

## 6.8 Fatigue in Sjögren's syndrome

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Fatigue in Sjögren's syndrome

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### Abstract

Fatigue is a common symptom described by people with Sjögren's syndrome. There are different patterns of fatigue and people with Sjögren's syndrome may experience tiredness of a different nature compared to a healthy individual. The aetiology of fatigue is not fully understood and likely to be multi-factorial. There are a number of fatigue outcome measures and disease activity scores used to assess and monitor fatigue. We discuss pharmacological therapies which have been studied in the context of fatigue and allude to non-pharmacological interventions to address fatigue. We also highlight the importance of incorporating assessment of fatigue due to the significant impact on the quality of life of patients and their abilities to carry out activities of daily living.

### Key words

Fatigue

Tiredness

Quality of life

Fatigue outcome measures

Pain

Depression

Treatment of fatigue

### **Fatigue in Sjögren's syndrome**

Fatigue is defined as a sense of overwhelming tiredness. It is also a feeling which may be experienced after strenuous mental or physical activities [1]. Fatigue is a multi-dimensional experience, often multi-factorial, and difficult to characterise from the clinical point of view.

Fatigue may be differentiated into central fatigue and peripheral fatigue. Central fatigue is defined as 'difficulty in initiating and sustaining voluntary activities' which require motivation to carry out tasks to completion, whereas peripheral fatigue pertains to neuromuscular stamina and strength [2]. It has been suggested that fatigue occurs when there is discordance between central aspects such as motivation, and perceived effort required to perform a task [2].

Fatigue is described as being experienced by 11-30% of the general population [3, 4]. In contrast, fatigue has been reported to occur in 38-88 % of patients with primary Sjögren's syndrome (pSS) [5-7]. A higher prevalence of fatigue has also been reported in women, patients of lower socioeconomic status, and patients with multiple rheumatologic diagnoses [8].

#### **Patterns of fatigue**

It has been suggested that the fatigue experienced by patients with pSS is unlike the tiredness experienced by a healthy individual. The fatigue described by these patients is that of a constant, unpredictable heaviness, not remedied by rest or a good night's sleep [9]. There is a difference in opinion regarding the nature of fatigue in patients with pSS. It has been reported that patients with pSS were more likely to experience more intense physical fatigue compared to mental fatigue [1]. However, some report no difference in the levels of fatigue across the different dimensions [7]. The pattern of fatigue in pSS has been described to have diurnal variability, with progressively worsening fatigue, with an improvement mid-morning, and a deterioration thereafter [10]. This is in contrast to patients with systemic lupus erythematosus (SLE), where a gradual worsening of fatigue, after an initial improvement after rising, is thought to occur [10]. Others report similar fatigue profiles between patients with rheumatoid arthritis (RA) and pSS, which showed a progressive worsening of both somatic and mental fatigue as the day progressed [11]. Fatigue in pSS has also been observed to remain largely constant with no significant changes over time [12].

#### **Outcome measures**

A range of assessment tools have been developed to measure fatigue - some disease-specific, whilst others are scores used across various disease types. In Table 6.8.1, we detail the most frequently used outcome measures for fatigue in pSS.

