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Effectiveness of pharmacological interventions for Sjogren syndrome - A systematic review

Ruchika Choudhary [1], Sujatha S. Reddy [2], Rakesh Nagaraju [3], Ravleen Nagi [4], Pooja Rathore [5], Ritu Sen [5], Haripriya [6]

[1] Assistant Professor, Jaipur Dental College and Hospital, Maharaja Vinayak Global University, Jaipur, Rajasthan
[2] Professor, Department of Oral Medicine and Radiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India
[3] Professor and Head, Department of Oral Medicine and Radiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India
[4] Reader, Department of Oral Medicine and Radiology, Saveetha Dental College, Velappanchavadi, Chennai, Tamil Nadu, India
[5] Post Graduate Student, Department of Oral Medicine and Radiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India
[6] Post Graduate Student, Department of Oral Medicine and Radiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore, Karnataka, India

Correspondence:
Jaipur Dental College and Hospital
Maharaja Vinayak Global University
Jaipur, Rajasthan, 302028
drruchikac@gmail.com

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Abstract

Background: Sjogren's Syndrome (SS) is characterized by xeropthalmia and/or xerostomia. Treating the associated salivary gland hypofunction has been challenging to the clinicians. A variety of topical and systemic therapies have been tried to restore/stimulate the gland function or replace saliva reducing the symptoms of xerostomia and to avoid the problems of diminished salivary flow.

Material and Methods: Four search engines (PUBMED/Medline, EMBASE, Google Scholar and The Cochrane) were used in conducting a systematic review using the terms "Sjogren's syndrome" with the combination of other terms. To define these study acceptability criteria, we used PICO model (Population, Intervention, Control and Outcome) and study design technique.

Results: Out of 47 articles initially screened, 28 studies met our selection criteria. Included studies showed positive results with interventions such as pilocarpine, rituximab, and interferon-alpha (IFN-α) for enhancing salivary flow and lacrimal secretion in SS condition. One study showed promising results for combination of prednisone and hydroxychloroquine in SS, however dose of prednisone is recommended to be tapered. Another study demonstrated comparable effects of dehydroepiandrosterone and the placebo in alleviation of dry mouth symptoms (p=0.006). Therapeutic effects have been reported with LASER therapy.

Conclusions: Pilocarpine was found to be highly beneficial whereas, rituximab and IFN-α were moderately effective in the reduction of hyposalivation in SS patient. Adverse events were common. Use of any alternative modalities for the management cannot be supported based on the current evidence; this demands more studies in future to be conducted staking into account adverse effects which might occur particularly with the pharmacological therapies.

Key words: *Sjogren's Syndrome, Xerostomia, Hyposalivation, Pilocarpine, Rituximab, Sialagogue.*

Introduction

Sjogren's Syndrome (SS) is considered autoimmune, chronic inflammatory condition, which mainly affects the exocrine glands with sicca symptoms following, such as xerostomia (dry mouth), xerophthalmia (dry eyes) and parotid gland enlargement. It is often times referred to as an autoimmune exocrinopathy' (Fox and Speight, 1996). Approximately, 0.5-1% of the population, involves middle-aged women more frequently as compared to men, with ratio of 9:1 (1). The condition usually arises between fourth to sixth decade of life, although it can appear at any age. Various factors found to be associated with the pathogenesis of disease include immunologic, inflammatory, genetic, epigenetic, environmental, hormonal, and infectious agents (Mavragani & Moutsopoulos, 2010). It can be primary sjogren's syndrome (pSS) which frequently occurs when there is no underlying cause for rheumatic disorder or secondary sjogren's syndrome (sSS) that is reported to be related with another rheumatic disease, such as systemic lupus erythematosus, scleroderma, rheumatoid arthritis (RA), dermatomyositis, or primary biliary cirrhosis.

Circulating autoantibodies (anti-Ro, anti-La, ANA, etc.) and lymphocytic infiltrates in exocrine glands are the characteristic autoimmune features of the condition. Both findings are considered in the diagnostic criteria (Vitali *et al*., 2002). In relation to the same context, the inflammatory cells play a major role in the pathogenesis, attacking the epithelial cells (Manoussakis & Kapsogeorgou, 2010). As suggested by an important body of evidence, other factors promote the loss of epithelial cell homeostasis, occurring in the pre-autoimmune phase or independent of inflammatory cells (Delaleu *et al*., 2011, Perez *et al*., 2000, Ewert *et al*., 2010). Many classification criteria have been suggested for pSS (2,3). The American-European Consensus Group (AECG) proposed a classification in 2002, which is widely accepted now-a-days. Other classifications that have been accepted as a diagnosis criteria are the ones proposed by the Sjogren's International Collaborative Clinical Allia and American College of Rheumatology (4).

