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Original article

Sleepiness or fatigue? Can we detect treatable causes of tiredness in primary Sjögren's syndrome?

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Abstract

Objective. To study the prevalence of fatigue and daytime sleepiness in primary SS (pSS) and analyse predicting sleep disturbing factors and other potential determinants of fatigue and sleepiness.

Method. Seventy-two consecutive pSS patients and 59 age-matched healthy controls were compared. Assessment instruments were profile of fatigue (ProF), visual analogue scale fatigue, Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale, restless legs syndrome (RLS) Diagnostic Criteria and Lund University Sleep Questionnaire. In addition, markers of immune disturbance, inflammation and disease activity using the European League Against Rheumatism SS Disease Activity Index were analysed in patients.

Results. Fatigue, especially somatic fatigue, is the main problem for pSS patients. Sleepiness is a minor problem. Patients had significantly more often anxiety, nocturia and woke up more frequently during the night than controls. The factors that predicted daytime fatigue in pSS patients were anxiety and nightly awakenings due to pain. Nocturia was frequent but was not associated with fatigue or sleepiness. RLS, depression and sicca symptoms contributed to fatigue in the univariate regression analysis only.

Conclusions. This is the first study demonstrating not only the presence of disturbed sleep, but also that nightly musculoskeletal pain and other sleep disturbing factors and anxiety significantly influence fatigue. Management strategies aimed at these aspects should therefore be included in future trials for treatment of fatigue in pSS.

Key words: Primary Sjögren's syndrome, Fatigue, Daytime sleepiness, Nightly pain, Sleep disturbances, Anxiety, Depression, Treatment, Systemic disease activity.

Introduction

Primary SS (pSS) is a disorder characterized by dryness due to dysfunction of exocrine glands and additional non-exocrine manifestations from various organ systems [1]. The most common non-exocrine symptom is an extraordinary debilitating fatigue, which has been studied in a number of research papers dealing with pathophysiology, causes, assessment or treatment attempts for fatigue. Despite that, these factors are still not well understood in pSS. Fatigue, defined as a general lack of energy not relieved by increased sleep, is not apparently caused by inflammatory activity in most cases of pSS. Attempts to explain fatigue in pSS by increased serum levels of pro-inflammatory cytokines, such as IL-6 or TNF-α, have failed [2]. However, a recent publication demonstrates clear correlation between pSS-associated reduction of health-related quality of life and serum IL-6 levels [3]. Treatment trials addressing inflammation with DMARDs including TNF-α blockers have not had convincing effects on fatigue in controlled trials (reviewed in [4]), nor have other pharmacological approaches, with e.g. gamma-linolenic acid and dehydroepiandrosterone, been successful [5, 6]. The only truly promising substance to date is rituximab [7, 8]. One controlled trial with physical exercise has been promising [9].

There is only one report focusing on another important aspect of tiredness—daytime sleepiness—in pSS [10]. Excessive daytime sleepiness is defined as the propensity

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to fall asleep at a time when the individual would usually be awake and alert. In a report from Australia, SS patients were not found to be significantly more tired than OA controls using the Functional Assessment of Chronic Illness Therapy for Fatigue Scale [11], but clearly more sleepy during the daytime, using the Epworth Sleepiness Scale (ESS) [12, 13]. A clear relationship to increased urinary tract symptoms such as awakenings due to nocturia could not be established, neither could an increased prevalence of obstructive sleep apnoea be definitively determined [14]. Another paper from Sweden using the Uppsala Sleep Inventory described sleep disturbances and reported subjectively experienced sleepiness without objective assessment in pSS [15].

As interest in fatigue has generally increased in rheumatology during the recent 10–15 years, an increasing number of assessment instruments have become available. The only SS-specific fatigue measurement instrument is the profile of fatigue (ProF), developed by the devoted activities of SS researchers in Birmingham, UK [16], presented in a long and a short version [17]. This instrument has been validated for the use in Sweden [18]. Often studies use a simple visual analogue scale (VAS) [19] or the general and widely validated instrument Medical Outcome Survey Short Form 36 (SF-36), and in particular its vitality item, as measurements of fatigue [20, 21].

