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ORIGINAL RESEARCH

Assessment and personalised advice for fatigue in systemic lupus erythematosus using an innovative digital tool: the Lupus Expert system for the Assessment of Fatigue (LEAF) study

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ABSTRACT

Background Fatigue is reported as the most prevalent symptom by patients with systemic lupus erythematosus (SLE). Fatigue management is complex due to its multifactorial nature. The aim of the study was to assess the usefulness of an innovative digital tool to manage fatigue in SLE, in a completely automated manner.

Methods The «Lupus Expert System for Assessment of Fatigue» (LEAF) is free digital tool which measures the intensity and characteristics of fatigue and assesses disease activity, pain, insomnia, anxiety, depression, stress, fibromyalgia and physical activity using validated patient-reported instruments. Then, LEAF automatically provides personalised feedback and recommendations to cope with fatigue.

Results Between May and November 2022, 1250 participants with SLE were included (95.2% women, median age 43yo (IQR: 34–51)). Significant fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue <34) was reported by 78.9% of patients. In univariate analysis, SLE participants with fatigue were more likely to be women (p=0.01), perceived their disease as more active (p<0.0001), had higher levels of pain (p<0.0001), anxiety (p<0.0001), depression (p<0.0001), insomnia (p<0.0001), stress (p<0.0001) and were more likely to screen for fibromyalgia (p<0.0001), compared with patients without significant fatigue. In multivariable analysis, parameters independently associated with fatigue were insomnia (p=0.0003), pain (p=0.002), fibromyalgia (p=0.008), self-reported active SLE (p=0.02) and stress (p=0.045). 93.2% of the participants found LEAF helpful and 92.3% would recommend it to another patient with SLE.

Conclusion Fatigue is commonly severe in SLE, and associated with insomnia, pain, fibromyalgia and active disease according to patients' perspective. Our study shows the usefulness of an automated digital tool to manage fatigue in SLE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fatigue is the most prevalent and most bothersome symptom in systemic lupus erythematosus (SLE).
⇒ The management of fatigue is complex, due to its multifactorial and multidimensional nature.

WHAT THIS STUDY ADDS

⇒ The Lupus Expert System for Assessment of Fatigue study shows the relevance of using digital tools to assess and manage fatigue in SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Personalised assessment and management of fatigue using digital tools can now be incorporated into the holistic management of SLE.

INTRODUCTION

Fatigue is a universal symptom that lacks a consensual definition. It is typically described as a subjective unpleasant sensation of exhaustion interfering with individuals' ability to function at their average capacity.[1] In chronic conditions, the experience of fatigue seems to differ from 'everyday tiredness', as being more frequent and unresolved by rest.[2 3]

In systemic lupus erythematosus (SLE), fatigue is the most prevalent manifestation, affecting 67%–90% of patients, and is reported as the most bothersome symptom.[4] Fatigue impairs the quality of life by impacting daily life activities, social interactions, work, cognition and emotions.[5–8] Therefore, assessing and treating fatigue is a key, but often neglected, aspect of SLE care.

However, managing fatigue is complex because of its multidimensional nature and

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many potential determinants. Psychobehavioural factors such as anxiety and depression, as well as pain, fibromyalgia and sleep disorders, have all been associated with fatigue in SLE. Conversely, the actual contribution of disease activity to SLE fatigue remains controversial.[2 9–15] Non-pharmacological management, including physical activity,[16 17] psychological interventions[18 19] and self-management[20] have all been associated with fatigue improvement in SLE. A better understanding of the individual characteristics and profiles of fatigued patient in SLE would help improve its management.

Consequently, optimising the management of fatigue in SLE would necessitate a person-centred approach, which requires time that clinicians might lack during routine consultations. Yet, patients with SLE have reported the importance of fatigue acknowledgement by physicians, as well as the need to be provided with information about fatigue coping strategies.[21]

Digital health tools are an area of growing interest and are increasingly used in clinical practice as well as for research purposes.[22] They offer promising opportunities to improve the care of chronic diseases, as these digital tools embody the concept of both distant and patient-centred approaches, to monitor health outcomes, implement personalised education and to support self-management.[22–24] Digital strategies enable patients to play an active role in managing their disease and could therefore increase therapeutic adherence and engagement in actively changing health behaviours.[25]

The aim of the Lupus Expert System for the Assessment of Fatigue (LEAF) study was to assess the feasibility, acceptance and usefulness of an innovative digital tool to manage fatigue in SLE. LEAF assesses fatigue intensity and its characteristics at the individual patient-level as well as the most common variables associated with fatigue, and provides personalised feedback with the aim of improving fatigue management, individually, remotely and in a completely automated manner.