The management of hypofunction of salivary glands associated to SS has been a challenging aspect for the clinicians (Montgomery-Cranny *et al*., 2014). Topical and systemic interventions have been used in several individuals with SS to attempt restoring/stimulating the functions of salivary glands or replacing saliva, so to lessen the distressing symptoms of xerostomia and preventing complications of decreased or deficient salivation (Saraux *et al*., 2016). Other alternatives for stimulating residual salivary function includes topical sialogogues such as sugar-free chewing gum and lozenges (Glore *et al*., 2009), and para-sympathomimetics drugs like cevimeline (Petrone *et al*., 2002) and pilocarpine (Vivino *et al*., 1999). In the conditions where the gland is irreversibly compromised, varied range of saliva substitutes including sprays and gels can be used (Saraux *et al*., 2016). Traditional disease-modifying anti-rheumatic drugs (DMARDs) are known to have little to no effect on salivation (van Nimwegen *et al*., 2016); however, more recent B cell-targeted agents have been recommended (Rituximab, an anti-CD20 agent) and/or suggested to represent the positive therapeutic/management strategy, including agents targeting B-cell homeostasis cytokines (e.g., IL-6 and BAFF) (Vivino *et al*., 2016, Cornec *et al*., 2013). Non-pharmacological therapies such as acupuncture (Cafaro *et al*., 2014) and salivary neuro-electrostimulation (Fedele *et al*., 2008) have also been used to improve saliva production and alleviate dry mouth symptoms. Overall, there is a scarcity of solid evidence to inform and guide the clinicians about the effectiveness of various therapies that can be utilized in the treatment of hypo-functioning of salivary glands and symptoms of xerostomia associated with SS.

The existing systemic reviews published in the literature have predominantly focused on the SS and have included the studies recruiting the investigations of SS and different treatment modalities in different etiological factors.

As a result, treatment decisions in everyday practice are likely to be relied on a combination of personal experience, expert opinion, and low-quality evidence from published studies. As a result, we conducted this multi-therapy systematic review in order to assess and estimate the efficacy of available treatment choices in individuals with SS.

Material and Methods

-Focused Questions

Based on the PRISMA guidelines and Preferred Reporting Items for Systematic Reviews, a focused question was constructed. The addressed focused questions were:

1. Effective management of oral manifestation of Sjogren's syndrome?
2. What are the most commonly prescribed treatment regimens for SS?
3. Adverse effect during or post-treatment?

-Study Inclusion Criteria/ Eligibility Criteria

Study inclusion criteria were (i) design: randomized controlled trials (RCT), original investigations, clinical studies: (ii) population: above 18 years diagnosed with SS (pSS or sSS) (iii) intervention: investigation and treatments designed to treat oral manifestation of SS; (iv) control group: placebo, another active intervention, no treatment or in conjunction of the aforementioned. Any route, formulation or dose can be used for administering the interventions. The studies that have been included should contain sufficient, clear information on the effect of the experimental treatment upon the clinical outcomes and written solely articles in English. Review

papers, experimental research, letter to the editors, and unpublished works were not taken into account.

-Literature search/ Search Strategy

For the identification of studies included for this review, we developed detailed search strategies and each database (PUBMED/Medline, Google Scholar, The Cochrane Central Register of Controlled Trials and EMBASE) were searched from 2000 to 2021. The following terms were used in the search of all trials registers and databases: xerostomia, hyposalivation, Sjogren's syndrome, treatment, sialagogue, saliva substitute etc. Two authors independently reviewed and double-checked the title and abstracts of articles. Using the abstract and title eligibility criteria, the whole texts of eligible articles were reviewed and independently assessed. The authors then discussed and agreed on reference lists for original and review research that they considered was relevant (Fig. 1). In the initial search 47 articles were screened. Out of them, 28 studies were included depending on the eligibility criteria and data was extracted. For summarizing the important data, the current study was designed. This systematic review strictly adheres to the PRISMA statement (Moher *et al*., 2009).

Results

The study selection process is represented in Figure 1, which included 28 studies in a systematic review. The following classification criteria were used in the diagnosis of patients with SS condition who were selected for this study: Fox's classification criteria (Fox *et al*., 1986), Copenhagen criteria for Sjogren's syndrome (Manthorpe *et al*., 1986), the preliminary criteria for the classification of Sjogren's syndrome (Vitali *et al*., 1993) and the American European Consensus Group (AECG) Sjogren's syndrome classification criteria (Revised Europe Community Study Group) (Vitali, 2002).

Interventions included topical saliva substitutes (1 studies), topical saliva stimulants (3 studies), systemic cholinergic agonists (4 studies), LASER therapy (2 studies), biologic response modifier biological agents (6 studies), disease modifying anti-rheumatic drugs (1 studies) and Dehydroepiandrosterone (1 studies), combination of systemic cholinergic agonist and anti-rheumatic drugs (1 studies), Corticosteroids (7 studies.

Discussion

● Topical salivary stimulants vs. Alternative salivary stimulants or placebo (lozenge)

Casey Means *et al*. (2017) (5) reported a case of a healthy male patient aged 10 years with the history of bilateral juvenile recurrent parotitis and bilateral floor-of-mouth ranulas. The patient's medical history was important for the subjective complaints of dry eyes and history of dental caries. The patient and his family denied a history of

