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Guidelines

The British Society for Rheumatology guideline for the management of adults with primary Sjögren's Syndrome

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GUIDELINES

Background

Primary Sjogren's Syndrome (pSS) is a classic, immune-mediated, condition of unknown aetiology characterized by focal lymphocytic infiltration of exocrine glands [1]. Patients characteristically complain of drying of the eyes and mucosal surfaces along with fatigue and arthralgia. There is an association with autoimmune thyroid disease, coeliac disease and primary biliary cirrhosis. Systemic features include inflammatory arthritis, scLE, immune thrombocytopenia (ITP), vasculitis with purpura, salivary gland inflammation, neuropathies, interstitial lung disease (ILD) and a 5–10% lifetime risk of B cell lymphoma [2, 3].

This guideline reviews the treatment of the glandular and systemic features of pSS The management of the glandular features includes conserving, replacing and stimulating secretions. Systemic features may require system-specific therapy and immunomodulatory treatment. Holistic

NICE has accredited the process used by the BSR to produce its guidance for the management of primary Sjögren's Syndrome in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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management is important and many patients benefit from non-pharmacological therapies and general support.

Diagnosis

Patients commonly present with dryness of the eyes [4] and mouth [5]. In the early stages they may complain of grittiness rather than dryness of the eyes, and the mouth symptoms may require prompting. Fatigue and arthralgia are almost universal. There is often a considerable delay between symptom onset and diagnosis. The most widely accepted current classification criteria for pSS and those referred to in this guideline are the American-European Consensus Group (AECG) criteria [6]. The 2016 ACR–EULAR criteria have just been published [7] derived from criteria proposed by the Sjögren's International Collaborative Clinical Alliance (SICCA) [8]. The populations described by both criteria are very similar.

For a definite diagnosis the AECG criteria require four out of six of dry eye symptoms, dry mouth symptoms, objective ocular dryness (Schirmer's test $\leqslant$5 mm in 5 min or van Bijsterveld score $\geqslant$4), objective oral dryness (unstimulated salivary flow rate $\leqslant$0.1 ml/min or positive salivary scintigraphy and sialography), positive anti-Ro/La antibodies, labial gland focus score $\geqslant$1 including at least one of the last two objective features.

The 2016 ACR–EULAR classification criteria are based on the weighted sum of five items and require a total score $\geqslant$4 to meet the criteria for diagnosis where the presence of anti-Ro antibodies or focal lymphocytic sialadenitis with a focus score of $\geqslant$1 score 3 each and where abnormal ocular staining score $\geqslant$5, Schirmer's test result of $\leqslant$5 mm/5 min and unstimulated salivary flow rate of $<$0.1 ml/min score 1 each.

Investigations

The best-described autoantibodies in pSS are the anti-Ro and anti-La antibodies, which are routinely identified as part of the ENA laboratory screen. About two-thirds of patients with primary SS have anti-Ro antibodies and/or anti-La antibodies. These figures, however, depend on the classification criteria used, referral bias and access to labial gland biopsy.

Need for guideline

pSS typically presents in women in their fifth or sixth decade, although up to 10% of cases occur in men and it is also seen in younger people. Studies using the AECG criteria have estimated the prevalence in women in the UK at 0.1–0.4% [9]. Patients present to primary care physicians, general physicians, ophthalmologists and dental practitioners many of whom lack specialist knowledge regarding the treatment of this patient cohort.

Objective of guideline

This document aims to provide a pragmatic, practical guideline for the management of adults with pSS.

Target audience

The target audience includes rheumatologists, general physicians, general practitioners, specialist nurses and other specialists (e.g. ophthalmologists, dental practitioners and ENT specialists) who will review patients with pSS during their clinical practice. The guideline should also be of relevance to specialist registrars in training and specialist nurses.

Areas not covered

The management of children with SS is not specifically covered by this guideline although the general management of children and teenagers with SS is similar to that for adults with special emphasis on the importance of good dental care and hygiene to preserve dental health.

SS is very rare in teenagers and there are only anecdotal reports worldwide of its occurrence in pre-pubertal children so we would recommend that children and teenagers presenting with symptoms suggestive of SS are referred to a specialist centre for evaluation and treatment.

In addition this guideline does not cover the detailed management of patients with secondary Sjögren's. Where patients have secondary SS their systemic management should address the primary disease but the advice on topical management contained in these guidelines is applicable to sicca symptoms from any cause. This guideline does not cover the detailed management of patients with lymphoma, who should be managed in conjunction with oncologists and haematologists.

Stakeholder involvement

The multidisciplinary team involved in producing these guidelines was led by Dr Elizabeth Price, Consultant Rheumatologist, who chaired the team, undertook the systematic review and led the development of the guideline. The management of eye disease was led by Miss Saaeha Rauz, Clinical Senior Lecturer and Clinical Ophthalmologist, who also acted as The Royal College of Ophthalmologists' representative. Dr Anwar Tappuni, Reader and Academic Lead for Oral Medicine, was the main contributor to the oral section and Dr Nurhan Sutcliffe, Consultant Rheumatologist, acted as the lead for the systemic section. Ms Katie L. Hackett was the British Health Professionals in Rheumatology's representative and lead for non-pharmacological management. Dr Francesca Barone, Clinician Scientist and Honorary Consultant Rheumatologist, was the lead for the Delphi process and supervised Dr Guido Granata, Visiting Fellow, who undertook the Delphi analysis. Professor Wan-Fai Ng, Consultant Rheumatologist, Dr Benjamin A. Fisher, Senior Clinical Lecturer and Honorary Consultant Rheumatologist, Dr Michele Bombardieri, National Institute for Health Research Senior Clinical Lecturer in Rheumatology, Dr Elisa Astorri, Clinical Research Fellow, Miss Genevieve Larkin, Consultant Ophthalmologist, and Professor Simon Bowman, Consultant and Honorary Professor of Rheumatology, provided further review and clinical input. Mrs Bridget Crampton contributed as a patient representative and Dr Benjamin Empson provided GP representation.

Conflict of interest statement

Any conflicts of interest among members of the working party were fully declared. The declared conflicts of interest are included at the end of the article.

Rigor of development and limitations

A search was undertaken for all relevant evidence in the Cochrane Library, MEDLINE (Ovid and PubMed) and EMBASE from 1990 to current (February 2015 and updated September 2015). Additional references were added through regular updates to the draft recommendations up to January 2016. Non-English language papers were excluded unless a translation was published. We also excluded treatments not currently available in the UK unless there was a significant likelihood they would become available in the near future. Identified papers were reviewed, categorized and the level of evidence graded according to international criteria from Ia through to IV and A through to B [10]. See supplementary data Search history and supplementary table S1, available at *Rheumatology* online, for full details of search criteria and level of evidence definitions.

The guideline was developed in line with the BSR Guideline Protocol using Appraisal of Guidelines for Research and Evaluation II methodology (http://www.agreetrust.org/). The wording and content of the recommendations were subjected to a formal Delphi process [11] using online surveys to determine the eventual strength of agreement (SOA) for each recommendation. The Delphi method was developed in the 1950s. It describes a process whereby a group of experts anonymously reply to questionnaires and subsequently receive feedback in the form of a statistical representation of the group response, after which the process repeats itself. The goal is to reduce the range of responses and arrive at something closer to expert consensus. In our case each recommendation was rated on a score from 1 (no agreement) to 10 (complete agreement). The results were collated and circulated to the group prior to the second round. We then included recommendations with a mean SOA score of $\geqslant 7$ plus $\geqslant 75\%$ respondents scoring $\geqslant 7$. This is expressed as the mean score with percentage $\geqslant 7$ in parentheses, for example, SOA 7 (75%) with a maximum of 10 (100%).

The guideline

Eligibility criteria

This guideline is primarily aimed at the management of patients with pSS as defined by the AECG [6] or ACR–EULAR (in press) criteria but the advice on topical management contained in these guidelines is applicable to sicca symptoms from any cause.

Exclusion criteria

Sicca symptoms can result from a variety of causes, some of which may be reversible if addressed. Drugs are a common cause of sicca and many different drug groups have been implicated. Potential causative agents include those with anti-cholinergic activity such as anti-depressants, anxiolytics and anti-psychotics; muscarinic anatagonists such as tamsulosin hydrochloride and ipratropium hydrochloride; anti-histamines; opiates; anti-hypertensives including beta-blockers and angiotensin converting enzyme (ACE) inhibitors; and proton pump inhibitors such as omeprazole. Avoiding these entirely may not be practicable, but use should be minimized in the presence of sicca symptoms if possible.

Sicca symptoms are commonly seen following head and neck radiotherapy and may respond to topical treatment and pilocarpine (see below). Dehydration and acute anxiety may cause temporary sicca symptoms. Rarely, primary salivary gland pathology other than SS including sarcoidosis, IgG4 disease [12] and graft *vs* host disease [13] may be implicated. Salivary gland aplasia and ductal atresia [14] are both rare causes of oral sicca and viral infections including hepatitis C and HIV can cause salivary gland disease with hypertrophy and sicca symptoms.