Excessive daytime sleepiness is not uncommon in other conditions [22, 23]. Among the most well-known causes are obstructive sleep apnoea and narcolepsy. Narcolepsy forms without cataplexy (48% of those with narcolepsy) are more difficult to diagnose and differentiate from other forms of chronic tiredness or sleepiness. A strong association of narcolepsy with HLA-DR2, mainly HLA-DQB1*0602, present in 95% of the patients with and 40% without cataplexy (*vs* 18–35% in healthy individuals), has stimulated thoughts about narcolepsy being an autoimmune disease [23]. Prevalence of narcolepsy in pSS patients is not known, but co-existence of autoimmune diseases is very common [24]. Other major causes for excessive daytime sleepiness are insufficient sleep at night, circadian rhythm disorders, idiopathic hypersomnolence, periodic limb movement disorder in association with restless legs syndrome (RLS), depression, head injury, other disorders such as chronic pain disturbing sleep or use of drugs such as hypnotics and anti-convulsants [23]. Some of these factors, such as chronic pain or sicca problems disturbing sleep, depression or RLS are plausible in pSS, but their prevalence and relationship to disturbed sleep and daytime fatigue or sleepiness are not or insufficiently studied.

The aim of the present study was to elucidate if excessive daytime sleepiness or fatigue is the main problem in pSS patients. Furthermore, this study is the first to analyse the relationship between sleep disturbing factors and daytime tiredness in pSS, thus trying to identify treatable factors worthwhile addressing in a multimodal management approach for pSS-related fatigue. Validated instruments for measurement of fatigue (ProF [16] and VAS [19]), sleepiness (ESS [12, 13]), RLS (International classification criteria for RLS [25, 26]), sleep disturbances (Lund University Sleep questionnaire), anxiety and depression [Hospital Anxiety and Depression Scale (HAD)] [27] were used. The EULAR SS Disease Activity Index (ESSDAI) was included as a measurement of systemic disease activity [28].

Materials and methods

Patients

After informed consent, 81 consecutive outpatients (90% of whom were women) with pSS according to the American–European Consensus criteria (AECC; [29]) filled in the questionnaires during an outpatient visit and had a blood sample drawn, mainly to exclude overt inflammation as the reason for fatigue. Oxygen saturation was measured. BMI was calculated. Systemic disease activity was evaluated by ESSDAI [28]. None of the patients refused participation, but two patients were excluded from the statistical analysis due to apparent problems with the Swedish language, restricting the usefulness of questionnaire results. Seventy-two [median age 60.5 (range 30–79) years] of the 79 patients could be age matched with controls and were included in the comparison analysis with healthy controls, whereas controls were not available for five of the oldest pSS patients. Data of all 79 patients were used for the correlation and predictor analysis for fatigue in pSS.

Controls

Fifty-nine age-matched healthy controls [median age 55 (range 32–81) years, 90% women] were recruited. Thirty-two were randomly chosen from the background population, and the other 27 were recruited among hospital staff and their friends and relatives. All were unrelated to pSS patients. They filled in the same questionnaires after informed consent and personal contact. All persons who were asked for participation agreed. No other procedures were performed, e.g. no laboratory results were available. Age and gender were not significantly different between patients and controls.

The questionnaires

For measurement of fatigue we used ProF with ProF-M (mental) and ProF-S (somatic) subscales [16] and VAS fatigue [19]. For assessment of sleepiness, the ESS [12, 13]; for determination of depression or anxiety, the HAD [27]; for RLS, the internationally accepted questionnaire for RLS [25]; and for sleep disturbances, Lund University Sleep Assessment Questionnaire was used. The latter collects information about sleep-related personal factors and habits, sleep-related problems, comorbidities and medication, and allows identification of patients at high risk for sleep apnoea syndrome, other severe hypersomnolence as well as narcolepsy, periodic limb movement disorder and circadian rhythm disorder, by including groups of specific questions addressing these abnormalities.

Clinical depression and anxiety was defined as a score of $\geqslant 11$ in the depression and anxiety domains of the HAD, and a patient was considered having RLS when the classical symptoms of an urge to move the legs during rest accompanied by uncomfortable leg sensations was present $\geqslant 2$ nights a week. Significant daytime somnolence was defined as a score of $\geqslant 13$ on the ESS.

Blood samples

Blood samples were drawn the same day as the questionnaires were filled in. We analysed haemoglobin, high-sensitive CRP (hsCRP), sedimentation rate, immunoglobulins, complement factors C3 and C4, ANA, antibodies to Ro/SSA and La/SSB, IL-6, thyroid-stimulating hormone, creatine kinase (CK), creatinine, electrolytes and vitamin-B status.