PATIENTS AND METHODS

Development of the digital LEAF tool

LEAF was developed as an innovative online digital tool by the French National Centre for Autoimmune Diseases (RESO) of Strasbourg,

Within a LEAF session, participants self-assess the intensity and characteristics of fatigue through three different questionnaires (*cf. infra*). Subsequently, the tool captures in a systematic and sequential manner several variables associated with fatigue, including self-assessed disease activity, pain, insomnia, anxiety and depression, stress, physical activity and, optionally fibromyalgia, using validated patient-reported outcome instruments (PROs, *cf. infra*). At each stage, patients receive feedback regarding these PROs, such as the total score and whether this meets any of the reported thresholds from the literature. On completion of all PROs, LEAF provides automated and personalised feedback about the intensity and type of fatigue as well as regarding the presence of any clinically significant element captured through the PROs. Then, LEAF provides advice to cope with fatigue as well as with the other variables based on recent and validated data from the literature (see online supplemental documents 1 and 2 eg, of feedback).

LEAF was originally developed in French and translated in English and Spanish by native speakers, and validated by the patient association Lupus Europe.

Study design

The LEAF study was a cross-sectional survey analysing participants' responses to the LEAF tool. If a participant did not fully complete the questionnaire, only the collected responses were used for descriptive and univariate analyses. Multivariable studies were conducted using responses from participants who completed the entire questionnaire.

Study population

Participants were recruited by sharing the internet link to LEAF with patient associations as well as on social media such as Twitter or Facebook, or during the medical consultation. Inclusion criteria was a self-reported diagnosis of SLE that had been confirmed by a medical doctor. We excluded participants under the age of 18 years. Second usage of LEAF by the same patient was not analysed. All participants gave informed consent before inclusion.

Assessment of fatigue among LEAF participants

Fatigue was primarily assessed using the Functional Assessment of Chronic Illness Therapy - Fatigue Scale (FACIT-Fatigue), a 13-item self-reported instrument validated in SLE.[26] FACIT-Fatigue evaluates the degree of fatigue and its impact in patients affected by chronic diseases, using a continuous score ranging from 0 to 52, with higher scores indicating less severe fatigue. Based on the literature,[27–30] significant fatigue was defined as scores <34. The intensity of fatigue was also collected using a Numerical Rating Scale (NRS) ranging from 0 to 10 and the main dimensions of fatigue were evaluated using the Multidimensional Fatigue Inventory (MFI), a 20 questions self-administrated questionnaire designed to assess 5 dimensions of fatigue (general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation) on 4–20 scales.[31]

Assessment of potential predictors of fatigue

Self-reported disease activity and pain were measured using NRS ranging from 0 to 10, and were considered clinically significant when >3.[9]

Anxiety and depression were assessed according to the Hospital Anxiety and Depression Scale (HADS), a 14-item self-reported questionnaire consisting of two subscales (one for anxiety and the other for depression) ranging from 0 to 21, with scores ≥11 for significant clinical anxiety and depression.[32]

Insomnia was evaluated using the Insomnia Severity Index, a 7-question instrument assessing the severity of

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both night-time and daytime components of insomnia, on a 0–28 scale with a cut-off of 15 for significant clinical insomnia.[33]

The level of stress was measured by the Perceived Stress Scale 10 (PSS-10), a 10-items tool[34] with norms determined by age[35]: the level of stress was defined as high when the PSS-10 score was superior to 70% of the general population of the same age, very high when >95% of the general population of the same age and extremely high when >99.7% of the population of the same age.

Levels of physical activity were assessed by the International Physical Activity Questionnaire (IPAQ), which is a self-questionnaire measuring the intensity of physical activity in Metabolic Equivalent for Task-min/week. Cut-off levels were based on the IPAQ scoring protocol of the WHO.[36]

Option to fill-in the Fibromyalgia Rapid Screening Tool (FiRST), was suggested to patients who reported chronic and diffuse pain and was used to screen for fibromyalgia. A FiRST score >4/6 has a 90.5% sensibility and 85.7% specificity for fibromyalgia.[37]

Assessment of LEAF usefulness

Patients evaluated how helpful LEAF was and how much they would recommend it to other patients with SLE using NRS ranging from 0 to 5.

