#### PROFAD ─ The Profile of Fatigue and Discomfort

While there are many available instruments for the psychometric measurement of fatigue [1, 2] the Profile of Fatigue and Discomfort (PROFAD) [3] was the first patient-reported outcome tool designed specifically for PSS patients. Initially, it was designed with 64 questions to assess different ‘facets’ of symptoms commonly experienced by PSS patients. As the original version was considered burdensome for the patient to complete, a shorter version was subsequently developed with 19 questions each reflecting a single ‘facet’ of the longer, original version. Each item is scored on an 8 point (0-7) Likert scale and an average is taken for the domain score. In this instrument, 6 questions assess somatic and mental fatigue along with a visual analogue score, ranging from 0 for absent to 100 for worst imaginable perceived fatigue levels. A score of above 2.0 and 1.8 are considered significant for the somatic fatigue and mental fatigue domains, respectively [3, 4].

#### ESS ─ Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) [5] is a measure of daytime somnolence. It measures daytime sleepiness in 8 typical situations such as while being a passenger in a car or while watching TV. Respondents are asked to score on a scale of 0 (‘would never dose off’ to 3 ‘high chance of dozing off’ for each given situation. The total ESS score is the sum of each situation and a score of ≥10 indicates significant daytime somnolence and a score of 8 to 10 indicates moderate daytime somnolence. Here we use Epworth sleepiness scale scores as a simple measure of sleep propensity rather than as a clinical diagnostic.

#### HADS ─ Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) [6] is a 14-item measure (7 items per subscale) of anxiety and depression. It was developed specifically for use in physical illness. The maximum score for each subscale is 21. A score of >10 indicates caseness for anxiety or depression.

#### ESSPRI ─ EULAR Sjogren's Syndrome Patient Reported Index

The EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) [7] was developed to assess key patient reported symptoms – pain, dryness and fatigue. A single 0-10 numerical scale measures each of these symptoms. The ESSPRI score is a global measure of the severity of symptoms experienced by the patient. It is calculated with the mean domain scores of limb pain, dryness and (somatic) fatigue.

#### ESSDAI ─ EULAR Sjogren’s Syndrome Disease Activity Index

The EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) [8] is a clinical index designed to measure disease activity in PSS. It includes 12 clinical domains, which are weighted to provide an overall possible 0-123 score of disease activity.

**References**

1. Neuberger GB. Measures of fatigue: The Fatigue Questionnaire, Fatigue Severity Scale, Multidimensional Assessment of Fatigue Scale, and Short Form-36 Vitality (Energy/Fatigue) Subscale of the Short Form Health Survey. Arthritis Care & Research. 2003;49(S5):S175-S83. doi: doi:10.1002/art.11405.

2. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. Journal of pain and symptom management. 2009;37(1):107-28. Epub 2008/12/30. doi: 10.1016/j.jpainsymman.2007.08.019. PubMed PMID: 19111779.

3. Bowman SJ, Booth DA, Platts RG, Group UKSsI. Measurement of fatigue and discomfort in primary Sjogren's syndrome using a new questionnaire tool. Rheumatology (Oxford). 2004;43(6):758-64. doi: 10.1093/rheumatology/keh170. PubMed PMID: 15039495.

4. Segal B, Thomas W, Rogers T, Leon JM, Hughes P, Patel D, et al. Prevalence, severity, and predictors of fatigue in subjects with primary Sjogren's syndrome. Arthritis Rheum. 2008;59(12):1780-7. doi: 10.1002/art.24311. PubMed PMID: 19035421; PubMed Central PMCID: PMCPMC3106978.

5. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. PubMed PMID: 1798888.

6. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70. PubMed PMID: 6880820.

7. Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Annals of the rheumatic diseases. 2011;70(6):968-72. doi: 10.1136/ard.2010.143743. PubMed PMID: WOS:000290149900015.

8. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Annals of the rheumatic diseases. 2010;69(6):1103-9. doi: 10.1136/ard.2009.110619. PubMed PMID: 19561361; PubMed Central PMCID: PMCPMC2937022.

