

ORIGINAL ARTICLE

Pain and depression are associated with both physical and mental fatigue independently of comorbidities and medications in primary Sjögren's syndrome

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ABSTRACT

Objectives To report on fatigue in patients from the United Kingdom primary Sjögren's syndrome (pSS) registry identifying factors associated with fatigue and robust to assignable causes such as comorbidities and medications associated with drowsiness.

Methods From our cohort (n = 608), we identified those with comorbidities associated with fatigue, and those taking medications associated with drowsiness. We constructed dummy variables, permitting the contribution of these potentially assignable causes of fatigue to be assessed. Using multiple regression analysis, we modelled the relationship between Profile of Fatigue and Discomfort physical and mental fatigue scores and potentially related variables.

Results Pain, depression and daytime sleepiness scores were closely associated with both physical and mental fatigue (all $p \leq 0.0001$). In addition, dryness was strongly associated with physical fatigue ($p \leq 0.0001$). These effects were observed even after adjustment for comorbidities associated with fatigue or medications associated with drowsiness.

Conclusions These findings support further research and clinical interventions targeting pain, dryness, depression and sleep to improve fatigue in patients with pSS. This finding is robust to both the effect of other comorbidities associated with fatigue and medications associated with drowsiness.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease

Key messages

What is already known about this subject?

► Patients with primary Sjögren's syndrome (pSS) often report fatigue as the symptom most in need of improvement.

What does this study add?

► This study identifies pain, depression and daytime sleepiness scores as those factors most closely associated with both physical and mental fatigue in pSS.
► This finding is robust to both the effect of other comorbidities associated with fatigue and medications associated with drowsiness.

How might this impact on clinical practice?

► Interventions directed at managing fatigue might be expected to have a significant impact on the patient's quality of life.
► These findings support an interdisciplinary clinical assessment with:

- an initial medication review,
- assessment for comorbidities associated with fatigue,
- screening for anxiety and depression,
- assessment for undiagnosed sleep disorders,
- pain management interventions and
- interventions targeting fatigue management directly.

characterised by functional impairment of the lachrymal and salivary glands. The disease can result in systemic involvement, which

may affect any organ, resulting in manifestations such as vasculitis, neuropathy, as well as skin, lung and kidney involvement.¹ Patients with pSS often report fatigue as an important symptom in need of management.² Defined as *an overwhelming sense of tiredness, lack of energy and a feeling of exhaustion*,^{3,4} fatigue is associated with poor health⁵ and functional impairment.⁶ Previous studies have shown that physical fatigue measured with the somatic component of the Profile of Fatigue scale (PROFAD)⁷ is more prevalent and severe in patients with pSS than mental fatigue as measured with the mental component of the same scale.^{7–9} Unsurprisingly, patients with pSS also report higher daytime sleepiness scores.⁹

For some patients with pSS, fatigue is likely to have an assignable cause other than pSS. For example, they may be taking medications associated with drowsiness, or have comorbidities associated with fatigue—including hypothyroidism, depression, obesity, coeliac disease, diabetes and anaemia.

While there have been several previous studies examining the relationship between pSS, fatigue and other factors, these were conducted with lower numbers of patients and without regard to confounding medications or comorbidities. Furthermore, few studies have used the PROFAD which is a fatigue measure developed specifically for pSS.⁷

The objective of this paper is to report on the fatigue symptoms of a large cohort of 608 patients diagnosed with pSS defined using the American European Consensus Group (AECG) classification criteria and to identify factors associated with fatigue, and robust to assignable causes such as comorbidities and medications associated with fatigue.

METHODS

Design

The United Kingdom primary Sjögren's syndrome registry (UKPSSR, www.sjogrensregistry.org) is a protocol-driven, multicentre, cross-sectional study using standardised patient-reported measures and physician-generated assessments of patients with pSS from across the UK.¹⁰ All patients are participants in the UKPSSR and fulfil the AECG classification criteria. Note that fibromyalgia was an explicit exclusion criterion for the UKPSSR. Informed consent was obtained from all participants according to the principles of the Helsinki Declaration. Research ethics approval was granted by the North West Research Ethics Committee in the UK. All clinical and laboratory data were collected prospectively using a standardised pro-forma at the time of recruitment as previously described.¹⁰ At the time of analysis, 639 patients had been recruited to UKPSSR and complete data were available for 608 patients.