Xerostomia can be a feature of oral dysaesthesias with no objective reduction in salivary flow rate. Oral dysaesthesia or burning mouth syndrome is a chronic pain condition currently classified as a neuropathic disorder. Such patients may complain of a constellation of oral symptoms, including burning sensations, unusual taste as well as oral dryness, and their symptomatology is not uncommonly associated with anxiety states and clinical depression. There may also be a history of low back pain, FM and irritable bowel syndrome [15].

A syndrome comprising histological evidence of sialadenitis, nodular osteoarthritis and xerostomia has been described [16], but in view of the frequency of the individual clinical features and the demographics of the individuals with these conditions, clustering of these entities could also be expected to occur on a simple statistical basis.

Ageing *per se* is not a cause of xerostomia. Although there is a broadly linear reduction in the amount of functional acinar tissue within the salivary glands over time, this does not lead to clinically significant salivary gland hypofunction in normal subjects [17]. Xerostomia in the ageing population is more a function of intercurrent disease and medication rather than loss of secretory ability [18].

The guideline

The guideline covers management of the eye and mouth manifestations, systemic dryness and systemic disease in general with comments on the management of pregnancy and lymphoma in patients with SS. For each section we have reviewed and summarized the available evidence and then listed the recommendations that achieved a mean SOA score of $\geqslant 7$ plus 75% of respondents scoring $\geqslant 7$ after the second round of the Delphi process as described above. In general we would recommend initial symptomatic treatment of sicca manifestations combined, if appropriate, with systemic management.

Treatment of sicca manifestations

All patients with pSS (and sicca from other causes) should be offered symptomatic treatment of dryness. The sicca

Table 1 Dry eye management summary

Level 1: mild dry eye	Level 2: moderate dry eye	Level 3/4: severe dry eye (ophthalmology only)
Features	Features	Features
Tear film break-up time: >9 s	Tear film break-up time: 5–9 s	Tear film break-up time: <5 s
Staining: VB score = 0–3, OSS = 0	Staining: VB score = 4–5, OSS = 1–6	Staining: VB score = 7–12, OSS = 5–12
Management	As for mild plus:	As for moderate plus:
Educational and environmental	Moisture chamber spectacles	Lubricants
Lubricants	Lubricants	High concentration hyaluronates 0.2–0.4%
Hypromellose	Carmellose 1% eye	Hyaluronates with Xanthan gum
Carbomer gels	Low concentration hydroxypropylguar eye drops	Soybean with phospholipids
Carmellose 0.5%	Sodium hyaluronate eye drops 0.1–0.18%	Mucolytics for filaments, e.g. acetylcysteine
Ointments	For corneal inflammation consider prednisolone 0.5% non-preserved 2–3× daily (ophthalmology only)	Higher strength topical steroids for short term use, e.g. dexamethasone 0.1%
Lid hygiene	For blepharitis consider metallomatrix proteinase inhibitors, e.g. doxycycline 50 mg od (ophthalmology only)	Ciclosporin-containing drops or ointment
Liposomal sprays available over the counter to replace tear film oil layer	Punctal plugging—punctal or intracanalicular plugs (ophthalmology only)	Nutritional tear substitutes
	Secretagogues	Autologous or allogeneic serum eye drops (available via specialist commissioned centres only)
	Oral pilocarpine max 5 mg 4× per day (start with 2.5 mg od and build up)	Permanent punctal occlusion via cautery of all four puncta
	Pilocarpine 4% (3 drops = 5 mg) for those who are unable to swallow (palliative care pathway [56])	Periorbital botulinum toxin for significant blepharospasm
		Bandage contact lenses
		Amniotic membrane overlay or corneal grafting for significant corneal ulceration and corneal melt or perforation

Based upon the DEWS workshop and the Meibomian Gland Dysfunction Workshop [19]. VB: van Bijsterveld Schema; OSS: ocular surface staining score.

symptoms classically affect eyes and mouth but many patients also experience a chronic, dry cough due to drying of the mucosal surfaces and, in women, vaginal dryness. In general treatment of sicca symptoms should aim to conserve, replace and stimulate secretions while reducing inflammation.

Management of ocular manifestations of SS

Dry eyes may be classified as mild, moderate or severe based on the presence of both symptoms and signs [19]. Definitions are included in Table 1 and rely on knowing the tear film break-up time and/or the ocular surface staining score. In the past, staging of eye disease has not routinely been carried out by optometerists and ophthalmologists but this is changing with routine staging being introduced for other eye diseases. In practice rheumatologists and GPs will either rely on patient reported symptoms or simple Schirmer's testing to assess severity of disease but, by definition the majority of patients with SS will have severe dry eye (Schirmer's $\leqslant$5 mm in 5 min and tear break-up time $\leqslant$5 s).

It should be remembered that in Sjögren's associated dry eye all three layers of the tear film are affected. There is mucosal layer deficiency, aqueous deficiency and meibomian gland deficiency, all of which need to be addressed.

Ocular—conservation of tears and meibomian gland secretions

Systemic medications that exacerbate dryness should be avoided if possible. These include those with anti-cholinergic activity (psychotropics including antidepressants, anxiolytics and anti-psychotics), muscarinic antagonists (e.g. tamsolusin hydrochloride; ipratropium hydrochloride), anti-histamines, opiates, anti-hypertensives (e.g. beta blockers; ACE inhibitors) and proton pump inhibitors (e.g. omeprazole), although the latter may have an important role in the treatment of laryngotracheal reflux.

Studies have shown that humidification of cabin air increases tear-film stability [20] in normal individuals and by extrapolation it is advised for dry eye. Patients consistently report feeling more comfortable in a humidified environment.

Two randomized placebo controlled trials showed improvements in symptoms of dry eye following oral supplementation with omega 3 fatty acids, with improvement in both Schirmer's test and markers of ocular inflammation [21, 22]. There is some low quality evidence that omega 7 derived from sea buckthorn oil provides some symptomatic relief of dry eye symptoms from both a small, open label, informal study [23] and a double-masked, randomized, parallel trial [24]. The evidence was felt to be of insufficient strength to include this as a recommendation within the final guideline.

Adequate meibomian gland secretion is essential to prevent evaporative tear loss. There is evidence that it is useful to enhance meibomian gland secretion using either warm compresses or commercially available microwavable lid warming compresses [25]. Patients should be advised to perform lid hygiene if required using proprietary wipes (available over the counter) or with a weak solution of bicarbonate. Useful guides for patients are available on both the National Health Service and the National Institute for Health and Care Excellence (NICE) websites [26, 27].

A recent report by the American Academy of Ophthalmologists reviewed the evidence for the oral antibiotics doxycycline, minocycline and azithromycin in the management of ocular surface disease arising from disorders of the meibomian glands. They identified eight studies that documented an improvement in meibomian gland-related ocular surface disease after treatment with these agents, although side effects were common. Only one study was a randomized, controlled trial. They concluded oral antibiotics may be an effective treatment for ocular surface disease that results from meibomian gland disease [28]. Two small observational, open label clinical studies of topical azithromycin ophthalmic solution 1% (twice daily for 2 days and once daily on days 3–28) in subjects with symptomatic meibomian gland disease, but not specifically SS, showed improvement in both clinical signs and symptoms of disease [29, 30]. Expert advice in the UK is to consider doxycycline 50 mg od for a minimum of 3 months in patients with persistent meibomian gland inflammation and blepharitis not responding to topical management. If treating young patients it is important to remember that doxycycline is contraindicated in those $<$12 years of age. Minocycline is avoided because of the small risk of causing drug-induced lupus.

Wearing spectacles reduces surface evaporation of tears by up to 30% and the effect can be optimized by the use of moisture chamber spectacles [31, 32]. The latter can be manufactured by opticians or purchased on-line. There is evidence supporting the early use of punctal plugs [33, 34], which improve symptoms of dry eye significantly more than artificial tears alone.

First line treatment should be with visible plugs. If this successfully improves symptoms or signs, and there is no evidence of excess watering or over flow of tears, then permanent punctal occlusion can be achieved with punctal cautery. Intracanalicular plugs are effective but increase the risk of granuloma and infection [35, 36] and are not visible on examination. Referral to an ophthalmologist is advised and it is important to remember that plugs are available in different sizes and the puncta should ideally be measured with a calliper prior to selection and insertion of an appropriately sized plug. Improperly sized plugs may fall out, with accompanying deterioration in symptoms; alternatively loose plugs will allow tear flow, or cause irritation.

