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Review Article

Primary Sjögren's Syndrome - A Review

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A B S T R A C T

Primary Sjögren's syndrome is a systemic autoimmune disease. The hallmark of the disease is exocrinopathy, which often results in dryness of the mouth and eyes, fatigue, and joint pain. These three symptoms are present in more than 80% of the patients with this disease and have a major effect on quality of life, primarily because of disabling fatigue, with associated loss of work productivity. The global prevalence calculated for the rarer pSS is 61 per 100 000 inhabitants. The patients' quality of life is reduced by the diverse manifestations of the disease. Pharmacists can help SjS(Sjögren's Syndrome) patients improve their quality of life.

Keywords: Autoimmune disorder, Vitiligo, Depigmentation.

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INTRODUCTION

Primary Sjögren's syndrome is a common systemic autoimmune disease, with a female-to- male predominance of 9:1 and peak incidence at approximately 50 years of age [1.] The hallmark of the disease is exocrinopathy, which often results in dryness of the mouth and eyes, fatigue, and joint pain. These three symptoms are present in more than 80% of the patients with this disease and have a major effect on quality of life, primarily because of disabling fatigue, with associated loss of work productivity [2.] This condition may occur in isolation or in association with organ-specific autoimmune diseases, such as thyroiditis or primary biliary cirrhosis or cholangitis, in which case the disease is referred to as primary Sjögren's syndrome. In contrast, the term secondary, or associated, Sjögren's syndrome has been used when the disease occurs in association with another systemic autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, or dermatomyositis.

EPIDEMIOLOGY

The heterogeneity of the available prevalence and incidence data for Sjögren's syndrome is explained by differences in study design and classification criteria. The global prevalence calculated for the rarer pSS is 61 per 100 000 inhabitants, with the highest prevalence encountered in Europe[1.] Women develop Sjögren's syndrome significantly more frequently than men; the sex difference ranges between 9:1 to 19:1. Mean age at time of first diagnosis of pSS is 56 years, with another peak occurring between 20 and 40 years. However, first symptoms may occur years before diagnosis. The overall prevalence of Sjögren's syndrome, including the more common secondary form of the disease, is assumed to be at least 0.4% [3.]

CLASSIFICATION CRITERIA

Recently the American College of Rheumatology (ACR)–European League against Rheumatism (EULAR) criteria were designed and validated for the purposes of classification in Sjögren's syndrome,[4] they may also be useful in establishing a diagnosis of primary Sjögren's syndrome in the context of these common symptoms.

Table 1: (below) details the 2017 ACR-EULAR classification criteria, and a diagnosis of Sjögren's syndrome is made when the score is 4 or more.

Item	Description	Score
Focus score of ≥ 1	A score determined by the number of mononuclear cell infiltrates containing ≥ 50 inflammatory cells per per $4mm^2$ of minor labial salivary gland obtained on biopsy	3
Presence of Anti SSA antibodies	Measured in serum; only anti-Ro60 antibodies have to be considered; Isolated anti-Ro52 antibodies are not specific for sjogrens syndrome	3
SICCA ocular staining score of ≥ 5	A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining;scores range from 0 to 12,with higher scores indicating greater severity	1
Schimer test of ≤ 5mm per 5 min	An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moistureon the paper	1
Unstimulated whole salivary flow of ≤ 0.1ml per min	An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5min after the patient has swallowed.	1
Total Score		**9**

On the basis of the listed classification criteria, a diagnosis of primary Sjogren's syndrome is defined as a score of 4 or more. These criteria apply to patients who have at least one symptom of ocular or oral dryness or the presence of sys- temic manifestations suggestive of primary Sjogren's syndrome. Exclusion criteria include active hepatitis C virus infec- tion on polymerase-chain-reaction assay, radiotherapy of the cervical spine, sarcoidosis, graft-versus-host disease, receipt of anticholinergic drugs, and igG4-related disease. ACR denotes American College of Rheumatology, EULAR European League against Rheumatism, SICCA Sjogren's International Collaborative Clinical Alliance, and SSA anti-Sjogren's syn- drome-related antigen A. Positive serologic results for anti-SSB/La antibodies in the absence of anti-SSA/Ro antibodies is not specific and is no longer considered to be a criterion for the diagnosis.

