Fatigue Measurements in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Fatigue is a frequent, disabling issue in systemic lupus erythematosus (SLE). It is, however, difficult to quantify. The Ad Hoc Committee on SLE Response Criteria for Fatigue in 2007 recommended using the Krupp Fatigue Severity Scale (FSS). Since then, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale has also been validated in SLE. We performed a review of instruments used to measure fatigue in adult SLE patients from 2007 onward.

Methods. We searched PubMed, Medline, and Embase (January 2008–October 2017), identifying clinical trials and observational studies in adult SLE, where fatigue was a specifically measured outcome. All English and French studies were reviewed to determine fatigue measures and results.

Results. Thirty-seven studies met inclusion criteria. Eight scales were used. The visual analog scale (VAS), FSS, and FACIT-Fatigue Scale were most frequent. FSS was the most often used instrument in both clinical trials and observational studies. Twenty-five of the 37 studies demonstrated a difference in fatigue that was statistically significant and clinically meaningful. Of the 12 studies that did not, 6 used FSS, 3 used VAS, 2 used the Multidimensional Assessment of Fatigue, and 1 used the Brief Fatigue Index. All 6 studies using the FACIT-Fatigue Scale detected clinically meaningful and statistically significant differences.

Conclusion. VAS, FSS, and FACIT-Fatigue Scale were the most frequently used instruments in adult SLE studies from 2008 to 2017. Many studies detected clinically important changes in fatigue. Fatigue remains a key measure in both clinical trials and observational SLE studies. (First Release June 15 2019; J Rheumatol 2019;46:1470–7; doi:10.3899/jrheum.180831)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS FATIGUE MEASUREMENT

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder with significant morbidity and mortality[1]. Fatigue in SLE is frequent and often debilitating[2,3]; however, it is a challenging concept to define and measure[4,5,6]. Numerous instruments have been used in past SLE studies, creating difficulties in interpreting and comparing studies. Because it is a subjective symptom that is difficult to define, fatigue is challenging to measure, which may be why so many instruments exist (a 2007 systematic review identified 71 fatigue-specific instruments available for use in research across all patient populations)[7].

In 2007, the Ad Hoc Committee on SLE Response Criteria for Fatigue conducted a systematic review of fatigue instruments used in SLE studies[8]. They performed a search of articles from 1970 to 2006 and identified 15 instruments. Among these, they recommended the future use of the Krupp Fatigue Severity Scale (FSS) for evaluating fatigue in these patients. It was selected because it was the most frequently used fatigue scale in SLE, had good psychometric properties in patients with SLE, and was validated in multiple languages. In 2011, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, was also validated in SLE[9,10].

The aim of our current study was to perform a review of the instruments used to measure fatigue in adult patients with SLE since the 2007 Ad Hoc Committee recommendations

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and to summarize fatigue research in patients with SLE over the past 10 years.

MATERIALS AND METHODS

With the assistance of a librarian, we performed a systematic search of PubMed, Medline, and Embase for all English language publications containing MESH terms "systemic lupus erythematosus/SLE" and "fatigue, asthenia, lassitude" (Supplementary material, available with the online version of this article). Our search was further limited to adults. Both clinical trials and observational studies were included. Case reports, reviews, and animal studies were excluded. Given the previous Ad Hoc Committee review article in 2007[8], we limited our search to articles published between 2008 and October 2017 inclusively. Duplicates were subsequently removed.

Abstracts of the articles obtained with the preliminary search were screened by a single reviewer (AB). After initial screening, full texts were reviewed for inclusion. Publications with a clearly defined adult SLE population, and studying fatigue as a primary or secondary endpoint, were included in our study. Only publications using validated fatigue instruments were retained; studies were excluded if they measured fatigue only through measures of disease activity or quality of life scores (e.g., Medical Outcomes Study Short Form-36). We extracted information from the included studies regarding their design, objectives, and results. In positive studies, we determined whether the results were clinically significant using the minimal clinically important difference (MCID) specific to the instrument used if one was available in the literature.

