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Interventions for dry mouth and hyposalivation in Sjögren's syndrome: a systematic review and meta-analysis.

Keywords: Sjögren's syndrome, xerostomia, cholinergic agent, electrostimulation, acupuncture, saliva substitutes

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Abstract

Objectives

Systematic review with meta-analysis of interventions for dry mouth symptoms and hyposalivation of Sjögren's syndrome (SS).

Materials and Methods

We searched MEDLINE, Cochrane Central and EMBASE up to February 2018 for randomized trials of interventions for dry mouth and hyposalivation of SS. The primary outcome was the mean change in xerostomia symptoms. The secondary outcomes included changes in salivary flow and quality of life. We used the Cochrane risk of bias tool for individual studies and the GRADE method to summarize the quality of evidence across studies for the included outcomes.

Results

Thirty-six studies (3,274 patients) were included in the systematic review. Results from the meta-analyses showed high-quality evidence that pilocarpine was superior to placebo in reducing dry mouth symptoms. We found moderate quality of evidence that pilocarpine, rituximab, and interferon-alpha were more effective than placebo in increasing salivary flow, with the relevant effect size being large for pilocarpine, and notably smaller for rituximab and interferon-alpha.

Conclusion

Clinicians should be very confident in the beneficial effects of pilocarpine upon dry mouth symptoms of SS, and moderately confident that pilocarpine, rituximab and interferon-alpha can have beneficial effects upon salivary flow. Adverse events are common. The use of other treatment modalities cannot be supported on the basis of current evidence.

Introduction

Persistent salivary gland hypofunction is one of the most common manifestations of Sjögren's syndrome (SS) (Carr et al., 2012). Reduced salivation typically causes chronic dry mouth sensation (xerostomia), intra-oral discomfort, difficulty with speaking (dysarthria), swallowing (dysphagia), and altered taste (dysgeusia) (Fox, 2005). It can also increase the risk of dental disease and other oral infections (Glore et al., 2009), and can interfere with the use of dental prosthetic appliances (Turner et al., 2008), as well as the sublingual absorption of systemic medications (Davies et al., 2016). As a consequence, affected patients often experience a significant reduction in their oral health-related and general quality of life (Sutcliffe et al., 1998, Strombeck et al., 2000, LÓPez-Jornet & Camacho-Alonso, 2008). In addition, ocular dryness and numerous extraglandular manifestations may occur, making SS a complex disease to characterize. A number of classification systems for SS have been introduced over the years (13 classification systems from 1965 to 2016), with the aim of facilitating comparability of findings within clinical trials and epidemiological studies. More recently, the criteria of the American-European Consensus Group (AECG) (Vitali, 2002), which had been widely used since 2002, have merged with the new sets of criteria suggested by the Sjögren's International Collaborative Clinical Alliance (SICCA) (Shiboski et al., 2012) so to develop the 2016 ACR/EULAR classification criteria for primary SS (Shiboski et al., 2017).

The treatment of salivary gland hypofunction of SS is notoriously difficult and a challenge for clinicians (Montgomery-Cranny et al., 2014). A range of topical and systemic interventions have been used in individuals with SS to attempt restoring/stimulating salivary gland function or replacing saliva, so to lessen the distressing symptoms of xerostomia and prevent the complications of reduced or absent salivary flow (Saraux et al., 2016). Residual salivary function can be stimulated with the use of topical sialogogues, such as sugar-free gums and pastilles (Glore et al., 2009), and parasympathomimetic drugs including pilocarpine (Vivino et al., 1999) and cevimeline (Petrone et al., 2002). Where glandular function is irreversibly compromised, a range of salivary substitutes in the form of gels or sprays can be considered (Saraux et al., 2016). Traditional disease-modifying anti-rheumatic drugs (DMARDs) are known to have little, if any, effect upon salivation (van Nimwegen et al., 2016); however, more recent B cell-targeted

agents have been recommended (Rituximab, an anti-CD20 agent) or suggested to represent a promising therapeutic strategy, including agents targeting cytokines of B-cell homeostasis (e.g., BAFF and IL-6) (Vivino et al., 2016, Cornec et al., 2013).

Other non-pharmacological interventions such as acupuncture (Cafaro et al., 2014) and salivary neuro-electrostimulation (Fedele et al., 2008) have also been used in the attempt to increase saliva production and lessen the associated dry mouth symptoms.

Overall there remains very little robust evidence to inform and guide clinicians regarding the effectiveness of available interventions in the management of salivary gland hypofunction and dry mouth symptoms of SS. Systematic reviews published in literature have not specifically focused upon SS and have included studies recruiting individuals with xerostomia due to a variety of causes (Furness et al., 2013). Others have focused on a single intervention for hyposalivation of SS (Do Valle Souza et al., 2016) or are limited by linguistic constraints and the inclusion of non-randomized studies (Higgins et al., 2011). As a consequence therapeutic decisions in daily practice are currently likely to be based upon a mix of personal experience, expert opinion, and low quality evidence from published studies (Saraux et al., 2016). We have therefore undertaken this multiple-treatment systematic review and meta-analysis to summarize and estimate the effectiveness of available treatment options for xerostomia, hyposalivation and quality of life in individuals with SS.

Methods

Literature search

For the identification of studies included for this review, we developed detailed search strategies for each database (Medline, Embase, The Cochrane Central Register of Controlled Trials). The last literature search was performed on the 26th February 2018. We used the following search terms to search all trials registers and databases: xerostomia, hyposalivation, Sjögren's syndrome, treatment, sialogogue, cholinergic agonists, saliva substitute, electrical stimulation, acupuncture. We also searched the reference lists of retrieved reports and textbooks for additional references. We have reported this systematic review and meta-analysis adhering to the PRISMA statement (Moher et al., 2009).

Study inclusion criteria

Study inclusion criteria were (i) design: randomized controlled trials; (ii) population: adults with diagnosis of SS-induced dry mouth symptoms and salivary gland hypofunction; (iii) intervention: treatments designed to stimulate saliva production and/or to reduce the symptoms of xerostomia; (iv) control group: placebo, another active intervention, no treatment 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 upon the clinical outcomes. No language restrictions were imposed.

Outcomes and outcome measures

The primary outcome of this review was the mean overall change in subjective dry mouth symptoms (xerostomia), which was assessed by a change in a 0-100mm visual analogue scale (VAS) (Pai et al., 2001), or a 0-10 numeric rating scale (NRS) (Sindhu et al., 2011), or subjectively assessed using a categorical outcome of improvement compared to baseline (e.g. worse, no change, better). We also considered studies using a global dryness VAS, dry mouth questionnaire such as xerostomia inventory questionnaire (XI), and other dry mouth-related patient-centred instrument.

Secondary outcomes included changes in salivary flow, patient-centred symptom severity score (e.g. the EULAR SS Patient Reported Index - ESSPRI), and quality of life (QoL) questionnaire scores relevant to general (e.g. Short-Form Health Survey “SF-36”) and oral health (e.g. Oral health impact profile “OHIP”). We also looked in detail at the time endpoints used for collection of the outcome measures; in particular, we considered whether measurements at endpoint were taken shortly after providing the intervention (e.g. few minutes or hours) or away from it, therefore measuring the short-term or long-term effects of the intervention respectively. The magnitude of the treatment effect and clinical meaningfulness were reported where available. Cohen’s effect size (small, medium and large) (McGough & Faraone, 2009, Cohen, 1988) was calculated where relevant data were provided.