CLINICAL FEATURES

According to the largest cohort published so far, sicca symptoms are the most common manifestation of Sjögren's syndrome, with up to 98% of cases [4]. Patients with keratoconjunctivitis sicca (KCS) complain about foreign-body sensation, burning or soreness of the eyes and increased sensitivity to light. Marked xerostomia as a sign of stomatitis sicca presents clinically as difficulties when talking for extended periods of time and while chewing or insalivating dry food. Compared with the general population, the prevalence of dental caries and early tooth loss is about twice as high in patients with Sjögren's syndrome and their oral health related quality of life is significantly reduced. Recurrent oral infections with Candida albicans occur 10 times more frequently than in the general population[5]. On the other hand, sicca symptoms are commonly reported with advancing age and polypharmacy: Approximately 5% to 35% of the general population suffer from dry eyes [6], and approximately 20% of dental patients experience dry mouth [7]. Thus, a thorough medical history, including medications, and physical examination, followed by special function tests, is crucial for the interpretation of these complaints. Table 1 lists the differential diagnoses for glandular complaints. In addition, attention should be paid to other sicca symptoms, such as dry cough in tracheobronchitis sicca or sicca symptoms in the nasopharynx or genital tract, manifesting as an increased susceptibility to infection or as dyspareunia.

Up to 34% of patients with Sjögren's syndrome report episodic or chronic, typically bilateral swelling of the parotid glands [9]. Here, it is essential to exclude malignant non-Hodgkin lymphoma (NHL) of B cell lineage which occurs in about 5% of patients with pSS [10] who are at a significantly increased risk of developing NHL compared with the general population (risk ratio [RR]: 13.7). Key predictors for the development of NHL include low complement levels (RR: 8.3), cryoglobulinemia (RR: 6.8), lymphadenopathy (RR: 3.7), histological finding of ectopic germinal centerlike structures, permanent swelling of parotid gland, and skin vasculitis [10, 11]. These patients belong to a high-risk group and require monitoring at closer intervals and, if necessary, further diagnostic investigations, such as chest radiography and abdominal ultrasound; however, valid recommendations for lymphoma screening are not available.

The most common extraglandular manifestations are arthralgia and a usually non-erosive polyarthritis which occur in approximately 50% of patients [9]. Pulmonary involvement beyond the sicca complex typically manifests as interstitial lung disease or follicular bronchiolitis, normally after many years of disease activity (9–12%) [9, 12]. About 10% of patients have cutaneous lesions, the majority in form of a vasculitis with involvement of small and medium vessels of the lower limbs. In addition, other less common skin manifestations may occur, such as annular erythema, urticarial vasculitis, or hypergammaglobulinemic purpura [9]. Renal involvement,

which is found in approximately 5% of patients, is usually associated with tubulointerstitial changes which frequently go along with distal renal tubular acidosis (RTA type 1) with hypokalemic muscular hypotonia; glomerulonephritis is rare in patients with pSS [9, 13.]