RESULTS

Our search protocol yielded 340 articles after duplicates were removed. Of these, 37 articles met our criteria and were included (Figure 1). Among the 37 studies, 8 fatigue instruments were used (Table 1). The visual analog scale (VAS), Krupp Fatigue Severity Scale (FSS), and FACIT-Fatigue scale were the most frequently used measurements (Table 2, Table 3, and Table 4). The FSS was the most frequently used instrument in both randomized controlled trials (RCT) and observational studies. Twelve of the 37 studies failed to demonstrate a statistically significant difference in fatigue levels related to the exposure of interest. Of these, 6 used the FSS, 3 used the VAS, 2 used the Multidimensional Assessment of Fatigue, and 1 used the Brief Fatigue Inventory (BFI). All 6 studies using the FACIT-Fatigue scale detected clinically meaningful and statistically significant differences. Time until end of followup did not appear to influence study results.

RCT. Among the articles analyzed, 12 consisted of RCT; 5 of these studied the effect of biologic drug therapies on fatigue in patients with SLE. Abatacept was associated with a clinically significant reduction in fatigue compared to placebo at a 12-month followup, using a VAS[11]. A small RCT of infliximab suggested improvement in fatigue scores but this failed to reach statistical significance in terms of MCID[12]. Finally, there have been 3 studies each assessing

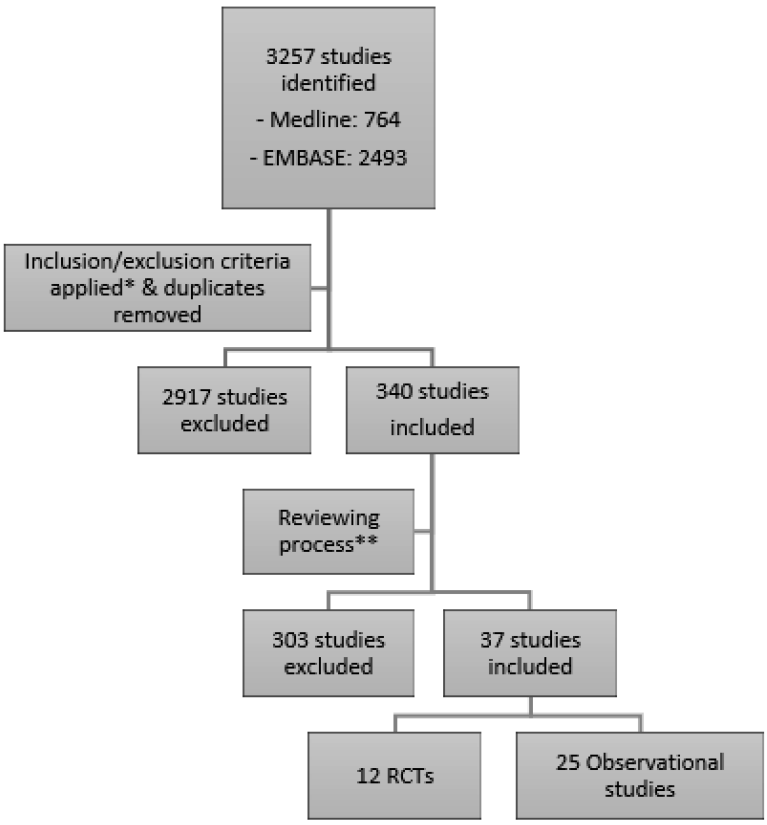

Figure 1. Flowchart of search strategy for selection of included articles. * Case reports, reviews, conference abstracts, and animal studies excluded; search limited to adults and studies in the English language. ** Studies with a clearly defined SLE population, studying fatigue as a primary or secondary endpoint, and using fatigue-specific instruments were included. RCT: randomized controlled trials; SLE: systemic lupus erythematosus.

Table 1. Fatigue scales used in studies of adults with SLE.

