



Towards a practical management of fatigue in systemic lupus erythematosus

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ABSTRACT

Significant fatigue is reported by two-thirds of patients with SLE and severe fatigue by one-third. The assessment and treatment of fatigue remains a major challenge in SLE, especially in patients with no disease activity. Here, we suggest a practical algorithm for the management of fatigue in SLE. First, common but non-SLE-related causes of fatigue should be ruled out based on medical history, clinical and laboratory examinations. Then, presence of SLE-related disease activity or organ damage should be assessed. In patients with active disease, remission is the most appropriate therapeutic target while symptomatic support is needed in case of damage. Both anxiety and depression are major independent predictors of fatigue in SLE and require dedicated assessment and care with psychological counselling and pharmacological intervention if needed. This practical algorithm will help in improving the management of one the most common and complex patient complaints in SLE.

SLE is a chronic autoimmune disease which may cause a broad spectrum of clinical manifestations as well as subjective symptoms^{1 2} such as fatigue. In SLE, fatigue is reported by 67% to 90% of patients^{1 3 4} and is rated as severe in up to one-third of patients using validated fatigue instruments, as shown in the recent multicentre FATILUP study.¹ Also, fatigue is often reported as the most debilitating symptom of the disease by patients^{5 6} and leads to both altered health-related quality of life^{4 7–9} and significant work disability with tremendous indirect costs.³ The rational assessment and treatment of fatigue remains a major challenge in SLE,⁵ especially in patients without active disease. Noteworthy, fatigue is a highly multifactorial concept¹⁰ which, in the context of SLE, may be due either to lupus-related or non-lupus-related general causes. Importantly, those causes can also be intricate with significant psychobehavioural determinants. Here, we suggest a practical step-by-step algorithm for the general assessment and management of fatigue in SLE (figure 1).

STEP 1: SEARCH FOR A GENERAL (NON-LUPUS-RELATED) CAUSE OF FATIGUE

In the primary care setting, a medical or psychiatric diagnosis can be found in at least two-thirds of patients presenting with acute fatigue. The most frequent causes of fatigue are summarised in table 1. It is crucial to understand the patient's perspective, the detailed history of fatigue and the impact on the patient's mood as well as on daily activities such as work, household chores, physical activity and leisure. Box 1 summarises the main questions to be asked when confronted with a patient with fatigue. A review of current medications is suggested, as some drugs may induce fatigue (eg, antihypertensive drugs such as beta blockers or sedatives). Lifestyle assessment is also essential: a significant association between smoking and fatigue has been reported in SLE.^{11–14} Also, obesity has been associated with increased fatigue both in the general population and SLE.¹⁵

A full clinical examination of the heart, lung, thyroid and nervous system¹⁶ is crucial. For women, a gynaecological examination is also recommended, especially in case of anaemia.^{17 18} Laboratory tests should rule out most common causes of fatigue (box 1) such as inflammation and infection, anaemia, renal or hepatic failure, viral hepatitis or HIV infection, and major endocrine or metabolic complications such as abnormal calcemia, hypothyroidism, diabetes or adrenal insufficiency (especially in patients who recently stopped glucocorticoids). Cancer screening should be updated, according to current guidelines, and indirect signs of malignancy (anorexia, weight loss and lymphadenopathy) should be carefully searched for. Although controversial,¹⁹ vitamin D deficiency has been associated with fatigue in SLE.²⁰ In an observational study of 80 patients with SLE, vitamin D supplementation improved fatigue in participants.²¹ Also, vitamin D supplementation was associated with a decrease



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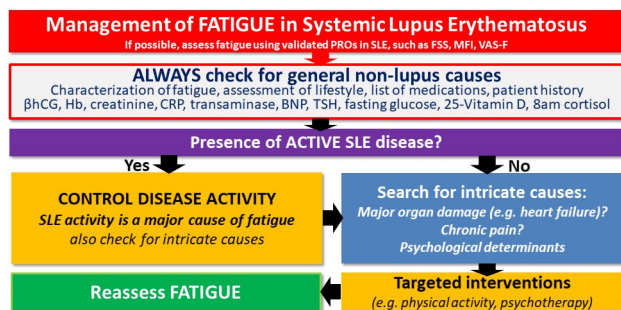


Figure 1 Practical algorithm for the management of fatigue in patients with SLE.