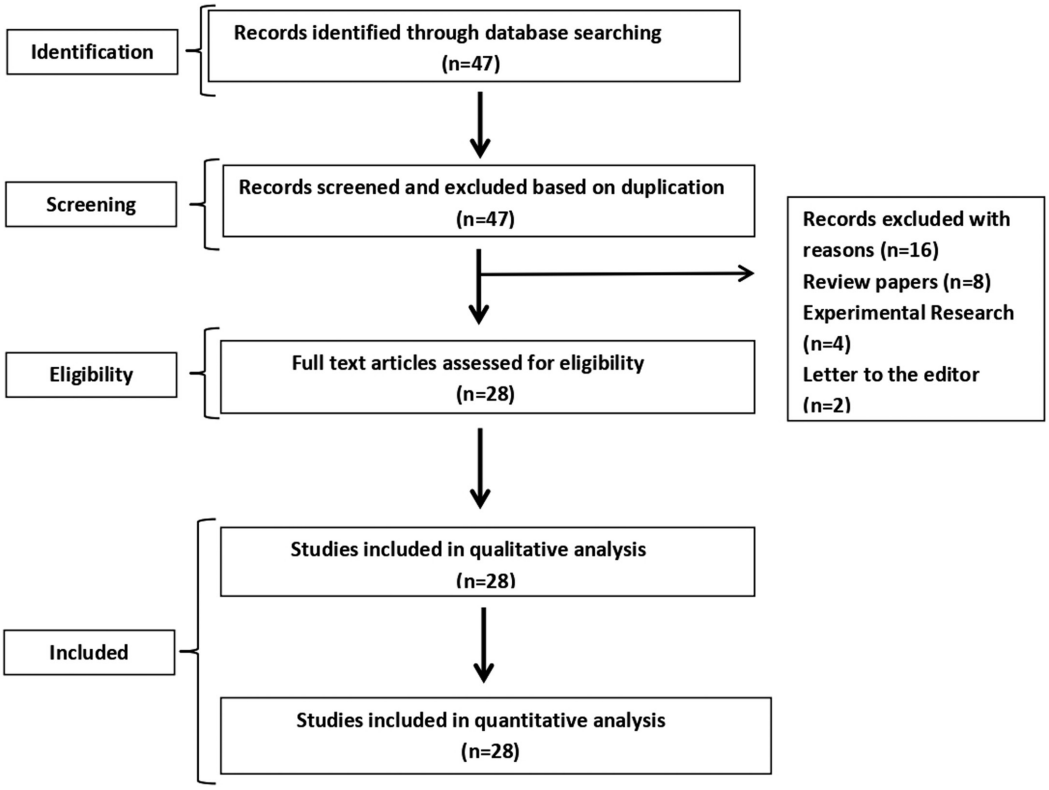

Fig. 1: Study Selection process.

trauma in relation to floor of the mouth, before the onset of swelling on both sides. He continued to have very frequent episodes of bilateral parotid gland swelling, treated with massage and sialagogues.

● Cholinergic agonists (Systemic) (cevimeline and pilocarpine) vs. placebo or saliva substitutes M. Cifuents *et al*. (2018) (6) reported double-blinded, randomized, controlled study in that 72 patients (69 women and 3 men) with SS were randomly assigned to receive 10 drops of pilocarpine (5mg) or 10 drops of artificial saliva, orally, three times/day for 12 weeks. They concluded that pilocarpine is more effective than artificial saliva for enhancing salivary and lacrimal secretion in patients with SS. Sialorrhea and nausea were two most common side effects reported.

Athena S. *et al*., (2004), (7) reported a trial that was placebo-controlled in 256 patients evaluating the effectiveness and safety of pilocarpine (orally) (20 mg -30 mg/daily) to relieve the symptoms of associated with SS. Symptoms and salivary flow changes were recorded over a 12-week period. Compared to placebo, the patients who received pilocarpine have shown significantly increased secretion after the first dose and through-out the study ($P \leq 0.0001$). Throughout the study, treated patients reported a positive improvement in the overall evaluation of patients with xerostomia/dry mouth (P 0.0001) and 5 out of 7 separate oral symptoms were alleviated ($P \leq 0.02$). At 12 weeks (5-7.5 mg dose), both pilocarpine groups were of the overall dry ice core, whereas 3 of the 8 ocular symptoms showed a slight difference at 6 weeks (5 mg dose). Significant improvement was shown ($P \leq 0.0001$) and 6 of the 8 associated symptoms ($P \leq 0.04$) were alleviated. At both the doses, the drug was reported to be well tolerated. The most commonly noted pilocarpine-related side effects were urinary frequency, sweating, flushing and chills. The authors found a significant improvement in xerostomia/dry mouth symptoms at 20 mg/daily and also reduced ocular symptoms, including a reduced need for artificial tears, after increasing the dose to 30 mg / day was noted.

Rose S. Fife *et al*. (2002) (8) For 6 weeks, researchers compared cevimeline 30 mg and 60 mg to placebo and found that there was no significant differentiation within the number of individuals who experienced a short-term (60 minutes) improvement in overall xerostomia score (3-point Likert). No changes were noted in VAS score (xerostomia) between the cevimeline and placebo groups (on a scale). However, the short-term changes in flow of saliva were significantly improved in the cevimeline group than reported in patients received placebo [0.194 vs. 0.015 mL / min (mean change). P0.05], clinical significance is unknown, but it shows a large effect size. In this study, risk of attribution obfuscation was considered unknown.

Dianne Petrone *et al*. (2007) (9) reported a study where patients had been randomly randomized to take either placebo, 15mg of cevimeline 3 times/daily, or 30mg of cevimeline 3 times/daily in a 12-week research. The authors concluded that treating patients of SS with cevimeline (dosage 30 mg 3times/day) resulted in remarkable improvements in tear and salivary flow, in addition, relieving of subjective feelings of dry eyes, dry mouth and overall dryness. Both the dosages were well tolerated by the patients, and the 15mg dosage reduced some symptoms.

Seong - Min Kweon *et al*. (2018) (10) presented a rare case of amyloidosis, localized to the lacrimal gland, with SS in 45 years old women, her diagnosis was pSS based on the presented symptoms and results of the Schirmer test, serological testing, and biopsy of minor salivary gland (SG). Pilocarpine (10mg/d) and hydroxychloroquine (200mg/d) were initiated for managing patients with SS. The symptoms of dry mouth and eyes did not worsen after 6 months of initial diagnosis and no lumps suggestive of localized amyloidosis were found.

