Fatigue Measurements in Systemic Lupus Erythematosus

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Abstract

Objective: Fatigue is a frequent, disabling issue in 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 (Jan. 2008-Oct. 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: 37 studies met inclusion criteria. Eight scales were used. The Visual Analogue 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 which did not, six used the FFS, three used the VAS, two used the Multidimensional Assessment of fatigue and one 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 2008-2017. Many studies detected clinically important changes in fatigue. Fatigue remains a key measure in both clinical trials and observational SLE studies.

Significance and Innovations

- This article consists of an update of fatigue instruments used in Systemic Lupus Erythematosus (SLE), since the 2007 Ad Hoc Committee systematic review.
- Both the Krupp Fatigue Severity Scale and Functional Assessment of Chronic Illness Therapy Fatigue scale have excellent properties.
- Just as RCTs now generally require fatigue scores, fatigue (ideally measured with FSS or FACIT Fatigue scale) should probably be a part of the core data collection for observational SLE studies.

Introduction

Systemic lupus erythematosus is a chronic multi-system 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 (4-6). 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 SLE patients 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 SLE patients since the 2007 Ad Hoc Committee recommendations and to summarize fatigue research in lupus patients over the past 10 years

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". 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 recent Ad Hoc Committee review article in 2007, 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, studying fatigue as a primary or secondary endpoint, were included in our study. Only publications using validated fatigue instruments were retained – studies measuring fatigue only through measures of disease activity or quality of life scores (e.g. SF-36) were excluded. We extracted information from these studies regarding their study 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, eight fatigue instruments were used (Table 1). The Visual Analogue Scale (VAS), Krupp Fatigue Severity Scale

(FSS) and Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale were the most frequently used measurements (Tables 2, 3 and 4). The FSS was the most frequently used instrument in both randomized-controlled trial (RCTs) and observational studies. Twelve of the 38 studies failed to demonstrate a statistically significant difference in fatigue levels related to the exposure of interest. Of these, six used the FFS, three used the VAS, two used the Multidimensional Assessment of fatigue and one used the Brief Fatigue Index. All 6 studies using the FACIT Fatigue scale detected clinically meaningful and statistically significant differences. Time until end of follow-up did not appear to influence study results.

Randomized-Controlled Trials

Among the articles analyzed, 12 consisted of RCTs; 5 of these studied the impact of biologic drug therapies on fatigue in SLE patients. Abatacept was associated with a clinically significant reduction in fatigue compared to placebo at a 12 month follow up, 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 three studies each assessing different 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 3 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 two studies, showing positive effects on fatigue, used the FACIT Fatigue scale, whereas the study of tabalumab used the Brief Fatigue Inventory (BFI).

Three RCTs addressed non-biologic drug therapies. One RCT studied the impact 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 3rd month of treatment, the long-term 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 towards improvement which did not reach statistical significance, possibly due to lack of power (19). Two RCTs 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 using 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, lupus patients were clinically more fatigued compared to age-matched controls (23). In terms of predictors, DHEA levels and obesity were not clearly associated with fatigue (24, 25). One study aimed to identify potential biomarkers for fatigue in neuropsychiatric lupus patients. It identified a clinically significant association between A proliferation-induced ligand

(APRIL) in cerebrospinal fluid hand 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 deficiency/insufficiency was corrected with supplementation, but this did not reach statistical significance (27). Of the four remaining vitamin D studies, two demonstrated clinically significant (i.e. met MCID) increased fatigue with low vitamin D levels (28, 29) while the other two 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 lupus patients (34-36). Finally, lower physical activity, sleep disturbances, pain, anxiety and depression were all found to be associated with fatigue levels in SLE (37-45). In terms of interventions, Belimumab was shown to clinically significantly decrease fatigue in lupus patients 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 (more than 100) demonstrated a clinically significant change in fatigue (29, 35-37, 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 2008-2017. The VAS is a simple analogue scale where patients mark with an X their level of fatigue on a 100mm 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 patients and does not consider fatigue's impact 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 impact 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 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 (less than 5 minutes). Interestingly, all studies that used the FACIT Fatigue scale found clinically significant associations in their studies (13, 14, 23, 35-37).

