RHEUMATOLOGY

Review

Primary Sjögren's syndrome: too dry and too tired

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Abstract

Chronic fatigue is one of the most prevalent and debilitating symptoms in primary SS (pSS). Approximately 70% of pSS patients suffer from disabling fatigue, which is associated with reduced health-related quality of life. In this article, we review the instruments used for evaluating pSS-related fatigue, our current understanding of the underlying psychosocial and physiological mechanisms of fatigue in pSS and the therapeutic strategies that have been studied in the management of fatigue in pSS.

Key words: Sjögren's, Fatigue, Outcome, Assessment, Quality of life, Therapy.

Introduction

Fatigue is a complex, multi-faceted and poorly understood phenomenon. When used as a common term, it may refer to the normal experience that most people report after inadequate rest or sleep or after excessive physical exertion. Many healthy individuals often also report a feeling of fatigue after intense mental activities or when they lack motivation to initiate activities. It is therefore not surprising that fatigue is relatively common in the general population [1] and is a common complaint in primary care settings [2].

Fatigue, however, is also one of the most prominent symptoms in patients with chronic diseases [3], cancers [4] and on medications such as atenolol, IFN-α [5] and oncological treatments [6]. In addition, fatigue is a major symptom in patients with chronic fatigue syndrome as well as depression [7]. Therefore, in assessing fatigue, it is important not only to quantify the intensity and define the variability, but also to describe in detail the dimension(s) of fatigue (e.g. physical, mental, motivational and affective) that is/are experienced by the patients. For this reason, different instruments have been designed to assess fatigue and each of these may reflect different balance of these components of fatigue. Additionally, the presence or absence of other medical conditions in which fatigue is a major symptom, the use of medications,

work and social circumstance should also be taken into consideration.

In this review, we will describe our current understanding of the underlying psychosocial and physiological mechanisms of fatigue, discuss the instruments that are available to assess fatigue and discuss potential therapeutic strategies to improve fatigue in patients with primary SS (pSS).

Instrument for fatigue assessment in pSS

A perfect instrument for measuring fatigue should be reliable, sensitive to change and easy to administer. The use of a 10-cm visual analogue scale (VAS) with the anchor points being 'No fatigue' and 'Worst possible fatigue' is one of the simplest methods of measuring the severity of fatigue. As a single item instrument, however, it does not measure individual dimensions of fatigue. Data from studies of patients with RA suggest that the VAS is useful in clinical research as well as in assessing response to treatment [8, 9]. Furthermore, the simplicity of the VAS makes it one of the most popular instruments used in the assessment of fatigue, either alone or alongside other multi-item instruments.

In addition to the VAS, several instruments have been developed based on self-administered multi-item questionnaires. These questionnaires collect more detailed information on the nature of fatigue suffered by the individuals. The primary objectives of these different instruments vary. Some assess the intensity of fatigue and the impact of fatigue on daily living and behavioural consequences {e.g. the fatigue severity scale (FSS) [10], the fatigue impact scale (FIS) [11], the functional assessment of chronic illness therapy-fatigue (FACIT-F) [12]} as well as the different dimensions of fatigue {e.g. the multi-dimensional fatigue inventory (MFI) [13] and