#### Statistical Methods - Supplemental

The main goal of the statistical modelling effort was to identify useful predictors of PROFAD-Physical and PROFAD-Mental fatigue scores robust to other comorbidities and medications associated with drowsiness. Inclusion of a predictor does not imply causation. Predictors may enter the model because they are correlated with causal variables. Conversely, causal variables may fail to be included because they are correlated with predictors already in the model. Causation cannot be inferred from such models: they can only hope to highlight those variables predictive of fatigue scores after adjustment for the presence of other covariates.

The multiple regression models presented in the main **Results** and in *Supplementary Table 2* are for the full model including all candidate predictors – AGE, SEX, SYMPTOMYRS, SEROPOSITIVITY, BMI, PAIN, DEPRESSION, ANXIETY, DRYNESS, DAYTIME SLEEPINESS, DROWSY MEDICATIONS and COMORBIDITIES (Coeliac, Thyroidism, Insulin-Dependent and Non-Insulin-Dependent Diabetes Mellitus, Anaemia, Clinical Depression and Obesity).

In addition, we repeated these analyses including disease activity ESSDAI as a covariate. ESSDAI was not statistically associated (p>0.25) for either PROFAD-Physical or PROFAD-Mental scores and was dropped from further analysis. Furthermore, there was no evidence to suggest that those patients prescribed anti-sicca medications had either improved dryness symptoms or improved fatigue symptoms. The UKPSSR contains historical and current data on immunosuppressive treatments – including corticosteroids, azathioprine, mycophenalate mofetil, methotrexate, leflunomide, cyclophosphamide, IVIg, etanercept, infliximab, and rituximab – and symptomatic treatments – including pilocarpine, civemiline, lachrymal substitutes, salivary substitutes, NSAIDs, and analgesics. Creating dummy variables permitted testing for the effects of individual medications in the regression. None of the anti-sicca medications had a statistically significant effect on fatigue scores. Nor was there a relationship between the number of anti-sicca medications prescribed and either PROFAD-Physical or PROFAD-mental scores. No medications were retained in the final model.

While just 20 patients received a clinical diagnosis of depression, some patients without a clinical diagnosis were prescribed anti-depressants and more than half of patients reported HADS scores warranting a clinical assessment for depression. Recognizing the potential for under-reporting of depression as a comorbidity, and in the light of the strong association of Depression on the HADS with both Physical and Mental Fatigue we repeated the analysis with Depression COMORBID recoded to include a new category – potentially undiagnosed depression (PUD) - those patients with a HADS Anxiety score > 8 or a Depression score > 8. Repeating the analysis, even after adjustment for potential undiagnosed Depression, the relationships of Pain, Depression, Dryness and Epworth Sleepiness remained statistically significant (p<0.0001).

We used backward elimination to simplify the two models of PROFAD-Physical and PROFAD-Mental scores, removing non-significant effects in a stepwise manner and re-evaluating at each step. In addition, we used a forward stepwise method - adding terms sequentially minimizing the Bayesian Information Criterion. While both methods gave more parsimonious models, the conclusions were unchanged: the main predictors maintained the same relative ordering and similar magnitudes. Similarly, the relative ordering of significant effects was preserved using both ten-fold cross validation, and 70:30 hold-out validation methods. The models are robust to the modelling method.

In addition, we considered performing separate analyses for different subgroups - those patients prescribed drowsy medications and those not, those with comorbidities and those not. We rejected this method on the basis that apparent differences between the sub-groups might arise as an artefact of the differences in sample size, or as a result of multiple testing of predictors in multiple subgroups compounding the problem of multiplicity. Instead, creating dummy variables and testing for interactions gives a direct statistical test for differences in drowsy medications and comorbidities. While this permits specific statistical tests of the primary questions of direct interest, for information only we present summary statistics for the sub-groups for the interested reader – see **Supplementary Table S2**.