Selection process and quality assessment

Titles and abstracts of the references were reviewed to exclude articles out of scope. Two independent reviewers screened the citations and full reports of potentially relevant studies were obtained (AH, VM). Any disagreements between reviewers were resolved by discussion until consensus was reached.

Data extraction

The following data were extracted: (i) study population; (ii) type, dosage, frequency and duration of the intervention, (iii) control group; (iv) xerostomia and salivary gland function outcome measures; and (v) effects on quality of life.

Assessment of risk of bias in included studies

We assessed risk of bias for individual studies using the "Risk of bias" tool of the Cochrane collaboration (Higgins et al., 2011).

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Meta-analysis

We summarized the effect size for continuous data using the mean difference (MD) with 95% confidence intervals (95% CI). For categorical data, we calculated odd ratio (OR) of improvement, with 95% CI. Heterogeneity between trials was investigated using the I^2 index. We used the following cut-offs for reporting heterogeneity: less than 25% no heterogeneity, 25% to 49% low heterogeneity, 50% to 74% moderate heterogeneity, and 75% or greater

high heterogeneity (Higgins et al., 2003). When I^2 was greater than 50%, we planned to consider the possible reasons. A fixed effect model was used unless statistical heterogeneity was significant ($p<0{\cdot}05$), after which a random effect model was used.

Quality of evidence and summary of findings

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of evidence across studies that contributed data to the meta-analyses for the pre-specified outcomes (Atkins et al., 2004). We created a 'Summary of findings' table to summarise the results and the quality of evidence for each outcome (Table 1). We used methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011), and GRADEpro software (GRADEpro GDT 2014) (GDT:). We justified all decisions to down- or up-grade the quality of studies in the footnotes.

Results

Figure 1 shows the process of study selection, leading to the inclusion of 36 studies in the systematic review, with a total of 3,274 participants. Table 2 shows a summary of trial characteristics. Fourteen studies out of the 36 provided sufficient information to be included in the quantitative meta-analysis; for the others a qualitative summary was prepared.

Table 3 provides a summary of the classification criteria, interventions, comparators, outcome and timing of outcome measurement adopted in the included studies.

Participants enrolled in the included clinical trials had SS diagnosed according to the following classification criteria: Fox's classification criteria (Fox et al., 1986) (2 studies), the Copenhagen criteria for Sjögren's syndrome (Manthorpe et al., 1986) (2 studies), the preliminary criteria for the classification of Sjögren's syndrome (Vitali et al., 1993) (7 studies) and the American-European Consensus Group Sjogren's syndrome classification criteria (Revised European

Community Study Group) (Vitali, 2002) (18 studies). In 7 studies the classification criteria were not reported.

Interventions included topical saliva substitutes (3 studies), topical saliva stimulants (2 studies), systemic cholinergic agonists (7 trials), electrostimulation (2 studies), acupuncture/laser acupuncture (2 studies), biologic response modifier biological agents (9 studies), disease modifying anti-rheumatic drugs (5 studies) and Dehydroepiandrosterone (2 studies). There was one study on gammmalinolenic acid, nizatidine, omega-3 supplements and traditional Chinese medicine respectively.

The majority of the studies (N=24) tested the efficacy of the experimental intervention against placebo. Eleven trials compared the study intervention with another agent or a sham intervention. In one trial the control group received no treatment.

Twenty-nine studies used xerostomia symptoms as an outcome, with outcome measures including changes in a 0-100mm VAS (n=16 studies), a VAS of 12.8 cm (N=1), the Xerostomia Inventory (N=1), a 3, 4, 5 and 6-point Likert scale for improvement (N=3, 1, 4, 1 studies respectively), a 0-10 numerical rating scale (N=1), and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (N=1). With respect to the time endpoints for outcome measurement, symptoms were assessed shortly after administration of the intervention in three studies and after 60 minutes in two trials, and therefore described to short-term effects of the interventions. Seven studies measured xerostomia symptoms one or more weeks after administration of the experimental treatment, therefore referring to long-term effects of the intervention. Timing of outcome measurement at endpoint was unclear in seventeen studies.

Salivary function assessed through changes in unstimulated or stimulated sialometry represented a study outcome in thirty-two trials, with one study using scintigraphy. At endpoint, salivary function was assessed shortly after administration of the intervention in four studies, after 60 minutes in four studies and after 90 minutes in one study, therefore indicating the short-term effects of the interventions. Three studies assessed salivary flow one or more weeks after the last administration of the experimental treatment, hence reporting on long-term effects. The timing of salivary flow measurement was unclear in twenty studies.

With respect to OH-QoL, one study used the General Oral Health Assessment Index [GOHAI] (Leung et al., 2008) whereas four studies used the SF-36 Survey to assess general QoL.

Risk of bias

Seventeen out of thirty-six studies were considered to be at low risk of bias (Figure 2). Adequate sequence generation and concealment was reported in 53% and 47% of studies respectively, which were therefore considered to be at low risk of selection bias. Blinding of participants to the allocated treatment by use of a placebo was done in 28 of the included studies and these trials were considered at low risk of performance bias. Outcome assessors were blinded to the allocated treatment in 27 trials, which were considered to be at low risk of detection bias. Over 90% of the included studies reported complete outcome data without selective reporting.

Systematic Review

Salivary substitutes vs. other salivary substitutes or placebo

Three controlled trials compared salivary substitutes vs other salivary substitutes or placebo. Klestov *et al* investigated a newly formulated salivary substitute based on a sodium phosphate (disodium hydrogenorthophosphate) mouthwash against a glycerine mouthwash in a randomised parallel study (Klestov et al., 1981), and reported that a higher number of patients (21.1% vs 5.3%; $P<0.05$) using the sodium phosphate mouthwash reported "excellent improvement" in their nocturnal dry mouth symptoms compared with those using the glycerine mouthwash (5-point Likert scale of improvement). The changes induced by the treatment were therefore clinically meaningful. No assessment of salivary flow was performed. We considered this trial to be at unclear risk of bias of sequence generation, allocation concealment and blinding. Van der Reijden *et al* reported no significantly different changes in xerostomia symptoms (on numeric rating scale) among SS patients using three different salivary substitutes spray [containing poly acrylic acid, high/low viscosity xanthan gum, and porcine gastric mucin] and placebo for one week in a cross-over (one week wash-out) double-blind trial at unclear risk

of selection bias (Van Der Reijden et al., 1996). The effects upon salivary flow were unclear. Johansson studied the effects of three-week use of Salinum with chlorhexidine (test group) and Salinum without chlorhexidine (control group) and found that more participants in the test group reported a clinically meaningful significant reduction in xerostomia symptoms on a 6-point Likert scale with respect to the control group (15 *vs.* 11; P<0.05) (Johansson et al., 2001). Changes in unstimulated salivary flow were not statistically significant. We considered this risk to be at unclear risk of bias of sequence generation and allocation concealment.