Fatigue assessment

The Profile of Fatigue and Discomfort (PROFAD)⁷ was designed specifically for patients with pSS. It includes

six questions which assess somatic and mental fatigue on an eight-point (0–7) scale. An average is taken for each domain score with a score of above 2.0 and 1.8 being considered significant for the somatic fatigue and mental fatigue domains, respectively.^{7,8} The PROFAD also includes a 10 cm visual analogue score of fatigue, which provides a score of 0 for absent to 100 for worst imaginable perceived fatigue levels.

Pain, depression and other assessments of patients with pSS

The following patient-reported outcome measures are collected for all UKPSSR pSS subjects: Epworth Sleepiness Scale (EPWORTH), Hospital Anxiety and Depression Scale (HADS—anxiety and depression), European League Against Rheumatism (EULAR) Sjögren's syndrome Patient Reported Index (ESSPRI) (measure of overall symptom burden and includes a 1–10 pain score), EULAR Sicca Score (ESS) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

All UKPSSR participants are asked to indicate which symptom they perceive as being the most in need of improvement (physical fatigue, mental fatigue, dryness or pain). At the time of recruitment, the presence of anti-Ro and/or anti-La antibodies are recorded, as well as levels of systemic inflammation including C-reactive protein and erythrocyte sedimentation rate. Additionally, body mass index (BMI) and co-morbidities and medications are recorded for each participant.

We captured the effect of multiple drugs and comorbidities using a comorbidity and polypharmacy score (CPS). This score is obtained by combining the number of comorbidities and the number of prescribed medications.¹¹ To identify *potentially* assignable causes for fatigue in patients with pSS, we analysed our cohort for existing comorbidities and medication status. We classified the following comorbidities as conditions potentially associated with fatigue independently of pSS: hypothyroidism, diabetes mellitus (insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM)), coeliac disease, anaemia (haemoglobin <10), a diagnosis of clinical depression and severe obesity (BMI ≥40).^{12,13} In addition, patients whose fatigue might be assignable to medications linked with drowsiness (eg, antidepressants, antipsychotics, opioids, etc) were identified—see online supplementary table S1. Using these data, we created dummy variables for each patient to adjust for medications associated with drowsiness (DROWSY Medications) or comorbidities associated with fatigue (COMORBID).

Statistical analysis

Multiple regression analysis was used to model the relationships between physical and mental fatigue and candidate variables, including age, sex, pain, dryness, anxiety, depression, daytime sleepiness scores, BMI, symptom years, drowsy medications (DROWSY) and comorbidities (Anaemia COMORBID, Hypothyroidism COMORBID, IDDM COMORBID, NIDDM COMORBID, Obesity COMORBID, Depression COMORBID, Coeliac COMORBID). Causation

cannot be inferred from such models: they can only hope to highlight those variables associated with fatigue after adjustment for the presence of other covariates. The assumptions underlying the multiple regression analysis were tested by lack-of-fit testing and inspection of residuals. Statistical analyses were performed using SAS JMP (V.13) Statistical Data Visualisation Software. Statistical significance was set at a p value of ≤ 0.05 .

RESULTS

The median age of our cohort ($n=608$) was 64 years (IQR: 53–71). The median number of symptom years for patients was 10 years (IQR: 5–17). Most UKPSSR patients experienced dryness as measured by objective measures of dryness such as Salivary Flow and Schirmer's Test. The median score on the ESSPRI scale was 5.67 (IQR: 3.67–7.00) and the EULAR Dryness Scale (ESS) was 6 (IQR: 4–8). The median disease activity score (ESSDAI) for the cohort was 3 (IQR: 1–7). While more than half of patients received one or more medications to manage their dryness symptoms, 40% of patients ranked fatigue or mental fatigue—rather than dryness—as the symptom 'most in need of improvement'. This is similar to the numbers ranking dryness as the most in need of improvement (45%), and rather more than those ranking pain as the symptom most in need of improvement (15%).

