

Management of salivary gland hypofunction of
Sjogren's syndrome: the evidence behind available
therapies and results of a feasibility study on a novel
intra-oral electro-stimulator of salivary glands.

Arwa Al-Hamad
(B.D.S, King Saud University, Saudi Arabia)
(MSc, University College London, UK)

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UNIVERSITY COLLEGE LONDON

EASTMAN DENTAL INSTITUTE

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ABSTRACT

Objective:

The effectiveness of available treatments of Sjogren's syndrome (SS) induced xerostomia remains unclear. The present thesis was aimed at determining the evidence of current therapies and to assess the efficacy of using an electrostimulation device for the treatment of xerostomia in patients with SS. Hence it comprises two studies to address the problem (a) a systematic review and (b) a clinical trial.

Methods:

For the systematic review the following databases were searched in November 2013 and in August 2015: MEDLINE, Cochrane Central, EMBASE and AMED. Randomized controlled trials comparing any topical or systemic intervention for the treatment of SS-induced xerostomia were included.

The clinical trial was a six-month double-blinded randomized sham-controlled feasibility trial of 30 patients with SS. Outcome measures were collected at baseline, month 1, month 3, and at end of the study. This was followed by a 6-month open label extension.

Results:

The systematic review identified 33 randomized controlled trials. The meta-analysis included 9 studies. The principal measure of effect size was the mean difference for continuous data and the odd ratio of improvement for categorical data. Results suggest that oral sialogogues are more effective than placebo in ameliorating dry mouth symptoms.

The clinical study found that unstimulated salivary flow increased more in participants receiving active devices compared to sham stimulation (1g/15min higher). The xerostomia inventory score reduced more in the active group by 3.3 points. Xerostomia VAS scores did not show any significant difference.

Conclusion:

The findings of the systematic review display statistically significant evidence that SS-induced xerostomia may be lessened by systemic pilocarpine, cevimeline or electrostimulation. The clinical trial reported that the electrostimulating device was well tolerated, increased salivary function and reduced dry mouth symptoms of SS. Thus there is merit in future studies being focused upon the use of sialogogues and electrostimulation devices.

DEDICATION

Dad & Mom, thank you for your faith, support, inspiration and prayers. Without you it would simply be impossible.

To my sister, brothers and true friends, you have for always been there for me.

My husband, you have always been my strength. Thank you for making my dream come true.

To my angel twin girls, for brightening my life.

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DECLARATION

“Except for the help listed in the acknowledgements, the content of this thesis are entirely my own work. This work has been not previously submitted, in part or in full, for a degree or diploma of this or any other University or Examination Board”.

.....

Arwa Al-Hamad (AH)

Oral Medicine

UCL Eastman Dental Institute

September 2015

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List of Acronyms

ACR	American College Of Rheumatology
ACE	Angiotensin-Converting Enzyme
AECG	American-European Consensus Group Criteria
AIDS	Acquired immunodeficiency Disease
ANA	Antinuclear Antibody
ANCOVA	Analysis Of Covariance
ASA	American Society Of Anaesthesiology
AZT	Azathioprine
BAFF	B Cell Activating Factor
CCHB	Congenital Complete Heart Block
CHB	Congenital Heart Block
CGvHD	Chronic Graft-Versus-Host Disease
CRF	Case Report Form
CNS	Central Nervous System
DCs	Dendritic Cells
DHEA	Dehydroepiandrosterone
DHEA-S	Metabolite DHEA Sulphate
DLBCL	Diffuse Large B-Cell Lymphoma
EC	European Criteria
ECIC	Eastman Clinical Investigational Centre
EDH	Eastman Dental Hospital
EBV	Epstein-Barr Virus
ENT	Ear, Nose And Throat
ER	Oestrogen Receptors
ESGCC	European Study Group On Classification Criteria
ESR	Erythrocyte Sedimentation Rate
ESSDAI	European League Against Rheumatism Sjögren's Syndrome Disease Activity Index
ESSPRI	European League Against Rheumatism Sjögren's Syndrome Patients Reported Index EULAR European League Against Rheumatism
EPZ	Epratuzumab
FLS	Focal Lymphocytic Sialadenitis
HBV	Hepatitis B Virus
HCO ³⁻	Bicarbonate
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus

HD	Hemodialysis
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
IFN	Interferon
IL	Interleukin
K ⁺	Potassium
KCS	keratoconjunctivitis Sicca
LEONIDAS-1	Long-Term Effectiveness Of A Novel Intra-Oral Electro-Stimulator For The Treatment Of Dry Mouth In Patients With Sjögren's Syndrome
M3Rs	Muscarinic Type-3 Receptors
MALT	Mucosa Associated Lymphoid Tissue
MCTD	Mixed Connective Tissue Disease
MRI	Magnetic Resonance
MSGB	Minor Salivary Gland Biopsy
MZBCL	Marginal Zone B-Cell Lymphoma
MZL	Marginal Zone Lymphoma
NHL	Non-Hodgkin Lymphoma
NOD	Non-Obese Diabetic
NSAIDs	Non-Steroidal Anti-Inflammatory
OHIP-49	The Oral Health Impact Profile
pSS	Primary Sjögren's Syndrome
QoL	Quality Of Life
RA	Rheumatoid Arthritis
RCT	Randomised Control Trial
RF	Rheumatoid Factor
RT	Radiotherapy
RTX	Rituximab
SF-36	Form (36) Health Survey Questionnaire
SFR	Salivary Flow Rate
SICCA	Sjögren's International Collaborative Clinical Alliance
SL	Sublingual
SLE	Systemic Lupus Erythematosus
SM	Submandibular
SMZL	Splenic Marginal Zone Lymphoma
SP1	Salivary Protein1
sSS	Secondary Sjögren's Syndrome

SS	Sjögren's Syndrome
SSDI	Sjögren's Syndrome Damage Index
SSDDI	Sjögren's Syndrome Disease Damage Index
SSFR	Stimulated Salivary Flow Rate
SSI	The Sicca Symptoms Inventory
TENS	Transcutaneous Electric Nerve Stimulation
Th	T Helper
TNF	Tumour Necrosis Factors
UCLH	University College London Hospital
US	Ultrasonography
UWSF	Unstimulated Whole Salivary Flow
VAS	Visual Analogue Scale
VIP	Vasoactive Intestinal Peptide
VRS	Verbal Categorical Rating Scale
WHO	World Health Organization
WSR	Whole Saliva Flow Rate
XI	Xerostomia Inventory

Chapter One:

Literature Review

1.1 Sjögren's Syndrome

1.1.1 History

The first case report describing what is now known to be Sjögren's syndrome (SS) was in 1882, when the German physician Theodor Leber described a condition of filamentary keratitis (mucous strands that attach to and inflame the cornea). In 1888, surgeon Johann Mikulicz presented to the Society of Scientific Medicine at Königsberg the case of a 42-year-old East Prussian farmer with painless parotid, lacrimal and submandibular gland swelling. The term *Mikulicz's syndrome* was commonly used to describe other conditions associated with parotid gland swelling, such as tuberculosis and lymphoma. Later that year, the London physician W. B. Hadden presented to the Clinical Society the case of a 65-year-old female with dry mouth and inability to tear, whose condition responded to tincture of jaborandi (pilocarpine).

It took 30 more years for evidence of a 'syndrome' to emerge. In 1926, Henri Gougerot in Paris described three patients with salivary gland enlargement, mucous membrane and vulvar atrophy and dryness. In 1927, Houwer observed an association of connected filamentary keratitis with arthritis. Of note however in 1933, the Swedish ophthalmologist Henrik Sjögren published his seminal monograph (not translated into English until 1943) in which he described a series of 19 patients with dry eyes and dry mouth, 13 of whom also had arthritis. He coined the term keratoconjunctivitis sicca having used rose Bengal staining to study the ocular surface for abnormalities due to dryness (Sjogren 1933; Wallace 2006).

In 1953, William Morgan and Benjamin Castleman rediscovered and popularized Sjögren's work (which had received little attention) and elaborated upon its

histopathological features as atrophy of the acinar parenchyma and diffuse lymphocytes infiltration (Fox et al. 1986). Kurt Bloch and colleagues reported in 1955 that Sjögren's syndrome could exist by itself or be secondary to other autoimmune disorders. In the 1950s and 1960s, Joseph Bunim and Norman Talal described the clinical presentation, natural history and laboratory features of large numbers of patients linked probably with Sjögren's syndrome, and for the first time, the syndrome with increased risk of lymphoma development. Although antibodies (anti-Ro/SSA and anti-La/SSB) linked to Sjögren's syndrome were discovered in the late 1960s, it took another 30 years for "autoimmune" Sjögren's to be differentiated from other causes of sicca symptoms, such as HIV infection, Hepatitis C infection and chronic graft-versus-host disease (CGvHD). The definition of disease, its classification and activity measures, are now permitting the development of more robust methodologies in designing clinical trials in Sjögren's syndrome (Wallace 2006). (Table 1)

Table 1. Key events in the history of the description of Sjögren's syndrome (Epstein and Stevenson-Moore 1992).

1888	Single case reports by Hadden and Rowlands
1892	Case report and histology described by Miculicz
1926	Three patients described by Gougerot
1928	Link with arthritis reported by Houwer
1933	Sjögren's thesis describing 19 patients with 'keratoconjunctivitis sicca'
1946	Sjögren's thesis translated into English
1953	The term 'Sjögren's syndrome' becomes established in the literature
1965	Primary versus secondary Sjögren's syndrome described
1970s	Autoantibodies Ro (SS-A) and La (SS-B) described.
1980s and 1990s	Extraglandular manifestations described
1990s	Trials of disease-modifying drugs
1993	Preliminary European classification criteria detailed
2002	Revised American–European consensus criteria detailed

1.1.2 Definition

Sjögren's syndrome is now known to be a chronic autoimmune disease, histopathologically characterized by lymphocytic infiltration of exocrine glands (Scully 1986; von Bultzingslowen et al. 2007; Bayetto and Logan 2010). Although salivary and lacrimal glands represent the most common targets of SS, it can also affect exocrine glands in the nose, ears, skin, vulva, vagina, respiratory and gastrointestinal systems (Al-Hashimi 2005; Bayetto and Logan 2010). Sjögren's syndrome can also give rise to a wide range of extra-glandular manifestations (Carsons 2001). The term 'sicca' has been used to describe dryness of the eyes and/or mouth and indeed in the past the term 'sicca syndrome' has been used to describe what is now known as primary SS. While SS can occur as a stand-alone disease (primary SS) (pSS) in which the dominants are those associated with lacrimal and salivary gland dysfunction, it can also be associated with other autoimmune disorders, particularly rheumatoid arthritis and lupus erythematosus but also scleroderma (sometimes termed systemic sclerosis), dermatomyositis, mixed connective tissue disease (MCTD), primary biliary cirrhosis and autoimmune hepatitis (Golding et al. 1970; Pérez et al. 1995; Al-Hashimi et al. 2001; von Bultzingslowen et al. 2007; Patel and Shahane 2014). Primary SS is usually seen with Raynaud's phenomenon, parotid gland enlargement, purpura, anti-Ro and anti-La autoantibodies and a strong association with HLA DR3 alloantigen (Moutsopoulos 2014).

1.1.3 Epidemiology

It is estimated that SS affects 0.2-3 % of the population (Carsons 2001; Hammi et al. 2005; Willeke et al. 2007; Margaix-Muñoz et al. 2009; Bayetto and Logan 2010; Reksten and Jonsson 2014), indeed it is considered the second most common autoimmune connective tissue disorder after rheumatoid arthritis (Fox, Stern, and Michelson 2000; Manoussakis and Moutsopoulos 2001; Porter, Scully, and Hegarty 2004). It is a disorder of middle to late age with most affected individuals diagnosed between 30 to 60 years of age (Carsons 2001; Jonsson et al. 2002; Margaix-Muñoz et al. 2009; Bayetto and Logan 2010; Reksten and Jonsson 2014). There is a female predominance of approximately 9:1 with a higher prevalence in menopausal women than other groups (Carsons 2001; Margaix-Muñoz et al. 2009; Bayetto and Logan 2010; Reksten and Jonsson 2014). Secondary Sjögren's syndrome (sSS) can affect up to one third of patients with other autoimmune disorders (i.e. rheumatoid arthritis, lupus erythematosus, scleroderma, mixed connective tissue disease and primary biliary cirrhosis) (Golding et al. 1970; Pérez et al. 1995; Carsons 2001; Vitali et al. 2002; Bayetto and Logan 2010).

In 2014, a review described three studies reporting the incidence of pSS (Patel and Shahane 2014). The first study was a retrospective study, and was undertaken in the USA between 1976 and 1992 (Pillemer et al. 2001). An annual incidence of pSS at 3.9 per 100,000 was estimated. Similarly an incidence of 3.9 per 100,000 was reported in the second prospective study between 2000 and 2002 in Slovenia (Rozman et al. 2004). While in Greece a prospective study carried out between 1982 to 2003, reported an incidence of 5.3 per 100,000 (Alamanos et al. 2006). With regards to prevalence rates, pSS can vary according to the classification criteria used (Patel and Shahane 2014). In a Norwegian study, the prevalence percentage

of pSS in individuals aged 40–44 years was 0.44 using the European criteria (EC), and 0.22 using the revised American-European Consensus Group (AECG) criteria (Rozman et al. 2004). In Denmark the prevalence of pSS was 0.6%–2.1% using the EC and 0.2%–0.8% using the Copenhagen criteria (Bjerrum 1997). And in Sweden it was 2.7% using the Copenhagen criteria (Jacobsson et al. 1989). A Turkish study reported the prevalence of pSS at 0.35 using the EC and 0.21 using the AECG criteria (Birlik et al. 2009). Furthermore, the prevalence was 1.56 using the EC and 0.72 using the revised criteria in women aged 18–75 in a cross sectional study in Turkey (Kabasakal et al. 2006). In Greece, the prevalence ranged from 0.09%–0.23% (Dafni et al. 1997; Alamanos et al. 2006; Anagnostopoulos et al. 2010) where the first study used the preliminary European criteria and the other two used the AECG criteria. And 0.60% in Slovenia applying the EC (Tomsic et al. 1999). According to the revised AECG criteria the prevalence was 1.6 in Manchester (Thomas et al. 1998) and 1.14 in Birmingham (Bowman et al. 2004). In China, according to the Copenhagen criteria the prevalence was 0.77% (Zhang et al. 1995), and 0.03% in Japan (Miyasaka 1995).

Recently in 2014 a systematic review and meta-analysis reported a high pooled (included 6 studies) incidence rate as 6.92 per 100,000 person/years and an overall pooled (included 18 studies) prevalence rate of 60.82 cases per 100,000 person/year. The female/male ratio was similar to previous studies with 9.15, and overall age of pSS patients was 56.16 years (Qin et al. 2014).

1.1.4 Classification and diagnostic criteria

The increased need to drink water during the night to lessen dryness of the mouth and/or throat and the need to have chewing gum and lozenges handy to help stimulate saliva production can be the first sign of xerostomia (Reksten and Jonsson 2014).

Sjögren's syndrome, especially in its early stages, is often under-recognized by clinicians and therefore under-diagnosed. In some instances it can take up to 6 to 10 years from the onset of initial symptoms to final definitive diagnosis (Talal 2000; Hammi et al. 2005). Such delay in diagnosis can be explained by the following: 1) symptoms of mouth and/or eye dryness can have many causes, particularly medication; 2) symptoms of cutaneous, oral and vaginal dryness/discomfort may be confused with those of menopause in middle-aged females; 3) the disease can present with initial non-specific systemic symptoms such as arthralgia and fatigue; 4) due to the multiple organ involvement, patients are often seen by different specialists each of whom detects only one element of the syndrome and 5) clinicians do not always apply international classification/diagnostic criteria (Jonsson, Haga, and Gordon 2000; Bayetto and Logan 2010). Furthermore prompt identification of SS can be compromised by the existence of other systemic diseases that can cause inflammatory infiltration of exocrine glands leading to glandular swelling and dryness. Examples include hepatitis C infection, HIV infection and CGvHD and rarely sarcoidosis and IgG4 disease (Gratwohl et al. 1977; Itescu, Brancato, and Winchester 1989; Jorgensen et al. 1996; Carsons 2001).

Since 1965, there have been 11 sets of classification criteria (Sankar, Noll, and Brennan 2014) for SS, suggested by different groups of specialists from different countries including Japan, America and Europe (Manthorpe et al. 1986; Homma et

al. 1986; Fox et al. 1986) although none of them were supported by robust validation (Vitali et al. 2002; Moutsopoulos 2014). Eventually a multicentre study was undertaken by a European Study Group in 1998, with the intention to: i) validate a simple questionnaire for sicca symptoms; ii) select the most sensitive and specific tests for the diagnosis of SS; iii) define a set of criteria for SS; iv) validate this criteria set (Vitali et al. 1993); see Table 2. The relevant European classification was initially accepted by the scientific community, but it was later criticized as histopathological evidence of disease (focal sialadenitis) or serology (anti Ro/La antibodies) were not considered necessary for the diagnosis- potentially leading to misclassification bias (Vitali et al. 2002).

In view of the criticism, the AECG modified this classification to include at least one objective finding, thereby redefining the rules of the ESGCC. They added a number of specifications to available criteria to make the classification accurate and acceptable (see Tables 3 and 4). This classification has shown a high sensitivity (89.5%) and specificity (95.2%) for the diagnosis of pSS (Vitali et al. 2002).

Table 2. The validated diagnostic/classification criteria for Sjögren's syndrome, as suggested by the European Community Concerted Action for SS (Vitali et al. 1996; Manoussakis and Moutsopoulos 2001).

Criteria	Definitions
1. Ocular symptoms	A positive response to at least one of the three selected questions: 1 Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than three times a day?
2. Oral symptoms	A positive response to at least one of the three selected questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary gland as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
3. Ocular Involvement	Objective evidence of ocular involvement defined as a positive result in at least one of the following two tests: 1. Schirmer's I test (less than or equal to 5 mm in 5 minutes) 2. Rose-Bengal score (greater than or equal to 4 according to van Bijsterveld's scoring system)
4. Salivary gland	Objective evidence of salivary gland involvement defined as a positive result in at least one of the following three tests: 1. Salivary scintigraphy 2. Parotid sialography 3. Unstimulated salivary flow (less than or equal to 1.5 ml in 15 minutes)
5. Histopathology	A focus score greater than or equal to 1 in a minor salivary gland biopsy (a focus is defined as an agglomerate of at least 50 mononuclear cells; the focus score is defined by the number of foci in 4 mm ² of glandular tissue)
6. Autoantibodies	Presence in the serum of the following autoantibodies: Antibodies to Ro(SSA) or La(SSB) or both

Rules for classification: In patients without any potentially associated disease the presence of any four of the six items is indicative of primary SS. In patients with a potentially associated disease (for instance another connective tissue disease) item 1 or item 2 plus any two from items 3, 4, 5 is indicative of secondary-SS.

Exclusion criteria: pre-existing lymphoma, acquired immunodeficiency disease (AIDS), sarcoidosis, graft-versus-host disease, sialadenosis. Use of anti-depressant and anti-hypertensive drugs, neuroleptics, parasympatholytic drugs.

Test should be excluded from the criteria or not considered indicative of a diagnosis of SS in elderly subjects (older than 60 years).

Table 3. Revised international classification AECG criteria for Sjögren's syndrome (Vitali et al. 2002).

I. Ocular symptoms, a positive response to at least one of the following questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms, a positive response to at least one of the following questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs, objective evidence of ocular involvement defined as a positive result for at least one of the following tests: 1. Schirmer I test, performed without anaesthesia (<5 mm in 5 minutes) 2. Rose bengal score or other ocular dye score (>4 according to van 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 focus score >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: 1. Unstimulated whole salivary flow (<1.5 ml in 15 minutes) 2. Parotid sialography showing the presence of diffuse sialectasis (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts ¹⁹ 3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
VI. Autoantibodies, presence in the serum of the following autoantibodies: 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Table 4. Revised rules for classification (AECG criteria) (Vitali et al. 2002)

<p><u>For primary SS</u></p> <p>In patients without any potentially associated disease, primary SS may be defined as follows:</p> <ol style="list-style-type: none"> The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI) The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical epidemiological survey
<p><u>For secondary SS</u></p> <p>In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS</p>
<p><u>Exclusion criteria:</u></p> <p>Past head and neck radiation treatment</p> <p>Hepatitis C infection</p> <p>Acquired immunodeficiency disease (AIDS)</p> <p>Pre-existing lymphoma</p> <p>Sarcoidosis</p> <p>Graft-versus-host disease</p> <p>Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)</p>

This AECG classification specified that the Schirmer I test in item III, which is a quantitative measurement of tear production over a specific period of time, should be performed without anaesthesia (Vitali et al. 2002). This test is considered as a simple and cost-effective test, but in mild cases of keratoconjunctivitis sicca it is difficult to reproduce accuracy (Bayetto and Logan 2010). As the severity of keratoconjunctivitis sicca increases, the Schirmer I test increases in reproducibility. The rose bengal eye stain, which stains the conjunctival surface, helps to reveal any breaks in the corneal epithelial surface (Lemp 2000). It may be used in conjunction with the Schirmer I test to increase diagnostic accuracy (Bayetto and Logan 2010). These tests are used to assess the function of the lacrimal glands and the integrity of the tear film layer (Sankar, Noll, and Brennan 2014).

In regards to item IV (histopathology), the focal lymphocytic sialadenitis (FLS) was defined as “multiple, dense aggregates of 50 or more lymphocytes in perivascular or periductal locations” (Chisholm and Mason 1968), with only a small proportion of plasma cells, and located adjacent to normal-appearing acini in gland lobules without showing any duct dilation or fibrosis (Daniels and Whitcher 1994). The term focal lymphocytic sialadenitis applies to labial salivary gland biopsy specimens having this pattern of lymphocytic infiltration and a focus score >1 focus/4 mm² (Daniels and Whitcher 1994; Vitali et al. 2002). Labial salivary gland biopsy had a limitation of a varied range of sensitivity and specificity, 63%–93% and 61%–100%, respectively (Sankar, Noll, and Brennan 2014). Yet the focal lymphocytic infiltrates of the labial salivary gland was found not to be specific for pSS, and can be observed in healthy individuals in a range of 7-32% (Pedersen et al. 1999). Stewart et al. (2008) reported poor reproducibility of the results, with variations across pathologists and gland section levels. On the other hand (Costa et al. 2015) studied the intraobserver and interobserver minor salivary gland biopsy (MSGb) reliability and considered it to be

substantial in pSS patients, with 12.6% of pathology samples resulting in a different diagnosis. They also noted that there was no standard process used to read the samples and to write the reports.

Furthermore, salivary gland hypofunction (criteria V) is one of the most common symptoms of SS, but due to the fact that it can be caused by many other co-existing factors such as anticholinergic drugs, systemic disease and psychological or physiological changes it thus has low specificity for SS (Daniels 2000). In this classification the positivity of parotid sialography was defined by the presence of diffuse sialectasis. According to Rubin and Holt the scoring system and the positivity of salivary scintigraphy should be defined as delayed uptake, reduced concentration and/or delayed secretion of the tracer (Rubin and Holt 1957). Low salivary flow can also be detected via salivary sialometry, using a threshold of 1.5ml/15 minutes (Al-Hashimi et al. 2001).

The presence of serum Ro (SSA) and in particular La (SSB) autoantibodies (criteria VI) is highly specific for SS, although healthy individuals and patients with rheumatoid arthritis and systemic lupus erythematosus (SLE) are occasionally proven to be positive for one or both antibodies (Talal 2000; Bayetto and Logan 2010).

Considering the different imaging techniques involved in the diagnosis, SS can give rise to a variety of salivary gland changes that can be detected with different radiological methods. Sialography involves the retrograde instillation of a contrast medium into the excretory duct where the architecture and configuration of glandular ducts can be determined. In SS the characteristic feature of sialography is a snowstorm-like (sialectasis) or Christmas tree pattern. Sialectasia is the dilatation of the acinar system; it is classified to punctate, globular, cavitary, and destructive

sialectasia. As these changes represent the glandular damage caused by the chronic salivary gland inflammation, the progression of the disease process can be monitored using sialography imaging (Kalk et al. 2002). However the test can be painful and time-consuming and relies upon easy identification of the opening of salivary gland duct (Scully 1986; Pedersen et al. 1999). Different stages of sialectasis can be found in patients with SS, but 15–29% of the healthy population may demonstrate some elements of sialectasis and other diseases such as non-specific chronic sialadenitis and recurrent parotitis of childhood can give rise to similar radiological features, hence reducing the specificity of the test (Soto-Rojas and Kraus 2002; Afzelius et al. 2014).

In a recent investigation 98 patients were enrolled (38 pSS patients, 38 sSS patients, 22 control subjects) the most common radiological finding in SS was sparsity of the branching pattern of the ducts. The most commonly affected ducts were the peripheral ducts rather than the main excretory duct. Asymmetric involvement of the parotid glands in pSS and the submandibular glands in sSS is commonly seen. Globally the parotid glands were more commonly involved than submandibular glands (Golder and Stiller 2014).

Scintigraphy with sodium pertechnetate of ^{99m}Tc evaluates the function of salivary glands. In addition, it can be used to examine glandular response to stimulation. The sensitivity of this test for the diagnosis of SS ranges from 75 to 87%, but has a low specificity (Vitali, Moutsopoulos and Bombardieri 1994). It has the disadvantage of being only performed in hospital settings and repetition is not appropriate in view of its invasive nature (Hermann, Vivino and Goin 1999).

Magnetic resonance (MRI) is mainly useful in the recognition of masses and cysts and provide excellent views of the parenchyma. In addition it can be useful in

selecting suitable places for biopsies of major salivary glands and assist in the diagnosis of lymphoma. Due to its high cost their cost and low sensitivity to identify SS, MRI is not considered to be a routine method of diagnosing SS (Soto-Rojas and Kraus 2002; Afzelius et al. 2014).

Ultrasonography (US) is an increasing useful and reliable method for diagnosis of SS; it has good correlation (~85%) with sialography and scintigraphy. Ultrasonography of the major salivary glands in recent studies have showed high specificity (73-99%) but lower sensitivity (59-87%) for the diagnosis of pSS (Hocevar et al. 2005; Salaffi et al. 2008; Milic et al. 2009). Indeed a report in 2010 showed that US of the salivary glands had a diagnostic sensitivity of 82% and specificity of 73% which can allow them to be an alternative imaging modality to sialography in the diagnosis of pSS. Milic et al (2012) reported that US had a high diagnostic accuracy, comparable to scintigraphy and biopsy, therefore US can be considered as a reliable diagnostic method, comparable with biopsy of major salivary glands. Nevertheless, the US changes seen in salivary glands can occur in disorders giving rise to xerostomia unrelated to SS such as HIV salivary gland disease and HCV sialadenitis.

An intra-study comparison between the preliminary EC and AECG in the same population, confirmed that the prevalence of pSS was lower using the AECG compared to the prevalence using previously the EC (Kabasakal et al. 2006; Haugen et al. 2008; Birlik et al. 2009). This gives an advantage in clinical trials as using the AECG criteria can lead to a much more homogenous group of patients, thus the AECG has been employed as an inclusion criteria in several randomized clinical

trials in pSS (Ramos-Casals et al. 2010; Baldini et al. 2011). Likewise the AECG criteria also has a benefit in clinical practice, Brun found that out of 203 outpatients with a clinical diagnosis of pSS, 116/203 (57.1%) satisfied the preliminary EC, when only 83/203 (40.9%) also fulfilled the AECG criteria (Brun et al. 2002). In the same way, Locht and co-workers reported that when using the AECG criteria on a cohort of 321 patients with pSS, initially diagnosed by the Copenhagen criteria¹, only 205/321 patients satisfied the criteria for pSS (Locht, Pelck and Manthorpe 2005).

Another study showed that only 23.5% of the patients classified with pSS according to the European preliminary criteria met the criteria of the AECG (Langeegger et al. 2007). A study carried out in China has shown a high sensitivity and specificity to the criteria of the AECG (Zhao et al. 2005; Gálvez et al. 2009). Nevertheless, there are patients who fulfil the Preliminary EC however not the AECG, although they have similar long-term disease complications. Thus giving rise to an argument on how to classify such patients.

Furthermore, the Sjögren's International Collaborative Clinical Alliance (SICCA) has highlighted some weaknesses of the AECG which were considered in developing a new criteria (Shiboski et al. 2012; Sankar, Noll, and Brennan 2014). These weaknesses were as following:

“(1 and 2) Ocular/oral symptoms²:

- Scales for scoring subjective measures vary and are not unique.

¹ The Copenhagen criteria (Manthorpe et al. 1986) set was confirmed if two criteria for keratoconjunctivitis sicca (schirmer-I test, break-up time and rose-Bengal score) and two for xerostomia (unstimulated whole sialometry, salivary gland scintigraphy and lower lip biopsy) were fulfilled.

² One strength was that these symptoms are the usual prompts that drive patients to seek out a diagnosis.

- Subjective tests lack specificity for SS and do not correlate with objective measures.
- The use of subjective tests potentially creates a heterogeneous pool of patients with SS, making it difficult to diagnose, assess efficacy of treatment, and determine the prognosis of patients with SS.

(3) Ocular signs assessed by Schirmer I test

- The test does not correlate with disease.
- The test lacks specificity for SS.

(4) Ocular signs assessed by ocular dye scores

This is a time-consuming grading system that is difficult to apply in clinical practice.

(5) Histopathology: none found

(6) Salivary signs assessed by salivary flow rates

- Types of saliva (whole vs individual gland) and collection techniques (spitting, drooling, suction devices, absorption, use of wafers, and use of iodine starch) vary. Other factors such as circadian variation, patient hydration, fasting state, medication, and possibly age and sex affect saliva production rates.
- Measures lack specificity for SS.

(7) Salivary signs assessed by sialography

- Technique is becoming obsolete.
- Technique cannot distinguish between various causes of glandular inflammation.

(8) Salivary signs assessed by scintigraphy

- Test scores correlate with flow rates but not FSs.
- The test may not provide sufficient diagnostic specificity to offset monetary expenses.
- The test lacks specificity for SS.

- The test requires referral to a tertiary-care facility and placement of intravenous access for radiographic dye isotope placement.

(9) Autoantibodies

- Found in only 60% of patients with SS.
- Found in other CTDs.
- The presence of these autoantibodies correlates with earlier onset of the disease, longer duration of SS, and is associated with extra-glandular features (parotid gland enlargement, vasculitis, splenomegaly)".

A new classification criteria of the American College of Rheumatology criteria (ACR) was proposed in 2012 (Shiboski et al. 2012; Maślińska et al. 2014), it recommended that preliminary criteria for SS should be at least 2 out of 3 of the following objective tests:

1. Positive serum anti-SSA and/or anti-SSB or [positive rheumatoid factor and ANA $\geq 1:320$]
2. Ocular staining score ≥ 3
3. Presence of focal lymphocytic sialadenitis with focus score ≥ 1 focus/4mm² in labial salivary gland biopsies.

In trying to avoid misclassification of asymptomatic patients, the ACR classification criteria do not include symptomatic manifestations (Hernández-Molina and Sánchez-Hernández 2013). Cornec considered the introduction of salivary gland US to the ACR as an improvement in the diagnostic value of this classification system (Cornec et al. 2014).

AECG and ACR performance were compared in 646 participants. Each potential participant was interviewed via phone using the six standardized and validated

questions in the subjective criteria of the revised AECG criteria, the responses were used to assess the presence of ocular and oral symptoms. Of the 646 study participants, 279 and 268 patients were classified as SS according to AECG and ACR criteria, respectively. Of the 303 participants classified by either system as SS, 244 (81%) individuals met both sets of criteria. This comparison shows that there are no significant differences between AECG and ACR. Participants classified as SS under the AECG criteria, 12.5% (35 of 279), were not considered SS when evaluated by the ACR criteria; conversely, 8.9% (24 of 268) met only the ACR criteria (Rasmussen et al. 2014).

On the other hand, 100 patients who met the AECG at Carolinas Center for Oral Health were assessed using the available data from the AECG criteria, and the specific criteria used in the ACR classification criteria were documented. The results indicated that of the 100 patients with pSS based on the AECG criteria, only 5 patients had adequate data available to meet the ACR criteria (Sankar, Noll, and Brennan 2014). Moreover, in comparing the AECG and ACR criteria, Tsuboi examined 302 patients with pSS, and reported that the sensitivity and specificity of the AECG criteria were slightly superior to those of the ACR criteria, 83.1 vs 79.1% and 90.9 vs 84.8%, respectively (Tsuboi et al. 2013).

In a prospective study patients previously diagnosed with SS were re-evaluated using the following classification criteria: the Copenhagen, European, Californian (also known as San Diego³), and AECG or the new ACR criteria. After 7.6 years of follow up, from the 34 patients with complete data, 25 (73%) fulfilled the same criteria as initially, 6 (18%) fulfilled different criteria as initially, and 3 (9%) could no longer

³ This criteria set diagnoses “definite SS” when patients meet all four of the following: KCS (Schirmer, rose Bengal or fluorescein staining), symptomatic xerostomia (resting and stimulated salivary flow), lymphocytic infiltration and at least one serum antibodies (rheumatoid factor, SS-A or SS-B antibody (Fox et al. 1986).

be classified as having SS by any criteria. The agreement between the initial and follow-up classification was the highest for the Californian and the AECG criteria (Plešivčnik Novljan et al. 2014).

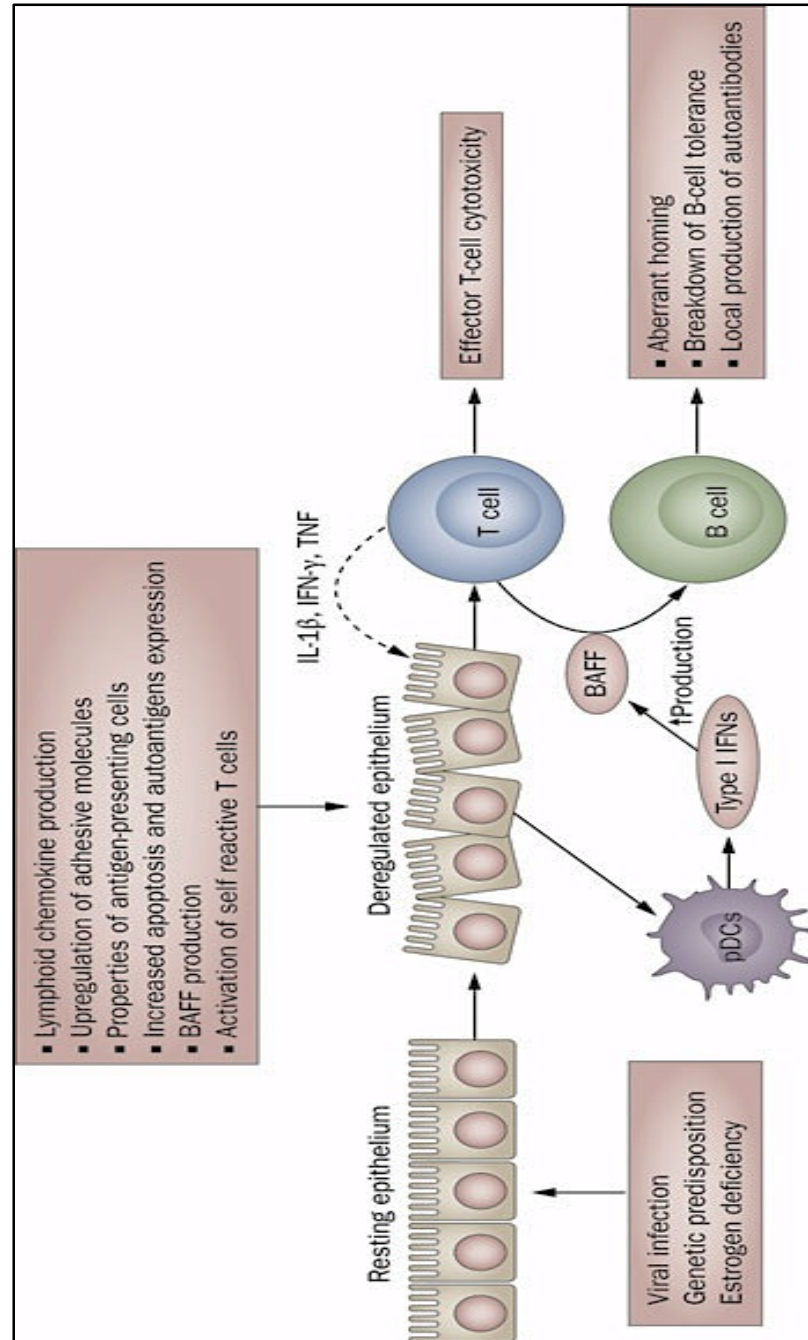
1.1.5 Aetiopathogenesis mechanisms in SS

The precise aetiology of SS is unknown. Previous studies have suggested that the pathogenesis consists of the following stages (Bultzingslowen et al. 2007; Margaix-Muñoz et al. 2009): i) initiation by an exogenous factor; ii) disruption of salivary gland epithelial cells; iii) T-lymphocyte migration and lymphocytic infiltration of exogenous gland; iv) B-lymphocyte hyper-reactivity and production of rheumatoid factor and antibodies to Ro(SSA) and La(SSB) (Konttinen and Käsnä-Ronkainen 2002) (Figure 1).

1.1.5.1 Risk factors

A family history can be associated with an increased risk of developing SS among family members compared to the general population, suggesting a role of genetic susceptibility in the aetiopathogenesis of SS (Al-Hashimi 2001a). Indeed a link between HLAB8, Dw3, HLA-DRw4 and SS has been reported (Margaix-Muñoz et al. 2009; Jonsson et al. 2002). The majority of pSS patients, regardless of racial and ethnic background, have the DQA1*0501 allele, suggesting that it may be a predictor of the susceptibility to pSS (Reveille et al. 1991; Tzioufas, Kapsogeorgou, and Moutsopoulos 2012). A study confirmed the genetic association of IRF5 rs2004640 T allele with predisposition to SS (Miceli-Richard et al. 2007). Another study found a correlation between IRF5 and STAT4 polymorphisms and SS development in a Swedish and Norwegian cohort (Nordmark et al. 2009; Vakaloglou and Mavragani 2011). Thirty five percent of patients with SS have relatives with other autoimmune disease which suggested a hereditary link (Reveille et al. 1984; Reksten and Jonsson 2014).

Figure 1. Pathogenic mechanisms in the initiation of Sjögren's syndrome (Voulgarelis and Tzioufas 2010).



A number of viruses have been proposed to have some sort of aetiological link with SS. Cytomegalovirus infection is known to cause SS-like features in animal models and it has been consequently suggested that this may represent a risk factor or a potential initiating event in SS (Al-Hashimi 2005; Delaleu, Jonsson, and Koller 2005). Other viruses reported to be potentially involved in SS pathogenesis are Epstein-Barr virus (EBV), Hepatitis C virus (HCV) and Human T-cell Leukaemia virus-1 (Mariette et al. 1991; Al-Hashimi 2005; Delaleu, Jonsson, and Koller 2005) but these are actually distinct disorders that have different clinical, histological and serological features from SS.

Of note however Iwakiri and his colleagues reported that SSA/SSB might be released by EBV infection through epithelial cell apoptosis, leading to the activation of TLR3 and the consequent activation of innate immunity (Iwakiri et al. 2009; Mariette and Gottenberg 2010). Reactivation of the EBV by environmental pollutants and virus complex formation with La/SSB autoantigen was associated with positivity for anti-Ro/SS-A and anti-La/SSB antibodies. (Pasoto, Ribeiro, and Bonfa 2014) Moreover, it was reported that perifollicular plasma cells displaying Ro52 immunoreactivity were often infected by EBV (Croia et al. 2014).

With regard to HCV, there is some evidence supporting its pathogenic role in autoimmune diseases. Certainly HCV infection can cause sialadenitis that may mimic the clinical and some of the histological features of SS but there is no constant presence of anti-Ro or anti-La antibodies (Ramos-Casals et al. 2001; Ramos-Casals, Muñoz, and Zerón 2008), as a consequence, HCV infection was added to the exclusion criteria list in the 2002 American-European revised classification criteria (Vitali et al. 2002). Conversely no conclusive evidence for any association between Hepatitis B virus (HBV) infection and autoimmune phenomena (Ramos-

Casals, Tzioufas, and Font 2005; Ram et al. 2008; Chen, Xue, and Wang 2012). There is substantial evidence that HBV is not the cause of SS. In Spain, Marcos analysed 603 patients with pSS, only 5 (0.83%) patients were detectable with HBsAg (Marcos et al. 2009; Chen, Xue, and Wang 2012). Similar results were found by Lu and colleagues (1997) as they reported that the HBsAg-positive rate was lower in patients with SLE than in controls (3.5% vs. 14.7%), while Zhao et al. (2010) detected HBsAG in 2.33% of patients with SLE and 9.57% of controls (Lu et al. 1997; Zhao et al. 2010). Additionally, bacteria from human commensal microbiota have also been suggested as potential triggers for autoimmunity in SS by molecular mimicry with Ro/SS-A autoantigen (Pasoto, Ribeiro, and Bonfa 2014).

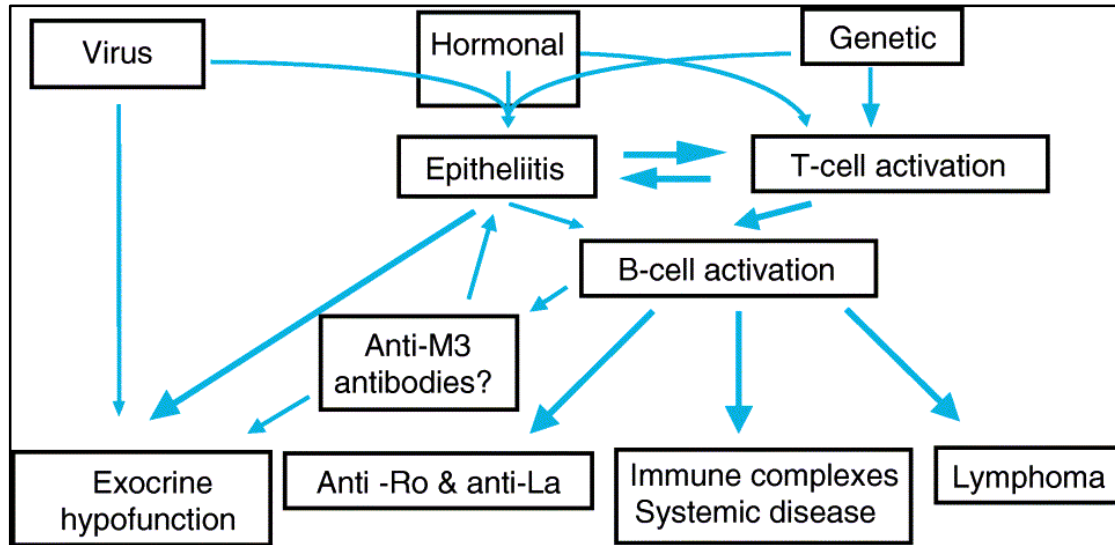
Sex hormones have also been reported as potential risk factors (Bayetto and Logan 2010), due to the high prevalence of SS in females (Talal 2000; Nakamura, Kawakami, and Eguchi 2006). The cellular immune response involved in the destruction of exocrine glands is known to be modulated by the ratio of androgen to oestrogen (Taiym, Haghighat, and Hashimi 2004). In animal models epithelial apoptosis was found to be influenced by oestrogen–androgen balance (Azzarolo et al. 1999). Oestrogen in particular, is an immune stimulator that has a role in lymphocyte growth, differentiation, proliferation, antigen presentation, cytokine production, antibody production, cell survival and apoptosis. Oestrogen can stimulate B-cell dependent responses leading to increased antibody production (Taiym, Haghighat, and Hashimi 2004). As women may be at of risk of developing SS during menopause it has been suggested that either the oestrogen decline or the difference in the oestrogen– androgen ratio is involved with disease onset (i.e. it is not the actual trigger but a factor that drives the destructive immune response

(Taiym, Haghighat, and Hashimi 2004; Bayetto and Logan 2010; Maślińska et al. 2014).

Valtysdottir reported that levels of dehydroepiandrosterone (DHEA) and its metabolite DHEA sulphate (DHEA-S) concentrations are 40–50% lower in patients with SS than in age and sex-matched controls (Valtysdóttir, Wide, and Hällgren 2001). Oestrogen deficiency can induce overexpression of the transcription factor RbAP48 and animal models of SS have been found to over-express RbAP48 (Ishimaru et al. 2008). Over expression of RbAP48 is associated with epithelial cell apoptosis and expression of several antigens (Ishimaru et al. 2008). Furthermore it has been shown in some studies that oestrogen receptors (ER) can be detected in cultured human non-neoplastic salivary gland epithelial cells (Leimola-Virtanen et al. 2000; Kassi et al. 2003; Maślińska et al. 2014). There is indirect evidence that oestrogen in fertile women may play a protective role, this comprising: (1) ovariectomized (estrogen-deficient) mice develop epithelial cell apoptosis and a SS-like condition; (2) aromatase knock-out (estrogen-deficient) mice spontaneously develop a lymphoproliferative SS-like autoimmune disease; and (3) aromatase-treated female breast cancer patients develop SS-like features (Konttinen et al. 2014).

Consequently it has presently been suggested that viruses (all be it unknown ones) may induce or promote autoimmune dysregulation, with a genetic susceptibility involving the type I interferon pathway causing SS (Croia et al. 2014) see (Figure 2).

Figure 2. Hypothetical model for the pathogenesis of Sjögren's syndrome (Venables 2004).