Topical saliva stimulants vs. other saliva stimulants or placebo

Two trials tested the effects of topical salivary stimulants versus other saliva stimulants or placebo. Gravenmade reported in a cross-over trial at high risk of selection bias that the use of mucin lozenge for two weeks led to a statistically larger and clinically meaningful reduction in xerostomia symptoms (1.7 vs 1 on a 5-point Likert scale; P<0.05) compared to placebo lozenges (Gravenmade & Vissink, 1993). Timing of outcome measurement was unclear. Da Silva Marques *et al* tested in a randomized parallel study at low risk of bias a novel malic acid-based gustatory salivary stimulant compared with a citric acid-based stimulant (da Silva Marques et al., 2011). The study failed to show any significant difference between the groups with regards to short-term (20 minutes) changes in salivary flow.

Systemic cholinergic agonists vs. placebo or salivary substitutes

Seven placebo-controlled trials tested the parasympathomimetic cholinergic agents cevimeline (3 studies) and pilocarpine (4 studies). Petrone reported a short-term (90 minutes) significantly higher increase in salivary flow rate in patients taking one tablet of 30mg cevimeline versus placebo, which was of unclear magnitude (Petrone et al., 2002). They also observed a short-term (60 minutes) significant difference in the mean change of VAS score (dry mouth) between the cevimeline group (-27mm) and placebo (-15mm), which corresponds to moderate effect size (P<0.05). Moreover, significantly more patients in the cevimeline group reported an improvement in global xerostomia symptoms (66% vs 37% on a 3-point Likert scale; P<0.05).

These findings therefore suggest a 27mm reduction in the 0-100mm dry mouth VAS to be clinically meaningful. This study was considered to be at unclear risk of allocation concealment and blinding bias. Fife tested 30mg or 60mg of cevimeline vs placebo for 6 weeks (Fife et al., 2002) and found no difference in the number of patients reporting a short-term (60 minutes) improvement in the global dry mouth evaluation (on a 3-point Likert scale) and no difference in the change of VAS score (dry mouth) between the cevimeline group and placebo. There was however a significantly higher short-term change in salivary flow in the cevimeline group compared to placebo [0.194 vs 0.015 mL/min (mean change); $P<0.05$)], which corresponds to a large effects size although clinical significance remains unknown. This study was considered to be at unclear risk of allocation concealment. Leung et al. reported in a cross-over trial with low risk of bias that the use of cevimeline for 24 week was associated with no significant change in xerostomia symptoms (Xerostomia Inventory), salivary flow or QoL (GOHAI, SF-36) between the intervention and placebo group (Leung et al., 2008). Of note, the significant improvement in xerostomia symptoms and Oral Health-related QoL claimed by the authors was expression of within-group separate analysis against baseline, which is well known to be highly misleading (Bland & Altman, 2011). Pilocarpine was tested in three placebo-controlled studies. Papas reported that 12-week use of pilocarpine 20-30mg/day (Papas et al., 1998) was associated with a short-term (60 minutes) significantly higher increase in salivary flow than placebo, which however was of unclear magnitude and clinical significance. There were more individuals in the pilocarpine group (61% vs 31%; $P<0.05$) reporting a reduction in xerostomia symptoms of at least 25mm (VAS), although the precise magnitude and clinical significance were unclear. This study was considered at unclear risk of detection bias. Vivino reported in a study deemed at unclear risk of selection bias that after 12 weeks of therapy with 5mg of pilocarpine more individuals in the intervention group (61% vs 31%; $P<0.05$) compared to the placebo group experienced a reduction in xerostomia symptoms of at least 25mm (VAS) (Vivino et al., 1999). The exact magnitude, clinical significance and the timing of xerostomia measurement were unclear. The study also reported a short-term (measured at 60 minutes) increase in salivation from baseline, which was higher in the intervention group compared to placebo [0.27 vs 0.06 mL/min (mean value); $P<0.05$), suggesting a large effect size, although the clinical significance remains unclear. Wu et al observed in a 12-week clinical trial at low risk of bias that a higher

proportion of patients taking 20mg/day of pilocarpine (69% vs 23%; P<0.05) reported a reduction in dry mouth symptoms of at least 25mm on VAS compared to those in the placebo arm (Wu et al., 2006). They reported that the number of individuals experiencing any short-term (60min) increase in salivary flow was higher in the intervention group (65% vs 28%; P<0.05) than in the placebo, although clinical significance was unclear. They also reported a significantly higher short-term increase in unstimulated whole salivary flow (uWSF) in the pilocarpine group than in those using placebo (0.05mL/min vs -0.02mL/min; median P<0.05), which was again of unclear clinical significance. The effect size could not be calculated.

Cifuentes et al observed in a clinical trial at low risk of bias a significantly higher unstimulated salivary flow rate at 12 weeks in patients taking ten drops of pilocarpine (5 mg) three times a day versus 10 drops of artificial saliva (Oral Schirmer Test: 0.924cm/min vs 0.297cm/min; P<0.05) (Cifuentes et al., 2018). These results suggest a large effect size but unclear clinical significance. Timing of outcome measurement was unclear. Changes in xerostomia symptoms were not reported.

Electrostimulation vs. placebo

Two double-blind studies investigated the use of an intra-oral electro-stimulating device vs a sham device. Steller reported a significant difference in post-stimulation salivary flow between the two groups [0.08 vs -0.01 mL/min (mean difference); P<0.05] at 4 weeks from baseline (long-term effect), which indicates a medium effect size but is of unclear clinical significance (Steller et al., 1988). This study was considered at unclear risk of selection bias. Talal reported in study at low risk of bias that participants using the electrostimulating device for four weeks had a short-term increase in salivary flow rate that was significantly different than those using a sham device [0.141 vs 0.051 mL/min (mean change); P<0.05]; however the increase was of unclear effect size and clinical significance (Talal et al., 1992).

Acupuncture/laser acupuncture vs. placebo or sham laser acupuncture

The effectiveness of acupuncture or laser acupuncture in reducing dry mouth symptoms or increasing salivary flow was assessed in two studies (List et al., 1998, Cafaro et al., 2014). List et al failed to show any significant difference in xerostomia (VAS) and salivary flow after 10 weeks treatment with acupuncture compared to no treatment in a trial at high risk of performance bias due to the unblinded designs (List et al., 1998). Cafaro et al investigated the effects of 5 weekly sessions of active versus sham laser acupuncture and reported a statistically significant short and long-term higher salivary flow (4.69 vs 0.91 mm/min at 6 months; $P<0.05$) in the active group (Cafaro et al., 2014), which suggests a large effect size, although clinical significance remains unclear. This study was considered at unclear risk of bias due to unclear blinding design.

Biologic response modifier vs placebo

Nine trials investigated the therapeutic efficacy of biologic response modifier agents (infliximab, etanercept, rituximab and interferon-α).

Mariette et al reported in a placebo-controlled trial at low risk of bias no significant changes in long-term (week 10) salivary flow rates or dryness (most disturbing site – xerostomia in 53% of cases, using an arbitrary 30% reduction as endpoint) after 3 infusions of infliximab 5mg/kg or placebo (week 0, 2 and 6) (Mariette et al., 2004).

Sankar et al investigated the effects of 25 mg of etanercept (twice a week for 12 weeks) versus placebo (Sankar et al., 2004) and reported no significant change in dry mouth symptoms or sialometry (using an arbitrary 20% improvement as endpoint). This study was considered to be at low risk of bias.