Comorbidities and medications associated with drowsiness

In addition to meeting AECG classification criteria for Sjögren's syndrome, patients in the UKPSSR cohort are an older cohort presenting with relatively complex health needs. The median CPS for the cohort was 6 (IQR: 3–9). Almost one-third of patients with pSS presented with one or more fatigue-related comorbidities. The most commonly reported comorbidity was hypothyroidism, see [table 1](#).

In addition, 130 patients with pSS were prescribed a number of different drugs associated with drowsiness. The most common drowsiness-associated medications included antidepressants, such as citalopram (18%), amitriptyline (12%) and fluoxetine (11%), or analgesics such as tramadol (13%). Some patients took two or more drowsiness-associated medications, see [table 2](#).

For information, summary statistics are reported separately for four separate subsets of patients: (a) patients with comorbidities associated with drowsiness, (b) patients with medications associated with drowsiness, (c) patients with both comorbidities and medications associated with drowsiness and (d) patients with neither comorbidities nor medications associated with drowsiness, see online supplementary table S2. Note that most patients presented with neither comorbidities nor medications associated with drowsiness. While apparent differences between subsets must be interpreted with caution—see online supplementary appendix—not surprisingly, there were statistically significant differences in both physical and mental PROFAD fatigue scores for patients with

Table 1 Numbers of patients presenting with comorbidities. While 170 patients presented with one and 22 presented with two or more comorbidities, most patients (416) presented with no comorbidities

Comorbidities	Number of patients
None	416
THYROID	114
COELIAC	16
DEPRESSION	16
DIABETES	10
OBESITY	8
THYROID+OBESITY	8
ANAEMIA	6
THYROID+DEPRESSION	3
THYROID+DIABETES	3
DIABETES+OBESITY	2
THYROID+ANAEMIA	2
DIABETES+DEPRESSION	1
ANAEMIA+COELIAC	1
THYROID+COELIAC	1
THYROID+DIABETES+OBESITY	1
Total	608

COMORBIDITIES Key: THYROID=hypothyroidism, COELIAC=coeliac disease, DEPRESSION=clinical depression diagnosis, DIABETES=IDDM or NIDDM diabetes, OBESITY=obesity, ANAEMIA=anaemia.

comorbidities associated with fatigue or medications associated with drowsiness (Kruskal-Wallis test, $p<0.0001$).

Models of fatigue

In order to identify variables associated with physical and mental fatigue, we ran multiple regression models separately for PROFAD physical and PROFAD mental fatigue scores. The models included the candidate variables: age, sex, symptom years, anti-Ro or anti-La positivity, pain, dryness, Epworth Sleepiness Scale and BMI. In addition, we included dummy variables for comorbidities associated with drowsiness—anaemia, obesity, hypothyroidism, IDDM, NIDDM, coeliac disease and a diagnosis of clinical depression (labelled respectively, Anaemia COMORBID, Obesity COMORBID, Hypothyroidism COMORBID, IDDM COMORBID, NIDDM COMORBID, Coeliac COMORBID and Depression COMORBID). The dummy variable DROWSY Medications captured those patients on medications associated with drowsiness. A list of medications associated with drowsiness is given in the online supplementary appendix. In addition, the model included anxiety and depression scores from the HADS. Given the large number of candidate variables, we used a Benjamini-Hochberg correction to adjust the false discovery rate (p value=0.05).¹⁴ Further statistical details are given in the online supplementary file. Full multiple regression equations for PROFAD physical and

Table 2 Numbers of patients prescribed drowsy medications. While 108 patients took one and 22 took two or more drowsy medications, most patients (478) took no drowsy medications. Of those taking one or more drowsy medications, citalopram, tramadol, amitriptyline, fluoxetine and zopiclone were the most frequently reported