Statistical methods

Patients and controls were compared by Student's *t*-test for independent samples and χ^2-statistics. Correlations of variables within the patient group were analysed by the Spearman correlation coefficient. For the predictor analysis we used general linear models. $P < 0.05$ was considered statistically significant.

Ethics

The study was reviewed and approved by Lund University Ethics Committee.

Results

Our patients represent an average pSS population with regard to autoantibodies and immune activation. The signs of systemic inflammation were only moderately increased. Systemic disease activity due to non-exocrine organ manifestations measured by ESSDAI was relatively low. Oxygen saturation, thyroid function and muscle enzymes were normal. Some patients had slightly lowered levels of haemoglobin, folate and cobalamine. Eight patients had a BMI > 30, whereas the median BMI was 25.1 (mean 25.4; Table 1).

Prevalence of fatigue and daytime sleepiness

Primary SS patients expressed significantly higher degree of fatigue than controls, but also higher degree of sleepiness. The difference between patients and controls was most prominent in fatigue, primarily in the somatic domain. The number of patients with abnormal fatigue was higher than in controls. Thus, fatigue clearly was the dominating problem in the patient group (Table 2). Two patients reported a diagnosis of narcolepsy, one successfully treated with modafinil, the other untreated due to medication intolerance. In three patients with unexplained high levels of somnolence, sleep apnoea syndrome was excluded by polysomnography.

Table 1 Disease characteristics of pSS patients

Disease duration, years[a]	12.24 (5.57)
SSA/SSB pos, %	66/38
ANA pos, %	76
IgM RF pos, %	52
ESR (ref. age dependent)[a], 1 h	26.8 (17.8)
hsCRP (ref. < 3 g/l)[a], g/l	4.8 (5.2)
IgG (ref. 6.7–14.5 g/l)[a], g/l	15.9 (6.2)
Serum IL-6 (ref. < 8 ng/l)[a], ng/l	11.4 (19.0)
Serum C3 (ref. 0.77–1.33 g/l)[a], g/l	1.21 (0.28)
Serum C4 (ref. 0.12–0.33 g/l)[a], g/l	0.25 (0.08)
Haemoglobin (ref. gender dependent)[a], g/l	130.2 (11.4)
CK (ref. 0.6–3.5 mkat/l)[a], mkat/l	1.39 (0.67)
ESSDAI (possible score 0–124)[a]	7.17 (7.08)
TSH (ref 0.4–4.0 mIU/l)[a], mIU/l	1.99 (1.33)
Oxygen saturation, %[a]	97.06 (1.41)
BMI[a]	25.5 (4.3)

None of the patients had overt untreated hypothyroidism, hypoxia, myositis or severe anaemia. [a]Mean (S.D.). pos: positive; IgG: immunoglobulin G; C3 and C4: complement factors 3 and 4; TSH: thyroid stimulating hormone.

Table 2 Measures and prevalence of fatigue and daytime sleepiness

Studied variable	Patients ($n = 72$)	Controls ($n = 59$)	*P*-value
ProF total score (0–112), mean (S.D.)	55.9 (23.7)	25.9 (23.6)	<0.001
ProF-M, mean (S.D.)[a]	2.5 (1.9)	1.4 (1.5)	<0.001
ProF-S, mean (S.D.)[b]	3.8 (1.5)	1.7 (1.5)	<0.001
VAS fatigue, mean (S.D.)	64.4 (22.2)	34.4 (11.8)	<0.001
ESS, mean (S.D.)	9.5 (5.2)	7.0 (4.0)	0.003
Abnormal fatigue, %[c]	38.9	11.9	0.001
Excessive sleepiness, %[d]	15.3	11.9	0.016
Both fatigued and sleepy, %	13.9	3.4	0.001
Neither fatigued nor sleepy, %	45.8	79.7	0.001

[a]ProF-M: calculated as sum of the facet scores within ProF items 13–16 divided by 2. [b]ProF-S: calculated as sum of the facet scores within ProF items 1–12, divided by 4. [c]cut-off for abnormal fatigue is defined as a score of greater than (mean + 1.64 × S.D.) of the healthy controls ($\geqslant 65$); [d]excessive sleepiness is defined as $\geqslant 12$ points in ESS [12].