Measure	Description	Construct Validity Studied[53]	MCID in SLE[51], %
Visual analog scale[53]	Single 100-mm line to measure fatigue	No*	Δ 10
Krupp Fatigue Severity Scale[48]	9-item questionnaire on effect of fatigue on specific types of functioning	Yes	Δ 9.7
Functional Assessment of Chronic Illness Therapy Fatigue Scale[9]	13-item questionnaire on aspects of physical and mental fatigue and its effect on daily living over the past 7 days	Yes	Δ 11.5
Multidimensional Assessment of Fatigue[48]	16-item scale that measures fatigue over the past week according to 4 dimensions: severity, distress, timing, and its effect on daily living	No	Δ 11.5
Multidimensional Fatigue Inventory[54]	20-item instrument that covers general, physical, and mental fatigue as well as reduced motivation and activity	No	Δ 14.3
Fatigue Assessment Scale[55]	10-item fatigue measure	No	N/A
Brief Fatigue Inventory[56]	9-item instrument that assesses the severity of pain and fatigue	Yes	N/A
Vanderbilt Fatigue Severity[8]	18-item fatigue questionnaire	No	N/A

* Validated in other populations, including chronic fatigue syndrome, and stroke. N/A: not available; SLE: systemic lupus erythematosus; MCID: minimal clinically important difference.

Table 2. Frequency of fatigue scales overall and subdivided by study type (clinical trial vs observational).

Measures	SLE Instruments Used, n = 38[1]	SLE Instruments in Observational Studies, n = 26[1]	SLE Instruments in SLE Clinical Trials, n = 12
Visual analog scale	9 (24)	7 (27)	2 (17)
Krupp Fatigue Severity Scale	15 (39)	10 (38)	5 (42)
Functional Assessment of Chronic Illness Therapy Fatigue scale	6 (16)	4 (15)	2 (17)
Multidimensional Assessment of Fatigue	2 (5.3)	2 (7.7)	–
Multidimensional Fatigue Inventory	3 (7.9)	2 (7.7)	1 (8)
Fatigue Assessment Scale	1 (2.6)	–	1 (8)
Brief Fatigue Inventory	1 (2.6)	–	1 (8)
Vanderbilt Fatigue Score	1 (2.6)	1 (3.8)	–

Values are n (%). [1] One study used 2 fatigue measures (37 studies included, but 38 instruments used). SLE: systemic lupus erythematosus.

different B-lymphocyte stimulator (BLyS) antagonists. Belimumab, the first BLyS antagonist on the market, was found to have clinically significant improvements in fatigue at 52 weeks of treatment in a phase III study[13]. Blisibimod was also associated with a significant reduction in fatigue[14]. A study of tabalumab did not show significant improvement in fatigue scores[15]. Interestingly, the first 2 studies, showing positive effects on fatigue, used the FACIT-Fatigue scale, whereas the study of tabalumab used the BFI.

Three RCT addressed nonbiologic drug therapies. One RCT studied the effect of N-acetylcysteine (NAC; thought to be by blocking mTOR in T lymphocytes) on disease activity and fatigue. NAC demonstrated a statistically significant reduction in fatigue, using the FAS. Given that the fatigue levels began to rise again during the third month of treatment, the longterm efficacy of NAC is questionable[16]. An RCT of fish oil did not improve fatigue in SLE[17]. A placebo-controlled trial involving dehydroepiandrosterone (DHEA) similarly failed to demonstrate improvement in fatigue using the Multidimensional Fatigue Inventory[18].

Acupuncture's benefits on fatigue and pain were studied in a small RCT. There was a trend toward improvement that did not reach statistical significance, possibly due to lack of power[19]. Two RCT of exercise in SLE demonstrated clinically significant reductions in fatigue. Of note, improvement in fatigue (using the FSS) was noted even in patients with low adherence in one of these studies, raising the question of bias in the intervention group[20,21]. Low glycemic index and low-calorie diets were also shown to decrease fatigue in SLE patients when measured by the FSS. Statistical significance was achieved with both diets but only the low glycemic index diet met the MCID[22].

