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Effectiveness of Nonpharmacologic Interventions for Decreasing Fatigue in Adults With Systemic Lupus Erythematosus: A Systematic Review

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Objective. **Survival of patients with systemic lupus erythematosus (SLE) has significantly improved over the past decades. As SLE patients live longer they inevitably experience a range of clinical manifestations and somatic symptoms. Quality of life may also be impacted through a range of subjective indicators. Among these parameters, fatigue is the most prevalent complaint. Nonpharmacologic strategies seem regularly utilized for fatigue management in SLE; however, their real effects are not known.**

Methods. **A systematic review was conducted to analyze the effectiveness of nonpharmacologic interventions to reduce fatigue in SLE patients. Medline/PreMedline, Embase, PsycINFO, SCI-EXPANDED, Social Sciences Citation Index, and the Cochrane Library were searched (June 2014). Studies were included and assessed for quality if they fulfilled prespecified criteria.**

Results. **A total of 12 studies were finally included (n = 549): 7 randomized trials, 1 nonrandomized trial, and 4 prospective observational studies. They assessed 5 main intervention categories: exercise, behavioral and psychological approaches, diets, acupuncture, and phototherapy. All interventions produced reductions in fatigue, as measured using at least 1 instrument. Aerobic exercise was found to be effective and suitable for reducing fatigue, but results were not always consistent across instruments used. The diversity of psychological interventions limits the significance of the results; however, data point to a positive impact on fatigue. There are still few data on the effect of acupuncture, diets, and ultraviolet A radiation.**

Conclusion. **Studies are few and heterogeneous; however, nonpharmacologic interventions applied to SLE patients can be effective in reducing fatigue.**

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with significant potential morbidity and mortality. The prevalence of SLE is 20–150 cases per 100,000 (1) and the estimated incidence is 1–25 per 100,000 in North America, South America, Europe, and Asia (2).

The spectrum of SLE is wide and variable, both in clinical manifestations and severity. SLE was considered a

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Significance & Innovations

- Nonpharmacologic interventions could be a valuable option for the treatment of fatigue in systemic lupus erythematosus (SLE).
- Psychological interventions and aerobic exercise are effective interventions to reduce fatigue in patients with SLE.

fatal disorder during the first half of the 20th century; however, significant advances in disease management have contributed to improve the survival of SLE patients (3). As a result of the better prognosis in SLE, increasing attention is now focused on the improvement of health-related quality of life (HRQOL).

Most SLE patients experience so-called minor symptoms, such as fatigue and pain; however, these symptoms still have a profound impact on their quality of life (4,5). Fatigue is a multidimensional phenomenon that affects individuals physically, emotionally, cognitively, and behaviorally (6). Besides, it is the most prevalent symptom in SLE, being present in up to 90% of patients (7). Moreover, fatigue has a major impact on the HRQOL of SLE patients. Therefore, every effort should be made to relieve fatigue in this population (7).

Recommendations for the management of fatigue usually combine pharmacologic and nonpharmacologic interventions (8); however, no specific drugs have proven useful for treating fatigue in SLE. Therefore, like other autoimmune conditions, nonpharmacologic strategies are essential for fatigue management in lupus (7).

An increasing number of nonpharmacologic therapies are available for patients with fatigue, including relaxation, programmed exercise, education, counseling, rehabilitation, and energy conservation (7,9), but their actual effect on SLE patients is not well known. Although some systematic reviews (7–10) and 1 meta-analysis reported on the effectiveness of nonpharmacologic interventions for fatigue (11), they excluded SLE patients (8,9) or focused on a limited subset of interventions (10,11).

For this reason, the aim of this study is to perform a systematic review to evaluate the available evidence on the effects of nonpharmacologic interventions for improving fatigue in adult patients with SLE.

MATERIALS AND METHODS

Information sources and search strategy. The following databases were searched (June 2014): Medline and Pre-Medline (OVID interface), Embase (Elsevier interface), PsycINFO (EbscoHost interface), Cumulative Index to Nursing and Allied Health Literature (CINAHL; EbscoHost interface), SCI-EXPANDED (Web of Science interface), Social Sciences Citation Index (SSCI; Web of Science interface), and the Cochrane Library, limited to trials (Wiley interface).