Rituximab was tested in three placebo-controlled studies at low risk of bias. Meijer studied the effect of two infusions of 1,000mg rituximab over 15 days and reported a significant long-term (at 12 weeks) increase in uWSF (mean 0.06 vs -0.01 ml/min; $P<0.05$) with respect to placebo, which suggests a large effect size (Meijer et al., 2010). Of note the magnitude of the effect

decreased beyond 12 weeks' endpoint. The study also reported a significant long-term reduction in xerostomia symptoms (VAS) and quality of life (SF-36) at week 24 (-21 vs +5 mm mean VAS; P<0.05), which indicates a large effect size. Of note, the effect was sustained up to week 48. However, the clinical significance of both salivation and xerostomia changes remains unknown. These results were however not replicated in the study of Devauchelle-Pensec et al, which failed to show an improvement in generalized dryness (using an arbitrary 30mm as endpoint) and salivary flow at 24 weeks (Devauchelle-Pensec et al., 2014). Recently, Bowman et al reported that the administration of second course of Rituximab 1000mg at 6 months (2 infusions at weeks 24 and 26 in addition to week 0 and 2) was not associated with a significant reduction in dry mouths symptoms (using an arbitrary 30% reduction as endpoint) at 48 weeks. However, there was a significantly different long-term increase in unstimulated salivary flow between groups (0.06 vs 0.04mL/min; P<0.05), which corresponds to a small effect size of unknown clinical significance (Bowman et al., 2017).

Four clinical trials investigated the use of interferon-α in SS. Shiozawa reported in a trial at high risk of performance, detection and reporting bias that a 6-months course of 150 IU interferon-α given orally three times a day vs sucralfate (250 mg) (Shiozawa et al., 1998) led to a significantly higher short-term increase in unstimulated salivary flow at 6-month (0.25 vs -0.05 mL/min; P<0.05) is to be considered of moderate to large effect size, althouth clinical significance remains unclear.

Ship studied in a 12-week trial at unclear risk of selection bias (Ship et al., 1999) the effects of different doses of interferon-α lozenges (150 IU once and three times a day, 450 IU once three times a day) vs. placebo. The study failed to show significant changes in xerostomia symptoms (defined as VAS 25mm improvement) and unstimulated salivary flow, whereas short-term stimulated salivary flow was increased in the 150 IU three times daily group compared to placebo at week 12 (0.158 vs 0.01 mL/min; P<0.05), which suggests a large effect size but unclear clinical significance.

Khurshudian reported in a trial at unclear risk of selection bias that participants receiving 150UI interferon-α three times a day for 24 weeks had a statistically significant short-term improvement in unstimulated salivary flow rate [0.10 vs 0.06 mL/min; P<0.05] and oral dryness

(22.1 vs 17.6 mm, VAS mean; P<0.05) with respect to placebo (Khurshudian, 2003), with unclear effect size and clinical significance.

The effects of the same dosage of interferon-α were investigated by Cummins in a 24-week study at low risk of bias. There reported no significant changes in xerostomia symptoms (VAS), but a significant increase in unstimulated salivary flow from baseline between the groups at 24-weeks endpoint (0.04 vs 0.02 mL/min; P<0.05) (Cummins et al., 2003). The effect size and clinical significance were unclear.

Disease modifying anti-rheumatic drugs (DMARD) vs. placebo

Five clinical trials investigated the effects of DMARD (cyclosporine A, hydroxychloroquine, azathioprine, rebamipide) upon dry mouth and salivary gland function. Drosos et al. reported in a 6-month placebo-controlled study at unclear risk of selection and reporting bias that significantly more patients taking Cyclosporin 5mg/kg reported a reduction in xerostomia compared to placebo (8 vs 2 ; P<0.05) (Drosos et al., 1986). Both the subjective outcome measure and the magnitude of the improvement were unclear. There was unclear difference in salivation changes between groups.

Two trials investigated the effects of hydroxychloroquine upon xerostomia and salivary gland function. Kruize reported in a 2-year cross-over study at low risk of bias no significant difference in the number of patients reporting an improvement in dry mouth symptoms or experiencing a change in salivary scintigraphy after 1-year treatment with hydroxychloroquine (400mg/day) compared to placebo (Kruize et al., 1993). Gottenberg similarly reported in a study at low risk of bias no difference in the number of participants having a 30% reduction in NRS (general dryness) after 6 months of therapy with hydroxychloroquine (400mg/day) vs placebo. There was no difference between groups in terms of sialometry or ESSPRI score (Gottenberg et al., 2014).

Price et al investigated the use of azathioprine 1 mg/Kg for 6 months in a placebo-controlled trial at low risk of bias (Price et al., 1998) and reported no significant change in oral dryness (VAS) or salivary flow between groups.

The efficacy of rebamipide (100mg 3 times/day) compared to placebo was tested in a study with unclear risk of selection bias by Sugai (Sugai et al., 2009), who reported no changed in xerostomia symptoms (VAS) and salivary function.

Others interventions vs. other interventions or placebo

Theander reported a 6-months trial investigating the use of gammalinolenic acid emulsion, which was suggested to have anti-inflammatory effects, compared to corn oil (placebo). The study failed to show any significant change in xerostomia symptoms; there was unclear difference among groups in salivary flow changes (Theander et al., 2002). The study was considered at unclear risk of selection, performance and detection bias.

Two studies at unclear risk of selection bias assessed the efficacy of oral dehydroepiandrosterone (DHEA) for 6 (Pillemer et al., 2004) or 12 months (Hartkamp et al., 2008). Pillemer reported no changes in salivary flow but a significant improvement in xerostomia symptoms (+9 vs -10 mm, VAS mean; $P<0.05$) with respect to placebo, which corresponds to a large effect size. Of note, the authors considered the change in VAS not to be clinically meaningful. The study by Hartkamp showed unclear difference in xerostomia symptoms (VAS) between groups after 12 months of therapy.

The effects of nizatidine (H2 receptor antagonist with the potential to stimulate salivary secretion) were compared to those of famotidine (another H2 antagonist) by Kasama in a 8-weeks parallel study with unclear risk of selection, performance, detection and reporting bias (Kasama et al., 2008). The authors reported that a higher proportion of participants using oral nizatidine (71% vs 15%; $P<0.05$) experienced an improvement in xerostomia symptoms (20% improvement in VAS score), although clinical meaningfulness and effect size was unclear. There was unclear difference in salivary flow changes between groups.

Singh reported in a study at unclear risk of selection bias no significant difference in the number of patients having a reduction in dry mouth symptoms or increase in salivary flow after 3-month use of different dosages of omega-3 and Vitamin E capsules (1750 mg linolenic acid/163 mg Vitamin E vs 144 mg of linolenic acid/3.63 mg Vitamin E) (Singh et al., 2010).

Hu investigated in a study at low risk of bias the effects of a 6-week course of traditional Chinese medicine compound (ShengJinRunZaoYangXue) vs placebo (Hu et al., 2014). They reported a significant difference in the change in xerostomia symptoms (0.83 vs 1.1 on an 11-point, mean NRS P<0.05) between groups of unclear effect size and clinical meaningfulness. There was no significant change in the salivary flow rates between groups.