Recommendations for conservation of tears and meibomian gland secretions

(i) Treatment should begin with conservation of tears by humidification and avoidance of systemic medication that exacerbates dryness. Level of evidence Ib/A; SOA 8.9 (97%).
(ii) Patients should be advised to stimulate meibomian gland secretion daily using either warm compresses or commercially available microwavable lid warming compresses or other devices and perform lid hygiene if required using proprietary wipes (available over the counter) or with a weak solution of bicarbonate. Level of evidence III/C; SOA 8.9 (93.3%).
(iii) In patients with persistent meibomian gland inflammation and blepharitis, treatment with doxycycline 50 mg od for a minimum of 3 months may be effective. Level of evidence IV/D; SOA 8.83 (92.9%).
(iv) Early referral to an ophthalmologist for review and consideration of insertion of punctal plugs or cauterization of puncta is recommended. Level of evidence II/B; SOA 9.27 (100%).

Ocular—replacement of tears and meibomian gland secretions

Liposomal sprays (available over the counter but not currently FP10 prescribable) reduce evaporative tear loss and replace the meibomian gland layer and have been shown to significantly reduce sicca symptoms [37].

To replace the aqueous tear film start with simple lubricating drops using the most cost-effective options. In general start with low viscosity simple drops such as hypromellose and escalate as symptoms dictate. Given the severity of dry eye disease in primary SS, it is unlikely, however, that simple drops will be sufficient to control the disease. When prescribing take into account the bottle or device used to apply the drops. In particular consider ease of application and expiry dates. See advice below and in accompanying Table 2 for preparations.

Multi-use ophthalmic preparations rapidly become colonized with bacteria and are associated with high rates of pathogenic organisms on conjunctival culture [38]. As a result, the majority of multi-dose preparations contain a preservative to limit bacterial, fungal and amoebic ocular infections and prolong shelf life by preventing biodegradation. High concentrations of certain preservatives

Table 2 Dry eye topical therapies

Viscosity	Compound	Preserved	Non-preserved
Low	Hypromellose	Hypromellose MD[a]	Artelac SDU
		Xailin Hydrate MD	Hydromoor SDU
		Tears Naturale MD[a]	Tears Naturale SDU
			Tear-Lac MD
	Polyvinyl alcohol	Liquifilm Tears MD[a]	Liquifilm Tears SDU
		Tubilux MD	Refresh SDU
Thin–medium	Carbomers	Viscotears	Viscotears SDU
		Gel Tears[a]	Visidic[b]
		Clinitas Carbomer Gel	
		Artelac Nighttime Gel	
	Carmellose	Optive 0.5% MD	Celluvisc 0.5 or 1% SDU
		Carmize 0.5% MD	Xailin Fresh 0.5% SDU
		Lumecare Advance 0.5% MD	Evolve Carmellose 0.5% MD
			Carmize 1% MD
	Guar gums	Systane MD	Systane SDU,
		Systane Ultra	Systane Ultra SDU
		Systane Gel	
		Systane Balance	
Thick–medium	Sodium hyaluronates	Xailin HA 0.2%	Vismed 0.18% SDU or MD
		Blink Intensive Tears 0.2% MD	Vismed gel 0.3%
			Clinitas 0.4% SDU
		Optive Fusion 0.1% MD	Clinitas Multi 0.4% MD
		Oxyal 0.15% MD	Hycosan[b]
		Artelac Rebalance 0.15% MD	Hylo-Forte 0.2%, Hylo-Care 0.1%, Hylo-Tear 0.1% (MD) Artelac Splash 0.2% SDU Blink Intensive 0.2% SDU Evolve Hyaluronate 0.4% MD Lubristil 0.15%/1% xanthan gum
High	Paraffin/white petroleum	—	Lacri-lube
			VitA-Pos
			Xailin Night
			HydraMed Night
Others	Liposomes[b]	—	Actimist[b]
			Vizulize Dry Eyes Eye Mist[b]
			Eye logic liposomal eye drops and spray (formerly Clarymist)[b]
	Soy bean/mineral oil	—	Emustil SDU
	Mucolytics[c]	Aceylcesteine (Ilube)[c]	Acetylcysteine 10% MD (unlicensed)[c]
	Anti-inflammatory or immune regulators[c]	—	Ciclosporin 0.2% (unlicensed, Optimmune®) veterinary preparation[c]
			Restasis® (not licensed EU)[c]
			Ciclosporin 0.1% (licensed, Ikervis® SDU)[c]
	Disaccharides[b]	—	Thealoz MD[b]
			Thealoz Duo MD[b]
			Thealoz Duo SDU[b]
			Thealoz Duo Gel SDU[b]
			HydraMed [sodium hyaluronate (0.2% w/v), polysaccharide (0.2% w/v)]

A selection of ocular lubricants available in preserved and non-preserved forms. Most are available both over the counter and on prescription, some are prescription only and others are over the counter only. [a]Contains benzalkonium chloride (should be avoided). [b]Over the counter only. [c]Prescription only. MD: multidose bottle; SDU: single dose units.

may damage and irritate ocular tissue and this effect is enhanced in those with ocular surface disease. Benzalkonium chloride is the most frequently used preservative in topical ophthalmic preparations and its epithelial toxic effects are well established [39]. Preserved preparations should be avoided in patients using eye drops long term (for >3 months), instilling drops >4 times daily or those with ocular surface disease (effectively the majority

of patients with pSS). Some eye drops are available as single-use preservative-free preparations. Although convenient these are often costly and require good manual dexterity to use. Increasingly eye drops are available in multi-use bottles with preservative systems that biodegrade on contact either with light or with the ocular surface. Other preservative-free multidose systems use a pump or vacuum system preventing regurgitation into the bottle and obviating the need for preservatives altogether.

Autologous or allogeneic serum eye drops are the only available nutritional tear substitutes and are effective and well tolerated by patients [40, 41]. However, they are very expensive to produce and are only available from commissioned specialist centres.

Recommendations for replacement of tears and meibomian gland

(i) Recommend liposomal sprays to reduce evaporative tear loss and replace the meibomian gland layer. Level of evidence III/C; SOA 8.29 (92.8%).
(ii) Start with simple lubricating drops using the most cost-effective options (see Table 2 for preparations). Level of evidence IV/D; SOA 9.3 (93.3%).
(iii) Avoid preservative-containing preparations. Level of evidence I/A; SOA 9.21 (92.9%).
(iv) Patients with severe dry eye, not responding to conventional treatment may be referred to specialist centres for consideration of autologous or allogeneic serum eye drops. Level of evidence IIb/B; SOA 9.5 (100%).

Ocular—anti-inflammatory

There is evidence supporting the use of topical anti-inflammatories under ophthalmic supervision in patients with persistent corneal inflammation. Low dose steroid-containing eye drops are recommended for short term use and have been shown to be both safe and effective [42]. Longer term use of topical steroids has been associated with an increased risk of glaucoma and cataract and should be avoided [43]. In general the use of topical steroids should be limited to patients under supervision by an ophthalmologist. For longer term use ciclosporin-containing eye drops have been shown to reduce subjective symptoms and improve objective signs of inflammation in patients with both primary and secondary SS [44–46]. Ciclosporin 0.1% (Ikervis®) is licensed and NICE approved as a possible treatment for people with dry eye disease that has not improved despite treatment with artificial tears (NICE TAG 369 December 2015 [47]) but must initially be prescribed by a sub-specialty ophthalmologist. An unlicensed veterinary ointment (Optimmune®, ciclosporin 0.2%) or a preservative-free eye drop available via Moorfields Pharmaceuticals may be used as alternatives. All forms of topical ciclosporin may be used off licence for patients <16 years of age.

Topical NSAIDs such as diclofenac and indomethacin have been shown to improve ocular discomfort but reduce corneal sensitivity and may predispose to further corneal damage and should therefore be used only with caution in patients with SS [48, 49].

Recommendation for anti-inflammatory treatment of dry eye

(i) Low dose steroid-containing eye drops are recommended for short term use under ophthalmic supervision only. Level of evidence Ib/A; SOA 9.64 (100%).
(ii) Longer term use of topical steroids should be avoided. Level of evidence Ib/A; SOA 9.64 (100%).
(iii) Ciclosporin-containing eye drops or ointments may be used under ophthalmic supervision in patients with evidence of chronic inflammation. Level of evidence Ib/A; SOA 9.38 (100%).
(iv) Topical NSAIDs such as diclofenac and indomethacin should be used with caution under ophthalmic supervision only. Level of evidence IIb/B; SOA 9.86 (100%).

Ocular—stimulate

Oral pilocarpine treatment can improve ocular dryness and tear film break-up time and increase goblet cell density thus improving the mucous layer [50–54]. Symptomatic and objective improvements are seen in more than a third of patients, although side effects (headache, increased sweating) may limit its use in some.