**Table 6.8.1: Outcome measures which have been used to assess fatigue associated with pSS.**

Fatigue	
Visual Analogue Scale (VAS) [1]	<ul style="list-style-type: none"> <li>• Measured from 0 (no fatigue) to 10 (severe fatigue)</li> <li>• Quick and easy to use</li> <li>• Uni-dimensional, and therefore inadequate to fully assess fatigue</li> </ul>
FACIT-Fatigue (Functional assessment of Chronic illness therapy – fatigue scale) [13]	<ul style="list-style-type: none"> <li>• 13 questions</li> <li>• Uses five-point Likert scale</li> <li>• Used in various chronic diseases including RA, MS, cancer</li> </ul>
SF-36 (Medical Outcome Survey Short Form) [14, 15]	<ul style="list-style-type: none"> <li>• Energy/fatigue are assessed by four questions:               <ol style="list-style-type: none"> <li>1. Did you feel full of life?</li> <li>2. Did you have a lot of energy?</li> <li>3. Did you feel worn out?</li> <li>4. Did you feel tired?</li> </ol> </li> <li>• Uses six-point Likert scale</li> </ul>
Fatigue Severity Scale (FSS) [14]	<ul style="list-style-type: none"> <li>• Measures severity/effect of fatigue</li> <li>• Nine questions</li> <li>• Uses seven-point Likert scale</li> <li>• Validated in SLE, also used in fibromyalgia</li> </ul>
Fatigue Impact scale (FIS) [16]	<ul style="list-style-type: none"> <li>• Assesses limitations as an effect of fatigue</li> <li>• Three main domains (cognition, physical, psychosocial)</li> <li>• 40 questions</li> <li>• Validated for MS, chronic fatigue syndrome, chronic obstructive pulmonary disease, primary biliary cirrhosis and chronic hepatitis C</li> </ul>
Multidimensional fatigue inventory (MFI) [17, 18]	<ul style="list-style-type: none"> <li>• Five domains (general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation)</li> </ul>

	<ul style="list-style-type: none"> <li>• 20 questions</li> </ul>
Nottingham Health Profile [19, 20]	<ul style="list-style-type: none"> <li>• Assessment of quality of life</li> <li>• 38 questions</li> <li>• Six domains: mobility, pain, social isolation, emotional reactions, energy, sleep</li> </ul>
Chalder Fatigue Scale (CFS) [14, 21], also known as Chalder Fatigue Questionnaire (CFQ), Fatigue Scale or Fatigue Questionnaire	<ul style="list-style-type: none"> <li>• Severity scale assessing physical and mental fatigue</li> <li>• 11 items: Seven questions pertaining to physical fatigue, four to mental fatigue</li> <li>• Measured using Likert or bimodal scale</li> </ul>
PROFAD-SSI score (profile of fatigue and discomfort sicca symptoms inventory) [22]	<ul style="list-style-type: none"> <li>• Assesses symptoms of somatic fatigue, mental fatigue, arthralgia, vascular symptoms, sicca (ocular and oral) symptoms, cutaneous and vaginal dryness</li> <li>• 64-point questionnaire</li> <li>• PROFAD-SSI-SF (short form) score is an abbreviated 19-point questionnaire which has been validated as a pSS outcome tool [22]</li> <li>• Fatigue VAS was found to most closely correlate with somatic fatigue</li> <li>• The somatic fatigue domain forms the PROF-S whilst the mental fatigue domain forms the PROF-M (derived from patient's descriptions of fatigue)</li> </ul>
ESSPRI (EULAR Sjögren's Syndrome Patient Reported Index) [23]	<ul style="list-style-type: none"> <li>• Patient questionnaire to assess symptoms associated with pSS</li> <li>• Three questions regarding dryness, fatigue, pain</li> <li>• Scale of 0-10</li> <li>• Independent predictor of health-related quality of life in pSS patients</li> </ul>
<b>Disease activity scores</b>	
SCAI (Sjögren's Systemic Clinical Activity Index) [24]	<ul style="list-style-type: none"> <li>• Utilises principles from British Isles Lupus Assessment Group (BILAG)</li> </ul>

	<ul style="list-style-type: none"> <li>• 42 questions from 8 domains (constitutional, musculoskeletal, cutaneous/vascular, respiratory, neurological, renal, salivary gland, haematological)</li> <li>• Scored as new, same, worse, improving or not present</li> </ul>
SSDAI (Sjögren's Syndrome Disease Activity Index) [23]	<ul style="list-style-type: none"> <li>• Eight domains: constitutional, salivary gland, articular, haematological, pleuro-pulmonary, vasculitis, renal, peripheral neuropathy</li> </ul>
ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index) [25]	<ul style="list-style-type: none"> <li>• 12 domains: constitutional, lymphadenopathy and lymphoma, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological, biological</li> </ul>
<b>Damage indices</b>	
SSDDI (Sjögren's Syndrome Disease Damage Index) [26]	<ul style="list-style-type: none"> <li>• Developed for the Italian cohort of patients</li> <li>• Six domains: oral/salivary damage, ocular damage, neurologic damage, pleuropulmonary, renal, lymphoproliferative</li> </ul>
Sjögren's Syndrome Damage Index [27]	<ul style="list-style-type: none"> <li>• Developed for the UK cohort</li> <li>• 10 domains: Ocular, oral, neurological, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, endocrine, malignancy</li> </ul>