Meta-analysis

A total of fourteen studies allowed data meta-analysis to evaluate the primary outcome of the mean overall change in xerostomia symptoms and changes in salivary flow rate. It was not possible to meta-analyse the QoL outcomes due to differences in the outcome measures among the studies.

In relation to the primary outcome of reduction in xerostomia symptoms two comparisons were sufficiently clinically homogenous to perform statistical pooling: systemic cevimeline vs placebo (n=2) and systemic pilocarpine vs placebo (n=3) (Figure 3). Three studies, with no heterogeneity (I^2=0%) and a pooled total of 517 participants showed that the patients using pilocarpine were significantly more likely to have a 25mm or higher reduction (probably short-term) in xerostomia VAS score compared to placebo (OR of 3.79, 95% CI 2.63-5.47; p<0.00001). Two homogeneous studies (I^2=0%) with a pooled total of 180 participants showed that the use of cevimeline was associated with a higher short-term reduction in dry mouth symptoms than placebo with a mean difference of 9.85 [95% CI 1.76-17.94; p=0.02].

In relation to the secondary outcome of salivary function increase we were able to compare the effect of cevimeline vs placebo (n=2), pilocarpine vs placebo (n=2), active electrostimulation vs sham electrostimulation (n=2), rituximab vs placebo (n=3), interferon- α vs placebo (n=3) on salivary flow rates (Figure 4).

Two moderately heterogeneous studies (I^2=37) with a total of 92 participants showed a mean difference in short-term unstimulated salivary flow change of 0.16mL/min [95% CI 0.09-0.22; p<0.00001] between the participants taking one tablet of cevimeline vs placebo.

Two heterogeneous studies (I^2=68%) with a total of 298 participants indicated a mean difference in short-term unstimulated salivary flow change of 0.15 ml/min [95% CI 0.08-0.22;

p<0.0001] between the group taking one tablet of pilocarpine vs placebo.

Two studies using the first generation electrostimulating device vs sham stimulation with no heterogeneity (I^2=0%) and a total of pooled 100 participants showed a mean difference in short-term unstimulated salivary flow change between groups of 0.17mL/min [95% CI 0.11-0.23; p<0.00001]. Three homogeneous studies (I^2=9) with a total of 283 participants showed a mean difference in long-term unstimulated salivary flow change of 0.04mL/min between the rituximab and placebo arm [95% CI 0.01-0.06; p=0.002].

Three homogeneous studies (I^2=35) with a total of 553 participants taking interferon-α showed a mean difference in short-term unstimulated salivary flow change of 0.01mL/min [95% CI 0.01-0.02; p<0.00001] with respect to placebo.

Adverse events

Adverse events including nausea, sweating, headache, palpitations were observed in up to 64% and 36% of patients taking pilocarpine and cevimeline respectively. No adverse events were associated with salivary electrostimulation. Infections, serum sickness and infusion reactions were observed in up to 52% of patients taking rituximab. Interferon-alpha was associated with gastro-intestinal adverse events in up to 34% of patients.

Withdrawal from the experimental intervention compared to control was observed in up to 30% vs 16% (pilocarpine), 22% vs 22% (interferon-alpha), 21% vs 15% (cevimeline), 20% vs 10% (rituximab) and 7% vs 26% (electrostimulation) of participants.

Quality of the evidence

We have summarised the GRADE quality of evidence in Summary of findings (Table 1). The quality of evidence for cevimeline in reducing dry mouth symptoms and increasing unstimulated whole salivary flow was downgraded to low due to unclear method of randomisation, concealment of treatment allocation and imprecision. The quality of evidence for pilocarpine was high in reducing dry mouth symptoms and downgraded to moderate with regards to increasing unstimulated whole salivary flow due to the risk of inconsistency.

The quality of evidence for electrostimulation in increasing unstimulated whole salivary flow was downgraded to low due to the risk of selection bias and indirectness. The quality of evidence for rituximab and interferon-alpha in increasing unstimulated whole salivary flow was downgraded to moderate due to the risk of heterogeneity.

Discussion

Sjögren's disease is associated with a high burden of illness, poor quality of life, and increased health care costs (Vivino et al., 2016). Dryness of the mouth is reported by the vast majority of affected individuals and remains a therapeutic challenge, with no clear evidence-based guidance for clinicians currently available. This is the first systematic review that focuses on the interventions for dry mouth symptoms and reduced salivary flow of SS; it assesses a range of outcomes (dry mouth symptoms, salivary function, and QoL), as well as the duration of the effect of the interventions as measured in the trials (short vs long term changes in salivation or xerostomia), with the aim of providing a clear interpretation of the study results. We have included 36 RCTs, with a total of 3,274 randomized SS patients, which specifically tested an intervention for the management of dry mouth symptoms, hyposalivation and quality of life. Meta-analyses were only possible for 14 studies relevant the use of pilocarpine (n=3), cevimeline (n=3), salivary electrostimulation (n=2), rituximab (n=3) and interferon-α (n=3), which were also assessed as per GRADE criteria.

Our results suggest that there is high quality evidence that the use of pilocarpine is associated with a significant reduction in dry mouth symptoms, although effect size, clinical significance and duration of effect remain unclear. There is moderate quality evidence that pilocarpine can lead to a large effect size of short-term increase in unstimulated salivary flow, which is however of unclear clinical significance. With respect to cevimeline therapy, there is low quality evidence supporting (i) its clinically meaningful, moderate effect size of short-term dry mouth symptoms reduction, and (ii) the large effect size of short-term increase unstimulated salivation (unclear clinical significance). There is low quality evidence behind the short-term increase in unstimulated salivary flow associated with intra-oral electrostimulation, which is of unclear clinical meaningfulness. There is moderate quality

evidence that rituximab therapy is associated with a long-term increase in unstimulated salivary flow (small to large effect size), of unclear clinical significance. There is moderate quality evidence that INF-alpha is associated with a short-term increase in unstimulated salivary flow of unclear effect size and clinical meaningfulness.

The results of our meta-analysis and GRADE rating have practical implications as clinicians managing SS-related xerostomia should be confident about pilocarpine leading to a reduction in dry mouth symptoms and increase in salivary flow, which is likely to be short-term, of possible large effect size, but unclear clinical significance. On the contrary, our confidence in the beneficial effects of cevimeline upon xerostomia and salivation, as well as of electrostimulation upon salivation, are limited by the low quality of evidence. Clinician should be moderately confident about the long-term effects of rituximab and interferon-alpha upon unstimulated salivary flow, which are of variable effect size and unclear clinical significance. Interestingly our conclusions are in partial agreement with the recent practice guidelines developed by the Sjögren's syndrome Foundation (Vivino et al., 2016) stating that rituximab may be considered as a therapeutic option for xerostomia in patients with evidence of residual salivary production and for whom conventional therapies have proven insufficient. Of note, with respect to the outcome of dry mouth, our systematic review showed no convincing evidence that rituximab, salivary electrostimulation, and INF-alpha (data not meta-analysed) can reduce symptoms of dry mouth.