The recommended starting dose is 5 mg once daily, escalating at weekly intervals as tolerated to 5 mg qds (with meals and at bedtime) but if response is insufficient, the dose can be increased to 30 mg daily, if tolerated well; discontinue if no improvement after 2–3 months. Contraindications include uncontrolled asthma and chronic obstructive pulmonary disease, uncontrolled cardiorenal disease and acute iritis. Common side effects include dyspepsia, diarrhoea, abdominal pain, flushing and increased urinary frequency. There is evidence from an observational study that it is both safe and effective in children and young people as young as 9 years of age [55]. In patients intolerant of pilocarpine tablets, using topical ocular drops orally allows delivery of a smaller dose of drug and may be better tolerated. The Palliative Care Formulary suggests 2–3 drops of pilocarpine 4% eye drops is equivalent to 4–6 mg oral pilocarpine; however this is an off-licence use [56].

Recommendations for stimulation of ocular secretions

(i) A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for patients with significant sicca symptoms and no contraindications to its use. Level of evidence IIb/B; SOA 9.08 (92.3%).

Miscellaneous treatments for dry eye and ocular complications

Mucolytic eye drops, for example, acetylcysteine 5–10% non-preserved, are useful for patients with mucous threads or ocular surface filaments [57] and have also

been shown to improve tear break-up time and Schirmer's tests in patients with meibomian gland disease [58].

Some patients with severe dry eye develop an associated blepharospasm. There are small case series describing a good response to botulinum toxin injections in these circumstances [59, 60].

For severe dry eye bandage scleral contact lenses, designed to protect the surface and create an optimized environment for healing, may be indicated. These lenses vault over the corneal surface and rest on the sclera. They are rigid and gas-permeable and require specialist fitting and manufacture. They are only available in specialist centres for severe corneal disease refractory to other treatment measures. A number of studies have shown significant decreases in corneal staining with scleral contact lens wear with significant improvements in dry eye symptoms and quality of life [61–63].

Corneal grafting or amniotic membrane overlay may occasionally be indicated for cases of significant corneal ulceration and corneal melt [64]. Neuropathic pain (when dry eye symptoms outweigh clinical findings) is a recognized entity. Neuropathic pain strategies should be considered for these patients [65].

Recommendations for severe, complicated dry eyes

(i) Mucolytic eye drops should be prescribed for patients with mucous threads or ocular surface filaments. Level of evidence III/C; SOA 9.38 (100%).
(ii) Patients with severe dry eye and associated blepharospasm may benefit from referral to a specialist centre for consideration of botulinum toxin treatment. Level of evidence III/C; SOA 9.17 (100%).
(iii) Patients with severe dry eye and corneal ulceration, not responding to conventional treatment, may be referred to specialist centres for consideration of bandage contact lenses or amniotic membrane grafting or corneal grafting for perforations. Level of evidence III/C; SOA 9.15 (92.9%).

Management of oral manifestations of SS

Dry mouth (xerostomia) is a hallmark of pSS and the majority of patients suffer from both reduced salivary flow rate and increased viscosity of saliva due to relative deficiency of the aqueous component, which may compromise oral health.

Complications of long-term xerostomia include oral discomfort and soreness and a burning sensation in the mouth. An increased rate of dental caries, excessive tooth wear and premature tooth loss are often observed. Patients struggle to achieve a high standard of oral hygiene and may suffer from halitosis. Patients tolerate dentures poorly and often complain of difficulty retaining them in the mouth with sore, ulcerated gums as a consequence of rubbing. Many patients suffer recurrent infections including parotitis, intraoral candidiasis and angular cheilitis. Dysarthria, dysphagia and dysgeusia (distorted sense of taste) are seen in established disease.

The evidence surrounding periodontal disease in Sjögren's is conflicting, with some studies suggesting an increased prevalence of periodontal disease [66] but others not [67].

Effective management of the dry mouth is important for the maintenance of oral health and to improve oral health-related quality of life as well as general health and quality of life.

Oral—conserve

Many patients with pSS anecdotally report improvement in symptoms following humidification of room air and patients frequently report worsening of symptoms in dry and air-conditioned environments.

Patients with pSS have higher rates of the cariogenic bacterium *Streptococcus mutans*, dental caries and dental loss compared with controls despite apparently good dental care [68, 69]. Dental caries is considered to be a diet-mediated disease, as sugars are essential in the caries process. This has been confirmed in several large-population-based studies that have shown a significant association between total sugar intake and the development of dental decay over time in a normal population. Twice daily use of fluoride toothpaste reduced but did not eliminate the association between diet and dental decay in these studies [70–72].

Given their enhanced risk of dental decay patients with pSS should be advised to practice excellent oral hygiene and avoid sweetened food and drink on a regular basis. Assessment by an Oral Medicine specialist and/or regular visits to a general dental practitioner are recommended to monitor and treat the oral manifestations of SS with the emphasis on preventative dental care.

The optimum concentration of fluoride in standard toothpaste has been calculated assuming a normal salivary flow rate and taking into consideration the availability of fluoride in normal saliva. Concentrations of fluoride in standard over-the-counter toothpastes vary from 500 to 1000 parts per million (ppm) and occasionally higher. Prescription toothpastes contain fluoride concentrations of between 2800 and 5000 ppm. Dry mouth patients will need a higher concentration of fluoride in toothpaste to compensate for the lack of salivary fluoride. A number of studies [73–75] and a Cochrane review [76] have concluded that caries protection is increased with higher fluoride concentrations. A systematic review of the literature and a Delphi consensus exercise by a national panel of experts in North America concluded that there was good evidence that a prescription strength, home-use, fluoride gel or paste should be used in all patients with pSS [77].

Acidic products and those containing sugar should not be prescribed for dentate patients since maintaining a neutral oral pH environment may reduce the development of dental caries [78].

There is evidence that in addition to the total sugar content of the diet, frequency of sugar intake is implicated in dental decay [77]. In light of this we recommend that patients with pSS avoid food and drinks other than plain

water between meals and from 1 h before bedtime and all through the night.

Patients should be advised to brush their teeth at least twice daily (but not immediately after eating) including before bed at night using a pea sized amount of high fluoride toothpaste and use fluoride-containing tooth mousse or gel on teeth twice daily. They should avoid alcohol-containing mouth washes, sugary or fizzy drinks and frequent snacking [77].

Chlorhexidine is an effective antiseptic that inhibits plaque formation on teeth and is useful for controlling gingivitis [79]. Many oral specialists and dentists recommend an alcohol-free chlorhexidine mouth wash in pSS patients as preventative treatment for gum disease. It can be used twice daily for a maximum of 2 weeks every 3 months but over use can lead to staining of teeth.

Recommendations for conservation of moisture and oral hygiene

(i) Patients should be advised to humidify the environment. Level of evidence IIV/D; SOA 9.13 (100%).
(ii) Patients should be advised to practice excellent oral hygiene, limit sugar intake and avoid food and drinks other than plain water between meals and from 1 h before bedtime and all through the night. Level of evidence IV/D; SOA 9.8 (100%).
(iii) Assessment by an oral medicine specialist and/or regular visits to a general dental practitioner typically at 3–6 monthly intervals are recommended to monitor and treat the oral manifestations of SS. Level of evidence IV/D; SOA 9.8 (100%).
(iv) Aim to avoid acidic products and those containing sugar when prescribing for dentate patients. Level of evidence IV/D SOA 9.87 (100%).
(v) Patients should be advised to brush teeth at least twice daily (but not immediately after eating) including before bed at night using a pea sized amount of high fluoride toothpaste and use fluoride-containing oral mousse or gel on teeth twice daily. Level of evidence I/A; SOA 9.8 (100%).
(vi) Alcohol-free chlorhexidine mouth wash used twice daily for a maximum of 2 weeks every 3 months can help prevent gum disease but over use can lead to staining of teeth. Level of evidence IV/D; SOA 9.0 (100%).

Oral—replace

It is common practice to manage mild symptoms by recommending that patients sip water, suck ice or chew sugar-free gum [77, 80]. More severe dryness can be managed with commercially available topical and systemic treatments for dry mouth.

Saliva substitutes provide symptomatic momentary relief of oral dryness. A Cochrane review of the effectiveness of topical treatments for dry mouth from any cause, including parallel and crossover randomized controlled trials of lozenges, sprays, mouth rinses, gels, oils, chewing gum and toothpastes did not find strong evidence for their effectiveness [81, 82], but in the experience of the working group patients report increased oral comfort from their use.

The ideal preparation will have neutral pH and contain fluoride and other electrolytes, mimicking the composition of natural saliva. Saliva substitutes are available commercially in the form of oral sprays, gels and rinses. Most are freely available over the counter and some are prescription only. The choice will depend upon patient preference and local availability. Fluoride-containing, neutral pH preparations should be prescribed for dentate patients (see Supplementary table S2, available at *Rheumatology* online, for products available in the UK). Preparations with acidic pH and/or without added fluoride should only be used in edentulous patients.

There is limited evidence that an oxygenated glycerol triester saliva substitute spray is more effective than a water-based electrolyte spray in older patients with dry mouth [83].