1.1.5.2 Pathogenesis

1.1.5.2.1 Autoantibodies

A variety of autoantibodies have been found in patients with pSS. This involve including antibodies to both ubiquitous autoantigens (e.g. SSA/Ro, SSB/La, a-fodrin) and to autoantigens that are limited to the target tissues e.g. islet cell antigen 69, muscarinic M3 receptor (Hansen, Lipsky, and Dörner 2003; Kassan and Moutsopoulos 2004; Hansen, Lipsky, and Dörner 2005).

Ro/SSA and La/SSB autoantibodies are the most common and are found in the serum of 60–70% of patients with pSS (Bultzingslowen et al. 2007; Bayetto and Logan 2010). Anti-Ro/SSA can be found in isolation (50–70%) or along with the presence of anti-La/SSB antibodies (30–60%), whereas exclusive anti-La/SSB positive is rare (Elkon et al. 1984).

The Ro/SS-A antigen is a RNP complex containing hY-RNAs and at least two proteins (Ro 52 kD and Ro 60 kD), while the La/SSB antigen consists of a 48kD protein (Ben-Chetrit 1993). The La protein is a transcription terminator factor of the

RNA polymerase III transcripts and lately the Ro protein has been recognized as an E3 ligase that regulates negatively cytokine production induced by the IFN γ pathway (Schulte-Pelkum, Fritzler, and Mahler 2009; Hernández-Molina, Leal-Alegre, and Michel-Peregrina 2011). Apoptosis of glandular cells may cause the exposure of nucleosomal and ribosomal particles to the immune system resulting in an autoantibody response- the target being these antigens (Waterman, Gordon, and Rischmueller 2000; Carsons 2001).

Early onset of disease, increased disease severity, longer duration of disease, recurrent parotid gland enlargement and extraglandular manifestations have been associated with the presence of these autoantibodies (Tishler et al. 2001; Al-Hashimi 2005b; Hammi et al. 2005; Reksten and Jonsson 2014). Thus, these autoantibodies may be used as a predictor of disease severity in newly diagnosed patients. The stability of the antibody profile of each patient is fixed at an early stage of disease and rarely changes (Davidson, Kelly, and Griffiths 1999). Patients with anti-La/SSB may have a higher lymphocytic infiltration of tissues than those with Ro/SSA alone, or those who are negative for both autoantibodies (Valesini et al. 1997; Hernández-Molina, Leal-Alegre, and Michel-Peregrina 2011). Furthermore levels of anti-Ro/SSA and anti-La/SSB antibodies are higher in HLA-DR3 and HLA-DR2 positive patients (Wilson et al. 1984; Harley et al. 1986). In one study, patients with younger onset disease had a higher prevalence (45% vs. 12%) of anti-Ro/SSA antibody than those patients with later onset, although a comparison of >70 and <70 year old patients did not find any variation in the prevalence of antibodies (García-Carrasco et al. 1999). Indeed younger onset SS patients can have higher serum levels of Ro/SSA and La/SSB antibodies and higher rheumatoid factor, which relates to more severe clinical symptoms (Tishler et al. 2001). Regarding the gender, some studies reported that male patients have a lower frequency of anti-Ro/La antibody compared with the

female population (Molina et al. 1986). Other studies reported that the positivity of these antibodies is associated with the salivary gland lymphocytic infiltration and abnormal oral and ocular tests (Hernández-Molina, Leal-Alegre, and Michel-Peregrina 2011).

Aqrawi reported a significantly higher degree of Ro52 expression in ductal epithelium in patients with SS compared to the non-pSS controls. Moreover, the level of inflammation was associated with the degree of ductal epithelial expression of Ro52. Yet, Ro52 protein could not be detected in serum and saliva samples of SS patients. The researchers concluded that the up-regulation of Ro52 in ductal epithelium could trigger the disease progression in SS (Aqrawi et al. 2014).

Onset of SS in young adults may be correlated with the presence of rheumatoid factor (RF). In addition RF can be related to the presence of extraglandular symptoms such as arthritis being present in about 74% of patients with pSS (Reksten and Jonsson 2014). Together with RF, the prevalence of antinuclear antibodies (ANAs) in pSS reaches 80%. ANAs can be a predictor of internal organ involvement and the development of lymphoproliferative disorders (Reksten and Jonsson 2014). Studies on animal models of SS have found antibodies to salivary protein1 (SP1) (Shen et al. 2012). A further study of the sera of 123 patients with SS, 50 patients with RA and 75 controls found that 63% of the patients expressed anti-Ro or anti-La whilst 52% expressed anti-SP1. Thirty-four percent of the pSS patients expressed anti-Ro, anti-La and anti-SP1 while 19% expressed only anti-SP1, 86% had anti-Ro/anti-La antibodies while only 41% had anti-SP1 antibodies, with a focus score equal or greater than 2 per 4 mm² (Shen et al. 2014).

1.1.5.2.2 Chronic lymphocytic infiltration and subsequent damage of the salivary acini

Abnormalities in epithelial cells before the infiltration by auto reactive lymphocytes have been found in the salivary glands of the non-obese diabetic mouse model of SS. These are such as disturbed cell proliferation at birth, increased apoptosis of acinar tissue, breakdown of secreted proteins and increased expression of IFN- γ (Cha, Peck, and Humphreys-Beher 2002). A high expression of laminin messenger RNA and protein prior to the lymphocytic infiltration was found in biopsy samples from patients with SS in comparison to controls, thus it is suggested that altered synthesis of the basement membrane of glandular epithelial cells is an early event that is accompanied with salivary gland pathology in SS (McArthur et al. 1997; Voulgarelis and Tzioufas 2010).

It is probable that epithelial cells in SS lesions have an active role in the initiation and maintenance of the inflammatory process (Xanthou et al. 2001; Voulgarelis and Tzioufas 2010). Although salivary gland epithelial cells are not considered to be antigen presenting cells, they hold all the features needed (Manoussakis et al. 1999; Matsumura et al. 2001; Manoussakis and Kapsogeorgou 2007). They have the ability to show higher expression of CD40 and adhesion molecules, additionally, they produces lymphoid chemokines, cytokines and B cell activating factor (BAFF) indicating that they could have a role in the accumulation of dendritic cells (DCs), T cell and B cells in the inflamed salivary glands and in the formation of lymphoid follicles (Xanthou et al. 2001; Tsunawaki et al. 2002; Dimitriou et al. 2002; Ohlsson et al. 2002; Lavie et al. 2004).

The focal lymphocytic infiltration of the salivary glands consists of T and B lymphocytes (at a high T to B ratio) and plasma cells (De Souza et al. 2014). The

lymphocytic infiltration has been suggested to cause acinar atrophy, ductal hyperplasia and replacement of acinar cells with fibrosis and / or fatty infiltration leading to functional impairment (Jonsson et al. 2002; Al-Hashimi 2005b; Fox 2007). T-cells produce cytokines, tumour necrosis factors (TNF) and interferon (IFN), that may increase the antigen presenting nature of epithelial cells, and together with interleukin-1 (IL-1) may inhibit the release of acetylcholine from cholinergic efferent nerves (Fox and Michelson 2000; Fox and Stern 2002). Interferon type 1 can also induce apoptosis of the salivary gland epithelial cells.

T helper (Th) cells are divided into two main subsets which control the polarization of the immune response. Th1 cells produce IFN-g, IL-2 and lymphotoxin and are implicated in cellular immunity. Th2 cells produce IL-4, IL-5 and IL-13, and have a major role in B-cell activation and humoral responses. In most autoimmune diseases this Th1/Th2 balance is altered. Recent evidence has shown that B cells are not strictly controlled by Th cells, but they may even regulate the levels of Th1 and Th2 cells (Mitsias et al. 2002; Youinou 2007; Cornec et al. 2012).

Th1 cells generally predominate in SS autoimmune lesions. On the other hand Th2 cells are the major cytokines in mild lesions (Fox and Kang 1992; Boumba, Skopouli and Moutsopoulos 1995; Mitsias et al. 2002; Manoussakis et al. 2007) while Th17 cell responses have been shown to correlate with lesion severity (Nguyen et al. 2008; Espinosa et al. 2009; Katsifis et al. 2009). The expression of IL-12 has been negatively correlated with parotid gland enlargement, while IL-18 has been positively correlated with C4 hypocomplementemia, suggesting that IL-12 and IL-18 can be considered prognostic factors for the development of lymphoma (Tzioufas, Kapsogeorgou and Moutsopoulos 2012). IL-6 levels were found to be increased in the serum and tissues of patients with a range of autoimmune diseases, including

pSS (Youinou and Jamin 2009; Cornec et al. 2012). In addition, IL-6 also plays a major role in the development of Th17 cells, a proinflammatory T-cell subset which has the capacity to secrete cytokines such as IL-17, TNF α or IL-22 (Miossec, Korn and Kuchroo 2009; Cornec et al. 2012).

Perforin, granzyme A and Fas/Fas ligand mechanisms, could lead to glandular destruction (Bolstad et al. 2003). Although only partial destruction of the gland occurs in most cases, yet the local production of cytokines, autoantibodies, and metalloproteinase is thought to lead to dysfunction of the residual glandular tissue (Konttinen et al. 1992; Konttinen and Käsä-Ronkainen 2002).

B-cells are known to produce immunoglobulins with autoantibody activity and can participate in antigen presentation (Jonsson et al. 2002). In addition, B cell activation can increase the tendency for lymphoma development (Masaki and Sugai 2004). B-cell-activating factor of the tumour necrosis factor family (BAFF) also termed (BLyS), supports B cell survival and antibody secretion (Mariette and Gottenberg 2010). BAFF-transgenic mice can develop polyarthritis, clinical features of lupus, and SS development. In patients with SS, serum BAFF levels correlate with levels of autoantibodies i.e. anti-SSA/SSB and rheumatoid factor (Mariette et al. 2003). An increase in serum BAFF levels correlates with a decrease in BAFF-R expression on B cells of patients with SS and SLE (Sellam et al. 2007), this decrease in BAFF-R is correlated with disease activity in both diseases (Mariette and Gottenberg 2010).

In SS, not only monocytes and dendritic cells express BAFF, but also T cells (Lavie et al. 2008), B cells (Pers et al. 2007) and salivary epithelial cells (Ittah et al. 2006; F. Lavie et al. 2008). IFNs are the main cytokines that stimulate BAFF secretion (Ittah et al. 2006; Lavie et al. 2008).

One fifth of patients investigated with SS can have ectopic germinal centre-like structures that correlate with abnormal B cell proliferation (Fox 2005). The formation

of these germinal centres is associated with increased glandular inflammation, elevated titres of rheumatoid factor, increased levels of auto antibodies and increased IgG levels compared with SS patients without germinal centres (Jonsson et al. 2007; Le Pottier et al. 2009; Voulgarelis and Tzioufas 2010).

1.1.5.2.3 Autoantibodies to muscarinic M3 receptors

IgG antibodies against muscarinic type-3 receptors (M3Rs) exist in the serum of patients with pSS and they may lead to salivary gland hypofunction (Bacman et al. 1996; Gao et al. 2004; Li et al. 2004; Jin et al. 2012). This is of great interest as it is recognized that M3Rs play a key role in the production of salivary fluid and electrolyte secretion (Jin et al. 2012).

The anti-muscarinic M3 acetylcholine receptor antibodies may cause synaptic inhibition of efferent nerve stimulation of salivary parenchyma (Fox and Stern 2002) and thus explain the occurrence of hyposalivation in 40-50% of patients with SS who do not have evidence of notable parenchymal destruction by lymphocytic infiltrate (Fox and Stern 2002). This is confirmed by observations that pilocarpine and other parasympathetic agents will induce an enhanced salivary flow via cholinergic nerve-stimulation of salivary parenchyma (Bayetto and Logan 2010).

Subsequent studies have confirmed the presence of anti-M3 to salivary glands in SS patients, and their selective inhibition of acetylcholine receptors of the bowel, bladder and salivary glands (Dawson et al. 2005; Kovács et al. 2008).

1.1.5.2.4 Autonomic nervous system abnormalities

Autonomic nervous system (ANS) abnormalities are common in SS (Andonopoulos et al. 1998; Kovács et al. 2003; Cai et al. 2008; Mandl et al. 2008; Nikolov and Illei 2009) and may have a role in its pathogenesis, as sympathetic and parasympathetic nerves control vascularity and secretory functions of salivary and lacrimal glands.

Autonomic nervous system dysfunction can lead to xerostomia and xerophthalmia independent from inflammatory infiltrate-mediated parenchyma destruction (Barendregt et al. 1998; Nikolov and Illei 2009).

1.1.5.3 Aetiopathogenesis Summary

As previously mentioned the exact initial event is still unknown. A general hypothesis is that the disease process is initiated by a virus. Viral infection may induce salivary gland epithelial cell expression/release of antigens, particularly Ro, La, and M3R and a triggering of secretion of cytokines and chemokines. Interferon may then induce the activation of BAFF and other cytokines, initiating the migration, and infiltration of T and B lymphocytes into the salivary gland cells. Further activation of these lymphocytes creates an autoimmune reaction and B cells start to produce anti-Ro and anti-La antibodies. Anti-M3R antibodies may inactivate the salivary acinar cells and together with the inflammatory damage of parenchyma to cause glandular dysfunction (Reksten and Jonsson 2014).

1.1.6 Manifestations

1.1.6.1 Oral manifestations

Patients with SS typically complain of dry mouth sensation which in turn can lead to difficulties with chewing and swallowing, dysesthesia, dysgeusia, burning sensation of the oral mucosa, pain in the salivary glands during meals and salivary gland swelling. Clinical signs comprise cracked, dry and desquamative lips, dry erythematous and fissured tongue and angular cheilitis. Rampant caries can be observed on atypical tooth surfaces and indeed patients with SS have higher than normal tooth loss (Fox 2005). Chronic erythematous candidiasis can affect up to 70–80% of SS patients (Torres et al. 2002; Margaix-Muñoz et al. 2009).

One of the complications affecting the salivary glands in SS is the bilateral enlargement, which can be found in 25% to 60%. The enlargement of the parotid glands can be acute or chronic. Pain is usually common with acute enlargement, which can be caused by obstruction of the salivary glands by mucous plugging, which can lead to retrograde contamination. Secondary inflammation also can cause swelling of the salivary glands (Turner 2014).

The oral manifestations of SS will be discussed in greater detail in section 1.2.

1.1.6.2 Ocular and lacrimal manifestations

Patient with SS can present with several ocular symptoms including foreign body sensation, scratching, grittiness, photophobia, redness and ocular fatigue. However ‘dry eyes’ is the most common complaint. An inability to tolerate contact lenses has been suggested to be an early manifestation of ocular involvement of SS prior to frank xerophthalmia. Rarely, patients present with swollen lacrimal glands (Carsons 2001).

Of note, the actual tear flow seems to correlate poorly with symptoms of ocular discomfort, although diminished tear secretion is a well known characteristic of SS. This is probably due to a reduction in mucin production (Jones et al. 1998; Fox, Tornwall, and Michelson 1999), as mucin provides stability to the tear film and decreases its viscosity. Indeed some studies have suggested that mucin production is reduced in the corneal epithelium of SS (Jones et al. 1998). Shimazaki suggested that a decreased number of functional Meibomian glands in the lower eyelid might contribute to the ocular symptoms of patients with SS (Shimazaki et al. 1998) via reduced lipid production and increased tear evaporation (Fox, Tornwall, and Michelson 1999; Fox 2005).

1.1.6.3 Dermatologic manifestations

Cutaneous manifestations in SS include dryness, leukocytoclastic vasculitis and hypergammaglobulinemic purpura (Nakamura, Kawakami, and Eguchi 2006). Occasionally dryness can lead to excoriation and secondary infection. Tishler suggested that patients with SS have a higher prevalence of contact dermatitis (40%) with respect to (20%) the patients with rheumatoid arthritis (Tishler, Paran, and Yaron 1998). A high frequency of erythema annulare has been reported in Japanese patients with SS (Ruzicka et al. 1991).

1.1.6.4 Respiratory and Pulmonary manifestations

Waiffenbach reported that 30% patients with SS had below normal odour identification score compared to 10% of controls (Weiffenbach et al. 1995). This was explained by the dry nasal mucosa, septal ulceration and crusting which affects the contact between odour molecules and olfactory receptors (Su, Poon, and Grushka

2014). In addition xerotrachea is reported to affect 17% of patients with pSS and may also present as a non-productive cough (Ienopoli and Carsons 2014).

Dysphonia and speech clarity were typically mildly affected based on an acoustic analysis in a study in the USA which included 11 patients with pSS. In contrast individuals with pSS considered their own overall voice severity as mild to moderate (Heller et al. 2014).

Pulmonary symptoms have been described to affect 9% to 75% of patients with pSS. Cough is the most common pulmonary manifestation. Dyspnea on exertion, chest pain, and wheeze also have been often reported. Dryness of the upper airway commonly occurs as a result of the decreased glandular function accompanying SS. Non-specific interstitial pneumonia has been reported in up to 61% of pSS lung manifestations (Ienopoli and Carsons 2014). The interstitial infiltrate of the lymphocytes around the bronchioles give rise to most lung lesions (Venables 2004).

1.1.6.5 Cardiac and vascular manifestations

Autonomic cardiovascular dysfunction may affect up to 50% of patients with SS (Andonopoulos et al. 1998), moreover Raynaud's phenomenon appears in about 30% of cases of SS. Purpuric vasculitis is also common, thought to be due to blood sludging in the small vessels due to hyperviscosity (Venables 2004). The prevalence of vasculitis in pSS has been reported to be between 5% and 10% (Ienopoli and Carsons 2014).

The prevalence of traditional cardiovascular risk factors in pSS patients was investigated in several studies, which reported variable outcomes due to the different methodologies used. Lodde reported that pSS patients had lower high-density lipoprotein (HDL) and total cholesterol levels than in xerostomic controls (Lodde,

Sankar, et al. 2006). Cruz reported similar lipid profiles in pSS patients and controls (Cruz et al. 2010). Perez de Lis found that diabetes mellitus and hypertriglyceridemia are more prevalent in pSS than in primary care patients in Spain (Pérez-De-Lis et al. 2010). Another study in the UK determined the prevalence of traditional cardiovascular risk factors in a large well-characterized pSS patient cohort: 543 patients with pSS (5 males, 538 females) were recruited from 30 centres, and with 473 healthy controls. The prevalence of hypertension, hypercholesterolemia, and hypertriglyceridemia was found to be higher among pSS patients compared to healthy controls. In addition there was a higher frequency of patients with pSS taking antihypertensive and statin therapies than control. Twenty-one percent of patients had hypertriglyceridemia compared to 9.5% of controls. The prevalence of hypertension was more in pSS patients than in controls (Juarez et al. 2014).

1.1.6.6 Gastrointestinal and renal manifestations

Sjögren's syndrome has been associated with several gastrointestinal manifestations including oesophageal dysmotility, cholestasis, atrophic gastritis and gastric mucosa-associated lymphoid tissue lymphoma (Ramirez-Mata, Pena Ancira, and Alarcon-Segovia 1976; Tsianos et al. 1985; I al-Hashimi 2001; Carsons 2001). A study in 1995 assessed dysphagia in patients with pSS, patients with sSS, and healthy controls by comparing the difference in swallowing a dry bolus with a water bolus. Results reported that patients with SS experienced significant clinical dysphagia compared to controls (Rhodus et al. 1995).

Glomerulonephritis can affect up to 55% of patients with SS (Skopouli et al. 2000), and one study found it to be associated with an increased risk of lymphoma development (Skopouli et al. 2000). Renal tubular acidosis and nephrocalcinosis

have also been reported (Rodríguez-Cuartero and González-Martínez 1998). In contrast, Venables reported that renal disease is rare in SS, and the majority of cases reported in the literature are based on single-case reports. In his study of 89 patients with SS, showed that clinically significant renal disease, as proteinuria, hyperchloraemia or acidosis, was identified in only four patients (Venables 2004). A significant renal disease was also reported in around 5% in a study of 471 patients (Goules et al. 2000).

1.1.6.7 Haematological manifestations and lymphoma

Haematologic manifestations of SS can range from mild asymptomatic laboratory abnormalities to life-threatening manifestations, particularly the development of lymphoma. The most common haematologic abnormalities reported in patients with pSS were anaemia and hypergammaglobulinemia (Baimpa et al. 2009).

Anaemia of chronic disease was by far the most common type of anaemia, and was associated with systemic involvement and circulating antibodies (i.e., ANA, SSA, SSB) that might reveal a state of generalized inflammation rather than disease limited to glandular sites. The high prevalence of hypergammaglobulinemia and its strong association with circulating autoantibodies (i.e., ANA, SSA, SSB) are harmonious with the polyclonal B-cell activation implicated in the pathogenesis of the disease (Baimpa et al. 2009).

In 25–66% of patients with pSS salivary gland enlargement can affect the parotid gland(s) (Moutsopoulos et al. 1980). The enlargement is usually firm, diffuse, non-tender, bilateral, recurrent or chronic (Daniels and Fox 1992). This presumably reflects the lymphocytic infiltrate and associated inflammation. The increased

production of BAFF caused by B-cell activity leads to an increased risk of lymphoma formation (Turner 2014).

An increased risk of lymphoma development in the course of pSS has been shown in different studies. Indeed, the relative risk of non-Hodgkin lymphoma (NHL) in SS, compared to the general population, is the highest of all autoimmune diseases studied, ranging from 6.1–to 44.4 fold (Kassan et al. 1978; Valesini et al. 1997; Smedby et al. 2006; Theander et al. 2006; Lazarus et al. 2006; Smedby et al. 2006; Mellemkjaer et al. 2008). There is robust evidence showing that patients with long standing SS are at an increased risk of developing lymphoma particularly mucosa associated lymphoid tissue (MALT) lymphoma. These are low-grade B cell lymphomas that can be located in glandular and/or extraglandular regions that typically have a progressive course (Fox 2005). Lymphoma is of a low-grade in SS and usually extra nodal. Of these low grade, 10% can convert to high-grade. It has been reported that the cumulative risk of lymphoma development at 5 years from diagnosis is 3-4% and 9-8% at 15 years (Solans-Laqué et al. 2011).

The most common subtype of lymphoma affecting patients with pSS was the extranodal marginal zone B-cell lymphoma (MZBCL) of the mucosa-associated lymphoid tissue (MALT), (Royer et al. 1997; Zintzaras, Voulgarelis, and Moutsopoulos 2005; Smedby et al. 2006). However, recent research has suggested an association between pSS and diffuse large B-cell lymphoma (DLBCL), (Baimpa et al. 2009). Three subtypes of B-cell marginal zone lymphoma (MZL) were reported by the World Health Organization (WHO) classification according to the sites involved: extranodal marginal zone of mucosa-associated lymphoid tissue (MALT) lymphoma, splenic MZL (SMZL) and nodal MZL (Swerdlow 2013).

In a cohort of 536 patients with pSS, Baimpa and colleagues reported forty cases of lymphoma with a median age at lymphoma diagnosis of 54 years, while the mean

time between pSS diagnosis and the development of lymphoma was 6.8 years. Only 1 of the 40 patients was male. Thirty-nine of the lymphomas were of the non-Hodgkin subtype, 38 of which were of B cell origin. They reported that the likelihood of a patient with pSS developing lymphoma is 4 times more likely to be MZBCL diagnosis than DLBCL (Baimpa et al. 2009). A systematic review reported that the risk of developing lymphoma was about 4% during the first 5 years, 10% at 15 years and 18% after 20 years of diagnosing SS. Parotid enlargement was considered a predictive factor. While palpable purpura was significantly associated with lymphoma development, only one study found it statistically significant as an independent risk factor. Lymphopenia was reported as an independent risk factor in half of the papers. Particularly, there was a statistically significant association between CD4+ T lymphopenia and NHL (Nishishinya et al. 2014). A retrospective study in the UK explored the data of 152 patients diagnosed with pSS from 1986–2011. The mean age of diagnosis was 54.4 years. Serologically, the presence of ANAs was the most frequent finding (75.7%) followed by anti-Ro/SSA antibodies and rheumatoid factor in just under 55%. Extraglandular manifestations were 3.4-fold more common than glandular manifestations. Of the glandular manifestations, parotid swelling was the most common (Abrol et al. 2014). Another retrospective study in Hungary investigated 547 patients diagnosed with pSS between 1975 and 2010. The mean age at the time of diagnosis of the 51 deceased patients was significantly higher than for the 496 patients still alive at the end of the study. Raynaud's phenomenon and serositis were established in the early phases of the autoimmune disease. Vasculitis and renal manifestations usually occur after the diagnosis of pSS. Thyroiditis was the most common accompanying disease with an incidence of 13.9% (Horvath et al. 2014).

Clonal expansion of B cells in salivary glands has been associated with an increased risk of lymphoma development and it has been suggested that patients with this feature should be monitored more closely. One small study reported that patients with paraproteins and antibodies against parietal cells can have a higher risk of gastric MALT lymphoma (Cain, Noble, and Matthay 1998; O'Donnell and Tung 1998; Jönsson et al. 1999).

It would be advantageous to be able to identify particular features of SS, either clinical or laboratory, at the time of diagnosis, to accurately predict subsequent progression to lymphoma, hence ensuring close follow-up of such high risk patients (Kassan et al. 1978; Skopouli et al. 2000). Patients with one or more of the following features (a) parotid enlargement; (b) palpable purpura; (c) low (complement) levels; or (d) mixed monoclonal cryoglobulinemia at the time of SS diagnosis have been reported to have a nine times increased risk of developing lymphoproliferative disease, but only the low complement levels were considered an independent predictor of lymphoma (Skopouli et al. 2000; Ioannidis, Vassiliou, and Moutsopoulos 2002). Significant increase in the size of the salivary glands, lymphadenopathy, splenomegaly, vasculitis, an increased sedimentation rate (ESR) and pulmonary infiltrates should be put into consideration as a suggestion of lymphoproliferation (Carsons 2001).

Neutropenia, cryoglobulinemia, splenomegaly, lymphadenopathy, or low C4 levels have been considered in the past as risk factors for lymphoma in pSS, although no study has identified risk factors for NHL subtypes. Baimpa found that the development of non-MZBCLs (most of which were DLBCLs) to be predicted by the presence of lymphopenia at diagnosis (Baimpa et al. 2009) (Table 5).

Table 5. Clinical manifestations and biomarkers associated with lymphoma development in pSS (Maślińska et al. 2014)

Clinical manifestations	Potential biomarkers
Vasculitis	Cryoglobulins
Salivary gland enlargement	Low C4 complement component
Salivary gland/parotid swelling	Anti-Ro/SSA antibodies
Lymphadenopathy	Leukopenia
Splenomegaly	Presence of RF expressing B cells
Peripheral neuropathy	Higher levels of BAFF/BLyS
Long duration of pSS Histopathology: germinal-like structures in minor salivary gland biopsy	

Treating lymphoma should be personalized according to disease stage. In the cases of low-grade lymphoma an observant strategy may be acceptable (Pollard et al. 2011). Patients with MALT lymphoma and high disease activity may benefit from early treatment in order to avoid transformation into more aggressive lymphomas (Pollard et al. 2011). The optimal treatment regimen may be a combination of rituximab with either alkylating agents (cyclophosphamide/chlorambucil) fludarabine or bendamustine (Zucca et al. 2013). The latter combination of rituximab and bendamustine has shown promising efficacy in recent studies concerning MZ and MALT lymphomas (Nocturne and Mariette 2014).

1.1.6.8 Neurological manifestations

In a large cohort study of 1010 patients with pSS, 110 patients (11%) had peripheral neuropathy (Ramos-Casals et al. 2008). Peripheral neuropathy can precede the diagnosis of SS in as many as 93% of patients, and can occur without sicca symptoms (Mori et al. 2005). In a study of 20 patients with SS associated neuropathy, 16 (80%) presented with burning feet and 12 (60%) with non-length

dependent sensory symptoms. Leg and thigh skin biopsies showed either reduced intraepidermal nerve fibre density or abnormal nerve fibre morphology (Chai et al. 2005). The cause of peripheral neuropathy secondary to pSS is not yet fully understood, vasculitis of the peripheral nerves is one of the suggested causes (Ienopoli and Carsons 2014). Skin biopsy was performed in 14 pSS patients with chronic neuropathic pain, small fiber neuropathy was detected in 13 patients (Fauchais et al. 2011; Carvajal Alegria et al. 2014).

The reported prevalence of pSS with CNS involvement in the literature has ranged from 20% to 2% and 10% (Ienopoli and Carsons 2014). In a retrospective study of 82 patients with neurologic manifestations of pSS, 56 patients (68%) had focal or multifocal CNS disorders. Twenty-nine patients had spinal cord involvement, 12 with acute and 16 with chronic myelopathy, 33 had brain involvement and 13 had optic neuropathy (Delalande et al. 2004; Chai and Logigian 2010).

Alexander and colleagues described a central nervous system disorder similar to multiple sclerosis, in up to 30% of patients (Alexander et al, 1986). Another report suggested that the multiple sclerosis-like syndromes can occur in about 1% of patients with SS (Vincent et al. 2003). SS patients with trigeminal neuralgia and Glove and Stocking-type peripheral neuropathy (Carsons 2001) have been occasionally reported.

The development of central nervous system disease in SS is rare and therefore it has been suggested that SS patients with demyelination, seizures, dementia, focal findings, or psychosis should be re-evaluated for the presence of an associated disease including SLE, multiple sclerosis or antiphospholipid syndrome (Carsons 2001).

Data of 93 patients were analysed retrospectively to assess the prevalence, clinical picture and outcome of CNS involvement. Twenty eight percent had neurological

involvement, 12.9% had only PNS involvement, 14% had only CNS disorders, and one had PNS and CNS involvement. The average age of CNS first manifestation was 47.29 ± 16 years (between 19 and 66 years). Neurological manifestations preceded pSS diagnosis in nine of the patients with CNS involvement (64 % of the 14 patients with CNS involvement). Three patients had movement disorders, two patients had epilepsy, two patients had motor and sensory deficits and two patients had migraine with aura. This study displays the great heterogeneity of CNS involvement in pSS patients (Moreira et al. 2014).

1.1.6.9 Pregnancy and foetal outcomes

Isolated congenital complete heart block (CCHB) develops around 16–24 weeks' gestation in fetuses with structurally normal hearts. CCHB is a rare disorder with an incidence of about one in 22,000 liveborn infants (Buyon and Clancy 2005). It has been linked with maternal connective tissue diseases like systemic SLE and SS, due to the transplacental passage of anti-SSA/Ro and anti-SSB/La antibodies from affected mother to fetus (Tincani et al. 2006). Almost half of the mothers with these antibodies do not have any manifestation of connective tissue disorders (Rivera et al. 2009). Anti-Ro/SSA antibodies are associated with congenital heart block (CHB) *in utero* and to other clinical manifestations in newborns, i.e. skin rash, liver abnormalities, and thrombocytopenia (Brucato et al. 1999).

Available studies do not consider SS to be associated with impaired foetal outcomes, although pregnancy outcome in pSS has not been widely studied (Mecacci et al. 2007). Moreover two studies described a higher rate of spontaneous abortion and foetal loss in pregnancies before SS diagnosis (Siamopoulou-Mavridou et al. 1988; Julkunen et al. 1995). In his study, Haga, applying the American-European

Consensus Group classification criteria for pSS, did not find significant differences in pregnancies in pSS before diagnosis when compared with controls (Haga et al. 2005).

Hussein et al confirmed in their study normal fertility and absence of excess numbers of foetal losses or preterm deliveries in pregnant mothers with pSS. However, maternal age at delivery is higher in patients with pSS, birth weight in pSS offspring lower and delivery by caesarean section or vacuum extraction was more frequent than controls. This complication (i.e. operative delivery) in delivery was caused by an increased risk of foetal growth restriction in the pSS pregnancies resulting in a higher risk of severe foetal complication (Hussein et al. 2011).

Pregnancy complications due to the presence of anti-Ro/ SSA and anti-La/SSB autoantibodies in the maternal serum are known as neonatal lupus and CHB (Lee 2005). The incidence of neonatal lupus in an offspring of a mother with anti-Ro/SSA antibodies is 1–2% (Brucato et al. 2001), however it may be as high as >20% if the mother has given birth to a child with neonatal lupus or CHB before (Buyon 1996). Complications of high risk of CHB, idiopathic cardiomyopathy, and neonatal lupus in sSS mothers have been reported in some studies to be even higher than in SLE patients (Gordon et al. 2004; Mecacci et al. 2007).

Some studies reported an improvement from second-degree to a first-degree block applying long-term dexamethasone therapy with 4 mg/d at 20 to 23 weeks of pregnancy (Copel, Buyon, and Kleinman 1995; Hughes 2004). At this time there is no evidence that steroid prophylaxis may possibly prevent CHB in SS patients at high risk.

Prolonged high-dose corticosteroid therapies in the past have been associated with numerous maternal–foetal complications. However, Brucato reported no association between high dose of dexamethasone during pregnancy and negative effects upon

the neuropsychological outcome of treated neonates (Brucato et al. 2006; Mecacci et al. 2007).

Recently 11 pregnancies with isolated fetal congenital CHB in India were reviewed retrospectively between July 2008 and July 2013. The study included positive anti-SSA/Ro or anti-SSB/La pregnant women with CCHB identified *in utero* by fetal echocardiography. Six mothers were asymptomatic; 2 had SS and 3 had SLE. Connective tissue disease was diagnosed before pregnancy. Four (36.3%) were anti-SSB/La-positive. There was no history of CCHB in previous pregnancies in any of the patients. Seven (63.6%) neonates were given a pacemaker; all were alive at the end of the follow-up period. Oral dexamethasone 4mg daily was given as an intrauterine treatment to all these patients after the diagnosis was made. None of the patients received prophylactic corticosteroids, beta-adrenergic agonists, plasmapheresis, intravenous immunoglobulin or hydroxychloroquine. The study concluded that the presence of underlying connective disorder in the mother does not worsen the prognosis of the affected neonate. Still, these results should be confirmed in larger prospective studies (Roy et al. 2014).

1.1.6.10 Other clinical manifestations

Subclinical musculoskeletal inflammation is seen in approximately 50% of SS patients (Ramos-Casals, Tzioufas, and Font 2005) leading to myalgia and arthralgia (Kassan and Moutsopoulos 2004). Arthritis appears in about 30% of patients with SS, and it may be similar to the arthritis of RA. However in comparison to RA, SS arthritis is usually more relapsing and remitting, and stiffness is less evident (Venables 2004). A study including 48 patients with pSS found that 26 (54%) had

symptoms or signs of arthralgia or arthritis, In 31% of these, arthralgia was reported as occurring before sicca symptoms developed (Pease et al. 1993).

In addition, chronic fatigue can be a prominent symptom in pSS. Studies using multi-dimensional assessment tools demonstrated that physical/somatic fatigue can be more severe and frequent than mental fatigue in patients with pSS (Tensing et al. 2001; Godaert et al. 2002; Bowman et al. 2004; Segal et al. 2008). It was described that 96% of pSS patients experience substantial physical fatigue with a mean score of 3.5, while only 48% of patients report significant mental fatigue with a mean score of 2.8 (Segal et al. 2008). Fibromyalgia syndrome has been reported to be present in approximately 20% of patients with pSS (Ienopoli and Carsons 2014).

Autoimmune thyroiditis has been found to be nine times higher among patients with SS. On the other hand the prevalence of SS is 10 times higher in patients with autoimmune thyroiditis than in normal individuals (Al-Hashimi et al. 2001).

The clinical presentation of SS was assessed in a retrospective study including 1115 patients with SS. Extraglandular pSS features were noted in 520/1115 patients (46.6%), while the remaining patients reported only sicca symptoms. Generally, the extra-glandular manifestations presented by the study sample were mild, including arthralgias, autoimmune cytopenia, mild to moderate polyneuropathy and mild to moderate pulmonary involvement. Immunosuppressive therapy was needed to treat severe extraglandular manifestations (15%). They were mainly synovitis (11.0%), sensory-motor neuropathy (2.0%), severe neutropenia or lymphopenia (14.0%) and diffuse purpura or ulcers related to cutaneous vasculitis (6.0%). NHL was reported in 50 patients with an overall prevalence of 4.5%. The majority of NHL cases were mucosa-associated lymphoid tissue, followed by diffuse large B cell lymphomas and nodal marginal zone lymphomas (Baldini et al. 2014) (Table 6).

Table 6. Extra-glandular manifestations in Sjögren's syndrome (Wu and Carsons 2014)

Skin	<ul style="list-style-type: none">• Xerostosis• Cutaneous vasculitis• Other skin lesions (erythema nodosum, livedo reticulares, lichen planus, vitiligo)
Joints/muscles	<ul style="list-style-type: none">• Arthralgia/arthritis• Myalgia/myopathy
Pulmonary	<ul style="list-style-type: none">• Interstitial lung disease• Pulmonary fibrosis• Pulmonary hypertension• Small airway obstruction• Bronchiectasis
Cardiovascular/ circulatory	<ul style="list-style-type: none">• Pericarditis• Arrhythmia• Raynaud's phenomenon
Nervous system	<ul style="list-style-type: none">• Peripheral neuropathy• Cranial neuropathy• Autonomic neuropathy• Central nervous system involvement
Gastrointestinal	<ul style="list-style-type: none">• Dysphagia• Esophageal dysmotility• Autoimmune hepatitis• Pancreatitis
Urogenital	<ul style="list-style-type: none">• Interstitial nephritis with renal tubular acidosis• Interstitial cystitis

1.1.7 Treatment in Sjögren's syndrome

Carson, in his review, divided the treatment of SS into phases. The first phase consists of moisture replacement. This is applied to the oral cavity, eyes, nose, skin, and genital tract. The second phase consists of stimulation of endogenous secretions that have been proven to be effective mainly for xerostomia. Finally, patients with systemic manifestations such as pulmonary disease, vasculitis, and pseudolymphoma may require corticosteroids, immunosuppressive and cytotoxic agents (Carsons 2001). This review of course was prior to the availability of biological agents such as the anti-TNF and anti-CD20 agents.

1.1.7.1 Treatment of glandular manifestations

1.1.7.1.1 Oral disease

To lessen the risk of dental caries (and other plaque-related oral diseases), frequent dental reviews are recommended (Fox 2005) together with office and home fluoride application in dentifrices and rinses (Selwitz, Ismail, and Pitts 2007). Patients should be advised to avoid retaining sucrose-containing foods in the mouth for long periods of time. Patients with SS should only chew sugar-free (usually sucrose-free) products to help control xerostomia associated caries (Wescott, Starcke, and Shannon 1975; Dreizen et al. 1977; Carsons 2001).

One of the suggested common complications secondary to dry mouth is intraoral candidiasis. Despite this being generally asymptomatic and unlikely to have a premalignant potential, many authors advocate its treatment. Therapy can be initiated with topical agents such as nystatin. The oral suspension (100,000 IU, qid for 10 days) is commonly used, although it contains significant amounts of sucrose and could be cariogenic. Thus, nystatin vaginal tablets (troches) dissolved orally can

be used instead. Cotrimazole lozenges (10-mg) dissolved in the mouth 5 times per day for 14 days also may be used. In addition miconazole gel can be used 4 times a day (Margaix-Muñoz et al. 2009). Patients wearing dentures should be advised to remove their dentures before sleep and store them in sodium hypochlorite solution or chlorhexidine. Oral candidiasis is recurrent and often requires retreatment (Walker et al. 1981). Acute suppurative sialadenitis is another complication of xerostomia induced by SS. It is an uncommon disorder characterised by painful swelling - usually of the parotid glands. Patients can experience purulent discharge from the duct of the affected gland, associated dysgeusia and cervical lymphadenopathy. Pyrexia, malaise and a risk of abscess formation can be present in severe cases. Acute suppurative sialadenitis can affect children and adults (Scully 1986; Khan, O'Sullivan, and McKiernan 2010; Özdemir et al. 2011). In addition acute suppurative sialadenitis of the parotid gland was the initial manifestation of pSS in a 7-year-old child (Alp et al. 2011). The causative organism of acute suppurative sialadenitis is often not found, however, facultative anaerobes, particularly *Staphylococcus aureus* and *Streptococcus viridans* have frequently been reported to be of aetiological significance. Effective hydration and antibiotics are the mainstays of therapy of uncomplicated acute suppurative sialadenitis. Typically employed antibiotics are anti-staphylococcal penicillins (e.g. flucloxacillin, amoxycillin or co-amoxiclav), cephalosporins or clindamycin (Brook 2009). Intra-ductal injection of antibiotics is unlikely to be of practical benefit (Troeltzsch et al. 2014).

The management of salivary gland hypofunction is discussed in detail in section 1.2.7.

1.1.7.1.2 Ocular disease

Managing SS complications affecting the eye should start with patient education on lifestyle modifications such as avoiding long periods of reading or watching television as it reduces the blink rate and eventually increase evaporative loss and indeed starting these periods with artificial tears. Similarly avoiding hot, windy or high altitude environments is necessary. Moreover patients with SS are advised to refrain smoking and avoid eye rubbing (Jackson 2009).

Next, tear supplementation, anti-inflammatory therapy, tear retention and tear stimulation can be an option. The main treatment for dry eye is artificial tears. They act as lubricants and have a wide variety of compositions, viscosity and osmolarity (Fazaa et al. 2014).

Patients should be encouraged to use tear substitutes often as a moisture replacement. Preservative-free tears may be used in cases of irritation (Kassan and Moutsopoulos 2004; Ramos-Casals, Tzioufas, and Font 2005). Artificial tears based on pilocarpine and cyclosporine at 0.05% concentration have been suggested (Kujawa and Rózycki 2005). The duration of tear retention can be increased in severe cases using high-viscosity agents such as sodium hyaluronate, however, this can cause visual blurring. Ophthalmic gels should be used during the night since they cause more blurring. On the other hand, low-viscosity agents such as methylcellulose are generally prescribed for mild-to-moderate dry eye. Tear evaporation can be decreased using lipid-containing artificial tears as they restore the lipid layer of the tear film (Lemp 2008).

Blocking the drainage of the tears or inhibiting their evaporation can retain the existing tears in the eye (Fox 2000). This may be accomplished by occluding the

puncta by inserting collagen or silicone plugs (temporary) or by electrocautery (permanent). Inhibiting tear evaporation can be accomplished by wearing goggles or glasses with specially built side chambers. Although these devices are sometimes not well accepted by patients they can be helpful in certain environmental conditions (i.e. wind). Inflammation of the meibomian glands (blepharitis) is treated with warm compression, cleaning the lids and topical antibiotic (Seal et al. 1990; Huber-Spitzy et al. 1991; Katayama, Koyano, and Nishioka 1994; Carsons 2001). Filamentary keratitis can be managed with frequent eyewashes and a topical mucolytic (acetylcysteine). Furthermore, using scleral lenses can be beneficial in creating a fluid-filled pre-corneal space to rest entirely on the sclera. They are recommended for treating severe, refractory ocular surface diseases (Fazaa et al. 2014).

Topical corticosteroids can improve signs and symptoms. However, these should not be used for long periods due to their potential adverse effects (cataract, steroid-induced glaucoma, risk of herpetic infection). Topical non-steroidal anti-inflammatory drugs can be used with caution as they can lead to corneal melting in patients with compromised ocular surfaces. Regarding immunomodulatory drugs, topical 0.05% cyclosporine emulsion, and 0.03% tacrolimus eye drops have been reported to enhance tear stability in patients with moderate-to-severe dry eye (Fazaa et al. 2014).

A number of trials were conducted to examine treatment options of dry eyes. A controlled trial evaluating 2 NSAIDs (0.1% diclofenac vs 0.1% indomethacin) reported that the diclofenac group showed more reduction in corneal sensitivity (Aragona et al. 2005). In two controlled trials and one prospective study, different topical glucocorticoids were examined. The first trial (Avunduk et al. 2003) reported that fluorometholone showed lower dry eye symptom compared to flurbiprofen and

artificial tears. The second trial (Pflugfelder et al. 2004) did not find any significant differences between 0.5% loteprednol etabonate and placebo in combined corneal staining score. The prospective study (Hong et al. 2007) reported significant improvement in ocular test scores using topical 1% methylprednisolone.

Three placebo-controlled trials of 1451 patients with moderate or severe dry eye disease were enrolled to assess topical cyclosporine. The largest trial (Sall et al. 2000) examined 2 doses (0.05% and 0.1%) and reported significant improvement in Schirmer test scores for both groups however improvement in corneal staining scores only in the 0.05% group. A 12-month extension of this trial using the 0.1% dose did not find any additional improvement in the outcomes (Barber et al. 2005). A controlled trial tested 4 doses of cyclosporine (0.05%, 0.1%, 0.2%, and 0.4%) found no linear dose/response results. However, best results were found in the 0.1% and 0.05% groups (Stevenson, Tauber, and Reis 2000).

Three controlled trials compared 0.05% cyclosporine with other therapies. In the first, Kim and his co-workers reported significant improvement in subjective evaluation of dry eye symptoms in 150 patients using either 0.05% cyclosporine or with 0.05% retinyl palmitate compared to artificial tears. Results showed no differences between cyclosporine and retinyl palmitate (Kim, Choi, and Joo 2009). Sall found an improvement in dry eye symptom and corneal staining scores using the combination of cyclosporine and glycolbased tears compared with cyclosporine and standard artificial tears in 60 patients (Sall et al. 2006). In another study when 0.05% cyclosporine, punctal occlusion and both 2 therapies combined were compared in 30 patients, no differences was seen between the cyclosporine/punctal occlusion combination and cyclosporine alone in Schirmer test (3.9 vs 3.0 mm over 3 minutes)

and in less daily artificial tear use (3.9 vs 3.2 fewer uses per day) (Roberts, Carniglia, and Brazzo 2007).