Correlations. In pSS patients, ProF total, ProF-S and ProF-M and VAS fatigue were highly correlated with each other, with the highest correlation coefficients for ProF total with VAS ($r = 0.67$; $P < 0.001$) and ProF-S with VAS ($r = 0.73$; $P < 0.001$). Weaker but significant correlations were found between ProF total and ProF-S and daytime sleepiness (ESS) ($r = 0.30$; $P < 0.01$ and $r = 0.33$; $P < 0.01$, respectively). Also VAS fatigue and ESS correlated weakly ($r = 0.27$; $P < 0.05$). There was no correlation between age and the outcome variables for fatigue (ProF and VAS) or sleepiness (ESS) in either group. Correlations within the control group were similar to those among patients (data not shown).

Correlation between biomarkers of disease or disease activity and fatigue or sleepiness in pSS patients. There was no difference in fatigue (ProF or VAS) or sleepiness (ESS) between patients seropositive or seronegative for antibodies to SSA or SSB. Inflammatory parameters such as IL-6, IgG, hsCRP and sedimentation rate did not correlate with ProF, VAS or ESS. Interestingly, however, serum IL-6 levels were increased in 40.3% of the patients and significantly ($P = 0.016$) higher in the patients with depression than in those without (19.6 *vs* 8.9 ng/l; $P = 0.026$). A similar trend without reaching significance was seen in relationship to anxiety (11.5 *vs* 9.4 ng/l; $P = 0.057$). The other markers of inflammation did not correlate with depression or anxiety. The ESSDAI (a disease activity index including articular, pulmonary, renal, nervous system, muscular, cutaneous, haematological, glandular, lymphatic, constitutional and biological activity) did not show any correlations with fatigue or sleepiness. BMI did not correlate with any fatigue or sleepiness measure, but clearly and expectedly with the level of hsCRP ($r = 0.39$; $P = 0.001$).

Prevalence of factors potentially disturbing sleep or causing fatigue

Patients spent ~45 min more in bed per night compared with controls (8.24 *vs* 7.72 h; $P = 0.048$). The estimated time to fall asleep was similar between the groups. Primary SS patients suffered from significantly more anxiety, nightly awakenings, nocturia and nightly sicca problems disturbing their sleep (Table 3).

Correlations. As shown in earlier works in pSS, fatigue correlated with psychological factors. ProF total significantly ($P < 0.001$ for all Spearman correlation coefficients below) correlated with depression and anxiety ($r = 0.64$ and 0.52), as did ProF-M ($r = 0.60$ and 0.51) and Pro-S ($r = 0.61$ and 0.42). In addition, the presence of pain during the night as a sleep disturbing factor was associated with the presence of depression and anxiety ($P = 0.002$ and 0.015). Nightly pain was also significantly correlated with the presence of abnormal fatigue ($P < 0.001$). Daytime sleepiness (ESS) did not correlate with these factors. Daytime sleepiness negatively correlated with insomnia, which represents a logical and expected finding, since sleepy people per definition easily fall asleep.

Table 3 Potential explaining factors for fatigue and sleepiness

Explaining factor	Patients ($n = 72$)	Controls ($n = 59$)	*P*-value
Anxiety (HAD), %	19.4	5.1	0.014
Depression (HAD), %	8.3	3.4	0.235
RLS, %	15.3	10.2	0.576
Time to fall asleep, min[a]	24.0 (28.8)	20.4 (20.6)	0.309
Awakenings/night, *n*[a]	2.7 (0.17)	1.7 (0.18)	0.031
$\geqslant$2 awakenings/night, %	56.4	14.8	<0.001
Nocturia disturbing sleep, %	53	26	0.001
Nightly pain disturbing sleep, %	19	9	0.076
Sicca symptoms disturbing sleep, %	13	0	0.008

[a]Mean (S.D.).

Predictors of fatigue and daytime sleepiness

In the patient group, the presence of RLS, a higher number of nightly awakenings, especially awakenings due to nightly pain, and the presence of anxiety and depression all were predicting fatigue during the day, whereas only depression seemed to have some impact on daytime sleepiness. In univariate analysis, anxiety explained 19% of the fatigue, 16% of pain at night and 14% of depression (Table 4).

When entering anxiety, depression, RLS and nightly awakenings due to pain or sicca problems into a multivariate analysis with age as covariate, 30% of the fatigue can be explained. Only anxiety and awakenings due to nightly pain were independent predictors of fatigue measured with ProF. ProF-S was only explained independently by night pain causing awakenings. ProF-M was not independently explained by any single variable (Table 5). Among controls, predictors of fatigue and sleepiness were not analysed due to the infrequency of abnormal fatigue and excessive sleepiness.