Also of clinical relevance is the involvement of the peripheral nervous system, especially later in the course of the disease, typically manifesting as sensory neuropathy (10–25%) [9, 14.] Rarer and more challenging to identify are CNS manifestations; for example, the differential diagnosis of multifocal CNS lesions on MRI includes multiple sclerosis lesions which are difficult to distinguish from pSS lesions [(15).] In this context, the coexistence of pSS with neuro myelitis optica spectrum disorders (NMOSD), which are characterized by autoantibodies to aquaporin-4, is of importance [(4).] If patients test positive for this antibody, this is of great differential therapeutic significance.By contrast, nonspecific complaints such as fatigue and diffuse pain are more difficult to evaluate. However, fatigue is the symptom experienced as most distressing by the patient, determining physician visit frequency, quality of life as well as fitness for work [(16).] Other conditions in the differential diagnosis of fatigue, such as hypo - thyroidism, anemia and sleep disorders, should be excluded and difficulties in coping with the disease should also be taken into account. Anti-Ro/SSA- and anti-La/SSB-positive women desiring to have children require special counseling. Placental transmission of these antibodies can cause inflammation with subsequent sclerosis of the atrioventricular (AV) node which carries the risk of the fetus developing a congenital heart block. In 80% of cases, complete irreversible heart block occurs and in 20% fetal mortality is significantly increased [17.] Weekly ultrasonographic monitoring of the cardiac rhythm of the fetus between 16 and 31 weeks' gestation is essential for both prognostic evaluation and management.

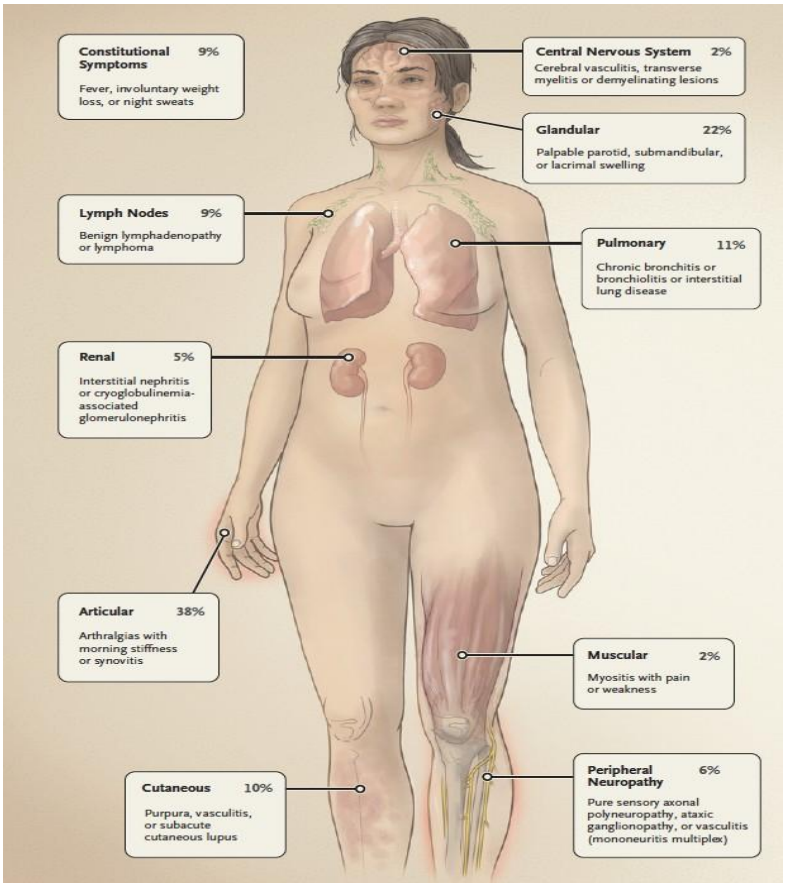


Figure 1: Depicting clinical features in Sjogren's syndrome

PROGNOSIS

Overall, the prognosis of Sjögren's syndrome is favorable. The life expectancy of pSS patients is comparable with that of the general population [18.] However, the patients' quality of life is reduced by the diverse manifestations of the disease. Cardiovascular disease, infections, solid tumors, and lymphoma are the main causes of death. In patients with sSS, life expectancy is determined by the primary disease.

PATHOGENESIS

As with most autoimmune diseases, the etiology of Sjögren's syndrome is not yet fully understood. Current concepts of its pathogenesis are summarized in the Figure 2.