● Disease modifying anti-rheumatic drugs (DMARD) vs. placebo (cyclosporine A, hydroxychloroquine, azathioprine, rebamipide)

Kristin Houghton *et al*. (2005) (11) published a case series which included 7 children diagnosed with pSS reported at British Columbia's Children's Hospital (BCCH) and were reviewed for pediatric and AECG criteria for pSS. Most of the patients were treated with hydroxychloroquine and it was found to be helpful in resolution of xerostomia and dysphagia with no additional anaphylactic episodes or new symptoms.

Alternative interventions vs. Alternative interventions or placebo (dehydroepiandrosterone)(DHEA)

A. Hartkamp *et al*. (2007) (12) reported a RCT (double blinded) which was placebo-controlled, 60 female patients having pSS received placebo or 200 mg oral DHEA. The outcome measures that were primarily noticed were depressive mood, mental well-being, general fatigue and physical functioning. Pain, sicca complaints, and disease activity indicators were also assessed. Patients were evaluated before starting the treatment and at 3rd, 6th, and 12th month after commencement of the medication, and at 6th month after stopping the medication. General weariness ($p = 0.001$), mental well-being ($p = 0.04$), and sad mood ($p = 0.008$) were all improved in both placebo-treated and DHEA groups. Physical performance remained unchanged ($p = 0.44$). Complaints of xerostomia reduced in both groups ($p = 0.006$), complaints of dry eyes were found to be improved with the placebo group ($p = 0.01$) and ESR decreased in the DHEA group ($p = 0.02$), according to the secondary outcome variables. Although both placebo and DHEA alleviated well-being and fatigue in female patients with pSS, this study did not demonstrate a stronger impact of DHEA when compared with placebo. This could point to need of potential cognitive behavioral therapies.

Rituximab

Z Touma *et al*. (2005) (13) reported a case report of 77-year-old women diagnosed with SS. With persistent enlargement of the parotid gland, sicca symptoms, active renal disease, and frequent recurrences of purpura and epigastric discomfort, the patient was managed with hydroxychloroquine, azathioprine, methotrexate, and cyclophosphamide (1 g/month for 6 months following with 1 g/3 months continued to be for 1 year). Prednisone was given on a daily basis but the dose was never tapered below 10 mg/day. Patient received 3 doses of infliximab 5 mg/kg due to the persistence of her symptoms, which resulted in a partial relief in her purpura and mouth dryness, but after the third treatment, patient developed pneumonia with sepsis, necessitating admission to the critical care unit. The authors decided to treat the patient with rituximab, an anti-CD20 antibody (375 mg/m2/week for 4 weeks) because her condition was refractory. Significant subjective improvement in dry eyes, parotidomegaly, dry mouth, disappearance of the purpura and decrease in the proteinuria were reported by the patient (Table 1, 1 cont-5). The patient was kept on prednisone 5mg/daily and remained in remission for 6 months following the last dose of rituximab. No side-effects were noted. Z touma *et al*. (13).conclude that favorable clinical efficacy and tolerability was demonstrated by rituximab and it also gave a promising alternative in specific patients with SS who were unmanageable with conventional treatment.

- Prednisolone

Marcosde Mendonca Invernici *et al*. (2014), (14) reported a case of 58-year-old female diagnosed with SS. She started the use of corticosteroid prednisone, 20 mg/daily, in order to control inflammation and pain. Authors concluded that it was possible to treat partially edentulous patients with SS associated with RA and diabetes, using corticosteroids and oral hyperglycemic therapy with dental implants and fixed prosthesis. Patient's comfort was significantly improved with this treatment and there was no bone loss reported even after 6 years.

Kaufman *et al*. (2008) (15) presented a rare case report of pSS with proteinuria and hypokalaemic tetraparesis due to sever interstitial nephritis, which was treated successfully with higher dosage of steroids (prednisone 20 mg/day), liquifilm eye drops and azathioprine. It was concluded that pSS patients with renal involvement can be treated with immunosuppressive therapy.

Catherine M *et al*. (2001) (16) reported a case report of African-American girl aged 14 years with bilateral parotid swelling and generalized tooth sensitivity, especially when drinking cold carbonated beverages. The patient was managed with systemic corticosteroids in low dose for the parotitis and the arthritis.

YO Ueda *et al*. (2014) (17) reported a case of 69-year-old female, diagnosed with pSS 23 years ago, developed

Table 1: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

S. No	Author	Year of Publication	Disease	Population	Case & Control	Age	Gender	Investigation Modalities	Treatment Modalities	Outcome	Follow-up
1.	Lisa Boge Christensens *et al*. (19)	2001	pSS	Denmark	Case - 53 Control- 53	27 to 61 = 24 patients; 62 to 84 years = 29 patients; mean age = 27 to 84	Female - 53; Male - 04	Interview for 30-40 minutes, Clinical Examination with artificial light, Plane Mirrors, Explores and standard Periodontal probe	Analysis of the DMFT score between pSS and control group.	Patient presented high risk of dental caries despite the relatively more regular oral health practices of these patient in comparison with the general population. PSS patient had excessive costs of dental caries.	10 years
2.	Gunvor Johansson *et al*. (26)	2001	SS	Sweden	22 Patients	The age range was 41 -84 years with mean age of 58 years	20 Female and 2 Male	Microbiological analysis, mirror friction test, and percentages of areas with tooth plaque and bleeding on probing. Oral symptom questionnaire due to decreased salivation.	Linseed extract Salinum® alone (Sal) or in addition with chlorhexidine (Sal/Cbx) was used for mouth rinsing during 3-week periods of rinsing separated by a 3-week "washout" period.	Positive effects on symptoms in patients with SS were seen after using Salinum® with or without chlorhexidine. Burning mouth symptoms, speaking problems, improved after use of Sal.	3 weeks