Statistical analysis

Quantitative variables were described in terms of median and 25th–75th percentile IQR, and qualitative variables were described using counts and percentages. Comparisons between groups were made using the Mann-Whitney test and χ^2 test, as appropriate. Variables associated with significant fatigue were studied using univariate and multivariable (using the enter method) logistic regression models. Correlations were analysed using Spearman's test. All tests were bilateral and statistical significance was established as a p value<0.05. Statistical analyses were performed using JMP V.17 software (SAS Institute, North Carolina, USA).

RESULTS

Between May and November 2022, 1647 participants used LEAF. Among them, 311 did not meet the inclusion criteria (figure 1), and 86 were further excluded because of an age <18 years. In total, 1250 participants were included in the study, and 688 completed entirely the series of questionnaires, including the screening for fibromyalgia, which was optional.

Characteristics of participants

As expected, most of the 1250 included participants were women (n=1190, 95.2%), with a median age of 43 years old (IQR: 34–51). Participants originated from 73 different countries, and a majority was European (n=820, 66.2%). SLE was reported as active by 66.9% (n=720/1077) of the patients, and clinically significant pain was reported by 69.1% (n=730/1057). A FiRST score >4, suggesting a possible diagnosis of fibromyalgia, was found in 57.6% of the patients reporting chronic diffuse pain (n=396/688). Clinically significant scores for anxiety, depression and insomnia were found in 42.3% (n=369/937), 25.4% (n=238/937) and 53.6% (n=559/1042) of participants, respectively. Stress level by PSS-10 was high in 66.2% (n=593/896) of participants. Low levels of physical activity according to IPAQ and WHO definitions were reported by 42.4% (n=400/944) of the patients (table 1).

Intensity and characteristics of fatigue

Significant fatigue (FACIT-Fatigue <34) was reported by 78.9% (n=987/1250) of patients. The median score for fatigue intensity was 7 (IQR: 6–8), on the 0–10 NRS. The median MFI scores were 15 (IQR: 12–17) for physical fatigue, 13 (IQR: 10–16) for mental fatigue, 14 (IQR: 11–16) for reduced activity and 14 (IQR: 11–17) for reduced motivation (table 2). Fatigue intensity on the 0–10 scale was strongly correlated with FACIT-Fatigue (r=−0.66, p<0.0001) and moderately correlated with the MFI for general fatigue (r=0.46, p<0.0001). The correlation between physical and mental fatigue was moderate (r=0.58, p<0.0001). Physical and mental fatigue were also

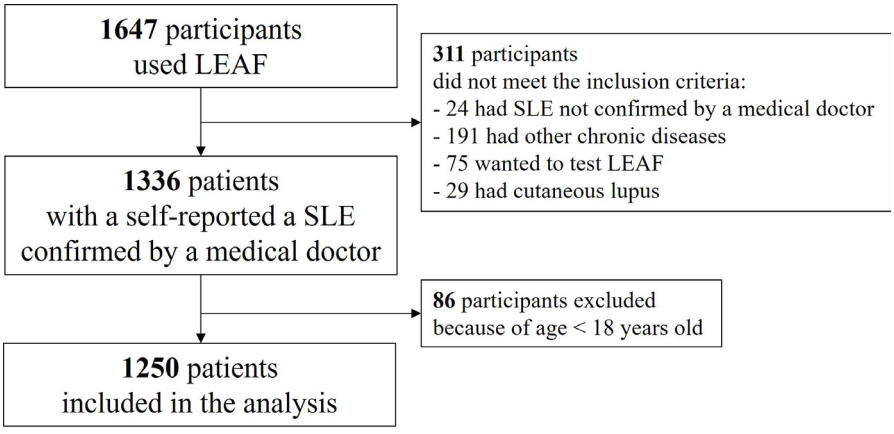


Figure 1 Flow chart of the LEAF study. LEAF, Lupus Expert System for the Assessment of Fatigue; SLE, systemic lupus erythematosus.

