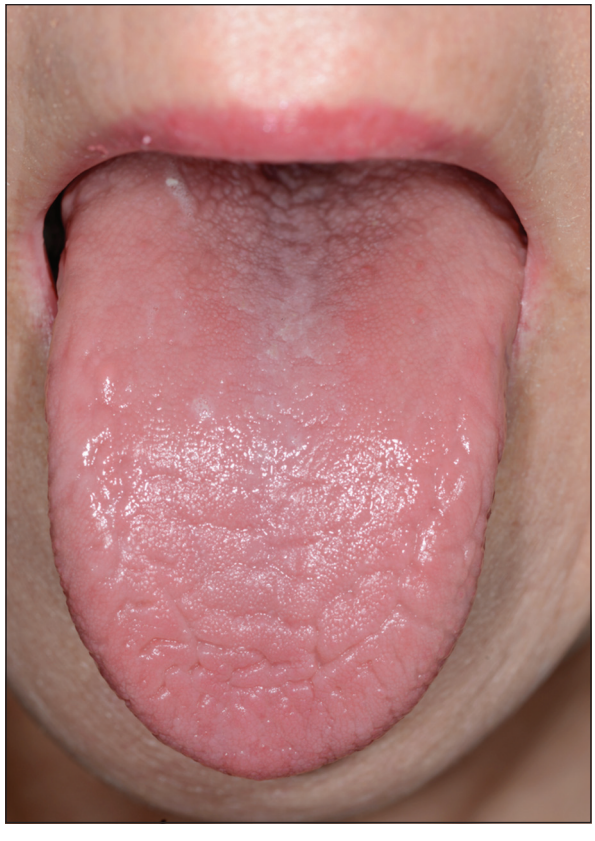
In those patients who complain of extra-oral dryness, namely ocular, it is prudent to perform investigations to look for Sjögren's syndrome (*Table 4*). Elevated levels of markers of inflammation, abnormal thyroid function, evidence of diabetes or positivity of autoimmune antibodies which are indicative of a relevant autoimmune condition, including Sjögren's syndrome, systemic lupus erythematosus and rheumatoid arthritis, may be detected by performing screening bloods (*Table 5*). Advances in imaging, especially ultrasound, are rapidly changing the way in which salivary gland pathology is diagnosed.

Diseases affecting the salivary glands

Sjögren's syndrome

Sjögren's syndrome is an autoimmune condition which has whole body effects but notably causes xerostomia as a result of lymphocytic infiltration of the salivary glands (as well as other exocrine glands) with progressive destruction of the acinar structure (Vitali et al, 2002). Along with the effects on salivary tissue, Sjögren's syndrome causes xerophthalmia, arthralgia, myalgia and fatigue. It is most commonly seen in women in the fifth to seventh decade of life but may affect those at the extremes of life, including children. The condition may be present as an autoimmune disease in its own right or can be secondary to various connective tissue disorders. Anti-Ro and anti-La antibodies may be positive in Sjögren's syndrome (*Table 6*).

Figure 4. Tongue appearance in a patient with xerostomia.



Primary Sjögren's syndrome

Primary Sjögren's syndrome carries a significantly increased risk of lymphoma in the salivary glands as well as extra-nodal sites with longstanding disease. Those with enlarged parotids are most at risk and regular surveillance with ultrasound imaging of the major salivary glands including the thyroid and lymph nodes of the neck is advised.

Secondary Sjögren's syndrome

Secondary Sjögren's syndrome most commonly develops after rheumatoid arthritis or systemic lupus erythemato-

Table 4. Investigations used in xerostomia

Sialometry	The measurement of unstimulated and/or stimulated saliva production in a set time
Schirmer's test	A measure of ocular wetting done by placing a strip of blotting paper under the eyelid and measuring the tear production by wetting length on the paper
Oral rinse	The patient rinses sterile saline around his/her mouth then spits it into a sample tube; microscopy is then performed to identify any potentially pathogenic microbes (oral candidosis may produce the sensation of xerostomia)
Ultrasound	This is both sensitive and specific for features of Sjögren's syndrome and may be used in conjunction with the older technique of sialography
Sialography	Cannulation and introduction of a radio-opaque contrast media into one of the major salivary glands with plain film radiographs taken at intervals during the procedure
Labial salivary gland biopsy	Harvesting a small collection of salivary glands usually from the lip for histopathological analysis; may show pathognomonic features in Sjögren's syndrome

Table 5. Blood tests used in investigation of xerostomia

Full blood count, C-reactive protein, erythrocyte sedimentation rate
Random glucose
Haematinics (vitamin B_{12}, folate and ferritin)
C3 and C4 complement levels
Rheumatoid factor
Autoantibodies including ANA, dsDNA and ENA (which includes anti-Ro and anti-La autoantibodies)
Immunoglobulins and serum electrophoresis