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Chalder fatigue scale (CFS) [14]}. One disadvantage of questionnaire-based tools is that they are language dependent, and, therefore, independent validation of the instrument is required when translated into different languages and used in difficult cultures. Another limitation is that these instruments were designed initially to measure fatigue in other disorders and therefore may not necessarily be suitable for use in pSS. Indeed, Lwin *et al.* [15] found that the CFS score of pSS patients was not significantly different from healthy controls, whereas data from other fatigue measurement tools from the same group of patients demonstrated significantly higher levels of fatigue than healthy controls. These observations highlight the importance of using appropriate instruments. It is for this reason that the UK Sjögren's Interest Group (UKSIG) developed an instrument, the profile of fatigue and discomfort-sicca symptoms inventory (PROFAD-SSI), to assess fatigue, dryness, pain and discomfort in patients with pSS. The PROFAD was constructed based on the patients' own vocabulary. The fatigue component (ProF) of the PROFAD instrument measures both somatic (ProF-S) as well as mental (ProF-M) fatigue. It also assesses different 'facets' of somatic (needing rest, poor starting, low stamina and weak muscles) and mental fatigue (poor concentration and poor memory). The PROFAD has been validated in other rheumatic diseases including SLE and RA. Interestingly, VAS fatigue scores correlated strongly with the score of fatigue in the 'somatic' but not 'mental fatigue' domain, suggesting that the VAS is a useful tool to assess physical fatigue, but a separate item is needed to assess mental fatigue. More recently, the European League Against Rheumatism (EULAR) has supported the development of a revised instrument (the EULAR SS patient reported index, ESSPRI) by shortening the PROFAD-SSI to its simplest elements with some additional items [16]. The validation of the ESSPRI is currently taking place in many centres across Europe.

Clinical characteristics of pSS-related fatigue

Several studies have shown that chronic fatigue is a prominent symptom in pSS using a variety of methods including the VAS, the 'vitality' domain of the Medical Outcome Survey Short Form 36-item questionnaire (SF-36), the 'energy' domain of the Nottingham health profile, the FSS, MFI and ProF. It is noteworthy that when the same instrument was used, the results obtained from different studies carried out in different countries were often similar [15, 17, 18].

Data from studies using multi-dimensional assessment tools showed that physical/somatic fatigue is more severe and frequent than mental fatigue in patients with pSS [17–20]. For instance, it has been reported that 96% of pSS patients suffer from significant physical fatigue (defined as a ProF-S score of >2) with a mean score of 3.5, whereas only 48% of patients report significant mental fatigue with a mean score of 2.8 [17]. Similarly, Godaert *et al.* [20] have shown that, after controlling for depression, pSS patients were more fatigued that healthy controls on the 'general fatigue', 'physical fatigue' and 'reduced activity' dimensions of the MFI, but not in the 'reduced motivation' and 'mental fatigue' dimensions. Similar findings were reported in another study after depression was adjusted for [21].

In the study of Godaert *et al.* [20], they also investigated the diurnal variation of fatigue in patients with pSS and SLE. These investigators made an interesting observation that although both patient groups suffer from substantially higher levels of fatigue than healthy volunteers, pSS patients report increasing levels of fatigue after rising, followed by an improvement in mid-morning before gradually worsening again later in the day. In contrast, SLE patients reported improvement after rising, followed by an increasing level of fatigue throughout the day [20]. Data on the variation in intensity and nature of fatigue, longitudinally, however, is lacking to date.

Pathogenesis of fatigue in pSS

Despite an increasing interest among clinicians and scientists, the underlying physiological basis of fatigue in pSS, or indeed in other conditions, remains poorly defined. Several non-mutually exclusive mechanisms have been proposed. A useful model to study fatigue is to consider the inter-relationships of biological, psychological and social factors on the feeling of fatigue. It should be emphasized, however, that the categorization of these factors into 'psychological', 'social' and 'physiological' is somewhat arbitrary and such categorization is mainly intended for facilitating discussion.

Psychosocial determinants of pSS-related fatigue

The prevalence of clinical depression among pSS patients varies depending on the instrument used to assess depression and the population being studied [15, 17, 20, 21]. In the majority of the studies, a moderate correlation between depression and fatigue was found, indicating that although affective symptoms are associated with fatigue in pSS patients, other factors are also important. It should be emphasized that the concurrence of depression and fatigue in pSS does not equate to causality. One possible explanation, for instance, is that fatigue and depression share common underlying biological mechanism(s). In this regard, it is interesting that dysregulation of neuroendocrine pathways has been linked to both depression [22] and fatigue. Furthermore, it is conceivable that chronic fatigue can lead to the development of depression.