Patients with Sjögren's are at increased risk of frictional oral ulcers [84]. There is evidence that polyvinylpyrrolidone and sodium hyaluronate oral gel (Gelclair) may be helpful in patients with recurrent oral ulceration post-chemotherapy but no published studies of its effectiveness in SS [85]. A list of commercially available oral preparations is provided for reference in Supplementary table S2, available at *Rheumatology* online.

Recommendations for replacement of oral secretions

(i) Patients should be advised to use a neutral-pH fluoride-containing mouth wash, gel or spray as required for symptomatic relief. Level of evidence III/C; SOA 9.43 (92.8%).

Oral—stimulate

Topical saliva stimulants

Although no study directly links improved salivary flow to caries prevention, expert opinion acknowledges that increasing saliva flow is likely to reduce caries incidence in the longer term.

Chewing sugar-free gum increases saliva production and there is some evidence that in addition to its value as a non-sugar sweetener xylitol may have a role in caries prevention in its own right [86, 87]. A recent Cochrane review of the evidence for xylitol concluded that over 2.5–3 years of use, a fluoride toothpaste containing 10% xylitol may reduce caries by 13% when compared with a fluoride-only toothpaste, but that there was insufficient evidence to determine whether any other xylitol-containing products could prevent caries in infants, older children or adults [88].

Many patients chew or suck sugar-free sweets and report benefit, but there is no published evidence supporting this. Certain foodstuffs may be more effective at stimulating saliva than others, but acidic products and those containing sugar should be avoided because of their cariogenic potential. A small cross-over study in normal volunteers assessed the efficacy of yogurt and lemon juice as salivary stimulants and found that both were

effective but yogurt more so than lemon juice compared with baseline, leading them to suggest that yogurt is a potential candidate for the treatment of dry mouth and warrants further study [89].

Some commercially available salivary stimulants are available in the UK. There is little convincing evidence of efficacy and conflicting results from the few reported studies [90, 91].

A small single-blinded, open-label, cross-over clinical study of a branded dry mouth product (Xerostom) containing olive oil, betaine and xylitol in a population with polypharmacy-induced xerostomia resulted in increased unstimulated whole salivary flow rates, reduced complaints of xerostomia and improved xerostomia-associated quality of life. No clinically significant adverse events were observed [92]. The preparation is non-acidic and contains both fluoride and calcium so may be suitable for patients with SS, although there are no published studies in this patient population.

Anhydrous crystalline maltose is available over the counter or on-line and has been shown to increase salivary flow rates with minimal adverse effects in small, observational studies [93] but is not available on prescription.

There is some experimental evidence for both acupuncture and mild electrical stimulation improving salivary flow rates. Published studies are generally small, usually observational and are not specifically looking at patients with SS [81]. There were adverse effects reported with the use of acupuncture, but these were mild and of short duration. There were no reported adverse effects from electrostimulation, with some evidence for improved salivary flow. Further larger studies are planned but neither is currently routinely available in the UK for the treatment of sicca [94]. A gel-releasing device (reservoir) worn in the mouth has been trialled and may be effective in some patients [95], but more research is needed.

Recommendations for mechanical stimulation of oral secretions

(i) Patients should be advised to chew xylitol-containing sugar-free gum. Level of evidence III/C; SOA 9.67 (100%).

Systemic stimulants

Pilocarpine hydrochloride (Salagen) is licensed for use in the UK for dry mouth and eyes in SS. It acts as an agonist on muscarinic-cholinergic receptors to stimulate secretion. It is effective in both primary and secondary SS. There are a number of randomized, controlled trials in patients with Sjögren's confirming significant symptomatic improvement and objective evidence of increased salivary flow in patients treated with pilocarpine [96–98]. Evidence suggests that at least half of patients respond although it can take up to 12 weeks to see a therapeutic benefit. In long term use levels of candida colonization reduce [99]. Side effects are common and dose dependent. They include sweating, palpitations and flushing. See 'Ocular—stimulate' section for more detail on the use of pilocarpine and adverse effects.

Cevimeline is another muscarinic agonist that stimulates fluid secretion generally [100, 101] but has higher affinity for muscarinic receptors located on lacrimal and salivary gland epithelium and may be associated with fewer side effects compared with pilocarpine [102]. However, this drug is not currently licensed for use in the UK.

There is some limited evidence that the H2 blocker nizatadine mildly improves (20% over baseline) objective and subjective measure of oral dryness and is well tolerated although it is not licensed for this indication in the UK [103].

Recommendations for systemic stimulation of secretions

(i) A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for patients with significant sicca symptoms and no contraindications to its use. Level of evidence IIb/B; SOA 9.77 (100%).

Treatment of oral candida

Oral candida is a frequent problem in patients with Sjögren's-associated dry mouth [104] and patients have high levels of candida carriage despite good dental hygiene [105]. Patients may have visible white plaques (simple infection) or erythematous infection, when they present with a red, raw tongue or oral cavity. Clinical experience suggests that whereas topical agents such as nystatin may be adequate to treat simple infection, oral fluconazole is required to treat erythematous infection. The presence of dentures creates an environment where candida may become persistent.

Angular cheilits, where patients present with dry, fissured erythematous lesions in the corner of their mouths, is another manifestation of candidal infection in SS. It can be effectively treated with miconazole topically for 2 weeks, using a clean cotton bud to apply to each side to prevent cross-contamination and persistence of infection [106].

Recommendations for treatment of oral candida

(i) In simple candida infection (visible white plaques) treat with oral nystatin liquid 1 ml five times daily for 7 days. Consider repeating the treatment for 1 week every 8 weeks if frequent recurrence. If the patient has erythematous infection manifesting as a red, raw tongue or oral cavity and commonly seen in denture wearers, use fluconazole 50 mg od for 10 days. Level of evidence IV/D; SOA 9.86 (100%).

(ii) Treat angular cheilitis with miconazole topically for 2 weeks, using a clean cotton bud to apply to each side to prevent cross-contamination and persistence of infection. Level of evidence IV/D; SOA 9.86 (100%).

Management of salivary gland enlargement

Some patients with pSS have recurrent or persistent salivary gland enlargement. This may occur during disease

activity flares or may reflect duct obstruction due to strictures, stones or inspissated secretions.

Parotid sialography is a very specific diagnostic test for pSS [107] that involves injection of contrast materials into the salivary ducts and is associated with a small risk of infection, ductal perforation and allergic reactions. Intraductal injection of contrast can assess the ductal system and exclude strictures [108]. Interventional sialoendoscopy has been reported to be useful in patients with SS with chronic obstructive sialadenitis unresponsive to medical therapy. Under local anaesthesia the orifice of the salivary gland is intubated and the scope advanced, with continuous saline lavage. This allows obstructing plaques to be washed out and any strictures dilated. Symptomatic improvement was achieved in 85% of patients using this technique [109]. However, sialoendoscopy is not widely available and no large scale or long term studies have been published.

In contrast salivary gland US is non-invasive, well tolerated by patients and easily repeatable. US allows assessment of the architecture of the major salivary glands and, used in conjunction with Doppler signals, it may help differentiate between benign and malignant lesions. In some centres salivary gland US is utilized as a diagnostic screening tool and studies confirm it has a high positive predictive value of 85% with good correlation between abnormalities on US and salivary gland histology [110]. Baseline ultrasound is recommended in patients with salivary gland swelling to look for active inflammation, infection and stones. Consider repeating the US if there is a history of new persistent or recurrent salivary gland swelling to monitor for disease progression and development of complications [111].

If there is acute inflammation in the absence of infection and stones then a short course of oral prednisolone or an intra-muscular injection of depomedrone (typically 120 mg) will often settle the glandular swelling promptly (anecdotal evidence). There is anecdotal evidence that massaging the glands can help reduce discomfort in chronically inflamed glands.

Recommendations for management of salivary gland enlargement

(i) Consider salivary gland US to look for active inflammation, infection and stones. Level of evidence IV/D; SOA 9.7 (100%).
(ii) If acute inflammation in the absence of infection and stones then a short course of oral prednisolone or an intra-muscular injection of depomedrone will often settle the glandular swelling. Level of evidence IV/D; SOA 9.01 (100%).
(iii) Massaging the glands can help reduce discomfort in chronically inflamed glands. Level of evidence IV/D; SOA 9.31 (92.8%).

Systemic dryness

Many patients report a chronic dry cough due to drying of mucosal surfaces. Humidification of inspired air is reported to help by some patients [112]. Pilocarpine improves secretions in general and anecdotally reduces the frequency and severity of dry cough. A mucolytic agent (i.e. carbocysteine) reduced the viscosity of sputum, improved the ability to cough up bronchial secretions, and reduced cough frequency and shortness of breath in a double blind controlled study of patients with chronic bronchitis [113]. There is anecdotal evidence it helps in patients with SS and an associated chronic, dry cough. Concomitant use of oral acetylcysteine with AZA and steroids should be avoided given evidence of increased hospitalization and death in a group of patients with pulmonary fibrosis (but not Sjögren's) treated with triple therapy *vs* placebo [114]. It should be remembered that chronic dry persistent cough may be a sign of ILD and should prompt appropriate investigations.