*RA – rheumatoid arthritis, MS - multiple sclerosis, SLE- systemic lupus erythematosus, pSS – primary Sjögren's Syndrome*

A French study demonstrated that the ESSDAI score, which measured the disease activity, did not correlate with the ESSPRI score, which comprises patient reported symptoms [28]. ESSDAI correlated more closely to physician global assessment, whilst the ESSPRI, on the other hand, correlated with patient global assessments. This reflects the different angles of the disease measured by the scores. The SCAI and SSDAI scores, however, correlated with the ESSPRI and ESSDAI but also with the PROFAD score [28], suggesting differences between the ability of different disease activity scores to correlate with patient reported outcomes.

The mechanisms of fatigue in pSS are not fully understood and the discrepancies between disease activity scores and patient reported outcomes suggest that it is more than likely to be a complex interplay of different factors rather than solely due to disease activity. Autoimmune diseases such as hypothyroidism may be an associated co-morbidity in some pSS patients which can contribute to symptoms of fatigue but this will not be discussed in this chapter. We detail below the most commonly researched associations between fatigue and biomarkers/symptoms in pSS.

### **Fatigue association with disease activity and biomarkers**

There is conflicting evidence about whether there are correlations between fatigue and levels of serological and haematological tests in patients with pSS, such as the presence of anti-nuclear (ANA) and anti-Ro antibodies [1]. Anecdotal experience suggests that patients complain equally of significant fatigue whether they are antibody positive or negative.

### **Associations with sicca symptoms**

An association between the discomfort caused by ocular sicca symptoms and mental/somatic fatigue has been identified in a small study of 39 patients (14 with pSS and 25 with RA) [11]. Patients with sicca symptoms were found to be affected by depression, fatigue and low quality of life scores whether or not they had pSS [29]. Vriezekolk *et al.* demonstrated that perceived ocular sicca symptoms did not correlate with objective measurements using the Schirmer's test. Interestingly, an increase in pain scores correlated with an increase in tear production rather than a decrease. There was also no association found between fatigue or depression with perceived ocular sicca symptoms or tear production [30].

### **Associations with pain, depression, cognition**

Pain, helplessness and depression were found to strongly correlate with fatigue on the FSS score and the PROF-S (somatic fatigue), whereas depression strongly correlated with the PROF-M (mental fatigue). Interestingly, lymphocyte count was found to predict FSS and VAS-fatigue [5].

A significant reduction in neuropsychological cognitive test scores was observed in female pSS patients compared to healthy subjects, as well as a significantly increased severity of depression, fatigue and poor quality of life (as assessed using the FSS scores and SF-36) [31]. A reduction in psychomotor processing and verbal reasoning has also been reported, independent of pain or depression scores [32].

Various psychological factors affect the way patients cope with fatigue and its effects. Van Leeuwen *et al.* stratified patients with pSS into four psychological profiles (reliant, self-reliant, alexithymic, dysfunctional) and assessed correlations with fatigue using the MFI score. They demonstrated that

patients who had dysfunctional coping mechanisms or who were alexithymic, reported higher fatigue scores compared to those who were self-reliant, which may indicate that pSS patients may benefit from a stratification of their profiles to guide prognosis and tailored management [33].

Patients with pSS were reported to engage less in moderate to vigorous activities, whereas sedentary activity levels were similar to that of healthy controls. Reduced physical activity was also found to correlate with fatigue, quality of life and depression [34].

### **Associations with sleep**

Sleep disturbance has been reported to be present more frequently in patients with pSS compared to normal subjects. Patients with pSS have been identified to have poorer sleep quality, which correlated to mental fatigue levels [11].