Topical 0.05% cyclosporine showed statistically significant improvements in a 6 month prospective study (Toker and Asfuroğlu 2010). Tauber conducted a placebo-controlled trial, he assessed 2 doses (1% and 2%) of topical ocular diquafosol, in 527 patients and found better corneal staining score but not improved clearing of foreign body sensation (Tauber et al. 2004; Ramos-Casals et al. 2010).

1.1.7.2 Treatment of extra-glandular/systemic manifestations

Concerning the general management of the extraglandular manifestations, no reliable treatment has yet been identified, but use can still be made of corticosteroids, nonsteroidal antiinflammatory drugs, immune regulators and immune suppressors (Ramos-Casals, Tzioufas, and Font 2005). However, Fox, Datiles and Atkinson reported that there was no improvement histologically or functionally in salivary and lacrimal glands from the use of prednisone (Fox et al. 1993). It was suggested in another study that the long-term side effects associated with this treatment far outweighed the benefits (Fox and Stern 2002).

Hydroxychloroquine (HCQ) at doses of 6 to 7 mg/kg/day is used to treat fatigue, arthralgia, and myalgia in pSS, although it has not been shown to improve dryness (Fox et al. 1996; Manoussakis and Moutsopoulos 1996; Tishler et al. 1999). A randomized multi-center placebo-controlled trial of HCQ of 120 patients found that this drug caused a reduction in IgG and IgM, yet no significant improvement of dryness, pain and fatigue seen at 12 months (Gottenberg et al. 2014). In current practice, hydroxychloroquine may be considered for the management of vascular purpura (Fazaa et al. 2014). Non-steroidal anti-inflammatory (NSAID) drug therapy can be used to control minor musculoskeletal symptoms. In the case of elderly patients or patients with peptic ulcer disease, cyclooxygenase-2 (COX-2) inhibitors can be considered. Infrequently, short courses of low-dose corticosteroid may be needed for very painful or disabling joint symptoms, Methotrexate in low doses weekly helps in managing arthralgia and myalgia, however it has a little effect in increasing the saliva flow (Skopouli et al. 1996).

Rituximab (anti-CD20) efficacy was assessed on several controlled trials. Seventeen patients with SS were included in the first trial (Dass et al. 2008). Fatigue was assessed using a visual analogue scale (VAS) as primary end point. Fatigue was significantly decreased in the rituximab group. Another study enrolled 30 patients and demonstrated efficacy in oral and ocular dryness and fatigue VAS (Meijer et al. 2010). Patients with recent disease-onset and/or systemic manifestations were enrolled in a recent multicenter trial. Pain, fatigue, dryness and disease activity were assessed using VAS. The proportion of patients with improvement was significantly higher in the rituximab group at week 6. However, at 6 months, no significant improvement was observed in the rituximab group (Devauchelle-Pensec et al. 2014a). Epratuzumab was tested in an open study included 15 patients with pSS (Jacobi et al. 2008). Improvement of dryness, fatigue and pain VAS were observed. Fifteen patients with pSS received 8 infusions of abatacept and were followed-up for 24 weeks. The ESSPRI and the ESSDAI were significantly improved. Stimulated whole saliva remained stable. The tolerance of abatacept was satisfactory (Meiners et al. 2014). Symptoms of dry skin can be improved with 20 to 30 mg/day of secretagogues such as pilocarpine (Carsons 2001). Tight or elastic clothing should be avoided in cases of hypergammaglobulinemic purpura. Intermittent use of a mild corticosteroid cream can be used to control pruritis. In severe cases, such as necrotic or ulcerating lesions, more aggressive therapy is needed. Initial suppression may be attained with moderate doses of corticosteroid (0.5 to 1 mg/kg/day of prednisolone), then tapered as rapidly as possible with continued immunosuppression maintained (Carsons 2001). Humidification and secretagogues can help in the management of xerotrachea. Cough and dyspnea may be treated with moderate-dose corticosteroid but may require low-dose oral cyclophosphamide (Carsons 2001).

Gastrointestinal extraesophageal reflux disease can be treated with antacids, histamine-2 blockers, and proton pump inhibitors. On occasion, endoscopic evaluation and intervention may be necessary (Carsons 2001).

Low-dose tricyclic antidepressants or anticonvulsants, such as gabapentin can be used to treat cranial and peripheral neuropathy. In resistant cases intravenous gammaglobulin is used (Pascual, Cid, and Berciano 1998; Carsons 2001). In cases of raynaud's phenomenon calcium channel blockers or angiotensin-converting enzyme (ACE), inhibitors appear to be sufficient in these patients (Mavragani and Moutsopoulos 2007).

1.2 Salivary gland hypofunction

1.2.1 Saliva: composition and physiology

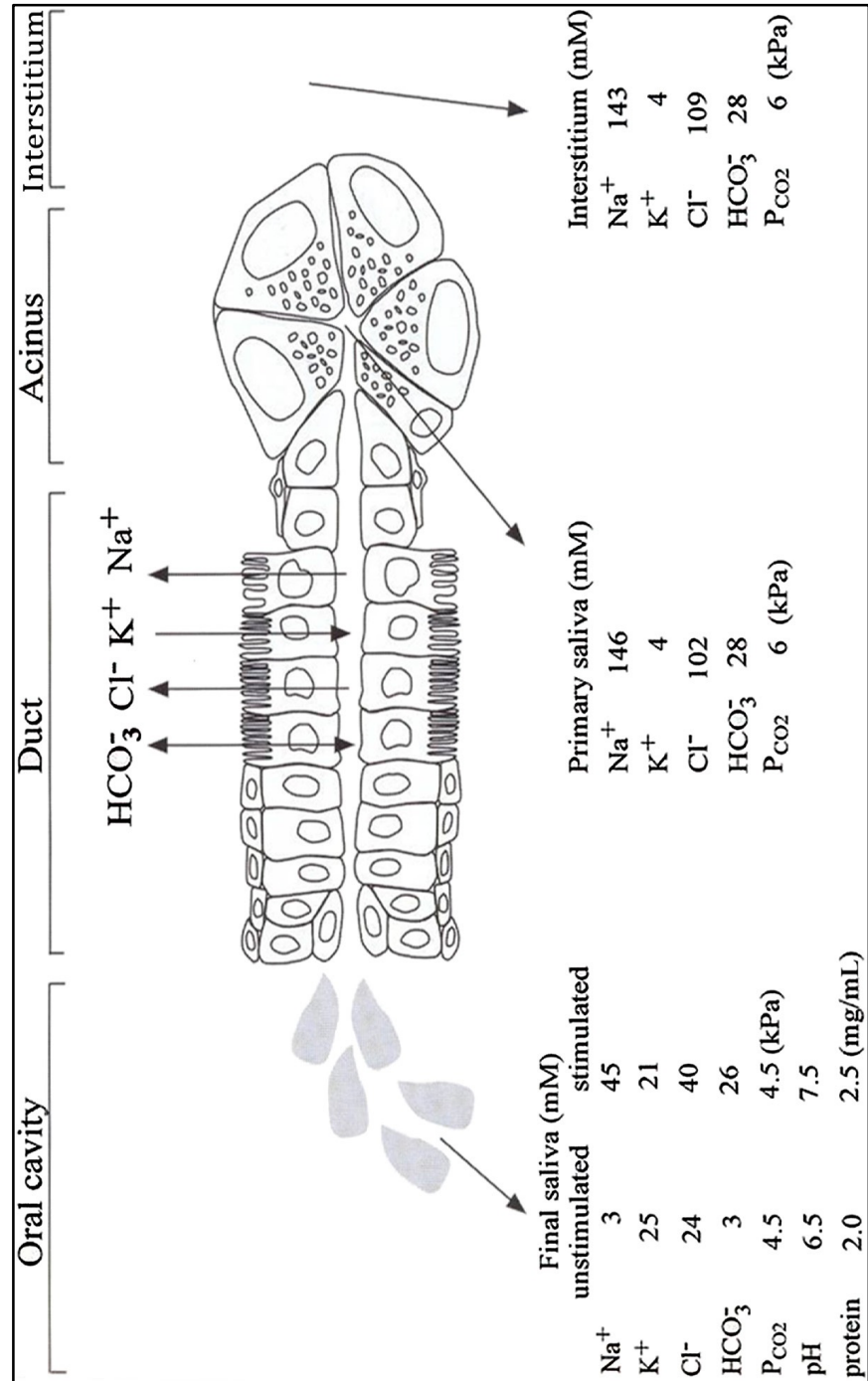
Whole saliva is composed of secretions from 3 pairs of major salivary glands (parotid, submandibular [SM], and sublingual [SL]) plus numerous minor glands. In addition, whole saliva comprises gingival crevicular fluid, microorganisms, food debris, and shed mucosal cells (Jensen and Vissink 2014). The amount of saliva secreted by an average adult is at least 500 ml over a 24-hour period. However, the salivary flow rates can differ greatly during any 24-hour period, according to the need or the current physiologic status of the patient. The unstimulated/resting flow rate is 0.3 ml/ min, while the flow rate during sleep is 0.1 ml/min; during eating or chewing, it can increase to 4.0 to 5.0 ml/min (Cooper et al. 1995; Guggenheimer and Moore 2003). Due to circadian rhythms, the flow rates were found to fluctuate by as much as 50 percent over a 24-hour period (Dawes 1987; Ship, Fox, and Baum 1991; Navazesh, Christensen, and Brightman 1992b; Ghezzi, Lange, and Ship 2000; Guggenheimer and Moore 2003).

The autonomic nervous system is responsible for controlling the secretion of the salivary glands, in addition to the action of various hormones. Salivary secretion depends on several modulatory influences, which perform either through a cyclic adenosine monophosphate–dependent, or a calcium-dependent pathway. Saliva is composed of two components that are secreted by independent mechanisms. Primary saliva is produced by the secretory end pieces (acini), which is isotonic, its ionic composition is similar to that of plasma (Melvin, He, and Baum 1988; Turner and Sugiya 2002) see Figure. 3. The primary fluid is then adjusted in the ductal system by the selective reabsorption of sodium and chloride, and by secretion of potassium and bicarbonate. Thus the secretion rate, and therefore the volume, of the

endproduct saliva are determined directly by the formation rate of primary saliva through the acinar cells (Jensen and Vissink 2014). Excitation of either sympathetic or parasympathetic nerves to the salivary glands stimulates salivary secretion, yet the effects of the parasympathetic nerves are usually stronger and long lasting (Guggenheimer and Moore 2003).

Both cholinergic and adrenergic agonists stimulate the ducts of the salivary glands causing an increase in the rate of secretion of potassium (K^+) and bicarbonate (HCO_3^-). In serous acinar cells, acetylcholine, norepinephrine, substance P, and vasoactive intestinal polypeptide are released by specific α - nerve terminals and increase the secretion of salivary amylase and the flow of saliva. Acetylcholine, substance P, and norepinephrine acting on α -receptors that increases the concentration of calcium ions in the serous acinar cells, resulting in copious secretion with a lower concentration of amylase. In contrast, norepinephrine acting on β -receptors and vasoactive intestinal polypeptide elevates the cyclic adenosine monophosphate concentration in acinar cells, eliciting a secretion that is rich in amylase. Accordingly, parasympathetic stimulation produces copious saliva of low protein concentration, whereas sympathetic stimulation produces little saliva but with high protein concentration, which may lead to the dry mouth sensation (Carlson 2000; Porter, Scully, and Hegarty 2004).

Figure 3. Ionic and protein composition of tissue fluid, acinar secretion, and oral fluid
(Jensen and Vissink 2014)



Therefore, not only the volume but the composition of mixed saliva in the mouth can differ depending on the role of different glands during reflex stimulation (Proctor and Carpenter 2007). The parotid gland has a very low secretory rate under resting (unstimulated) conditions compared to during stimulation. Conversely, the submandibular/sublingual glands secrete relatively more saliva under resting conditions, see Table 7 (Shannon, Suddick, and Chauncey 1969; Proctor and Carpenter 2007). It has been reported that different afferent stimuli can change the composition of saliva secreted by a single gland. A relatively greater amount of IgA was present in chewing-stimulated human parotid saliva when compared to citric acid evoked saliva (Proctor and Carpenter 2002). Other studies showed that sweet stimulated human parotid saliva has higher protein concentration compared to acid stimulated saliva (Mackie and Pangborn 1990). The effects of different reflex stimuli have been studied in animal models, they showed that higher concentrations of salivary amylase and other proteins were secreted in a rabbit, when parotid saliva was evoked by carrots compared to standard pelleted chow (Gjörstrup 1980; Ikawa, Hector, and Proctor 1991). Additionally hormones were found to have a role in salivary secretion; thus women tend to have lower salivary flow rates than men. And these rates can differ in women according to different events as puberty, menstruation, pregnancy and menopause (Saluja et al. 2014).

Table 7. Relative (%) contribution of different gland types to whole saliva under various conditions (Jensen and Vissink 2014).

Salivary Gland	Sleep	Unstimulated Whole Saliva	Stimulated (Mechanical) Whole Saliva	Stimulated (Acid) Whole Saliva
Parotid	0	21	58	45
SM	72	70	33	45
SL	14	2	2	2
Minor glands	14	7	7	8

1.2.2 Clinical features and complications of salivary gland hypofunction

Saliva plays a major role in oral function (Table 8). It carries food particles onto the taste buds in an appropriate dilution to aid in taste perception. In addition amylase and lipase aid initial digestion of starch and fat (Valdez and Fox 1991). Saliva eases the formation of the food bolus, and the salivary lubricatory glycoproteins, which permanently coat oral surfaces assisting in food mobility and reducing friction between the different oral structures (teeth, tongue, cheeks and lips) and between these structures and foreign elements (food, dental prostheses) (Levine et al. 1987). It aids in lubrication, repair, lavage, antimicrobial, and buffering properties which all contribute extensively to the protection of oral hard and soft tissue integrity (Mandel 1987). The presence of saliva allows the tongue, cheeks and lips to rub against the teeth and reduce bacteria accumulation on the tooth surfaces and oral cavity (Napeñas and Rouleau 2014).

Table 8. Main salivary function (Jensen and Vissink 2014)

- Protecting the mineralized tissues against wear and demineralization
- Wetting the oral mucosa, thereby forestalling oral desiccation and infection
- Promoting speech and the digestion of food.

The term xerostomia is the abnormal reduction of saliva. It can effect between one-fifth to one-third of the adult population. It is also known to affect women more commonly (Sreebny 1992; Billings, Proskin, and Moss 1996; Nederfors et al. 1997). It is more common with increasing age, and indeed 25 percent of the elderly can complain of daily dryness. Occasionally it could be subjective with no evidence of changed salivary flow. In this condition, xerostomia is usually due to psychological factors (Orellana et al. 2006).

In cases of salivary gland hypofunction, patients will often complain of a feeling of dryness of all the oral mucosal surfaces, involving even the throat (Wolff and Kleinberg 1998; Bretz et al. 2000; Guggenheimer and Moore 2003). Additionally, patients may complain from difficulty in chewing, swallowing, or speaking (dysphagia and dysarthria). Patients may report the need to drink fluids to aid in swallowing while eating or difficulties in swallowing dry foods. Many patients will report carrying fluids at all times for comfort and to help in speaking and swallowing (Loesche et al. 1995; Guggenheimer and Moore 2003). The lips can sometimes stick with the oral mucosa or to their teeth. Pain is another common complaint as the oral mucosa may become sensitive to spicy or coarse foods, which can interfere with a patient's diet and satisfaction at meal times. Retention of removable dentures can be negatively affected due to lack of lubrication (Niedermeier and Krämer 1992; Fox 2008).

The lips may appear cracked and atrophic, the buccal mucosa can be pale and look corrugated, and the tongue smooth and reddish with loss of papillation (Guggenheimer and Moore 2003). In addition the tongue was reported to have the appearance of ground beef because of the presence of the deep fissures and sticky appearance (Napeñas and Rouleau 2014). Regarding the hard tissues, there can be an increase in erosion and dental cavities either at the gingival margin or cusp tips. Carious lesions can sometimes be progressive despite the presence of excellent oral hygiene, though this is unusual, it can be due to the lost buffering action and cleansing that saliva provides (Guggenheimer and Moore 2003). Patients with SS usually have an increased number and frequency of cariogenic microorganisms as *Lactobacillus* spp and *Streptococcus mutans* in supragingival plaque, and *Candida albicans*. In addition, the mucosal immunity is deteriorated due to the reduction in IgA and therefore the defense against caries is lowered (Napeñas

and Rouleau 2014). As a consequence, Fox and colleagues found that greater number of dental visits, more decayed teeth, and more dental restorations were reported in patients with pSS in comparison with control subjects (Fox et al. 2008). Erythematous candidiasis may occasionally lead to mucosal sensitivity, and give rise to erythema of the oral mucosa (especially the palate and tongue), while thrush can give rise to white, curd-like patches of the soft palate and rarely other oral sites. The corners of the mouth can be inflamed giving rise to angular cheilitis (Rossie and Guggenheimer 1997; Guggenheimer and Moore 2003). Food pocketing in vestibules and around teeth is a common finding in patients with SS due to the lack of mechanical cleaning forces (Napeñas and Rouleau 2014) (Table 9).

The salivary glands must be assessed for enlargement, changes in texture, and pain, and also to observe the ability for saliva to be excreted from the main excretory ducts. Saliva should be expressed in a clear, watery and copious form. In cases where saliva appears as a cloudy exudate, that may be seen as sign of bacterial infection i.e. acute suppurative sialadenitis (Fox 2008). Parotid gland swelling in particular has been reported to occur in 30% to 40% of patients with SS (Napeñas and Rouleau 2014) this can be due to the inflammation of the disease process , acute suppurative sialadenitis and lymphoma.

Table 9. Effects of long-standing xerostomia

Increased frequency of caries (particularly cervical caries)
Proclivity toward acute gingivitis
Dysarthria
Dysphagia
Dysgeusia
Proclivity toward candidal infection (e.g. acute pseudomembranous candidiasis, median rhomboid glossitis, denture-associated stomatitis, angular cheilitis)
Burning tongue/depapillation of tongue
Oral mucosal soreness
Dry, sore, cracked lips
Salivary gland enlargement (various causes)

A study assessed the data of 35 patients with SS in order to describe variable oral circumstances. Feeling of a dry mouth and ingesting liquids to manage the dry mouth sensation was reported in all patients. Moreover, intraoral wounds were found in 71% of the subjects. Level of hyposalivation was found to be related to the duration of disease (Olate et al. 2014).

1.2.3 Objective hyposalivation measuring methods

Measuring salivary output can be easily done in an office setting by determining the total unstimulated output of saliva, termed the whole saliva flow rate (WSR). Salivary flow is classified as unstimulated, or resting, and stimulated, as it arises when an exogenous factor is acting on the secretory mechanisms (Dawes 1987). Whole saliva is basically the mixed fluid contents of the mouth. In 1992, Navazesh and colleagues suggested that salivary output can be measured and collected, less than 0.12 to 0.16 mL/min (unstimulated) is considered a criteria for hypofunction (Navazesh, Christensen and Brightman 1992; Pesce and Spitalnik 2007; Fox 2008). Another study indicated that unstimulated whole saliva flow rates less than 0.1 mL/min and stimulated whole saliva flow rates less than 0.7 mL/min are considered abnormally low (Jensen and Vissink 2014).

Some different methods of assessing salivary gland function are presented in Table 10, including sialochemistry which analyses the saliva composition (Kalk et al. 2001; Kalk et al. 2002), impression cytology of the buccal mucosa (Aguilar, Fonseca, and Croxatto 1991; Maragou et al. 1996), salivary electrophoresis (Al-Hashimi, Haghighat, and Fox 1998), saliva ferning (Aguilar, Fonseca, and Croxatto 1991; Maragou et al. 1996; el-Miedany, el-Hady, and el-Baddin 1999), and the use of iodine–starch reaction to identify the number of lip salivary gland ostia (Inamura et al. 2001). Salivary function assessment can also be performed using the following methods: the wafer test (Sánchez-Guerrero et al. 2002), the Saxon test (Kohler and Winter 1985), the oral Schirmer test (López-Jornet, Camacho-Alonso, and Bermejo-Fenoll 2006), the candy weight loss test (Sreebny and Valdinì 1988), the palatal (Márton et al. 2006), and parotid gland saliva flow (Skopouli et al. 1989), the capsaicin-stimulated salivary flow using filter paper (Kanehira et al. 2011) and more

commonly the whole saliva collection, with or without stimulus (Speight, Kaul, and Melsom 1992; Vitali, Moutsopoulos, and Bombardieri 1994) see Table 10. Some of the most frequently used methods are explained in the next section with further details.

1.2.3.1 Resting whole saliva

Four techniques have been described to estimate resting whole saliva flow rate: the draining method, the spitting method, the suction method, and the swab technique. In the draining method, collections should be performed after an overnight fast, between 8 and 11 a.m., or at least at a regular time. Patients are instructed not to brush, use mouthwashes, drink, chew (e.g., food, gum) or smoke at least 90 minutes before the collection time. The test should be carried out in a quiet area. The patient is then seated in a chair, in an upright position with the head tilted down, given a funnel and a test tube, and is asked to swallow. Following this, they are asked to sit quietly for a period of 5 minutes and to allow the saliva to accumulate in the mouth and passively drain into the funnel. The volume of saliva is measured and the rate of flow is recorded as mL/min. Alternatively, the saliva may be collected into a weighing boat. In such cases, the boat is tared (zeroed) on a precision balance, the saliva is allowed to drool into the boat, and the boat is then weighed again after the test period. Results may be expressed as g/min or as mL/min. The spitting technique is similar to the draining method. The difference is that the patient allows the saliva to accumulate in the mouth and then spits it into the collecting vessel, 1–2 times per minute. The saliva may be collected either into the weighing boats, into test tubes, or into the sialometer. The suction method involves the use of the standard, plastic, dental saliva ejector. The swab method is conducted by placing preweighed cotton rolls or gauze sponges into the mouth, leaving them for a fixed period, and then

reweighing them after the test. However, regardless of the method used, the conditions of the test should be the same for each patient each time that saliva is collected (Sreebny and Vissink 2010).

1.2.3.2 Stimulated whole saliva

Whole saliva is generally stimulated by either chewing or tasting citric acid. Both methods are reliable. Flow rates using citric acid are generally greater than those induced by wax. When applying the masticatory method, the patient is either given a piece of paraffin wax, a piece of gum base, or a piece of Parafilm to chew for 5 minutes. The accumulated saliva is then actively spat into the collecting vessel every minute. The gustatory method uses a 2% solution of citric acid to stimulate flow. The solution is applied to the lateral borders of the tongue with a cotton applicator every 30 seconds for 5 minutes. As with the chewing method, the saliva is expectorated into the collecting vessel every minute (Vissink et al. 1983).

1.2.3.3 Parotid saliva

The orifice of the parotid gland is accessible for cannulation, but usually a (modified) Lashley or Carlsson-Crittenden cup is used. The Lashley cup is a bi-chambered device, which measures about 2 cm in diameter. The inner chamber is placed directly over the orifice of the Stensen duct and connected, via plastic tubing, to a (graduated) test tube. The outer chamber is attached to a rubber bulb or a suction device via plastic tubing and is secured to the mucosa by vacuum. Parotid saliva is usually collected under stimulated conditions because the flow rate of unstimulated parotid saliva is usually very low or even absent in healthy individuals. The most commonly applied stimulus is a 2% to 4% citric acid solution. This stimulus is applied to the lateral borders of the tongue at 30-second or 60-second intervals with a cotton swab. It is usually collected for 10 minutes (Navazesh 1993; Burlage et al. 2005).

1.2.3.4 Submandibular/sublingual (SM/SL) saliva

About 70% of the oral secretions stem from the combined SM/SL glands. Therefore, most studies consider that the flow and composition of saliva obtained from the SM/SL glands are similar to that gained with whole saliva. The suction method is mostly used to collect these secretions. In this technique, the Stenson ducts are blocked with either Lashley cups or cotton roles. This strategy allows SM/SL saliva to flow from the Warthin the Bartholin ducts. Saliva which accumulates on the floor of the mouth, can be aspirated with a syringe, micropipette, or with gentle suction. The SM/SL saliva can be collected in the resting or stimulated state (Sreebny and Vissink 2010).

1.2.3.5 Minor salivary gland secretions

The advent of the Periotron®, has allowed the development of a simple to measure the volume of saliva from the minor salivary glands and to calculate the thickness of the salivary film on the oral mucosa. In practice, a small piece of pan-shaped filter paper (Sialopaper TM) is placed at a selected site on the mucosa and held there for 5 seconds. The Sialopaper TM is then removed, placed between the 'jaws' (electronic sensors) of the Periotron®, and the reading is shown on the screen. The Periotron® is a micro moisture meter that reads volumes up to 3 µL. The Sialopaper TM strips collect 0–3µL of fluid. To calculate the thickness of the mucosal film (in µm), one divides the volume of the collected saliva by the area of the Sialopaper TM test strip (31.7 mm^2).

Several papers have now recorded the normal values for various sites in the mouth (DiSabato-Mordarski and Kleinberg 1996; Wolff and Kleinberg 1998a; Won et al. 2001; Lee et al. 2002). Of particular interest is the one that is located on the hard palate. It is the driest site in the oral cavity. The thickness of the salivary film at this

site may well be a valid sialometric indicator of the subjective feeling of oral dryness (Sreebny and Vissink 2010).

Table 10. Objective salivary hypofunction tests (Hernández-Molina and Sánchez-Hernández 2013)

Test	Method	Abnormal test	Disadvantage
Whole saliva flow collection	Un-stimulated: saliva collection is performed during 5 min to 15 min by the spitting method. Stimulated: after chewing wax or gum for 1 min, the volume of saliva expectorated during that time is measured.	Non-stimulated ≤ 1.5 ml/15 min Stimulated ≤ 0.6 ml in 1 min	Clinical practice test. Affected by age, time of the day and drugs.
Palatal saliva flow	Dry weighed 8 mm disks are placed on both sites of the palate, at the level of the upper first molars. Collection is carried out for 30 s and then the disk is weighted.	$1.35 \pm 2.5 \mu\text{cm}^{-2}\text{min}^{-1}$	Clinical practice test. Affected by age, time of the day and drugs.
Stimulated parotid saliva flow	Saliva is collected under a stimulus with a cannula or other collection device.	1.5 ml/5 min	Clinical practice test. Special collection material needed.
Wafer test	After swallowing any residual saliva, the wafer is put on the centre of the subject's tongue, and wafer dissolution time is measured.	>4 min	Screening/clinical practice test. Affected by age, time of the day and drugs.
Oral Shirmer test	After placing a filter paper on the floor of the mouth, the wetted length after 5 min is measured.	≤ 30 mm/5 min	Screening/clinical practice test. Affected by age, time of the day and drugs.
Candy weight loss test	The weight loss of a standard hard sugar candy after 3 min of passive incubation between tongue dorsum and palate is tested.	<0.23 g	Screening/clinical practice test. Affected by age, time of the day and drugs.
Impression cytology	Cellulose acetate paper is applied on the internal surface of the inferior lip and the obtained sample is stained with hematoxylin and PAS.	Keratinized epithelium is abnormal	Research test. Light microscopy needed. Age dependent.
Iodine–starch reaction	A test tape of $1 \times 1 \text{ cm}^2$ containing iodine and starch is set on the labial mucosa anterior to the labial frenulum for 30 s. The number of blue spots corresponds to the number of salivary gland ostia.	Controls 9.4 ± 2.5 spots Oral dryness 4.5 ± 3.1 spots Sjögren's 2.1 ± 1.3 spots	Screening/clinical practice test. Age dependent.
Capsaicin-stimulated salivary flow	An assay system comprising 5 spots containing starch, potassium iodide and a colouring reagent with or without capsaicin is placed in the mouth.	In controls the capsaicin-stimulated salivary flow increased from 1.2 ± 1.4 to 2.9 ± 1.3 coloured spots No change in the hyposalivation group	Screening/clinical practice test. Age dependent.
Sialochemistry	Measurement of specific proteins (lactoferrin and lysozyme), carbohydrate, and electrolytes.	Laboratory kits Cut-offs	Research test. No agreement about significant cut-offs. Variation between resting and stimulated saliva. Moderate amount of saliva is required.

1.2.4 Subjective hyposalivation measuring methods

Though subjective dryness does not associate well with assessable salivary gland dysfunction, some symptoms have been found to have a predictive value (Fox, Busch, and Baum 1987). It is useful to note that around a 50% reduction in saliva is required to take place before the xerostomia becomes evident (Dawes 1987).

The use of a questionnaire accompanied with saliva collection has been useful in determining subjective measures of salivary gland dysfunction (Pai, Ghezzi, and Ship 2001). Since measuring xerostomia is a complex process, it is necessary to include the measurement of subjective symptoms and therefore, it is advised to use scales with different items that evaluate the range of the xerostomia (Sreebny and Valdini 1987; Nederfors et al. 1997; Baker, Pankhurst and Robinson 2006).

1.2.4.1 Visual analogue scale (VAS)

VAS has been widely used in the measurement of pain. One potential advantage over dichotomous/categorical measures of xerostomia is its ratio properties, which could be useful in analysing relative changes in salivation over time (Pai, Ghezzi, and Ship 2001), when compared to dichotomous/categorical measures which have a limited use in detecting change in xerostomia over time (Langley and Sheppard 1985). A VAS is a 100 mm horizontal straight line; the end anchors are labelled as the extreme boundaries of the sensation or response to be measured. The subjects are asked to mark their response by placing a vertical line between the two ends of the line (Wewers and Lowe 1990). This rating scale approach provides a continuous score which would allow more accurate discrimination among individuals with respect to the severity of their symptoms, thus reducing the potential for misclassification which may occur with single-item approaches ('xerostomic' vs. 'normal') defining the condition. (Price et al. 1983; Pai et al. 2001)

1.2.4.2 Verbal categorical rating scale (VRS)

The VRS consists of a set of word descriptors such as mild, moderate, and severe. Patients select a word that best represents the severity of symptoms (Langley and Sheppard 1985). The VRS may correspond to different values on the VAS in the same patient on different occasions. Thus, a categorical scale should be used only as a coarse screening instrument, and more accurate intensity assessment should rely on a VAS, even in routine clinical assessment (Breivik et al. 2008).

1.2.4.3 Subjective clinical evaluation

Investigations have already shown that the complaint of xerostomia (the feeling of oral dryness) by itself is not a reliable predictor of salivary gland hypofunction (Fox 1985; Navazesh et al. 1992; Närhi 1994; Wang et al. 1998). In fact a study by Field showed that only 54% of patients complaining of xerostomia actually had objective evidence of salivary hypofunction (Field et al. 1997). However, Fox demonstrated that specific questions concerning symptoms of oral dysfunction can be helpful in identifying patients with salivary gland hypofunction (Longman et al. 2000). In clinical trials patients can be asked a series of standardised questions concerning symptoms of dry mouth. Longman demonstrated that oral dryness, assessed by the clinician, was indicative of a reduced salivary flow rate and a significant predictor of salivary hypofunction in patients attending a Dry Mouth clinic (Longman et al. 2000).

1.2.4.4 Xerostomia inventory (XI)

XI is an 11-item summated rating scale resulting in a single continuous scale score, which represents the severity of chronic xerostomia. The constituent items cover both experiential and behavioural aspects of the condition and is used to score the symptoms of dryness (Hernández-Molina and Sánchez-Hernández 2013). Measures such as the XI can be used for a diagnostic or evaluative purpose

(Thomson and Williams 2000). With the former, the aim is to discriminate individuals with mild (or no) symptoms from those with more severe symptoms at one point in time; with the latter, the measure's ability to accurately depict change in symptoms is the key consideration (Locker et al. 2004), particularly if they are to be used as outcome measures in intervention studies. A change in XI score of 6 or more points appears to be clinically meaningful (Thomson 2007).

1.2.4.5 The Sicca symptoms inventory (SSI)

This is the first disease-specific score intended to assess ocular, oral, vaginal, and skin dryness in patients with pSS over a period of 2 weeks (Bowman et al. 2003). The severity of each domain is scored by a 0–7 Likert scale, with an overall maximal score of 28. The oral domain includes five facets: difficulty eating, dry throat, bad breath, wet mouth, and oral problems. However, the sensitivity to change of this questionnaire is not clear yet (Hernández-Molina and Sánchez-Hernández 2013).

1.2.4.6 Sjögren's Syndrome Damage Index (SSDI)

This index is used to assess cumulative permanent damage in pSS. It includes the following domains (maximal score =27): ocular, oral, neurological, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, endocrine, and malignancy (Barry et al. 2008).

1.2.4.7 Sjögren's syndrome Disease Damage Index (SSDDI)

This index is also used to assess cumulative permanent damage in pSS. SSDDI approach was based on expert validation and includes the following domains (maximum score =16): oral, ocular, neurologic, pleuropulmonar, renal, and lymphoproliferative (Vitali et al. 2007).

1.2.5 Assessing treatment efficacy in SS

In 2010 Seror and colleagues developed an international consensus Sjögren's activity score on the umbrella of European League against Rheumatism (EULAR). The first index was a patient administered questionnaire to assess subjective features, the EULAR SS Patients Reported Index (ESSPRI). It is a 0–10 numerical scale, one for assessment of each of the three domains: dryness, fatigue and pain (articular and/or muscular), the final score is the mean of the score of each domain (Seror et al. 2010). The second index was a systemic activity index to assess systemic complications, the EULAR SS Disease Activity Index (ESSDAI). It includes 12 domains (i.e. organ systems). Each domain includes three to four levels, according to their degree of activity (Seror et al. 2010). Seror included data of 96 patients retrospectively to assess the sensitivity to change of the ESSDAI, which showed that changes over time were detected more accurately than with other known indices. Meiners (2012) in a prospective study, also assessed responsiveness to change of ESSPRI and ESSDAI in pSS patients treated with rituximab. The results confirmed that ESSPRI and ESSDAI are certainly sensitive to measure the changes in disease activity following a treatment method, which indicates the usefulness of these indices for future clinical trials (Vissink et al. 2012). In addition assessing the effect of a treatment can be monitored using US imaging of the salivary glands, as US is not considered only a method to diagnose pSS. It is also useful to note that involvement of submandibular salivary glands is earlier in SS than the parotid glands (Vissink et al. 2012).

Moreover, parotid gland biopsies can have a role in assessing the efficacy of an intervention. It has the advantage that parotid gland tissue can be easily harvested, repeated biopsies from the same parotid gland are possible, and the histopathological results can be compared with other diagnostic results derived from

the same gland, e.g. secretory function, sialographic appearance, and ultrasound (Vissink et al. 2012).

1.2.6 Xerostomia related quality of life

Xerostomia is known to be unpleasant, and due to its chronicity in nature it can lead to a reduced quality of life (QoL). As xerostomia is the perception of dry mouth, a number of epidemiological studies have shown that actual salivary flow rates correlate very poorly with this subjective complaint (McMillan et al. 2004). Earlier European studies have found a significant reduction of health related quality of life in patients with pSS (Thomas et al. 1998; Sutcliffe et al. 1998; Belenguer et al. 2005; Champey et al. 2006; Bowman et al. 2007).

QoL in patients with pSS can be measured using the Medical Outcome Short Form (36) Health Survey questionnaire (SF-36), a health-related questionnaire that reflects the patient's perception of their physical, emotional and social function and the disease and treatment-related symptoms. The standard version of the Health Questionnaire SF-36 contains eight areas: physical functioning, physical role limitations, bodily pain, general medical health, vitality, social functioning, role limitations: emotional and mental health. High scores indicate better health; hence 0 is the worst state of health and 100 is the ideal state of health (Alonso, Prieto and Antó 1995; Lopez-Jornet and Camacho-Alonso 2008). The SF-36 is used to compare the general state of health in patients (Lopez-Jornet and Camacho-Alonso 2008).

The Oral Health Impact Profile (OHIP-49) was developed for a thorough measurement of the levels of dysfunction, discomfort and disability related to oral disorders (Locker 1988; Slade 1998; Locker, Jokovic, and Clarke 2004; Lopez-

Jornet and Camacho-Alonso 2008). The OHIP-49 is focused on measuring oral health. Each of its items was scored: 'never', score 0; 'hardly ever', score 1; 'occasionally', score 2; 'fairly often', score 3; 'very often', score 4. The OHIP-49 is divided into seven different domains and the possible score range for each one is: 'functional limitation' (nine items) – from 0 to 36; 'physical pain' (nine items) – from 0 to 36; 'psychological discomfort' (five items) – from 0 to 20; 'physical disability' (nine items) – from 0 to 36; 'psychological disability' (six items) – from 0 to 24; 'social disability' (five items) – from 0 to 20; 'handicap' (six items) – from 0 to 24; and finally 'Overall OHIP score' (49 items) – from 0 to 196. In this model, the higher scores indicate a poorer state of health (Lopez-Jornet and Camacho-Alonso 2008). This questionnaire was intended to measure self-reported dysfunction, discomfort and disability concerning oral conditions. Both questionnaires (SF-36 and OHOP-49) have been widely used internationally and both are validated (Lopez-Jornet and Camacho-Alonso 2008).

QoL assessments have been used in some studies to estimate the effects of xerostomia in patients with pSS, (Strömbeck et al. 2000; Hay, Morton, and Wall 2001; Rostron et al. 2002). In his study, Sutcliffe showed that, with the exception of oral damage, end organ damage was uncommon in pSS, still the amount of functional disability was as great in patients with pSS (Sutcliffe et al. 1998).

In a study of 42 Swedish women with pSS investigating health related quality of life, all 8 scales of the SF-36 were significantly reduced and the percentage of patients not employed due to disability was similar among patient with pSS, RA and fibromyalgia. Patients with pSS scored worse on the psychological scales and had better physical function than the RA patients, while the fibromyalgia patients had

lower levels of health quality on all 8 SF-36 scales in comparison to both patients with RA and pSS (Strömbeck et al. 2000).

Another study on a Chinese population of patients with SS, the SF-36 scores in physical function, role-physical and general health domains were lower in SS patients, indicating the direct influence of the condition on health related quality of life (McMillan et al. 2004). In the same study when applying the dry mouth measure, it showed that most patients with SS had problems related to a subjective feeling of dry mouth particularly when eating and speaking. Moreover sticky saliva and coughing were also features in more than half of the primary cases (McMillan et al. 2004). Champey emphasised, in his study of 111 patients with pSS, the role of the psychological dimension on results of the SF-36. Fatigue and pain, but not dryness, were associated with quality of life and psychological distress (Champey et al. 2006). In 2009 Murukutla and colleagues reported reduced function in patients with pSS in each domain of the SF-36, and a higher utilization of health care services in comparison to controls, in addition they reported a greater work disability. For emotional well being, the main unique predictor of quality of life was depression, counting on its own for 25% of the variance in the index amongst patients with pSS. Murukutla demonstrated that morbidity associated to sicca symptoms was high. Additionally on both the SF-36 and in the impact questions, patients with higher sicca severity reported poorer functioning (Segal et al. 2009). Segal and colleagues pointed out that one of the causes that can give rise to psychological distress is the delay in the diagnosis of SS. Therefore earlier diagnosis could possibly decrease morbidity related to sicca complications such as corneal scarring and tooth loss (Segal et al. 2009).

In a Dutch population, Meijer and colleagues reported that patients with SS had a large impact on HRQOL and employment, which was suggested by lower SF-36

scores and employment rates, and higher disability rates when in comparison to the general Dutch population. These striking results allow us to apply them in different populations due to the huge difference between the SS patients group and the control group. Fatigue was reported as a main explanation for reduced physical and mental HRQOL (Meijer et al. 2009). In his study, Hackett reported that functional capacity in a wide spectrum of daily activities significantly reduced in pSS patients (Hackett et al. 2012).

Patients with pSS in Korea were found to have low HRQOL and significantly higher ESSPRI scores in a prospective study compared to 42 non-SS sicca patients. Furthermore, ESSPRI scores had a significant association with all SF-36 scales (Cho et al. 2013). Lendrem showed that higher scores on the ESSDAI, EULAR sicca score and ESSPRI happen to be associated with poorer health states (Lendrem et al. 2014).

Furthermore, the impaired chemosensory perception was found to influence health-related QoL in a clinical situation other than SS itself (Epstein et al. 2002). In 2009, a study confirmed that impaired QoL in patients with SS can also be due to the abnormal chemosensory perception that leads to impaired smell and taste. Kamel reported in this study a high degree of impairment, particularly for smell, as 50% of the patients with SS demonstrated clinical hyposmia. They pointed out some factors that could lead to such impairment, such as decreased mucin (an odorant carrier) and recurrent rhinosinusitis. The recurrent epistaxis, due to dryness, leads to scab formation and nasal blockage that also gives rise to a reduced smell sensation (Kamel, Maddison, and Whitaker 2009). Within the SS group, the threshold for sweet taste was the least reduced due to the fact that sweet taste is independent of saliva, unlike the other tastes (Kaneda et al. 2000). There was a significant reduction in the

composite physical and mental components of SF-12 in SS patients compared with controls and appeared to be influenced by chemosensory impairment, particularly loss of taste (Doty et al. 1991; Kamel, Maddison, and Whitaker 2009).

All these findings increasingly recognise QoL assessments as a valid, appropriate and significant indicator of treatment need and intervention outcomes (Locker 1988; Slade 1998; Locker, Jokovic, and Clarke 2004).

1.2.7 Salivary gland hypofunction treatment methods

The management of long-standing xerostomia is chiefly directed towards the avoiding factors that may exacerbate dry mouth, applying salivary substitutes, the use of sialogogues and the prevention of the accompanying oral complications (Walls and Murray 1993; Jonsson, Haga and Gordon 2000; Porter, Scully and Hegarty 2004).

1.2.7.1 Salivary substitutes

It is essential to note that because these substances are removed from the mouth during swallowing, it leaves them with a short effect (Al-Hashimi and Taylor 2001). Regardless of the duration of saliva substitutes, they have a function in hydrating and lubricating the oral cavity tissues (Porter, Scully, and Hegarty 2004).

1.2.7.1.1 Water

Patients with xerostomia usually sip water on a regular basis. Olsson & Axell compared the efficacy of water with that of artificial saliva in patients with xerostomia of different etiologies in a double-blind study. Patients were asked to rinse 15ml of the solutions. Both subjective and objective, i.e. mucosal friction measurements, effects were noted. It was found that water lead to a mean duration of subjective improvement of 12 minutes, while the mean duration of objective improvement was 5.5 minutes. These values were about half the values seen with artificial saliva (Olsson and Axéll 1991).

1.2.7.1.2 Topical artificial saliva

Artificial salivas are the most commonly prescribed salivary substitutes. They are normally based on either mucin or carboxymethylcellulose (Levine et al. 1987). Mucin is found in saliva, and the mucin-based artificial salivas show more

effectiveness and better tolerance than the carboxymethylcellulose- based ones ('S-Gravenmade, Roukema, and Panders 1974; Vissink et al. 1983; Visch et al. 1986). Yet, even the mucin based artificial salivas are not considered good saliva substitutes (Levine et al. 1987). One study reported that the mean duration of subjective improvement in xerostomia with a mucin-based artificial saliva was 18 minutes, while the mean duration of objective improvement in mucosal friction was 11.5 minutes (Olsson and Axéll 1991). This short duration of action has also been reported by other investigators (Vissink et al. 1983). However, the mucin-based artificial saliva is considered to have a longer duration when compared with carboxymethylcellulose-based agents (Vissink et al. 1983).

Mucin-based artificial saliva was compared to flavoured water, and its non-mucin base in a double-blind study, it was found that the mucin-based saliva is more effective in reducing xerostomia (Duxbury, Thakker, and Wastell 1989). Nevertheless, water was considered the best treatment more often than the mucin-based artificial saliva (Vissink et al. 1983; Visch et al. 1986).

Patients using Carboxymethylcellulose-based artificial salivas can complain of sticky accumulations in the mouth, which can lead to irritation of the underlying mucosa ('S-Gravenmade, Roukema, and Panders 1974; Vissink et al. 1983), whereas this is not apparent with mucin-based ones. In general all types of artificial salivas are not typically associated with systemic side effects.

Lubricating agents in the form of gels, mouthwashes, lozenges (Senahayake, Piggott, and Hamilton-Miller 1998), and toothpastes (Warde et al. 2000), have been used with different results to lessen the symptoms of xerostomia (Epstein et al. 1999). The qualities of a lubricating agent that increase patient acceptance and compliance are: lubrication, taste, duration of action, the delivery system, severity of xerostomia, and cost (Epstein and Stevenson-Moore 1992). Some available

proprietary preparations include Luborant (Antigen, UK), Saliva Orthana (AS Pharma, Sweden), Salivace, and Oral Balance (Anglian, UK), all have been approved for dry mouth related to radiation or SS (Samarawickrama 2002).

1.2.7.1.3 Glycerine

Greenspan has recommended the use of glycerine in combination with lemon to be used as a salivary substitute (Greenspan 1990). Still, glycerine was reported to be subjectively less effective than artificial saliva in comparative studies (Klestov et al. 1981; Poland et al. 1987).

1.2.7.1.4 Others

The use of a standard bedside humidifier and supersaturated humidification have been of slight benefit (Criswell and Sinha 2001). An intraoral device containing saliva substitute, which slowly releases the lubricant into the mouth, has been reported more acceptable to patients with xerostomia than the use of the lubricant on its own (Frost et al. 2002) although there is a little supportive data.

1.2.7.2 Topical saliva stimulants

Stimulation of taste, touch, pressure and proprioceptive receptors in and around, the oral cavity can generate a number of stimuli that can lead to an increase in salivary flow. Saliva stimulants include two categories: those that stimulate the aforementioned receptors (afferent pathways), e.g. organic acids and chewing gum, and those that act directly on the parasympathetic nerves (efferent pathways), e.g. pilocarpine (Davies 1997).