Females with SS frequently complain of vaginal dryness [115]. Pilocarpine may help this by non-specifically stimulating secretions. There is evidence supporting the use of non-hormonal moisturisers in the treatment of vaginal dryness from any cause [116–118]. Vaginal moisturizers applied on a regular basis have an efficacy equivalent to local hormone replacement for the treatment of local urogenital symptoms such as vaginal itching, irritation and dyspareunia [116]. Patients with SS have both vaginal dryness and atrophy of the genital skin [119]. There is evidence supporting the use of topical oestrogen-containing products in patients with post-menopausal vaginal atrophy and dryness [116]. Creams and pessaries are equally effective and although systemic absorption can occur with local preparations, there is no current evidence of an increased risk of endometrial thickening [116]. The use of local hormone replacement therapy can reduce the frequency of recurrent urinary tract infections in post-menopausal women [116].

Recommendations for management of systemic dryness

(i) A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for all patients with significant systemic dryness and no contraindications to its use. Level of evidence IV/D; SOA 9.08 (92.3%).
(ii) Patients with vaginal dryness should be advised to use a non-hormonal vaginal moisturiser with or without a topical oestrogen-containing product. Level of evidence I/A; SOA 9.8 (100%).

Treatment of systemic disease

Systemic (extra-glandular) features are seen in ~70% of patients with SS and are severe in about 15% [120]. The most commonly involved organs are joints, lungs, skin and peripheral nerves [3]. Raynaud's and thyroid disease tend to be commoner in females and lung involvement and peripheral neuropathies are commoner in those with a disease duration of > 10 years [2]. Other systemic features may include autoimmune liver disease, renal involvement, scLE, ITP, myositis, monoclonal gammopathy of uncertain significance and lymphoma. There are also common overlapping conditions, most notably thyroid disease in up to

20% [121], primary biliary cirrhosis in 8% [122] and coeliac disease in 4.5% [123].

Although significant systemic complications are more common in the Ro/La positive group [3] recent evidence suggests that systemic complications also affect a reasonable proportion of the antibody negative group with SS [124] suggesting that all patients with SS warrant consideration of active treatment.

Non-pharmacological interventions for systemic disease

A recent systematic review evaluated the evidence for non-pharmacological interventions for pSS and found that much of the evidence was inconclusive [125]. The available studies suggest that patients with SS benefit from moderate to high intensity exercise with improvements in aerobic capacity, fatigue scores, physical functioning and depression [126].

Lifestyle management strategies may benefit SS patients if fatigue is significantly affecting their ability to perform daily activities. Strategies recommended by NICE guidance for fatigue include sleep management, activity management, relaxation techniques, cognitive behavioural therapy and graded exercise therapy. See relevant NICE guidance on management of fatigue in adults.

Many patients report benefit from joining a Sjögren's support group. The British Sjögren's Syndrome Association provides information and advice for members via their website, a quarterly magazine and a dedicated telephone helpline (www.bssa.uk.net). Arthritis Research UK (www.arthritisresearchuk.org) provides helpful information and leaflets on SS, anti-rheumatic drugs and lifestyle advice.

Recommendations for non-pharmacological interventions for systemic disease

(i) Regular exercise and, where appropriate, a graded exercise programme are recommended for patients with SS presenting with fatigue. Level of evidence IIb/B; SOA 9.33 (93.3%).
(ii) Provide written patient information and details of appropriate support groups and on-line resources. Level of evidence IV/D; SOA 9.8 (100%).

Immunomodulation for systemic disease

Early and aggressive immunomodulation is recommended for RA and increasingly for other autoimmune diseases but not well established for SS. An evidence base is lacking and patients with SS often tolerate these drugs poorly. There is, however, increasing insight into the pathogenesis of SS and interest in its therapeutic management with an increase in the use of conventional disease modifying drugs and research interest in the development of targeted biological agents. The guideline working group considered the evidence supporting the use of corticosteroids, disease modifying drugs, biologics and other drugs alongside their own experience. Where disease modifying drugs are used they should be monitored in accordance with the recommendations of the latest BSR DMARD guidelines (in press). Biologics are not currently NICE approved or funded for the treatment of SS.

Systemic pulmonary manifestations of Sjogren's include ILD and cysts. Usual interstitial pneumonitis and non-specific interstitial pneumonitis are the most commonly reported. In general systemic steroids are recommended as first line treatment, then subsequently various immunosuppressives, including CYC and AZA, rituximab and anti-malarials depending on steroid responsiveness [127–129]. A broad range of neurological complications have been described in Sjögren's. A diffuse sensorimotor neuropathy, confirmed on nerve conduction testing, may affect $>15\%$ of patients with Sjögren's [130]. There are anecdotal reports of benefit from rituximab, immunoglobulins, AZA and HCQ [130].

Trigeminal neuropathy/neuralgia has been described in up to 5% of patients with Sjögren's. It does not usually respond to treatment with steroids and in general is treated as for trigeminal neuralgia of unknown cause. Mononeuritis multiplex is probably seen in $<3\%$ of Sjögren's patients over their lifetime. It is associated with vascultis and may respond to treatment with steroids and CYC [131]. Autonomic neuropathy is common and correlates with patient reported outcomes [132]. It may respond to simple, symptomatic treatment. SS myelopathy can mimic multiple sclerosis. Patients may present with paraplegia, sensory changes and bladder dysfunction. Steroids and CYC may be helpful [133].

Signal hyperintensities on brain MRI have been described in patients with Sjögren's and have been postulated to indicate the presence of an underlying cerebral vasculopathy [134]. Correlation with serological abnormalities and clinical symptoms is poor, however. Neuromyelitis optica spectrum disorder is associated with the presence of aquaporin-4 antibodies and although seen in association with Sjögren's may not be a direct neurological complication of Sjögren's. This patient group benefits from aggressive and ongoing immunosuppression [135].

Although significant renal impairment is rare, tubulointerstitial nephritis and, more rarely, immune complex glomerulonephritis are well described renal manifestations of Sjögren's. In those patients with tubulointerstitial nephritis there is a mononuclear lymphocytic infiltrate on renal biopsy, and treatment with mycophenolate and steroids improves the renal function [136].

Corticosteroids

Prednisolone has been shown to help systemic features including lung disease [127–129] cytopaenias [137], and, in combination with CYC or chlorambucil, neurological involvement [138, 139]. Small studies of low dose prednisolone (5–7.5 mg per day) have shown improvements in sicca symptoms and modest improvements in salivary flow [140].

There are no controlled trials of pulsed i.v. methylprednisolone or i.m. depomedrone in Sjögren's, although there are anecdotal reports of successful use of pulsed steroids in patients with Sjögren's associated lung disease [141], ganglionopathy [142], myelopathy [133] and renal involvement [143].

Recommendations for corticosteroids

(i) Corticosteroids are not recommended for the routine treatment of pSS although intermittent short courses of oral or intramuscular steroid are effective for systemic flares of disease and steroids may be used for significant organ manifestations with or without additional immunosuppressive treatment. Level of evidence III/C; SOA 9.2 (100%).
(ii) Low dose oral prednisolone is effective in treating persistent constitutional symptoms in patients who have failed to respond to HCQ or other immunosuppresants. Level of evidence IIb/B; SOA 8.92 (100%).

Recommended DMARDs

HCQ

Evidence of efficacy of HCQ in SS is variable. A number of studies [144–147] suggest modest improvements in ocular and oral dryness, lowering of ESR and immunoglobulin levels, together with reductions in fatigue levels and joint pain in patients treated with HCQ.

The JOQUER study, a randomized controlled trial of HCQ 400 mg daily, which studied a group with mild disease (i.e. no systemic disease), failed to reach its primary outcome of a 30% improvement in two out of three outcomes (visual analogue scale (VAS) of pain, dryness, fatigue) at 6 months, but it did confirm a decrease in immunoglobulin levels and ESR in treated patients. The study was extended to 48 weeks with all patients being prescribed HCQ between weeks 24 and 48. Although there was a suggestion of clinical and serological improvement in the cohort taking a full 12 months of HCQ, in the open-label extension this did not reach statistical significance [148].

A meta-analysis of six earlier trials involving 140 female patients failed to identify a clear benefit of antimalarials but commented that the available evidence was of poor quality and called for more and better quality research [149].

All members of the guideline working group recommended a therapeutic trial of HCQ treatment in patients with evidence of systemic disease starting at 400 mg once daily decreasing after 6 weeks to 200 mg once daily with monitoring as per BSR guidelines.

Recommendations for HCQ

(i) HCQ up to a maximum dose of 6 mg/kg is recommended for patients with pSS especially those with skin and joint disease and fatigue. Patients should be monitored for evidence of a clinical and/or biological response (e.g. falling immunoglobulin levels). If no response after 12 months of treatment consider stopping. Level of evidence IIa/B; SOA 9.64 (100%).