Apart from fatigue, excessive sleepiness was also more frequently seen in pSS patients compared to healthy controls. They also were observed to experience twice the frequency of apneic-hypopnoeic episodes on polysomnography compared to normal subjects. However, the sleep parameters did not seem to correlate significantly with fatigue levels [35].

A higher level of discomfort in the evening was found to correlate with a higher level of fatigue the following day, compounded by poor sleep. Interestingly, a higher level of anxiety was found in pSS patients, alongside increased frequency of awakenings at night, nocturia and nocturnal sicca symptoms. However, only anxiety and nocturnal awakenings due to pain were found to predict daytime fatigue [11]. Priori *et al.* reported significantly worsened perceived quality of sleep and increased frequency of sleep disturbances resulting in impaired quality of life, but this did not correlate to fatigue scores or disease activity [36].

### **Associations with fibromyalgia**

Fibromyalgia may co-exist with Sjögren's syndrome or any other rheumatologic conditions. Fatigue is recognised as one of the features of fibromyalgia. The prevalence of fibromyalgia in the general population ranges from 2-7% [37]. The prevalence of fibromyalgia in pSS has been estimated to be 13% although these were derived from low sample size studies [37]. There is conflicting evidence whether the presence of fibromyalgia as a co-morbidity associated with a rheumatic condition is the cause of associated fatigue. Giles *et al.* did not identify a significant number of patients with co-morbid fibromyalgia features, despite the majority of the patients with pSS reporting fatigue [38]. Other studies have demonstrated no difference in fatigue reported on VAS between pSS patients with or without fibromyalgia [39], suggesting that although fibromyalgia may result in fatigue, this is unlikely to be the only explanation for the fatigue experienced in pSS patients.

### **Fatigue and the brain**

pSS patients have been found to have significantly low cerebrospinal Flt3 ligand, similar to that of patients with Alzheimer's disease, compared to patients with fibromyalgia. The Flt3 ligand correlated significantly with the presence of tau proteins in pSS patients, with the conjecture that ongoing degradation of proteins and remodeling may be occurring in these patients [40]. A recent small study comparing cerebrospinal fluid between fatigued and non-fatigued pSS patients have also suggested differences in the proteome of these patients. Some of the proteins implicated have important functions in the brain and have been reported in the context of depression and chronic fatigue syndrome [41].

### **Autonomic nervous system dysregulation**

Autonomic nervous system dysregulation has been suggested to contribute to fatigue in patients with pSS. A significant negative correlation was identified between supine plasma noradrenaline and fatigue in patients with pSS, but this was not the case with adrenaline. There were no significant correlations found in this study between blood pressure and fatigue [42]. Another study, however, reported that low blood pressure, particularly the diastolic component, correlated with fatigue [43].

### **Associations with serum/plasma biomarkers**

Dysregulation in the cytokine milieu has been described to be responsible for the manifestations in pSS, with pro-inflammatory cytokines such as IFN- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, TNF- $\alpha$ , B-cell activating factor implicated [44, 45]. Whilst some have shown no correlation between serum cytokine (IL-2, IL-6, IL-10, TNF- $\alpha$ ) levels and fatigue [7], there is emerging data suggesting associations between cytokines and fatigue. D'Elia *et al.* hypothesised the existence of a link between IL-6 and the hypothalamic-pituitary–adrenal (HPA) axis and reported in a small study that IL-6 levels were found to have an inverse correlation to fatigue and that dehydroepiandrosterone (DHEA) substitution reduced the level of soluble IL-6 receptors [46]. A recent UK-based study on a validation cohort found pro-inflammatory cytokines, TNF- $\alpha$  and LT- $\alpha$  levels, to inversely correlate with severity of fatigue suggesting that pro-inflammatory cytokines may not be directly responsible for symptoms of fatigue. This study also describes a predictive model of fatigue severity which included cytokines, routine laboratory haematological/biochemical indices, clinical scores, depression, anxiety and pain indices [47].

Heat shock protein, HSP90 $\alpha$ , has been found to be significantly raised in pSS patients with high fatigue scores. It has been suggested that HSP may play a role in central nervous system signalling responsible for causing fatigue [48].