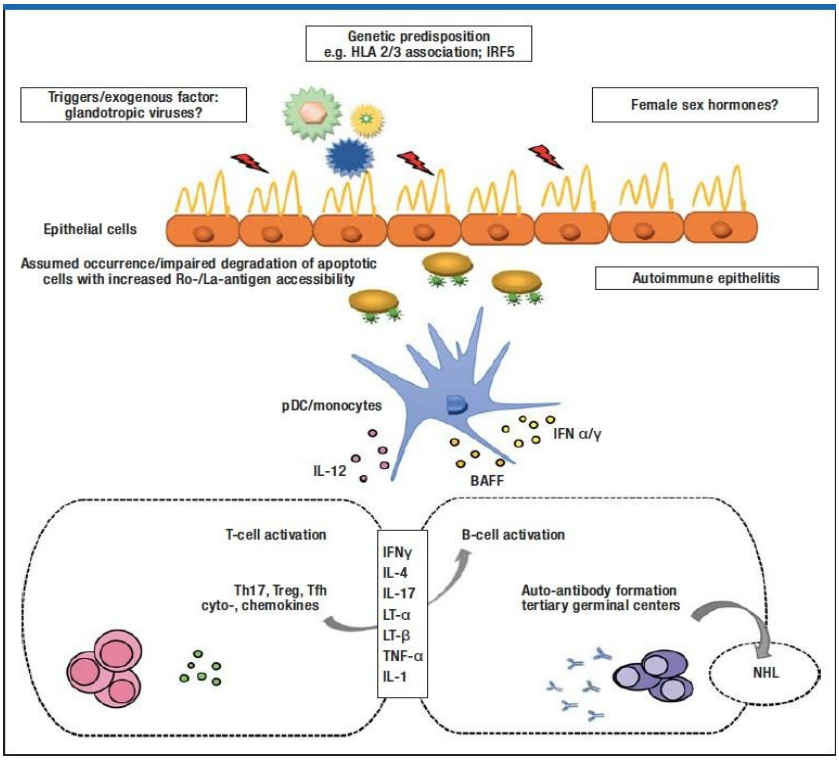


Figure 2: Diagram of the pathogenesis of Sjögren's syndrome

Genetic predisposition, exogenous triggering factors (e.g. glandotropic viruses) and hormonal changes are thought to initiate and maintain the immunopathogenesis of the disease. Glandular epithelial cells supposedly play a central pathophysiological role in the development of auto-immune epithelitis, especially with regard to antigen presentation of Ro/SSA- and La/SSB-protein complexes which are found on the surface of apoptotic cells [19]. Both the innate (e.g. pDC/monocytes) and the adaptive immune system (T-/B- cells) are involved in the initiation of the disease and perpetuation of the immune response (e5, e6). Via the activation of various CD4+ T-helper cell subsets, B cells play an important role in auto-antibody production, from the formation of ectopic germinal center-like structures to the malignant transformation to NHL [(11)].

BAFF, B cell-activating factor of the tumor necrosis factor family; HLA, human leukocyte antigen; IFN α/γ, interferon α/γ; IL-1, -4, -12, -17, interleukin 1, 4, 12, 17; IRF5, interferon regulatory factor 5; LT-α, lymphotoxin α; LT-β, lymphotoxin β; NHL, Non-Hodgkin lymphoma; pDC, plasmacytoid dendritic cells; Tfh, follicular T cells; Th17, T helper cells 17; TNF-α, tumor necrosis factor α; Treg, regulatory T cells.