AZA

AZA has been reported as helpful in case reports for systemic complications such as lung disease [150], myelopathy [151] and cytopaenias [152], but a double blind placebo controlled trial in a small cohort of patients with uncomplicated disease suggested that it did not have a routine role in treatment and was associated with a high frequency of side effects [153]. There is, however, some evidence for efficacy of AZA in both usual interstitial pneumonitis and non-specific interstitial pneumonitis, the most commonly reported forms of ILD in Sjögren's [128, 129, 154, 155]. Discontinuation rates of AZA due to non-respiratory side effects may be higher than for mycophenolate although efficacy is similar in patients with ILD [156].

Recommendations for AZA

(i) AZA is not routinely recommended for management of uncomplicated Sjögren's but may be considered in patients with systemic complications, for example, lung disease, myelopathy and cytopaenias. Level of evidence III/C; SOA 9.09 (100%).

MTX

MTX is the drug of choice for patients with significant inflammatory arthritis [157]. There are case reports of successful treatment of Sjögren's associated inclusion body myositis [158] and myelopathy [159] with MTX. An open label, pilot study of weekly MTX in 17 patients showed improvement in sicca symptoms, parotid swelling, dry cough and purpura but no improvement in objective parameters of dry eyes and mouth [160].

Recommendations for MTX

(i) MTX may be useful for those patients with an associated inflammatory arthritis but there is not enough evidence for its routine use as a disease-modifying drug for those with sicca symptoms alone. Level of evidence IV/D SOA 9.54 (100%).

Mycophenolate

A single centre, open-label pilot trial of mycophenolate in 11 patients reported subjective improvement of ocular dryness and reduction in artificial tear use, but objective evidence of significant glandular improvement in only two patients with short disease duration. There was significant reduction in hypergammaglobulinaemia and RF levels and increase in complements and white cell levels [161]. A case report [162] documents successful treatment of refractory agranulocytosis with mycophenolate in a patient with primary Sjögren's. There is emerging evidence supporting the use of mycophenolate in patients with CTD related ILD including SS [163, 164]. Mycophenolate has been show to stabilize scleroderma associated ILD in a randomized controlled trial [165]. There are to date no similarly robust clinical trials supporting mycophenolate in Sjögren's associated ILD, but there are anecodatal reports and small case series suggesting benefit [166, 167].

Recommendations for mycophenolate

(i) The use of mycophenolate may be considered in patients with systemic complications such as cytopaenias or lung disease. Level of evidence III/C; SOA 9.1 (100%).

Ciclosporin A

There are anecdotal reports of successful treatment of Sjögren's associated interstitial cystitis [168], annular erythema [169, 170], red cell aplasia [171] and pneumonitis [172] with oral ciclosporin. An open-label phase II study of low dose ciclosporin A (2 mg/kg) showed reductions in joint swelling and tenderness, a fall in the EULAR SS Disease Activity Index and Hospital Anxiety Questionnaire and improvements in both the physical and mental health domains of the Short Form 36 [173].

Recommendations for ciclosporin A

(i) Ciclosporin A is not routinely recommended for management of uncomplicated Sjögren's, although it may be helpful in patients with significant joint involvement. Level of evidence III/C; SOA 8.58 (85.7%).

CYC

There are no controlled trials of CYC in SS and in general its potential toxicity would preclude routine use. However, there are published case reports and series documenting successful treatment of Sjögren's associated myelopathy [133, 138] with pulsed monthly CYC, refractory thrombocytopaenia [174] with pulsed followed by oral CYC, glomerulonephritis [143, 175] with both pulsed and oral CYC and lung disease [176] with pulsed intravenous CYC.

Recommendations for CYC

(i) The use of CYC (usually in combination with steroids) may be considered in patients with organ threatening systemic complications such as CNS, renal or lung disease. Level of evidence III/C; SOA 9.09 (100%).

DMARDs not routinely recommended

LEF

Two phase II open label pilot studies found very modest benefits and multiple side effects [177, 178].

Recommendations for LEF

(i) LEF is not routinely recommended for pSS. Level of evidence III/C; SOA 9.8 (100%).

Penicillamine

A prospective open label study found very modest benefits and multiple side effects [179].

Recommendations for penicillamine

(i) Penicillamine is not routinely recommended for pSS Level of evidence III/C; SOA 10 (100%).

Biologics for systemic disease

Rituximab

There is accumulating evidence from published case studies and case series supporting the use of rituximab in patients with active, systemic pSS.

Rituximab has evidence of efficacy from small case series and case reports in the treatment of Sjögren's related lymphoma, ITP, cryoglobulinaemia and neurological disease [180–190].

A number of open label studies and randomized controlled trials have looked at the effect of rituximab on the fatigue and sicca manifestations (see Supplementary table S3, available at *Rheumatology* online, for a summary). An open label study of 12 patients [191] observed modest improvements in patient reported fatigue and oral dryness at 26 weeks following a single treatment course of rituximab. The TEARS (Tolerance and Efficacy of Rituximab in primary Sjogren's syndrome) study [192] found no significant differences between treatment and placebo arms in the primary end point (an improvement of at least 30 mm in 2 of 4 VAS scores at week 24 following a single treatment course of rituximab). However, there was a significant improvement in the fatigue VAS scores in the treatment group at 6 and 16 weeks. The multicentre UK based TRACTISS (TRial of Anti-B Cell Therapy In patients with primary Sjogren's Syndrome) trial [193] has recently been completed. Although preliminary analysis has shown no consistent benefit on fatigue, dryness and salivary flow, further analysis of data is being conducted. A recent study has suggested that patients with higher levels of B cell infiltration within the parotid glands are more likely to respond to rituximab, suggesting that we may in future be able to target therapy more effectively [194]. There is evidence that B cell activating factor is upregulated after rituximab treatment [195] and this may explain the observation in the TEARS study that patients had improved at 4 months but deteriorated again by 6 months [192].

The dose, duration between doses and treatment response in the smaller studies and case series are listed in Supplementary table S3, available at *Rheumatology* online, but in the TEARS study [192] patients received just two 1 g pulses of rituximab 2 weeks apart at baseline, whereas in the TRACTISS study [193] this was repeated at 6 months.

In conclusion there is currently insufficient evidence to recommend routine use of rituximab in those with predominantly fatigue and sicca manifestations but good evidence for its use in systemic complications and lymphoma. Use of Rituximab in pSS is not currently NICE approved and is not routinely funded for the treatment of SS with the exception of those patients presenting with lymphoma.

Recommendations for rituximab

(i) Rituximab is recommended for specialist use in patients with significant systemic manifestations refractory to treatment with steroids and other immunosuppressives. It has a role in those with lymphoma, ITP, vasculitic neuropathy and cryoglobulinaemias. Level of evidence IIb/B; SOA 9.43 (100%).

Biologics where more evidence of efficacy is required

Belimumab

Belimumab is a human mAb that inhibits B cell activating factor. An open-label study of belimumab, in 30 patients

with pSS demonstrated a significant improvement in the EULAR SS Disease Activity Index Score from baseline with particular improvement in non-malignant glandular swelling [196]. Although not currently routinely used in Sjögren's syndrome, belimumab has also been reported to be of benefit in case reports in combination with rituximab [197] and further trials of belimumab, including a combined study with rituximab, are currently underway.

Recommendations for belimumab

(i) Belimumab is not currently recommended although it merits further study. Level of evidence IIb/B; SOA 9.46 (92.8%).

Abatacept

Abatacept was well tolerated in one open label pilot study and fatigue and health related quality of life improved significantly over a 24-week treatment period [198]. There is a phase II study currently underway (https://clinicaltrials.gov/ct2/show/NCT02067910).

Recommendations for abatacept

(i) Abatacept is not currently recommended although it merits further study. Level of evidence III/C; SOA 9.46 (92.8%).

Biologics not currently recommended

Anti-TNF therapy

Initial open label studies of anti-TNF agents suggested some benefit [199–201] but subsequent randomized double-blind controlled trials have failed to show clinical or serological improvement in patients with Sjögren's following treatment with anti-TNF in the form of etanercept [201] or infliximab [203].

Recommendations for anti-TNF therapy

(i) Anti-TNF therapies are not recommended for treatment of pSS. Level of evidence Ib/A; SOA 9.38 (85.7%).

IFNα

IFNα therapy via the oro-mucosal route is not currently available in the UK for the treatment of SS, although there is some evidence of efficacy with moderate improvements in unstimulated salivary flow rates in phases II and III studies [204–207].

Recommendations for IFNα

(i) IFNα therapy via the oro-mucosal route is not currently recommended for the treatment of SS. Level of evidence Ib/B; SOA.

Anti-IL1 (anakinra)

A double-blind, placebo-controlled parallel group study [208] of anakinra in pSS failed to reach its primary end point, although more patients on the active drug than on placebo reported a 50% reduction in fatigue.