Although the theory is that only subjects with residual salivary gland function can benefit from agents that stimulate salivary glands, it is unfeasible to determine if the cellular infiltrate in SS has destroyed the entire salivary gland parenchyma. It is

possible that residual function may exist in minor salivary glands, which can be undetectable by the clinicians. Therefore, stimulating agents may be of benefit in excreting even a small amount of saliva that may lessen the symptoms of oral dryness (Sreebny and Valdin 1987; Wolff et al. 2012).

1.2.7.2.1 Ascorbic acid (vitamin C)

Although there is little evidence to support the use of ascorbic acid tablets treating xerostomia (Davies and Singer 1994), a study in Sweden compared the efficacy of ascorbic acid with artificial saliva and a number of other saliva stimulants in patients with xerostomia of varying aetiology (Björnström, Axéll, and Birkhed 1990). Ascorbic acid was subjectively more effective than artificial saliva, but less effective than the other saliva stimulants (Davies and Singer 1994). Furthermore, long term use of ascorbic acid may cause dental demineralization (Anneroth, Nordenram, and Bengtsson 1980).

1.2.7.2.2 Citric acid

Citric acid is found in some hard-boiled sweets (Twycross and Lack 1986). Patients with non-radiation-induced xerostomia in an uncontrolled study, reported that a mouthwash containing 1% citric acid was effective (Spielman et al. 1981). Although patients with radiation-induced xerostomia did not report improvement using the mouthwash. Interestingly, subjective improvement in the sense of dryness of the mouth was related to an objective increase in salivary flow in only 55% of cases. Only three out of 34 patients discontinued this preparation due to burning sensation. Citric acid, similarly to ascorbic acid, can have a detrimental effect upon the teeth causing erosion and caries (Newbrun 1981).

1.2.7.2.3 Malic acid

Malic acid is a naturally developed acid which can be found in apples, pears and certain other fruit. At the end of Bjornstrom's study, 44% of the patients preferred to continue with the malic acid pastilles (Björnström, Axéll, and Birkhed 1990). Local irritation was not a major problem. However, yet again, malic acid does cause demineralization of the teeth (Anneroth, Nordenram, and Bengtsson 1980) and therefore it should not be used for long durations in dentate patients.

1.2.7.2.4 Sugar-free confectionary

Confectionaries containing citric and malic acid are frequently used to treat xerostomia (Davies 1997). Mints were reported to improve salivary flow in patients with xerostomia. But, subjective improvement in the sensation of dryness of the mouth, duration of the effect, and acceptability of the treatment, were not recorded (Abelson, Barton, and Mandel 1990). Additionally, patients often do not wish to use such confectionary on a long-term basis (Al-Hashimi and Taylor 2001).

1.2.7.2.5 Chewing gum

Chewing can result in an increase in saliva output, and this is usually according to taste, especially sour and bitter (Fox 2004). Chewing gum includes a gustatory action (i.e. via taste) although the physical action of chewing may also be beneficial to increase salivary outflow from the major salivary glands (Abelson, Barton, and Mandel 1990). However, these actions are probably short-lived and full dentures users may be unable to use it (Itthagarun and Wei 1997). Several studies have shown that chewing gum can increase salivary flow in patients with xerostomia of varying aetiology (Markovic, Abelson and Mandel 1988; Abelson, Barton and Mandel 1990; Olsson and Axéll 1991; Aagaard et al. 1992; Risheim and Arneberg 1993) but the duration of the effect was still not recorded. This objective improvement in

salivary flow was linked with subjective improvement in xerostomia, 56±79% of patients preferred to continue using the chewing gum at the end of the study (Olsson and Axéll 1991; Aagaard et al. 1992). Definitely, in the Bjornstrom study, chewing gum was the mostly preferred treatment (Davies 1997). Chewing gum, in addition, did not give rise to any notable adverse side effects (Aagaard et al. 1992).

1.2.7.3 Systemic saliva stimulants

Muscarinic receptors are the receptor sites for acetylcholine, the neurotransmitter of the parasympathetic autonomic nervous system. These receptors are located at the ends of parasympathetic nerve pathways on the postsynaptic cell membranes of various tissues, principally muscles and glands (Broadley and Kelly 2001). There are two types of acetylcholine receptors, nicotinic and muscarinic. Two types of drugs act as agonists of muscarinic cholinergic receptors: choline esters (acetylcholine) and cholinomimetic alkaloids (muscarine and pilocarpine). The alkaloid muscarine was isolated from the mushroom *Amanita Muscaria* by Schmiedeberg in 1869 (Broadley and Kelly 2001). Five subtypes of muscarinic acetylcholine receptors have been identified (M1–M5), with M1 and M3 predominating in the salivary glands, and M3 in the lachrymal glands (Zoukhri and Kublin 2001). Two muscarinic agonists (pilocarpine and cevimeline) are licensed for the treatment of sicca symptoms in SS due to their ability to stimulate muscarinic acetylcholine receptors, stimulating watery secretions (Fox, Konttinen, and Fisher 2001; Brito-Zerón et al. 2013).

1.2.7.3.1 Pilocarpine

Pilocarpine is an alkaloid found in the leaves of two of the Jaborandi plants Maranham Jaborandi and Pernambuco Jaborandi, also referred to as *Pilocarpus Microphyllus* and *Pilocarpus Jaborandi*, respectively (Broadley and Kelly 2001).

Pilocarpine was first extracted and named in 1875 by Gerrard of University College Hospital in London (Berk 2008). The same year, Langley described the effects of Jaborandi extract on the heart (Langley 1875). The prime effect was the slowing and ultimately stopping of the heart. In his discussion of Jaborandi, he mentions that the effect of the extract, that is pilocarpine, includes 'producing a copious flow of saliva'. Marshall (1904) published on the physiologic actions of pilocarpine, he found that 5 mg of pilocarpine injected intraperitoneally into a rat rapidly produced dyspnea, depression and salivation lasting nearly 2 hours. He described the effects of self-administration: 'At first hypodermic injections were used, but later the substances were taken by mouth. The symptoms were salivation and sweating and with larger doses, a curious feeling about the eyes and fullness of the head, increased pulse-rate and slight nausea'. The smallest dose causing this effect was 5 mg (Berk 2008). Pilocarpine is a non-specific muscarinic acetylcholine receptor agonist (Berk 2008). There are five muscarinic receptors (M1–M5). Of these, pilocarpine chiefly acts to increase salivary flow throughout the M3 receptors. These are expressed on smooth muscle and glandular tissues (Ishii and Kurachi 2006). Stimulation of central muscarinic receptors can lead to confusion, agitation and seizures. Moreover, stimulation of central M4 receptors can lead to a Parkinsonian-like resting tremor (Mayorga et al. 1999). Stimulation of peripheral muscarinic receptors produces salivation, lacrimation, rhinorrhea, bronchospasm, bronchorrhea, urinary frequency, defecation, increased peristalsis, vomiting, sweating, miosis and bradycardia. Unlike acetylcholine and acetylcholinesterase compounds, pilocarpine does not stimulate nicotinic receptors (Hendrickson, Morocco, and Greenberg 2004a).

Aromdee and colleagues reported that pilocarpine absorption is from the gastrointestinal tract, and the peak plasma concentrations are reached within around

1 hour. It is metabolised in the liver and excreted principally by the kidneys, with an elimination half-life of around 1 hour (Aromdee et al. 1999).

It was predicted that patients with SS might satisfactorily respond to treatment of xerostomia with pilocarpine, due to the greater residual functional salivary components when compared to xerostomia due to irradiation (Nusair and Rubinow 1999). In an early trial, Fox and colleagues tested pilocarpine on a heterogeneous population of patients with salivary hypofunction (Fox et al. 1991). Thirty-one patients were randomly assigned over the course of 5–6 months of pilocarpine and 1 month of placebo. Salivary function, as measured by stimulated flow and scintigraphy, increased during pilocarpine use in 21 of the patients and there was subjective improvement in 27 of the patients.

Oral pilocarpine has been evaluated in several placebo-controlled trials. The first trial assessed 2 doses (2.5 and 5 mg every 6 hours) and found a higher frequency of improvement in dry mouth and dry eye in the 5-mg group but not in the 2.5-mg group (Vivino et al. 1999b). In the second trial Papas evaluated the use of 5 mg and 7.5 mg during 6 weeks with placebo (Papas et al. 2004). Salivary flow rates were significantly increased in the pilocarpine groups. In 2006, a dose-escalating trial was performed (from 5 to 7.5 mg every 6 hours) and similarly reported a higher frequency of improvement in dry mouth and dry eye in the 5 mg group (Wu et al. 2006a). Vivino found a higher frequency of sweating was reported and increased urinary frequency compared with placebo (Vivino et al. 1999b). In a dose-escalating trial (Wu et al. 2006a) 23% of patients switched from a regimen of 7.5 mg every 6 hours to 5 mg because of adverse effects.

In a placebo-controlled double-blind randomized clinical trial on healthy volunteers, the effect of pilocarpine mouthwash on the salivary flow was tested using 0.5 mg, 1 or 2% pilocarpine or 0.9% saline. Before the trial the patients completed an analogue

scale to record the intensity of anxiety, tremors, sudoresis, facial flushing, abdominal and/or thoracic distress, lacrimation, salivation, palpitation, nausea, visual disturbance and hunger. Blood pressure and heart rate were monitored and the salivary flow was quantified by weighing a piece of cotton that was kept under the tongue for 1 minute. Patients were instructed to keep the solutions in their mouth for 1 minute without swallowing and after 75 minutes pre-trial examinations were repeated. It was found that mouth rinsing with 1 and 2% pilocarpine solution was able to induce a significant and dose-dependent elevation in salivary flow perceived subjectively and objectively without giving rise to any adverse effect (Bernardi et al. 2002).

Another study reported that juvenile SS patients could respond better using pilocarpine, than adult patients, which could be due to the more severely salivary gland damage in adult patients (Tomiita et al. 2010).

The results of most clinical trials imply that pilocarpine is safe and well tolerated, with no serious adverse effects (Scully and Epstein 1996), but it is sensible to avoid pilocarpine in patients with respiratory disease (e.g., asthma, chronic bronchitis, chronic obstructive pulmonary disease) and those on antihypertensive drugs, since interactions with β -blockers would seem possible (Porter, Scully, and Hegarty 2004). Yet it is noted, that in controlled trials of oral pilocarpine, no serious reactions or toxicities have been reported. Rather, only mild muscarinic symptoms seem to be common in therapeutic use and are dose related. On the other hand, clinical toxicity has infrequently occurred from excessive application or ingestion of ophthalmic preparations of pilocarpine (Hendrickson, Morocco, and Greenberg 2004a). Topical ophthalmic pilocarpine caused bradycardia and muscarinic toxicity (Epstein and Kaufman 1965). Likewise, Littman reported a similar case that resulted in atrioventricular dissociation and bradycardia (Littmann et al. 1987). Another study

reported the accidental subcutaneous injection of 80 mg of pilocarpine ophthalmic solution, which lead to muscarinic symptoms (Lum and Kastl 1987).

Hendrickson reported a case of muscarinic toxicity secondary to an accidental pilocarpine overdose due to patient-doctor miscommunication. Within one half-hour after ingestion, the patient reported sweating, and crampy, intermittent, and diffuse abdominal pain. Six hours later, the patient developed excessive salivation, lacrimation, vomiting, anxiety, tremor and profuse watery diarrhoea (Hendrickson, Morocco, and Greenberg 2004).

1.2.7.3.2 Cevimeline

Cevimeline is a cholinergic agent specific for the M1 and M3 receptors, and since the majority of muscarinic receptors on salivary glands are M3 (Fox, Kontinen, and Fisher 2001), it is suggested that it would have more efficacy and fewer cardiac side effects (associated with the M2 receptor) and tremor (associated with M4 receptor) than pilocarpine (Fox 2004; Atkinson and Baum 2001; Hendrickson, Morocco, and Greenberg 2004).

It was found that doses of 30 mg of cevimeline 3 times daily significantly improved symptoms of dry mouth and increased the salivary output in patients with SS (Petrone et al. 2002a). Cevimeline has a similar pharmacological profile to pilocarpine, however the onset of increased salivation may be later and the duration of action longer than the latter agent. The safety and adverse event profiles are similar to those of pilocarpine, patients can complain of sweating and nausea secondary to cevimeline use.

The efficacy of cevimeline has been examined in large, well-controlled trials. A trial assessed 2 doses (15 and 30 mg every 8 hours) and reported a higher frequency of improvement in dry mouth in the 30 mg group (Petrone et al. 2002a). Another trial

assessed 2 doses (30 and 60 mg every 8 hours) and found a higher frequency of improvement in dry mouth in the 30 mg group (Fife et al. 2002a). However, a third trial there was a significant difference in subjective sicca symptoms in the 20-mg group yet not in the 30-mg group (Ono et al. 2004), whereas the fourth trial, which tested 30 mg of cevimeline every 8 hours using a crossover design, and found no significant results (Leung et al. 2008). A higher frequency of nausea and sweating in the 30-mg group compared with placebo (Petrone et al. 2002a) and a higher frequency of nausea sweating and rigors in the 60-mg group in comparison with placebo (Fife et al. 2002a).

1.2.7.4 Systemic immunologically active agents

In SS, cases with severe systemic involvement or when improvement has failed with conventional therapies, the use of immunological therapies can be justified. However, because the role of biologic therapies in pSS patients with sicca syndrome and/or fatigue alone is not yet clear, it is not justifiable to use these agents for patients without systemic involvement. Additionally it is critical to note the cost to the patient and health care service (Bowman and Barone 2012). On this point, the literature has provided three disappointing messages concerning the use of immunological agents: 1) limited benefit for sicca features, 2) the lack of a specific analysis of extraglandular features and 3) the high rate of adverse events (ranging between 41% and 100%) (Ramos-Casals et al. 2010; Brito-Zerón et al. 2013).

Several studies were conducted to assess some immunomodulatory and immunosuppressive drug available.

1.2.7.4.1 Immunomodulatory or immunosuppressive agents

No difference was reported between groups in salivary flow rate (SFR), Schirmer test, rose bengal staining score, or histopathological focus score in a controlled trial comparing oral prednisone (30 mg per day) with piroxicam (20 mg per day) and placebo (8 patients in each group) (Fox et al. 1993). A prospective study reported that glucocorticoids did not have an effect in improving SFR, as it was worse in 60 patients with pSS (Meijer et al. 2007). Conversely, another prospective study of 20 patients found that oral prednisolone improved SFR (Miyawaki, Nishiyama, and Matoba 1999).

A 2-year crossover trial using 400 mg of HCQ per day in 19 patients reported no significant differences in HCQ vs placebo for sicca symptoms, parotid enlargement, fatigue, myalgia, and arthralgia, and no significant difference in ocular tests (Kruize et al. 1993). Similar results were found in a prospective study of HCQ in 14 patients, as no effects on sicca symptoms and fatigue were found (Tishler et al. 1999). The efficacy of HCQ was examined in a recent double-blinded placebo controlled trial in France. The results did not show efficacy in the main disabling symptoms (dryness, pain, and fatigue) of pSS compared to placebo (Gottenberg et al. 2014).

Azathioprine (Price et al. 1998) and oral cyclosporine (Drosos, Skopouli, Galanopoulou, et al. 1986) in 13 and 20 patients, respectively, were compared in two placebo-controlled trials. The first trial reported no significant differences in of the outcomes. The second trial found a higher rate of improvement of xerostomia in patients treated with cyclosporine, without significant differences in the Schirmer test score and SFR.

Three prospective studies evaluated the use of methotrexate (Skopouli et al. 1996), leflunomide (van Woerkom et al. 2007), and mycophenolic acid (Willeke et al. 2007) and all showed inadequate improvements in sicca symptoms. However all these

studies reported a high rate of adverse events (41% for methotrexate, 63% for mycophenolic acid, and 100% for leflunomide). Severe adverse events lead to the early termination of a controlled trial of thalidomide (Pillemer et al. 2004).

Three controlled studies assessed oral interferon-alfa (IFN- α) (150 IU daily). The first trial (12 patients) suggested a favourable effect on unstimulated SFR and ocular or oral dryness. The SG biopsies were evaluated in nine patients after treatment with IFN- α , they showed significant histopathological improvement, including reduced mononuclear infiltration. These patients in particular experienced a two-fold or greater increase in saliva output in response to treatment (Shiozawa and Tanaka 1998). A single-blinded, sucralfate-controlled trial (Khurshudian 2003) reported a significant time-dependent improvement in the production of whole saliva at 3 months but not at 6 months. Conversely, a large placebo controlled trial including 497 patients reported significant improvement in only 1 of 28 outcomes evaluated (unstimulated whole saliva) and a higher percentage of adverse events (40% vs. 25% in the placebo group) (Cummins et al. 2003). Two other trials reported an increase in stimulated whole saliva flow in a proportion of patients treated with IFN- α 150 IU t.i.d (Gf et al. 1995; Ship et al. 1999).

1.2.7.4.2 Biological agents

Infiximab was evaluated in a placebo controlled trial (Mariette et al. 2004) in 103 patients, the study did not find any significant differences in the primary outcome. Although a previous prospective study on 16 patients found significant improvements in subjective and objective sicca measures (Steinfeld et al. 2001). Thus the Mariette trial failed to support the favourable results reported in Steinfelds study (Tobón et al. 2010).

A placebo-controlled trial assessed etanercept in 28 patients with SS and found no significant differences in the primary outcome, with only 20% improvement in the values on 2 of 3 domains: oral, ocular, and laboratory. In addition, no significant differences were found for the secondary outcomes (Sankar et al. 2004). Parallel negative results were found in a prospective study in 15 patients with SS (Zandbelt et al. 2004).

A placebo-controlled trial assessed the use of rituximab (RTX) as two 1000-mg doses 15 days apart (Meijer et al. 2010). It included 30 patients and has reached the primary outcome (improvement of stimulated SFR) at 12 weeks but not at the end of the study. Only the VAS score for dry eye significantly improved at 48 weeks while other secondary outcomes improved at different study time points but not at 48 weeks. Another study (Dass et al. 2008) included 17 patients but did not achieve the primary outcome.

Two prospective studies found significant improvement in sicca and general symptoms compared with baseline values (Pijpe et al. 2005; Devauchelle-Pensec et al. 2007). Several retrospective surveys have studied RTX effect. One study on 6 patients with pSS treated with RTX for associated lymphoma (n=2) or systemic manifestations (n=4), reported significant improvement in subjective feeling of dryness in 3 patients. In addition, 1 of the 2 patients with lymphoma achieved full remission (Gottenberg et al. 2005). Another retrospective study described 5 patients with pSS treated with RTX for NHL and 11 for systemic manifestations. Only a small number of patients experienced relief from dryness. However, the extraglandular manifestations improved in 9 of 11 patients (Seror et al. 2007). Guzman Moreno evaluated the efficacy and tolerance of RTX in 31 patients with pSS in a retrospective study. A total of 22 benefited from improvement in arthritis and myalgias, 16 of them had subjective improvement in sicca symptoms (Guzman Moreno 2009).

Fifteen patients with pSS were enrolled in a study where biopsies were taken. The patients were then treated with two cycles of i.v. infusions of 1000 mg RTX on days 1 and 15 (at time 0 and then after 6 months). After 48 weeks, another biopsy was taken. RTX was shown to be effective in improving whole saliva flow rate (Ciccia et al. 2014). Yet, a randomized placebo-controlled multi center study was conducted between March 2008 and January 2011. Patients received 1 g of RTX (at weeks 0 and 2), or placebo. In this trial, RTX did not significantly increase the proportion of patients achieving the primary end point. However, RTX did show clinically significant improvements at week 6, suggesting transient efficacy that was not maintained throughout the 24-week period. The authors concluded by not supporting the use RTX with recent onset systemic pSS (Devauchelle-Pensec et al. 2014a).

Epratuzumab (EPZ) was evaluated in a study of 14 women and 2 men with pSS. Patients received four 360mg/m² EPZ infusions at 2-week intervals. 14 individuals received all four infusions without significant adverse side effects. After 6 months 20% showed improvement in Schirmer test, unstimulated whole salivary flow, fatigue, ESR and IgG levels (Steinfeld et al. 2006).

Belimumab has been tested in patients with RA or SLE (Dall'Era et al. 2007; Furie et al. 2008). Both studies established the safety and tolerability of Belimumab. Patients with SS enrolled in an open label study where they received Belimumab infusion, as an improvement in VAS dryness score was reached in 11 (37%); VAS fatigue score in 7 (23%); VAS pain score in 7 (23%) (Mariette et al. 2013). An open label trial in Japan reported that abatacept IV significantly decreased patients' VAS for dry mouth and dry eye at 24 weeks (Tsuboi et al. 2014).

1.2.7.5 Gene transfer

Re-engineering the function of the surviving non-fluid secreting ductal cells in damaged glands to a secretory phenotype was considered to be a conventional therapy for damaged salivary glands (Atkinson and Baum 2001). In salivary glands, due to their anatomy, gene transfer can be accessible orally using conventional cannulation techniques to introduce viral or non-viral vectors into the gland.

In 1994, the first peer-reviewed paper on gene transfer to salivary glands was published (Mastrangeli et al. 1994). Several laboratories have transferred different genes successfully to salivary glands since then (Baum and O'Connell 1999). Most of these studies have utilised viral vectors, specifically adenoviral vectors, to mediate gene transfer. Viral vectors are considered very effective at transferring genes, but can give rise to a safety risk by stimulating a potent immune response (Atkinson and Baum 2001).

Several target genes are considered in gene therapy for hyposalivation caused by SS, they include inflammatory mediators, cytokine inhibitors, apoptotic molecules, cell–cell interaction, and intracellular molecules. Kok demonstrated the effect of a recombinant AAVhIL10 vector administered to the salivary glands of non-obese diabetic (NOD) mice on the stimulated salivary flow rate. He reported that animals receiving the rAAVhIL10 demonstrated noticeably higher salivary flow rates than those in the sham group of animals (Kok et al. 2003).

In another study, the ability to slow down the progression of SS dysfunction in NOD mice was explored by administering a recombinant serotype 2 adeno-associated virus encoding the human vasoactive intestinal peptide (VIP) transgene (rAAV2hVIP) into the submandibular gland. Higher salivary flow rates were shown but without any difference in focus scores or apoptotic rates. There was an increase of the expression of VIP in the submandibular gland and serum and a decrease in

IL2, IL10, IL12 and TNF- α in the experimental group compared to the control, therefore the study suggests that local delivery of rAAV2hVIP can demonstrate a disease-modifying and immunosuppressive action in the submandibular gland of the NOD (Lodde et al. 2006).

The effect of Adenoviral vector encoding hAQP1 gene has been assessed in a small group of patients with radiation induced parotid gland hypofunction. This trial demonstrated the safety and efficacy of this strategy with a persistent expression of hAQP1. This method could possibly be used in the future for the long-term treatment of salivary gland hypofunction induced by irradiation. Additionally, this strategy might also be applicable to the treatment of SG hypofunction caused by SS (Lodde et al. 2006).

Using gene transfer for the repair of damaged glands can be an option in cases where epithelial tissue survives either the irradiation or autoimmune damage. However, when the entire parenchymal cells are destroyed, in cases where a gland has been fully replaced by fibrotic tissue, gene transfer cannot cause an improvement of saliva production given that no system exists to produce and transport fluid into the mouth (Atkinson and Baum 2001). Adeno-associated virus vectors encoding human IL-10, or vasointestinal peptide may also prove to be of benefit as indicated from the results of salivary flow in NOD mice (Fazaa et al. 2014).

1.2.7.6 Acupuncture

Acupuncture has long been a well known treatment for xerostomia in Chinese medicine (Hansen 1975). However, it is quite recent that it has been embraced by western medicine. The mechanism by which acupuncture increases salivary flow has yet to be determined, although it is known to cause an increase in blood flow

within the mouth (Blom et al. 1993). One group has recognised at least two neuropeptides (vasoactive intestinal peptide and calcitonin gene-related peptide) which increases in saliva following acupuncture treatment (Dawidson et al. 1998; Dawidson et al. 1999). Since these can stimulate salivary function, it is possible that generation of increased amounts of neuropeptides could be responsible for any increase in salivation found (Fox 2004).

It has been reported that acupuncture is effective treating in patients with xerostomia of varying aetiology. In a Swedish controlled study, the active group received traditional Chinese acupuncture utilising local, distant and auricular points, whilst the control group received 'placebo acupuncture', i.e. superficial needling of non acupuncture points. Each group received a 6-week course of twice weekly treatments, which was repeated after a gap of 7±10 days. The interesting finding was that there was an increase in salivary flow in both groups, though it was more marked and longer lasting in the active group. Without a doubt, the increase in salivary flow continued for at least a year in the active group, while it only lived for the period of the study in the placebo group (Blom, Dawidson, and Angmar-Månsson 1992). One of the difficulties with these trials is the small sample size in the studies, a lack of double-blinding and the subjective nature of the reporting (Fox 2004). It is also important to consider the significant placebo effect (Blom, Dawidson, and Angmar-Månsson 1992).

In another controlled study by List, 20 patients with pSS were included in a study where they received manual acupuncture and no treatment for the control group. Outcome measurements included salivary flow rate, subjective symptoms of burning sensation in the mouth, dry mouth, and dry eyes obtained using a VAS, but there was no significant difference between groups (List et al. 1998a; Jedel 2005). In a pilot randomized placebo-controlled trial, Cafaro used laser acupuncture and

showed that true laser acupuncture significantly improved saliva production in patients with SS (Cafaro et al. 2014).

1.2.7.7 Acupressure

Acupuncture is known to be an invasive procedure that must be delivered by licensed practitioners. In contrast, acupressure is a massage technique of Chinese origin. It differs from acupuncture in that pressure is put on acupoints on the surface of the body to relieve obstruction and to balance the energy flow; its effects are thought to be comparable to those achieved by acupuncture. Acupressure uses the hands as a tool to press acupoints on the skin (Maa 2005; Ma, Chang, and Lin 2007). Pressure is usually applied for a minimum of 15 s, but it can last for between 30 seconds and 5 minutes (Matsumura 1993). The amount of pressure applied depends on patient tolerance, as it can be applied until the patient experiences numbness, pressure, heaviness, soreness or a feeling of distention (Maa 2005).

The effectiveness of acupressure in managing the symptom of dry mouth and improving salivary flow for patients with SS has however, not been tested. One single-blinded study evaluated acupressure in stimulating salivary flow rates and improving hemodialysis (HD) patients with dry mouth symptoms (Yang et al. 2010). There is some evidence that acupressure on the acupoints CV23 and TE17 increased the salivary flow rates in HD population and are similar to the results obtained in studies using actual acupuncture techniques in improving symptoms related to radiation-induced xerostomia.

1.2.7.8 Dietary supplementation

Simple dietary advice can have an influence in aiding xerostomia patients. That could include types of food to avoid and increase fluid intake (Davies 1997).

A placebo-controlled study suggested that a herbal based agent with vitamin supplements (LongoVital, LV, Denmark) led to a extended increase in unstimulated salivary flow and a reduction in rose bengal dye scores in a group of patients with SS (Pedersen et al. 1999). It was also suggested that evening primrose oil, rich in fatty acids and important in inhibiting 2-series prostaglandins, may possibly improve salivary flow in some individuals with SS (Horrobin 1986; Oxholm et al. 1986; Belch and Hill 2000). Moreover, the use of linseed extract Salinum with or without chlorhexidine led to improvement in symptoms in patients with SS (Johansson. et al. 2001).

1.2.7.9 Electrostimulation

In patients with SS, electrostimulation has been reported to increase the salivary flow (Erlichman 1990). In 1850 Ludwig discovered that electrical stimulation of the chorda tympanilingual nerve in the dog caused a copious secretion of submandibular saliva (Ami and Wolff 2010). In 1992 a study demonstrated an improvement in xerostomia symptoms in a group of patients with SS who were treated with electrostimulation (Talal, Quinn, and Daniels 1992b).

This will be discussed in further detail in the next section.

1.3 Electrostimulation in the treatment of salivary gland hypofunction in Sjögren's syndrome

Electrostimulation of neural and muscular structures has a therapeutic significance in several areas of medicine (e.g. pacemakers and phrenic nerve stimulators) and as the autonomic control of salivary secretion is known, a similar approach could potentially be applied to the management of salivary gland hypofunction (Fedele et al. 2008). Physiologically, xerostomia can be due to an interruption of the reflex that induces salivation. It can be at the receptor site, the neural pathway of the afferent limb, the efferent pathway, the peripheral ganglion or the effector site (Fedele et al. 2008).

The salivary reflex engages a response from both divisions of the autonomic nervous system (i.e. sympathetic and parasympathetic). Myoepithelial cells are usually contracted by both parasympathetic and sympathetic nerves (Emmelin 1987; Garrett 1987). In addition, blood vessels receive a dual innervation: the parasympathetic stimulus causes vasodilation as part of secretion, whereas sympathetic vasoconstriction is part of a general response and not a direct part of the salivary reflex. Parasympathetic impulses provide the main stimulus for fluid formation and secretion by the secretory cells; sympathetic impulses act in collaboration with the parasympathetic drive and increase the output of pre-formed elements from certain cells (Emmelin 1987; Garrett 1987; Steller, Chou, and Daniels 1988a).

Electrical stimulation of the sympathetic nerve supply to salivary glands in anaesthetized animals experiments leads to a vasoconstriction of glandular blood vessels and the activation of parenchymal cells. In contrast, under reflex conditions only sympathetic secretomotor nerve fibres and not vasoactive nerve fibres to

salivary glands are activated. Hence vasoconstriction is not part of the salivary reflex (Proctor and Carpenter 2007) see Table 11.

In view of the presence of autoimmune SS muscarinic receptor-blocking autoantibodies, the sicca component of SS may not be solely caused by an irreversible structural damage of the secretory acinar cells, thus it can be considered potentially reversible and treatable (Jonsson, Gordon, and Konttinen 2003).

Table 11. Effects of autonomic nerves on salivary gland function (modified from Garrett, 1987)

Parasympathetic stimulation:

- 1) Is mediated mainly by acetylcholine in combination with NANC peptides (e.g. VIP)
- 2) Evokes most of the salivary fluid secreted. Mainly acts through M3 and to a lesser extent M1 muscarinic cholinergic receptors
- 3) Causes variable degrees of exocytosis from salivary cells but is responsible for most mucin secretion by mucous glands
- 4) Induces contraction of myoepithelial cells
- 5) Increases glandular blood flow as part of the salivary reflex.

Sympathetic stimulation:

- 1) Is mediated mainly by noradrenaline and acts essentially on cells receiving parasympathetic impulses, which tends to produce synergistic effects, but exerts little effect on mucous gland secretion
- 2) Often does not cause much mobilization of fluid but does not inhibit salivary secretion
- 3) Tends to modulate the composition of saliva by increasing exocytosis from salivary cells
- 4) Induces contraction of myoepithelial cells
- 5) Exerts control on glandular blood flow but not as part of the salivary reflex.

Through the application of electric impulses to one or more of the three components of the salivary reflex arch there is an, at least theoretical, possibility of improving salivary secretion and consequently to lessen the different long-term effects of hyposalivation.

Animal studies have reported that the application of electrical current on this reflex arch can increase salivary production and relieve symptoms of xerostomia (Izumi and Karita 1995). In one study it was shown that electric neurostimulation in the rat is more effective than pilocarpine to induce salivary secretion via reflex stimulation (Schneyer and Hall 1965). Likewise, the application of an electrical current via the

oral mucosa on afferent neuronal receptors and pathways increased the salivary production and lessened xerostomia in patients with salivary gland hypofunction (Weiss et al. 1986; Steller, Chou, and Daniels 1988a; Talal, Quinn, and Daniels 1992b).

It has been suggested that the stimulation of the autonomic nervous system may increase the release of specific neuropeptides that have trophic effects to salivary gland parenchyma, causing regeneration of functional tissue and thereby causing the effect of electrostimulation to be sustained (Schneyer et al. 1993).

In order to electrically stimulate sympathetic salivation, it is required to use impulses of higher frequency and longer duration to generate sparse viscous saliva (Beal 1989). In contrast, electric stimulation of parasympathetic nerves of the salivary glands produces copious amounts of watery saliva at lower frequencies, which is clinically most useful for managing xerostomia (Erichman 1990). Within this dual autonomic system it is clear that salivation is primarily under parasympathetic control (Shiba et al. 2002).

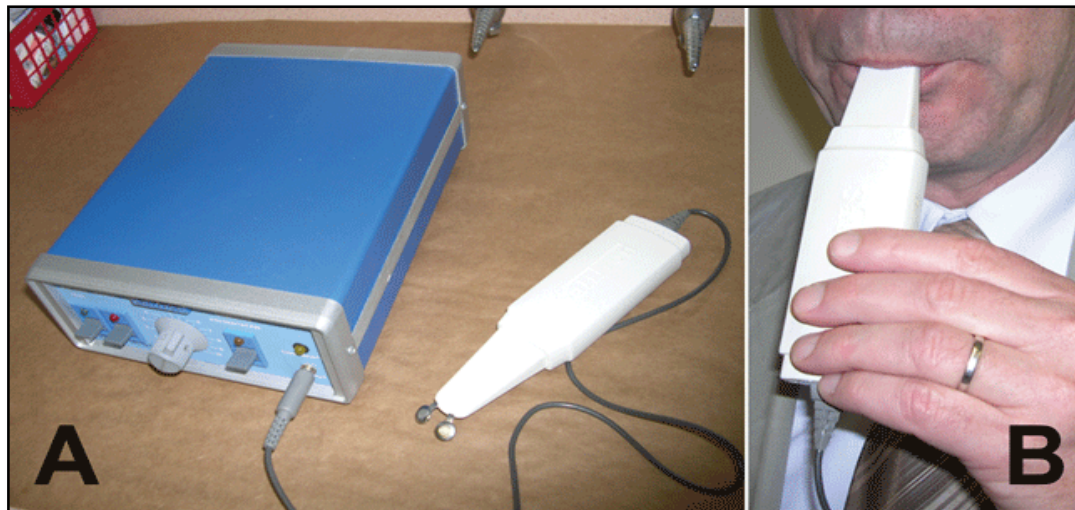
1.3.1 Intraoral electrostimulation devices

1.3.1.1 First-generation and novel electrostimulating devices

The electronic stimulation device (Biosonics Salitron System, SAL II model, Biosonics, Inc., Mt. Laurel, NJ) is powered by a 9-volt battery. It consists of a small hand-held probe tipped with stainless steel electrodes, and a console. The console houses the battery, wave-form generator and associated electronics, switches, an intensity control dial, automatic 3-minute timer control, a counter to record the number of uses, and status-indicator lights. The device induces an electrical stimulus that is delivered to the oral cavity through the electrodes, which are placed on the

dorsum of the tongue and pressed against the hard palate. An intensity control knob with intervals from 0-10 sets peak stimulus output between 0 and 6 volts. The maximum average current output is 9 microamperes and corresponds to a maximum average power dissipation of 0.2 microwatts (Steller, Chou, and Daniels 1988b).

Figure 4. First-generation electrostimulation device (Salitron) (Fedele et al. 2008).



An effort to utilize neuro-electrostimulation to increase salivary secretion gave rise to the production of a device that was marketed in the USA (Salitron; Biosonics, Fort Washington, PA, USA) (Figure 4). The probe of the device was applied to the intraoral mucosal surfaces by the user (between the dorsum of the tongue and palate) for a few minutes each day, and delivered a stimulating signal (Weiss et al. 1986; Steller, Chou, and Daniels 1988b; Talal, Quinn, and Daniels 1992b). It was found that this device when used repeatedly, led to both an immediate (direct) response (increase of salivation as a result of the stimulation) and a cumulative long-term (indirect) response (sustained increase of basal salivary flow rate) as well as subjective improvement in symptomatic xerostomia, regardless of the fact that it was a fairly clumsy device (Weiss et al. 1986; Steller, Chou, and Daniels 1988b; Talal, Quinn, and Daniels 1992b).

In 1986 Weiss demonstrated the efficacy of a first generation device in a group of patients with dry mouth due to different causes, including Sjögren's syndrome (n=9) and radiotherapy to the head and neck (n=13) (Weiss et al, 1986). This open-label uncontrolled study showed an improvement in oral wetness in 50% of patients as measured by visual inspection. Looking in more detail at the subgroup of individuals with SS-related dry mouth, all treated patients showed objective improvement (increased moisture on visual examination) and reported slight-to-substantial symptomatic improvement.

A more robust study design and reliable outcome measures were employed by Steller and collaborators, who designed a placebo-controlled clinical trial and assessed device efficacy through sialometry in 29 SS patients (Steller et al. 1988). Objective improvement (sialometry) was observed in 13 subjects on active device, and subjective improvement (patients' complaints and non- validated questionnaire) in 5 patients allocated on active device.

The same device was investigated by Talal in a multicentre, double blind study including 77 Sjögren's patients (Talal et al. 1992). The electrostimulation patient group showed a difference of 116% greater than the placebo group between the pre- and post-stimulation salivary production. The duration of experimental treatment was 3 visits in a total of 4 weeks, the same as the other two previous trials. These initial studies demonstrated that salivary electrostimulation could lead to an objective increase in salivation and a subjective improvement of dry mouth sensation.

As the device gave promising results in proof-of-principle clinical studies (Table 12) and did not give rise to any associated local or systemic adverse effects, it was approved by the US Food and Drug Administration in 1988 (PMA No. P860067).

However its wider use was hindered by its large size, high price, and lack of user-friendliness (Fedele et al. 2008).

Table 12. Human trial using generation I electrostimulating device in the treatment of xerostomia

Authors	Number of patients	Diagnosis	Methods and Design	Results
Weiss 1986	24	SS (9) RT (13) Other (2)	Short duration stimuli (1-3 minutes) for 3 weeks. Open label non-randomised trial	Objective improvement (assessment of oral wetness via visual examination). Subjective improvement (patients' complaints).
Steller 1988	29	SS (29)	Short duration stimuli (3 minutes)/day per 4 weeks. Double blind placebo-controlled randomised trial	Objective improvement (uWSF sialometry) in 13 subjects on active device. Subjective improvement (patients' complaints and non-validated questionnaire) in 5 patients on active device
Talal 1992	77	SS (77)	Short duration stimuli (3 minutes)/day for 4 weeks. Double blind placebo-controlled multi-centre trial	Objective improvement (uWSF sialometry) in subjects on active device. Subjective improvement (patients' complaints and non-validated questionnaire) in patients on active device
* SS: Sjögren's syndrome; RT: radiotherapy; uWSF: unstimulated whole salivary flow				

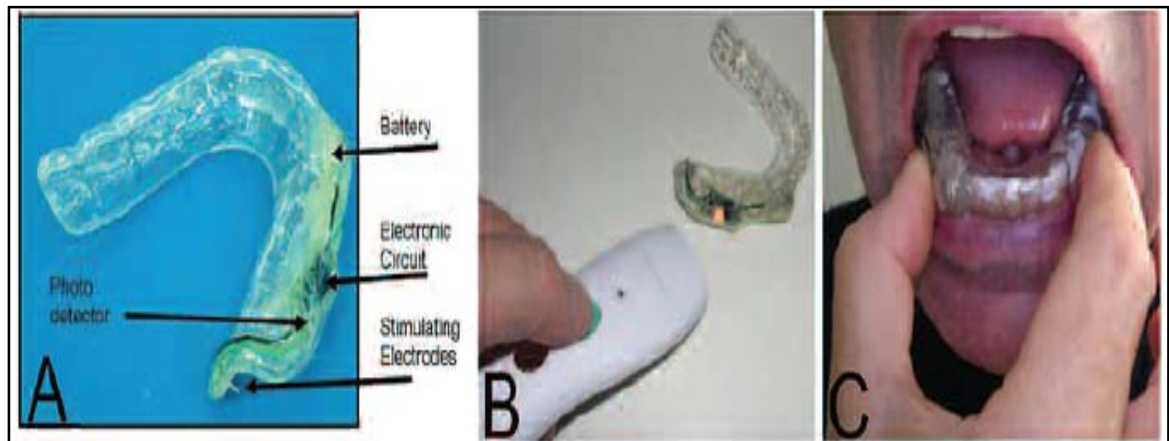
1.3.1.2 Second-generation electrostimulating device

To overcome the limitations of the first-generation device, an EU-funded Consortium developed and tested a second-generation electrostimulating device. The novel device is a removable intraoral thermoplastic polyurethane-made appliance (Figure 5) similar to mouth-guards (splints) used by individuals with temporomandibular disorder or bruxism. It is custom made on the individual patient by using their teeth pattern moulds and its size is much smaller than the Salitron.

The electrical circuit and the battery have been miniaturized and are embedded within the device to avoid saliva contamination. Two electrodes protrude through the appliance to deliver the electrical impulses to the trigeminal and lingual nerves via

the oral mucosa. An external remote control regulates device function by means of infrared light transmission at a wavelength of 940nm–950nm.

Figure 5. Second-generation electrostimulation device (GenNarino) (Fedele et al. 2008).



The efficacy of the novel device was initially tested in a small feasibility study on 23 patients with dry mouth associated with SS (n=10), medications (n=7), and in individuals with idiopathic xerostomia (n=6). This was a double-blind crossover, sham-controlled randomised multicentre feasibility trial aimed at investigating safety and short-term effectiveness (Strietzel et al. 2007) see Table 13. The investigated device was equipped with a wetness sensor, embedded within the appliance, to record real-time changes of wetness during stimulation. The experiment consisted of each patient having one stimulation test for 10 minutes, followed by 35 minutes wash-out and another 10-minute test. The allocation of active vs. sham test was cross-over randomised at stage one. Each experiment was repeated on average 6 times in each patient. After the performance of 158 experiments, a significant reduction of oral dryness for the active mode was objectively registered by the wetness sensor, as well as subjectively by patients' judgement. The device was well tolerated by all patients and did not give rise to adverse side effects. The second generation device was granted CE mark on the basis of the results of this initial feasibility short-term study.

In order to clarify whether prolonged use of electrostimulation can provide long-term benefits, a multicentre longer-term clinical trial was performed in 2011. Strietzel designed a randomised, multicentre crossover sham-controlled double-blind trial with primary endpoint being defined as a subjective improvement in the severity of xerostomia, as assessed by VAS (Strietzel et al. 2011). Unstimulated and stimulated salivary flow rates as assessed by sialometry as well as QoL questionnaire were the second outcome measure of this study. The randomised controlled trial had a 2-month duration and was followed by a subsequent uncontrolled phase aimed at investigating long-term effectiveness. In the initial randomised double-blind phase, the electrostimulating device was used for 10 minutes at a time, each for 1 month, on average 4 times per day, in either sham mode or active mode. 66 patients with SS, 14 with radiation-induced dry mouth and 64 with xerostomia of other causes were enrolled (Total 144). Analysis of results of the randomised controlled phase showed a better performance in terms of dryness severity (subjective symptoms) for the active intervention vs. the sham experiments. No statistical difference, however, was found with respect to unstimulated and stimulated flow rates and oral discomfort. The subsequent second open-label phase consisted of a 3-month investigation of active devices in a subset of patients (n=79). Approximately 70% of treated individuals reported improvement in dryness severity and 63% of them showed increased unstimulated salivary flow rates at the end of the 3-month treatment period. No changes were detected regarding stimulated salivary flow and quality of life scores. Alajbeg subsequently reported the outcomes of extended long-term follow up (after additional 6 months of device usage) confirming previous positive outcomes. (Alajbeg et al., 2012).

Table 13. Human trial using II generation electrostimulating device in the treatment of xerostomia

Authors	Number of patients	Diagnosis	Methods and Design	Results
Strietzel 2007	23	SS (10) Drug-induced (7) Other causes (6)	Two 10-minute stimuli with an interval of 35 minutes(158 experiments). Cross-over, randomised, sham-controlled, double blind, multi-centre trial	Objective improvement (assessed via an electronic wetness sensor) during active experiments. Subjective improvement (patients' complaints and non-validated questionnaires) in 60% of the experiments patients
Strietzel 2011	114	SS (66) RT (14) Other causes (64)	Application of the device for 10 minutes at a time for 1 month. Stage I was a double blind cross-over randomised trial. Stage II was a 3-month open-label study	Objective improvement (uWSF sialometry) in 63% of the participants. Subjective improvement (assessed via a validated questionnaire) in 70% of participants
Alajbeg 2012	94	SS (56) RT(9) Other causes (29)	Application of the device for either 1, 5, 10 minutes at a time, not more than once every hour. Open-label uncontrolled 9-month study	Objective improvement (uWSF) and subjective improvement (a validated questionnaire) in study participants
* SS: Sjögren's syndrome; RT= Radiotherapy; uWSF: unstimulated whole salivary flow				

1.3.1.3 Third- generation electrostimulation device

Electrostimulation with implanted devices is not a new concept, and has been used in the treatment of pain, deafness, bone healing, micturition (urination) disorders, cardiac arrhythmia (pacemakers), muscle weakness, respiratory malfunction, seizures, and essential or parkinsonian tremors (Ami and Wolff 2010).

The third-generation is a dental implant-based, intra-oral device designed for patients that may require frequent and/or constant stimulation of salivary glands. Thus, a miniature neuro-electrostimulating device to be permanently implanted into the oral cavity was developed (the Saliwell Crown) (Figures 6 and 7). It is designed to be placed in close proximity (1-5 mm) to the lingual and long buccal nerves (Kiesselbach and Chamberlain 1984; Alling 1986).