***Supplementary Table S1:*** *Medications Associated with Drowsiness*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|

|  |
| --- |
| Amitriptyline hydrochloride |
| Baclofen |
| Carbamazepine |
| Chlorpromazine |
| Citalopram |
| Clomipramine hydrochloride |
| Clonazepam |
| Diazepam |
| Dosulepin hydrochloride |
| Duloxetine |
| Escitalopram |
| Fluoxetine |
| Gabapentin |
| Imipramine hydrocholoride |
| Lamotrigine |
| Levetiracetam |
| Lithium citrate/lithium carbonate |
| Mirtazapine |
| Nitrazepam |
| Nortriptyline |
| Olanzapine |
| Paroxetine |
| Quetiapine |
| Risperidone |
| Ropinirole |
| Sertraline |
| Sodium valproate |
| Temazepam |
| Topiramate |
| Tramadol hydrochloride |
| Venlafaxine |
| Zolpidem |
| Zopiclone |

 |

***Supplementary Table S2:*** *Descriptive statistics summarizing key variables for the four subsets of patient: patients with comorbidities associated with fatigue; patients prescribed medications associated with drowsiness; patients with neither comorbidities nor medications associated with drowsiness; and patients with both comorbidities associated with fatigue, and medications associated with drowsiness. Counts or medians and quartile ranges with the sample sizes for each subset.*

|  |  |  |
| --- | --- | --- |
|  |  | Subsets |
|  Variable (units) |   | Neither | Comorbidities | Drowsy Meds | Both |
| SEX | Male | 23 | 5 | 3 | 3 |
| (count) | Female | 303 | 147 | 74 | 50 |
|   | N | 326 | 152 | 77 | 53 |
| Anti-Ro Positive | Yes | 282 | 130 | 69 | 39 |
| (count) | No | 40 | 21 | 7 | 14 |
|   | Not Done/Not Known | 4 | 1 | 1 | 0 |
|   | N | 326 | 152 | 77 | 53 |
| Anti-La Positive | Yes | 212 | 102 | 51 | 22 |
| (count) | No | 98 | 46 | 21 | 30 |
|   | Not Done/Not Known | 16 | 4 | 5 | 1 |
|   | N | 326 | 152 | 77 | 53 |
| AGE | Median | 63 | 65 | 64 | 66.5 |
| (years) | Quartile Range | 54-70 | 51-71 | 51-72.7 | 55.2-75 |
|   | N | 299 | 143 | 72 | 48 |
| SYMPTOMYRS | Median | 9 | 10 | 12 | 11 |
| (years) | Quartile Range | 5-16 | 5-18 | 5-17.5 | 3.5-20 |
|   | N | 326 | 150 | 77 | 53 |
| BMI | Median | 25 | 25.3 | 27.5 | 25.9 |
| (kg/m2) | Quartile Range | 22.3-28.4 | 22.6-28.8 | 24-31.2 | 24-30.6 |
|   | N | 314 | 147 | 75 | 52 |
| SALFLOW | Median | 0.2 | 0.2 | 0.5 | 0.1 |
| (ml/min) | Quartile Range | 0-1 | 0-1.1 | 0-1.5 | 0-1.8 |
|   | N | 318 | 149 | 76 | 53 |
| SCHIRMER | Median | 2.5 | 3 | 5 | 5.5 |
| (mm/5 min) | Quartile Range | 0.5-7.5 | 0.5-9 | 1.6-12.5 | 1.5-11 |
|   | N | 317 | 146 | 76 | 51 |
| ESR number | Median | 21 | 19 | 17 | 16 |
| (mm/h) | Quartile Range | 11-37 | 10-44 | 8-38 | 8-35.5 |
|   | N | 316 | 148 | 75 | 52 |
| CRP number | Median | 4 | 5 | 5 | 5 |
| (mg/l) | Quartile Range | 2-5 | 3-5 | 3-5 | 5-6 |
|   | N | 322 | 148 | 75 | 53 |
| ESDDAI | Median | 3 | 3 | 4 | 4 |
| (score) | Quartile Range | 1-7 | 2-7 | 2-8 | 0.5-8 |
|   | N | 322 | 152 | 77 | 53 |
| ESSPRI | Median | 5 | 5.6 | 6.6 | 6.3 |
| (score) | Quartile Range | 3-6.6 | 4.3-6.9 | 5-8 | 5.3-7.6 |
|   | N | 326 | 152 | 77 | 53 |
| EULAR Sicca Score | Median | 5.6 | 6.3 | 7 | 6.6 |
|  (score) | Quartile Range | 3.5-7.6 | 4.6-8 | 5.1-8.8 | 4.3-8 |
|   | N | 326 | 152 | 77 | 53 |
| Continued Continued Part 1/2  |  |  |  |  |  |