Strombeck *et al.* [23] found that 33% of pSS patients suffered from clinical anxiety as determined by a score of >10 on the Hospital Anxiety and Depression Scale. Furthermore, anxiety was found to be associated with the level of fatigue using the CFS, although the association was not maintained after linear regression analysis [23].

Learned helplessness, originally described by two American psychologists, Seligman and Maier, refers to a perceived lack of control over the outcome (usually

negative) of a situation. Learned helplessness has been linked to depression, negative attribution style (i.e. broadly speaking, 'pessimism') and impaired cognitive function. Recently, Segal *et al.* [17] reported that learned helplessness, as measured by the Rheumatology Attitudes Index, correlated with depression as well as fatigue in patients with pSS. The clinical significance of this finding is that, if true, psychological therapy such as cognitive behavioural therapy may be a useful approach in the management of fatigue.

Physiological factors of pSS-related fatigue

Disease activity. Although fatigue is very common among pSS patients, the link between 'biological' disease activity and fatigue remains to be fully defined. While several studies have shown correlations between the levels of fatigue and various surrogate 'disease activity' markers such as serum levels of immunoglobulins, ANA, lymphocyte counts and anti-Ro (SSA) antibodies [17, 18, 24, 25]. The results from these studies, however, were inconsistent and sometimes conflicting. Furthermore, it remains unclear whether these markers faithfully reflect disease activity in pSS. Indeed, there has been no standardized tool for measuring disease activity until recently. It would be interesting to re-evaluate the relationship between fatigue and disease activity using the recently devised instruments of disease activity such as the EULAR SS Disease Activity Index (ESSDAI) [26].

Cytokines. It has been suggested that IL-6 may play an important role in the pathogenesis of fatigue in RA [27], cancer [28] and over-trained athletes [29], as increased levels of IL-6 are found in these conditions and preliminary data suggest that IL-6 blockade improved symptoms of fatigue in RA [30]. IL-6 acts through binding to its receptor. The IL-6 receptor (IL-6R) complex consists of the IL-6 binding molecules and the signal transduction molecule, gp130. In addition to the membrane form of IL-6R, a soluble form of the IL-6R also exists and upon binding to IL-6 can also form an association with membrane-bound gp130 molecules leading to a process known as transactivation [31].

In pSS, the levels of IL-6 are elevated in the serum, tears as well as in saliva [32–35], although conflicting data have also been reported [36]. Recently, Konttinen and colleagues [37] have shown that baseline serum soluble IL-6R (sIL-6R) inversely correlated with fatigue as measured by MFI and VAS and positively correlated with vitality score of SF-36. Furthermore, serum IL-6 also correlated inversely with general fatigue domain of MFI in patients with detectable levels of serum IL-6. At first glance, these findings seem at odds with the current understanding of the link between IL-6 and fatigue. However, these investigators postulated that the IL-6 system was activated in pSS patients to counteract fatigue through the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the subsequent release of stress hormones [38, 39]. This may explain their observation that treatment with dehydroepiandrosterone (DHEA) suppressed the serum levels of sIL-6R. A number of anti-IL-6 therapies are currently under development for the treatment of RA and they may potentially be worth investigating for use in pSS as well.

IFN-α is another candidate molecule that may contribute to pSS-related fatigue. Induction of fatigue in patients treated with IFN-α has been well documented [5]. It has been reported that 80% of patients who received IFN-α developed symptoms of fatigue within 3 months of therapy. The underlying mechanisms remain to be elucidated, but altered basal ganglia activity has been implicated [40]. There is now an increasing body of evidence to suggest that the IFN-α pathway may be involved in the pathogenesis of pSS (reviewed in [41]). For instance, polymorphism of IFN regulatory factor 5 (IRF5), a transcription factor involved in type I IFN secretion, has been shown to be a strong risk factor for pSS [42] and a prominent pattern of over-expressed genes that are inducible by IFN are found in pSS patients [43]. In addition, the levels of IFN-α mRNA in peripheral blood cells and IFN-α proteins in plasma from patients with pSS were significantly higher than in healthy controls. Furthermore, IFN-α$^+$ lymphocytes and ductal epithelial cells were also detected in labial gland biopsies [44, 45]. Similarly, increased type I IFN activity has been detected in the salivary glands and the peripheral blood of pSS patients [46]. Therefore, it is plausible that over-activity of the IFN-α pathway may contribute to the symptoms of fatigue in pSS although direct evidence to support this hypothesis is needed.