This generation was introduced to overcome the inconvenience related to the repeated application and removal of a splint-based stimulator. The same components of the second-generation device were miniaturized and packaged into a device that has the dimensions and shape of a molar tooth. The device can be mounted on to a commercially available osteointegrated implant. A wetness sensor has been embedded into the device to detect changes in wetness/dryness (Fedele et al. 2008). To ensure close proximity to the lingual nerve that carries both afferent and efferent salivary impulses, and to avoid interference with normal oral function, the osteointegrated implant is situated in the region of the lower third molar. The posterior location of the device ensures that there are no aesthetic concerns (Fedele et al. 2008). This technique has the advantage that patients can make use of saliva production while eating, as it is an intra-oral device (Ami and Wolff 2010).

The aim of this device was 1) to generate a continuous stimuli, 2) to be applied in the oral cavity without interfering with normal oral function, 3) to sense the wetness/dryness status of the oral cavity and accordingly automatically increase or decrease the stimulus and 4) to include a remote control (Fedele et al. 2008). The use of a Saliwell Crown in an 81 year old female resulted in notable improvement of subjective parameters and increase in salivary secretion. In this case not only oral dryness symptoms as quality of life, and oral functional parameters (speech and swallowing) improved, but the oral burning sensation has also improved (Ami and Wolff 2010). This could be explained by the findings of Eliav and colleagues that 82% of patients with burning mouth syndrome were found to have chorda tympani dysfunction (Eliav et al. 2007). This is because the Saliwell Crown is designed to stimulate the chorda tympani

through the lingual nerve stimulation. Although a placebo effect cannot be ruled out, due to the well-recognized psychogenic component of burning mouth syndrome.

Figure 6. Third-generation electrostimulation device (Saliwell Crown) (Fedele et al. 2008).

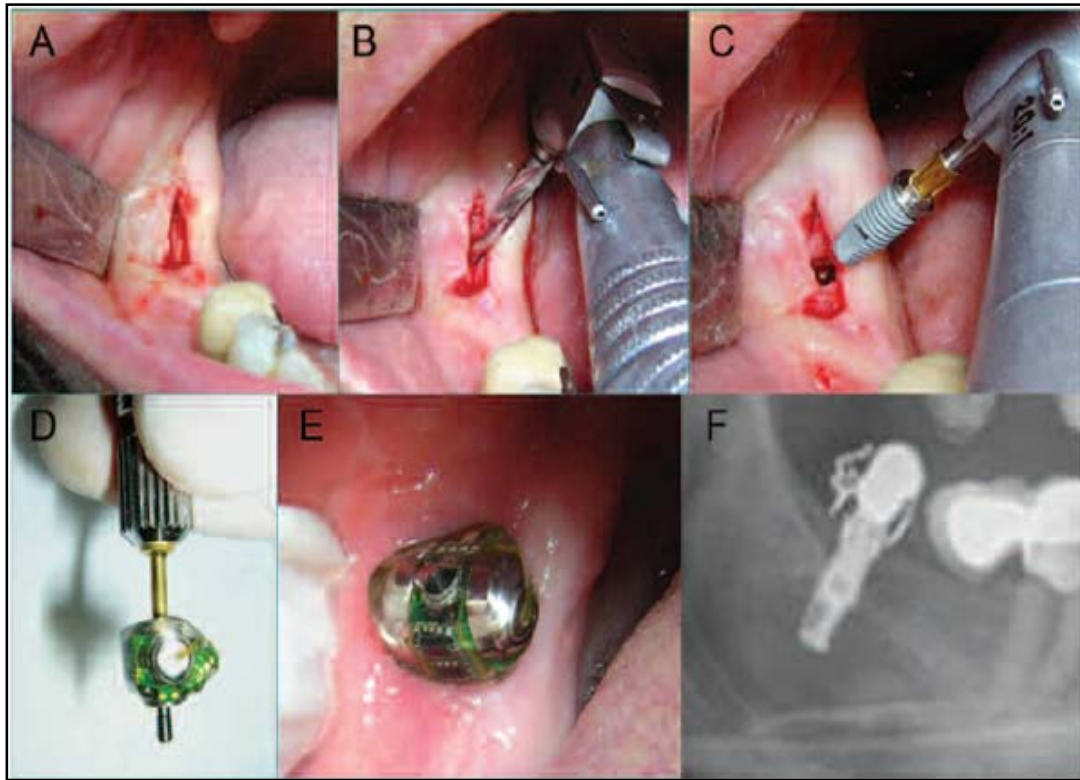
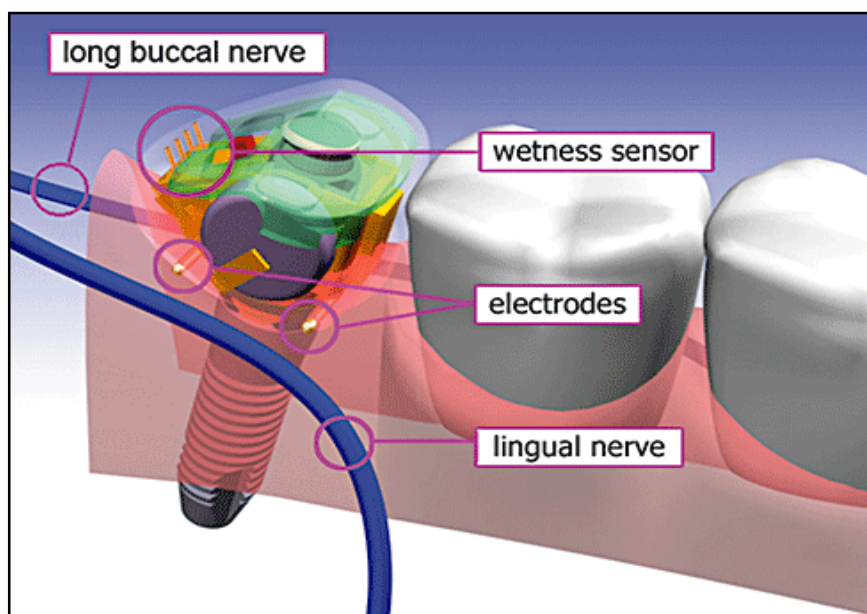


Figure 7. Saliwell Crown location to the different nerves responsible for stimulation of salivation (Ami and Wolff 2010).



1.3.2 Extraoral electrostimulation devices

1.3.2.1 Transcutaneous electrical nerve stimulation

Transcutaneous electric nerve stimulation (TENS) is widely used in pain management; it is a safe and widely accepted means of treatment. An electrical current passes using surface electrodes. The mechanism of extraoral neurostimulation is not fully understood. It has been postulated that transcutaneous electric nerve stimulation (TENS) could directly stimulate the auriculotemporal nerve, which supplies the parotid gland, whereas it remains unclear whether there is also an indirect action (via afferent pathways) onto the salivary reflex arch (Figure 8).

Improvement in salivary function by 0.045-0.02 ml/min was achieved using TENS in a study including 50 patients with xerostomia (Mittal, Keluskar, and Kapoor 2014).

Figure 8. Transcutaneous electric-nerve stimulation (TENS)



The use of TENS unit has been studied by Hargitai and colleagues in 2005 as a means of stimulating salivary production in a pilot study (Hargitai, Sherman, and Strother 2005). Fifteen of the 22 subjects experienced an increased parotid salivary flow when stimulated via the TENS unit. The mean unstimulated salivary flow rate was 0.02418 mL/min (SD 0.03432) and mean stimulated salivary flow rate was 0.04946 mL/min (SD 0.04328). The subjects that had the greater change in salivary flow were those who had an initial saliva flow prior to entry to the study. TENS was unable to stimulate saliva where the salivary flow was 0 at baseline. Therefore, it can be appreciated that TENS may act more efficiently as an accelerator of salivary flow rather than an initiator, and may be more effective in cases with decreased salivary gland function rather than absolute absence of function.

TENS was assessed with 30 oral cavity and oropharyngeal cancer patients who received post-adjuvant (n=26) or definitive radiotherapy (n=4). The electrode pads were placed overlying the parotid glands. Unstimulated whole saliva was collected for 5 min using the spitting method. Then TENS was activated and stimulated saliva was collected for an additional 5 min. A statistically significant increase in saliva flow during stimulation was seen in 29 of 30 patients. The mean unstimulated saliva flow was 0.056 ml/min and the mean stimulated saliva flow was 0.12 ml/min with a median increase of 0.06 ml/min (Vijayan et al. 2014).

Chapter Two:

Systematic Review and Meta-Analysis of Treatments of Xerostomia Due To Sjögren's Syndrome

2.1 Knowledge gap

Sjögren's syndrome is a chronic autoimmune disease, histopathologically characterized by lymphocytic infiltration to exocrine glands (al-Hashimi 2001b; Devauchelle-Pensec et al. 2007; Margaix-Muñoz et al. 2009; Bayetto and Logan 2010), clinically characterized by dry mouth and dry eyes. Sjogren's syndrome can also cause a wide range of extra-glandular manifestations. It is considered the second most common autoimmune connective tissue disorder after rheumatoid arthritis (Fox, Stern and Michelson 2000; Porter, Scully and Hegarty 2004).

Saliva has the important function of lubrication and protection of the oral cavity and upper pharynx, modulating the microbial population and providing stabilisation and remineralisation of teeth. In healthy adults up to one and a half litres of saliva are produced daily, mostly by paired parotid, sublingual and submandibular glands (Porter, Scully and Hegarty 2004). As a consequence of the salivary gland dysfunction, patients with SS typically experience a dry mouth sensation possibly accompanied by dysarthria, dysphagia, dysaesthesia and dysgeusia (Fox 2005). Perhaps unsurprisingly there can be a significant reduction in health related quality of life (QoL) of patients with SS (Sutcliffe et al. 1998; Strombeck et al. 2000; Tensing et al. 2001; Rostron et al. 2002; Belenguer et al. 2005; Champey et al. 2006; Bowman et al. 2007).

Although a wide range of systemic and local therapeutic strategies to ameliorate the symptoms of SS associated xerostomia and related symptoms, the majority of the patients rely on drinking frequent sips of water (Cassolato and Turnbull 2003; Ramos-Casals and Font 2007) which only provide transient relief of symptoms and do not prevent the complications of hyposalivation.

Salivary stimulation techniques with topical and systemic sialogogues may be appropriate for use by patients with some degree of salivary gland function. Topical sialogogues, such as sugar-free chewing may reduce the sensation of mouth dryness and facilitate speech and swallowing. Systemic saliva stimulation with parasympathomimetic drugs (the most widely used being pilocarpine hydrochloride), enhances salivary secretion by stimulating the parasympathetic nervous system. Where salivary glands have been irreversibly damaged or there are contraindications to pharmacological therapies, topical application of salivary substitutes can offer some benefit by providing a moisture coating over the oral mucosa. Non-pharmacological interventions, such as acupuncture, have also been used to increase saliva production, by enhancing peripheral blood flow.

The effectiveness of available treatments for SS-induced xerostomia remains unclear; the reason being that the systematic reviews in literature included participants with dry mouth due to different causes. Therefore, current therapeutic decisions are likely to be based upon a mix of personal experience, expert opinion, and reported studies. Hence we have therefore undertaken this systematic review and meta-analysis to summarize and estimate the effectiveness of available treatment options for xerostomia caused by SS.

2.2 Methods

2.2.1 Literature search

For the identification of studies included for this review, we developed detailed search strategies (Appendix 1) for each database (Medline, Embase, The Cochrane Central Register of Controlled Trials).

We searched reference lists of retrieved reports and textbooks for additional references. Citations were screened and full reports of potentially relevant studies obtained.

2.2.2 Study inclusion criteria

Study inclusion criteria were (i) design: randomized controlled trials; (ii) population: adults with diagnosis of SS induced salivary gland hypofunction (iii) intervention: techniques designed to stimulate saliva production (sialogogues, acupuncture and electrostimulation) or to mimic the presence of saliva (saliva substitutes); (iv) control group: placebo, another active intervention or a combination of the aforementioned. The interventions could be given by any route, formulation, or dose. Studies had to contain sufficient, clear information on the effect of the experimental treatment on clinical outcome to be included. No language restrictions were imposed.

2.2.3 Outcome measure

The primary subjective outcome measure of this review was the mean overall change in xerostomia symptoms, which was assessed by change in a visual analogue scale (VAS) or be subjectively assessed as a dichotomous outcome either improved, or not compared to baseline. Dry mouth symptoms may also be measured using a validated questionnaire such as xerostomia inventory questionnaire (XI) or similar.

Secondary objective outcome measure were the QoL and the saliva flow rate of SS patients. Finally we considered incidence of adverse effects.

2.2.4 Selection process and quality assessment

Titles and abstracts of the references were reviewed to exclude articles out of scope. Full-text articles of potentially relevant records were assessed for eligibility by two independent reviewers (AH, VM). Any disagreements between reviewers were resolved by discussion until consensus was reached.

The risk of bias assessment of the selected trials was performed according to the Cochrane Collaboration tool for assessing risk of bias, documenting the method of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

2.2.5 Data extraction

The following data were extracted by AH and MV: (i) study population; (ii) type, dosage, frequency and duration of intervention, (iii) control group; (iv) xerostomia outcome measures; and (v) effects on psychosocial outcomes (QoL).

2.2.6 Meta-analysis

We summarized effect size for continuous data as xerostomia intensity assessed using a 100 mm visual analogue scale, with the mean differences with 95% confidence intervals (95% CI). For categorical data, reported xerostomia relief was dichotomised into two categories (improvement or no improvement), and we calculated odd ratio (OR) of improvement, with 95% CI.

2.3 Results

The search strategy yielded 694 articles and 12 more through other sources. Of these, 33 articles met the inclusion criteria and read in full. Data were extracted according to the pre-established protocol. These studies were included in the qualitative analysis with a total of 3170 participants. Nine studies out of the 33 provided sufficient data to allow a meta-analysis (Figure 9).

The majority were parallel (two arms) studies (30 studies). In the crossover studies, washout period ranged from 1-3 weeks. Ten trials were conducted in the United States, five in The Netherlands, three in Japan, two in Sweden, France, China and the UK, one in Australia, Portugal and Taiwan. Fourteen trials were funded by the pharmaceutical industry. Five trials received government funding, one study received university funding and 3 received non-governmental support. Studies recruited between 12 and 497 participants and lasted 3 weeks to 24 months. Tables 14 to 19 show study populations, interventions, and extracted outcome measures for eligible trials.

Participants enrolled in these clinical studies had SS diagnosed according to the following diagnostic criteria: Fox et al (Fox et al. 1986) (2 studies), Copenhagen (Manthorpe et al. 1986) (2 studies), Daniels and Talal (Daniels and Talal 1987) (1 study), Preliminary criteria (Vitali et al. 1993) (7 studies) and the American-European Consensus group (Revised European Community Study Group) (Vitali et al. 2002) (15 studies). In 6 studies the classification criteria were not reported. Topical salivary substitutes were assessed in three studies (Reijden et al. 1996; Klestov et al. 1981; Johansson et al. 2001). Topical saliva stimulants were tested in two studies (Gravenmade and Vissink 1993a; da Silva Marques et al. 2011) Interferon- α used in four studies (Shiozawa et al. 1998; Ship et al. 1999;

Khurshudian 2003; Cummins et al. 2003). Electrostimulation was tested in two trials (Steller et al. 1988; Talal et al. 1992). Salivary sialogogues were included in seven trials (Papapoulos et al. 1998; Vivino et al. 1999; Fife et al. 2002a; Petrone et al. 2002a; Wu et al. 2006; Leung et al. 2008; Sugai et al. 2009). Biological agents were tested in four studies (Sankar et al. 2004b; Mariette et al. 2004; Meijer et al. 2010; Devauchelle-Pensec et al. 2014). Immunomodulatory agents were tested in four studies (Drosos, Skopouli, Costopoulos, et al. 1986b; Kruize et al. 1993; Price et al. 1998; Gottenberg et al. 2014). One trial tested acupuncture (List et al. 1998b). One study tested Gammalinolenic acid (Theander et al. 2002). Two trial tested Dehydroepiandrosterone (Pillemer, Brennan, et al. 2004; Hartkamp et al. 2008). Nizatidine tested in one trial (Kasama et al. 2008a). One study included Omega-3 supplements (Singh et al. 2010) and one trial tested a traditional Chinese medicine (Hu et al. 2014).

Most of studies tested the efficacy of a treatment option against placebo; only 11 trials compared a treatment with another agent or another dose of the test agent (Klestov et al. 1981; van der Reijden et al. 1996; Papas et al. 1998; Shiozawa et al 1998; Vivino et al. 1999; Ship et al. 1999; Johansson et al. 2001; Petrone et al. 2002; Fife et al. 2002; Theander et al. 2002; da Silva Marques et al. 2011).

The majority of the studies used whole unstimulated saliva flow (WUSF) and whole stimulated saliva flow (WSSF) as the objective outcome measures, whereas stimulated parotid saliva was used in two studies only. One study considered the findings of the investigator's examination as an objective clinical evaluation (Sugai et al. 2009). On the other hand the most common subjective assessments used was the visual analogue scale of dryness (VAS), in addition a numerical analogue scale (NAS), numerical rating scale (NRS), and a categorical

subjective response collected either in the form of a degree scale (i.e. 0=absence of complaints to 4=severe complaints) or a response percentage (i.e. Excellent, moderate, slight, no difference, worse). One study used the xerostomia inventory (XI) as a subjective assessment method.

Dry mouth symptoms at endpoint were assessed immediately after intervention administration in one trial (Steller, Chou, and Daniels 1988). And one hour after administration of the intervention in three studies (Fife et al. 2002; Petrone et al. 2002; Wu et al. 2006) and therefore results here were relevant to acutely improved dry mouth symptoms.

Salivary function was assessed shortly after the intervention in three studies (Steller, Chou, and Daniels 1988b; Talal, Quinn, and Daniels 1992a; da Silva Marques et al. 2011). Some studies repeated salivary function assessment after 30, 45 minutes (Vivino et al. 1999; Papas et al. 2004), after 60 minutes in four studies (Vivino et al. 1999; Fife et al. 2002; Papas et al. 2004; Wu et al. 2006) and after 90 minutes in two studies (Vivino et al. 1999; Petrone et al. 2002).

2.3.1 Risk of bias results:

Eleven (27%) out of thirty-three studies were considered with low overall risk of bias (Figure 10). Adequate sequence generation and concealment was reported in 45% and 42% of studies respectively, which were therefore considered to be at moderate risk of selection bias. Blinding of participants to the allocated treatment by use of a placebo was done in 25 of the included studies (75%) and these trials were assessed at low risk of performance bias. Outcome assessors were blinded to allocated treatment in 24 trials (72%), which were considered to be at low risk of detection bias. Over (90%) of the included studies reported

complete outcome data, and (85%) of studies without selective reporting, which led to low attrition and reporting bias. Figure 11 reveals each bias item for studies individually.

2.3.2 Results: Qualitative analysis of individual studies

2.3.2.1 Saliva substitutes vs. other saliva substitutes or placebo

Three trials evaluated different salivary substitutes, with a total of 173 participants enrolled (Table 14), all were considered of an unclear risk of bias. Klestov et al in 1981 tested a newly formulated salivary substitute against a glycerine mouthwash as a placebo. Participants were instructed to swill 5ml of the salivary substitute or the placebo for one minute as frequently as desired. In the participant's response to the two forms of therapy: 21.1% of test group reported excellent benefit and 5.3% of placebo group reported excellent benefit ($P<0.01$), this can represent minimal clinical significance. When assessing the symptoms they benefited completing a questionnaire; dry mouth at night time had the only statistical significant between test and control group (46% vs. 21% respectively) $P<0.02$. And in the same time 30.7% of the test group and 37.5% of placebo group reported lack of benefit in any of the symptoms assessed; yet it didn't reach statistical significance. In this study the timing of outcome measurement was not clear and only the percentage of responders were reported with out reporting the magnitude of improvement. Furthermore it is unclear whether these endpoints were assessed at resting salivary function or with acutely enhanced salivary function. Another study evaluated different polymer-based substitutes (poly acrylic acid (PAA), high and low xanthan gum (XG), porcine gastric mucin (SO)) and placebo (van der Reijden et al. 1996). This study consisted two parts, in the

first part 43 participants were included, each substitute was used for one week with a one-week washout period, with a total of 7 weeks test period. Unstimulated salivary flow and paraffin-stimulated whole saliva were collected on day 1 (first day of week 1) and day 56 (last day of week 7). The efficacy of the different substitutes were assessed using 3 self-administered questionnaires, questionnaire 1 was completed at the beginning of each test week, questionnaire 2 completed at the end of each test week and questionnaire 3 completed at the end of the 7 week period. Author reported that there was no carry over effect of each substitute as a one-week wash-out period was adequate. PAA, high viscosity XG and SO were equally preferred, were as placebo was preferred in only 2 of the 43 participants. There was no significant difference in the reduction of patient's symptoms using the substitutes; and the magnitude of reduction was not clear. Patients that preferred PAA had lower stimulated salivary flow than patients who preferred SO ($P<0.05$). Effect size of participant's preference and salivary flow in the first part of the study was only displayed in figures. High (HVXG) versus low (LVXG) viscosity xanthan gum were tested in the second part of the trial were 33 of the participants were included. The efficacy of HVXG and LVXG was not significant. Unstimulated salivary flow rates did not show any significance, yet patients that had a reduction in symptoms using LVXG had significant lower stimulated flow rate than patients with symptoms reduced using HVXG or reduced by both, these were significant for decreasing dry mouth in general ($P<0.05$) and at day time ($P<0.01$). Yet it was not reported if these results had any clinical significance. And it was not clear when measurements were taken; therefor it is not possible to consider these results short or long-lived. In the third study Salinum (SAL) without/ with chlorhexidine (CHX) was assessed

(Johansson et al. 2001), for 9 weeks (3 test weeks, 3 week washout period between agents). This study included 22 patients; they were instructed to rinse 10ml of intervention preparation for one minute each morning and evening. Unstimulated saliva flow was collected (values varied between 0-4.6 ml/15 minutes), but without any significant changes during the trial. A mucosal mirror friction test using a 3-degree scale was employed. Friction was reduced to normal in all nine patients in the SAL group (which are patients with elevated initial values) ($P<0.01$). In the SAL/CHX group mirror friction was also reduced in 8 out of 10 participants ($P<0.05$). 11 patients reported reduced oral dryness symptoms in the SAL group and 15 patients in the SAL/CHX group. The reduction in symptoms using Sal and Sal/Chx was significant ($P<0.05$ and $P<0.001$ respectively) yet meaningfulness to participants was not reported. Timing of clinical recording was not reported, likewise magnitude of improvement was not reported; author only presented number of participants with improvement.

2.3.2.2 Topical saliva stimulants vs. placebo

Two studies tested salivary stimulants with a total of 122 participants (Table 14). Mucin lozenges and placebo were tested each for two weeks each, with a two week wash out period, participants were instructed to be use intervention and placebo as required (Gravenmade and Vissink 1993), this study had a high-risk selection bias due to the fact that all participants were members of the national association of SS. Four self-administered questionnaires were used: questionnaire(I) was about dryness related symptoms and was completed before dispensing the preparations; questionnaire(II) was on the efficacy of the lozenges after two weeks of using the preparation; questionnaire(III) was similar to the initial one, and completed before the second preparation was

dispensed; questionnaire(IV), was similar to the second one and was completed by the end of the 6 weeks. Twenty-eight (67%) participants in the active group reported that their general complaints were diminished, 13(31%) reported no change and 1 (2%) reported more complaints. Oral dryness during the day was largely relieved in 8 (19%), moderately relieved in 26 (62%) and not changed in 7 (17%). Using the placebo lozenges did not reduce the sensation of oral dryness during the day or night. Thirty-two patients (76%) ($P<0.001$) preferred the mucin lozenges, 4 patients (14%) preferred placebo, which gives the investigation a good clinical significance. Mucin lozenges resulted in a larger reduction in complaints ($P<0.001$) and a reduction in the sensation of dry mouth ($P<0.01$). This study reported the magnitude of improvement clearly but timing of outcome measurement collection was not clear. Another trial compared a new malic acid gustatory stimulant with a placebo citric acid gustatory stimulant with 80 participants (da Silva Marques et al. 2011). This study is considered of high quality as it has an overall low risk of bias. Stimulated salivary flow was collected as a secondary outcome immediately after administration of intervention; therefore the study results represent an acute enhancement (short-lived). Both groups elicited a significant increase in salivary flow ($P<0.05$) followed by a decrease, and reaching the basal levels after 20 min. Yet the difference in salivary flow between groups was not significant. Of note the magnitude of improvement was not reported neither the clinical significance.

2.3.2.3 Systemic saliva sialogogues vs. placebo

A total of 7 studies were analysed, 3 tested cevimeline, 3 trials tested pilocarpine, 1 tested rebamipide, with a total of 1099 patients enrolled (Table 15). Petrone et

al. enrolled 197 patients in a 12 week study (Petrone et al. 2002a), testing 30 mg of cevimeline vs. placebo. The primary endpoint was the patient's global evaluation of dry mouth (worse, no change or better) which was assessed 60 minutes after cevimeline administration. At the end of the study 66% of the cevimeline group, reported their mouth to feel better compared to 37% in the placebo group ($P=0.0004$). We consider these results to indicate the effects of long-term therapy, which are likely to be short-lived as assessment was taken 60 minutes after medication administration. However the effect size was not reported. The secondary endpoint of dry mouth VAS was collected each visit before and 1 hour after medication administration, and therefore represents the short-lived effects of 1 single tablet of cevimeline. There was statistical significance difference ($P=0.038$) between the long-term use of 30mg (-27.0 ± 30.4) and control group (-15.0 ± 33.4). The unstimulated salivary flow, which was collected 90 minutes after medication administration showed a statistical significant difference between placebo and 30mg groups in the baseline to 90 minutes post dose values, likewise salivary flow represented acute salivary enhancement (short-lived). Of note the magnitude of salivary flow enhancement was not reported nor the clinical meaningfulness. Thirty mg of cevimeline vs. placebo was tested in another trial for 6 weeks (Fife et al. 2002), recruiting 75 patients. Primary endpoints were the global patient evaluation of dry mouth (better, no change or worse) and the VAS, which were collected 1 hour after administration of medication. At endpoint 76% percent of the 30mg group and 35% placebo group had a response of better long-term results in the global dry mouth evaluation, without reporting the magnitude of improvement. At endpoint the change in predose to postdose in the dry mouth VAS was -16.59 ± 22.54 in the

30mg group and -8.27 ± 14.24 in the placebo group but without statistical significance. The mean change predose to postdose (short-term use) in salivary flow was 0.194 ± 0.179 in the 30mg group and 0.015 ± 0.064 in the placebo group ($P < 0.01$), yet it was not clear when the postdose measurements exactly taken and the meaningfulness to participants was not reported. Leung et al. tested the 30 mg cevimeline with placebo in a 24 week crossover trial (Leung et al. 2008). This trial was considered at overall low risk of bias. Assessment was performed (1) before treatment, (2) at the end of first period, (3) before second trial and (4) at the end of second trial. Subjective assessment included the xerostomia inventory questionnaire (XI), the general oral health assessment index (GOHAI), the medical outcomes short form (SF-36), patient satisfaction and preference. Objective assessment involved stimulated salivary flow and parotid saliva. Participants in the cevimeline group had significant (long-term) improvement in the XI. Mean XI change in active group was -2.6 (5.9) and -0.9 (5.9) in the placebo group ($P = 0.198$). Mean GOHAI change in active group 1.4 (4.2) and -1.1 (3.4) in the placebo group ($P = 0.057$). No statistical significance difference seen in the SF-36 scores. Furthermore, salivary flow rates did not show statistical significance between the (long-term use) cevimeline and placebo groups. No significant differences were seen in patient's satisfaction scores between cevimeline and placebo. The results of this trial are unclear if represents long or short term effects. However the magnitude of outcomes were correctly reported except for the SF-36. In the previous studies more adverse events were seen in the cevimeline groups than placebo.

Pilocarpine was tested in three studies (Table 15), Papas et al. evaluated the use of 5mg for 6 weeks then 7.5mg for the next 6 weeks vs. placebo (Papas et

al. 1998). Efficacy was assessed at week 6 and week 12, pre and post drug administration. Patients completed a VAS (response was >25mm) and a 3-point categorical questionnaire evaluating dry mouth improvement. Results showed a high significance in subjective global improvement in dry mouth at both 6 and 12 week, responders 61% in the pilocarpine group and 31% in the placebo group at week 12, yet meaningfulness to participants was unknown. Salivary flow was collected predose and 30,45 and 60 minutes postdose. Predose salivary flow rates were not changed throughout the study. However 30,45 and 60 minutes post dose salivary flow values showed statistical significance ($P \leq 0.0001$) in the pilocarpine group. These represent the short-term use results and are considered as short-lived effects. Authors did not display the magnitude of improvement. Vivino et al tested pilocarpine with 2.5mg or 5mg dose vs. placebo (Vivino et al. 1999). Subjective assessment was using a VAS (response was >25mm) and a 3-point categorical questionnaire completed at week 6 and week 12, post drug administration. The 5mg group had a greater improvement compared to placebo in the global assessment of dry mouth (61.3% and 31.1% respectively), without presenting the magnitude of improvement and with unknown clinical significance. The salivary flow rate 60 minutes post dosing demonstrated a statistically significant increase in salivary flow compared with the placebo group at endpoint (0.37 ± 0.46) and (0.17 ± 0.19) respectively. Again the results represent acute effect of investigation (short-lived effect). The third study testing pilocarpine was a 12 week trial using 5 mg (Wu et al. 2006), it demonstrated high level of evidence as it showed overall low risk of bias. There were a significant proportion of patients with an improvement in global postdose assessment in dry mouth using a VAS

(response was >25mm). In the pilocarpine group it was (69.6%) compared to placebo (23.8%). The clinical significance was not reported nor the magnitude of improvement. At the end of the study 65.2% percent of the pilocarpine group had a higher response in the 60-minute post-dose saliva production compared to placebo (28.6%). The median increase was 0.05g/minutes vs. -0.02g/minute in the pilocarpine and placebo group respectively ($P=0.0014$), results were short-lived. Salivary function results display short-term effects. Adverse events were seen more in pilocarpine groups.

Rebamipide 100mg 3 times/day vs placebo was tested in one study by Sugai et al. in which 104 participants were included in this 8-week study (Sugai et al. 2009) (Table 15). Dry mouth at week 2, 4 and 8 improved by 26.0%, 44.0% and 46.9% respectively in the rebamipide group compared to 20.0%, 27.1% and 39.1% in the placebo group, yet no significance was found between groups. Rebamipide's clinical significance was not clear. On the other hand the mean increase in salivary secretion was 0.14 ± 0.40 , 0.24 ± 0.46 and 0.35 ± 0.54 g/2 minutes. Timing of assessment was not clear. Higher adverse events were seen in the test group.

2.3.2.4 Electrostimulation vs. placebo

Two studies examined the use of an electrically stimulating device in a total of 106 patients (Table 16). In the first study 29 participants were instructed to use the device (active, sham) for three minutes, three times a day for 4 weeks (Steller et al. 1988). Subjective and objective assessment was performed before and immediately after the use of the device. The pre stimulation salivary flow rates (long-lived) during the 4 weeks were as follow in the active group: at

week 0 (0.05 ± 0.06) and at week 4 (0.09 ± 0.15), and in the placebo group it was: (0.08 ± 0.16) and (0.07 ± 0.19), yet these were not significant. In addition the net increase between pre and post stimulation values of each visit did not reach statistical significance. However the post stimulation salivary flow values were in the active group at week 0 (0.08 ± 0.08) and week 4 (0.24 ± 0.33), and in the placebo group (0.11 ± 0.15) and (0.08 ± 0.18), the difference between the active and placebo group was statistically significant and these values represent the acute enhancement in salivary function (short-lived). Only five patients using the active device reported subjective slight increase in salivary flow, yet clinical importance was unclear. The second study included 77 patients (Talal et al. 1992). The electrostimulation device was again used for three minutes, three times a day for 4 weeks. Salivary function was assessed before and right after using the device. Mean pre stimulation salivary flow rates in the active group were at week 0 (0.060) and at week 4 (0.102), and in the placebo group it was (0.071) and (0.094), these values represented the resting condition of salivary flow (long-lived effects). However the mean post stimulation salivary flow values were in the active group at week 0 (0.330) and week 4 (0.385), and in the placebo group (0.209) and (0.196), these values on the other hand represent the acute enhancement in salivary function (short-lived). This study displayed high level of evidence as it had an overall low risk of bias. Of note the magnitude of improvement in salivary function in these trials were clearly reported however not the subjective outcomes.

2.3.2.5 Acupuncture vs. placebo

One randomised controlled study assessed the effects of acupuncture on dry mouth of SS (List et al. 1998) (Table 16). This included 21 participants,

randomized in two groups, group 1 received treatment twice/week for 10 weeks. Group 2 acted as a control for 10 weeks as they did not receive any kind of treatment, later group 2 received treatment twice/week for 10 weeks. In group 1 there was a significant increase in the stimulated saliva ml/5min, before and after treatment 0.6(0.0-1.2) and 1.2 (0.05-2.6) respectively $P \leq 0.05$. However no statistically significant was found between groups in before and after salivary flows. Subjective assessment showed a significant reduction in mouth dryness before and after treatment in group 1 7.2(4.5-10.0) and 5.5 (3.2-10.0) respectively. Still no significance was found between groups in subjective assessments. Timing of outcome measurements was not clear in this study. We considered this study to be at high risk bias, due to the unblinded nature of the study, the incomplete outcome data and the selective reporting.

2.3.2.6 Biological agents vs placebo

Four studies on the effectiveness of biological agents (infliximab, etanercept and rituximab) have been reported (Table 17). A total of 281 patients have been examined in these studies. The first study had the largest number of patients as it included 103 participants and tested infliximab IV infusion (5mg/kg) vs. placebo, infusions were given on week 0, 2 and 6. Outcome measurements were collected on week 10 and week 22. (Mariette et al. 2004). This study was considered at low risk of bias and therefore high level of evidence. The primary endpoint was the overall response ($\geq 30\%$ improvement as measured on 2 of 3 factors (fatigue VAS, joint pain VAS and most disturbing dryness VAS). Secondary endpoints were the values of each VAS, salivary flow, labial salivary gland biopsy (taken before treatment and at week 10), schirmer test and the SF-36. At week 10, 27.8% of patients in the infliximab group and 26.5% in the placebo group had a

favorable response ($P=0.89$), fulfilling the definition of a primary response. At week 22 it was 16.7% in the active group and 20.4% in the placebo group ($P=0.62$). The Effect size of outcomes was clearly reported. Yet, none of the endpoints differed between the active and placebo group. Assessment was not performed immediately after infusions; therefore we can consider the results representing resting condition. The test group was accompanied with more side effects compared to placebo. The second study enrolled 28 participants to assess the efficacy of etanercept 25mg subcutaneous injections twice/week for 12 week vs. placebo (Sankar et al. 2004). Five patients in the active group and 3 in the placebo group had improvement in primary outcomes (20% improvement in 2 of the 3 SS disease domains: oral, ocular and laboratory tests), but no statistical significance was found between test and placebo groups in the primary outcomes. Magnitude of improvement was not clear for primary endpoints; rather only number of responders was reported. On the other hand secondary end point effect size were reported. No statistical significant changes were found in any of the secondary end points except for ESR. This study assessed the long-term effect of investigated intervention. More adverse events were seen in the Etanercept group. Rituximab IV infusion was tested in two studies, first study tested long-term use of 1000mg vs. placebo given on day 1 and day 15 assessed in 30 participants (Meijer et al. 2010). The follow up was performed on week 5, 12, 24, 36 and 48. This study provided an overall low level of bias. With the primary endpoint (significant improvement in stimulated whole salivary flow in the test group compared to placebo), there was a significant improvement in the rituximab group at week 5 ($P=0.018$) and at week 12 ($P=0.004$), there was also a significant difference in the mean change from baseline to week 12 between

active and placebo groups in the stimulated salivary flow ($P=0.038$), outcome measurements were not taken immediately after intervention, thus they represent resting salivary function. In addition (SF-36) showed higher improvement in the rituximab group. VAS for oral symptoms improved in the active group and there was a significant difference in the mean change in VAS scores from baseline between groups. Magnitude of improvement was reported clearly in this trial, however the clinical importance was not addressed here. Rituximab group experienced more adverse events compared to placebo. The second study tested 1g IV infusion of rituximab given at week 0 and week 2 in 120 participants (Devauchelle-Pensec et al. 2014b). Efficacy was evaluated at week 6, 16 and 24. The primary outcome was $\geq 30\text{mm}$ improvement at week 24 in at least 2 of the 4 VAS. Secondary outcome was the change from baseline in ESSDAI, individual VAS, basal flow rate at week 6 and 16. Primary endpoints results were displayed as percentage of responders and secondary endpoints were displayed as magnitude of improvement. The percentage of patients with at least 30mm decrease in at least 2 of the 4 VAS was larger in the rituximab group only at week 6 (difference 13.3 percentage points ($P=0.036$)), however for the primary outcome, at week 24 the difference was not significant. In the secondary outcomes, the 30mm decrease in VAS fatigue was more in the rituximab group (absolute difference 26.6 percentage points ($P<0.001$) at week 6 and 18.3 percentage points ($P=0.012$) at week 16). VAS dryness was not significant at week 6, 16 and 24. In addition pain VAS was not improved by rituximab at any time point neither there was a decrease in ESSDAI in the test group. There was no improvement in the mean salivary flow rate in the test group. Results of this trial represent intervention long-term effect. VAS effect size was not reported,

rather results were displayed as percentages, and however secondary outcomes effect size was reported in this study. Still the clinical meaningfulness was not reported. Adverse events were reported more in patients in the rituximab group.

2.3.2.7 Immunomodulatory or immunosuppressive agents vs. placebo

The systemic agents tested were cyclosporine A, hydroxychloroquine and azathioprine (Table 18). Interferon- α was tested in four trials. Drosos et al. assessed cyclosporine A 5 mg/kg for 6 months with 20 patients (Drosos et al. 1986). Patients only improved in subjective measurement of xerostomia as 8 out of the 10 patients in the active group reported an improvement in dry mouth symptoms, without reporting the magnitude of the improvement. There was no change in parotid flow between test and placebo groups. It is unclear whether results refer to resting salivation or enhanced salivary flow. Adverse events were nearly similar between groups except for hirsutism, which was seen in 6 of the 10 participants in the test group compared to none in the control group. In a 2 year study, 19 patients received hydroxychloroquine 400 mg daily vs placebo in a crossover design (Kruize et al. 1993). Assessment measurements were collected every 3 months (more likely results represent resting salivary function); patients were asked in a questionnaire to rate the severity of symptoms compared to the previous visit. There was no clear preference between hydroxychloroquine and placebo in improving clinical symptoms as dry mouth and parotid swelling, the study did not report magnitude of improvement in these subjective parameters nor the it found clinical significance (as there was no preference to either test or control). Another study evaluated the efficacy of 400mg daily of hydroxychloroquine vs. placebo for 24 weeks (Gottenberg et al. 2014). Primary endpoints were evaluated at week 24: proportion of patients with $\geq 30\%$ reduction

from baseline in 2 of 3 (dryness, fatigue and pain) on a 0-10 numerical analogue scale (NAS). Secondary endpoints were each of the three NAS, ESSPRI, ESSDAI, SF-36, salivary flow rate and schirmer test. At Week 24, the proportion of responders in the active group was 17.9% and in the placebo group 17.2% ($P=0.96$). There was no difference in the change from week 0 between the active and control groups in the dry mouth subjective and objective assessments. This study most likely represents resting salivary gland assessment. It did not find any significant clinical importance. Azathioprine 1mg/kg for 6 months was assessed vs. placebo in 25 patients (Price et al. 1998). Participants completed pre and post treatment xerostomia VAS questionnaire, and unstimulated salivary flow also was performed pre and post treatment. This study did not find any significant changes between test and placebo group in any of the outcome measurements. Outcomes of this study are more likely to represent salivary gland function at rest. A total of 679 participants were enrolled in 4 studies of interferon- α (Table 18). In the first trial 150 IU interferon- α vs sucralfate 250mg three times a day for 6 months was assessed (Shiozawa et al. 1998). The mean change from baseline to month 6 in the test group was 0.50 and in the control group it was -0.10. Fifty percent of patients who received 150 IU interferon- α orally had at least a 100% increases in baseline whole saliva flow level at month 6. However this study displayed a high-risk performance, detection and reporting bias, in addition the timing of collecting the measurements was not clear. A second trial of 119 patients (Ship et al. 1999) compared different doses of interferon- α orally in lozenges (150 IU once, 150 IU three times, 450 IU once and 450 three times) vs. placebo. A complete response was defined as at least a 25-mm increase in VAS for oral dryness and an increase of unstimulated salivary flow of at least 0.05

g/min, yet the analysis of the primary efficacy endpoints did not show any significant treatment effect based on the complete response definition. The secondary outcome (stimulated salivary flow) was significantly increased in the 150 IU 3 times daily group compared to placebo at week 12. However other subjective measurements (oral comfort VAS, difficulty in swallowing VAS, difficulty in speaking VAS and eye dryness VAS) only showed a suggestion of benefit in the interferon- α 150 IU 3 times daily group. Furthermore timing of outcome measurements was unclear. In a third study twelve patient were enrolled in a 24 week study receiving either 150 IU interferon- α or placebo orally three times daily (Khurshudian 2003), participants were assessed every 6 weeks. At week 12 there were no significant changes in mouth comfort, burning sensation, furthermore there were no significant changes in the stimulated or unstimulated salivary flow. However, in week 24 there was a statistical significant increase in unstimulated whole salivary flow in the test group [median in test group: baseline (0.081), week 24 (0.192) and median in control group: baseline (0.069), week 24 (0.181)] and a statistical significance improvement in oral dryness VAS in the test group [median in test group: baseline (26), week 24 (41), median in control group: baseline (16), week 24 (29.5)]. Meaningfulness of treatment to participants was not addressed in the study. The last study included 497 patients which received 150 IU interferon- α or placebo three times/ day for 24 weeks via oromucosal rout (Cummins et al. 2003). This trial displayed high level of evidence with overall low risk of bias. The efficacy primary endpoints were oral dryness VAS and the stimulated salivary flow. At week 24, patients in the test group had a significant $P=0.01$ increase in unstimulated salivary flow rates compared to placebo, although the primary endpoints (stimulated whole salivary flow and oral dryness

VAS) did not significantly improve. Magnitude of effect was not clearly described in this study and the clinical significance cannot be obtained.

2.3.3.8 Others interventions vs. placebo

Ninety participants were assessed in one study using gammalinolenic acid (800 mg or 1600 mg) vs corn oil as placebo for 6 months. Gammalinolenic acid did not improve dry mouth VAS or increase unstimulated salivary flow rates (Theander et al. 2002). A total of 88 participants were enrolled in two studies to assess the efficacy of oral Dehydroepiandrosterone (DHEA) 200 mg. In the first study Pillemer et al with 28 participants assessed the efficacy of DHEA 200mg/daily for 24 weeks. The primary outcome was the improvement of 2 out of 3 of SS domains; oral, ocular, laboratory. Oral improvement was defined as $\geq 20\%$ improvement in dry mouth VAS or 20% improvement in stimulated salivary flow. The study did not find significant improvement in the DHEA group compared to placebo in the stimulated whole salivary flow. However dry mouth VAS was statistically significantly improved (change of measurement at final visit compared to baseline; active (9), placebo (-10) $P=0.02$, though author reported that this improvement was not clinically meaningful. Timing of measurements was unclear (Pillemer et al. 2004). The second study enrolled 60 participants assessing DHEA 200mg/daily or placebo for 12 months. Secondary outcomes included dry mouth VAS, which was significantly changed in both groups (Hartkamp et al. 2008). The timing of assessment in the DHEA studies was not clear, nor clinical importance. Nizatidine (H₂ receptor antagonist) 300mg/twice a day and famotidine 20mg/twice a day as a control for 8 weeks was assessed for twenty-seven participants. Primary outcomes assessed were the salivary flow (saxon's test) and global xerostomia improvement VAS. Nizatidine significantly improved

stimulated salivary flow rates compared to famotidine, and more participants in the test group did achieve a 20% improvement in the sensation of dry mouth VAS compared to famotidine. Additionally, more frequent patients in the test group did reach a prominent relief in xerostomia symptoms which was indicated by a 50% improvement in VAS dry mouth (Kasama et al. 2008), however this study was presented an overall non clear risk of bias, in addition timing of assessment was not clearly reported. Omega-3 and Vitamin E supplements vs. germ oil as control was tested in one study which included 61 participants (Singh et al. 2010). The difference in unstimulated, stimulated salivary flow and dry mouth VAS between active and control group did not show statistical significance ($P=0.38$, $P=0.346$, $P=0.817$ respectively). A traditional Chinese medicine (ShengJinRunZao YangXue) once a day was tested in a 6 week trial compared to placebo (Hu et al. 2014). The primary endpoint was schimer I test, sugar test and salivary flow (15 min). The secondary endpoint was dry mouth and dry eyes evaluated on an 11-point numerical rating scale (NRS). The magnitude of improvement was reported in this study. In regards to the primary endpoint the difference between the active and control groups were not significant at week 6. Yet in the secondary endpoint, the improvement in the NRS dry mouth was significant between the two arms of the study. Clinical meaningfulness was not reported.

These treatment modalities are displayed in table 19.

Table 14. Qualitative analysis: Saliva substitutes and topical saliva stimulants (NR= not reported, NS=not significant).

	Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control/dose	Outcome measure	Results	Adverse events
Saliva substitutes	(Klestov et al. 1981)	Australia (Non-governmental)	108 (10)	Not clear	Salivary substitute (SS) 5ml/ use for one minute/as frequently as desired.	Glycerine mouthwash As Placebo 5ml/ use for one minute/as frequently as desired.	Subjective: -Response to form of therapy -Assessment of benefited Symptoms	Active: 21.1% reported excellent benefit. Placebo: 5.3% reported excellent benefit. $P<0.01$. Active: 30.7% reported lack of benefit Placebo: 37.5% reported lack of benefit $P<0.02$	None.
	(van der Reijden et al. 1996) <i>Part 1.</i>	Not clear (Industry)	43 (3)	7 weeks (Each agent tested for one week) one week wash out period)	Poly acrylic acid (PAA), Xanthan gum (XG) and Porcine gastric mucin (PM)	Placebo	Subjective: -3 self-administered questionnaires Objective: WUSF, WSSF	PAA, XG and PM were equally preferred. Patients preferred PAA had lower stimulated salivary flow than patients who preferred SO ($P<0.05$)	None
	<i>Part 2.</i>	Not clear (Industry)	33 (3)	3 weeks	High Xanthan gum	Low Xanthan gum	Subjective: -2 self-administered questionnaires Objective: -uWSF -sWSF	Patients that had a reduction in symptoms using LVXG had significant lower stimulated flow rate than patients with symptoms reduced using HVXG or reduced by both. ($P<0.05$) LVXG vs. HVXG uWSF: NS sWSF: Low viscosity: 0.093 ± 0.107 (general xerostomia) 0.069 ± 0.089 (daytime xerostomia)	None
	(Johansson et al. 2001)	Sweden (Academic)	22 (2)	9 weeks (3 test weeks, 3 wash out period)	Salinum without chlorhexidine (SAL)	Salinum with chlorhexidine (SAL/CHX)	Objective: -Mirror friction test -Unstimulated salivary flow	SAL group, friction was reduced to normal in 9 of patients with initial elevated values $P<0.01$. SAL/CHX group also was reduced in 8 out of 10 $P<0.05$. 11 patients reported reduced oral dryness symptoms in the SAL group and 15 patients in the SAL/CHX group. Speaking problems and burning mouth symptoms improved after SAL but not SAL/CHX.	NR
Topical saliva stimulants	(Gravenma de and Vissink 1993)	Netherlands (not clear)	42 (1)	6 weeks: 2 test week 2 week wash out	Mucin lozenges used as required	Placebo lozenges Used as required	Subjective: -3 self-administered questionnaires	Oral dryness during the day was largely relieved in 8 (19%), moderately relieved in 26 (62%) and not changed in 7 (17%) in the active group. Thirty-two patients (76%) preferred the mucin lozenges, 4 patients (14%) preferred placebo. Mucin lozenges resulted in a larger reduction in complaints ($P<0.001$) and a reduction in the sensation of dry mouth ($P<0.01$)	NR
	(da Silva Marques et al. 2011)	Portugal (not clear)	80 (none)	Not clear	Gustatory stimulus (malic acid)	Gustatory stimulus (citric acid)	Objective: -Stimulated salivary flow	Both groups obtained a significant increase in salivary flow.	NR

Table 15. Qualitative analysis: Saliva sialogogues (NR= not reported, NS=not significant).

	Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control	Outcome measure	Results	Adverse events
Saliva sialogogues	(Petrone et al. 2002a)	USA (Industry)	197 (10)	12 weeks	Cevimeline 15 mg tid or 30 mg tid	Placebo	Primary efficacy endpoints: <i>-Global evaluation of dry mouth (1 hour post-dose)</i> Secondary efficacy endpoint: <i>-Salivary flow (90 min post-dose)</i> <i>-Dry mouth VAS (1 hour post-dose)</i>	45% in the 15mg group and 66% of the 30mg group, reported a better response, compared to 37% in the placebo group. The change from baseline to postdose was statistically significant between placebo and 30mg. The mean postdose salivary flow at endpoint also was statistically significant between placebo and 30mg. Change between baseline and final visit value: 15mg: mean±SD -17.7±25.5 30mg: mean±SD -27.0±30.4 Placebo: mean±SD -15.0±33.4 Statistically significant difference between placebo and 30 mg group.	82.2% reported at least one adverse event. 25.7% in the placebo group, 30.8% in the 15-mg group and 48.4% experienced drug-related adverse events.
	(Fife et al. 2002)	USA (Industry)	75 (10)	6 weeks	Cevimeline 30 mg tid or 60 mg tid	Placebo	Objective measurement: <i>-Whole unstimulated salivary flow (post-dose)</i> Subjective measurement: <i>-Global patient evaluation (1 hour post-dose)</i> <i>-Dry mouth VAS (1 hour post-dose)</i>	Change, mean±SD ml/min (predose to postdose) 30mg 0.194±0.179 / 60gm 0.258±0.310 Placebo 0.015±0.064 Statistical significance to favor the active treatment. 19 patient receiving 30 mg (76%) 18 patients receiving 60 mg (67%) 8 in the placebo group (35%) had a response of “better” Change, mean±SD, mm (predose to postdose), 30mg:-16.59±22.54/ 60mg:-19.95±22.10 Placebo: -8.27±14.24	Patients received 60 mg had at least one adverse event. Significant difference between 60 mg and placebo were in: Sweating Nausea Rigors
	(Leung et al. 2008)	China (not clear)	50 (none)	10 weeks first period 4 washout period 10 weeks second period	Cevimeline 30 mg / three times	Placebo 3 times/day	Objective measurement: <i>-Whole stimulated saliva: ml/min</i> <i>-Stimulated Parotid flow: ml/min</i> Subjective measurement: <i>-Xerostomia inventory (XI)</i>	Pre/ active 0.56 (0.67), placebo 0.59 (0.64) Post/ active 0.60 (0.59), placebo 0.55 (0.60) Change: active 0.04 (0.3), placebo -0.04 (0.1) Pre/ active: 0.08 (0.11), placebo:0.08 (0.08) Post/ active: 0.11 (0.12), placebo: 0.08 (0.11) Pre / Active 34.3 (8.7)/ placebo 34.3 (7.7) Post/ Active 31.7 (8.4)/ placebo 33.4 (9.2) Change: active 0.03(0.1)/ placebo 0(0.1)	18.2% in the cevimeline group developed side effects. Including: Sweating, gastrointestinal disturbance, palpitation and heat sensation.

(Continue table 15)

Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control	Outcome measure	Results	Adverse events
(Papas et al. 2004)	USA (Industry)	256 (14)	12 weeks	Pilocarpine 5mg or 7.5mg	Placebo	Objective measurement: -Whole unstimulated saliva (30,45, 60 minutes post-dose) Subjective measurement: -Subjective 3-point categorical question -Dry mouth VAS	Significant increase post dose in the pilocarpine group. $P \leq 0.0001$ Global Improvement in mouth dryness. Proportion of responders, week 12 Active 61% Placebo 31% $P \leq 0.0001$	Most frequent reported adverse experience: sweating, headache, urinary frequency, and nausea.
(Vivino et al. 1999)	USA (Industry)	373 (16)	12 weeks	Pilocarpine 2.5mg or 5mg / 4times a day	Placebo	Objective measurement: -Whole unstimulated saliva (ml/min) (60 min post-dosing) Subjective measurement: -Global improvement in dry mouth -Dry mouth VAS	5mg 0.37 (± 0.46). vs Placebo 0.17(± 0.19). Significant finding favoring 5mg (61.3%), compared to placebo (31.1%). Significant findings favoring pilocarpine group.	Most frequent reported adverse experience: Sweating, headache, flue syndrome and nausea
(Wu et al. 2006)	Taiwan (not clear)	44 (5)	12 weeks	Pilocarpine 5mg / four times	Placebo	Objective measurement: -Whole unstimulated saliva (g/min) (60 min post-dosing) Subjective measurement: - Global improvement in dry mouth -Dry mouth VAS	Active: 65.2% had a higher response Placebo 28.6 had a higher response The median increase in saliva production in the pilocarpine group was significantly greater than placebo group, 0.05g/min vs. -0.02g/min respectively. Active: 69.6% of had improvement Placebo: 23.8% of had improvement. Significant results favoring pilocarpine.	21.7% in pilocarpine group experienced perspiration Palpitation was reported in 4.3% in the pilocarpine group.
(Sugai et al. 2009)	Japan (not clear)	104 (3)	8 weeks	Rebamipide 100 mg / three times a day	Placebo	Objective measurement: -Saxone test, g/2min Subjective measurement: -Self-assessed overall severity of dry mouth (4-grade scale) -Dry mouth VAS	Mean increase in salivary secretion Week 8: Active: 0.35 ± 0.54 Control: 0.17 ± 0.58 NS Improvement rates favoring rebamipide was Week 8 46.9% vs. 39.1% NS NS	Adverse events were observed in 60.4% in rebamipide group, and 66.7% in the placebo group. The most frequent was gastrointestinal disorders in both groups.

Table 16. Qualitative analysis: Electrostimulation and acupuncture (NR= not reported, NS=not significant).

	Study	Country (Funding source)	Number of participants (Male)	Study duration	Intervention/ dose	Control	Outcome measurements	Results	Adverse events
Electrostimulation	(Steller et al. 1988)	USA (Industry)	29 (2)	4 weeks	Electrostimulation Three min/ 3times a day	Sham device	Objective measurement: -Whole unstimulated saliva (g/2min)	Pre stimulation (resting condition) Week 0 week 4 Active 0.05±0.06 0.09±0.15 Placebo 0.08±0.16 0.07±0.19 NS Post stimulation (acute enhancement) Week 0 week 4 Active 0.08±0.08 0.24±0.33 Placebo 0.11±0.15 0.08±0.18 P=0.04 Net increase (post-pre stimulation) at week 4 Active: 0.15±0.24 Placebo 0.02±0.03 Subjective measurement -Subjects evaluated the increase in saliva	None
	(Talal et al. 1992)	USA (Industry)	77 (3)	4 weeks	Electrostimulation Three min/ 3times a day	Sham device	Objective measurement: -Whole unstimulated saliva (g/2min)	Pre stimulation (resting condition) Week 0 week 4 Active 0.060 0.102 Placebo 0.071 0.094 P≤0.05 Post stimulation (acute enhancement) Week 0 week 4 Active 0.330 0.385 Placebo 0.209 0.196 P≤0.05 Difference between active and placebo post stimulation scores Week 0 +0.121 Week 4 +0.190 -Subjective measurement Significant improvement in difficulty in swallowing and burning tongue.	NR
Acupuncture	(List et al. 1998)	Sweden (Governmental)	21	10 weeks	Acupuncture Twice a week	No treatment	Objective measurement: -Whole unstimulated saliva: median (minimum and maximum), before and after acupuncture treatment (ml/15 min) -Stimulated salivary flow: median (minimum and maximum), before and after acupuncture treatment (ml/5 min) Subjective measurement: -Mouth dryness VAS: median (minimum and maximum), before and after acupuncture treatment	Active: before 0.0(0.0-0.2). after 0.0(0.0-0.6) NS Placebo: before:0.0(0.0-0.7). after 0.0(0-0.2) NS Active: before 0.6(0.0-1.2). after 1.2(0.05-2.6) P≤0.05 Placebo: before 0.5(0.0-2.4). after 0.6(0.1-2.5) NS Active: before 7.2(4.5-10.0). after 5.5(3.2-10.0) P≤0.05 Placebo: before 6.3(0.0-9.5). after 6.8(0.0-9.5) NS	NR

Table 17. Qualitative analysis: Biologic agents. (NR= not reported, NS=not significant)

Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control	Outcome measurements	Results	Adverse events
(Mariette et al. 2004)	France and Belgium (not clear)	103 (not clear)	Infusions on week 0, 2 and 6 Assessed on week 10 and up for 22 weeks	Infliximab Infusions 5mg/kg	Placebo	Primary endpoint -Overall response to treatment ≥ 30% improvement as measured on 2 of 3 factors (fatigue VAS, joint pain VAS and most disturbing dryness VAS) Secondary endpoint -Salivary flow rate (ml/min)	Week 22 <i>Fulfilled the overall response:</i> Active 16.7% Placebo 20.4% <i>P=0.62</i> Week 22 Active=0.03±0.15 Placebo= 0.02±0.19 <i>P=0.24</i>	Infusion reactions (2). Isolated cutaneous facial eruption (1). Autoimmune hepatitis (1). Pneumococcal septicemia (1). Breast cancer (1).
(Sankar et al. 2004)	Netherlands (not clear)	28 (2)	12 weeks	Etanercept 25 mg S/Q injections /twice a week	Placebo	Primary endpoint -20% improvement in 2 of the 3 SS disease domains: oral, ocular and laboratory tests <i>-Stimulated salivary flow (ml/min)</i> <i>-Dry mouth VAS</i>	Improvement in primary outcomes Active: 5 patients Placebo: 3 patients <i>P=0.2</i> Median (25 th , 75 th percentiles) Active -0.033 (-0.31,0.16) Placebo -0.22 (-0.56,0.13) <i>P=0.63</i> Median (25 th , 75 th percentiles) Active -2(-13,2) Placebo 3(-11,10) <i>P=0.44</i>	Injection-site reactions (2). Multiple actinic skin lesions (1).
(Meijer et al. 2010)	Netherlands (Industry)	30 (1)	Followed up week 5, 12, 24, 36 and 48.	Rituximab IV infusion of 1000mg on day 1 and 15	Placebo	Primary endpoint -Stimulated salivary flow: (ml/min) Secondary endpoint -Unstimulated salivary flow: (ml/min) <i>-Oral dryness VAS: significant results at week 24, 36 and 48.</i> <i>-SF-36: significant results at week 36</i>	Significant results in week 5 and 12. Week 5 Active=0.84±0.71 Placebo=0.41±0.24 Week 12 Active=0.87±0.87 Placebo=0.28±0.17 Significant results in week 5 and 12. Week 5 Active= 0.24±0.22 Placebo=0.09±0.07 Week 12 Active= 0.23±0.22 Placebo=0.05±0.05 Week 24 Active=34±27 Placebo=64±27 Week 36 Active=51±28 Placebo=68±26 Week 48 Active=50±28 Placebo=69±25 Week 36 Active=60±17 Placebo 63±16	Early infusion reaction (2). Late infusion reaction (2). Serum sickness (1). Infections within two weeks after infusion (2). Infections within forty-eight weeks after infusion (10).
(Devauchelle et al. 2014)	France (Governmental, industry)	120 (8)	Infusion at week 0 and 2 Follow up week 6, 16 and 24	Rituximab IV infusion of 1g at week 0 and 2	Placebo	Primary endpoint at week 24 -≥30mm improvement in at least 2 of 4 VAS Secondary endpoint at week 16 -Change in individual VAS <i>-Unstimulated salivary flow (ml/min)</i>	Week 24 Active 23% Placebo 22% <i>P=0.91</i> Fatigue VAS Active 34.7% Placebo 8.2% <i>P<0.001</i> Dryness VAS Active 21.1%, placebo 13.6% NS Active -0.01, placebo -0.03 NS	Infusion reaction, respiratory disorder, shortness of breath, dry cough, sneezing.

Table 18. Qualitative analysis: Immunomodulatory/ immunosuppressive agents. (NR= not reported, NS=not significant).

Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control	Outcome measurements	Results	Adverse events
(Drosos et al. 1986)	Greece (not reported)	20 (1)	6 months	Cyclosporin A 5mg/kg daily	Placebo	Subjective measurement: -Xerostomia improved Objective measurement: -Parotid flow (ml/5min)	Active= 8 patients Placebo= 2 patients Active Pre: 0.62±0.67 Post: 1.14±1.28 Placebo Pre: 0.62±0.66 Post: 1.06±1.08 NS	Hirsutism (6). Infections (4). Hypertension (1). Gingival hypertrophy (1). Nausea, vomiting (1).
(Kruize et al. 1993)	Netherlands (Industry)	19 (none)	24 months Crossover	Hydroxychloroquine 400 mg daily	Placebo	-Questionnaire reporting the presence and severity of dry mouth symptoms.	Participants had no clear preference to test medication with respect symptoms of dry mouth.	Mild deterioration of liver function (1).
(Gottenberg et al. 2014)	France (Governmental, Industry)	120 (10)	24 weeks	Hydroxychloroquine 400 mg daily	Placebo	Primary endpoint: -Proportion of patients with ≥30% reduction from baseline in 2 of 3 (dryness, fatigue and pain) on a 0 to 10 numeric scale, at week 24 Secondary endpoint: -Each of 3 primary endpoint -ESSPRI, ESSDAI, SF-36 -Unstimulated salivary flow (ml/min) at week 24	Week 24 Active=17.9% Placebo=17.2% P=0.96 No difference between both groups in the change from week 0 seen in each numerical scale, ESSPRI, ESSPRI and SF-36 Mean (SD) Active: 0.18 (0.21) Placebo 0.22 (0.21) P=0.45	Urinary lithiasis (1) Breast cancer (1)
(Price et al. 1998)	UK (Non-governmental)	25 (2)	6 months	Azathioprine 1 mg/kg	Placebo	Objective measurement: -Unstimulated salivary flow (ml/5min) Subjective measurement: -Dry mouth VAS	Active: Pre 0.2(0.1) Post 0.3(0.1) Placebo: Pre 0.2 (0.05) Post 0.2 (0.09) NS Active: Pre 76.6 (10.7) Post 72.8 (10.9) Placebo: Pre 77.4 (5.10) Post 78 (4.2) NS	Nausea, abnormal liver function test, perforated large bowel
(Shiozawa et al. 1998)	Japan (Industry)	60 (2)	6 months	Interferon-α 150 IU orally three times a day	Sucralfate 250mg three times a day	Objective measurement: -Salivary flow (g/2min) -Mean change from baseline at month 6	At month 6 Active 1.17± 0.98 Placebo 0.58±0.48 P < 0.001 Active 0.50 Placebo -0.10 P<0.001	Depression (2).
(Ship et al. 1999)	USA (Industry)	109 (8)	12 weeks	Interferon-α 150 IU once 150 IU three times 450 IU once 450 IU three times orally	Placebo	Primary endpoint: -Complete response Objective measurement: -Unstimulated salivary flow (g/5min) -Stimulated salivary flow (g/5min) Subjective measurement: -Dry mouth VAS	Non-significant, but a suggestion of benefit in the 150 IU tid group. Non-significant, but 150 IU tid and 450 IU tid groups had greater percentage of participants with positive response. 150IU TID 0.79±0.46 Placebo 0.06±0.11 P=0.04 Non-significant, however there was a trend over time for 150 IU tid and 450 IU tid groups.	None.

Immunomodulatory or immunosuppressive agents

(Continue table 18)

	Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control	Outcome measurements	Results	Adverse events
Immunomodulatory or immunosuppressive agents (cont.)	(Khurshudian 2003)	USA (not clear)	12 (2)	24 week	Interferon-α 150IU 3times orally	Placebo	Objective measurement: -Unstimulated salivary flow (ml/min) -Stimulated salivary flow (ml/min) Subjective measurement: Dry mouth VAS	<i>Week 24, mean\pmsem(median)</i> Active 0.242 \pm 0.06 (0.192) Placebo 0.176 \pm 0.06 (0.181) NS <i>Week 24, mean\pmsem(median)</i> Active 0.507 \pm 0.14 (0.399) NS Placebo 0.696 \pm 0.27 (0.704) NS <i>Week 24: mean\pmsem(median)</i> Active 46 \pm 11.1 (41) Placebo 35.7 \pm 11.2 (29.5) NS	None.
	(Cummins et al. 2003)	USA (Industry)	497 (37)	24 week	Interferon-α 150IU 3times orally	Placebo	Primary endpoint -Stimulated salivary flow (gm/5min) -Dry mouth VAS Secondary endpoint -Unstimulated salivary flow (gm/5min)	No significant improvement compared with placebo. No significant improvement compared with placebo. <i>Week 24</i> Test group showed a significant increase compared to placebo $P=0.01$	Gastrointestinal adverse event.

Table 19. Qualitative analysis: Other agents (NR= not reported, NS=not significant).

Study	Country (Funding source)	Number of participants (Males)	Study duration	Intervention/ dose	Control	Outcome measurements	Results	Adverse events
(Theander et al. 2002)	UK (Industry)	90 (8)	6 months	Gammalinolenic acid 800 mg or 1600 mg	Corn oil	Secondary endpoint -Unstimulated salivary flow (ml/15min) -Dry mouth VAS	Month 6, (median, interquartile range) Active (1600 mg): 0.4 (-0.4;1.1) Placebo: 0.1 (-0.1;0.4) NS	Mild gastrointestinal side effects.
(Pillemer et al. 2004)	Not clear (not clear)	28 (none)	6 months	Dehydroepiandrosterone 200mg	Placebo	Primary outcome ≥20% improvement in dry mouth VAS or 20% improvement in stimulated salivary flow -Stimulated salivary flow (ml/min) -Dry mouth VAS	Change at week 24 (Mean (SEM)) Active 0.086(0.09) Placebo -0.09(0.09) P= 0.17 Change at week 24 (ml/min) (Mean (SEM)) Active 9(5.5) Placebo -10(5.5) P= 0.02	Acne, facial hirsutism, post-dose chills, disseminated streptococcal infection.
(Hartkamp et al. 2008)	Netherlands (Non-governmental)	60 (none)	6 months	Dehydroepiandrosterone 200mg	Placebo	Secondary outcomes -Dry mouth VAS	Both groups showed a significant change.	NR
(Kasama et al. 2008)	Japan (not clear)	27 (5)	8 weeks	Nizatidine 150 mg/ twice	Famotidine 20mg/twice/day	Objective measurement -Saxone test (g/2min) Subjective measurement -Dry mouth VAS	Active : Pre 0.57±0.39 Post 0.90±0.65 P<0.05 More patients in the test group achieved a 20% improvement 71.4 vs 15.4 P<0.05	None.
(Singh et al. 2010)	USA (Governmental)	61 (4)	3 months	Omega-3 and Vitamin E supplements Once daily	Wheat germ oil	Objective measurement -Unstimulated salivary flow (ml/ 5min) -Stimulated salivary flow (ml/ 5min) Subjective measurement -Dry mouth VAS	Difference from baseline to month3 (mean(SD)) Active 0.064(0.173) Placebo 0.029(0.09) Active 0.242(0.64) Placebo 0.101 Month 3 (mean(SD)) Active 1.69(2.19) Placebo 1.56(2.16)	NR
(Wei et al. 2014)	China (Governmental)	240 (11)	6 weeks	ShengJinRunZao YangXue Once daily	Placebo Once daily	Primary endpoint (week 6) -Saliva flow rate (ml/15min) Secondary endpoint (week 6) -Dry mouth numerical scale (NRS-11)	Improved salivary flow by 0.04 ml/15 min NS difference Improved difference by 0.83 P<0.01 between groups	Liver dysfunction (4) Diarrhea (4) Upper respiratory tract infection (4) Leucopenia (4)

Others

2.3.3 Results: Quantitative analysis (meta-analysis)

The meta-analysis compared 9 studies; none of them had any high-risk bias item. Statistical analysis of subjective xerostomia symptoms (5 studies) and objective assessment of salivary function changes (8 studies) was possible. QoL outcome assessment was not possible due to the statistically lack of homogeneity.

In relation to the primary outcome (change measured on a 100-mm visual analogue scale (VAS), evaluating degree of mouth dryness), pilocarpine versus placebo: Three studies with a pooled total of 638 participants, with no heterogeneity among them, indicated that systemic pilocarpine use for 12 weeks is 3.58 times more likely to have a long-term effectiveness in ameliorating dry mouth symptoms than placebo. These studies indicated that the magnitude of effect is having more than 25mm change on dry mouth VAS. The OR was 3.58 [95% CI 2.55-5.03] (Figure 12).

Cevimeline versus placebo: Two studies again with no heterogeneity and a total of 180 participants indicated that long-term use of 60mg of cevimeline is associated with higher reduction in dry mouth symptoms than placebo with a MD of 10.11 [95% CI 2.52-17.69] (Figure 13).

Concerning the secondary outcomes we were able to compare the (short and long term) effect of electrostimulation vs sham stimulation, pilocarpine vs placebo, cevimeline vs placebo and interferon- α vs placebo in improving unstimulated salivary flow (ml/min) (Figure 14). Electrostimulation versus placebo: Two studies using 1st generation device with no heterogeneity and a total of pooled 101 participants showed a moderate evidence that electrostimulation leads to an increase in the unstimulated salivary flow with a small effect size (0.05mL/min) [95% CI 0.02-0.09]. The clinical relevance remains unclear and the effect is likely to be short-lived. The effects of long-term use were not significant (0.01ml/min) [95% CI -0.14, 0.16].

Pilocarpine versus placebo: Two homogeneous studies ($I^2=21$) with a total of 594 participants indicated that one tablet of pilocarpine is more effective in increasing unstimulated salivary flow in a short-term (measured at 60min) (0.22 ml/min) [95% CI 0.17-0.28]. Long-term effect of pilocarpine is unknown.

Cevimeline versus placebo: Two studies ($I^2=61$) with a total of 180 participants reported an effect in regards to the short term salivary flow enhancement (measured at 90 min) of one tablet of cevimeline to increase unstimulated salivary flow. The effect size was small (0.08mL/min) [95% CI 0.03- 0.14]. Long-term benefits remain unknown.

Interferon- α versus placebo: With two studies ($I^2=17$) comparing interferon- α did not show efficacy in increasing unstimulated salivary flow compared to placebo (0.01 [95% CI -0.00 - 0.02]).

2.4 Discussion

Treating dry mouth aspects in patients with SS can be challenging especially with the absence of an evidence-based guide for clinicians. One systematic review on the treatment of salivary gland hypofunction of SS has been published in 2010 (Ramos-Casals et al. 2010). This review has a number of limitations including linguistic constraints (only papers in English were reviewed) and the inclusion of non-randomized studies (Grégoire, Derderian and Le Lorier 1995, Higgins et al. 2013). Hence we have designed this systematic review and meta-analysis with the aim of overcoming limitations of previous reviews providing accurate estimate of effectiveness of available treatments. The objective is to support the development of evidence-based practice guidelines for the management of SS-induced hyposalivation and xerostomia. We have considered a number of study characteristics that were not included in reviews, which we believe are important to assess the efficacy of interventions. These include the type of outcomes (dry mouth symptoms, salivary function, quality of life), the timing of collecting outcome measurements at endpoint (shortly after administration of the intervention or away from treatment completion) and timing of outcome changes, e.g. whether they reflect long or short term changes in salivation or xerostomia (after weeks/months or a few minutes/hours of therapy). Table 20 displays these characteristic for each study.

The results of 33 RCTs with a total of 3170 randomized patients were summarized to estimate the effectiveness of treatment on SS-induced xerostomia and hyposalivation where possible. The meta-analysis was possible only for 9 studies. Results of this review suggest that the long-term use (12 weeks) of systemic pilocarpine provides improvement in dry mouth sensation of SS. Individuals using pilocarpine were 3.58 times more likely to perceive a reduction in dry mouth symptoms of at least 25mm. Effect size was however unclear and clinical significance was unknown. With respect to cevimeline, our meta-analysis shows that the short-term use of one tablet of cevimeline is associated with a small 10.11 [2.52, 17.69] reduction in dry mouth symptoms. Nothing is known regarding its clinical meaningfulness of cevimeline on VAS scores.

This meta-analysis suggests that electrostimulation, pilocarpine and cevimeline can increase the salivary flow in patients with SS. Short-use of the electrostimulation device can lead to a small increase in salivary flow of unknown clinical significance. Whereas long-term use does not seem to provide a very notable effect. One tablet of cevimeline also improved salivary flow; effect size was (0.08 ml/min [0.03, 0.14], yet it did demonstrate high clinical significance. The use of 1 tablet of pilocarpine can increase salivary flow with a moderate effect size (0.22 ml/min [0.17, 0.28]) but unknown clinical significance. No information is available for cevimeline and pilocarpine effect on salivary function in resting conditions. Interferon- α had a small effect size of (MD 0.01 [-0.00, 0.02]) furthermore the clinical significance was unknown nor the timing of outcome assessment.

Some practical implications can be withdrawn from these results when managing SS induced xerostomia. It is helpful to consider two aspects: reducing dry mouth symptoms and increasing salivary flow. Prescribing pilocarpine and cevimeline can both provide an improvement in salivary flow (larger effect seen using pilocarpine), yet both are likely to be short-lived, as no available evidence supports their long-term effect. However in the same time both are expected to reduce dry mouth symptoms, which is clinically important to patients. Short use of electrostimulation can provide a small symptomatic benefit but failed to provide evidence regarding beneficial effect of longer use of the device. Clinical significance also remains unknown. The toxicity of pilocarpine and cevimeline seems similar, possibly with a tendency for cevimeline to be better tolerated, although evidence is not robust as no direct comparison is available. And on the other hand electrostimulation did not give rise to any adverse events.

With respect to interventions that were not included in the meta-analysis, this systematic review suggests that there is no evidence that acupuncture, infliximab, etanercept, azathioprine, cyclosporine, hydroxychlorquine, gammalinolenic acid, dehydroepiandrosterone and omega-3/ vit E can have an effect on reducing dry mouth symptoms, improving salivary flow or improving quality of life in SS patients with xerostomia. However Salivary substitutes (mouth washes) and topical salivary stimulants (lozenge) provided low level of evidence suggesting that they might have potentials in relieving in mild dry mouth cases without having adverse effects. Furthermore interferon- α , rituximab and nizatidine provide low-quality evidence of beneficial effect as they were of an unclear/high risk of bias.

This systematic review has some limitations. We detected significant heterogeneity between the studies. Most heterogeneity could be accounted for by variations in doses and application procedures. In addition to the type of treatment in the experimental and control groups, there were discrepancies in the baseline characteristics of the patients. The studies included were conducted between 1981 and 2014. During this time the classification criteria of SS has changed, leading to different characteristics of study samples. The low number of studies included in the meta-analysis highlights the limited evidence available to determine the effectiveness of dry mouth therapy.

2.4.1 Summary

- Heterogeneity among studies was high. Data pooling for quantitative meta-analysis was possible in only 9 studies out of the 33 included in the systematic review. The 9 selected studies were of moderate/good quality with low risk of bias.
- Dry mouth symptoms can be effectively reduced with long-term use of pilocarpine. Effect seems notable (at least 25 point on 0-100 VAS) but the precise effect size and its clinical meaningfulness remain unclear.
- There is limited evidence regarding the efficacy (long) of cevimeline in lessening xerostomia. Effect size seems small (10 points on 0-100 VAS).
- With respect to salivary gland function, there is robust evidence that short-term use (60 minutes after 1 tablet) of pilocarpine can increase unstimulated whole salivary flow rate by 0.2ml/min more than placebo. Clinical significance of this effect is unknown. Long-term effects of pilocarpine could not be evaluated.

- The effects of cevimeline upon salivary flow are similar to those of pilocarpine, although the effect size seems to be significantly smaller (0.08 vs 0.2 mL/min).
- There is some limited evidence that the short-term use of the 1st generation electrostimulating device is associated with an increase in salivation. However, the effects size seems very small (0.05 mL/min).
- For most the studies the beneficial effects seem short-lived and longer-term effects are unknown.
- This review did not conclude with much of a good evidence of a suitable therapy for the oral aspects of SS – yet some promising evidence that electrostimulation may provide a cheap, reliable, safe method of controlling this problem. However ultimately the burden of this disease will only fall once the primary cause is identified and appropriate therapy developed.

Figure 9. Flow diagram of the strategy search.

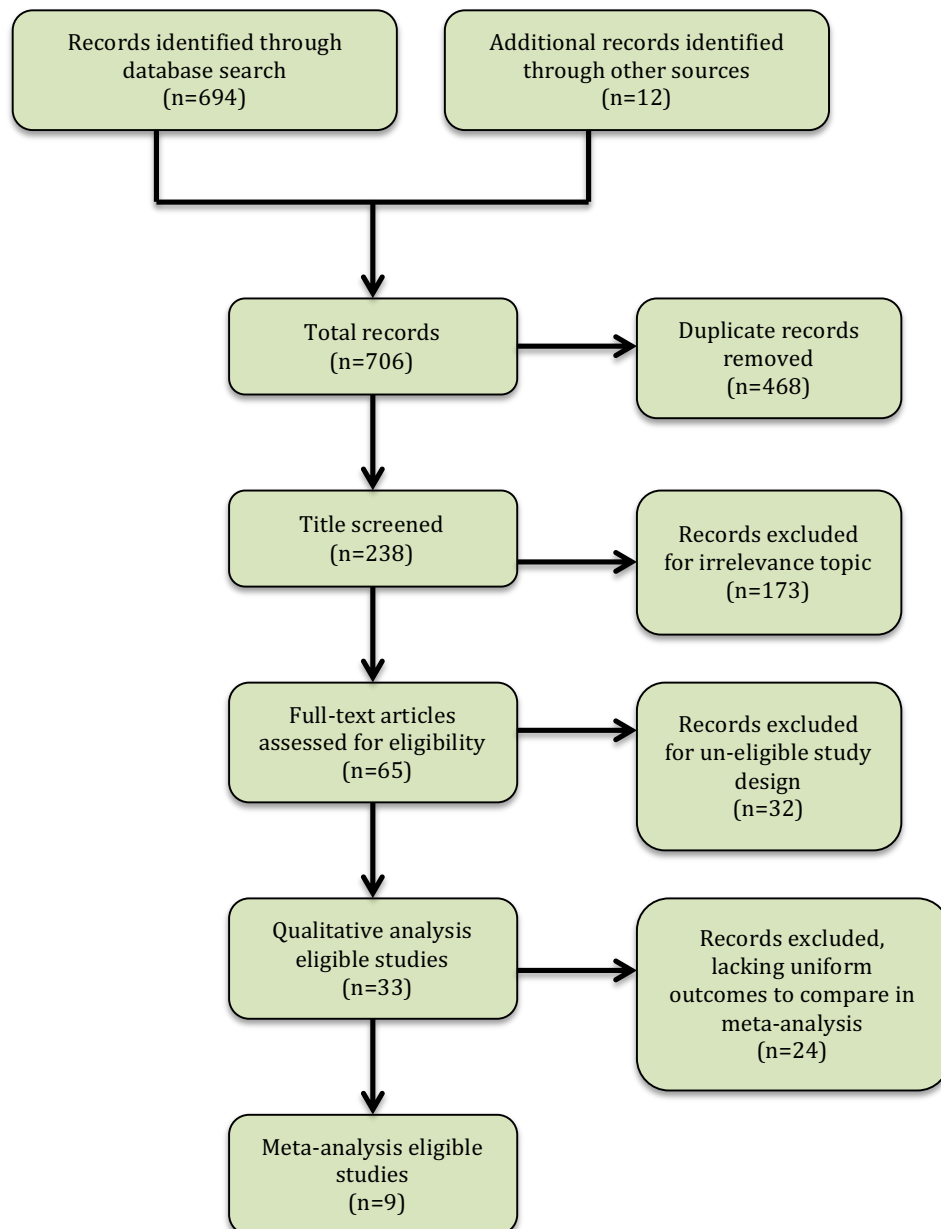


Figure 10. Risk of bias summary: each bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cummins 2003-IFN α	+	+	+	+	+	+	+
Devauch. 2014- rituximab	+	+	+	+	+	+	+
Drosos 1986-cyclosporin	?	?	+	+	+	+	+
Fife 2002-cevimeline	?	?	+	+	+	+	+
Gottenberg 2014- HC	+	+	+	+	+	+	+
Gravenmade 1993-stimulant	-	-	+	+	+	+	+
Hartkamp 2008-DHEA	?	?	+	+	+	+	+
Johansson 2001-substitute	?	?	+	+	+	+	+
Kasama 2008-nizatidine	?	?	?	?	?	?	?
Khurshudian 2003-IFN α	?	?	+	+	+	+	+
Klestov 1981-substitute	?	?	+	+	?	+	+
Kruize 1993-HC	+	+	+	+	+	+	+
Leung 2008-cevimeline	+	+	+	+	+	+	+
List 1998-acupuncture	?	?	-	-	-	-	-
Mariette 2004-infliximab	+	+	+	+	+	+	+
Marques 2011-stimulant	+	+	+	+	+	+	+
Meijer 2010-rituximab	+	+	+	+	+	+	+
Papas 1998-pilocarpine	+	+	+	?	+	+	+
Petrone 2001-pilocarpine	+	?	?	?	+	+	+
Pillemer 2004-DHEA	?	?	?	?	+	?	+
Price 1998-azathioprine	+	+	+	+	+	+	+
Reijde 1996-substitute	?	?	?	?	+	+	+
Sankar 2004-etanercept	+	+	?	?	+	+	+
Shiozawa 1998-IFN α	?	?	-	-	+	-	+
Ship 1999-IFN α	?	?	+	+	+	+	+
Singh 2010-Omega3	?	?	+	+	+	+	+
Steller 1988-electrostim	+	?	+	+	+	+	+
Sugai 2009-rebamipide	?	?	+	+	+	+	+
Talal 1992-electrostim	+	+	+	+	+	+	+
Theander 2002-GLA	?	?	?	?	+	?	+
Vivino 1999-pilocarpine	?	?	+	+	+	+	+
Wei 2014, shingjinrunzao.	+	+	+	+	+	+	?
Wu 2006-pilocarpine	+	+	+	+	+	+	+

Figure 11. Risk of bias graph: percentages across all included studies

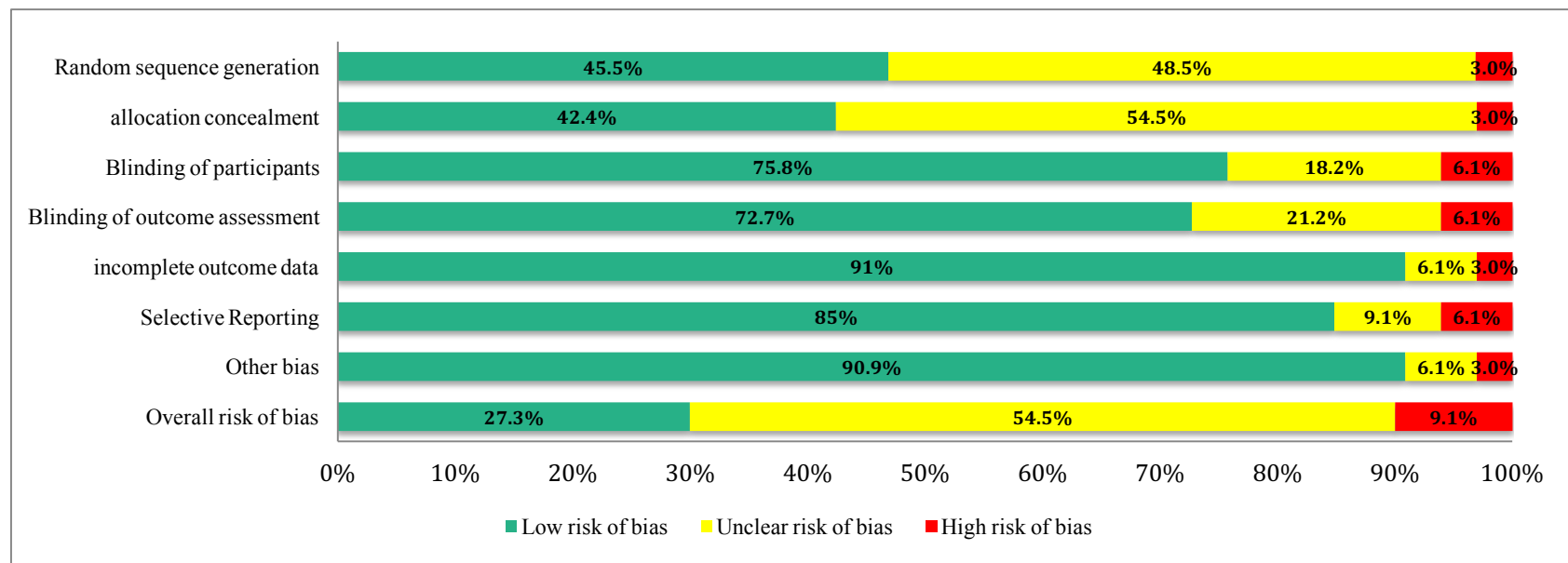


Figure 12. Forest plot. Primary outcomes: oral dryness VAS. (pilocarpine vs. placebo)- dichotomous data.

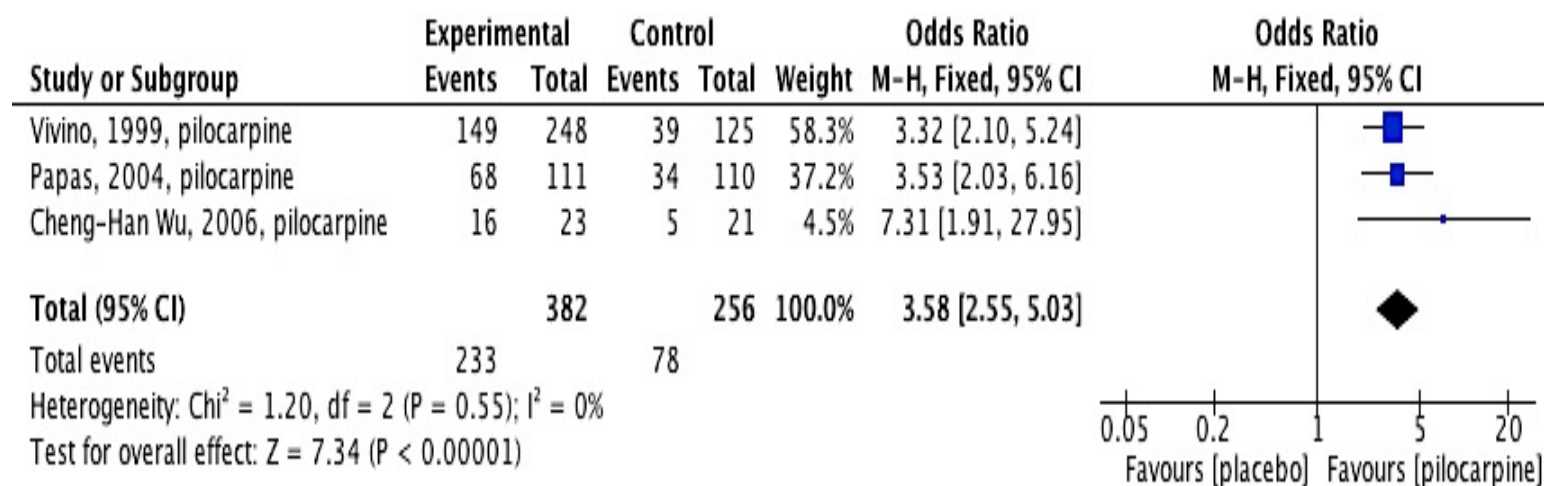


Figure 13. Forest plot. Primary outcome: oral dryness VAS. (cevimeline vs. placebo)- continues data.

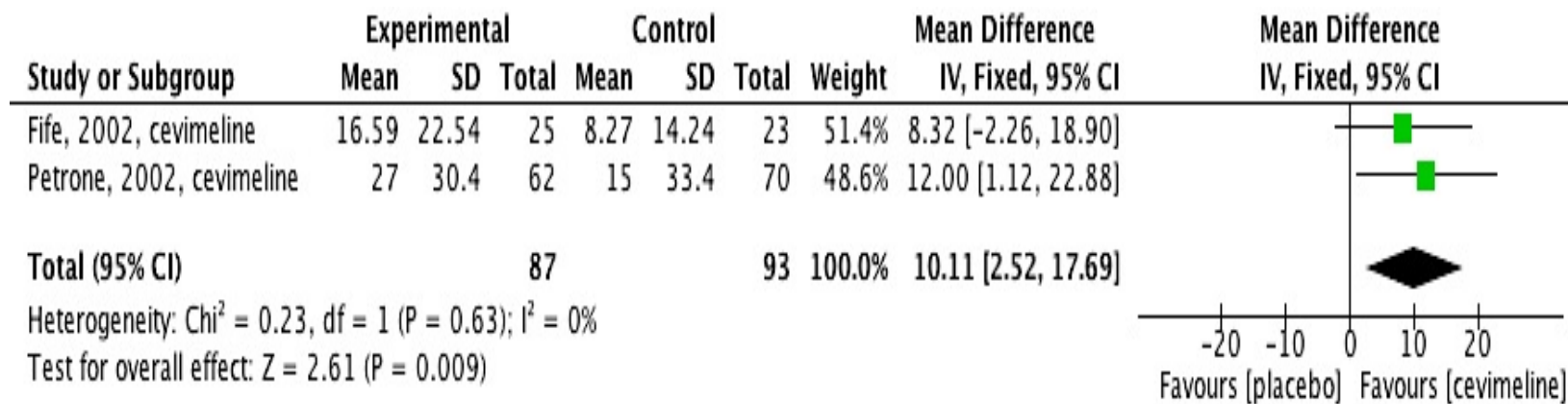


Figure 14. Forest plot Secondary outcome: unstimulated salivary flow ml/min. (electrostimulation, pilocarpine, cevimeline, biologic agents and Interferone- α vs. placebo)- continues data.