in fatigue scores in a randomised controlled trial in juvenile-onset SLE.²²

STEP 2: OBJECTIVE ASSESSMENT OF FATIGUE USING VALIDATED PROS

Because fatigue is a highly subjective symptom, the standardised assessment of fatigue using validated patient-reported outcomes (PROs) is an important step. The use of validated PROs also allows for an individual follow-up of fatigue intensity and symptoms over time, and may help in underlining the benefit of a therapeutic intervention at the patient level. It is also a way to show that the physician is genuinely interested in understanding and treating the cause of fatigue, which is important from the patient’s perspective, and helps in establishing a trusting physician–patient relationship. Among a total of 16 different fatigue PROs which have been used in SLE, the FSS (Fatigue Severity Scale) and the short-FSS are the most used ones, but the MFI (Multi-dimensional Fatigue Inventory) and the Fatigue-VAS have also been used, although less commonly¹⁶ (see table 2). The FACIT-Fatigue score is

Box 1 Checklist for the initial assessment of fatigue in SLE

1. **Characterisation of fatigue:**
 - Onset: acute or insidious
 - Evolution: recent (<1 month), persistent (<6 months) or chronic (>6 months)
 - Presence of fatigue-free periods
 - Is fatigue ameliorated by rest?
 - Physical and mental impact of fatigue
2. Assessment of **lifestyle** (work, restrictive diet or obesity, physical activity), **habitus** (smoking, drinking) and **sleep quality**
3. Presence of **concurrent manifestations**
 - Lupus flare?
 - Any other (non–SLE-related) disorder?
4. List of **medications**
5. List of **previous or current associated medical conditions**

commonly used in clinical trials but has been infrequently used in routine clinical practice.¹

STEP 3: IDENTIFYING A LUPUS-RELATED CAUSE OF FATIGUE

Fatigue can be a manifestation of active SLE but can also be related to organ damage (figure 2). The relationship between disease activity and fatigue remains controversial in SLE and has been shown to be less strong than with other factors such as anxiety or depression.^{1 23 24} Its association with serological markers (C3, anti-dsDNA antibodies) is also controversial.¹¹

Fatigue has been associated with several SLE-specific organ manifestations:

- ▶ Several studies found an association between neurological involvement,^{11 25} including white matter hyperintensities,²⁶ and fatigue.

Table 1 Frequent causes of fatigue and suggested first-line assessment

Common causes of fatigue		First-line assessment
Drug-induced fatigue	Steroids, anti-arrhythmic, anti-hypertensive, benzodiazepines or other antidepressant and sedative agents, anti-histaminic, diuretics	Medication review
Pregnancy		β-HCG
Anaemia	Iron or vitamin deficiencies	C-reactive protein, haemoglobin, Coombs test, ferritin, B ₉ and B ₁₂ vitamins
Metabolic disorders	Hypothyroidism, adrenal insufficiency, panhypopituitarism	TSH, fasting glucose...
Vitamin D insufficiency		Vitamin D levels
Infection	Chronic bacterial (mycobacterial) or viral (HIV, hepatitis B and C, EBV) infections	C reactive protein Hepatitis B/C, EBV and HIV serology Quantiferon
Organ failure	Cardiac insufficiency Respiratory insufficiency Liver insufficiency Kidney insufficiency	BNP, chest X-ray, echocardiography creatinine, full hepatic tests
Sleep disorders	Obstructive sleep apnoea syndrome Jet lag syndrome in frequent travellers	Polysomnography

b-HCG, b-human chorionic gonadotropin hormone; BNP, brain natriuretic peptide; EBV, Epstein-Barr virus; TSH, thyroid-stimulating hormone.

Table 2 Most frequently used fatigue patient-reported outcomes (PROs) in SLE

Fatigue PROs	Description
Fatigue Severity Scale (FSS)	9-item scale covering the general aspects of fatigue Originally derived for people with multiple sclerosis and SLE
Multi-dimensional Fatigue Inventory (MFI)	20-item scale divided into five domains: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity The threshold for significant fatigue depends on age and gender
Visual analogue scale to evaluate fatigue severity (VAS-F)	The scale consists of 18 items related to the subjective experience of fatigue, using fatigue and energy subscales
Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue)	13-item self-reported questionnaire assessing aspects of physical and mental fatigue, and their effects on function and daily living

- ▶ Renal failure can be an important cause of fatigue. It is crucial to assess whether it is related to active kidney disease or to chronic lesions (damage).^{27 28}
- ▶ Cardiac failure is an obvious cause of fatigue.
- ▶ Hepatic failure and cirrhosis can (rarely) be due to lupus hepatitis, and overlap with autoimmune hepatitis or less frequently sclerosing cholangitis.^{29 30}