Table 6. Antibody positivity in Sjögren's syndrome

Autoantibody	Primary Sjögren's syndrome	Secondary Sjögren's syndrome
SS-A (anti-Ro)	10%	Up to 80%
SS-B (anti-La)	Up to 70%	5%
Rheumatoid factor	Over 50%	Over 90%

sus is diagnosed. Patients with other connective tissue disorders may also go on to develop Sjögren's syndrome. This group is less at risk of lymphoma than those with primary disease (Risselada et al, 2013). Diagnosis of either form of the disease is made on the basis of patients fulfilling the revised version of the guidelines developed during the 1988–96 European Study Group on Classification Criteria of Sjogren's Syndrome (Vitali et al, 2002) (*Tables 7* and *8*).

Table 7. Revised classification criteria for Sjögren's syndrome

For primary Sjögren's syndrome	In patients without any potentially associated disease, primary Sjögren's syndrome may be defined as follows:	The presence of any four of the six items is indicative of primary Sjögren's syndrome, as long as either item IV or VI is positive (*Table 8*)
		The presence of any three of the four objective criteria items (III, IV, V or VI)
		The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in the clinical-epidemiological survey
For secondary Sjögren's syndrome	In patients with a potentially associated disease (e.g. another well-defined connective tissue disease), the presence of item I or item II plus any of the two from among items III, IV and V may be considered as indicative of secondary Sjögren's syndrome	
Exclusion criteria	Past head and neck radiation treatment	
	Hepatitis C infection	
	Acquired immunodeficiency disease (AIDS)	
	Pre-existing lymphoma	
	Sarcoidosis	
	Graft *vs* host disease	
	Use of anticholinergic drugs (for a time shorter than four times the half life of the drug)	

From Vitali et al (2002)

Diabetes mellitus

Between 10 and 20% patients with type 1 diabetes complain of xerostomia (Moore et al, 2001), as do 14% of those with type 2 diabetes mellitus (Bajaj et al, 2012). Both xerostomia and salivary hypofunction have been reported in diabetic patients without other significant medical comorbidity or medications known to cause xerostomia. As glycaemic control worsens, both resting and stimulated salivary flow declines in patients with type 1 diabetics (Vitali et al, 2002). This may be caused by the effect of elevated blood glucose causing a relatively high osmotic gradient leading to dehydration and therefore reduced salivary production. In addition in longstanding diabetes mellitus, autonomic dysfunction occurs and peripheral neuropathies may lead to dysregulation of salivary function.

Graft *vs* host disease

Graft *vs* host disease takes acute and chronic forms which may present with various oral manifestations, but salivary hypofunction is seen most in the chronic state where it is common but not pathognomonic (Hymes et al, 2012). On a histopathological scale, the salivary tissue is actually damaged in the same way that we see in Sjögren's syndrome and is largely indistinguishable (Imanguli et al, 2009).

Table 8. The diagnosis of Sjögren's syndrome

I. Ocular symptoms: a positive response to at least one of the following questions	Have you had daily, persistent, troublesome dry eyes for more than 3 months?
	Do you have a recurrent sensation of sand or gravel in the eyes?
	Do you use tear substitutes more than three times a day?
II. Oral symptoms: a positive response to at least one of the following questions	Have you had a daily feeling of dry mouth for more than 3 months?
	Have you had recurrently or persistently swollen salivary glands as an adult?
	Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs (i.e. objective evidence of ocular involvement defined as a positive result) for at least one of the following two tests	Schirmer's test, performed without anaesthesia (≤5 mm in 5 minutes)
	Rose bengal score or other ocular dye score (greater than or equal to Bijsterveld's scoring system)
IV. Histopathology	In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a score more than or equal to 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests	Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
	Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitatory or destructive pattern), without evidence of obstruction in the major ducts
	Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
VI. Autoantibodies: presence of the following in the serum	Antibodies to Ro or La antigens or both

From Vitali et al (2002)

Management of dry mouth

The role of oral medicine in the management of hypofunction is to identify those with systemic disease driving their symptoms and to liaise with other medical specialities to ensure underlying medical disorders are managed appropriately. Oral medicine specialists are able to manage individuals with dry mouth and patients with proven Sjögren's syndrome may be monitored in the medium to long term if they are not routinely reviewed by a rheumatologist. Management aims to alleviate the symptoms of xerostomia and salivary hypofunction and this may need be continued in primary care on discharge (Porter et al, 2004; Scully and Felix, 2005). A structured guide to management of xerostomia and salivary hypofunction is highlighted in *Table 9*.