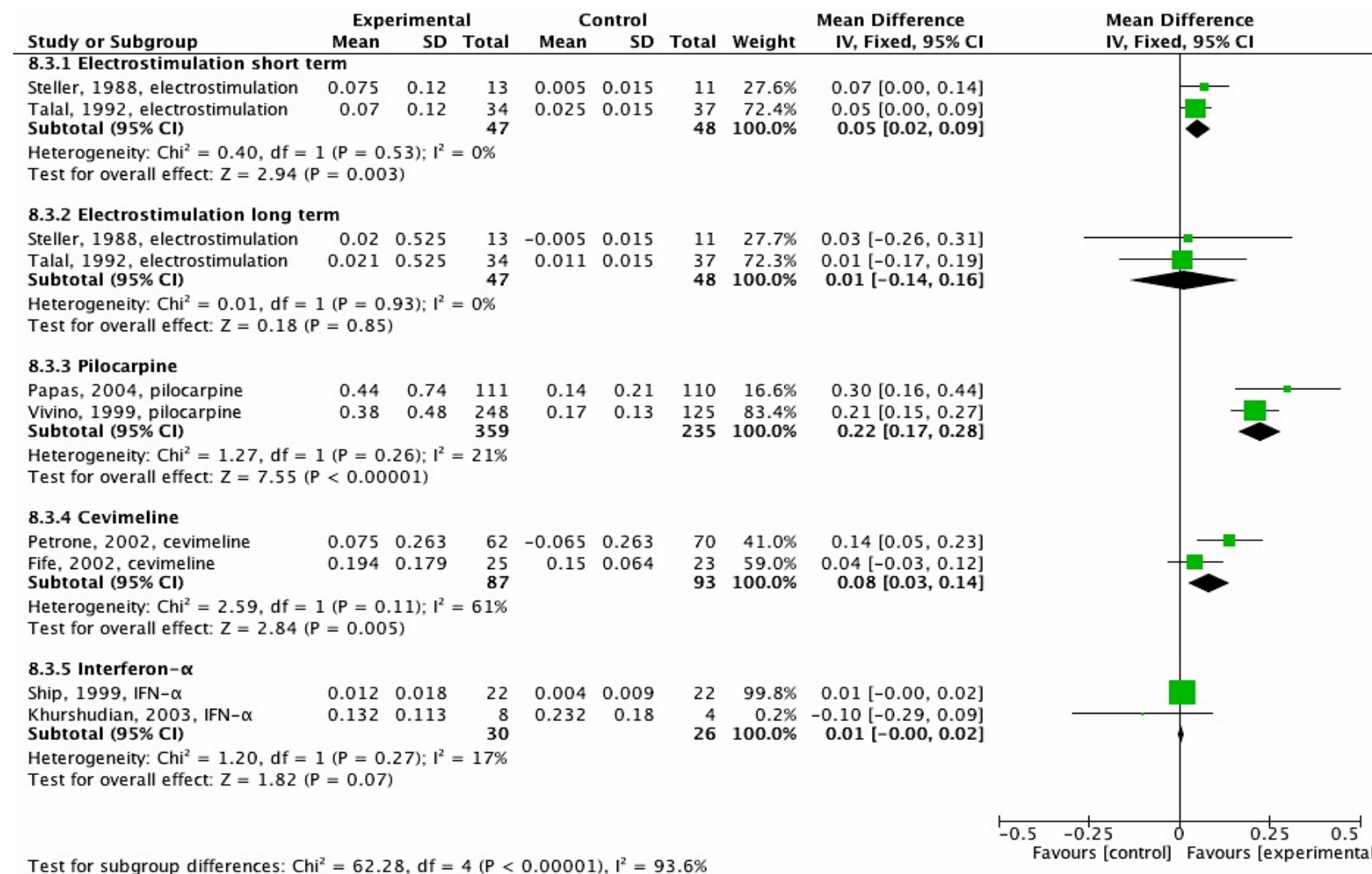


Table 20. Individual study characteristics.

Authors	Number of participants	Intervention	Dry mouth symptoms	Salivary function	Quality of Life	Bias risk	Included in the meta-analysis
SALIVA SUBSTITUTES vs PLACEBO OR ANOTHER SUBSTITUTE (N=3)							
Klestove	108	New developed salivary substitute vs glycerine mouthwash	Significantly more participants on the new salivary substitute vs glycerine mouthwash had less dry mouth at night. Effect size unknown. Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	N.A	N.A.	Unclear	No
van der Reijden (part 1)	43	Poly acrylic acid (PAA), Xanthan gum (XG) and Porcine gastric mucin (PM) vs placebo	No Significant difference in reduction of patient's symptoms between groups. Effect size unknown. No Clinical significance was seen between groups. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	sWSF was significantly lower in patients that preferred PAA compared to who preferred SO. Effect size unknown. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	Unclear	No
van der Reijden (part 2)	33	High Xanthan gum vs Low Xanthan gum	No significant difference in the efficacy of High and low XG. Effect size unknown. Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	Patients with a reduction in symptoms using LVXG had significant lower stimulated flow rate than patients with symptoms reduced using HVXG or reduced by both. Effect size: mean sWSF using LVXG was 0.093 ml/min (in general xerostomia) and 0.069 ml/min (in day time xerostomia). Clinical significance unknown. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A	Unclear	No

(Continue table 20)

Johansson	22	Salinum without chlorhexidine (SAL) vs Salinum with chlorhexidine (SAL/CHX)	Significant reduction in dry mouth symptoms in Sal ($P<0.05$) and Sal/Chx ($P<0.001$). Effect size unknown. Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	-No significant changes in uWSF. -Friction was reduced to normal in all nine patients (with elevated initial values) in the SAL group ($P<0.01$). And in the SAL/CHX group mirror friction was also reduced in 8 out of 10 participants ($P<0.05$). Effect size unknown. Clinical significance unknown. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A	Unclear	No
TOPICAL SALIVA STIMULANT vs ANOTHER STIMULANT OR PLACEBO (N=2)							
Gravenmade	42	Mucin lozenges vs placebo	Significantly more participants on mucin lozenges vs placebo reported a reduction in general complaints $P<0.001$. Effect size: mean change 1.7 vs 1 (on a five point scale) Clinical significance : 76% preferred mucin lozenges $P<0.001$. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	N.A	N.A.	High	No
Da Silva Marques	80	Malic acid gustatory stimulant vs citric acid gustatory stimulus	N.A	Significant short-term (20 minutes) increase in sWSF in both groups. Difference between groups was not significant. Effect size: unknown. Clinical significance unknown. Results refer to enhanced salivary flow (short-lived).	N.A.	Low	No

(Continue table 20)

CEVIMELINE vs PLACEBO (N=3)							
Petrone	197	Cevimeline vs placebo	<p>-Significant difference in patient's global evaluation of dry mouth. Effect size unclear (graphs only). Clinical significance favouring long-term use of cevimeline (66% responded better in the test group).</p> <p>-Significant difference in dry mouth VAS between Long-term use of cevimeline 30mg vs placebo. Effect size: mean -27.0 vs -15.0 ($P=0.038$). Results refer to enhanced salivary flow (60 min post dose) (short-lived).</p>	<p>Significant long-term change in uWSF 30mg vs placebo. Effect size unclear (graphs only). Clinical significance unknown. Results refer to enhanced salivary flow (90 min post dose) (short-lived).</p>	N.A.	Unclear	Yes
Fife	75	Cevimeline vs placebo	<p>-Significant difference in dry mouth favouring long-term use of cevimeline. Effect size unknown. Clinical significance favouring cevimeline (76% with cevimeline responded better).</p> <p>-No statistical significance found at endpoint in change in dry mouth VAS between 30mg cevimeline and placebo (short-term use) . Effect size: mean -16.59 vs -8.27. Results refer to enhanced salivary flow (60 min post dose) (short lived).</p>	<p>Significant higher change in mean uWSF in short-term use of cevimeline group compared to placebo. Effect size: mean 0.194 vs 0.015 ml/min. Clinical significance unknown. Results refer to enhanced salivary flow (short-lived).</p>	N.A	Unclear	Yes
Leung	50	Cevimeline vs placebo	<p>No statistical significance change in XI between groups. (long-term use) Effect size: mean -2.6 vs -0.9. Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.</p>	<p>No statistical difference in sWSF and parotid SF (long-term use). Effect size: mean change: uWSF: 0.04 vs -0.04 ml/min. Parotid: 0.03 vs 0 ml/min. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.</p>	<p>-No statistical significance change in GOHAI between groups (long-term use) Effect size: mean 1.4 vs -0.1.</p> <p>-SF-36 did not show any significance. Effect size unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.</p>	Low	No

(Continue table 20)

PILOCARPINE vs PLACEBO (N=3)							
Papas	256	Pilocarpine vs placebo	Significant (long-term use) improvement in oral dryness symptoms favouring pilocarpine. Effect size unclear (> 25mm on VAS). Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced (more likely) salivary flow.	Significant improvement in short-term use of pilocarpine post does uWSF rates. Effect size: unclear (figures only) Results represent acutely enhanced salivary function (30,60 and 90 min) post dosing (short-lived).	N.A	Unclear	Yes
Vivino	373	Pilocarpine vs placebo	Significant (long-term use) improvement in mouth dryness favouring pilocarpine. Effect size: unclear (> 25mm on VAS). Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced (more likely) salivary flow.	Statistical significance uWSF in the pilocarpine group (short-term use) in the 60 min post dose sample at end point. Effect size: mean 0.37 vs 0.17 ml/min. Results represent acutely enhanced salivary function (60 min) post dosing (short-lived).	N.A	Unclear	Yes
Wu	44	Pilocarpine vs placebo	Significant (long-term use) improvement in mouth dryness favouring pilocarpine. Effect size: unclear (> 25mm on VAS). Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced (more likely) salivary flow.	Significantly greater increase in uWSF in (short-term use) pilocarpine group. Effect size: median 0.05 vs -0.02 g/min Results represent acutely enhanced salivary function (60 min) post dosing (short-lived).	N.A	Low	Yes

(Continue table 20)

REBAMIPIDE vs PLACEBO (N=1)							
Sugai	104	Rebamipide vs Placebo	No significant difference seen in dry mouth between groups. Effect size: unclear (figure only) Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	No statistical difference seen between groups in the saxone test. Effect size: mean at end point 0.35 vs 0.17 g/2min. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	Unclear	No
ELECTROSTIMULATION vs PLACEBO (N=2)							
Steller	29	Active vs sham Electrostimulating device	Only five patients using the active device reported subjective slight increase in salivary flow. Effect size unknown. Clinical significance unknown.	-Significant increase in the post-stimulation uWSF (short-term use). -No statistical significance difference in pre-stimulation uWSF (long-term use) neither in the changes in uWSF. Effect size: mean change from week 0 to week 4: 0.15 vs 0.02 g/2min Clinical significance unknown. Results were measured to represent resting salivation and enhanced salivary flow (short and long lived results).	N.A.	Unclear	Yes
Talal	77	Active vs sham Electrostimulating device	No significance found in dry mouth symptoms. Effect size unknown. Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	Significant difference between active and placebo in post-stimulation uWSF (long-term). Effect size: mean difference in post-stimulation at week 4 is +0.190 g/2min. Clinical significance unknown. Results were measured to represent resting salivation and enhanced salivary flow (short and long lived results).	N.A.	Low	Yes

(Continue table 20)

ACUPUNCTURE vs NO TREATMENT (N=1)							
List	21	Acupuncture vs no treatment	No significant difference between groups on dry mouth VAS. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	No significant difference between groups in uWSF or sWSF. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	High	No
BIOLOGICAL AGENTS vs PLACEBO (N=4)							
Mariette	103	Infliximab vs placebo	No significant difference in dry mouth symptoms. Effect size: mean 22.2 vs 22.5. Results represent symptoms perceived during resting salivary condition.	No significant difference in WSF. Effect size: mean 0.05 vs 0.01 ml/min. Results represent resting salivary condition.	No significant difference in SF-36 between groups. Effect size: mean change <i>Physical component</i> 4.3 vs 2.2 <i>Mental component</i> 2.1 vs 4.9	Low	No
Sankar	28	Etanercept vs placebo	No significant difference in dry mouth symptoms. Effect size: median -2 vs 3. Results (more likely) represent symptoms perceived during resting salivary condition.	No significant difference in sWSF. Effect size: median -0.033 vs -0.22 ml/min. Results (more likely) represent resting salivary condition.	N.A.	Unclear	No
Meijer	30	Rituximab vs placebo	Significant difference in the mean change in VAS dry mouth scores between groups. Effect size: mean at week 48: 50 vs 69 Clinical significance unknown. Results represent symptoms perceived during resting salivary condition (long-term changes).	Significant difference in the mean change of sWSF at week 12 was found in between groups. Effect size: mean 0.87 vs 0.28 ml/min Clinical significance unknown. Results represent resting salivary condition (long-lived changes).	Significant improvement in SF-36 score (from baseline to week 36) in the test group. Effect size: mean at week 36: 60 vs 63 Results represent resting salivary condition.	Low	No

(Continue table 20)

Devauchelle	120	Rituximab vs placebo	No significant difference in VAS oral dryness. Effect size unclear (at least 30 mm improvement) Results represent symptoms perceived during resting salivary condition.	No significant difference in the mean change of UWSF. Effect size: at week 16: -0.01 vs -.03 ml/min. Results represent resting salivary condition.	No significant differences in the SF-36 between groups. Effect size: at week 16: <i>Physical component</i> 3.2 vs 2.2 <i>Mental component</i> 3.2 vs 0.8 Results represent resting salivary condition.	Low	No
IMMUNOMODULATORY/ IMMUNOSUPPRESSIVE AGENTS vs PLACEBO (N=8)							
Drosos	20	Cyclosporin A vs placebo	Significant improvement in dry mouth symptoms in the test group. Effect size unknown. Unclear whether results refer to symptoms perceived during resting salivation (more likely) or enhanced salivary flow.	No significant change in the parotid salivary flow. Effect size unknown. Unclear whether results refer to collection during resting salivation (more likely) or enhanced salivary flow.	N.A.	Unclear	No
Kruize	19	Hydroxychloroquine vs placebo	No improvement in dry moth symptoms in both groups. Effect size unknown. Unclear whether results refer to symptoms perceived during resting salivation (more likely) or enhanced salivary flow.	N.A	N.A	Low	No
Gotten	120	Hydroxychloroquine vs placebo	No significant change in dryness numerical scale between groups at week 24. Effect size: mean 6.22 vs 5.85. Unclear whether results refer to symptoms perceived during resting salivation (more likely) or enhanced salivary flow.	No significant change in uWSF between groups at week 24. Effect size: mean 0.22 vs 0.18 ml/min. Unclear whether results refer to collection during resting salivation (more likely) or enhanced salivary flow.	No significant change in dryness numerical scale between groups at week 24. Effect size: mean <i>Physical component</i> 54.5 vs 48.1 <i>Mental component</i> 63.1 vs 54.4 Unclear whether results refer to symptoms perceived during resting salivation (more likely) or enhanced salivary flow.	Low	No

(Continue table 20)

Price	25	Azathioprine vs placebo	No significant difference in dry mouth VAS. Effect size: mean at end point 72.8 vs 78 Unclear whether results refer to symptoms perceived during resting salivation (more likely) or enhanced salivary flow.	No significant difference in uWSF. Effect size: mean at end point 0.3 vs 0.2 ml/5min Unclear whether results refer to collection during resting salivation (more likely) or enhanced salivary flow.	N.A.	Low	No
Shioza	60	Interferon- α vs Sucralfate	N.A.	Significant difference in the mean change from baseline between groups (long-term use). Effect size: mean change: 0.50 vs -0.10 g/2 min Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	High	No
Ship	109	Interferon- α vs placebo	No significant difference in dry mouth VAS. Effect size unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	-No significant difference in uWSF. -Significant difference in sWSF at week 12. Effect size: mean 0.79 vs 0.06 g/min Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	Unclear	No
Khurshud	12	Interferon- α vs placebo	Significant improvement in dry mouth VAS at week 24 in the test group only (long-term use). Effect size: mean at week 24 46 vs 35.7 Clinical significance unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	Significant improvement in uWSF at week 24 in the test group only (long-term use). Effect size: mean at week 24 0.242 vs 0.176 ml/min Clinical significance unknown. Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	Unclear	No
Cummins	497	Interferon- α vs placebo	No improvement in dry mouth VAS. Effect size unknown. Unclear whether results refer to symptoms perceived during resting salivation or enhanced salivary flow.	-No significant difference in sWSF between groups -Significant difference in uWSF between groups(long-term use). Effect size: ACNOVA on mean (week 24) 252.2 vs 244.2 gm/5min Unclear whether results refer to collection during resting salivation or enhanced salivary flow.	N.A.	Low	No

(Continue table 20)

OTHER AGENTS/COMPOUNDS (N=6)							
Theander	90	Gammalinolenic acid vs corn oil	No significant improvement in dry mouth VAS. Effect size unknown. Unclear whether results refer to symptoms perceived during resting salivation (most likely) or enhanced salivary flow.	No significant improvement in uWSF. Effect size: median 0.4 vs 0.1 ml/15 min Unclear whether results refer to collection during resting salivation (most likely) or enhanced salivary flow.	N.A.	Unclear	No
Pillemer	28	Dehydroepiandrosterone vs placebo	Significant improvement in dry mouth VAS in test group. Effect size: change in mean 9 vs -10. Clinically meaningful unclear (author reports improvement was not clinically meaningful) Unclear whether results refer to symptoms perceived during resting salivation (most likely) or enhanced salivary flow.	No significant improvement in sWSF. Effect size: median 0.086 vs -0.09 ml/5 min. Unclear whether results refer to collection during resting salivation (most likely) or enhanced salivary flow.	N.A.	Unclear	No
Hartkamp	60	Dehydroepiandrosterone vs placebo	Both groups had significant improvement in dry mouth. Effect size unknown. Timing of outcome unclear.	N.A.	N.A.	Unclear	No
Kasama	27	Nizatidine vs famotidine	Significantly more participants in the test group had an improvement in global assessment of xerostomia at week 8 (long-term use). Effect size unclear (20% improvement in VAS). Clinical significance unknown. Timing of outcome unclear.	Significant improvement in Saxon's test at week 8, in the test group only (long-term use). Effect size: mean at week 8 0.90 vs 0.71 g/2min Clinical significance unknown. Timing of outcome unclear.	N.A.	Unclear	No

(Continue table 20)

Singh	61	Omega-3 and Vitamin E supplements vs wheat germ oil	No significant difference in dry mouth VAS seen between groups. Effect size unclear. Timing of measurement unclear.	No significance in difference in uWSF at month 3. Effect size: mean 0.064 vs 0.029 ml/min. No significance in difference in sWSF at month 3. Effect size: mean 0.242 vs 0.101 ml/min. Timing of measurement unclear.	N.A.	Unclear	No
Hu	240	ShengJinRunZao YangXue vs placebo	Significant difference in dry mouth NRS between groups at week 6. Effect size: mean 0.83. Clinical significance unknown Timing of measurement unclear.	No significant difference in WSF between groups at week 6. Effect size: mean 0.04 ml/15min. Timing of measurement unclear.	N.A.	Unclear	No

Chapter Three:

Study Aim, Patients and Methods

3.1 Knowledge gap and research need

The use of intra-oral second-generation devices may represent an ideal therapeutic strategy for individuals with SS-induced dry mouth. The device sits comfortably in the patient's mouth and can be easily applied and removed; it stimulates natural salivation with no notable adverse side effects; and there is even some suggestion that electrostimulation may also have cumulative and trophic effects on glandular parenchyma (Schneyer et al. 1993).

As discussed previously the evidence supporting its efficacy is however limited. More importantly, the design and overall quality of published clinical trials is debatable.

As a consequence it remains unclear whether the second-generation intraoral electrostimulating device is indeed effective in providing (i) long-term reduction in dry mouth symptoms and (ii) increase of salivary flow. It is also unknown whether it could lead to a significant improvement in quality of life. Finally, the magnitude of any potential benefit is also unclear.

3.2 Trial design

LEONIDAS-1 (Long-term Effectiveness Of a Novel Intra-oral electro-stimulator for the treatment of Dry mouth in Patients with Sjögren's Syndrome) is a feasibility multicentre randomised double-blind trial of 6 months therapy. It was followed by a 6 month uncontrolled phase aimed at investigating long-term effectiveness.

3.2.1 Hypothesis

The study tested the hypothesis that long-term application of the removable intraoral electrostimulation device will:

- 1) Reduce dry mouth symptoms (i.e. reduction in dry mouth VAS score)
- 2) Improve salivary function (i.e. an increase of resting salivary flow rates)
- 3) Improve quality of life in individuals with dry mouth due to SS.

We also investigated whether adaptation mechanism would reduce its beneficial effect over time.

3.2.2 Study aim

The main objective of LEONIDAS-1 was to obtain preliminary data regarding the effectiveness of this new intra-oral removable device for the long-term relief of distressing symptoms of reduced salivation (xerostomia) resulting from SS.

3.2.3 Primary objective

That long-term (6 months) application of the removable electro-stimulation device will reduce dry mouth symptoms (primary outcome). The hypothesis was addressed through comparisons of outcomes between patients randomised to an active device (releasing electronic stimuli) and a device that is not active (determining mechanical/tactile stimulation only).

3.2.4 Secondary objectives

To ascertain whether the device also improved salivary function. The device's frequency of use by patients and their acceptability of the intervention were also determined.

3.2.5 Randomisation and blinding

3.2.5.1 Sequence generation

A blocked random list, which allocated the patient identification numbers to the specific type of stimulation was prepared by an independent study coordinator (central randomisation at Leeds clinical trial unit) see figure 15 and figure 16. The method of sequence generation was a random-number generator on a computer. The randomisation code was disclosed only at the end of the trial after statistical analysis.

3.2.5.2 Allocation concealment

Allocation concealment, was aimed at keeping clinicians and participants unaware of upcoming assignments, this was guaranteed as the computer-generated list was prepared and maintained by the independent study coordinator based at a different study centre. The independent study coordinator had no contact with the patients and had undertaken the randomisation, allocated the study devices, and held the trial codes which was disclosed only after the termination of the study and completion of the statistical analysis.

3.2.5.3 Implementation

The 'implementation process', consisting of enrolling participants and assigning the next available study number, has been performed by clinical researchers at the clinical centres, who had no contact with the individual responsible for sequence generation.

3.2.5.4 Blinding

The study is a double-blind controlled randomised trial, during which patients have been randomly assigned to electrical or sham tactile stimulation (e.g. controls used a device that does not release electricity but provides tactile stimulation only). Neither clinical investigators nor participants knew which devices are active and which are not. The double-blind design was feasible as (1) the computer-based randomisation was performed in a centre other than the clinical centre and remained blinded to the clinicians, (2) the electronic stimulus was completely asymptomatic and the patients could not possibly realise whether or not they were using an active or sham device.

**Figure 15. Recruitment Form
(Eastman Dental Institute –
University College Hospital)**

Centre 1: UCL/UCLH				
Randomisation Number (Send this information to the laboratory along with the impression)	Participant's initials	Screening number (From CRF)	Staff member recruiting the participant (Sign)	Date
UCL1				
UCL2				
UCL3				
UCL4				
UCL5				
UCL6				
UCL7				
UCL8				
UCL9				
UCL10				
UCL11				
UCL12				
UCL13				
UCL14				
UCL15				
UCL16				
UCL17				
UCL18				
UCL19				
UCL20				
UCL21				
UCL22				
UCL23				
UCL24				
UCL25				

Figure 16. Recruitment Form
(Birmingham Dental Hospital)

Centre: Birmingham				
Randomisation Number (Send this information to the laboratory along with the impression)	Participant's initials	Screening number (From CRF)	Staff member recruiting the participant (Sign)	Date
BIR1				
BIR2				
BIR3				
BIR4				
BIR5				
BIR6				
BIR7				
BIR8				
BIR9				
BIR10				
BIR11				
BIR12				
BIR13				
BIR14				
BIR15				

3.3 Endpoints

3.3.1 Primary endpoints

1. Reduction of dry mouth symptoms as evaluated through a 0-100 mm VAS (Appendix 2) between baseline and end of trial.
2. VAS scores of dry mouth symptoms recorded during treatment. This was evaluated at baseline, 1 month, 3 months and 6 months.
3. Reduction of Xerostomia Inventory (XI) (Appendix 3) and questionnaire scores recorded at baseline and end of the trial.
4. Reduction of EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (Appendix 4) recorded at baseline and end of the trial.
5. XI and ESSPRI questionnaire scores during the treatment (on the basis of serial measurement recorded during patients' appointments).

3.3.2 Secondary endpoints

1. Changes in salivary flow (recorded via standardized sialometry) at baseline and end of the trial.
2. Salivary flow during the treatment (on the basis of serial measurement recorded during patients' appointments).
3. Intervention compliance and acceptability as recorded in the Patient diary.

3.3.3 Exploratory analysis

1. Changes between baseline and month 12 on the VAS, XI, ESSPRI questionnaire and salivary flow scores was explored.

3.4 Endpoint analysis

The effect of treatment over time on the VAS scores, salivary flow, the XI and ESSPRI scores was examined graphically using individual patient response profiles and overall mean profile plotted against time, estimated using regression, to assess the relative patterns of response between active and placebo (non-active device) groups.

Summary statistics for reduction from baseline to 6 months and scores at each time point was presented by treatment arm from VAS scores, salivary flow, XI and ESSPRI.

An exploratory analysis of data collected during the open-label phase up to 12 months was undertaken. This analysis was restricted to patients at UCL for which the data were recorded. As this is an exploratory analysis the differences and 95% CIs of the changes from baseline are quoted but no formal tests were completed.

3.5 Patients

After obtaining a favourable ethical approval on the 13th January 2012 (REC reference 11/YH/0423) from the NRES committee Yorkshire and the Humber – Sheffield, patients with pSS were invited to a screening visit in the Eastman Clinical Investigational Centre (ECIC), they were provided with a patient information sheet at the oral medicine clinic at the Eastman Dental Hospital (EDH) or at the Rheumatology clinic at the University College London Hospital (UCLH).

Other subjects contacted EDI after the posting of an advert about the trial on the British Sjögren's Syndrome Society website and including it in its newsletter.

A screening appointment was arranged to answer and clarify any issues that patients might have, explain the trial in detail, show patients a model of the device and insure that patients are diagnosed with pSS according to the 2001 EU-USA classification criteria.

Inclusion criteria (Appendix 5)

- Subjects being ≥ 18 years old.
- Have clinical symptoms of xerostomia (dry mouth) due to primary SS syndrome diagnosed on the basis of 2001 EU-USA classification criteria.
- 50 mm minimum degree of dryness on a 100 mm VAS scale.
- Unstimulated salivary flow higher than 0 ml/15min.
- Evidence of residual salivary function by having an increase in salivary flow with proper stimulation using a piece of parafilm wax during saliva collection for 15min.
- No sialogogue therapy during the study.

- Not to be pregnant or trying to have children.

Exclusion criteria

- Severe systemic disease (on the basis of the classification of the American Society of Anaesthesiology: ASA 3 or more).
- Known allergy to materials similar to those used in the investigational product.
- Wearing of other active implants such as cardiac pacemaker, defibrillator, or hearing aids.
- Unstimulated whole salivary flow of 0ml/15min (complete absence of unstimulated salivary flow as measured via sialometry for 15 minutes).
- To have evidence of no residual salivary gland function (via citric acid stimulation or chewing paraffin wax test).
- Use of pilocarpine as systemic sialogogue therapy.
- Pregnant or trying to become pregnant.

Subsequently, after subjects fulfilled the inclusion criteria and where happy to take part in the study, they were asked to sign three copies of the consent form (1 copy to patient, 1 copy to clinical notes, 1 copy added to the case report form (CRF)) and sign all pages of patient information sheet with their initials.

3.6 Intervention

Electrostimulating devices had been manufactured for each participant using impressions taken from the lower dental arch. Participants have been randomly assigned to either:

- Group A (cases): patients who received a fully functioning electrostimulating device. or

- Group B (controls): patients who received a device that did not release electric stimuli (but provided mechanical/tactile stimulation).

The general structure of experimental procedures consisted of: (Appendix 6)

A: Screening/Enrolment

B: Impression

C: Delivery of individualised device at start of experimental treatment

D: Follow-up (end of month 1, 3)

E: Study closure and end of randomised part at month 6

F: Uncontrolled visit at month 12

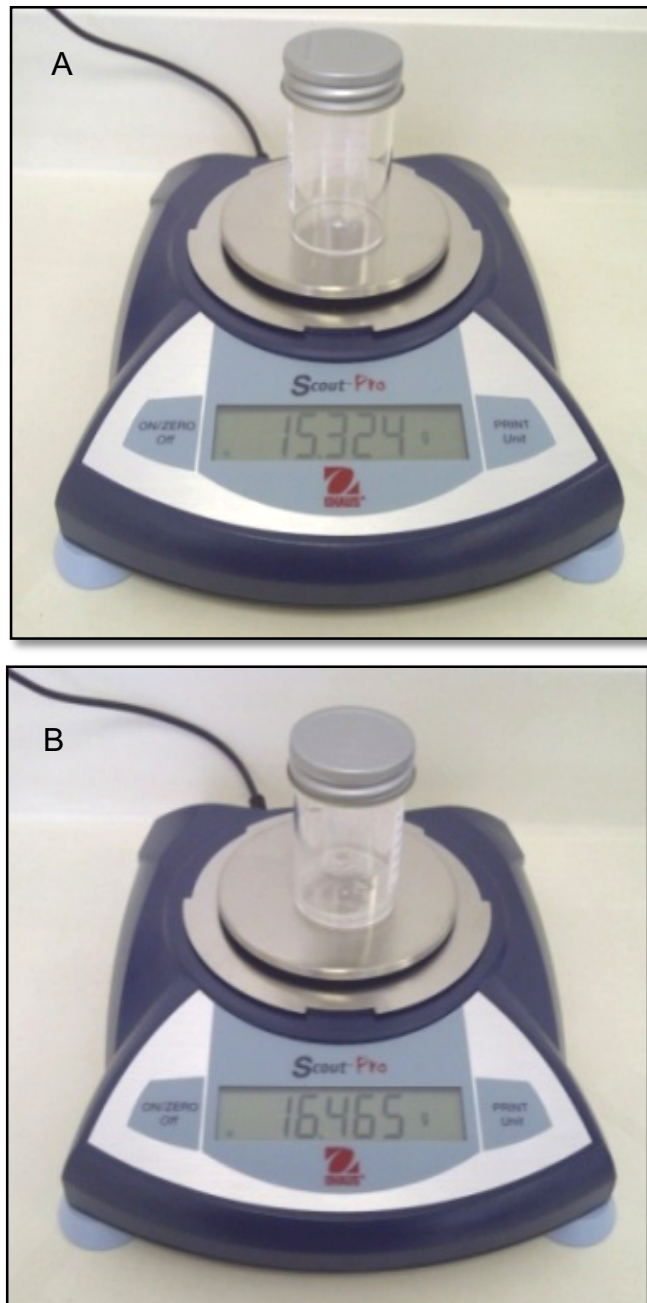
3.6.1 Screening/ enrolment

Potential participants identified during routine clinical sessions were invited to attend an initial screening appointment, which included collection of detailed information on SS. A dedicated Case Report Form was used to gather clinical data. The forms have been stored at the UCL (EDI), London, UK and Birmingham Dental Hospital in locked facilities.

As the device was designed to stimulate the salivary glands, only patients with demonstrated residual salivary gland function capable of a significant response to stimuli were included. For this purpose, unstimulated and stimulated (after the patient has chewed paraffin wax for 15 minutes) whole saliva was collected and measured gravimetrically using pre-weighted tubes (Sterilin, UK, catalog n.185CM) and a precision balance (Scout Pro SPU123, Ohaus, NJ). Salivary flow rates was measured via standardised sialometry: participants were asked

to (i) avoid eating and drinking for 90 minutes before the measurement, and (ii) to collect saliva for 15 minutes into pre-weighted tubes (Figure 17).

Figure17. Sialometry steps. (A) Weigh empty pot. (B) Weigh pot with saliva.



All assessments were performed at a fixed time of the day to minimise fluctuations related to the circadian rhythm of salivary secretion. The grade of

dry mouth symptoms was also assessed using the dedicated XI / SSPRI and dry mouth VAS score.

When entry criteria was satisfied, patients were provided with the relevant Patient Information Sheet (Appendix 7) and given all the time they needed to consider participation, ask further questions and provide written consent (Appendix 8).

3.6.2 Impression and manufacturing

A dental impression using polyvinylsiloxane material (Figure 18) was taken by one of the clinical investigators and shipped to Saliwell Ltd for device manufacturing.

Figure 18. Lower arch impression taken



3.6.3 Delivery of individual device

On the insertion appointment, the device was taken out of its packaging (Figure 19) and inspected visually and manually for any sharp edges (Figure 20). When the safety was insured, the device was inserted by a clinician and seated on the lower arch. Participants were asked if they had any issues with comfort or if any part of the device gave rise to any pain. If an area of discomfort was present due to flanges of the acrylic being too long, an acrylic bur on a low-speed hand piece was used to trim and smooth flanges until participant was happy (Figure 21. A). In cases where the electrodes were impinging on the oral mucosa, the electrodes were shortened and smoothed until comfort was insured. It was explained to patients that electrodes should touch but not injure the mucosa for the device to stimulate the lingual nerve (Figure 21. B).

After insuring comfort, participant was asked to hold a mirror to observe clinician when inserting and taking the device out. Afterwards the participant was instructed to insert the device by taking the side with the electrodes in first, then seating the rest of the device. Afterwards participant was instructed to take it out.

Participants were asked if they were confident in inserting the device and if they needed to practice more or had any questions. Participants were instructed to contact the clinician whenever they had any complaints so they could be seen in clinic to address any issues.

Figure 19. Electrostimulation device + Remote control



Figure 20. Electrostimulation device to be inspected for any sharp edges

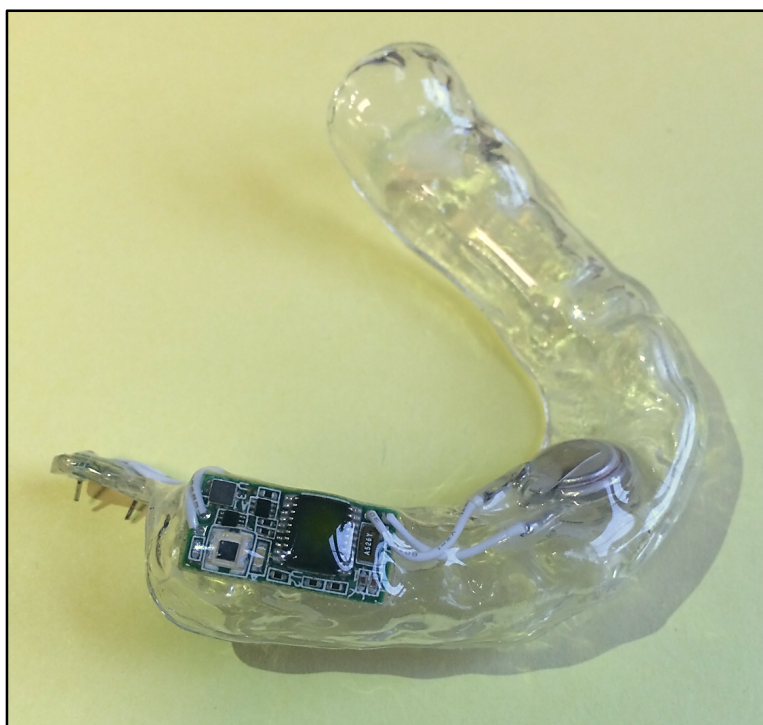
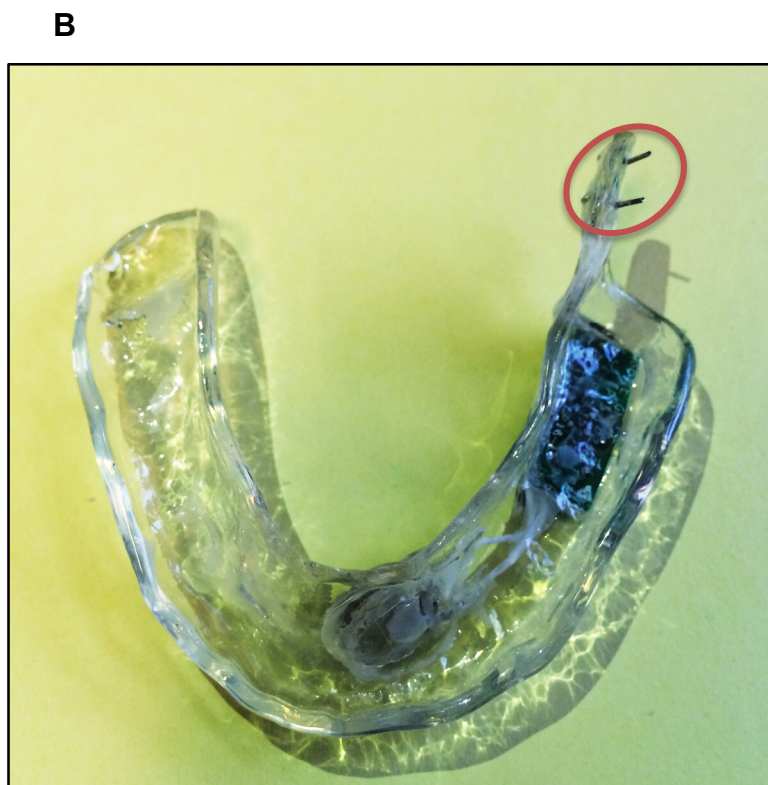
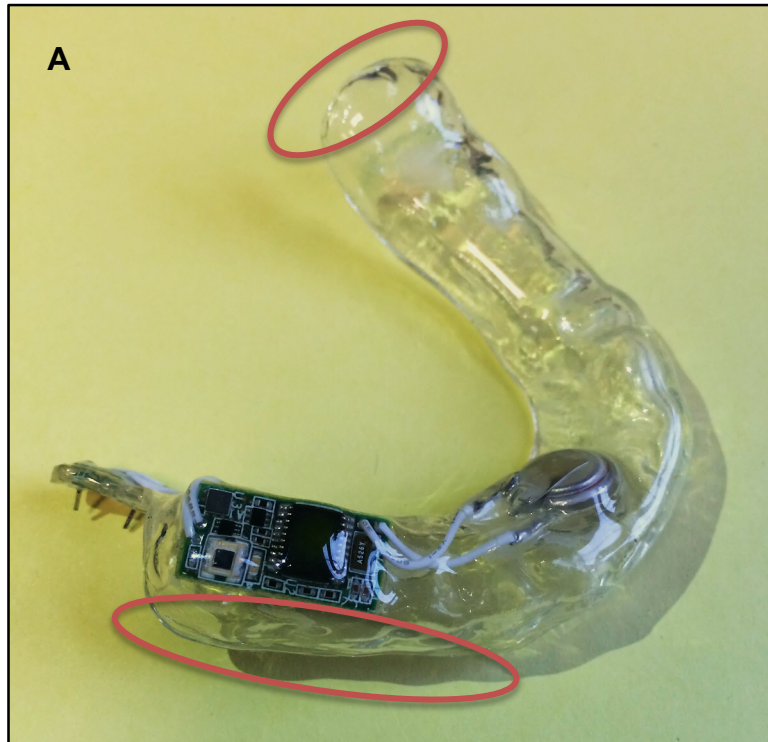


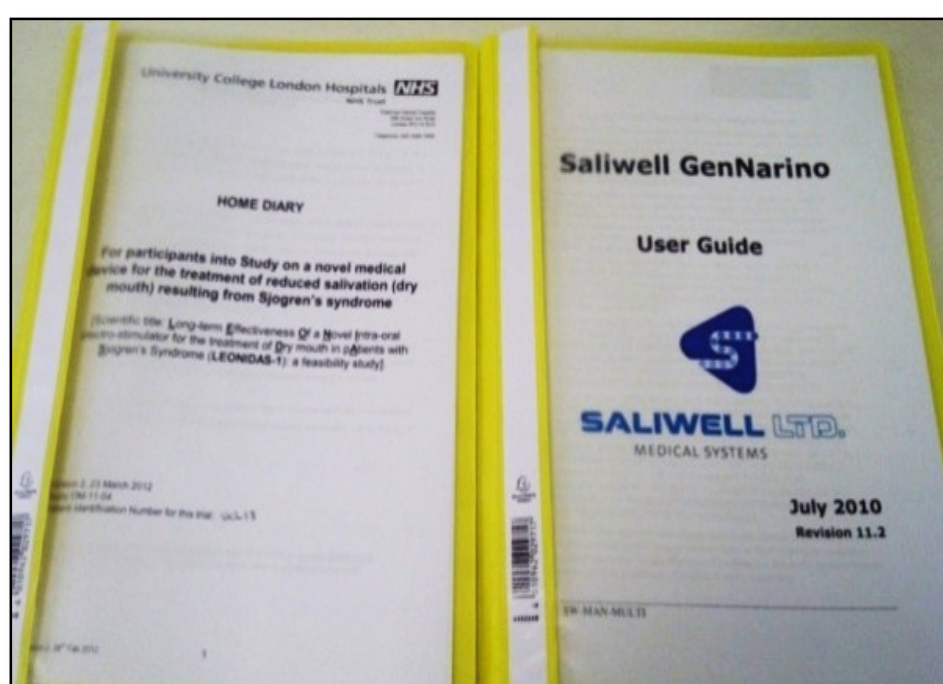
Figure 21. Areas of possible adjustments on electrostimulating device

(A) Too long acrylic flanges. (B) Sharp electrodes impinging the oral mucosa.



Participants were informed and trained by the clinical investigators regarding the modality of use of the device during the study period. Patients were asked to use the device with a frequency of 5 minutes/hour, as many times as they wanted during the day. Participants received a 'guide for user' and were asked to complete a diary of the frequency of application of the device per day (Figure 22) (Appendix 9).

Figure 22. Home diary and User guide



3.6.4 Follow-up

After the delivery of the individualised device to the patient (baseline), follow up visits and relevant study measurements were scheduled at 4 time points: end of the 1st, 3rd, 6th, 12th months. Measurements included dry mouth VAS score, XI and ESSPRI and sialometry. As safety-related secondary outcome measures, vital signs, changes in health condition and oral mucosal status were assessed. Any oral mucosal abnormality or oral discomfort caused by the electrostimulating device was also recorded.

3.7 Statistical analysis

Statistical support and supervision of this study was provided by a dedicated statistician at CTRU. Changes in the effect of treatment over time on the VAS scores, salivary flow and the XI scores was initially examined graphically using individual patient response profiles plotted against to assess the relative patterns of response between active and placebo groups. In doing so, the optimal timing of the primary outcome was judged. The difference in proportions achieving a reduction in xerostomia was estimated and adjusted for baseline score, to assess the possible size of difference that was achieved with the device and to inform sample size calculations for a larger study. For the secondary outcomes of salivary flow as measured by sialometry, data was compared between groups at the final visit using an analysis of covariance (ANCOVA) to control for any potential baseline differences. Adjusted mean differences and associated 95% confidence intervals was calculated. Rates of recruitment and compliance will be summarised and used to plan a larger study.

Chapter four:

Results

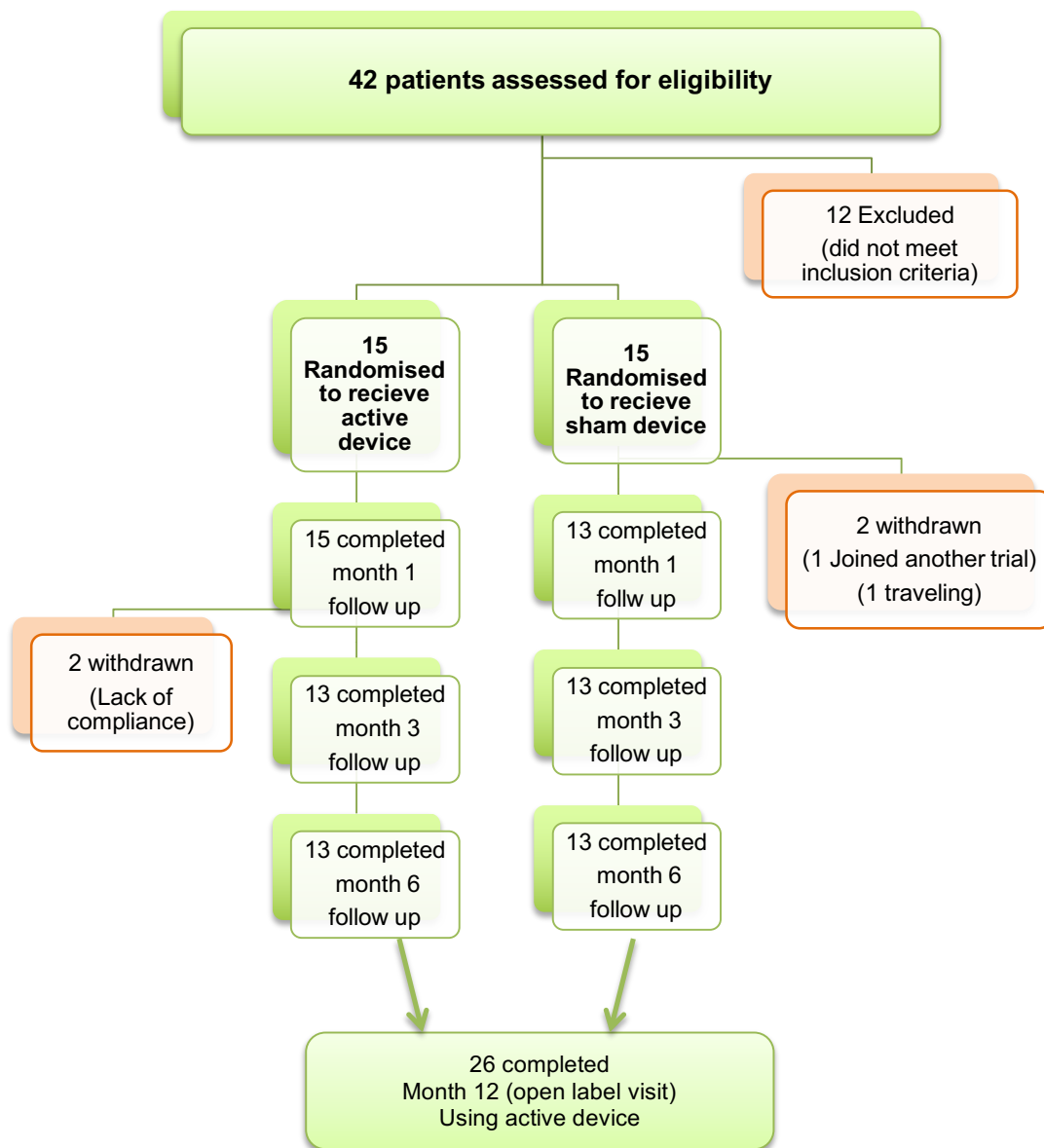
4.1 Feasibility and Demographics

Two study sites (UCLH and Birmingham University) recruited participants. Forty-two patients with pSS-induced xerostomia were screened and 30 were recruited on the basis of the inclusion and exclusion criteria (screening/recruitment ratio: 42:30), 12 patients did not meet entry criteria (Table 21) and (Figure 23). The 30 participants were recruited over 11 months (recruitment rate: 2.7/month). Acceptability to participate and to be randomised was 100%, as no eligible participants decided not to participate. The drop out rate was 13.3% (4/30). Reasons for drop out were: perceived no benefit (n=2), travelling abroad (n=1), and joined another trial (n=1). Twenty-six participants thus completed the study. The majority of participants (93%) were females. The mean age was 61.6 years (range 31 to 82 years). No adverse side effects were noted.