Discussion

In pSS, we are far from having solved the problem of treating fatigue. Some positive effects have been seen in treatment trials with anti-B-cell therapy [7, 8], but treatment effects are hardly in parity with costs and unknown long-term effects of repeated (as would be necessary) or life-long application: neither have studies convincingly confirmed that inflammation or immune disturbances cause fatigue in pSS. The most recent study analysing correlations between pro-inflammatory cytokines and health-related quality of life in pSS could, however, demonstrate a correlation between increased IL-6 levels and decrease in the somatic composite score of the SF-36, which includes bodily pain, but not vitality (fatigue). The mental composite score was not significantly correlated to IL-6 [3]. This finding is partly in contrast to our present

Table 4 Univariate analysis of predictors of fatigue and sleepiness

Predictor	Depending variable							
	ProF total score		ProF-S		ProF-M		ESS	
	R^2	β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)
RLS	0.06	17 (1.9, 32)*	0.05	1.9 (0.02, 2.0)*	0.06	1.3 (0.15, 2.5)*	0.03	2.6 (−0.53, 5.76)
Anxiety	0.19	28 (14, 41)***	0.12	1.4 (0.50, 2.3)**	0.15	1.9 (0.86, 3.0)**	0.03	2.4 (−0.58, 5.3)
Depression	0.14	34 (15, 54)**	0.11	2.0 (0.70, 3.2)**	0.15	2.8 (1.3, 4.3)***	0.07	4.8 (0.64, 9.0)*
Awakenings, *n*	0.10	5.8 (1.6, 10)**	0.14	0.44 (0.180.70)**	0.002	0.06 (−0.28, 0.40)	0.03	0.63 (−0.25, 1.5)
Nocturia	0.001	1.3 (−10, 12)	0.004	0.20 (−0.52, 0.92)	0.00	0.00 (−0.86, 0.85)	0.00	−0.04 (−2.3, 2.3)
Pain at night	0.16	26 (12, 39)***	0.17	1.7 (0.81, 2.5)***	0.12	1.7 (0.64, 2.7)**	0.02	1.7 (−1.2, 4.6)
Sicca at night	0.06	19 (2.1, 36)*	0.08	1.4 (0.27, 2.5)*	0.02	0.81 (−0.53, 2.14)	0.03	2.9 (−0.64, 6.5)
High IL-6	0.02	0.13 (−7.3, 17)	0.03	0.55 (−0.24, 1.3)	0.00	−0.05 (−1.1, 0.69)	0.02	1.6 (−0.87, 4.0)

β: slope; high IL-6: serum levels ⩾ 8 ng/l. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 5 Multivariate analysis of predictors of fatigue and sleepiness

Predictor	Depending variable					
	ProF total score		ProF-S		ProF-M	
	R^2	β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)
RLS		2.8 (−13, 18)		0.057 (1.5, 4.6)		0.40 (−0.82, 1.6)
Anxiety		17 (1.4, 32)*		0.60 (−0.41, 1.6)		1.1 (−0.11, 2.4)
Depression		13 (−9.2, 36)		0.91 (−0.56, 2.4)		1.3 (−0.41, 3.16)
Awakening, *n*						
Nocturia	0.30		0.25		0.24	
Pain at night		15 (0.42, 29)*		1.1 (0.14, 2.1)*		0.86 (−0.31, 2.02)
Sicca at night		7.1 (−11, 25)		0.7 (−0.45, 1.9)		0.045 (−1.4, 1.4)
High IL-6						
Age		0.023 (−0.35, 0.39)		0.004 (−0.02, 0.03)		−0.000 (−0.03, 0.29)

Age is used as covariate. *$P < 0.05$. β: slope; high IL-6: serum levels ⩾ 8 ng/l. R^2-values take into account all the variables together.

result of higher IL-6 levels in depressed pSS patients (with similar trends in anxious and fatigued patients). More in-depth analyses of cytokine levels in relation to SS using SS-specific assessment instruments for subjective distress, which are soon available [European League Against Rheumatism (EULAR) 2009, personal communication], will probably clarify further the impact of these biochemical markers on patients' well-being. Systemic disease activity measured by ESSDAI mirroring mainly non-exocrine organ involvement did not correlate with fatigue or sleepiness in the present investigation. On the other hand, several reports describe psychological distress as part of pSS and a recent study by Segal *et al.* [30] confirms that psychosocial variables determine fatigue but only account for part of it.