With respect to interventions that were not included in the meta-analysis, the present systematic review suggests that there is no evidence that the use of DMARDs, acupuncture, laser acupuncture, infliximab, etanercept, and other interventions (gammalinolenic acid, dehydroepiandrosterone, omega-3/ vit E, nizatidine, a traditional chinese medicine compound) can reduce symptoms of dry mouth or increase salivary flow in individuals with SS. Salivary substitutes and topical salivary stimulants are widely used in the management of xerostomia of SS (Ramos-Casals et al., 2010). We found high heterogeneity among the studies included in this systematic review and therefore no data pooling was possible. Our results indicate that there is no robust evidence that any of the salivary substitutes or topical salivary stimulants tested in the included trials is effective in reducing dry mouth symptoms or

increasing salivary flow of SS patients, due to unclear or high risk of bias, as well as unclear magnitude and effect size. Furthermore, one trial at low risk of bias reported that pilocarpine is superior to salivary substitutes at increasing salivary flow.

Assessment of changes in oral or general quality of life was performed in five studies (cevimeline n=1, infliximab n=1, rituximab n=3), and there remains no evidence that any of these interventions can lead to an improvement in the quality of life outcomes with the exception of the Rituximab study by Meijer et al.

Limitation of the study

Moderate degree of heterogeneity was observed for two of the interventions of the meta-analysis (cevimeline and pilocarpine), as indicated by an I^2 statistic value of 65-68%, which was probably due to differences in the risk of bias and led to a downgrade in the quality of evidence on the basis of inconsistency. An additional limitation of this study is that the included trials were conducted between 1981 and 2017. During this time the classification criteria of SS has changed, possibly leading to different characteristics of study populations.

Conclusion

- Clinicians should be very confident in the beneficial effects of pilocarpine upon dry mouth symptoms of SS. However adverse events are common and contributing to the reported 30% withdrawal from treatment. Similar convincing evidence with regards to cevimeline is lacking.
- With respect to increasing salivary flow of individuals with SS, there remains limited confidence in the beneficial effects of cevimeline and electrostimulation. Clinicians should be moderately confident that pilocarpine, rituximab and interferon-alpha might have beneficial effects upon salivary flow, although the effect size seems large for pilocarpine, and much smaller for rituximab and interferon-alpha. Indeed the two latter agents failed to show a significant reduction in dry mouth symptoms. Adverse events are common with these agents, contributing to the reported 30%, 20% and 22% withdrawal from treatment, respectively.
- The use of other treatment modalities cannot be supported on the basis of current evidence.

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Table 1: Summary of findings

Quality assessment							№ of patients		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Placebo/ controls**	
QUESTION: CEVIMELINE COMPARED TO PLACEBO									
Xerostomia symptoms reduction (assessed with: VAS; Scale from: 0 to 100)									
2 (Petrone et al., 2002; Fife et al., 2002)	randomised trials	serious [a]	not serious	not serious	serious [b]	none	87 (Cevimeline)	93 (Placebo)	⊕⊕◯◯ LOW
Unstimulated salivary flow (ml/min)									
2 (Fife et al., 2002; Leung et al., 2007)	randomised trials	serious [a]	serious [c]	not serious	not serious	none	75 (Cevimeline)	73 (Placebo)	⊕⊕◯◯ LOW
QUESTION: PILOCARPINE COMPARED TO PLACEBO									
Xerostomia symptoms (reduction of at least 25mm on VAS)									
3 Papas et al., 2004; Vivino et al., 1999; Wu et al., 2006	randomised trials	not serious	not serious	not serious	not serious	none	261 (Pilocarpine)	256 (Placebo)	⊕⊕⊕⊕ HIGH
Unstimulated salivary flow (ml/min)									
2 (Vivino et al., 1999; Wu et al., 2006)	randomised trials	not serious	serious [c]	not serious	not serious	none	150 (Pilocarpine)	148 (Placebo)	⊕⊕⊕◯ MODERATE
QUESTION: ACTIVE ELECTROSTIMULATION COMPARED TO SHAM ELECTROSTIMULATION									

Unstimulated salivary flow (ml/min)									
2 (Steller et al., 1988; Talal et al., 1992)	randomised trials	serious [a]	not serious	serious [d]	not serious	none	48 (Active electrostimulation)	52 (Sham electrostimulation)	⊕⊕◯◯ LOW
QUESTION: RITUXIMAB COMPARED TO PLACEBO									
Unstimulated salivary flow (ml/min)									
3 (Bowman et al., 2017; Devauchelle-Pensec et al., 2014; Meijer et al., 2010)	randomised trials	not serious	serious [c]	not serious	not serious	none	150 (Rituximab)	133 (Placebo)	⊕⊕⊕◯ MODERATE
QUESTION: INTERFERON-ALPHA COMPARED TO PLACEBO									
Unstimulated salivary flow (ml/min)									
3 (Cummins et al., 2003; Khurshudian, 2003; Ship et al., 1999)	randomised trials	not serious	serious [c]	not serious	not serious	none	330 (Interferon-alpha)	223 (Placebo)	⊕⊕⊕◯ MODERATE

GRADE Working Group grades of evidence:

• **High**: we are very confident that the true effect lies close to that of the estimate of the effect.

• **Moderate**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

• **Low**: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

• **Very low**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Quality of evidence downgraded one level on the basis of unclear risk of selection bias

b. Quality of evidence downgraded one level on the basis of imprecision due to wide 95% CI

c. Quality of evidence downgraded one level on the basis of heterogeneity

d. Quality of evidence downgraded one level on the basis of indirectness

Table 2. Randomised controlled trials investigating treatment for xerostomia and/or hyposalivation of Sjögren's Syndrome

	Authors	Number of patients	Study design	Intervention	Xerostomia (dry mouth symptoms)	Salivary function	Quality of Life	Bias risk	Included in the meta-analysis
SALIVA SUBSTITUTES vs PLACEBO OR ANOTHER SUBSTITUTE (N=3)									
1	Klestov et al., 1981	108	Parallel double-blind controlled	New developed salivary substitute based on a sodium phosphate vs glycerine mouthwash	Significantly more participants on the new salivary substitute vs glycerine mouthwash had less dry mouth at night and reported "excellent improvement" (21.1% vs 5.3% on 5-point Liker questionnaire; P<0.05) after one course of treatment. Unclear magnitude and effect size.	N.A	N.A.	Unclear	No

2	Van Der Reijden et al., 1996	43	Parallel double-blind placebo-controlled	Spray containing Poly acrylic acid (PAA), Xanthan gum (XG) and Porcine gastric mucin (PM) vs placebo	No significant difference in reduction of patient's symptoms (NRS) between groups.	Unclear effects upon uWSF.	N.A.	Unclear	No
3	Johansson et al., 2001	22	Cross-over double-blind controlled	Salinum without chlorhexidine (SAL) vs Salinum with chlorhexidine (SAL/CHX)	More participants in the test group (15 vs 11; P<0.05) reported a reduction in xerostomia symptoms on a 6-point Likert scale with respect to the control group. Unclear magnitude and effect size.	No significant changes in uWSF.	N.A	Unclear	No
TOPICAL SALIVA STIMULANT vs OTHER STIMULANT OR PLACEBO (N=2)									
4	Gravenmade & Vissink, 1993	42	Cross-over double-blind placebo-controlled	Mucin lozenges vs placebo	Significantly larger reduction in xerostomia symptoms compared to placebo lozenges (magnitude 1.7 vs 1 on a 5-point Likert scale; P<0.05). Unclear effect size.	N.A.	N.A.	High	No
5	Da Silva Marques et al., 2011	80	Parallel double-blind controlled	Malic acid gustatory stimulant vs citric acid gustatory stimulus	N.A	No significant difference in WSF changes between groups.	N.A.	Low	No
SYSTEMIC CHOLINERGIC AGONISTS vs PLACEBO or SALIVARY SUBSTITUTES (n=7)									