Drowsy medications	Number of patients
None	478
CITALOPRAM	23
TRAMADOL	17
AMITRIPTYLINE	16
FLUOXETINE	14
ZOPICLONE	4
DIAZEPAM	3
DOSULEPIN	3
GABAPENTIN	3
PAROXETINE	3
BACLOFEN	2
DULOXETINE	2
IMIPRAMINE	2
MIRTAZAPINE	2
SERTRALINE	2
TEMAZEPAM	2
ZOLPIDEM	2
CARBAMAZEPINE	1
CLOMIPRAMINE	1
CLONAZEPAM	1
LAMOTRIGINE	1
LEVETIRACETAM	1
NORTRIPTYLINE	1
RISPERIDONE	1
SODIUM VALPROATE	1
CARBAMAZAPINE ESCITALOPRAM AMITRIPTYLINE	1
DIAZEPAM DOSULEPIN	1
DULOXETINE AMITRIPTYLINE CITALOPRAM	1
ESCITALOPRAM DIAZEPAM	1
GABAPENTIN FLUOXETINE	1
LAMOTRIGINE CITALOPRAM	1
TOPIRAMATE MIRTAZAPINE AMITRIPTYLINE	1
TRAMADOL AMITRIPTYLINE	1
TRAMADOL CITALOPRAM	3
TRAMADOL DOSULEPIN	1
TRAMADOL FLUOXETINE DIAZEPAM	1
TRAMADOL GABAPENTIN	1
TRAMADOL SERTRALINE LITHIUM CHLORPROMAZINE TEMAZEPAM	1
TRAMADOL ZOPICLONE	1
VENLAFAXINE ROPINIROLE QUETIAPINE	1
ZOLPIDEM SERTRALINE	1
ZOPICLONE AMITRIPTYLINE	1
ZOPICLONE FLUOXETINE	1
ZOPICLONE LAMOTRIGINE FLUOXETINE	1
ZOPICLONE OLANZAPINE GABAPENTIN DIAZEPAM	1
Total	608

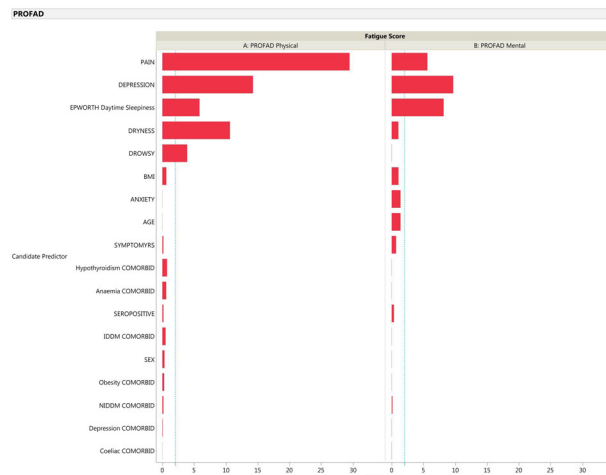


Figure 1 Summary multiple regression charts for (A) PROFAD physical fatigue and (B) PROFAD mental fatigue scores. Log worth values indicate the relative importance of each variable in the model. The broken, blue, vertical reference line is for Log worth=2.0 equivalent to an false discovery rate-adjusted p value of 0.01. Note that both pain and depression are closely associated with both physical and mental fatigue. See text. BMI, body mass index; PROFAD, Profile of Fatigue and Discomfort.

PROFAD mental scores are presented in online supplementary table 3. These analyses are summarised in figure 1. Note that while there was a weak association between ESSDAI disease activity scores and PROFAD fatigue scores, this was not robust to the inclusion of other covariates, see online supplementary appendix.

Interestingly, pain and depression scores are correlated with both PROFAD physical fatigue and PROFAD mental fatigue scores. The physical fatigue model identified pain, depression, dryness and scores on the Epworth daytime sleepiness scale as the most important variables associated with PROFAD physical fatigue scores (all $p \leq 0.0001$). The mental fatigue model identified pain, depression and scores on the Epworth daytime sleepiness scale as the three most important variables associated with PROFAD mental fatigue scores (all $p \leq 0.0001$).

The strong association of depression on the HADS with both physical and mental fatigue prompted us to repeat the analysis with depression COMORBID recoded to include a new category—those patients with a HADS score ≥ 8 or a depression score ≥ 8 . Such patients warrant further assessment for depression and may represent a subset of those patients with currently undiagnosed depression. Repeating the analysis, even after adjustment for potential undiagnosed depression, the relationships of pain, depression, dryness and Epworth daytime sleepiness scores remained statistically significant ($p \leq 0.0001$).