The United States Food and Drug Administration strongly encourages the use of patient reported outcomes (PRO) as secondary end-points in SLE clinical trials. Both the FDA and European Medicine Agency emphasize fatigue as being one of the most important PROs 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 a MCID calculated for SLE patients (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, 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 SLE patients (9, 52). The content validity for FSS has not yet been studied (53). In summary, fatigue remains an important issue in SLE patients. Our literature review revealed a small number of clinical trial studies with important reductions in fatigue with medications and non-pharmacologic 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 long-term observational studies, has not been validated in SLE and does not capture fatigue's functional impact 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 demonstrate a statistically significant change in fatigue (24, 29, 35-37, 39-43, 45). This suggests that some of the smaller studies included were underpowered (26, 28, 31, 34, 48). Regarding RCT results, most had follow-up time less than 52 weeks, and hence limits our ability to comment on long-term effects.

In summary, the VAS, FSS and FACIT Fatigue scale were the most frequently used instruments in adult SLE studies from 2008-2017. Many studies detected clinically important changes in fatigue. Fatigue remains a key measure in both clinical trials and observational SLE studies. Just as RCTs 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.

References

1. Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2014;66:608-16.

2. del Pino-Sedeno T, Trujillo-Martin MM, Ruiz-Irastorza G, Cuellar-Pompa L, de Pascual-Medina AM, Serrano-Aguilar P, et al. Effectiveness of Nonpharmacologic Interventions for Decreasing Fatigue in Adults With Systemic Lupus Erythematosus: A Systematic Review. Arthritis Care Res (Hoboken). 2016;68:141-8.

3. Ahn GE, Ramsey-Goldman R. Fatigue in systemic lupus erythematosus. Int. 2012;7:217-27.

4. Mattsson M, Moller B, Stamm T, Gard G, Bostrom C. Uncertainty and opportunities in patients with established systemic lupus erythematosus: a qualitative study. Musculoskelet. 2012;10:1-12.

5. Ramsey-Goldman R, Rothrock N. Fatigue in systemic lupus erythematosus and rheumatoid arthritis. Pm R. 2010;2:384-92.

6. Cleanthous S, Tyagi M, Isenberg DA, Newman SP. What do we know about self-reported fatigue in systemic lupus erythematosus? Lupus. 2012;21:465-76.

7. Hjollund NH, Andersen JH, Bech P. Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. Health and Quality of life Outcomes. 2007;5:12.

8. Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue. Measurement of fatigue in systemic lupus erythematosus: a systematic review. Arthritis and rheumatism. 2007;57:1348.

9. Kosinski M, Gajria K, Fernandes AW, Cella D. Qualitative validation of the FACIT-fatigue scale in systemic lupus erythematosus. Lupus. 2013;22:422-30.

10. Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue Scale in Patients with Moderately to Severely Active Systemic Lupus Erythematosus, Participating in a Clinical Trial. J Rheumatol. 2011;38:672-9.

11. Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62:3077-87.

12. Uppal SS, Hayat SJ, Raghupathy R. Efficacy and safety of infliximab in active SLE: a pilot study. Lupus. 2009;18:690-7.

13. Strand V, Levy RA, Cervera R, Petri MA, Birch H, Freimuth WW, et al. Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials. Ann Rheum Dis. 2014;73:838-44.

14. Petri MA, Martin RS, Scheinberg MA, Furie RA. Assessments of fatigue and disease activity in patients with systemic lupus erythematosus enrolled in the Phase 2 clinical trial with blisibimod. Lupus. 2017;26:27-37.

15. Merrill JT, van Vollenhoven RF, Buyon JP, Furie RA, Stohl W, Morgan-Cox M, et al. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75:332-40.

16. Lai ZW, Hanczko R, Bonilla E, Caza TN, Clair B, Bartos A, et al. N-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2012;64:2937-46.

17. Arriens C, Hynan LS, Lerman RH, Karp DR, Mohan C. Placebo-controlled randomized clinical trial of fish oil's impact on fatigue, quality of life, and disease activity in Systemic Lupus Erythematosus. Nutr J. 2015;14:82.

18. Hartkamp A, Geenen R, Godaert GL, Bijl M, Bijlsma JW, Derksen RH. Effects of dehydroepiandrosterone on fatigue and well-being in women with quiescent systemic lupus erythematosus: a randomised controlled trial. Ann Rheum Dis. 2010;69:1144-7.