A “fatigue signature” has also been proposed by another recent study using proteomic analysis which identified 16 differentially expressed serum proteins comparing pSS patients with and without fatigue. The main proteins found to be upregulated were neuroactive synaptosomal-associated protein 25 (SNAP-25), alpha-enolase (ENO1) and ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1), which have been described to be important for central nervous system function and implicated in conditions such as Alzheimer’s disease [49].

### **Genetic associations**

No individual genes were found to be associated with fatigue in a large registry study; however differences in metabolic pathways associated with 55 genes were identified between pSS patients with high levels compared to low levels of fatigue [50]. Differences in DNA methylation have also been described in patients with pSS with low versus high levels of fatigue, inferring that epigenetic changes could represent regulatory mechanisms associated with fatigue in pSS [51].

### **Therapies for fatigue**

Hydroxychloroquine 400mg daily was used in a two-year double blind crossover trial [52] and a randomised-controlled trial (RCT) [53] which both found no significant benefit in fatigue, myalgia, arthralgia, sicca symptoms, when compared to placebo. Similar results were also seen in a small prospective study of 14 patients where hydroxychloroquine therapy did not have any significant benefit on fatigue and sicca symptoms, although there were significant improvements in inflammatory markers and IgG levels and 2 out of the 14 patients had improvement in sleep [54].

Improvement was seen in the general fatigue domain of the MFI score after 24 weeks of leflunomide in a small open label study of 15 patients but no difference was seen in the other four domains (physical fatigue, mental fatigue, reduced activity, reduced motivation) [55]. In another small open label study, zidovudine treatment was administered to 7 pSS patients (with no history of retroviral infections) over 3 months with improvement in fatigue VAS was seen in all patients [56].

Infliximab was found to be ineffective in controlling symptoms of fatigue associated with pSS [57]. In an open label pilot study of 15 patients treated with etanercept for 12 weeks, 4 patients reported an improvement in fatigue as assessed by MFI score [58].

A randomised, double-blind, placebo-controlled trial with IL-1 inhibitor, anakinra did not show a significant benefit when analysed as a group but a significantly higher number of patients treated with anakinra reported more than 50% improvement in fatigue compared to patients given placebo [59].

Abatacept has been shown to improve ESSDAI and ESSPRI scores, as well as pain and fatigue, in an open label study [60].

Rituximab outcomes in clinical trials have been varied, with improvement seen in ESSDAI scores with treatment [61, 62]. A small open label study of low dose rituximab (375mg/m<sup>2</sup>) 1 week apart showed improvement in fatigue scores [63]. Two RCTs reported improvement in fatigue (fatigue VAS [64] and MFI [65]) in patients treated with rituximab (2 doses of 1g) compared to placebo. Another RCT of rituximab (2 doses of 1g) or placebo did not meet its primary endpoint of improvement in 2 out of 4 VAS scores but showed greater improvement in fatigue in the rituximab treated arm at 24 weeks [62]. However, Bowman et al. demonstrated no improvement in fatigue scores (ESSPRI, VAS, PROFAD) in an RCT of rituximab (2 doses of 1g per course, for 2 courses 24 weeks apart) compared to placebo. The study also demonstrated that rituximab treatment in this context was not cost-effective [66]. Two meta-analyses have also reported no differences in fatigue outcomes with rituximab treatment [67, 68].

BAFF has been implicated in the pathogenesis of pSS. In an open label phase II study, 60% of patients treated with belimumab achieved the primary outcome of improvement in two of the following domains: sicca symptoms, fatigue, pain, systemic activity, and B-cell markers [69]. However, although there was a reduction in mean fatigue VAS, this was not found to be significant.

An open-label study identified significant improvements in fatigue and patient global assessment scores with the anti-CD22 drug - epratuzumab. Interestingly, this study identified an over-expression of CD22 in peripheral B-cells in pSS patients, which were down-regulated by epratuzumab therapy [70].