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Table 1 Characteristics of LEAF participants

Demographics, n=1250	
Female, n (%)	1190 (95.2)
Age, median (IQR)	43 (34-51)
Geographical origin, n=1238	
Europe, n (%)	820 (66.2)
South America, n (%)	178 (14.4)
North America, n (%)	151 (12.2)
Africa, n (%)	69 (5.6)
Asia, n (%)	16 (1.3)
Australia, n (%)	4 (0.3)
Disease activity, n=1077	
NRS disease activity, 0–10 scale, median (IQR)	5 (3-7)
Self-reported active SLE (NRS>3), n (%)	720 (66.9)
Pain, n=1057	
NRS pain, 0–10 scale, median (IQR)	5 (3-7)
Clinically significant pain (NRS>3), n (%)	730 (69.1)
Fibromyalgia, n=688	
FiRST score positive (>4), n (%)	396 (57.6)
Depression, n=937	
HADS depression, 0–21 scale, median (IQR)	8 (4-11)
No depression (HADS 0–7), n (%)	458 (48.9)
Subclinical depression (HADS 8–10), n (%)	241 (25.7)
Clinical depression (HADS 11–21), n (%)	238 (25.4)
Anxiety, n=937	
HADS anxiety, 0–21 scale, median (IQR)	9 (6-13)
No anxiety (HADS 0–7), n (%)	325 (34.7)
Subclinical anxiety (HADS 8–10), n (%)	216 (23.1)
Clinical anxiety (HADS 11–21), n (%)	396 (42.3)
Insomnia, n=1042	
ISI, 0–28 scale, median (IQR)	15 (10-19)
No insomnia (ISI 0–7), n (%)	176 (16.9)
Subclinical insomnia (ISI 8–14), n (%)	307 (29.5)
Moderate insomnia (ISI 15–21), n (%)	445 (42.7)
Severe insomnia (ISI 22–28), n (%)	114 (10.9)
Stress, n=896	
PSS-10, 0–40 scale, median (IQR)	22 (17-28)
Low level of stress, n (%)	36 (4.0)
Level of stress similar to general population of the same age, n (%)	267 (29.8)
High level of stress (>70% of general population of same age), n (%)	593 (66.2)
Very high level of stress (>95% of general population of same age), n (%)	320 (35.7)
Extremely high level of stress (>99.7% of general population of same age), n (%)	93 (10.4)
Physical activity (WHO), n=944	
Low level of physical activity, n (%)	400 (42.4)
Moderate level of physical activity, n (%)	258 (27.3)
High level of physical activity, n (%)	286 (30.3)

FiRST, Fibromyalgia Rapid Screening Tool; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; NRS, Numerical Rating Scale; PSS-10, Perceived Stress Scale 10.;

correlated with reduced activity and motivation (data not shown).

Parameters associated with significant fatigue

In univariate analysis, SLE participants with significant fatigue (FACIT-Fatigue <34) were more likely to be women (p=0.01), to perceive their disease as more active (p<0.0001), to have higher levels of pain (p<0.0001), anxiety (p<0.0001), depression (p<0.0001), insomnia (p<0.0001), stress (p<0.0001) and were more likely to have a positive FiRST score (p<0.0001), compared with patients without significant fatigue (table 3).

In multivariable analysis, the parameters independently associated with significant fatigue were clinical insomnia (OR 3.31 (95% CI: 1.73 to 4.34), p=0.0003), pain (OR 2.83 (95% CI: 1.44 to 5.54), p=0.002), FiRST score >4 (OR 2.50 (95% CI: 1.26 to 4.96), p=0.008), self-reported active SLE (OR 2.26 (95% CI: 1.17 to 4.40), p=0.02) and a high level of stress (OR 1.97 (95% CI: 1.01 to 3.83), p=0.04) (table 4).

Usefulness and acceptability of the digital tool LEAF

Of participants, 93.2% found LEAF helpful (NRS≥3/5) and 92.3% would recommend it to another patient with SLE (NRS≥3/5) (figure 2).

Table 2 Fatigue scores in LEAF participants

Fatigue prevalence, n=1250	
FACIT-Fatigue, 0–52 scale, median (IQR)	21 (15-29)
Significant fatigue (FACIT-Fatigue <34), n (%)	987 (78.9)
Fatigue intensity, n=1250	
NRS fatigue, 0–10 scale, median (IQR)	7 (6–8)
Fatigue characteristics, n=1100	
MFI general fatigue, 4–20 scale, median (IQR)	17 (14-19)
MFI physical fatigue, 4–20 scale, median (IQR)	15 (12-17)
MFI mental fatigue, 4–20 scale, median (IQR)	13 (10-16)
MFI reduced activity, 4–20 scale, median (IQR)	14 (11-16)
MFI reduced motivation, 4–20 scale, median (IQR)	14 (11-17)

FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy - Fatigue Scale; MFI, Multidimensional Fatigue Inventory; NRS, Numerical Rating Scale.