Other cytokines that have been implicated in fatigue include TNF-α and IL-10. Of note, Hartkamp *et al.* [47] compared the serum levels of IL-1β, IL-2, IL-6, IL-10 and TNF-α of 60 pSS patients and 139 healthy controls and found no correlation between the levels of fatigue (assessed using MFI) and the levels of these cytokines.

Neuroendocrine disturbances. Many common symptoms of pSS, such as fatigue, depression, arthralgia and myalgia, resemble that of hypoadrenalism. Therefore, it is possible that pSS-associated fatigue may be a consequence of altered HPA axis function. Indeed, significantly lower basal adrenocorticotrophin and cortisol levels have been reported in patients with pSS and were associated with a blunted pituitary and adrenal response to corticotrophin releasing hormone compared with normal controls [48]. These observations suggest that the defect is at the pituitary or hypothalamic level. Nevertheless, no direct evidence on the causal role of these neuroendocrine abnormalities to the level of fatigue in pSS is available to date.

Dysregulation of the hypothalamic–pituitary–gonadal system may be another contributory factor to fatigue. Patients with pSS have low serum levels of DHEA [49], and the levels correlate with mental well-being [50, 51]. However, treatment with DHEA did not show superior effect on improvement of fatigue over placebo [52], even though treatment with DHEA but not placebo led to a reduction of plasma sIL-6R [37].

Another candidate neuroendocrine system is the serotonin (also known as 5-hydroxytryptamine) pathway. In men, increased levels of tryptophan and the subsequent

stimulation of serotonin production and release is thought to be responsible for fatigue after prolonged physical activity [53]. Furthermore, increased synaptic level of serotonin induced by selective serotonin uptake inhibitors is associated with reduced physical performance in healthy volunteers [54], whereas treatment with serotonin antagonists, such as ondansetron, reduces the levels of fatigue in patients with chronic hepatitis, primary biliary cirrhosis (PBC) and chronic fatigue syndrome [55–57]. It has also been postulated that reduced levels of synaptic serotonin may contribute to cancer-related fatigue. This is largely based on the observation that many pro-inflammatory cytokines, such as IL-2, IFN-γ and TNF-α, stimulate the production of indoleamine 2,3-dioxygenase, which degrades serotonin. This may also explain the frequent association between fatigue and depression, which is also characterized by reduced serotonin levels in the brain. One unifying hypothesis is that the synaptic level of serotonin is linked to fatigue in a U-shaped manner [58]. To date, little is known regarding the role of the serotonin pathway in pSS but is an area worthy of further exploration.

Autonomic dysfunction. Dysregulation of the autonomic nervous system has been thought to be an important factor in chronic fatigue [59–61]. For instance, neurally mediated hypotension, exaggerated blood pressure variation, abnormal heart rate variability and tilt-table responses have all been reported in chronically fatigued individuals. Symptoms and signs of both sympathetic and parasympathetic dysfunction have been reported in patients with pSS [62–68]. Barendregt *et al.* [21] studied 49 pSS patients and found no correlation between resting supine systolic blood pressure and fatigue, although there was an inverse relationship between plasma levels of noradrenaline and the 'general fatigue' domain of the MFI. In contrast, d'Elia *et al.* [69] recently reported that high level of fatigue is associated with low blood pressure. The reasons for the discrepant data between these studies are not clear and further studies are warranted to investigate the link between fatigue and autonomic function.