None of the comorbidities associated with fatigue had a statistically significant relationship with either PROFAD physical or PROFAD mental scores. However, patients prescribed medications associated with drowsiness had higher PROFAD physical fatigue scores ($p = 0.0001$).

DISCUSSION

Fatigue is important to patients with pSS

This is the largest study to date investigating fatigue in patients with pSS. Our study confirms previous observations that fatigue is an important symptom in need of improvement.¹⁵ The main objective was to report on fatigue in patients with pSS after separating out effects attributable to assignable causes such as comorbidities and medications. Our data suggest that while patients with pSS may present with complex comorbidities and medications associated with fatigue, these account for a relatively small proportion of the variation in fatigue symptoms.

Pain, depression and dryness

Fatigue symptoms are important to patients with pSS and there is an association between fatigue and other symptoms such as pain and depression.¹⁶⁻¹⁷ Howard Tripp *et al*¹⁸ identified pain and depression scores, in association with the pro-inflammatory cytokines inducible protein 10 and interferon gamma, as the two symptoms best predicting fatigue groups.¹⁸

Pain is associated with both mental and physical fatigue.¹⁹ The origin of pain in pSS is unclear, although research points towards neuropathic pain being the most common type of pain in pSS, followed by nociceptive pain.¹⁶ The relationship between pain and fatigue is reported in other conditions including rheumatoid arthritis (RA), systemic lupus erythematosus and ankylosing spondylitis (AS).²⁰⁻²² Previous research using anti-tumour necrosis factor inhibitors in RA suggests that the reductions in reported fatigue were attributable to a reduction in pain, rather than direct effects on fatigue itself²³ and pain may be a mediator of fatigue. Pain can be modified through medications which have an association with drowsiness such as amitriptyline and gabapentin. This contribution gives a possible explanation as to why drowsy medications do not have a major role in predicting mental fatigue.

Interestingly, we found that a diagnosis of clinical depression was not associated with higher fatigue. It is possible that those patients with a pre-existing depression diagnosis have been successfully treated for their depression and consequently are less likely to experience fatigue. However, less than 5% of our cohort had a clinical diagnosis of depression—rather less than that for other rheumatic diseases²⁴—and yet more than half presented with HADS scores suggesting they be screened for depression or were treated with antidepressants. If depression were under-reported, then this might lead to an apparent association between depression scores and fatigue. However, the relationship between depression scores and fatigue was robust to the introduction of an additional classification capturing those patients with a potentially undiagnosed depression.

Dryness is one of the characteristic symptoms of pSS and we observed a strong relationship between dryness symptoms and physical fatigue. Dryness may be directly related to fatigue, or it may act as an indicator of either severity or disease activity. In a recent qualitative study

of pSS fatigue, patients described experiencing ‘ocular fatigue’, where they experienced tiredness in their eyes, which for many, related to their ocular dryness symptoms such as feeling gritty or sore.²⁵ High dryness scores may simply indicate that the disease is highly active, or needs to be more closely managed in the clinic. Dryness symptoms may be an indicator of autonomic dysfunction, and fatigue may be a result of autonomic dysfunction. In addition, dryness symptoms may be associated with changes in nocturnal behaviour—see below.

Sleep

The Epworth Sleepiness Scale can be used as a screening tool to identify patients who potentially have obstructive sleep apnoea and other primary sleep disorders.²⁶ We observed that the scores on the Epworth scale were associated both with physical and mental fatigue. This finding is similar to a recent study in RA, which found that both physical and mental fatigue were associated with poor sleep.²⁷ While there are limitations to the Epworth scale, this does suggest that patients with pSS be screened for sleep problems. This could include incorporating information from a caregiver, partner or others, using other sleep instruments, polysomnography and other tests with referral to specialists in sleep disorders. A recent review has identified that a range of sleep disturbances, including night awakenings, are common in patients with pSS.²⁸ Troublesome sicca symptoms, pain and nocturia have been identified as symptoms which can potentially disturb sleep causing a reduction in sleep quality.²⁸ Identification of specific sleep disturbances in this patient group is essential, and a combination of objective and subjective measures is required to identify specific primary sleep disorders,²⁹⁻³⁰ thereby ensuring that patients have access to appropriate interventions. Treatment of sleep disturbances in other rheumatic diseases has resulted in a reduction of pain, fatigue and depression.³¹