Table 1 cont.: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

3.	Roses Fife *et al.* (8)	2002	SS	Los Angeles, US	75 Patients with SS, 61 participants were included in the study.	Not Mentioned	Not Mentioned	**pSS-** clinical diagnosis ;1) at least 1 positive response to ocular and oral symptoms yes/no question; (2) SG and lacrimal dysfunction; and (3) positive anti-Ro and/or anti-La antibodies, rheumatoid factors, or anti-nuclear antibodies. **sSS -** (1) at least 1 positive response to either ocluar or oral symptoms yes/no questions; (2) SG and lacrimal dysfunction; (3) positive anti-Ro and/or anti-La antibodies, rheumatoid factors, or anti-nuclear antibodies. abnormal Schirmer test and abnormal unstimulated whole salivary flow rate.	For six weeks, participants were given either cevimeline 30 mg three times/day, 60 mg of cevimeline three times/day, or placebo.	Cevimeline, 30 mg three times/day, reported to be well accepted and to provide significant relief from xerostomia symptoms.	Not Mentioned
4.	Dianne Petrone *et al.* (9)	2002	SS	Dallas	197 patients were includedin a multicenter, double-blind, randomized, parallel-group study	Patients between 18 and 75 years of age	Not Mentioned	Diagnosed of SS, either pSS or sSS, with accompanying lacrimal and SG dysfunction. Negative pregnancy test in female patients (if applicable).	In a multicenter, double-blind, randomized, parallel-group investigation, 197 patients were included. Patients were assigned to groups based on a computer-generated regimen (70 patients in the control group, 65 in the 15-mg cevimeline group, and 62 in the 30-mg cevimeline group). The study medicine was to be taken at the following times: dose 1 between 6 and 8 a.m., dose 2 between 1 and 3 p.m., and dose 3 between 7 and 9 p.m. On visit days, patients were told not to take one of their regularly scheduled dosages. Patients having morning visits were advised not to take morning dose, and patients who had afternoon appointments were advised not to take afternoon dose until pre dose assessments at the clinic were completed.	Patients with Sjogren's syndrome who took cevimeline 30 mg for three times/day reported with a considerable improvement in their keratoconjunctivitis sicca symptoms and xerostomia. Both the 15-mg and the 30-mg dosages were well tolerated, and the 15-mg dosage alleviated certain symptoms.	Not Mentioned

Table 1 cont.-1: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

5.	MARTIN J. CUMMINS *et al.* (17)	2003	pSS	Boston, Massachusetts	497	Above 18	Both male and female	Not Mentioned	Oral administration was given at 150 IU of human IFN-α 3 times/daily for 24 weeks or placebo	Low-dose orally administered IFN-α can significantly increase the UWS flux in patients with pSS without causing significant side effects.	Not Mentioned
6.	Artur V. *et al.* (23)	2003	pSS	Texas	2 phase III clinical trials in which a total of 497 subject with pSS	Ranged between 26 to 88 years, Mean age = 58.2 years	Male and Female both. Mostly female (92.6%)	Complete physical and oral examination, medical history review, pregnancy test (if applicable), salivary flow, Schirmer score, percentage of patients positive for SSA / SSB antibody, and percentage of patients positive for minor salivary gland biopsy, EC criteria.	At baseline, subjects were randomized to 24 weeks of daily treatment with either 150 IU IFN-α, 3 times/day or placebo at 3:2 ratio. Approximately at 8:00 am, 2:00 pm and 8:00 pm, subjects were instructed to take the lozenges/daily.Subject were instructed to allow each lozenge to dissolve in the mouth and not to chew or swallow. They were also instructed to wait for 5 minutes before consuming each lozenge and 15 minutes afterward to eat, drink, use oral wetting agents, or brush their teeth. Lozenges were not used within 60 min of study visit	Low-dose orally administered IFN-α can significantly increase the UWS flux in patients with pSS without causing remarkable side effects.	Not Mentioned
7.	Athena S. Papas *et al.* (7)	2004	SS	Caucasian, Black, East Asian, others	Total 256; Case = 128 in Pilocarpine group and; Control = 128 in Placebo Group. Female 117 in case and 125 in control; Male 11 in Case group and 3 in Control group	Not Mentioned	Male and Female both	Questionnaire in 2 formats at each visit (1) VAS of 100 - mm; and (2) categorical questions (3-point). UWSF measurement predose and post dose	Case group - Treated with Pilocarpine (20mg to 30mg daily). Most commonly side effects associated with pilocarpine include sweating, pollakiuria, flushing, and chills.	At 20mg/day, there was significant alleviation in dryness of mouth, and at 30mg/day, there was relief in ocular symptoms, including a reduction in the need for artificial tears.	6 to 12 weeks