Table 2: Differential Diagnosis og Glandular Manifestations [8]

<table>
<tr><th colspan="2">Dry eye/keratoconjunctivitis sicca</th></tr>
<tr><td>Normal tear production (Schimers test unremarkable)
-Environmental factors(air conditioning, smoking, computer work)
-meibomian gland dysfunction,rosacea
-Contact lenses
-Corneal hypoesthesia after LASIK surgery, along with diabetes
-Incomplete lid closure</td><td>Reduced tear production (abnormal Schimers test)
-Drug –induced: Anticholinergics, antihistamine, tricyclic antidepressants, diuretics
-Age related/menopause
-Status post head/neck radiation
-Chronic viral infections (HCV,HIV)
-Sarcoidosis, lymphoma
-Sjogrens syndrome (primary and secondary)
-IgG4-related disease</td></tr>
<tr><td colspan="2">Xerostomia

- Drug –induced: Anticholinergics, antihistamine, tricyclic antidepressants, diuretics, antihypertensives ,among them
-anxiety disorder, endogenous depression, fibromyalgia, bulimia/anorexia
- Status post head/neck radiation
-Systemic disease (sarcoidosis,amyloidosis,HCV,HIV)</td></tr>
<tr><td colspan="2">Parotid swelloing</td></tr>
<tr><td>Mainly unilateral

-Acute: Bacterial infection,actinomycosis,mechanical obstruction by salivary duct stones

-Chronic: Chronic sialadenitis,neoplasia (pleomorphic adenoma of the parotid gland)</td><td>Mainly bilateral

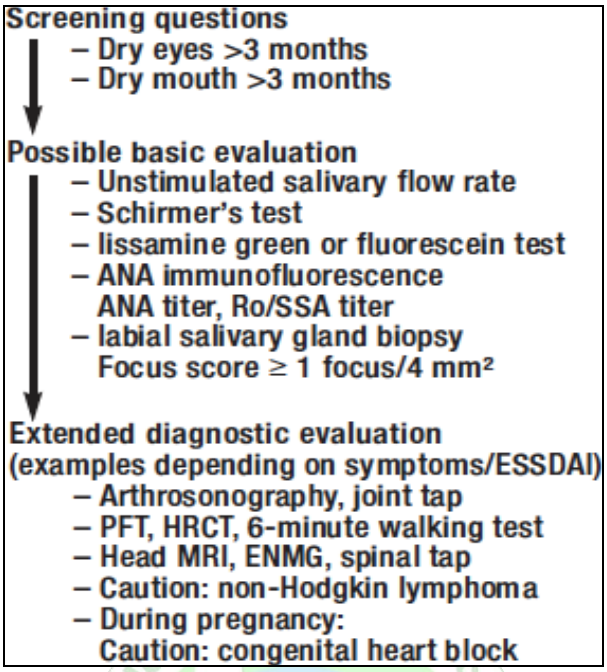
-Acute : viral infection(mumps, EBV,CMV)

-Chronic: Chronic infections (HCV<HIV),Diabetes mellitus,alcoholism,anorexia,amyloidosis,IgG4 related disease, hyperlipoprotenemia</td></tr>
</table>

Diagnostic Algorithm of Sjögren's Syndrome

ANA, antinuclear antibodies; ENMG, electro neuromyography; ESSDAI, EULAR— Sjögren´s syndrome disease activity index; HRCT, high-resolution computed tomography; PFT, pulmonary function test.

Diagnostic Evaluation



Objective tests for sicca symptoms

Schirmer's test and Saxon's test are easy to perform, but their results do not correlate well with patient complaints and should be evaluated in the overall context. Here, cooperation with the ophthalmology department is crucial: Topical application of vital stains (lissamine green or fluorescein) is used to visualize and grade corneal and conjunctival lesions

associated with keratoconjunctivitis sicca. Direct measurement of salivation is the diagnostic gold standard, but it is time consuming in daily clinical practice. Parotid sialography and salivary gland scintigraphy lack sufficient specificity. As a noninvasive method, ultrasonography of the major salivary glands is an integral part of daily clinical practice. However, the method is not yet sufficiently validated to be include in the classification criteria [21.]