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Table 3 Comparison of LEAF patients with or without significant fatigue

Parameters	Patients with significant fatigue (n=987)	Patients without significant fatigue (n=263)	P value
Age, median (IQR)	43 (34-52)	41 (33-49.5)	0.19
Female, n (%)	954/992 (96.2)	162/177 (91.5)	0.01*
NRS disease activity, median (IQR)	6 (3-7)	3 (1-5)	<0.0001*
NRS pain, median (IQR)	6 (3.25-7)	2 (1-4.5)	<0.0001*
Score FiRST positive, n (%)	379/611 (62.0)	17/77 (22.1)	<0.0001*
HADS anxiety, median (IQR)	10 (7-14)	7 (4-10)	<0.0001*
HADS depression, median (IQR)	8 (5-11)	4 (2-7)	<0.0001*
ISI, median (IQR)	16 (11-19)	10 (5-15)	<0.0001*
High level of stress, n (%)	540/878 (69.4)	53/118 (44.9)	<0.0001*
Low level of physical activity, n (%)	354/816 (43.4)	46/128 (35.9)	0.12

*P value<0.05.
FiRST, Fibromyalgia Rapid Screening Tool; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; NRS, Numerical Rating Scale.

DISCUSSION

In the LEAF study, we developed an online digital tool to assess fatigue intensity and characteristics, and its potential predictors at the individual patient level and provide automated personalised advice to cope with fatigue in SLE. LEAF provides patients with the possibility to be actively involved in their own care by allowing them to assess their fatigue level at any time, to understand the main-related factors, and to impulse lifestyle changes based on tailored advice. This innovative digital tool is the first automated tool to offer personalised fatigue management in SLE and has been successfully used by a large international cohort of 1250 patients with SLE with a very high satisfaction rate.

Fatigue was frequent in the LEAF study (reported by 78.9% of participants), which is consistent with previous studies from our group.[4 9] One of the limitations of this study was the possible selection bias, as patients feeling fatigued may have been more interested in using LEAF than patients not feeling fatigued, which could have influenced the result for the prevalence of fatigue. As expected, fatigue had a negative impact on daily activities and motivation to accomplish tasks, as shown by the MFI scores. Altogether, these results confirmed the urgent need to develop new tools to assess and improve fatigue specific management in SLE.

Importantly, the FACIT-Fatigue scores, the MFI and the NRS for fatigue intensity were well-correlated, which reinforces the internal validity of our study. Although not as detailed as the other two fatigue scores, a 0–10 NRS, therefore, appears as a quick and valid alternative to assess fatigue globally in SLE.

Among all potential predictors of fatigue tested, the multivariable analysis revealed a significant association with clinical insomnia, pain, fibromyalgia, stress and self-perceived disease activity.

The prevalence of clinical insomnia was high in the LEAF study since it affected 53.6% of the participants

Table 4 Multivariable analysis of associations with significant fatigue

	Univariate analysis		Multivariate analysis	
Parameters	OR (95% CI)	P value	OR (95% CI)	P value
Female	2.10 (0.69 to 6.43)	0.26	–	–
Self-reported active SLE	4.55 (2.63 to 7.89)	<0.0001*	2.26 (1.17 to 4.40)	0.02*
Clinically significant pain	5.68 (3.26 to 9.90)	<0.0001*	2.83 (1.44 to 5.54)	0.002*
Positive score FiRST	4.87 (2.67 to 8.85)	<0.0001*	2.50 (1.26 to 4.96)	0.008*
Clinical anxiety	2.24 (1.27 to 3.96)	0.006*	0.94 (0.46 to 1.93)	0.88
Clinical depression	4.14 (1.75 to 9.80)	0.0003*	1.92 (0.74 to 4.99)	0.18
Clinical insomnia	4.46 (2.45 to 8.11)	<0.0001*	3.31 (1.73 to 4.34)	0.0003*
High level of stress	3.71 (2.15 to 6.41)	<0.0001*	1.97 (1.01 to 3.83)	0.045*
Low level of physical activity	1.42 (0.81 to 2.48)	0.27	–	–

*P value<0.05; R^2 for multivariable model: 0.23.
FiRST, Fibromyalgia Rapid Screening Tool; SLE, systemic lupus erythematosus.