Table 1 cont.-2: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

8.	Xavier Mariette *et al.* (27)	2004	pSS	France and Belgium	103 Patients	Not Mentioned	Not Mentioned	The new AECG criteria for SS (focus score ≥ 1 or tested positive for anti-RO antibodies and/or anti-LA antibodies (13) and had disease at the time of examination. VAS (0–100 mm) that evaluated fatigue, joint pain and the most disturbing buccal, ocular, vaginal, skin and bronchial dryness (range - 0 for absence of dryness and 100 for worst imaginable dryness).	Out of 103 patients, 54 patients were given infliximab and 49 patients has received placebo.	Randomized, double-blind clinical trial, of an anti-TNF agent didn't present any evidence of effectiveness of infliximab in pSS. Seven patients experienced severe adverse events. Six of the adverse events occurred in the influx imab group (1 an isolated cutaneous facial eruption without any anti-DNA anti bodies, 2 were infusion reactions, 1 autoimmune hepatitis, 1 pneumococcal septi cemia, and 1 breast cancer) and 1 occurred in the placebo group (polyclonal lymph node enlargement)	Evaluated at 0, 10th, and 22nd week.
9.	A. Hartkamp *et al.* (18)	2008	pSS	Netherland	60 female patients with pSS received 200mg of placebo or oral DHEA. 30= allocated to DHEA; 30 = allocated to placebo	Not Mentioned	Female	European criteria for classification of pSS including a focus score ≥ 1 on minor SG biopsy, and were ≥ 8 years, Schirmer I test, ESR, Hemoglobin concentration, and Serum - Ig. The patient reacted to four statements suggesting weariness during the preceding three days on the general fatigue scale of the Multidimensional Fatigue Inventory (MFI, range 4-20). The Zung self-rating scale was used to analyse the depressive mood's psychological and physical aspects. The RAND health survey was used to measure the parameters like Mental Component Summary (MCS) score and Physical Component Summary PCS).	Dehydroepiandrosterone (DHEA)	Female patients diagnosed with pSS, DHEA has a better effect than placebo. DHEA and placebo both enhance fatigue and overall well-being.	At baseline, after 3, 6, & 12th month on study medication and 6 months after stopping of the treatment.

Table 1 cont.-3: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

10.	Sangar Maripuri *et al.* (22)	2009	PSS with Renal Involvement	Rochester, Minnesota	24 patients	Range between 13 to 84	Female - 21; Male - 3	Patient were classified as having pSS using the 2002 AECC Criteria, Renal biopsy in PSS diagnosed patient. After 1990, routine Ro and La antibody test done, Renal function test.	20 patients were treated initially with corticosteroids (prednisolone 40mg for 3 week); 8 patients remained on corticosteroids more than 1 year, with a median low dose of 5mg; out of remaining 4 patients who have not received prednisolone, 3 received no immunosuppressive treatment because of the mild nature of their kidney disease, and the other 1 patient has received plasma exchange due to cryoglobulins. 2 patients, both with TIN, received cyclophosphamide with corticosteroid, 1 patient was given rituximab in addition to corticosteroid (at the time of biopsy). Only 6 out of these patients with pSS were given the treatment with hydroxychloroquine before KB.	pSS patient with kidney involvement should receive corticosteroids course as first- line treatment. Chronic TIN with monolymphocytisc infiltrate is the prototype renal manifestation in pSS, the authors have proposed that a KB representing these findings should be considered as an additional criterion to the classification criteria for pSS.	17 to 19 months
11.	J. M. Meijer *et al.* (28)	2010	pSS	Netherlands	30 Patients			Patients with active pSS, as determined by the revised AECG criteria, and a rate of SWS secretion of >0.15 ml/minute. Determination of the complete blood cell count and Serum biochemical analyses was done as laboratory assessments. Levels of IgA, IgG, and IgM and IgM-RF were measured by nephelometry. Numbers of circulating CD8, CD4, and CD19 T cells were quantified and analyzed using FACSCalibur flow cytometer in TruCOUNT tubes.	Patients were assigned randomly to a treatment group in a ratio of 2:1 (rituximab: placebo). 20 were treated with IV infusions of rituximab 1,000 mg (Roche, Woerden, The Netherlands). On days 1 and 15th, 10 patients were treated with placebo's IV infusions to reduce the side effects (serum sickness, infusion reactions), all patients were pretreated with methylprednisolone (100 mg IV), clemastine (2 mg IV), acetamino phen (1,000 mg orally), and received 60 mg oral prednisone on days 1 and 2, on day 3 and 4, 30 mg was given and and 15 mg was given on day 5 after each infusion.	Rituximab can be considered as safe and effective treatment strategy in patients with pSS. Mild serum sickness–like disease was reported in 1 patient with rituximab group.	Evaluation was done at 5th, 12th, 24th, 36th, and 48th weeks.