The search strategy was developed initially in Medline using controlled vocabulary and free-text terms, and then it was adapted for each of the other databases. The strategy combined the following terms: ([therapy] OR [rehabilitation] OR [psychology] OR [therapy intervention] OR [exercise] OR [diet therapy] OR [psychotherapy] OR [psychological therapy] OR [psychological treatment] OR [psychological intervention]) AND ([fatigue] OR [asthenia] OR [tiredness]) AND ([Systemic Lupus Erythematosus] OR [SLE] OR [lupus]). Searches were limited to English and Spanish languages and no date restriction was imposed. The Medline search strategy is presented in Table 1 and the full search strategy is available from the study authors.

To complete the systematic search, the reference lists of included studies were reviewed for additional reports of studies meeting the inclusion criteria. The references were imported into a Reference Manager (version 10) database and duplicate records were removed. The remaining records were uploaded to an Excel file for subsequent selection of references relevant to the investigation.

Selection criteria. Studies were eligible for inclusion if they assessed the effectiveness of nonpharmacologic strategies for reducing fatigue in adults diagnosed with SLE, even if fatigue was not a primary outcome measure. Randomized controlled trials (RCTs), nonrandomized controlled trials (non-RCTs), and observational studies published in English or Spanish were included. Comparison groups could be given standard of care, placebo, no treatment, or alternative treatments.

Studies focused on patients age <18 years, with fewer than 5 study participants or with fatigue results not identifiable from composite data were excluded. Cross-sectional and qualitative research designs, reviews, meeting abstracts, and protocols were also excluded.

Screening process. The study selection process was conducted by 2 independent reviewers in order to reduce the possibility of rejecting relevant articles. The reviewers followed the blinded and structured hierarchical strategy: first, a screening of titles and abstracts; second, a comprehensive reading of full-text articles selected in the first phase; and third, a definitive selection of studies fulfilling the pre-determined inclusion and exclusion criteria. Differences between reviewers were resolved through discussion with the research team until consensus was reached.

Data collection process and quality assessment. A data extraction form was developed by the authors, pilot tested on 2 studies, and refined accordingly. One author extracted the following data from the included studies: study design, methodology, participants (selection criteria, demographics, and comorbidities), interventions and results for incidence, severity, impact, and duration of subjective fatigue. Health outcomes measuring HRQOL, mood or functional ability, when available, were also recorded. A second reviewer subsequently verified the extracted data. If any required information was missing or unclear in the published article, an effort was made to contact authors.

Two reviewers independently assessed the quality of included studies using the criteria of the Scottish Intercollegiate Guidelines Network (12), which is based on a

Table 1. Medline/PreMedline search strategy*

1. exp Lupus Erythematosus, Systemic/
2. Systemic Lupus Erythematosus.mp
3. SLE.tw
4. (Lupus adj5 erythematosus).mp
5. (Lupus erythematosus or Lupus nephritis).tw
6.*Lupus Nephritis/
7. exp Lupus Erythematosus, Cutaneous/or exp Renal Dialysis/or exp Kidney Transplantation/or exp Kidney Failure, Chronic/
8. (Cutaneous lupus erythematosus or Chronic Kidney Failure or kidney failure or Renal Dialysis or dialysis or Kidney Transplantation or transplantation).mp
9. 7 or 8
10. Or/1–6
11. 10 not 9
12.*Fatigue/
13.*Asthenia/
14. (Fatigue or asthenia or tiredness).tw
15. Or/12-14
16.*Rehabilitation/
17.*Psychotherapy/
18.*Physical Therapy Modalities/
19. (Therapy or Rehabilitation or drug therapy or psychology or Therap* intervention* or exercise* or diet therapy or psychotherap*).tw
20. (Physic* adj2 therap*).tw
21. (Psycholog* adj2 (therap* or treatment* or intervention*)).tw
22. Or/16–21
23. 11 and 15 and 22
24. limit 23 to (English or Spanish)
25. remove duplicates from 24

* SLE = systemic lupus erythematosus.

number of key questions that focus on those aspects of the study design with demonstrated significant influence on the validity of the results and conclusions. These key questions vary between studies with different designs, and a range of checklists are used to bring a degree of consistency to the assessment process. Any disagreements between both reviewers were resolved first by verifying the protocol criteria and subsequently by consensus.