Table 21. Study demographics and baseline measurement

	Active	Sham	Total
Number of participants	15	15	30
Mean age	64.8	56.3	61.6
Number of males	0	2	2
Number of withdrawals	2	2	4
VAS¹ (mean, sd)	7.4 (1.8)	7.5 (1.5)	7.5 (1.6)
Sialometry² (mean, sd)	0.68 (0.61)	0.69 (0.88)	0.68 (0.74)
XI³ (mean, sd)	47.3 (6.5)	45.4 (6.1)	46.4 (6.3)
ESSPRI⁴ (mean, sd)	8.4 (1.4)	8.3 (1.1)	8.3 (1.2)
¹ Dry mouth visual analogue scale. ² Sialometry (ml/15min). ³ Xerostomia inventory questionnaire. ⁴ The European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index.			

Figure 23. Study flow chart



4.2 Outcome results

The median use of the device was 3 times/day in both active and sham groups.

The range was 0-11 times/day in the active group and 0-10 times/day in the sham group. Table 22 details the outcome results baseline vs. month 6 visit and Table 23 details the outcome results through study visits.

Table 22. Clinical assessments: baseline and at month 6 (controlled part of trial)

	Mean VAS ¹ (cm)		Mean Sialometry (g/15min)		Mean XI ²	
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6
Sham	7.5	7.3	0.69	0.75	45.4	45.3
Active	7.4	6.9	0.68	1.9	47.3	43.5

¹ Dry mouth visual analogue scale. ² Xerostomia inventory questionnaire.

Table 23. Clinical assessment trends during follow up visits.

			Controlled visits results			Uncontrolled visit results
			Baseline	Month 1	Month 3	Month 6
VAS ¹ (cm)	Sham	7.5	7.7	7.3	7.3	7.5
	Active	7.4	6.8	6.3	6.9	7.1
Sialometry (g/15min)	Sham	0.69	0.56	0.56	0.75	0.5
	Active	0.68	1.1	1.4	1.9	2.4
XI ²	Sham	45.4	44.9	45.5	45.3	45.5
	Active	47.3	45.5	43.6	43.5	43.1

¹ Dry mouth visual analogue scale. ² Xerostomia inventory questionnaire.

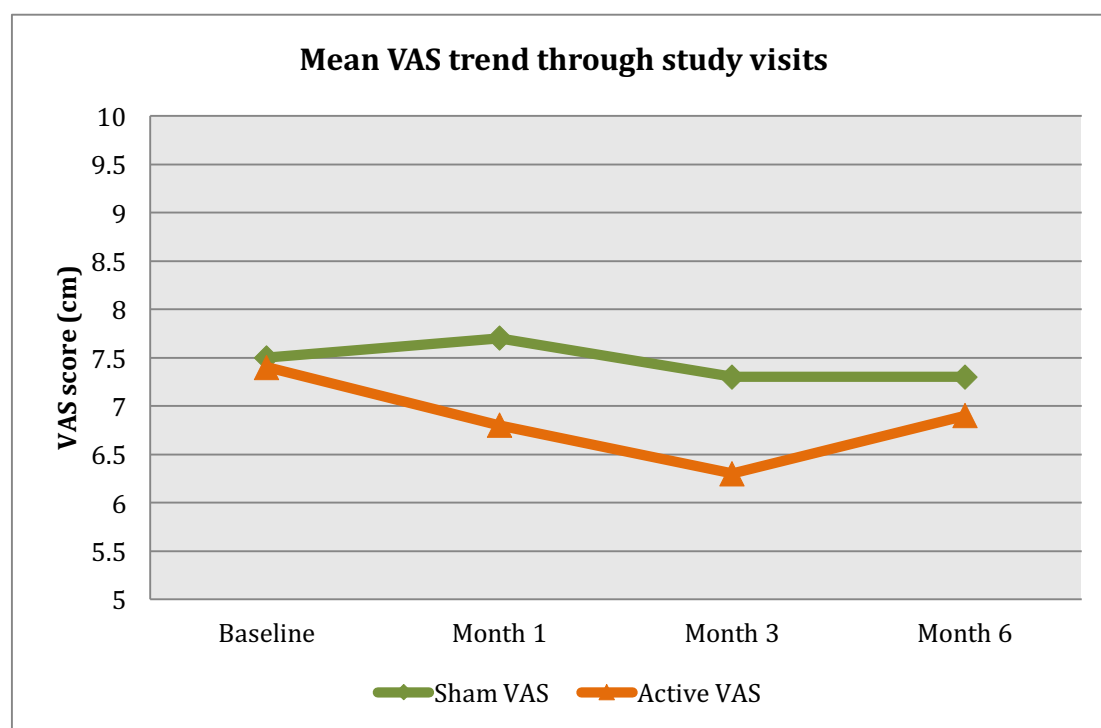
4.2.1 Visual analogue scale (VAS)

There was no obvious pattern of response for the (dry mouth) VAS. There was an initial reduction in VAS in the active group with a maximum reduction at 3 months. By 6 months the gap between the groups had almost closed. The mean difference between the groups in VAS change at 6 months was -0.3 (95% CI -2.8 to 2.1) (Table 24) (Figure 24). VAS had an effect size of 0.24 (P=0.54). This gap was further reduced in the open-label period up to 12 months.

Table 24. VAS Two –sample t test (month 6).

Group	Mean	Std. Err.	Std. Dev.	95% Conf. Interval	
Active	- 0.7230769	0.4603725	1.659897	-1.726142	0.2799885
Sham	- 0.3615385	0.355459	1.281626	-1.136017	0.4129401
Difference	- 0.3615384	0.5816304		-1.561965	0.8388876

Figure 24. Mean VAS by group



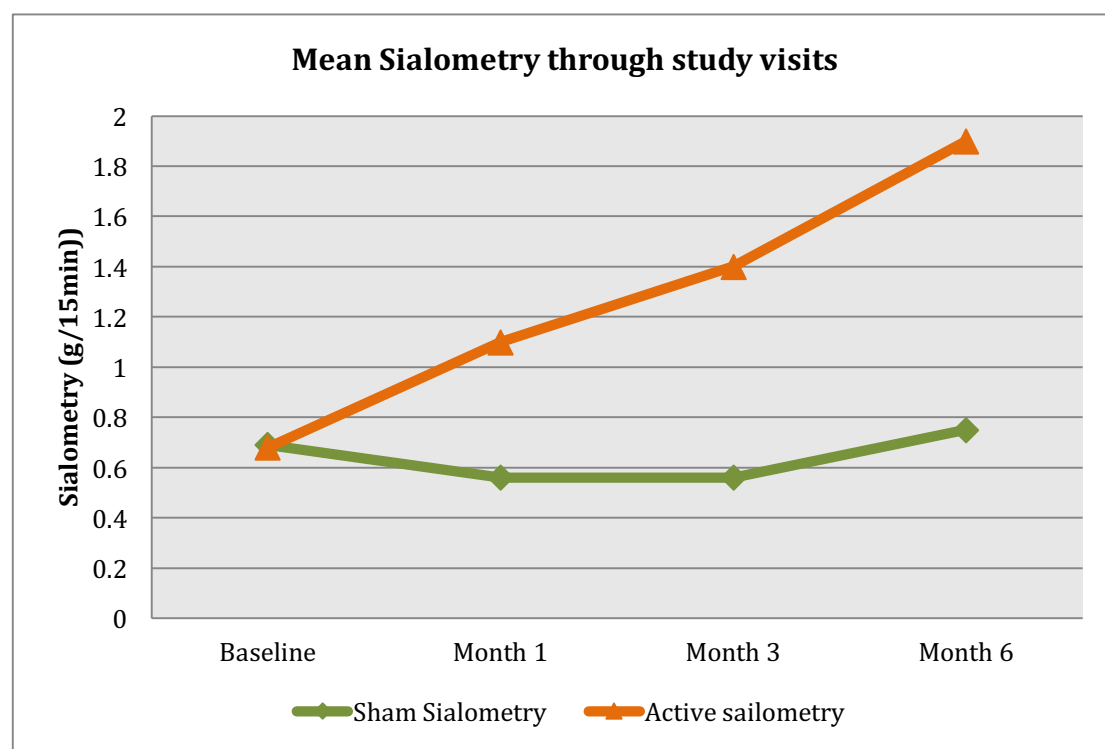
4.2.2 Sialometry

There was an increase in salivary flow rate in the active group at 6 months being 1g/15 min higher (95% CI -0.5 to 2.4 g/15 min) (Table 25) (Figure 25) and effect size 0.54 ($P=0.17$). The mean difference between the groups in sialometry change at 12 months is 1.7 (95% CI -0.5 to 3.9).

Table 25. Sialometry Two –sample t test (month 6).

Group	Mean	Std. Err.	Std. Dev.	95% Conf. Interval	
Active	1.214385	0.6898906	2.487436	- 0.2887579	2.717527
Sham	0.2329768	0.1700454	0.6131076	- 0.1384203	0.6025741
Difference	0.9823077	0.7105382		- 0.484171	2.448786

Figure 25. Mean sialometry by group



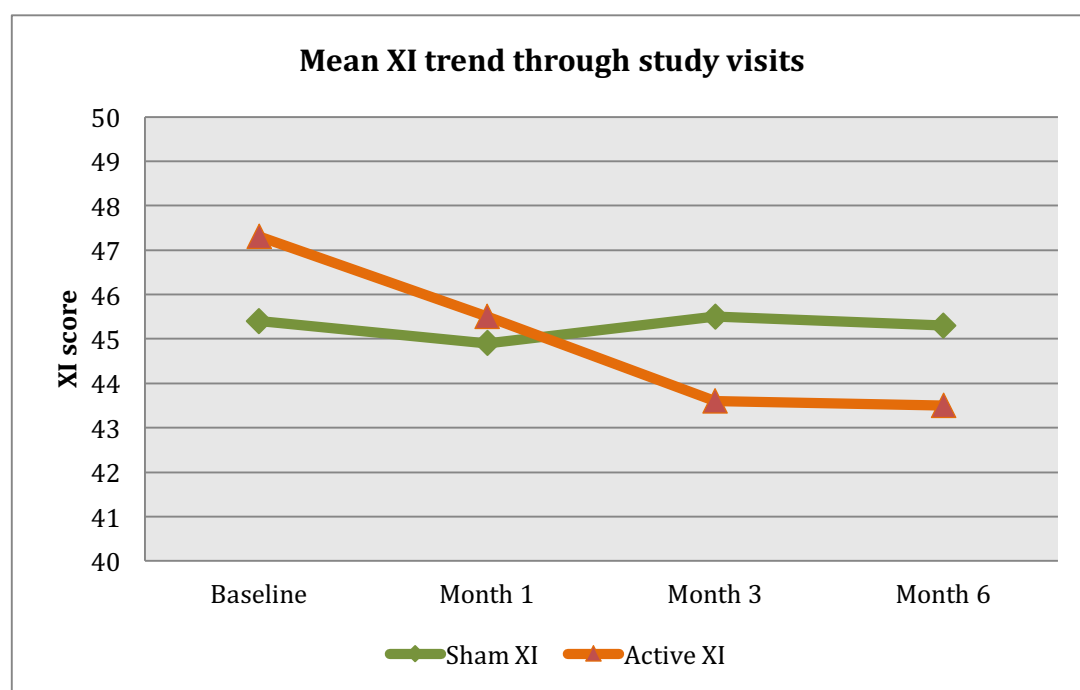
4.2.3 Xerostomia inventory (XI)

XI score reduced more in the active group than in the sham group at endpoint (6 months) by 3.3 points (95% CI -6.2 to -0.4) (Table 26) (Figure 26). XI results related to effect size 0.93 ($P=0.02$). The mean difference between the groups in Xerostomia Inventory change at 12 months is -4.2 (95% CI -8.5 to 0.04).

Table 26. XI Two –sample t test (month 6)

Group	Mean	Std. Err.	Std. Dev.	95% Conf. Interval	
Active	- 3.461538	1.124411	4.054121	-5.911419	-1.011658
Sham	- 0.1538462	0.8231129	2.967776	-1.947255	1.639563
Difference	- 3.307692	1.39349		-6.183714	- 0.4316701

Figure 26. Mean XI score by group



4.2.4 EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)

There was no difference between the groups in terms of overall dryness as measured by ESSPRI Q1 (dryness). The mean difference between the groups in ESSPRI Q1 (dryness) change at month 6 was -0.2 (95% CI -1.6 to 1.1) (P=0.73) (Table 27). This persisted in the open label period.

There appears to be no difference between groups in terms of overall ESSPRI. The mean difference between the groups in ESSPRI (overall) change at month 6 was -0.6 (95% CI -2 to 0.7), effect size 0.36 (P=0.37) (Table 28). The mean difference between groups in overall ESSPRI change at 12 months is -1.5 (95% CI -3.1 to 0.2). Again there is some evidence that the difference between the groups increases during the open label phase.

Table 27. ESSPRI Q1 (dryness) Two –sample t test (month 6)

Group	Mean	Std. Err.	Std. Dev.	95% Conf. Interval	
Active	- 1.307692	0.5925241	2.136376	-2.598691	-0.0166932
Sham	- 1.076923	0.3293649	1.187542	-1.794548	-0.3592985
Difference	- 0.2307692	0.677913		-1.629913	1.168374

Table 28. ESSPRI (overall) Two –sample t test (month 6)

Group	Mean	Std. Err.	Std. Dev.	95% Conf. Interval	
Active	- 0.358974	0.4810683	1.734516	-1.407132	0.6891834
Sham	- 0.256410	0.479128	1.727521	-0.7875205	1.300341
Difference	- 0.615384	0.6789628		-2.016695	0.7859258

Chapter Five:

Discussion

At present there remains no cure for SS and thus regarding the dry mouth aspects of the disease, patients rely greatly on frequent sips of water (Cho et al. 2010). While this may transiently lessen the symptoms of oral dryness patients would be missing a great deal of benefits that saliva provides in addition to lubrication such as: repair, antimicrobial, and buffering properties which all contribute extensively to the protection of oral hard and soft tissue integrity (Mandel 1987). In addition it contains amylase and lipase which aid initial digestion of starch and fat (Valdez and Fox 1991). All the benefits that saliva can provide, likewise can be absent with salivary substitutes as these agents provide mainly moisture only. Furthermore the physical properties of salivary substitutes can be different from natural saliva and they only provide short-term relief (Vissink et al. 1983; Olsson and Axéll 1991).

For these reasons it would be of advantage to provide a treatment option that can stimulate existing functioning salivary gland tissue to produce saliva, thus attaining saliva moisture and the other aforementioned functions. Studies have shown that salivary sialogogues (pilocarpine and cevimeline) can reduce dry mouth symptoms and increase salivary gland function (Vivino et al. 1999a; Fife et al. 2002b; Petrone et al. 2002c; Papas et al. 2004a) yet these non-selective M-agonists can often cause adverse side effects: sweating, headache, increased urinary frequency, bronchospasm, bradycardia, dizziness and gastrointestinal upset. In addition it is estimated that treating patients with SS would cost the health service in the UK (in 2004) £2188 per patient (annual direct health cost) (Callaghan et al. 2007; Sada, Isenberg and Ciurtin 2014). Pilocarpine 5 mg tid would cost around £534.82 / year, while in contrast the second-generation electro stimulation intra-oral device costs us

\$575, where the batteries last for a year or possibly more and did not give rise to notable adverse effects. Therefore when considering the therapy for xerostomia associated with SS, it is crucial that the treatment can stimulate/increase natural saliva, be free of side effects, be self administered by patients and not notably expensive.

These criteria might be achieved by electrostimulation. It has been reported that electrostimulation increases the salivary flow (Erlichman 1990), and in 1992 a study demonstrated an improvement in xerostomia symptoms in a group of patients with SS who were treated with electrostimulation (Talal, Quinn, and Daniels 1992b). Yet there is no available robust evidence of the efficacy of the second-generation electrostimulation device in treating xerostomia caused by SS. Previous studies included patients with dry mouth due to different causes (radiotherapy, medications, etc) they also had an open-label and uncontrolled design in some of them, additionally these studies assessed the short-term effectiveness only of the device (Strietzel et al. 2007; Strietzel et al. 2011; Alajbeg et al. 2012). Consequently these studies did not provide robust evidence for the use of electrostimulation for xerostomia of SS. The present study was advanced due to the promising data in regards to the effectiveness of treating SS induced dry mouth with electrostimulation, and to provide a high quality study investigating the long-term effectiveness of the second-generation electrostimulation device.

In the present study the use of the second-generation electrostimulation device for 5 minutes as needed in LEONIDAS-1 did not result in any side effects or any kind of erythematous reaction at the site of stimulation. Any complaints of

discomfort were easily solved by adjusting the electrodes and flanges till participants were satisfied.

The unstimulated salivary flow (USF) in the present results favour the active group, at month 6 (end of the randomised controlled part of trial). The USF difference between baseline and month 6 in the active group was 0.08ml/min and in the sham group 0.015ml/min, these results were better than that of previous trials on electrostimulation treating xerostomia: active: 0.02 ml/min vs. sham: -0.005 ml/min (Steller, Chou, and Daniels 1988c), active: 0.021 ml/min vs. Placebo: 0.017 ml/min (Talal, Quinn, and Daniels 1992b), active: 0.033 ml/min vs. Placebo: -0.033 ml/min (Strietzel et al. 2011). In the present study at month 12 the difference from baseline in USF reached 0.11ml/min in the active group and -0.0012ml/min in the control group and thus demonstrates more improvement in the active group with longer use.

The VAS of dry mouth symptoms in the active group improved in the initial 3 months, however by 6 months and with further completing the 12 months, the active and sham VAS scores are almost identical, this may suggest that participants were more sensitive to changes in the symptoms of oral dryness when they were newly enrolled in the trial. In addition SS is considered a chronic condition, where patients may live with it for years and adapt to the sensation of dry mouth, therefore a larger objective improvement (higher increase in salivary function) may be needed in order for symptoms of oral dryness to improve.

Indeed, it is suggested that for XI to be of use the minimally important difference should be 6 units. At 6 months the XI score in the present study has reduced by 3.3 points more in the active group than in the sham group. At month 12

further widening of the differences between the groups XI score were observed. The XI is not only used to assess subjective feelings of dry mouth, it also involves the habitual behaviour in reaction to xerostomia (i.e. sipping liquids when swallowing, sucking sweet or feeling dry skin, hands and inside of nose), hence it is likely that although subjective symptoms have been improved using electrostimulation device, the habits may persist. It is also vital to consider the small sample size in this study, which might explain the small differences seen between the two arms of the trial.

With regards to the ESSPRI, the overall ESSPRI includes 3 domains covered in three questions; (1) general dryness, (2) fatigue and (3) pain. Question one in the ESSPRI covers general dryness (eye, cutaneous, vaginal etc.). The present results revealed that the ESSPRI did not change in either the active or sham groups, this is not unexpected as the present device influenced a local reflex loop affecting the salivary gland function, hence it is unlikely to have an effect on eye, skin and vaginal dryness or demonstrate a significant change particularly as the XI did not.

Using the second-generation intra-oral electrostimulation device is limited with few contraindications as wearing active pacemakers, defibrillators, hearing aids and mental disease/depression. Yet these are not absolute contraindications; built-in safety features are included in pacemakers to protect them from other electrical devices that may affect their operation. Also professional pre-assessment is necessary for patients with pacemakers or defibrillators (by a cardiologist) or hearing aids (by an ear, nose and throat

(ENT) specialist) and psychiatric patients (by a psychiatrist) (Strietzel et al. 2007).

The present results of the efficacy of the use of an electrostimulation device on the salivary gland in patients with SS are promising. However although a cumulative improvement in salivary function was found, an improvement in subjective symptoms was not definitely detected. Thus a larger study is coloured by the present results is now warranted to confirm these results.

Future study:

A 12- month multicentre, parallel group, double-blind, randomised sham-controlled trial (RCT) in patients with primary Sjogren's Syndrome is now anticipated.

A total of 124 patients are required to have 90% power for detecting an effect size of 2.5 units for the change in XI score at 12 months post randomisation (informed by the feasibility study and clinical opinion), assuming a between patient standard deviation of 4 units, 2-sided 5% significance level and 10% dropout.

The Primary Objective of this study will be:

- Is salivary electro-stimulating device over 12 months of use superior to the sham device in terms of reducing dry mouth symptoms in patients with Primary Sjogren's Syndrome (pSS)?

While the Secondary Objectives will be:

- Will 12-month use of the salivary electro-stimulating device result in an increase in salivary flow in individuals with pSS?
- Will 12-month use of the salivary electro-stimulating device result in improved oral health-related quality of life in individuals with pSS?

- To what extent do patients adhere to the device protocol over a 12-month period?
- What is the safety profile of the salivary electro-stimulating device?

Cost-effectiveness: To assess whether the use of a salivary electrostimulating device is cost effective when compared with the sham device.

To conclude this detailed study successfully demonstrated feasibility of recruitment and randomization into a sham-controlled salivary electrostimulation trial. The device was safe and well tolerated. Although the study was not designed to investigate effectiveness, we looked at changes in dry mouth symptoms and salivary flow before and after treatment, so to identify a “clinical signal” or “preliminary suggestion” that supported conducting a full definitive RCT. The present study will be used to identify the primary outcome and estimate the variability, in order to calculate the sample size for the definitive RCT. Out of the 4 study outcome measures, XI and uWSFR captured changes in dry mouth symptoms and salivation and suggested that the device can lessen dry mouth symptoms (3.3 units on XI score) and increase salivation (1g/15min).

Appendices

Appendix 1. Systematic review search strategy

Medline (Ovid):

Xerostomia
Hyposalivation
Asialia
Mouth Dryness
Dryness, Mouth
xerostomia.mp.
xerostomi*
(dry\$ adj2 (oral or mouth\$)).mp.
(asialia or "salivary gland hypofunction" or hyposalivat\$).mp.
or/1-9
salivary gland dysfunction
Sjogrens Syndrome
Syndrome, Sjogren's
Sjogren Syndrome
Sicca Syndrome
Syndrome, Sicca
or/ 11-16
Therapeutic
Treatment
Treatments
parasympathomimetic*
cholinergic agonists
sialogogue\$.mp.
("anticholinergic drug\$" or "anti-cholinergic drug\$").mp.
"sympathomimetic drug\$".mp.
pilocarpine
acetylcholine
bethanechol
carbachol
methacholine chloride
cholinesterase inhibitors
ambenonium chloride
edrophonium
neostigmine
paraoxon
physostigmine
pyridostigmine bromide
choline esters
cholinomimetics
aceclidine hydrochloride
choline alfoscerate
exp mucin/
(carboxymethylcellulose or cellolax or cethylose or "croscarmellose sodium" or "carboxymethyl cellulose"
or hydroethylcellulose or polyglycerylmethacrylate or "polyethylene oxide" or
hydroxypropylmethylcellulose).mp.
(CMC or HEC or PGM).ti,ab.
exp Candy/
(lozenge\$ or candy or candies or "chewing gum" or sweet\$).mp.
"malic acid\$".mp.
(xylitol adj3 gum\$) or (xanthan adj3 gum\$)).mp.
"saliva substitut\$".mp.
Mouthwashes/
(mouthwash\$ or mouth-wash\$ or "mouth wash\$" or mouthrins\$ or mouth-rins\$ or "mouth rins\$").mp.
(linseed\$ or rape\$ or canola\$ or aloe\$).mp.
Hyperbaric Oxygenation/
"hyperbaric oxygen\$".mp.
Electrical Stimulation/

((electric\$ adj3 stimulat\$) or neuroelectrostimulation or “masticatory stimulation”).mp.
intra-oral device\$”.mp.
Acupuncture/
acupuncture.mp.
Lasers/
laser\$.mp.
or/ 18-61
9 and 17 and 62

The above subject search will be linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE:

#64 randomized controlled trial.pt.
#65 controlled clinical trial.pt.
#66 randomized.ab.
#67 placebo.ab.
#68 drug therapy.fs.
#69 randomly.ab.
#70 trial.ab.
#71 groups.ab.
#72 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
#73 exp animals/ not humans.sh.
#74 72 not 73

Cochrane Central register for controlled trials:

Sjogrens Syndrome
Syndrome, Sjogren's
Sjogren Syndrome
Sicca Syndrome
Syndrome, Sicca
or / 1-5
MeSH descriptor Xerostomia explode all trees
xerostomia
(dry* near/2 oral) or (dry near/2 mouth*)
(asialia or "salivary gland hypofunction" or hyposalivat*)
or / 7-10
MeSH descriptor Parasympathomimetics, this term only
MeSH descriptor Pilocarpine, this term only
MeSH descriptor Arecoline, this term only
MeSH descriptor Oxotremorine, this term only
MeSH descriptor Cholinesterase Inhibitors, this term only
MeSH descriptor Quaternary Ammonium Compounds explode all trees
MeSH descriptor Physostigmine, this term only
MeSH descriptor Pyridostigmine Bromide, this term only
MeSH descriptor Mucins explode all trees
cholinergic agonists #
sialogogue\$
acetylcholine
bethanechol
carbachol
methacholine chloride
amibenonium chloride
edrophonium
neostigmine
paraoxon
choline esters
cholinomimetics
aceclidine hydrochloride
bethanechol chloride
choline alfoscerate
mesh descriptor carboxymethylcellulose, this term only
carboxymethylcellulose or cellolax or cethylose or "croscarmellose sodium" or "carboxymethyl cellulose"
or hydroethylcellulose or polyglycerylmethacrylate or "polyethylene oxide" or
hydroxypropylmethylcellulose
(cmc or hec or pgm): ti,ab,kw
mesh descriptor candy explode all trees
lozenge* or candy or candies or "chewing gum" or sweet*
"ascorbic acid tablet*"
"malic acid*"
((xylitol near/3 gum*) or (xanthan near/3 gum*))
"saliva substitut*"
mesh descriptor mouthwashes explode all trees
mouthwash* or mouth-wash* or "mouth wash*" or mouthrins* or mouth-rins* or "mouth rins*"
linseed* or rape* or canola* or aloe*
mesh descriptor hyperbaric oxygenation, this term only
"hyperbaric oxygen*"
mesh descriptor electric stimulation explode all trees
electric* near/3 stimulat*
neuroelectrostimulation or "masticatory stimulation"
"intra-oral device*"
mesh descriptor acupuncture, this term only
acupuncture
or/ 12-55
6 and 11 and 56

EMBASE (OVID):

Sjogrens Syndrome
Syndrome, Sjogren's
Sjogren Syndrome
Sicca Syndrome
Syndrome, Sicca
or/ 1-5
xerostomia.mp.
(dry\$ adj2 (oral or mouth\$)).mp.
(asialia or "salivary gland hypofunction" or hyposalivat\$).mp.
(radioxerostomia or radio-xerostomia).mp.
or/7-10
parasympathomimetics
cholinergic agonists
sialogogue\$.mp.
("anticholinergic drug\$" or "anti-cholinergic drug\$").mp.
"sympathomimetic drug\$".mp.
acetylcholine
bethanechol
carbachol
methacholine chloride
pilocarpine
cholinesterase inhibitors
ambenonium chloride
edrophonium
neostigmine
paraoxon
physostigmine
pyridostigmine bromide
choline esters
cholinomimetics
aceclidine hydrochloride
choline alfoscerate
anticholinesterases
ambenonium
demecarium bromide
distigmine
eseridine salicylate
galantamine hydrobromide
cevimeline
exp Mucin/
Carboxymethylcellulose/
(CMC or HEC or PGM).ti,ab.
exp Candy/
(lozenge\$ or candy or candies or "chewing gum" or sweet\$).mp.
"ascorbic acid tablet\$".mp.
"malic acid".mp.
((xylitol adj3 gum\$) or (xanthan adj3 gum\$)).mp.
"saliva substitut\$".mp.
Mouthwashes/
(mouthwash\$ or mouth-wash\$ or "mouth wash\$" or mouthrins\$ or mouth-rins\$ or "mouth rins\$").mp.
(linseed\$ or rape\$ or canola\$ or aloe\$).mp.
Hyperbaric Oxygenation
"hyperbaric oxygen\$".mp.
Electrical Stimulation/
((electric\$ adj3 stimulat\$) or neuroelectrostimulation or "masticatory stimulation").mp.
"intra-oral device\$".mp.
Acupuncture/
acupuncture.mp.
or/12-58
6 and 11 and 59

The above subject search will be linked to the Cochrane Oral Health Group filter for EMBASE via OVID:

random\$.ti,ab.
factorial\$.ti,ab.
(crossover\$ or cross over\$ or cross-over\$).ti,ab.
placebo\$.ti,ab.
(doubl\$ adj blind\$).ti,ab.
(singl\$ adj blind\$).ti,ab.
assign\$.ti,ab.
allocat\$.ti,ab.
volunteer\$.ti,ab.
CROSSOVER PROCEDURE.sh.
DOUBLE-BLIND PROCEDURE.sh.
RANDOMIZED CONTROLLED TRIAL.sh.
SINGLE BLIND PROCEDURE.sh.
or/61-73
6 AND 11 AND 60 AND 74

AMED (OVID):

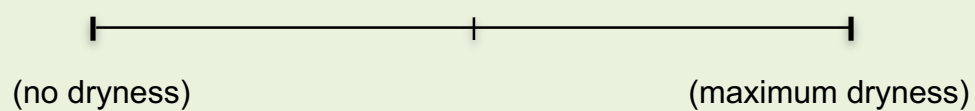
xerostomia.mp.
(dry\$ adj2 (oral or mouth\$)).mp
(asialia or "salivary gland hypofunction" or hyposalivat\$).mp.
(Sjogrens Syndrome or Syndrome, Sjogren's or Sjogren Syndrome or Sicca Syndrome or Syndrome, Sicca).mp.
or/1-4

The above subject search will be linked to the Cochrane Oral Health Group filter for AMED via OVID:
exp randomized controlled trials/
exp double blind method/
exp random allocation/
(random\$ or control\$ or placebo\$ or factorial).mp.
(double adj blind).mp.
(single adj blind).mp.
exp comparative study/
or/6-12
5 AND 13

Appendix 2. Dry mouth visual analogue scale

Please place a mark on the line below representing the degree of dryness in your mouth today (as one end indicates no dryness and the other maximum dryness)

How severe is your dry mouth today?



Appendix 3. Xerostomia Inventory (XI)

Please score the following statements referring to the preceding 4 weeks

	Never	Hardly ever	Occasionally	Fairly often	Very often	
I sip liquids to aid in swallowing food						
My mouth feels dry when eating a meal						
I get up at night to drink						
My mouth feels dry						
I have difficulty in eating dry foods						
I suck sweets or cough lollies to relieve dry mouth						
I have difficulties swallowing certain foods						
The skin of my face feels dry						
My eyes feel dry						
My lips feel dry						
The inside of my nose feels dry.						Final
<i>Scores</i>						

Scoring Never = 1; Hardly ever = 2; Occasionally = 3; Fairly often = 4; Very often = 5

Appendix 4. Eular Sjögren's Syndrome Patient Reported Index

ESSPRI

EULAR Sjögren's Sndrome Patient Reported Index

Your physician has asked you to answer several questions relating to your disease. To answer to these questions, please take into account how bad your symptoms have been at their worst during the last two weeks only.

Please tick one box only that best reflects your response. Please take care to answer all the questions.

Example:

No pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable pain
	0	1	2	3	4	5	6	7	8	9	

1) How severe has your dryness been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10	

2) How severe has your fatigue been during the last 2 weeks?

No fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable fatigue
	0	1	2	3	4	5	6	7	8	9	10	

3) How severe has your pain (joint or muscular pains in your arms or legs) been during the last 2 weeks?

No pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable pain
	0	1	2	3	4	5	6	7	8	9	10	

Appendix 5. Trial inclusion criteria

	Yes	No
≥ 18 years old		
Have clinical symptoms of xerostomia (dry mouth) due to primary SS syndrome diagnosed on the basis of 2001 EU-USA classification criteria		
Degree of dry mouth symptoms: a minimum degree of dryness of 50mm (≥50mm) on a 100mm VAS scale (0= no dryness; 100= maximum dryness).		
To have unstimulated whole salivary flow higher than 0 ml/15min (unstimulated salivary flow as measured via sialometry for 15 minutes)		
No systemic sialogogue therapy (e.g. pilocarpine) for the duration of the study		
To have evidence of residual salivary gland function, by demonstrating an increase in salivary flow on appropriate stimulation [eg citric acid stimulation or chewing paraffin wax]		
Not be pregnant or trying to have children for the length of their participation. Female participants of child bearing potential would need to take measures to avoid pregnancy		

Appendix 6. Study visits

Procedures		Study visit (n.)
1	Information (verbal and written) regarding the study	1
2	Consent	
3	Medical and drug history	
4	Vital signs	
5	Clinical oro-facial examination and questionnaires: Examination of oral and dental tissues Dry mouth VAS score Measurement of stimulated vs unstimulated salivary flow	
6	Confirmation that inclusion/exclusion criteria are met. Enrolment into the study	
7	Generation of study codes (for randomization). Dental impression (to build individualized device)	2
8	Delivery and fitting of the device, usage instruction and start of 12 month trial. BASELINE value of Dry mouth VAS score, XI and ESSPRI questionnaire, salivary flow.	3
9	Hospital appt month 1: - Salivary flow rate + Dry mouth VAS score + XI and ESSPRI questionnaires	4
10	Hospital appt month 3: - Salivary flow rate + Dry mouth VAS score + XI and ESSPRI questionnaires	5
11	Hospital appt month 6 - Salivary flow rate + Dry mouth VAS score + XI and ESSPRI questionnaires. Final assessment – discharge from trial	6

Appendix 7. Participant information sheet

University College London Hospitals

NHS Trust

Study Number: OM-11-04
Subject Initials: _____
Screening Number: _____
Randomization Number: _____

Eastman Dental Hospital
256 Gray's Inn Road
London WC1X 8LL
Telephone: 020 3456 7891

Participant Information Sheet

(Version 5, 3rd July 2012)

STUDY ON A NOVEL MEDICAL DEVICE FOR THE TREATMENT OF REDUCED SALIVATION (DRY MOUTH) RESULTING FROM SJOJOREN'S SYNDROME

Please read this sheet carefully. Please ask if you do not understand or would like more information

1. Invitation to participate

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have.

You have been selected as a potential participant because you might have the appropriate condition that we are studying. The following information is provided so that you can make an informed decision regarding your willingness to participate. Please discuss with family and friends and ask us if there is anything which is not clear or if you would like more information.

2. What is the purpose of the study?

Sjogren's syndrome often causes permanent damage to the salivary glands and consequent reduction in salivation – also known as dry mouth. Dry mouth can be very distressing and affect the way you talk and eat. Unfortunately, current therapies of dry mouth are often unsatisfactory, and may result in adverse side effects. Preliminary studies indicated that a device that releases mild and painless electric stimuli to skin of the mouth can increase salivation and reduce the sensation of dry mouth.

The main purpose of this study is to investigate whether this device will reduce dry mouth symptoms in patients with Sjogren's syndrome.

The medical device to be investigated in this research was introduced few years ago, showed to be effective and safe in humans and was recently granted approval for commercialization in EU.

We also aim at analyzing and comparing levels of salivary components before and after treatment with device as it has been suggested that electrostimulation may also alter the composition of saliva and the function of cells that secrete saliva.

3. Why have I been invited?

You have been identified as a potential participant by doctors in your hospital because you have persistent dry mouth due to primary Sjogren's syndrome.

4. Do I have to take part?

It is up to you to decide whether to join the study. We will describe the study and go through this information sheet in details. You can take as much time as you need to decide upon taking part in this study, although we will ask you to confirm your participation within a time compatible with the scheduled end of the study (November 2012). The latest date to confirm participation into this study is, at the present moment – the end of October 2012. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive. Participation in this study will in no way affect your legal rights.

5. What will happen to me if I take part?

A total of 30 individuals with dry mouth caused by primary Sjogren's syndrome will participate in this study. If you decided to take part, an appointment will be arranged at the study centre to see whether you fulfil the criteria for participation. Individuals who fulfil the criteria will participate into the study and will be divided into 2 groups of 15 each (group A and group B). Participants will be allocated into these 2 groups casually (a process known as randomisation) and neither participants nor investigators will know which patients belong to group A or B (known as "double blind design") until the end of the study. Participants of both groups will receive an individual customised device that is shaped on a cast (model) of their dentition taken with a routine dental impression (the same as that taken for dentures) and a remote control to switch the device on/off. Participants will be explained how to use

the device and will be asked to bring it home and test it for 6 months. Participants of Group A (cases) will receive a device that releases electric stimuli when switched ON by the associated remote control. Participants of Group B (controls) will receive a device that does not release electric stimuli as it will not be switched ON by the remote control. You will not be able to tell the difference between the active and the inactive devices as the electric stimuli are very mild and well below human sensing ability. During this time, participants will be asked to attend 4 predefined hospital appointments (at start of the trial and month 1, 3 and 6; each appointment lasting about 30-40 minutes) in order to let doctors to assess the potential benefits of the device (doctors will measure salivation and will ask participants to complete 2 questionnaires – they will also check the device and examine the mouth of study participants). After measurement, saliva will be stored in freezer (in anonymised containers) and subsequently analysed for changes in its composition. After study is completed, we may store remaining saliva samples in our tissue bank for possible use in future research upon review by ethical committee. Participants will also be asked to report into a home diary the frequency of device application per day.

6. Expenses and payments

We will reimburse your travel expenses and will compensate you for your time you will spend to attend hospital appointments relevant to the study.

7. What will I have to do?

You will be asked to bring the device home and use it as directed for the duration of the study (6 months). A dedicated remote control will also be provided to switch the device on/off.

We shall recommend keeping the device in its protective case to avoid damage (such as breaks or heat deformation).

You will not be allowed to use pilocarpine tablets (a medication which is sometimes prescribed for dry mouth) during the study but you can continue to use your usual topical treatment (e.g. spray, mouthwash) for dry mouth control.

You will also be asked to attend pre-arranged hospital appointments for measurement and to fill questionnaires regarding the degree of dry mouth.

We will provide a home diary for you to report the frequency of device application per day.

8. Alternatives

Current treatment options for dry mouth consist of:

(I) Salivary substitutes (mouthwash, spray, gel), which are applied into the mouth and typically provide only mild and transient benefit;

(II) Tablets of pilocarpine, a medication that can stimulate your own salivation but is often burdened by adverse side effects.

Overall treatment modalities for dry mouth are unsatisfactory and many individuals attempt to lessen dry mouth sensation with frequent sips of water.

9. What are the possible disadvantages and risks of taking part?

Previous studies showed that the device is safe and its use does not cause discomfort as it is custom-made on the shape of individual dentition. Occasionally the device may cause friction and irritation to the lining of the mouth – this can be promptly resolved by the Investigators (study doctors) who can easily re-shape the device and remove the irritating parts. The device may affect your speech but only while you are wearing it.

Although no significant risk is expected, it is a sensible precaution in clinical research not to include participants who are pregnant or trying to have children; also female participants of child-bearing potential would need to take measures to avoid pregnancy for the length (6 months) of the study.

10. What are the possible benefits of taking part?

Study participants will benefit from using a novel medication-free therapeutic means that – based on previous research – is likely to lessen their dry mouth sensation. Also participants in the control group (those using the non-functional device) should benefit from increased salivation due to tactile stimulation of the device onto the mouth – although this is expected to be lower than that caused by the electric stimuli.

11. What happens when the research study stops?

2 of 3

Participant Initials _____

On study completion, you can retain the device until battery expires (if you wish so). You will be asked to return the remote control you used during the study and provided with a new remote control to switch your device on/off. The new Remote Control will activate the device of all participants (both group A and B). On battery expiration, you will be asked to return the device/remote control and offered currently available treatment modalities to lessen dry mouth symptoms. You can tell that battery is expired by looking at the small red LED light on the device: If it does not blink when you try to switch the device ON/OFF with the remote control, the battery is expired. Information will be provided regarding the modality of purchasing a new device from the manufacturer (should you wish so).

12. Will my taking part in the study be kept confidential?

The investigator (study doctor) will make every possible effort to keep your personal information confidential. All the information collected will be kept by the research coordinator. The Chief Investigator is responsible for safety and security of the data. Medical records which identify you and the consent form signed by you may be inspected by an Institutional Review Board or Ethical Review Committee. The results of this research project may be presented at meetings or in publications; however, any research data released or published will not identify volunteers by name. All data and results will be completely anonymised and it will be impossible to identify you from them.

13. What if there is a problem?

Any complaint about the way you have been dealt with during or as a consequence of the study or any possible harm you might suffer will be addressed. Contact numbers of study investigators are provided at the end of this document – as an alternative, you can also complain directly to UCLH. If you are harmed by taking part in this research project, there are no special compensation arrangements – although the normal NHS complaints mechanisms will still be available to you (where appropriate). If you are harmed due to someone's negligence, you may have legal grounds for compensation, but you may have to pay for it.

14. Study results

The results of this research study may be presented at meetings and may be published, likely at least one year after the end of the project. No patients will be identified in any report. If you would like to receive the results of the study, please contact the Chief/Principal Investigator, Dr S Fedele by phone, letter or email.

15. Who is organising and funding the research?

The study is sponsored by UCLH and funded by Arthritis Research UK.

16. Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favorable opinion by Sheffield Research Ethics Committee

17. Whom to ask questions regarding this study or to make a complaint to?

You have the right to ask questions concerning this study at any time - please contact Dr Stefano Fedele at 020 3456 1004.

Complaints

- To Study Investigators: please contact Dr Stefano Fedele or Professor Stephen Porter.
- To UCLH: please speak to the person in charge of the ward or clinic, or to our Patient Advice and Liaison Service (PALS) who will help with your problem quickly and informally. Contact PALS on 020 7380 9975.
- You can also make formal complaint. Please write with full details to the Complaints Manager at: Governance Department, UCLH, 2nd Floor West, 250 Euston Road, London, NW1 2PG (Fax: 02073809595- email: complaints.officer@uclh.nhs.uk).

A copy of this information sheet and a signed consent form will be given to you.

Appendix 8. Consent form

University College London Hospitals

NHS Trust

Version 4, 3rd July 2012
Study Number: OM-11-04
Subject ID:

Eastman Dental Hospital
256 Grays Inn Road
London WC1X 8LD

EASTMAN CLINICAL INVESTIGATION CENTRE
Enquiries and Appointments: Tel: 020 3456 1278

CONSENT FORM

Title of project:

Study on a novel medical device for the treatment of reduced salivation (dry mouth) resulting from Sjogren's syndrome

[Scientific title: Long-term Effectiveness Of a Novel Intra-oral electro-stimulator for the treatment of Dry mouth in patients with Sjogren's Syndrome (LEONIDAS-1): a feasibility study.]

Name of Chief and Principal Investigator: **Dr. Stefano Fedele**

Please Initial box

1. I confirm that I have read and understood the Information sheet Version 5 dated 3rd July 2012 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by the researchers and responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to my General Practitioner and General Dental Practitioner being informed of my participation in the study. ☐
5. I understand that the medical device to be investigated meets the requirements of all relevant European Directives (CE Marking) ☐
6. I understand that this study will investigate whether a novel medical device will lessen dry mouth sensation caused by Sjogren's syndrome. I also understand that saliva samples will be stored in freezers during the study and analyzed for changes in composition of saliva. ☐
7. I understand that the saliva sample may be stored after study is completed and used for potential future research at a later date upon review by ethical committee. I understand that these results will remain anonymous. ☐
8. I agree to take part in the above study ☐

Name of patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature



UCL Hospitals is an NHS Foundation Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.



Appendix 9. Home diary

Patient Initials: _____	Study (Randomisation) n: _____
<u>Long-term Effectiveness Of a Novel Intra-oral electro-stimulator for the treatment of Dry mouth</u> <u>in pAtients with Sjogren's Syndrome (LEONIDAS-1)</u> <u>Study OM-11-04</u>	

Study start date (first day of use of the device): __/__/__

Month 1

Day	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Frequency (per day)							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Frequency (per day)							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Frequency (per day)							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Frequency (per day)							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Frequency (per day)							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Frequency (per day)							

End of Month 1: __/__/__

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