Sleep disturbance. Gudbjornsson *et al.* [70] have shown that pSS patients have a significantly higher level of sleep deficit (defined as the difference between the time needed for sleep and the actual sleep time). pSS patients also reported more difficulty in trying to fall asleep and more frequent and prolonged night awakening. Furthermore, polysomnography confirmed the presence of sleep disturbances—reduced sleep efficiency, increased number of awakenings and increased wakefulness surrounded by sleep—in a large proportion of pSS patients. In this study, many patients attributed their daytime fatigue to sleep disturbance [70]. However, the symptom of fatigue was not investigated in detail in this study and no formal statistical analysis on whether the degree of sleep disturbance was associated with fatigue was reported. The presence of sleep disturbances in pSS patients was subsequently confirmed in other studies [71, 72], but none

has determined the relationship between sleep disturbance and fatigue.

Impact of pSS-related fatigue

In two recent studies, fatigue has been a major predictor of reduced health-related quality of life in pSS [73, 74]. Other symptoms such as dryness and arthralgia are also likely to play a role, but the dominant contribution of fatigue is striking. However, it remains to be determined whether fatigue has adverse effects on other aspect(s) of physical and psychological well-being of pSS patients. In this regard, it is noteworthy that in other chronic conditions, such as PBC, as well as in older adults, fatigue has been linked to increased mortality and coronary heart disease [75, 76]. Recently, the UKSIG has embarked on a nationwide project (the UK primary SS registry, UKPSSR) to establish a cohort of 500 clinically well-characterized pSS patients together with a research biobank [77]. Data from this cohort should be able to address some of these issues.

Management of pSS-related fatigue

Effective management of fatigue in pSS remains a major challenge. Both pharmacological and non-pharmacological approaches have been tried with various degrees of success. The multi-dimensional nature of fatigue suggests that effective management of pSS-associated fatigue may require a combined pharmacological and non-pharmacological multi-disciplinary approach. Furthermore, the management should be tailored to individual patients according to the severity and nature of fatigue.

Pharmacological approach

Only a limited number of clinical trials in pSS used fatigue as the primary outcome measure. For the majority of the therapies discussed below, fatigue was measured as a secondary outcome and therefore subject to the potential pitfalls of multiple analyses, and inadequately powered as the sample size is usually calculated based on the primary outcome.

Non-biological therapies
HCQ. HCQ is one of the commonest 'disease-modifying' drugs being used empirically in pSS. However, there are surprisingly few published papers on the efficacy of HCQ in pSS [78–82]. Furthermore, the number of patients in these studies was small and the outcome usually focused on its effectiveness in improving symptoms of dryness, rather than fatigue. Nevertheless, it is widely used in clinical practice specifically to treat fatigue and arthralgia in pSS.

LEF. LEF is used in RA as a disease-modifying anti-rheumatic drug. In a phase II open-labelled study, 15 patients with pSS were given LEF 20 mg daily. At 24 weeks, there was a statistically significant improvement in the general fatigue score (from 17 to 11) and an increase (improvement) in the SF-36 physical function

domain score (from 39.8 to 43.8). Serum levels of IgG, IgA and IgM also decreased. However, five patients developed a lupus-like rash that resolved with topical corticosteroid. Two patients with pre-existing hypertension required escalation of anti-hypertensive therapies [83].

Zidovudine. Retroviral infections have been thought to play a role in the pathogenesis of pSS [84–87] and hence anti-retroviral therapy, such as zidovudine, was considered a potential treatment. In an open-labelled study, seven pSS patients were treated with zidovudine 250 mg twice daily for 3 months, and followed up for 4 months in total. All patients had very early disease (<1 year of duration) and evidence of active disease as defined by the presence of extraglandular features and either hypergammaglobulinaemia or elevated ESR. None of the patients had either HIV or hepatitis C virus infection. Remarkably, six out of seven patients showed marked improvement of their symptoms of dryness and fatigue. The mean fatigue VAS reduced from 65.1 (13.4) to 16.8 (9.1), and the treatment was well tolerated [88].