Laboratory testing

Immunofluorescence testing for antinuclear antibodies (ANA) is highly relevant for the diagnosis of connective tissue disorders. Up to 83% of patients with pSS test positive for ANA [22.] However, low-titer (<1:160) and unspecific ANA patterns are also found in 5% to 20% of the general healthy population [23.] In patients with positive ANA titers, a fine speckled fluorscence pattern is strongly indicative of anti-Ro/SSA and/or anti-La/SSB antibodies, which is revealed in approximately 40% to 75% and 23% to 52% of pSS patients, respectively [24.] With the recent increase in diagnostic value assigned to anti-Ro/SSA antibodies in the current classification system, it can be expected that significantly more newly classified Sjögren's syndrome patients will have elevated antibody levels compared with historical cohorts. Positive antibody titers correlate with early onset of disease, more intense tissue infiltration, and higher prevalence of extraglandular manifestations. However, patients with other connective tissue disorders may also test positive for anti- Ro/SSA antibodies. Here, the clinical context is vital, especially to differentiate between overlapping disease entities. Interestingly, serological autoimmune phenomena have been detected up to 20 years before the appearance of the first signs and symptoms of the disease [25.] Other serological abnormalities include the presence of rheumatoid factors (60–75%) as well as polyclonal hypergammaglobulinemia as a sign of increased B cell activity.

The development of biomarkers, providing prognostic information and a means to monitor disease progression, has now reached the establishment phase. An increase in beta2-microglobulin and free light chains of immunoglobulins is associated with an increased risk of lymphoma [26.] Siglec-1 has recently emerged as a new biomarker. This indirect interferon marker correlates with a high level of disease activity as well as extraglandular manifestations [27.]

Histopathology

The histopathological finding of focal periductal localized lymphocytic infiltrates in exocrine glandular tissue along with otherwise intact acinar units is pathognomonic for Sjögren's syndrome. These infiltrations mostly consist of

CD4+ T cells, with some additional CD8+ T cells and CD19+ B cells, plasma cells and dendritic cells. Deep expertise in line with international recommendations on the interpretation of histopathological findings is required to differentiate Sjögren's syndrome from other disease entities [28]. A minimum number of 50 monocytic cells/4 mm² was defined as a focus score (FS) of 1. A focus score ≥1 correlates with the phenotypical characteristics of Sjögren's syndrome.

MANAGEMENT

Despite continued advances in our understanding of the mechanisms involved in the pathogenesis of the disease, a targeted treatment of Sjögren's syndrome is not available at present. Treatment is decided on an individual basis according to disease activity and the presence and extent of extraglandular manifestations. In patients with sSS, the indication for treatment is based on the underlying disease. In general, treatment should be provided by an interdisciplinary team, including family physicians, rheumatologists, ophthalmologists and ETN specialists, as well as dentists. Subject to the organ(s) involved and the presenting symptoms, consultation of other specialists (gynecologists, pulmonologist, neurologists, etc.) may be required. Disease-modifying therapy is reserved for patients with extraglandular involvement. To measure systemic disease activity, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is used.

Management of sicca symptoms

In most patients, the main aim of therapy is to improve quality of life by treating the sicca and fatigue symptoms. At the same time, this is a very challenging task for physicians as evidence- based treatment options are scarce and most therapeutic approaches are only symptomatic (Table 2).

Patient education plays an important role, focusing on compliance with everyday behavioral

rules[30] targeting environmental factors (e.g., air humidification), prevention (e.g., fluoride for caries prevention, quit smoking), and avoidance of factors that increase fatigue (e.g., sleep hygiene) as well as physical fitness (aerobic endurance training to fight fatigue).

Various tear substitutes are available to treat keratoconjunctivitis sicca. The composition of the tear substitutes varies in accordance with the complex physiology of the three-layered preocular tear film (lipid layer, aqueous layer, and mucin layer). Since immune-mediated mechanisms play a central role in the pathogenesis of dry eye, anti-inflammatory treatment with cyclosporine A eye drops has gained significant importance. Their efficacy has been proven in randomized controlled trials (RCTs) and, based on data from these studies, 0.1% cyclosporine A cationic emulsion received marketing authorization from the European Medicines Agency[31]. Additional measures significantly increasing the quality of life of these patients include the use of punctal plugs and the fitting of extra-large contact lenses ("scleral lenses") with water storage function [32]. Thus, cooperation with ophthalmologists is essential.