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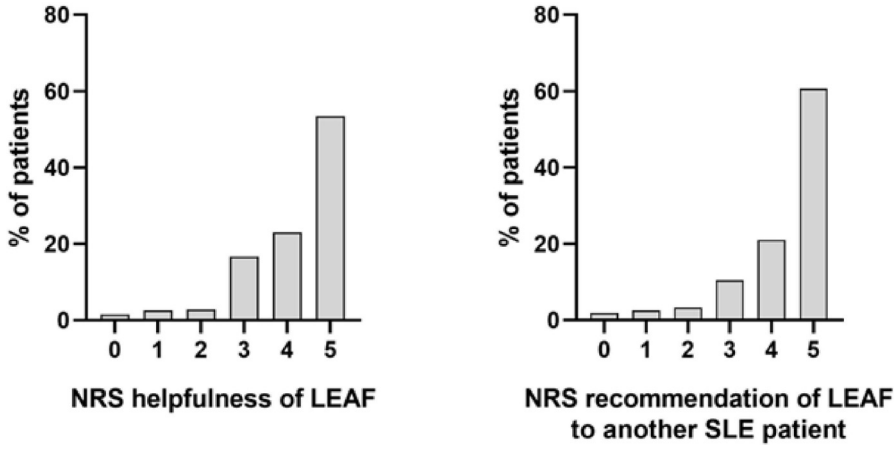


Figure 2 Usefulness of the digital tool LEAF. LEAF, Lupus Expert System for the Assessment of Fatigue; NRS, Numerical Rating Scale; SLE, systemic lupus erythematosus.

and 60.0% of those with significant fatigue. More importantly, insomnia was the determinant that had the strongest association with fatigue (OR 3.31, 95% CI: 1.73 to 4.34). Our results further strengthen the importance of assessing sleep quality in fatigued patients with SLE.[38 39]

Pain and fibromyalgia are already well-described major contributors of fatigue in SLE,[9 13 40] whereas only a few studies have analysed the association between stress and fatigue in patients with SLE.[41 42] Here, we showed that stress is more frequent in patients with SLE than in the general population, since two-thirds of participants had levels of stress higher than 70% of the general population and that stress was a significant contributor to fatigue in SLE. Hence, promoting stress-relieving strategies, including mindfulness, shall be considered in patients with SLE with high-stress levels.[43 44]

The role of disease activity in the occurrence of fatigue in SLE remains controversial.[9 12] In LEAF, we found a significant association between fatigue and self-reported active disease, but the interpretation of this result has to be cautious since patients' and physician global assessments of disease activity are commonly discrepant.[45 46] Moreover, self-perceived disease activity can be influenced by fatigue itself.[47 48]

In the LEAF study, patients with significant fatigue had higher HADS depression and anxiety scores than patients without fatigue. However, we did not find an independent association between these variables and fatigue in multivariable analysis.[9] This is likely explained by the fact that anxiety and depression might be potential cofounders influencing other predictors that had stronger associations with fatigue, such as stress, fibromyalgia or insomnia.

With the LEAF study,[49] we showed that a digital tool to assess fatigue in SLE and provide personalised advice is feasible, well-accepted and considered helpful by patients. The satisfaction rate was very high and most participants found LEAF extremely helpful. One of the main strengths of LEAF is the use of PROs, which enables a valid and patient-centred approach to monitor fatigue and measure health outcomes. Moreover, a digital tool has the advantage of being accessible anytime between medical consultations and to provide a large amount of information to which patients can go back to if needed. Among the limitations of the LEAF tools are its cross-sectional design, the fact that disease activity was self-assessed, and the lack of formal demonstration that the tool actually improves fatigue in SLE. Assessing the impact of lifestyle adjustments suggested by LEAF will prove useful. Yet, the feedback provided by the participants was very encouraging, many of which were for the first time able to understand the contribution of insomnia, anxiety, depression, stress, fibromyalgia and physical activity to their fatigue status.

CONCLUSION

Fatigue is frequent in patients with SLE and has a significant impact on daily activities. Insomnia, pain, fibromyalgia, stress and self-reported disease activity are independent predictors of fatigue and should routinely be assessed in fatigued patients with SLE. A digital tool such as LEAF, which evaluates fatigue and provides automated and personalised advice to cope with fatigue, is well-accepted and considered helpful by patients with SLE and may therefore be incorporated into the holistic care of SLE.

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Patient and public involvement statement Patients were actively involved during the study.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by COMITE D'ETHIQUE des Facultés de Médecine, d'Odontologie,de Pharmacie, des Ecoles d'Infirmières, de Kinésithérapie, de Maïeutique et des Hôpitaux, reference: CE-2021-23. Participants gave informed consent to participate in the study before taking part.

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