Table 1 cont.-4: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

12.	Jacques-Eric Gottenberg *et al.* (25)	2014	pSS	France	120 patients, 56 to hydroxychloroquine quine and 64 to placebo	Not Mentioned	Not Mentioned	PSS according to AECG Criteria.	120 patients in total were randomized: 56 to hydroxychloroquine and 64 to receive placebo until 24th week. Hydroxychloroquine was prescribed to all the patients between weeks 24 and 48	In individuals with anti-Ro autoantibodies, systemic involvement, high IgG levels and/or, hydroxychloroquine had no effect. There were 2 serious adverse effects in the hydroxychloroquine group and during the first 24 weeks in placebo groups, 3 were reported; there were 3 serious adverse effects in the hydroxychloroquine group and 4 in the placebo group during the last 24 weeks. During 24 weeks of treatment, hydroxychloroquine did not alleviate symptoms in patients with pSS in comparision with placebo.	Participants were assessed at baseline, 12th week, 24th week (primary outcome), and 48th week. The last follow-up update for the patient was May 15, 2012.
13.	Vale´rie Devauchelle-Pensec *et al.* (24)	2016	pSS	France	120 patients, Randomization (1:1 ratio) to rituximab (1 g at weeks 0 and 2) or placebo	Not Mentioned	Most patients were women;	Fulfilled the AECG criteria for pSS (16) was diagnosed with active disease, defined with scores of at least 50 mm on at least 2 of 4 VAS (scores ranging from 0 [none] to 100 mm [worst]) for global disease, pain, fatigue, and dryness. In addition, onset of pSS symptoms (first visit for any sign) in approximately past 10 years and biologically active pSS (defined as autoantibodies [anti-Ro antibodies or rheumatoid factor], hypergammaglobulinemia, cryoglobulinemia,2-microglobulin elevation, or hypocomplementemia) or systemic pSS with at least 1 extra glandular features or parotid gland enlargement on the time of examination.	Patients were assigned to a blinded intravenous infusion treatment in a 1:1 ratio randomly and was given rituximab (1 g) or placebo at weeks 0 and 2. All investigators, study personnel, and patients remained blinded to the treatment group throughout the entire study. Infusions were prepared by the pharmacist after a telephone call to the statistics department who were not involved in any other study procedure and the treatment group were not disclosed to the investigators. All patients had received the same amount of volume, but the infusion contained the solvent only (normal saline or 5% glucose) in control group and the solvent plus rituximab in the rituximab group. The patients were given 500 mg of acetaminophen orally and 100 mg of methylprednisolone intravenously before each placebo and rituximab infusion.	Rituximab did not reduce symptoms or progression of disease in pSS patients at week 24, but initially did reduce some symptoms.	Efficacy was evaluated at 6th , 16th , and 24th week.

Table 1 cont.-5: Charaterstics of included studies based on Population, Intervention, Comparison, and Outcome(PICO) model.

14.	M. Cifuentes *et al.* (6)	2018	SS	Chile	Double-Blind RCT study. 72 patients with symptomatic SS were randomly assigned in group and received either 10 drops of pilocarpine orally or ten drop of artificial saliva	Mean Age 52.5 years (range- from 24 to 74 years)	69 Women and 3 Men	(1) Whole saliva test (WST) determined the non-stimulated salivary flow. (2) The Schirmer test was used to measure non-stimulated lachrymal flow using a Wathman paper strip for 5 minutes. (3) Patients' symptoms, such as xerostomia, dysphagia, dysgeusia, and ocular symptoms, were analyzed using a 10-cm long VAS scale.	72 patients with symptomatic - randomly divided into two group. **Group I** – 10 drops of Pilocarpine (equivalent to 5mg) orally, 3 times a day for 12 weeks. **Group II** - 10 drops of artificial saliva, 3 times/day for 12 weeks, directly after or during the meals.	Pilocarpine improves salivary flow more effectively than artificial saliva.	Not Mentioned
15.	Achille marino *et al.* (20)	2021	cSS (Children SS)	Italian	12 cases (9 female)	Range between 4-17 years; disease onset was 10.2 years	Female	ANA, Anti-Ro antibodies, Schirmer test, Biopsy of minor SG, USG of SG.	Not Mentioned	A cluster of association between younger patients (< 11 years) and parotid involvement. Recurrent parotid swelling was the most recorded features	5 months
16.	Edelstein R *et al.* (21)	2021	SS	Bratislava Slorakia	50 patients in that 39 patient with SS. From those 27 had positive lip biopsy remaining 12 patients with SS, had a negative lip biopsy	Average age 51, Oldest patient was 78 years and youngest 6 years at the time of clinical examination.	Female - 37, Male 13	Biopsy of Minor (labial) SG	Not Mentioned	Minor (labial) SG biopsy is the criterion for the diagnosis with the highest specificity and sensitivity and should be used in all the patients who are suspected for SS, who had negative test result for anti-Ro antibodies. This method is having high sensitivity (63.5 - 93.7%) and specificity (61.2-100%).	Not Mentioned

interstitial cystitis [IC]was successfully treated with tacrolimus and prednisolone combination therapy.

● Biologic response modifier vs placebo

MARTIN J. CUMMINS *et al*. (2003) (18) reported a clinical trial of 2 phase III in pSS patients which included 497 subjects who received 150 IU of human IFN-α or matching placebo 3 times/day by the oral route for 24 weeks. IFN-α administered by the oral route at a lower dosage can lead to remarkable increase in UWS flow in the patients with pSS, without causing and significant adverse events.

Adverse events

Patients administered with the pilocarpine and cevimeline were reported with the adverse events like sweating, nausea, headache, palpitations respectively. No adverse events association was noted with salivary electrostimulation. Infections, serum sickness and infusion reactions were also observed in patients taking rituximab. Adverse effects on gastro-intestinal system were found to be linked with IFN-α.

Conclusions

Analysis of studies showed favorable effects of pilocarpine, rituximab and IFN-α in the reduction of dry mouth symptoms. The use of other treatment strategies such as low-level LASER therapy, cognitive behavioral therapy, electrostimulation, etc. cannot be generalized based on the current evidence. Studies based on cognitive behavioral therapy should be carried out for SS patients as this therapy has been documented to have potential to improve QoL of patients. Effectiveness of therapies such as hydroxychloroquine, immunosuppressants, hydroxychloroquine, infliximab should be validated by further RCTs in SS patients.