Doxycyline. The use of low-dose doxycycline has been studied in a double-blind, randomized, placebo-controlled cross-over study in 22 pSS patients. Doxycycline is an antibiotic, but low-dose doxycycline has been shown to inhibit MMPs with no significant anti-microbial effect [89]. However, not only was there no clinical benefit, there was only a slight, but statistically significant, worsening of fatigue as measured by VAS [90].

DHEA. As mentioned earlier, in a double-blind, randomized, placebo-controlled trial of 60 pSS patients, Hartkamp *et al.* [52] demonstrated that both DHEA and placebo significantly reduced the levels of fatigue as assessed by MFI. Further analyses revealed that the belief to have used DHEA was a stronger predictor for improvement of fatigue and well-being than the actual use of DHEA [52]. Similar results were also reported in another double-blind, placebo-controlled trial, although in the latter study fatigue was not measured [91].

Gamma-linolenic acid. It has been suggested that abnormalities of essential fatty acids may be important in the pathogenesis of pSS [92]. Gamma-linolenic acid (GLA) is an essential omega-6 fatty acid and a major component of evening primrose oil. However, a double-blind, randomized, placebo (corn oil)-controlled trial of 90 pSS patients treated with high dose of GLA showed no statistically significant improvement in fatigue VAS [93].

Biological therapies
TNF-α blockade. TNF-α blockade therapies were the first biological therapies to be studied in pSS. Despite promising data in open-labelled studies [94–96], data from double-blind, randomized, placebo-controlled trials of either infliximab [97] or etanercept [98] were disappointing, with neither drug demonstrating significant benefits over placebo in improving fatigue in pSS patients.

B-cell blockade. Clinical features such as autoantibody production, hypergammaglobulinaemia, the presence of B-cell infiltrates in the salivary glands and the propensity to the development of B-cell lymphomas suggest that B cells play a key role in the pathogenesis of pSS. Therefore, B-cell blockade is an attractive therapeutic option. Indeed, data from several prospective [99–101] and retrospective [102, 103] studies have demonstrated that rituximab may potentially be effective in the treatment of dryness and fatigue in pSS. For instance, in a double-blind, randomized, placebo-controlled trial, Dass *et al.* [101] have shown that a single course of rituximab (2 × 1 g of rituximab), but not placebo, significantly reduced fatigue VAS scores at 6 months. Similar results were also reported in an open-labelled prospective study [100]. Interestingly, in the study by Pijpe *et al.* [99], significant improvement in MFI fatigue scores and vitality score of SF-36 was demonstrated at 12 weeks in patients with early disease (<4 years duration), but not in patients with mucosa associated lymphoid tissue lymphoma despite good clinical responses to the lymphoma. Furthermore, the dryness and fatigue returned to baseline levels by 48 weeks, and a similar degree of improvement can be achieved following re-treatment with rituximab [99, 104]. Based on these observations, at least two large double-blind, randomized, placebo-controlled clinical trials of rituximab are underway.

Epratuzumab (a humanized anti-CD22 antibody) is another anti-B-cell therapy. In an open-labelled, phase I/II study, 16 pSS patients received four infusions of 360 mg/m^2 epratuzumab fortnightly. Over 40% of the patients reported at least 20% improvement in the fatigue VAS and the levels of improvement were sustained over the entire follow-up period of 6 months [105].

Although the above data suggest that B-cell blockade is a promising therapeutic strategy for the management of fatigue, the levels of fatigue gradually returned to baseline in these studies, indicating that regular treatment may be necessary. However, the risk of long-term depletion of B cells is still unclear. In addition, the cost associated with such an approach is substantial and should be carefully evaluated from a health economic perspective. Furthermore, the clinical significance of the relatively modest levels of reduction in fatigue achieved with anti-B-cell therapy remains to be defined.