|  |  |  |
| --- | --- | --- |
|  |  | Subsets |
|  Variable |   | Neither | Comorbidities | Drowsy Meds | Both |
| PAIN | Median | 3 | 5 | 6 | 7 |
| (score) | Quartile Range | 1-6 | 2.2-7 | 3.5-8 | 4.5-8 |
|   | N | 326 | 152 | 77 | 53 |
| FATIGUE | Median | 5 | 6 | 7 | 7 |
| (score) | Quartile Range | 3-7 | 4-7 | 5-9 | 5-8 |
|   | N | 326 | 152 | 77 | 53 |
| DRYNESS | Median | 6 | 7 | 7 | 6 |
| (score) | Quartile Range | 4-8 | 5-8 | 5-8.5 | 4-8 |
|   | N | 326 | 152 | 77 | 53 |
| ANXIETY | Median | 7 | 8 | 9 | 10 |
| (HADS-A score) | Quartile Range | 4-10 | 5-10 | 6-12.5 | 7-14 |
|   | N | 326 | 152 | 77 | 53 |
| DEPRESSION | Median | 5 | 5 | 8 | 9 |
| (HADS-D score) | Quartile Range | 2-7 | 2-8.7 | 5-12 | 4.5-11 |
|   | N | 326 | 152 | 77 | 53 |
| EPWORTH | Median | 8 | 8 | 9 | 10 |
| (score) | Quartile Range | 4-11 | 4-11.7 | 6-15 | 4-15 |
|   | N | 312 | 148 | 75 | 50 |
| CPS | Median | 4 | 7 | 9 | 12 |
| (score) | Quartile Range | 2-7 | 5-9 | 5-11 | 8.5-15 |
|   | N | 326 | 152 | 77 | 53 |
| PROFAD-Physical | Median | 3.5 | 4 | 5.25 | 5 |
| (score) | Quartile Range | 2-4.75 | 2.75-4.75 | 4-6 | 4-6 |
|   | N | 322 | 151 | 75 | 51 |
| PROFAD-Mental | Median | 2.5 | 3 | 4 | 4 |
| (score) | Quartile Range | 1-4 | 1.5-4.375 | 2-5 | 2.5-5.25 |
|   | N | 325 | 152 | 76 | 53 |
| PROFAD-VAS | Median | 51.5 | 60 | 69 | 72.5 |
| (mm) | Quartile Range | 26.75-71.25 | 41-76 | 58-86.75 | 59.25-82 |
|   | N | 318 | 147 | 76 | 52 |
| Continued Continued Part 2/2  |  |  |  |  |  |
|  |  |  |  |  |  |

*Key: BMI – Body Mass Index, ESSDAI – EULAR Sjögren's Syndrome Disease Activity Index, ESSPRI - EULAR Sjögren’s Syndrome Patient Reported Index, CPS – Comorbidity and Polypharmacy Score , EPWORTH – Epworth Sleepiness Scale, N – Sample Size.*

***Supplementary Table S3:*** *Multiple Regression Prediction Equations for Physical and Mental Fatigue. The P-Values are the ‘raw’ probabilities before adjustment for multiplicity.*