6	Petrone et al., 2002	197	Parallel double-blind placebo-controlled	Cevimeline vs placebo	Short-term (60min) significant difference in VAS score change between the groups (-27mm vs -15mm; P<0.05). Moderate effect size. Clinically meaningful as more patients using cevimeline reported an improvement in global xerostomia symptoms (3-point Likert scale).	Short-term (90min) higher increase in uWSF in individuals taking 30mg cevimeline vs placebo. Magnitude and effect size unclear. Clinically meaningful.	N.A.	Unclear	Yes
7	Fife et al., 2002	75	Parallel double-blind placebo-controlled	Cevimeline vs placebo	No difference in the number of patients reporting a short-term (60 minutes) improvement in the global dry mouth evaluation (on a 3-point Likert scale) and no difference in the change of VAS score (dry mouth) between the cevimeline group and placebo	Significantly higher short-term change in uWSF in the cevimeline group compared to placebo (0.194 vs 0.015 mL/min; P<0.05). Large effects size. Clinical significance unknown	N.A	Unclear	Yes
8	Leung et al., 2007	44	Cross-over double-blind placebo-controlled	Cevimeline vs placebo	No statistical significance change in XI between groups.	No statistical difference between groups in sWSF and parotid SF.	No statistical significance change in GOHAI and SF-36 between groups.	Low	Yes

9	Papas et al., 2004	256	Parallel double-blind placebo-controlled	Pilocarpine vs placebo	More individuals in the pilocarpine group (61% vs 31%; P<0.05) reported a reduction in xerostomia symptoms of at least 25mm (VAS). Unclear magnitude, effect size and clinical significance.	Significantly higher short-term (60 minutes) increase in uWSF than placebo. Unclear magnitude, effect size and clinical significance.	N.A.	Unclear	Yes
10	Vivino et al., 1999	252	Parallel double-blind placebo-controlled	Pilocarpine vs placebo	More individuals in the intervention group (61% vs 31%; P<0.05) compared to the placebo group experienced a reduction in xerostomia symptoms of at least 25mm (VAS). Unclear magnitude, effect size and clinical significance.	Significantly higher short-term (60 minutes) increase in uWSF than placebo (0.27 vs 0.06 mL/min; P<0.05). Large effect size. Unclear clinical significance.	N.A	Unclear	Yes

11	Wu et al., 2006	44	Parallel double-blind placebo-controlled	Pilocarpine vs placebo	More individuals in the intervention group compared to the placebo group (69% vs 23%; P<0.05) experienced a reduction in xerostomia symptoms of at least 25mm (VAS). Unclear magnitude, effect size and clinical significance.	More individuals in the intervention group than in the placebo (65% vs 28%; P<0.05) experienced any short-term (60min) increase in uWSF. Unclear effect size and clinical significance. Also greater increase in median uWSF change in the pilocarpine group (0.05 mL/min) vs placebo. (0.02 mL/min) P<0.05. Unclear effect size and clinical significance.	N.A	Low	Yes

12	Cifuentes et al., 2008	72	Parallel double-blind controlled	Pilocarpine vs salivary substitutes	N.A.	Significantly higher unstimulated salivary flow rate at 12 weeks in patients taking ten drops of pilocarpine (5 mg) three times a day versus 10 drops of artificial saliva (mean UWSF 0.924cm/min vs 0.297cm/min ; P<0.05). Large effect size but unclear clinical significance.	N.A	Low	No
ELECTROSTIMULATION vs SHAM STIMULATION (N=2)									
13	Steller et al., 1988	29	Parallel double-blind sham-controlled	Active vs sham Electrostimulating device	Unclear effects upon dry mouth symptoms	Significantly higher long-term (4 weeks) increase in sWSF than sham stimulation (mean change 0.08 vs -0.01 mL/min; P<0.05). Medium effect size. Unclear clinical significance.	N.A.	Unclear	Yes

14	Talal et al., 1992	77	Parallel double-blind sham-controlled	Active vs sham Electrostimulating device	No statistical significant change in dry mouth symptoms (not validated questionnaire) between groups.	Significantly higher short-term (immediately after application) increase in uWSF than sham stimulation (0.141 vs 0.051 mL/min; mean; P<0.05). Unclear effect size and clinical significance.	N.A.	Low	Yes
ACUPUNTURE/LASER ACUPUNCTURE vs NO TREATMENT or SHAM LASER ACUPUNCTURE (N=2)									
15	List et al., 1998	21	Open-label	Acupuncture vs no treatment	No statistical significance change in dry mouth symptoms (VAS) between groups.	No significant difference between groups in uWSF or sWSF.	N.A.	High	No
16	Cafaro et al., 2014	26	Open-label	True laser acupuncture vs sham laser acupuncture	N.A.	Significantly higher short-term (immediately after application) and long-term (6 months) increase in uWSF than sham laser acupuncture (4.69 vs 0.91 mL/min; mean; P<0.05); Large effect size. Unclear clinical significance.	N.A.	High	No
BIOLOGICAL RESPONSE MODIFIER vs PLACEBO (N=9)									

17	Mariette et al., 2004	103	Parallel double-blind placebo-controlled	Infliximab vs placebo	No significant difference in dry symptoms between groups (using an arbitrary 30% VAS reduction as outcome) at 10-week endpoint.	No significant difference in uWSF between groups at 10-week endpoint.	No significant difference in SF-36 between groups.	Low	No
18	Sankar et al., 2004	28	Parallel double-blind placebo-controlled	Etanercept vs placebo	No significant difference in dry mouth symptoms between groups (using an arbitrary 20% VAS change as outcome).	No significant difference in sWSF between groups (using an arbitrary 20% change as outcome) at 12-week endpoint.	N.A.	Low	No
19	Meijer et al., 2010	30	Parallel double-blind placebo-controlled	Rituximab vs placebo	Significant difference in dry mouth symptoms between groups (-21 vs 5mm; VAS mean change; P<0.05) at 24-week endpoint. Large effect size. Unclear clinical significance.	Significantly higher long-term increase in uWSF in the active group vs placebo at 12-week endpoint (0.06 vs -0.01 ml/min; P<0.05). Large effect size. Unclear clinical significance.	Significant improvement in SF-36 score (from baseline to week 36) in the test group. Effect size: mean at week 36: 60 vs 63. P<0.05	Low	Yes

20	Devauchelle-Pensec et al., 2014	120	Parallel double-blind placebo-controlled	Rituximab vs placebo	No significant difference in dry mouth symptoms between groups (using an arbitrary >30mm VAS change as outcome) at 24-week endpoint	No significant difference in uWSF between groups at 24-week endpoint.	No significant differences in the SF-36 between groups at 24-week endpoint.	Low	Yes
21	Bowman et al., 2017	133	Parallel double-blind placebo-controlled	Rituximab vs placebo	No significant difference in dry mouth symptoms between groups (using an arbitrary 30% VAS reduction as outcome) at 48-week endpoint.	Significantly different increase in uWSF between groups (0.06 vs 0.04mL/min; P<0.05) at 48-week endpoint. Small effect size. Unclear clinical significance	No significant differences in the SF-36 between groups.	Low	Yes
22	Shiozawa et al., 1998	60	Parallel single-blind controlled	Interferon-α vs Sucralfate	N.A.	Significant difference in uWSF short-term changes (0.25 vs -0.05 mL/min; P<0.05) between groups after 6-month of therapy. Moderate to large effect size. Unclear clinical significance.	N.A.	High	No