Observational studies. Twenty-five observational studies were included. As previously described in the literature, patients with SLE were clinically more fatigued compared to age-matched controls[23]. Regarding predictors, DHEA levels and obesity were not clearly associated with fatigue[24,25]. One study aimed to identify potential biomarkers for fatigue in patients with neuropsychiatric SLE. It identified a clinically significant association between A proliferation-induced ligand (APRIL) in cerebrospinal fluid and fatigue[26]. Five observational studies assessing vitamin D levels and fatigue in SLE demonstrated somewhat different results. One study suggested a trend in improved fatigue levels when vitamin D

Table 3. Summary of clinical trials with fatigue as an outcome in SLE.

Authors	Data Collection	Scale	Intervention	Followup, weeks	N	Findings	Country
Greco, *et al*[19]	2004–2006	FSS	Acupuncture vs minimal needling	5–6	24	No difference detected	USA
Avaux, *et al*[21]	2012–2013	FSS	Exercise vs controls	12	45	Clinically significant improvement*	Belgium
Davies, *et al*[22]	Published 2012	FSS	Low GI diet and LC diet vs placebo	6	23	Clinically significant improvement with GI diet*, but only statistically significant improvement with LC diet (did not meet MCID)	UK
Bogdanovic, *et al*[20]	Published 2015	FSS	Aerobic and isotonic exercise	6	60	Clinically significant improvement*	Serbia
Arriens, *et al*[17]	Published 2015	FSS	Fish oil vs PBO	26	50	No difference	USA
Strand, *et al*[13]	2007–2010	FACIT-Fatigue	Belimumab or PBO	52 (n = 865); 76 (n = 819)	1684	Clinically significant improvement*	Multicenter
Petri, *et al*[14]	2010–2012	FACIT-Fatigue	Blisibimod or PBO	24	547	Clinically significant improvement*	USA and Brazil
Uppal, *et al*[12]	Published 2009	VAS	Standard therapy ± infliximab (anchor not specified)	24	27	No difference detected	Kuwait
Merrill, *et al*[11]	Published 2010	VAS	Abatacept vs placebo (anchor not specified)	52	175	Clinically significant improvement*	Multicenter
Hartkamp, *et al*[18]	Published 2010	MFI	DHEA vs PBO	52	60	No difference detected	the Netherlands
Lai, *et al*[16]	2009–2011	FAS	PBO vs escalating doses of N-acetylcysteine	12	36	Statistically significant improvement	USA
Merrill, *et al*[15]	2011–2014	BFI	Tabalumab vs PBO	52	1124	No difference detected	Multicenter

* Met MCID (therefore both statistically and clinically significant difference detected). MCID: minimal clinically important difference; FSS: Krupp Fatigue Severity Scale; GI: glycemic index; LC: low-calorie; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue Scale; PBO: placebo; VAS: visual analog scale; MFI: Multidimensional Fatigue Inventory; DHEA: dehydroepiandrosterone; BFI: Brief Fatigue Inventory; FAS: Fatigue Assessment Scale; SLE: systemic lupus erythematosus.

deficiency/insufficiency was corrected with supplementation, but this did not reach statistical significance[27]. Of the 4 remaining vitamin D studies, 2 demonstrated clinically significant (i.e., met MCID) increased fatigue with low vitamin D levels[28,29] while the other 2 were unable to demonstrate associations[30,31]. Two studies aimed to determine the relationship between muscle strength and fatigue in SLE. One study demonstrated decreased strength with increased fatigue[32], while the other was unable to establish this relationship[33]. Three studies demonstrated a clinically significant association between work disability and fatigue in patients with SLE[34,35,36]. Finally, lower physical activity, sleep disturbances, pain, anxiety, and depression were all found to be associated with fatigue levels in SLE[37–45]. Regarding interventions, belimumab was shown to clinically significantly decrease fatigue in patients with SLE in an observational study[46]. A study of a fatigue and activity management education intervention, administered by occupational therapists, was unable to demonstrate decreased fatigue in SLE[47].

Among observational studies, most studies with large sample sizes (> 100) demonstrated a clinically significant change in fatigue[29,35,36,37,39–43,45]. Smaller studies were unable to demonstrate changes, suggesting that they were underpowered[26,28,31,34,48].