19. Greco CM, Kao AH, Maksimowicz-McKinnon K, Glick RM, Houze M, Sereika SM, et al. Acupuncture for systemic lupus erythematosus: a pilot RCT feasibility and safety study. Lupus. 2008;17:1108-16.

20. Bogdanovic G, Stojanovich L, Djokovic A, Stanisavljevic N. Physical Activity Program Is Helpful for Improving Quality of Life in Patients with Systemic Lupus Erythematosus. Tohoku J Exp Med. 2015;237:193-9.

21. Avaux M, Hoellinger P, Nieuwland-Husson S, Fraselle V, Depresseux G, Houssiau FA. Effects of two different exercise programs on chronic fatigue in lupus patients. Acta Clin Belg. 2016;71:403-6.

22. Davies RJ, Lomer MC, Yeo SI, Avloniti K, Sangle SR, D'Cruz DP. Weight loss and improvements in fatigue in systemic lupus erythematosus: a controlled trial of a low glycaemic index diet versus a calorie restricted diet in patients treated with corticosteroids. Lupus. 2012;21:649-55.

23. Mishra R, Dhir V, Aggarwal A. The relationship of fatigue with quality of life in patients with systemic lupus erythematosus having low disease activity. 2015;10:125-8.

24. Overman CL, Hartkamp A, Bossema ER, Bijl M, Godaert GL, Bijlsma JW, et al. Fatigue in patients with systemic lupus erythematosus: the role of dehydroepiandrosterone sulphate. Lupus. 2012;21:1515-21.

25. Rizk A, Gheita TA, Nassef S, Abdallah A. The impact of obesity in systemic lupus erythematosus on disease parameters, quality of life, functional capacity and the risk of atherosclerosis. Int J Rheum Dis. 2012;15:261-7.

26. Hopia L, Thangarajh M, Khademi M, Laveskog A, Wallstrom E, Svenungsson E, et al. Cerebrospinal fluid levels of a proliferation-inducing ligand are increased in patients with neuropsychiatric systemic lupus erythematosus. Scand J Rheumatol. 2011;40:363-72.

27. Ruiz-Irastorza G, Gordo S, Olivares N, Egurbide MV, Aguirre C. Changes in vitamin D levels in patients with systemic lupus erythematosus: Effects on fatigue, disease activity, and damage. Arthritis Care Res (Hoboken). 2010;62:1160-5.

28. Salman-Monte TC, Torrente-Segarra V, Almirall M, Corzo P, Mojal S, Carbonell-Abello J. Prevalence and predictors of vitamin D insufficiency in supplemented and non-supplemented women with systemic lupus erythematosus in the Mediterranean region. Rheumatol Int. 2016;36:975-85.

29. Abaza NM, El-Mallah RM, Shaaban A, Mobasher SA, Al-Hassanein KF, Abdel Zaher AA, et al. Vitamin D Deficiency in Egyptian Systemic Lupus Erythematosus Patients: How Prevalent and Does It Impact Disease Activity? Integr. 2016;11:27-33.

30. Stockton KA, Kandiah DA, Paratz JD, Bennell KL. Fatigue, muscle strength and vitamin D status in women with systemic lupus erythematosus compared with healthy controls. Lupus. 2012;21:271-8.

31. Fragoso TS, Dantas AT, Marques CD, Rocha Junior LF, Melo JH, Costa AJ, et al. 25-Hydroxyivitamin D3 levels in patients with systemic lupus erythematosus and its association with clinical parameters and laboratory tests. Rev. 2012;52:60-5.

32. Balsamo S, da Mota LM, de Carvalho JF, Nascimento Dda C, Tibana RA, de Santana FS, et al. Low dynamic muscle strength and its associations with fatigue, functional performance, and quality of life in premenopausal patients with systemic lupus erythematosus and low disease activity: a case-control study. BMC Musculoskelet Disord. 2013;14:263.

33. Cezarino RS, Cardoso JR, Rodrigues KN, Magalhaes YS, Souza TY, Mota L, et al. Chronic low back pain in patients with systemic lupus erythematosus: prevalence and predictors of back muscle strength and its correlation with disability. Rev. 2017;57:438-44.