**PROFAD-Physical:**

| **Term** | **Estimate** | **Std Error** | **t Ratio** | **Prob>|t|** |
| --- | --- | --- | --- | --- |
| Intercept | 1.218887 | 0.630978 | 1.93 | 0.0539 |
| DRYNESS | 0.1389932 | 0.019551 | 7.11 | <.0001\* |
| PAIN | 0.2321898 | 0.018639 | 12.46 | <.0001\* |
| ANXIETY | 0.0016852 | 0.013419 | 0.13 | 0.9001 |
| DEPRESSION | 0.134022 | 0.016055 | 8.35 | <.0001\* |
| EPWORTH Daytime Sleepiness | 0.0532503 | 0.010277 | 5.18 | <.0001\* |
| Coeliac COMORBID[NO] | -0.007923 | 0.140203 | -0.06 | 0.9550 |
| IDDM COMORBID[NO] | -0.387187 | 0.271659 | -1.43 | 0.1547 |
| NIDDM COMORBID[NO] | 0.1232045 | 0.174408 | 0.71 | 0.4802 |
| Depression COMORBID[NO] | 0.0482652 | 0.127363 | 0.38 | 0.7049 |
| Obesity COMORBID[NO] | -0.158313 | 0.155112 | -1.02 | 0.3079 |
| DROWSY[NO] | -0.249082 | 0.059569 | -4.18 | <.0001\* |
| SEROPOSITIVE[Negative] | 0.0561825 | 0.072699 | 0.77 | 0.4400 |
| SEX[Female] | 0.1100897 | 0.095309 | 1.16 | 0.2486 |
| SYMPTOMYRS | 0.003011 | 0.004774 | 0.63 | 0.5285 |
| Anaemia COMORBID[NO] | 0.3844507 | 0.23895 | 1.61 | 0.1082 |
| Hypothyroidism COMORBID[NO] | -0.115473 | 0.061334 | -1.88 | 0.0603 |
| AGE | -0.0006 | 0.003788 | -0.16 | 0.8742 |
| BMI | -0.017076 | 0.010048 | -1.70 | 0.0898 |

**PROFAD-Mental:**

| **Term** | **Estimate** | **Std Error** | **t Ratio** | **Prob>|t|** |
| --- | --- | --- | --- | --- |
| Intercept | 1.7257553 | 0.844528 | 2.04 | 0.0415\* |
| DRYNESS | 0.0555285 | 0.026105 | 2.13 | 0.0339\* |
| PAIN | 0.1268643 | 0.024723 | 5.13 | <.0001\* |
| ANXIETY | 0.0453448 | 0.017849 | 2.54 | 0.0114\* |
| DEPRESSION | 0.1482141 | 0.021374 | 6.93 | <.0001\* |
| EPWORTH Daytime Sleepiness | 0.0854361 | 0.013625 | 6.27 | <.0001\* |
| Coeliac COMORBID[NO] |  -0.099033 | 0.188111 |  -0.53 | 0.5988 |
| IDDM COMORBID[NO] |  -0.109989 | 0.364098 |  -0.30 | 0.7627 |
| NIDDM COMORBID[NO] |  -0.184016 | 0.223063 |  -0.82 | 0.4098 |
| Depression COMORBID[NO] | 0.0777249 | 0.170647 | 0.46 | 0.6490 |
| Obesity COMORBID[NO] | 0.0266188 | 0.210453 | 0.13 | 0.8994 |
| DROWSY[NO] |  -0.033636 | 0.079043 |  -0.43 | 0.6706 |
| SEROPOSITIVE[Negative] | 0.116616 | 0.094631 | 1.23 | 0.2184 |
| SEX[Female] | 0.0245507 | 0.127787 | 0.19 | 0.8477 |
| SYMPTOMYRS | 0.0108779 | 0.006384 | 1.70 | 0.0890 |
| Anaemia COMORBID[NO] | 0.0619097 | 0.320677 | 0.19 | 0.8470 |
| Hypothyroidism COMORBID[NO] |  -0.006449 | 0.081581 |  -0.08 | 0.9370 |
| AGE |  -0.013186 | 0.005043 |  -2.61 | 0.0092\* |
| BMI |  -0.029451 | 0.01338 |  -2.20 | 0.0281\* |

***Supplementary Figure 1*:** *Medications Treemap capturing patients taking one or more medications associated with drowsiness. A minority of patients in the cohort, 21.4%, were taking medications associated with drowsiness - mostly Citalopram, Amitriptyline, Tramadol and Fluoxetine or combinations of two or more of these drugs – see Text.*

INSERT SUPPLEMENTARY FIGURE 1 HERE