Other clinical manifestations of SLE have been associated with fatigue: in the FATILUP study,¹ we found arthritis and oral ulcers to be individual SLE Disease Activity Index score components associated with severe fatigue. This may underline a more specific role for painful disease manifestations in SLE.^{11 23}

Finally, the prevalence of fibromyalgia is estimated to range between 6.2% and 22% of patients with SLE^{31 32} and has been strongly associated with fatigue.³³ Sjögren's syndrome should also be thought of in patients with sicca syndrome and has been associated with significant fatigue across several studies.^{34 35}

STEP 4: LOOKING FOR INTRICATE PSYCHOLOGICAL DETERMINANTS

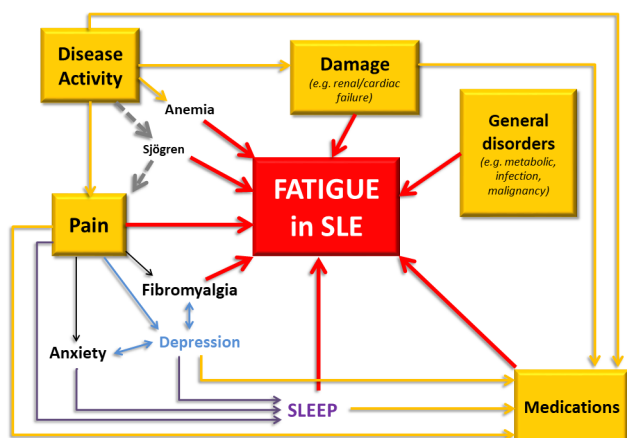
Emotional and functional well-beings as well as abnormal illness-related behaviours strongly correlate with depression and fatigue in SLE.^{1 36 37} Pain, stress and depression have been shown to be the most important predictors of fatigue in patients with SLE³⁸ and their intensity and

consequences should be assessed, with the help of a psychologist or psychiatrist if needed. Mood disorders are reported in up to 13% of patients with SLE and attributed to SLE in about 40% of cases.³⁹ Sleep disorders are also common in the general population as well as in SLE, and have been associated with fatigue^{40–42} and depression.⁴¹

TOWARDS A PRACTICAL MANAGEMENT OF FATIGUE IN PATIENTS WITH SLE

In patients with significant disease activity, the main therapeutic target is remission (or alternatively low-disease activity) and reaching these goals can be sufficient to improve fatigue.^{43 44} However, a common situation is the presence of significant fatigue contrasting with the absence of disease activity or any underlying organic cause. In these patients, immunosuppressive treatment escalation is not indicated and other non-pharmacological interventions such as psychological and behavioural assessment or physical activity workshops should be favoured.⁴⁵ Importantly, lack of optimal physical activity as well as sedentary behaviour have been associated with fatigue in SLE.^{44 46 47}

Physical exercise is recommended for the management of pain and fatigue in patients with inflammatory arthritis in the last European League Against Rheumatism recommendations.⁴⁸ Physical activity has been shown to improve fatigue in patients with SLE,^{44 49} with more time spent in moderate or high physical activity associated with less fatigue.⁵⁰ Patients with SLE with otherwise unexplained fatigue should undergo dedicated psychological assessment, and behavioural issues should be specifically taken care of using appropriate psychological counselling^{51–55} and pharmacological intervention, when needed. The exact benefit of antidepressants on fatigue is difficult to assess in SLE because there is no specific trial, but there is no reason to believe that those treatments would not be appropriate, keeping in mind the potential interaction with hydroxychloroquine, which may lead to QT prolongation. Tobacco smoking cessation should be encouraged as it significantly reduces therapeutic efficacy of many drugs and could promote flares.¹⁴ Last but not least, hydroxychloroquine observance should be evaluated and if needed, non-scheduled hydroxychloroquine serum

**Figure 2** Main determinants of fatigue in patients with SLE.

concentrations should be measured to verify therapeutic adherence and adjust daily posology.^{56 57}

CONCLUSION

Significant fatigue is reported by two-thirds of patients with SLE and severe fatigue by one-third.¹ As in the general population, general non-SLE-related causes of fatigue should be ruled out. Then, it is important to assess whether fatigue may be related to disease activity or damage. In the former situation, disease remission is the most appropriate therapeutic target, with an emphasis on painful manifestations. Importantly, both anxiety and depression are major independent predictors of fatigue in several studies. These manifestations should be thoroughly assessed and taken care of using appropriate psychological counselling and pharmacological intervention, when needed. We believe this practical algorithm will help in improving the management of one of the most common and complex patient complaints in SLE.

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