More experimental methods for promoting salivation and giving relief of xerostomia include acupuncture and electrostimulation but their safety profiles, efficacy and validity are not completely evaluated (Furness et al, 2013).

Often it is possible to put elements of management in place before a diagnosis is confirmed. General advice includes adequate oral intake of at least 2 litres of water a day divided into frequent small sips, and avoiding sugar-containing beverages and sweets as a means to lubricate the mouth because of their cariogenicity. All patients should be advised to register with a general dental practitioner for routine surveillance, preventative advice, and restorative and periodontal care. Salivary hypofunction causes a higher rate of decay than a normally lubricated oral cavity and use of high fluoride content toothpastes, mouthwashes and even varnishes applied by the general dental practitioner should be considered. Patients may wish to suck sugar-free mints or use chewing gum to stimulate salivary flow.

Various dry mouth preparations are available and it is good practice to give the patient the choice of preparation where possible as the ease of use and texture of product heavily influences patient preference. It is important to note that some of the products available for prescription in the British National Formulary should be avoided in dentate patients as they have an acidic pH (including Biotene Oralbalance gel and Glandosane spray). Also, some agents are animal-derived products and a patient's cultural background may need to be considered when prescribing (these include AS Saliva Orthana spray and lozenges; Biotene Oralbalance gel; BioXtra gel, spray, toothpaste and mouth rinse) (UK Medicines Information, 2013).

Other measures which may be appropriate in the management plan may be referral to colleagues in ophthalmology, rheumatology, infectious disease or a diabetologist for assessment of extra-oral signs and symptoms. It may be necessary for the patient's dentist to work with restorative dentistry or prosthodontics as rampant caries in a dry mouth poses a significant challenge to constructing suitable and functional fixed restorations and dentures. A multidisciplinary approach is often necessary to fully address the patient with salivary hypofunction.

In patients whom have radiotherapy-induced xerostomia or primary Sjögren's syndrome with no major medical comorbidity including cardiovascular disease or respiratory disease, use of the cholinergic agent pilocarpine can be considered to stimulate the patient's residual saliva production (Lovelace et al, 2014). Unfortunately, the adverse effects can be intolerable to patients, particularly the sweating, flushing and dizziness patients commonly report.

Conclusions

Dry mouth is a common problem. It is often multifactorial and frequently the causal factors are irreversible. Management involves the interface with various specialities and primary care practitioners, both medical and dental, to provide the best quality patient care. Investigation of xerostomia in the oral medicine setting seeks to rule out or identify potentially serious underlying disease. Patients need educating with regards to their condition and should be offered psychological support when this is appropriate, for instance when patients present with a perceived xerostomia in the absence of a definable cause or objective salivary hypofunction. It is important to appreciate that xerostomia may often be iatrogenic as a byproduct of medication prescribed to treat other conditions and doctors should not underestimate the impact that xerostomia has on patients' quality of life. As patients live longer and polypharmacy becomes more widespread, it is likely that we will see more patients with dry mouth as a result of multiple factors and therefore its management may become more complex. **BJHM**

Table 9. Structured management of xerostomia and salivary gland hypofunction

General advice	Smoking cessation
	Limit caffeinated drink intake
	Maintain hydration levels with adequate oral fluids daily
	Minimize sugary food and drink intake; chew sugar-free gum or 'sweets' to stimulate salivation
	Advise the patient to register with a general dental practitioner for preventative and restorative treatment
Medication review	Check the patient's drugs for xerostomia-inducing agents – avoid or replace if possible
	Prescribe saliva substitutes, e.g. BioXtra toothpaste, mouthwash and gel
	Ensure dentate patients are not prescribed acidic saliva substitutes
Referral to oral medicine	For complex, multifactorial cases
	When suspecting Sjögren's syndrome or other underlying systemic disease
	Those not improving with above measures
Prescription of pilocarpine	Reserved for cases of primary Sjögren's syndrome or post-radiotherapy to the salivary gland region
	Initiated by oral medicine, continued in primary care
	Titrate dose slowly, monitor for side effects (e.g. sweating, light-headedness)

Conflict of interest: none.

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KEY POINTS

- Saliva is important in maintaining oral health.
- Dry mouth can be disabling for the individual and challenging for the clinician to manage.
- Oral effects of dry mouth include increased risk of oral candidosis and caries, taste disturbances and sore mouth.
- There are numerous causes for xerostomia and management should include ruling out underlying diseases such as Sjögren's syndrome.
- Various saliva substitutes and stimulants are available but most provide just temporary relief.
- In some patients with dry mouth systemic therapy with pilocarpine may be advised.
- Oral medicine specialists play a key role in the diagnosis and management of patients with xerostomia and salivary hypofunction.