Xerostomia is treated jointly by dentists and otolaryngologists. The oral mucosal surface is comparatively large and different structures in the oral cavity need to be moistened (tongue, teeth, gum, oral mucosa). In addition, saliva composition varies with function and time of day. Optimal therapeutic compensation of the complex functions of saliva cannot be achieved. Two systematic reviews on topical/nonpharmacological treatments arrive at the conclusion that, while symptoms can be alleviated, the flow of saliva cannot be increased [33, 34]. Dental care for patients with xerostomia is particularly challenging, as the lack of saliva reduces the tolerability of removable dental restorations. By contrast, in patients with Sjögren's syndrome good outcomes are achieved with dental implant treatment [35].

Table 3: Treatment Recommendations for sicca symptoms and fatigue in patients with primary Sjogrens syndrome [30]

Indication	Treatment (grade of recommendation)
Keratoconjunctivitis sicca	-Patient education/avoid anticholinergics/tear substitutes (A) - Secretagogues: pilocarpine, cevimeline* (A) **Caution:** sweating, flush, headache, nausea -Cyclosporine A eye drops 0.1% (B) **Caution:** burning of eyes in case of moderate to severe corneal damage -Short term topical corticosteroids (C) **Caution:** glaucoma, cataract -Punctal plugs (C),sclera lenses (C)
Stomatitis sicca	-Patient education/avoid drugs that promote xerostomia(A) -Topical fluorides for caries prevention(A) -Secretagogues: pilocarpine, cevimeline (A) **Caution:** sweating, flush, headache, nausea -Saliva substitutes, sugar free chewing gum, electrostimulation of salivary glands (C)
Rhinitis sicca	-Nasal oil **Caution:** No decongestant nasal drops
Tracheobronchitis sicca	-Pilocarpine, brohexine, inhalation with saline, avoiding dehydrating substances (e.g. chamomile)
Dyspareunia	-Estrogen containing vaginal suppository
Fatigue	-Aerobic endurance training (B) -Hydroxychloroquine (C) **Caution:** annual ophthalmological follow ups

Grades of recommendation according to Centre for evidence Based Medicine in Oxford:

- Evidence obtained from meta analyses or at least one randomized controlled trail.
- Evidence from at least one well designed experimental study.
- Evidence from at least one well designed descriptive study or case control studies.
- Evidence from expert opinion.

Disease-modifying therapy

The decision to intensify treatment is dependent on disease activity and the organ system involved. However, the few RCTs evaluating the use of conventional disease-modifying antirheumatic drugs (DMARDs) or biologic agents in patients with Sjögren's syndrome did not provide conclusive evidence supporting their efficacy [30, 36]. Treatment decisions are frequently based on experiences with related rheumatic disease entities, such as systemic lupus erythematosus. Analog to other connective tissue disorders, hydroxychloroquine, an agent with a favorable side- effect profile, is the drug of choice for various mild to moderate systemic manifestations,

such as arthralgia, arthritis, cutaneous lesions, and fatigue. The example of hydroxychloroquine highlights the challenges with regard to study design and the selection of patients who may benefit from treatment. A randomized controlled trial on pSS found no difference between hydroxychloroquine und placebo regarding sicca symptoms, pain and fatigue after 24 weeks [37]. However, this study had significant limitations: The disease activity in these patients was low, the follow-up period short, and the primary endpoint not validated. To increase the validity of future RCTs investigating this heterogeneous disease, it is essential to recruit representative patient groups and select robust primary endpoints.

With regard to fatigue, a pilot study demonstrated moderate efficacy for rituximab [38]. Unfortunately, this was not confirmed by a large RCT conducted some years later [39].