References

1. Aframian DJ, Konttinen YT, Carrozzo M, Tzioufas AG. Urban legends series: Sjögren's syndrome. Oral Dis. 2013;19:46-58.
2. Baldini C, Talarico R, Tzioufas AG, Bombardieri S. Classification criteria for Sjogren's syndrome: A critical review. J Autoimmun. 2012;19:9-14.
3. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014;6:247-55.
4. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version for the European criteria proposed by the American-European Consensus Group. ARD. 2002;61:554-8.
5. Means C, Aldape MA, King E . Pediatric primary Sjögren syndrome presenting with bilateral ranulas: a case report and systematic review of the literature. International Journal of Pediatric Otorhinolaryngology. 2017;101:11-19.
6. Cifuentes Mutinelli M, Del Barrio Díaz P, Vera Kellet CA. Pilocarpine and artificial saliva for the treatment of xerostomia and xerophthalmia in Sjögren syndrome: a double-blind randomized controlled trial. Br J Dermatol. 2018;179:1056-1061.
7. Papas AS, Sherrer YS, Charney M, Golden HE, Medsger Jr TA, Walsh BT, et al. Successful treatment of dry mouth and dry eye symptoms in Sjögren's syndrome patients with oral pilocarpine: a randomized, placebo-controlled, dose-adjustment study. J Clin Rheumatol. 2004;10:169-77.
8. Fife RS, Chase WF, Dore RK, Wiesenhutter CW, Lockhart PB, Tindall E, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. Arch Intern Med. 2002;162:1293-300.
9. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis & Rheumatism. 2002;46:748-754.
10. Kweon SM, Koh JH, Lee HN, Kim E, So MW, Shin HJ, et al. Primary Sjogren syndrome diagnosed simultaneously with localized amyloidosis of the lacrimal gland: A case report. Medicine (Baltimore). 2018;97:e11014.
11. Houghton K, Malleson P, Cabral D, Petty R, Tucker L. Primary Sjögren's syndrome in children and adolescents: are proposed diagnostic criteria applicable? The Journal of rheumatology. 2005;32:2225-2232.
12. Christensen LB, Petersen PE, Thorn JJ, Schiødt M. Dental caries and dental health behavior of patients with primary Sjögren syndrome. Acta Odontologica Scandinavica. 2001;59:16-120.
13. Touma Z, Sayad J, Arayssi T. Successful treatment of Sjogren's syndrome with rituximab. Scandinavian journal of rheumatology. 2006;35:323-325.
14. de Mendonça Invernici M, Finger Stadler A, Vale Nicolau G, Naval Machado MÂ, Soares de Lima AA, Compagnoni Martins M. Management of Sjogren's syndrome patient: a case report of prosthetic rehabilitation with 6-year follow-up. Case Rep Dent. 2014;2014:761251.
15. Means C, Aldape MA, King E. Pediatric primary Sjögren syndrome presenting with bilateral ranulas: a case report and systematic review of the literature. International Journal of Pediatric Otorhinolaryngology. 2017;101:11-19.
16. Flaitz CM. Parotitis as the initial sign of juvenile Sjogren's syndrome. Pediatric dentistry. 2001;23:140-142.
17. Cummins MJ, Papas A, Kammer GM, Fox PC. Treatment of primary sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: Combined phase III results. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2003;49:585-593.
18. Hartkamp A, Geenen R, Godaert GL, Bootsma H, Kruize AA, Bijlsma JW, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: a randomised controlled trial. Annals of the rheumatic diseases. 2008;67:91-97.
19. Hosoda C, Hosaka Y, Ryu K, Kinoshita A, Saito K, Kuwano K. Pleuritis associated with primary Sjogren syndrome. Respirology Case Reports. 2008;6:e00285.
20. Marino A, Romano M, Giani T, Gaggiano C, Costi S, Singh R, et al. Childhood Sjogren's syndrome: An Italian case series and a literature review-based cohort. In Seminars in Arthritis and Rheumatism. 2021;51:903-910.
21. Edelstein R, Kilipiris GE, Machalekova K, Mouzalini E, Slobodianuk A, Javorka V. Accuracy of minor salivary gland biopsy in the diagnosis of Sjögren syndrome. Bratislavske Lekarske Listy. 2021;122:454-460.
22. Colaci M, Cassone G, Manfredi A, Sebastiani M, Giuggioli D, Ferri C. Neurologic complications associated with Sjögren's disease: case reports and modern pathogenic dilemma. Case Reports in Neurological Medicine. 2014;2014:590292.
23. Khurshudian AV. A pilot study to test the efficacy of oral administration of interferon-α lozenges to patients with Sjögren's syndrome. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2003;95:38-44.
24. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S., Berthelot JM, Perdriger A, Puéchal X, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Annals of internal medicine. 2014;160:233-242.
25. Gottenberg JE, Ravaud P, Puéchal X, Le Guern V, Sibilia J, Goeb V, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. Jama. 2014;312:249-258.
26. Johansson G, Andersson G, Edwardsson S, Björn AL, Manthorpe R, Attström R. Effects of mouthrinses with linseed extract Salinum®

without/with chlorhexidine on oral conditions in patients with Sjögren's syndrome. A double-blind crossover investigation. Gerodontology. 2001;18:87-94.
27. Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2004;50:1270-1276.
28. Meijer JM, Meiners PM, Vissink A, Spijkervet FKL, Abdulahad W, Kamminga N, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatism. 2010;62:960-968.

Conflict of interest
Find the attached no conflict of interest form.