Non-pharmacological management

Reduction of aerobic capacity has been linked to fatigue [23]. Strombeck *et al.* [106] investigated the effect of moderate to high-intensity exercise programme on the aerobic capacity and fatigue in patients with pSS. Eleven pSS patients were given a medium- to high-intensity aerobic exercise programme and 10 were given low-intensity home exercises. The level of fatigue was assessed before and after the 12-week study period using ProF and VAS. Patients allocated to the medium- to high-intensity programme reported a significant improvement of fatigue VAS and aerobic capacity compared with the home exercise group. There were reductions in the

total, somatic and mental components of the ProF score in both interventional groups.

Another non-pharmacological approach that may be useful in the management of fatigue in pSS is cognitive behavioural therapy (CBT). Evidence supporting a role for CBT includes the prominent placebo effect observed in many interventional trials of fatigue in pSS and the association of learned helplessness and fatigue in pSS. CBT may also be beneficial for a subgroup of pSS patients who also suffer from depression. Therefore, further investigation into the effectiveness of CBT in the management of pSS-related fatigue is warranted.

Patient education is also an important aspect of the fatigue management. For clinicians caring for patients with pSS, the lack of proven strategies in the management of fatigue may lead to a tendency of avoiding any discussion of fatigue with their patients. Indeed, data from a recent audit carried out in a single teaching hospital with a dedicated connective tissue clinic have shown that only 40% of patients had been given advice from their rheumatologists on the management of fatigue, although 86% of patients would welcome more advice from their doctors. Moreover, all patients who had received advice from their rheumatologists found it helpful in the management of their fatigue [107].

Unanswered questions and future work

Our understanding of the underlying psycho-physiological basis of fatigue remains limited. Therefore, the number of unanswered questions is high and the spectrum of future work is wide. We highlight below a few areas of research that we believe are important to be addressed in the near future. First, can we define physiological fatigue? For instance, can we identify an association between levels of cytokines and fatigue in larger patient samples that could give us a clearer answer to this question? This is an important issue because the identification of biomarker(s) of fatigue will enhance the development of targeted therapeutic strategies for pSS-related fatigue. Similarly, because the sample size in the majority of studies of fatigue in pSS was relatively small, these studies may not have had sufficient power to address the importance of the various inter-related psycho-physiological factors that can contribute to the symptoms of fatigue in pSS. We hope that the data from the UKPSSR will be able to shed light into this, once the recruitment target is achieved. Secondly, the data on aerobic exercise and fatigue is interesting. Perhaps, collaboration with sports physiologists in future studies of fatigue in pSS will be beneficial. Thirdly, the role of sleep disturbance in pSS-associated fatigue is still relatively unexplored and future studies are warranted. Fourthly, longitudinal data on pSS-related fatigue will be useful in understanding the evolution of this important symptom as well as the impact on the physical and psychological health of pSS patients. Finally, development of a management guideline for pSS-related fatigue, based on the current understanding of the mechanisms of fatigue and data from clinical trials, will facilitate a systematic approach to the management of this debilitating symptoms as well as supporting audit and future research.

Conclusion

Fatigue is a common and debilitating symptom in pSS. The pathogenesis of pSS-associated fatigue is unclear and an effective management strategy has not been identified. The difficulty in reliably measuring fatigue adds to the challenge in research into fatigue. Future research in pSS-associated fatigue will require a comprehensive assessment of different aetiological factors and their relative contributions to the symptoms of fatigue in pSS, as well as longitudinal assessment. Our goal should be to obtain sufficient evidence-based data to inform the development of a systematic guideline on the management of fatigue in pSS.

> **Rheumatology key messages**
> - Fatigue is a common and debilitating symptom in pSS.
> - Further research to define the underlying psycho-physiological mechanisms and to develop effective management strategies is needed.

Acknowledgements

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