Treatment recommendations with regard to immunosuppression vary according to organ involvement (Table 3). In patients with severe organ manifestations, the use of high-dose methylprednisolone and cyclophosphamide is of proven effectiveness. For severe vasculitis, especially with concomitant cryoglobulinemia, rituximab or plasmapheresis are the recommended treatment options. In patients with NHL, treatment is chosen based on subentity and stage according to current guidelines on the treatment of hemato-oncological disorders. The recommended treatment for pregnant women with Sjögren's syndrome and a high risk for congenital heart block is hydroxychloroquine to minimize risk; however this recommendation is solely based on evidence from retrospective studies [40].

New treatment approaches, targeting pathophysiological mechanisms, are currently being evaluated in RCTs with validated instruments (ESSDAI): modulation of B-cell hyperactivity (e.g., belimumab), antagonizing T-cell co-stimulation (e.g., abatacept), effector cytokines (e.g., interleukin-6-receptor/tocilizumab; interferon α/anifrolumab), as well as prevention of the formation of ectopic germinal center-like structures (e.g., lymphotoxin-βR blockade). These studies face the challenge to demonstrate efficacy for the three symptom complexes—sicca, fatigue, and extraglandular manifestations.

Table 4: Treatment recommendations for systemic manifestations of primary Sjogrens syndrome[30]

Indication	Treatment (Grade of Recommendation)
Parotid swelling	-NSAIDS and short term corticosteroids(< 20 mg/d for max,1 month) (D) Consideration for contraindications -Antibiotic treatment, if required (D)
Arthritis	-Hydroxychloroquine (C) Caution:annual ophthalmological follow ups. -NSAIDS, short term oral/intraarticular corticosteroids (C);Consideration of contraindications -Second line DMARDs as with rheumatoid arthritis (C), (especially methotrexate (D)---**caution:** renal failure
Interstitial pneumopathy	-Corticosteroids,oral or intravenous (C) Consideration of contraindications -Cyclophosphamide for active alveolitis (C) **Caution:** hemorrhagic cystitis,pancytopenia,fertility -Pirfenidone, Nintedanib(C) **Caution:** Hepatic impairment
Tubulo interstitial nephritis	-Potassium and bicarbonate replacement (D) 3×1-2 g/day
Peripheral neuropathy	-Antidepressants,gabapentin (D) **Caution :** sicca -Corticosteroids, oral printravenous IVIg (D) Consideration of contraindications
Cryoglobulinemic vasculitis with organ involvement	-Methylprednisolone, plasmapheresis (C) Consideration of contraindications -Rituximab (C) **Caution:** Infusion reaction,formation of immune complexes, infections

Close monitoring of patients treated with DMARDs or immunosuppressants according to the recommendations of the German society of Rheumatology (dgrh.de/therapieueberwachen.html)

Grades of recommendation according to Centre for evidence Based Medicine in Oxford:

- Evidence obtained from meta analyses or atleast one randomized controlled trail.
- Evidence from atleast one well designed experimental study.
- Evidence from atleast one well designed descriptive study or case control studies.
- Evidence from expert opinion

DMARDs- disease modifying antirheumatic drugs;
IV Ig -, Intravenous immunoglobulins
NSAID- nonsteroidal anti inflammatory drugs

PHARMACIST'S ROLE

Pharmacists can help SjS patients improve their quality of life. The most important thing to remember is that therapy must be tailored to the individual patient[41-44]

- Offer counseling on prescription and nonprescription medications, including moisturizing products for the skin, nose, and vagina.
- Advise patients to avoid windy or drafty environments and to wear sunglasses when outdoors.
- Discuss the benefits of indoor humidifiers.
- Remind patients to practice good oral hygiene (chewing sugarless gum, sucking on sugarless candy, staying well hydrated, visiting the dentist 3 times annually).
- Suggest that patients who work at a computer or read extensively remind themselves to blink.
- Encourage smoking cessation and advise avoiding smoky environments.
- Advise against wearing eye makeup.
- Address showering: patients can pat dry (leave beads of water on the skin) and apply an emollient on damp skin within 3 minutes.

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