34. Utset TO, Chohan S, Booth SA, Laughlin JC, Kocherginsky M, Schmitz A. Correlates of formal work disability in an urban university systemic lupus erythematosus practice. J Rheumatol. 2008;35:1046-52.

35. Mok CC, Cheung MY, Ho LY, Yu KL, To CH. Risk and predictors of work disability in Chinese patients with systemic lupus erythematosus. Lupus. 2008;17:1103-7.

36. Strand V, Galateanu C, Pushparajah DS, Nikai E, Sayers J, Wood R, et al. Limitations of current treatments for systemic lupus erythematosus: a patient and physician survey. Lupus. 2013;22:819-26.

37. Kasitanon N, Achsavalertsak U, Maneeton B, Wangkaew S, Puntana S, Sukitawut W, et al. Associated factors and psychotherapy on sleep disturbances in systemic lupus erythematosus. Lupus. 2013;22:1353-60.

38. Petri M, Naqibuddin M, Carson KA, Wallace DJ, Weisman MH, Holliday SL, et al. Depression and cognitive impairment in newly diagnosed systemic lupus erythematosus. J Rheumatol. 2010;37:2032-8.

39. Waldheim E, Elkan AC, Pettersson S, van Vollenhoven R, Bergman S, Frostegard J, et al. Health-related quality of life, fatigue and mood in patients with SLE and high levels of pain compared to controls and patients with low levels of pain. Lupus. 2013;22:1118-27.

40. Fischin J, Chehab G, Richter JG, Fischer-Betz R, Winkler-Rohlfing B, Willers R, et al. Factors associated with pain coping and catastrophising in patients with systemic lupus erythematosus: a cross-sectional study of the LuLa-cohort. Lupus sci. 2015;2:e000113.

41. Pettersson S, Bostrom C, Eriksson K, Svenungsson E, Gunnarsson I, Henriksson EW. Lifestyle habits and fatigue among people with systemic lupus erythematosus and matched population controls. Lupus. 2015;24:955-65.

42. Mahieu MA, Ahn GE, Chmiel JS, Dunlop DD, Helenowski IB, Semanik P, et al. Fatigue, patient reported outcomes, and objective measurement of physical activity in systemic lupus erythematosus. Lupus. 2016;25:1190-9.

43. Moraleda V, Prados G, Martinez MP, Sanchez AI, Sabio JM, Miro E. Sleep quality, clinical and psychological manifestations in women with systemic lupus erythematosus. Int J Rheum Dis. 2017;20:1541-50.

44. Moldovan I, Cooray D, Carr F, Katsaros E, Torralba K, Shinada S, et al. Pain and depression predict self-reported fatigue/energy in lupus. Lupus. 2013;22:684-9.

45. Somers TJ, Kurakula PC, Criscione-Schreiber L, Keefe FJ, Clowse ME. Self-efficacy and pain catastrophizing in systemic lupus erythematosus: relationship to pain, stiffness, fatigue, and psychological distress. Arthritis Care Res (Hoboken). 2012;64:1334-40.

46. Parodis I, Sjowall C, Jonsen A, Ramskold D, Zickert A, Frodlund M, et al. Smoking and pre-existing organ damage reduce the efficacy of belimumab in systemic lupus erythematosus. Autoimmun Rev. 2017;16:343-51.

47. O'Riordan R, Doran M, Connolly D. Fatigue and Activity Management Education for Individuals with Systemic Lupus Erythematosus. Occup Ther Int. 2017:4530104.

48. 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 Res (Hoboken). 2003;49(S5).

49. US Department of Health and Human Services. Guidance for industry: Systemic lupus erythematosus – developing medical products for treatment. US Food and Drug Administration wfgdDG.

50. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46:1121-3.

51. Goligher EC, Pouchot J, Brant R, Kherani RB, Avina-Zubieta JA, Lacaille D, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. J Rheumatol. 2008;35:635-42.

52. Ramsey-Goldman R, Rothrock N. Fatigue in systemic lupus erythematosus and rheumatoid arthritis. Pm&R. 2010;2:384-92.

53. Holloway L, Humphrey L, Heron L, Pilling C, Kitchen H, Hojbjerre L, et al. Patient-reported outcome measures for systemic lupus erythematosus clinical trials: a review of content validity, face validity and psychometric performance. Health Qual Life Outcomes. 2014;12:116.