In a case report, bortezomib, a proteasome inhibitor, was used in refractory pSS with improvement in fatigue levels, hypergammaglobulinemia and hyperviscosity [71].

Studies have also investigated treatments such as dehydroepiandrosterone [72, 73], doxycycline [74] and gammalinolenic acid (evening primrose oil) [75] with no evidence of improvement on fatigue scores in pSS.

In Table 6.8.2, we detailed the therapeutic agents used for fatigue associated with pSS, and their associated benefit.

**Table 6.8.2: Table of studies investigating therapeutic options for fatigue associated with pSS.**

<b>Medication</b>	<b>Study design</b>	<b>Number of patients</b>	<b>Impact on fatigue</b>
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Hydroxychloroquine	Double blind crossover RCT [52]	19	No difference
	RCT [53]	120	No difference
	Prospective open-label study [54]	14	No difference
	Retrospective open-label study [76]	40	Improvement in fatigue noted in 15 participants
	Retrospective, multi-centre study [77]	221	Of the patients reporting fatigue (n = 30), 83% were not on hydroxychloroquine
Leflunomide	Phase II, open label study	15	Improvement in general fatigue domain of MFI score (no improvement in other 4 domains)
Zidovudine	Open label study	7	Improvement in fatigue VAS
Infliximab	RCT [78]	103	No improvement
Etanercept	Open label study [58]	15	4 out of 15 reported improvement
Abatacept	Open label study [60]	15	Significant improvement in fatigue, HRQoL and ESSDAI/ESSPRI scores
Anakinra	RCT [59]	26	No significant difference when analysed as a group but significantly more patients on anakinra

			achieved 50% reduction in fatigue
Rituximab	Open label [63]	16	Improvement
	RCT [64]	17	Improvement
	RCT [65]	30	Improvement
	RCT [62]	120	Primary endpoint of trial not met but greater improvement with rituximab at 24 weeks
	RCT [66]	133	No improvement
Belimumab	Open-label phase II study [69]	30	Primary endpoint met, significant improvement in ESSDAI and ESSPRI but not fatigue score
Epratuzumab	Open-label phase I/II study [70]	16	Improvement

RCT – randomised-controlled trial, MFI - Multidimensional Fatigue Inventory, VAS – Visual Analogue Scale, HrQoL – Health-related Quality of Life, ESSDAI - EULAR Sjögren’s Syndrome Disease Activity Index, ESSPRI - EULAR Sjögren’s Syndrome Patient Reported Index

### Non-pharmacological interventions for fatigue

Exercise has been reported to reduce fatigue as well as improve aerobic capacity and mood in pSS and therefore is recommended as a therapeutic option to manage fatigue [79]. There is limited evidence to support the use of non-pharmacological intervention and therefore, better quality RCTs are needed. A further exploration of non-pharmacological interventions is detailed in **Chapter 6.9**.

### Impact on quality of life

Fatigue affects the ability to get through activities of daily living in multiple ways - from the motivational aspect, to the ability for higher cognitive processing, to muscle strength. For a number of patients, fatigue may be the most debilitating symptom. Patients with pSS have been reported to have impaired health-related quality of life and lower employment rates [80]. A UK study showed pSS patients have impaired EuroQoL-5 dimension scores, reflecting impaired quality of life with significant

associations with depression and pain [81]. ESSPRI has been shown to predict quality of life more accurately compared to ESSDAI a disease activity score. These scores should be interpreted in conjunction to guide decision-making and management of fatigue [82]. From a patient perspective, fatigue not only affects activities of daily living but also negatively impacts on social life [83]. In addition, there may be effects of fatigue or the disease as a whole which may not be fully captured by disease activity scores or patient reported outcomes, such as concerns about the future and concerns of being a burden to family [83]. Therefore, a holistic approach is needed in the assessment and management of patients with pSS which goes beyond standard disease activity measures and patient reported outcomes.

### Key conclusions

1. Fatigue is more common in patients in pSS compared to the general population.
2. The aetiology of fatigue in pSS is multi-factorial.

Disease activity scores should be used in conjunction with patient reported scores, such as ESSPRI and other measure of fatigue to guide management.

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