The interactions between sleep and fatigue on the one hand and other factors such as pain or psychosocial distress on the other are complicated and convincingly bilateral. Thus, improving sleep may improve pain, anxiety and depression. Also, the improvement of pain, anxiety and depression may result in better sleep and less fatigue. Heavily impaired sleep (as in obstructive sleep apnoea) will cause daytime sleepiness. Therapies are available for anxiety, depression, insomnia/sleep disorders, pain, sleepiness, but not for fatigue. However, their efficacy for improving pSS-related fatigue has not been studied, probably due to a lack or proof of causality between these factors in pSS.

Our study has clarified some of these points.

(i) Fatigue is more important than sleepiness in pSS, despite the fact that daytime sleepiness occurs and may deserve treatment in some patients.
(ii) Sleep disturbances are prevalent in pSS as previously demonstrated in older studies [31, 32], but they also correlate with fatigue, which is a new finding.
(iii) Sleep disturbing factors are not equally important for fatigue. Although nocturia is prevalent (53% of patients spontaneously mention it as awakening factor), it does not predict fatigue according to the regression analysis. Pain at night was reported in 19% of the patients (not significantly more often

than in controls), but was highly predictive, and beside anxiety, the only independent explaining factor for fatigue.

Thus, a conclusion to be drawn from our results is that improving sleep by specifically aiming at management of nightly pain may, in combination with approaching anxiety/depression, result in reduced fatigue. This has to be shown in a multimodal intervention trial.

Our study confirms some earlier findings, such as associations between various variables of fatigue [18, 33], the higher scores for somatic than for mental fatigue in pSS [30, 34, 35] and potential causes such as psychosocial distress, frequent sleep disturbances and awakenings [31, 33]. We cannot confirm Walker *et al.*'s [10] results of the dominance of sleepiness over fatigue [10], possibly due to another measurement tool for fatigue and the fact that their control group consisted of OA patients in whom (nightly) pain might have caused considerable fatigue as well. Neither can we confirm Gudbjörnsson's finding of difficulties falling asleep in our patients in comparison with healthy controls [31].

Measures of inflammation and immune activation were not related to fatigue, with the exception of IL-6 levels, which were higher in depressed, anxious and fatigued patients, and in patients positive for anti-SSA and those having pain at night. Only in depressed patients was statistical significance reached. However, measured IL-6 levels were generally only moderately increased, the numbers of extremely tired, depressed and anxious patients was limited, and IL-6 in serum may not be the ideal test variable. Still, on the background of the positive findings of anti-B-cell treatment and the availability of an anti-IL-6 drug, this finding should be followed up in further studies focusing on IL-6, psychological distress, sleep disturbance and fatigue.

Although our study is the first one to objectively analyse the importance of treatable night-time sleep disturbing factors for daytime fatigue, it has some drawbacks. First, sleep disturbances and daytime sleepiness are diagnosed by questionnaire, instead of the gold standards of polysomnography and sleep latency tests. These methods would not have been possible to be performed in such a large number of patients and controls as in this investigation. Secondly, it would be an advantage to have combined the study with an intervention part to confirm our results. Thirdly, only 30% of the fatigue is explained in our model, which means that there are additional factors of importance not included or even not recognized. In an earlier study, we have shown that aerobic exercise may improve fatigue [36]. Thus, physical inactivity as a learned behaviour or helplessness [30] is probably an additional factor to be taken into account when choosing management strategy or proposing self-help programmes for the patients.

In conclusion, treating fatigue in pSS is challenging and no intervention will fit all patients, but instead an individually tailored combination of drug and non-pharmacological approach will be necessary. Despite the fact that we investigate a patient population regularly cared for by rheumatologists, simple measurements such as adequate pain management or sicca management are not sufficiently used and should be optimized and combined with other methods such as physical activity and cognitive behavioural therapy where available. Also, drugs like modafinil or melatonin may deserve to be studied in subgroups of SS patients. Especially in patients with more severe systemic disease manifestations and in those where conventional therapy is optimized and fatigue is still predominant, biological treatment with anti-B cell or IL-6 blocking agents may be used, preferably in controlled trials, as there are some encouraging results from small trials [7, 8] and new associations documented in a recent [3] and the present investigation. Combined evaluation instruments for subjective distress including sicca, pain and fatigue are under development and will facilitate intervention studies in pSS patients (EULAR 2009, personal communication).

Rheumatology key messages

- Fatigue is the main problem in pSS and not daytime sleepiness.
- Treatable causes for fatigue can be identified and addressed with available treatment modalities.
- Nightly musculoskeletal pain and anxiety or depression are the main determinators of pSS-associated fatigue.

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