DISCUSSION

This review is an important update of instruments used to measure fatigue in SLE in the past 10 years. In this systematic review the VAS, FSS, and FACIT-Fatigue scale were the most frequently used instruments to measure fatigue in adult SLE studies from 2008 to 2017. The VAS is a simple analog scale in which patients mark with an "x" their level of fatigue on a 100-mm line. The advantages are its ease of use and quick administration. Unfortunately, although validated in other populations, this instrument has not yet been studied in SLE and does not consider fatigue's effect on daily living. Additionally, many studies fail to provide the anchors used with the scale, rendering it difficult to compare their results.

Krupp's FSS was the most frequently used instrument in our study and was the instrument recommended for use by the 2007 Ad Hoc Committee[8]. It was designed to measure the effect of fatigue on functional outcomes such as exercise, motivation, and daily activities. It has been validated for use in SLE[48].

The FACIT-Fatigue scale is a 13-item questionnaire (originally developed in cancer patients) that measures aspects of physical and mental fatigue and their effects on daily living and functioning. The FACIT-Fatigue scale had not yet been validated in SLE when the Ad Hoc Committee made its recommendations in 2007. The first validation

Table 4. Summary of observational studies reporting fatigue as an outcome in SLE.

Authors	Data Collection	Scale	Predictor (Independent) Variables	N	Findings	Country
Balsamo, *et al*[32]	2009–2011	FSS	Dynamic muscle strength	25	Clinically significant association between increased fatigue & lower strength*	Brazil
Petri, *et al*[38]	2003–2004	FSS	Depression	160	Clinically significant association*	USA
Utset, *et al*[34]	2004–2005	FSS	Work disability	143	Clinically significant association*	USA
Hopia, *et al*[26]	Published 2011	FSS	APRIL cerebrospinal fluid level	28	Clinically significant association*	Sweden
Mahieu, *et al*[42]	2011–2012	FSS	Depression, anxiety, and low physical activity	129	Clinically significant association*	USA
Rizk, *et al*[25]	Published 2012	FSS	Obesity	90	No difference detected	Egypt
Stockton, *et al*[30]	Published 2012	FSS	Vitamin D levels	45	No difference detected	Australia
Cezarino, *et al*[33]	Published 2017	FSS	Maximum voluntary isometric contraction of back muscles	25	No difference detected	Brazil
O'Riordan, *et al*[47]	Published 2017	FSS	FAME intervention	21	No difference detected	Ireland
Pettersson, *et al*[41]	Published 2015	FSS + MAF	Lifestyle habits	616	Clinically significant association between fatigue and anxiety, depression, and decreased physical activity*	Sweden
Mok, *et al*[35]	Published 2008	FACIT-Fatigue	Work loss	147	Clinically significant association*	China
Strand, *et al*[36]	2009–2010	FACIT- Fatigue	Corticosteroid use, unemployment, and disease activity	886	Clinically significant association with steroid use and unemployment; no change with disease activity	Sweden
Kasitanon, *et al*[37]	2009–2011	FACIT- Fatigue	Sleep disturbances	56	Clinically significant association *	Thailand
Mishra, *et al*[23]	Published 2015	FACIT- Fatigue	Fatigue level in SLE vs control	88	Clinically significant difference*	India
Ruiz-Irastorza, *et al*[27]	2008	VAS	Vitamin D levels† (anchor: 0 = no fatigue; 10 = intense fatigue)	80	No difference detected	Spain
Fragoso, *et al*[31]	2009–2010	VAS	Vitamin D levels (anchor not specified)	142	No difference detected	Brazil
Somers, *et al*[45]	2010–2011	VAS	Race, disease activity, and pain	74	Clinically significant association with pain only; no association with race and disease activity	USA
Moldovan, *et al*[44]	2013	VAS	Pain, depression, and socioeconomic variables	125	Clinically significant association for pain and depression; no association with socioeconomic variables*	USA
Salman-Monte, *et al*[28]	2012–2014	VAS	Vitamin D deficiency and insufficiency†	102	Clinically significant association* between increased fatigue and low vitamin D	Spain
Parodis, *et al*[46]	2011–2015	VAS	Belimumab (anchor not specified)	58	Clinically significant improvement*	Sweden and France
Abaza, *et al*[29]	Published 2016	VAS	Vitamin D levels†	90	Clinically significant association* between increased fatigue and low vitamin D	Egypt
Fischin, *et al*[40]	2009	VFS	Pain, coping, and catastrophizing	447	Statistically significant association (MCID not available)	Germany
Waldheim, *et al*[39]	Published 2013	MAF	Pain severity	175	Statistically significant association (MCID not available)	Sweden
Moraleda, *et al*[43]	Published 2017	MFI	Sleep quality	41	Statistically significant association between poorer sleep quality and fatigue	Spain
Overman, *et al*[24]	Published 2012	MFI	DHEA	120	No difference detected	the Netherlands