Recommendations for anti-IL1

(i) Anakinra (an anti-IL-1 receptor antagonist) is not recommended for the treatment of pSS. Level of evidence Ib/A; SOA 9.82 (100%).

Tociluzimab

Tocilizumab, an anti-IL-6 receptor antibody, is used routinely in the treatment of patients with RA but is not licensed for use in SS. A single case report describes successful treatment of refractory organizing pneumonia associated with Sjögren's [209], but there is insufficient evidence to recommend its use pending further studies.

Recommendations for tociluzimab

(i) Tociluzimab (an anti-IL-6 receptor antibody) is not recommended for the treatment of pSS. Level of evidence III/C; SOA 9.82 (100%).

Efalizumab

A small, open label study of three patients showed no clinical improvement and a significant increase in inflammation on minor salivary gland biopsy with the development of new anti-dsDNA antibodies in two of the three subjects [210].

Recommendations for efalizumab

(i) Efalizumab is not recommended for the treatment of pSS. Level of evidence III/C.

Other potential treatments for systemic disease

IVIG

There is evidence supporting the use of immunoglobulin therapy in Sjögren's associated sensorimotor and non-ataxic sensory neuropathy from retrospective and observational cohorts and case reports [211, 212]. Immunoglobulin treatment has also been used successfully in refractory Sjögren's associated myositis not responding to conventional treatment [213]. There is no evidence for its routine use in patients without significant complications.

Recommendations for IVIGs

(i) Immunoglobulin treatment is not routinely used in pSS, although it may be effective in Sjögren's associated myositis and neuropathies and its use in these conditions may be justified if the patient has failed to respond to treatment with steroids and conventional immunosuppression. Level of evidence III/C; SOA 9.43 (100%).

Colchicine

There are case reports describing successful treatment of Sjögren's associated hypergammaglobulinaemic purpura [214], granulomatous panniculitis [215] and pericarditis [216] with colchicine.

Recommendations for colchicine

(i) Colchicine may be considered as adjunctive treatment in patients with cutaneous manifestations or pericarditis not responding to HCQ or other treatments. Level of evidence III/C; SOA 8.45 (85.7%).

Dapsone

There are case reports describing successful treatment of Sjögren's associated scLE and urticarial vasculitis [217], pyoderma gangrenosum [218] and cutaneous vasculitis [219] with dapsone.

Recommendations for dapsone

(i) Dapsone may be considered as adjunctive treatment in patients with cutaneous manifestations not responding to HCQ. Level of evidence III/C; SOA 8.8 (100%).

Topical tacrolimus

There are case reports describing successful treatment of annular erythema associated with SS [220] with topical tacrolimus. Studies of tacrolimus suggest an increased incidence of skin cancer, so it should be used sparingly for a limited amount of time.

Recommendations for tacrolimus

(i) Topical tacrolimus may be considered as adjunctive treatment in patients with cutaneous manifestations not responding to HCQ. Level of evidence III/C; SOA 8.75 (100%).

Other drugs not recommended

Dehydroepiandrosterone substitution treatment

Two double-blinded, randomized studies of DHEA treatment in SS failed to show any symptomatic improvement or changes in clinical or serological measures in treated patients compared with placebo [221, 222].

Recommendations for DHEA

(i) DHEA substitution treatment is not recommended in pSS. Level of evidence Ib/A; SOA 9.45 (100%).

Management of pregnancy

Fertility is normal in patients with pSS, although there is an increased risk of recurrent miscarriage in the Ro/La$^+$ group [223–225]. Neonatal lupus rash occurs in about 5% of live births in Ro/La positive women usually appearing at 6 weeks of age and lasting about 17 weeks before fading and clearing completely. A few children have persistent depigmentation or telangiectasia [226]. Congenital heart block occurs in $< 2\%$ of pregnancies in women with anti-Ro or anti-La antibodies and may be detected by US scanning from about 16 weeks' gestation [227]. There is evidence that in anti-Ro positive women, fetal atrioventricular (AV) time intervals are longer and heart rates slightly lower compared with controls. Fetuses with normal AV time intervals at 18–24 weeks had normal electrocardiographic results at birth. Hence serial Doppler echocardiographic measurement of AV time intervals is suggested as a useful method for surveillance of these high-risk pregnancies [228]. Following an affected pregnancy the risk of congenital heart block goes up to 17% for subsequent pregnancies. Seventy per cent of affected children survive, but nearly all require pacemakers in the first few months of life [229]. There is some evidence from longitudinal, observational studies that primary SS mothers deliver significantly earlier, give birth to babies with lower birth weight and have complications during deliveries more frequently than women in the general population [227]. Other, very rare, complications include hepatitis and cytopenias affecting the newborn. Only a handful of cases have been reported in the literature and in the majority of cases the child has improved spontaneously [230].

Successful pregnancies are, however, increasingly common in patients with Sjögren's. There is evidence that low-dose aspirin initiated in early pregnancy improves placental implantation and reduces the incidence of both pre-eclampsia and intra-uterine growth retardation [231, 232]. The working group therefore recommended that in Sjögren's pregnancy one should consider low dose aspirin to improve placental implantation and monitor closely with serial US. It is safe to continue HCQ throughout pregnancy with evidence in patients with SLE of improved outcomes for the mother and no detrimental effects on the child [233–236]. Refer to the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding [235, 236].

Recommendations for management of pregnancy

(i) Consider low dose aspirin to improve placental implantation. Level of evidence IIb/B; SOA 8.27 (92.8%).
(ii) Monitor closely with serial US if anti-Ro and/or anti-La positive and consider referral to specialist centre. Level of evidence IIb/B; SOA 9.71 (100%).
(iii) Review all medication in pregnancy. HCQ may be continued throughout pregnancy and breastfeeding. Level of evidence I/A; SOA 7.91 (85.7%).

Assessment of lymphoma risk

The risk of lymphoma development in patients with primary SS increases from 3% in the first 5 years to 9.8% at 15 years, that is, up to 40 times the population risk [237–239]. The presence of lymphadenopathy, parotid enlargement, palpable purpura, low serum C4 levels and cryoglobulins are the most consistent predictors of future risk [240] and may increase the risk of future development of lymphoma up to 5-fold [238]. The detection of germinal centre-like structures or a focus score $\geqslant 3$ on light microscopy in diagnostic salivary gland biopsies from patients with pSS may suggest a future higher risk for lymphoma development [241]. The majority of lymphomas are of the mucosa-associated lymphoid tissue type. The median age of onset is mid-50s and the diagnosis of Sjögren's generally predates the lymphoma by a mean of 7 years [237].

Commonest sites of presentation include the parotid and other salivary glands, followed by the orbits, stomach, thyroid, lung, upper airways and rarely other sites [242]. Presentation is usually with a firm, palpable swelling within the gland. GI tract lymphoma may present with chronic diarrhoea, malabsorption and weight loss [243].

Recommendations for assessment of lymphoma risk

(i) Review high risk patients regularly and warn patients to report firm, painless glandular swelling that does not settle. Level of evidence IV/D; SOA 9.86 (100%).

Management of lymphoma

US allows assessment of any new swelling within the major salivary glands and, used in conjunction with Doppler signals, may help differentiate between benign and malignant lesions [111].

Biopsy is usually necessary to confirm the diagnosis. CT scanning is helpful for staging. Treatment can be variable and may include a watch and wait approach in patients with localized low-grade lymphoma or radiation alone but is generally with surgical excision followed by radiotherapy, chemotherapy, generally including rituximab, or a combination of the two. There are regularly updated UK guidelines available. The prognosis is generally good with a complete response to initial treatment in >90% and 5-year disease-free survival >75% [242], but splenomegaly, low serum C3, levels, neutropenia and lymphopenia may indicate a higher risk of poor outcome [240]. Refer to Haematology/Oncology for detailed advice on management.

Recommendations for management of lymphoma

(i) Investigate suspicious lesions with local US, biopsy and CT chest, abdomen and pelvis for staging. Level of evidence III/C; SOA9.77 (100%).

Conclusion

pSS is a chronic, debilitating condition that warrants effective management. All patients should be counselled and offered topical management for sicca symptoms. Systemic treatment should be considered early in those with constitutional symptoms.

Applicability and utility

Key standards of care and potential organizational barriers to implementation

pSS is associated with significant direct and indirect costs and represents a significant impact on the healthcare system [244, 245]. The initial management of SS includes educating the patient on appropriate management and initiating simple treatments such as moisturizing eye drops and fluorinated mouth gels. This is best done by a physician with an interest and some background knowledge. Patients also benefit from the additional time and expertise of an appropriately trained specialist nurse. A baseline ophthalmic and oral medicine specialist assessment are recommended. Appropriate early management will improve outcomes for patients and prevent the development of excess dental caries and potentially reduce the future health care needs of these patients. A multi-disciplinary clinic setting has been shown by one specialist unit to provide a cost effective and high quality environment for patient care while facilitating involvement in research [246].

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is available on the BSR website.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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