54. Tseng BY, Gajewski BJ, Kluding PM. Reliability, responsiveness, and validity of the visual analog fatigue scale to measure exertion fatigue in people with chronic stroke: a preliminary study. Stroke research and treatment. 2010;2010.

55. Gentile S, Delarozière J, Favre F, Sambuc R, San Marco J. Validation of the French 'multidimensional fatigue inventory'(MFI 20). Eur J Cancer Care. 2003;12:58-64.

56. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. Journal of psychosomatic research. 2003;54:345-52

57. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Brief Fatigue Inventory. STOP, THAT and One Hundred Other Sleep Scales: Springer; 2011. p. 75-7.

Table 1: Fatigue scales used in studies of adults with systemic lupus (SLE)

Measure	Description	Construct validity studied (53)	Minimal Clinically Important Difference (MCID) in SLE(51)
Visual Analogue Scale (VAS) (55)	Single 100mm line to measure fatigue	No[1]	Δ 10%
Krupp Fatigue Severity Scale (FSS) (48)	9-item questionnaire on impact of fatigue on specific types of functioning	Yes	Δ 9.7%
Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT F) (9)	13-item questionnaire on aspects of physical and mental fatigue and its impact on daily living over the past 7 days.	Yes	Δ 11.5%
Multidimensional Assessment of Fatigue (MAF) (48)	16 item scale that measures fatigue over the past week according to four dimensions: severity, distress, timing and its impact on daily living.	No	Δ 11.5%
Multidimensional Fatigue Inventory (MFI) (55)	20-item instrument that covers general, physical and mental fatigue as well as reduced motivation and activity.	No	Δ 14.3%
Fatigue Assessment Scale (FAS) (56)	10 item fatigue measure	No	N/A[2]
Brief Fatigue Index/Inventory (BFI) (57)	9 item instrument that assesses the severity of pain and fatigue	Yes	N/A
Vanderbilt Fatigue Severity (VFS) (8)	18-item fatigue questionnaire	No	N/A

[1] Validated in other populations, including chronic fatigue syndrome, and stroke.

[2] N/A= not available

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

Measure	# SLE instruments used (n=38)[1]	# SLE instruments in Observational studies (n = 26)[1]	# SLE instruments Number of SLE Clinical Trials (n = 12)
Visual Analogue Scale (VAS)	9 (24%)	7 (27%)	2 (17%)
Krupp Fatigue Severity Scale (FSS)	15 (39%)	10 (38%)	5 (42%)
Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT F)	6 (16%)	4 (15%)	2 (17%)
Multidimensional Assessment of Fatigue (MAF)	2 (5.3%)	2 (7.7%)	-
Multidimensional Fatigue Inventory (MFI)	3 (7.9%)	2 (7.7%)	1 (8%)
Fatigue Assessment Scale (FAS)	1 (2.6%)	-	1 (8%)
Brief Fatigue Index/inventory (BFI)	1 (2.6%)	-	1 (8%)
Vanderbilt Fatigue Score (VFS)	1 (2.6%)	1 (3.8%)	-

[1] One study used 2 fatigue measures (37 studies included, but 38 instruments used)

Table 3: Summary of Clinical Trials with Fatigue as an Outcome in SLE

Authors	Data Collection	Scale	Intervention	Follow-up (weeks)	N	Findings	Country
Greco et al. (19)	2004-2006	FSS	Acupuncture versus minimal needling	5 to 6	24	No difference detected	USA
Avaux et al. (21)	2012-2013	FSS	Exercise versus controls	12	45	Clinically significant improvement *	Belgium
Davies et al. (22)	Published 2012	FSS	Low glycemic index (GI) diet and low-calorie (LC) diet versus 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 versus placebo	26	50	No difference	USA
Strand et al. (13)	2007-2010	FACIT-F	Belimumab or placebo	52 (N=865) 76 (N=819)	1684	Clinically significant improvement *	Multicenter
Petri et al. (14)	2010-2012	FACIT-F	Blisibimod or placebo	24	547	Clinically significant improvement *	USA & 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 versus placebo *Anchor not specified*	52	175	Clinically significant improvement *	Multicenter
Hartkamp et al. (18)	Published 2009	MFI	Dehydroepiandrosterone versus placebo	52	60	No difference detected	Netherlands
Lai et al. (16)	2009-2011	FAS	Placebo versus escalating doses of N-acetylcysteine	12	36	Statistically significant improvement	USA
Merrill et al. (15)	2011-2014	BFI	Tabalumab vs. placebo	52	1124	No difference detected	Multicenter