* Met MCID (therefore both statistically and clinically significant difference detected). † Anchor: 0 = no fatigue; 10 = intense fatigue. APRIL: A proliferation-induced ligand; MCID: minimal clinically important difference; DHEA: dehydroepiandrosterone; FSS: Krupp Fatigue Severity Scale; FAME: Fatigue and Activity Management Education; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue Scale; VAS: visual analog scale; MFI: Multidimensional Fatigue Inventory; SLE: systemic lupus erythematosus; MAF: Multidimensional Assessment of Fatigue.

study of FACIT-Fatigue scale in SLE was published in 2011[10]. Like FSS, the FACIT-Fatigue scale has been shown to have good psychometric properties and is easy and quick to administer (< 5 min). Interestingly, all studies that used the FACIT-Fatigue scale found clinically significant associations[13,14,23,35,36,37].

The US Food and Drug Administration (FDA) strongly encourages the use of patient-reported outcomes (PRO) as secondary endpoints in SLE clinical trials. Both the FDA and European Medicine Agency emphasize fatigue as being one of the most important PRO to consider. Though no specific scale is recommended, they state that the instrument used should be well defined and have been validated in SLE trial populations[49]. Difficulty in showing effects of an intervention on fatigue in SLE may well be due to study power for many of the studies that we reviewed.

The FACIT-Fatigue scale and FSS have good construct validity[9,50]. Both scales have an MCID calculated for patients with SLE[51], which allows them to demonstrate changes in fatigue that are both statistically and clinically (in terms of MCID) significant. FACIT-Fatigue scale has been reported to have superior internal consistency and greater sensitivity to change than FSS[51]. FACIT-Fatigue scale may be more sensitive to detect subjectively important changes in fatigue levels and potentially able to detect a change in smaller sample sizes[51]. Using focus groups, the FACIT-Fatigue scale has been shown to have good content validity, which means that it appears to be relevant and sufficient for properly assessing fatigue in patients with SLE[5,9]. The content validity for FSS has not yet been studied[52]. Fatigue remains an important issue in patients with SLE. Our literature review revealed a small number of clinical trial studies with important reductions in fatigue with medications and nonpharmacologic approaches. Many of these studies used either the FSS, which was recommended for use by the 2007 Ad Hoc Committee, or the FACIT-Fatigue scale, which has demonstrated both superior internal consistency and greater sensitivity compared to FSS[51]. The VAS, though easy to use and often used in longterm observational studies, has not been validated in SLE and does not record fatigue's functional effect on patients.

As in any review, our results have potential limitations, and these are partially driven by limitations in the literature. We found that observational studies with larger sample sizes more consistently demonstrated a statistically significant change in fatigue[24,29,35,36,37,39-43,45]. This suggests that some of the smaller studies included were underpowered[26,28,31,34,48]. Regarding RCT results, most had a followup time of < 52 weeks, and hence limited our ability to comment on longterm effects.

The VAS, FSS, and FACIT-Fatigue scale were the most frequently used instruments in adult SLE studies from 2008 to 2017. Many studies detected clinically important changes in fatigue. Fatigue remains a key measure in both clinical trials and observational SLE studies. Just as RCT now generally require fatigue scores, fatigue (for example, measured with the FSS or FACIT-Fatigue scale) should be a part of the core data collection for observational SLE studies.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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