RECOMMENDATIONS

Our data confirm the importance of fatigue symptoms—both mental and physical—to patients with pSS and permit identification of factors contributing to fatigue including other comorbidities and medications associated with drowsiness. Given the wide variety of potential factors contributing to fatigue, we support the view that a multidisciplinary approach is essential for the clinical management of fatigue in pSS.³²

► We observe that many patients with pSS are taking multiple medications and we recommend a medication review be undertaken to identify drowsy medications which could be contributing to fatigue. If these medications are discontinued, then a review should be arranged and if the fatigue does not improve, then treatment of comorbidities should be considered. However, as pain is a major contributor of both mental and physical fatigue, the contribution of some pain-modifying medications may be beneficial, despite their association with drowsiness.

- ▶ Patients with pSS should be tested for common comorbidities which can contribute to fatigue, including anaemia or hypothyroidism and offered appropriate treatments.
- ▶ We recommend screening for depression and anxiety and offering patients appropriate interventions to address these symptoms. Non-pharmacological interventions (such as talking therapies) may reduce the need for antidepressants and anti-anxiolytics, many of which are associated with drowsiness.
- ▶ We recommend that patients undergo a more detailed sleep assessment in order to screen for a primary sleep disorder. Patients identified with conditions such as obstructive sleep apnoea should be offered assignable causes such as Continuous Positive Airway Pressure (CPAP) treatment.³³ Interventions such as cognitive behavioural therapy for insomnia (CBT-I) are a first-line treatment for insomnia associated with other medical conditions³⁴ and may prove beneficial to patients with pSS.²⁸
- ▶ Patients with pSS should be offered appropriate pain management interventions. If pain is associated with poor sleep, then CBT-I with a pain adjunct has been suggested as a feasible treatment.³⁵
- ▶ Finally, in the absence of good evidence to support effective drug treatments, fatigue interventions in pSS might focus on a multidisciplinary approach incorporating activity management, graded exercise/ activity and CBT.³²

There are limitations to this study. While the PROFAD system is an established and well-validated tool, there is still a need for a good objective measure of fatigue. Though a sample population of 608 patients gives some assurance that this study is a reasonable cross section of patients in the UK, it would be useful to have comparative data in the future from other cohorts. While there was no evidence of biases arising from missing data, we note that data were incomplete for some measures and these are noted in the relevant tables of summary statistics. In addition, this was an observational study using cross-sectional data. We cannot infer causality and are only able to report associations. Prediction models do not imply causation.

CONCLUSIONS

Our data support that of others in recognising the importance of fatigue in the clinical management of patients with pSS.^{3 5 36–40} Furthermore, our analysis permits the identification of contributing factors—such as comorbidities and drowsiness-associated medications. In addition, we identified multiple factors associated with both physical and mental fatigue in pSS. Most notable of these are pain scores measured on the ESSPRI and depression scores measured on the HADS. These associations are robust and observed in patients with pSS even after adjustment for assignable causes such as other comorbidities and use of medications associated with drowsiness. Interventions directed at managing fatigue might

be expected to have a significant impact on the patient's quality of life. We recommend that the management of fatigue in pSS be multidisciplinary, and personalised to each patient depending on potential contributors to what is a debilitating and complex symptom.

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Collaborators See Appendix 1 for the full list of members.

Contributors SJB, BG, W-FN conceived the UKPSSR study. Study coordination and data collection for the UKPSSR was coordinated by SM. Data collection was performed by SM, SJB, EP, CTP, PE, PL, JH, MG, MB, NS, CP, JMCL, AC, MR, IG, DI, SV, DC, BD, NMCh, SY-M, RM, NG, MA, BG and W-FN. BH performed data management and data processing. DWL advised and KLH, KD, JRT, STM and RB performed the analyses. The paper was drafted by KLH, KD, DWL and W-FN. All authors reviewed and approved the final manuscript.

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