23	Ship et al., 1999	109	Parallel double-blind placebo-controlled	Interferon-α vs placebo	No significant difference in dry mouth (using an arbitrary 25mm improvement as outcome) VAS between groups.	No significant difference in uWSF changes between groups. Significant difference in sWSF short-term (60 min) changes between groups at week 12 (0.158 vs 0.01 mL/min; P<0.05). Large effect size. Unclear clinical significance.	N.A.	Unclear	Yes
24	Khurshudian, 2003	12	Parallel double-blind placebo-controlled	Interferon-α vs placebo	Significant difference in VAS score change between the groups at 24 weeks (22.1 vs 17.6 mm; P<0.05). Unclear effect size and clinical significance.	Significant short-term difference in uWSF between groups at week 24 [0.10 vs 0.06 mL/min; P<0.05]. Unclear effect size and clinical significance.	N.A.	Unclear	Yes

25	Cummins et al., 2003	497	Parallel double-blind placebo-controlled	Interferon-α vs placebo	No significant difference in the mean change in VAS dry mouth scores between groups.	Significant difference in uWSF between groups at week 24 (0.04 vs 0.02 mL/min; P<0.05). Unclear effect size and clinical significance. No significant difference in sWSF between groups.	N.A.	Low	Yes
DISEASE MODIFYING ANTI-RHEUMATIC DRUG vs PLACEBO (N=5)									
26	Drosos et al., 1986	20	Parallel double-blind placebo-controlled	Cyclosporin A vs placebo	Significantly more patients taking Cyclosporin reported a reduction in xerostomia compared to placebo (8 vs 2; P<0.05). Unclear magnitude, effect size and clinical significance.	Unclear difference in uWSF between groups.	N.A.	Unclear	No
27	Kruize et al., 1993	19	Cross-over double-blind placebo-controlled	Hydroxychloroquine vs placebo	No significant difference in the number of patients reporting an improvement in dry mouth symptoms between groups.	No significant difference in salivary scintigraphy measurements between groups	N.A	Low	No

28	Gottenberg et al., 2014	120	Parallel double-blind placebo-controlled	Hydroxychloroquine vs placebo	No significant difference in the number of participants having a 30% reduction in NRS (general dryness) between groups. No difference between groups in terms of ESSPRI score	No significant change in uWSF between groups.	N.A	Low	No
29	Price et al., 1998	25	Parallel double-blind placebo-controlled	Azathioprine vs placebo	No significant difference in dry mouth (VAS) between groups.	No significant difference in uWSF between groups.	N.A.	Low	No
30	Sugai et al., 2008	104	Parallel double-blind placebo-controlled	Rebamipide vs Placebo	No significant difference seen in dry mouth (VAS) between groups.	No statistical difference in sWSF (Saxon's test) between groups .	N.A.	Unclear	No
OTHER AGENTS/COMPOUNDS (N=6)									
31	Theander et al., 2002	90	Open-label parallel	Gammalinolenic acid vs Corn oil	No significant change in dry mouth (VAS) between groups.	Unclear difference in uWSF between groups	N.A.	Unclear	No

32	Pillemer et al., 2004	28	Parallel double-blind placebo-controlled	Dehydroepiandrosterone vs placebo	Significant difference in dry mouth between groups at 6 months (9 vs -10 mm, VAS; P<0.05). Large effect size. Clinical significance unclear (Authors considered VAS change not to be clinically meaningful due to arbitrary 20% symptoms reduction as an outcome).	No changes in sWSF between groups.	N.A.	Unclear	No
33	Hartkamp et al., 2008	60	Parallel double-blind placebo-controlled	Dehydroepiandrosterone vs placebo	Unclear difference in xerostomia symptoms (VAS) between groups after 12 months of therapy.	N.A	N.A	Unclear	No
34	Kasama et al., 2008	27	Open-label controlled	Nizatidine vs famotidine	Higher proportion of participants using oral nizatidine (71% vs 15%; P<0.05) experienced an improvement in xerostomia symptoms (20% improvement in VAS score) at week 8. Unclear clinical significance and effect size.	Unclear difference in sWSF (Saxon's test) between groups	N.A.	Unclear	No
35	Singh et al., 2010	61	Parallel double-blind placebo-controlled	Omega-3 and Vitamin E supplements vs wheat germ oil	No significant difference in dry mouth (VAS) seen between groups after 3 months of therapy.	No significance in difference in uWSF and sWSF between groups at 3 month endpoint.	N.A.	Unclear	No

36	Hu et al., 2014	240	Parallel double-blind, placebo-controlled	ShengJin RunZao YangXue vs placebo	Significant difference in the change in xerostomia symptoms (0.83 vs 1.1 on an 11-point, mean NRS; P<0.05) between groups after 6 weeks of therapy. Unclear effect size and clinical meaningfulness	No significant difference in WSF between groups at week 6.	N.A.	Unclear	No
uWSF: unstimulated whole salivary flow. sWSF: stimulated whole salivary flow									

Table 3. Characteristics of included studies

Studies included in the review and meta-analysis (n)	Systematic review (36) Meta-analysis (14)
SS Classification criteria used in the reviewed studies (n)	Fox's classification criteria (2) The Copenhagen criteria for Sjögren's syndrome (2) Preliminary criteria for the classification of Sjögren's syndrome (7) American-European Consensus Group Sjogren's syndrome classification criteria (18)
Interventions used in the reviewed studies (n)	Topical saliva substitutes (3) Topical saliva stimulants (2) Systemic cholinergic agonists (7) Electrostimulation (2) Acupuncture/laser acupuncture (2) Biologic response modifier/biological agents (9) Disease modifying anti-rheumatic drugs (5) Dehydroepiandrosterone (2) Gammmalinolenic acid (1) Nizatidine (1) Omega-3 supplements (1) Traditional Chinese medicine (1)
Comparators used in the reviewed	Placebo (24)

studies (n)	Another active intervention (8) Sham intervention (3) No treatment (1)
Outcomes used in the reviewed studies (n)	**Xerostomia symptoms (29)** 0-100 mm VAS (16) 0-12.8 cm VAS (1) Xerostomia Inventory (1) Likert scale of improvement (9) 0-10 numerical rating scale (1) ESSPRI (1) **Salivary function (32)** Sialometry (31) Scintigraphy (1) **Quality of Life (5)** GOHAI (1) SF-36 (4)
Timing of outcome measurement in reviewed studies (n)	**Xerostomia symptoms:** Shortly after administration of the intervention (3) 60 minutes after administration of the intervention (2) One or more weeks after the intervention (7) Unclear (17) **Salivary function:** Shortly after administration of the intervention (4) 60 minutes after administration of the intervention (4) 90 minutes after administration of the intervention (1) One or more weeks after the intervention (3) Unclear (20)