*Met minimal clinically important difference (MCID) (therefore both statistically and clinically significant difference detected)

Table 4: Summary of Observational Studies Reporting Fatigue as an Outcome in SLE

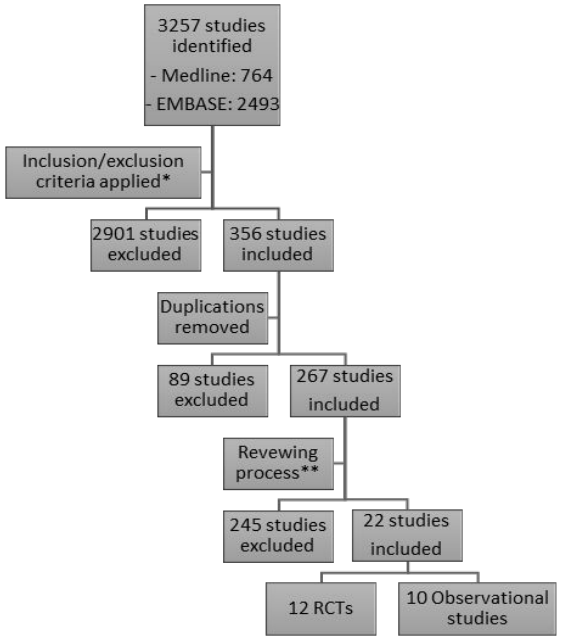
Authors	Data collection	Scale	Predictor (independent) variable	N	Findings	Country
Balsamo et al. (32)	2009-2011	FSS	Dynamic muscle strength	25	Clinically significant association between increased fatigue & lower strength*	Brazil
Petri et al. (38)	2003-2004	FSS	Depression	160	Clinically significant association*	USA
Utset et al. (34)	2004-2005	FSS	Work disability	143	Clinically significant association*	USA
Hopia et al. (26)	Published 2011	FSS	A proliferation-induced ligand (APRIL) CSF 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 2011	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	Fatigue and Activity Management Education (FAME) intervention	21	No difference detected	Ireland
Pettersson et al. (41)	Published 2015	FSS + MAF	Lifestyle habits	616	Clinically significant association between fatigue & anxiety, depression and decreased physical activity*	Sweden
Mok et al. (35)	Published 2008	FACIT-F	Work loss	147	Clinically significant association*	China
Strand et al. (36)	2009-2010	FACIT-F	Corticosteroid use, unemployment & disease activity	886	Clinically significant association with steroid use & unemployment	Sweden

					No change with disease activity	
Kasitanon et al. (37)	2009-2011	FACIT-F	Sleep disturbances	56	Clinically significant association *	Thailand
Mishra et al. (23)	Published 2015	FACIT-F	Fatigue level in SLE versus 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 & disease activity	USA
Moldovan et al. (44)	2013	VAS	Pain, depression and socio-economic 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 & insufficiency *Anchor: 0=no fatigue; 10=intense fatigue*	102	Clinically significant association* between increased fatigue & low vitamin D	Spain
Parodis et al. (46)	2011-2015	VAS	Belimumab *Anchor not specified*	58	Clinically significant improvement*	Sweden & France
Abaza et al. (29)	Published 2016	VAS	Vitamin D levels *Anchor: 0=no fatigue; 10=intense fatigue*	90	Clinically significant association* between increased fatigue & 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	MFI	Sleep quality	41	Statistically significant	Spain

	2017					association between poorer sleep quality and fatigue	
Overman et al. (24)	Published 2012	MFI	Dehydroepiadrosterone (DHEA)	120	No difference detected		Netherlands

*Met minimal clinically important difference (MCID) (therefore both statistically and clinically significant difference detected)

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 using fatigue specific instruments were included