Statistical analysis. Stata statistical software (Stata 13) was used for effect size estimations. The effect size (Cohen's *d*) was calculated according to the data provided by each study. The information used to generate Cohen's *d* and correlation values was based upon group differences at the final measurement point for the intervention group (nonpharmacologic intervention) and the comparison group. In a few cases, the articles did not report enough information to calculate the effect size. In these cases, we described the results from the original studies.

RESULTS

The results of the search and selection process followed to identify pertinent references are shown in Figure 1. Among 319 potentially relevant reports initially identified after eliminating duplicates, 12 studies (n = 549), published in English from 1989 to 2012, were finally eligible for inclusion (13–24). Seventeen studies were excluded on the basis of the full paper examination (see Figure 1 for exclusion reasons).

Characteristics of studies. The main characteristics and quality appraisal of selected studies are summarized in Table 2. Over half of the included studies were RCTs (13,14,17–21,23), 1 study was a non-RCT design (15) and 4 studies had a prospective observational design, 2 of them with a control group (16,24) and 2 uncontrolled (18,22).

All studies assessed a single nonpharmacologic intervention and almost every one of them a different intervention. In order to simplify analyses and results presentation, we have grouped interventions into 5 main categories: exercise (15,19–22), behavioral and psychological approaches (13,16,21,23,24), diets (14), acupuncture (17), and phototherapy (18).

Fatigue was the primary outcome measure in 7 trials (13,14,17,19–22,24). A total of 6 different instruments were used to quantify fatigue, with 2 studies using more than 1 measuring instrument (19,20). The most frequently used instruments were the Fatigue Severity Scale (13–15,17,19,21,22), followed by Likert scales (18), and a visual analog scale (20,21,23). Other scales were the Profile of Mood States Subscale for fatigue (20), the Chalder Fatigue Scale (21), the Fatigue Intensity Scale (16), and the Multidimensional Assessment of Fatigue (24).

The results of the methodological quality assessment of the included studies are shown in Table 2. Most of them fulfilled some of the criteria (+) or most of or all (++).

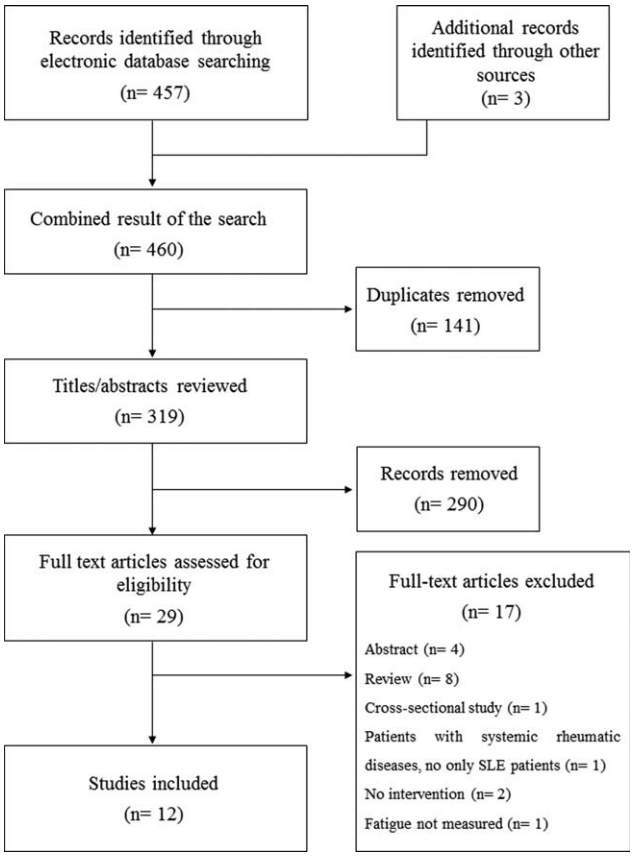

Figure 1. Flow diagram of the selection process of studies. SLE = systemic lupus erythematosus.

Among 6 trials reported as randomized, only 1 specified the method for sequence generation (computer generated) with an adequate allocation concealment (17). Two trials employed some type of blinding procedure: in Greco et al (17), patients and physicians were blinded, and in Austin et al (13) outcome assessment was blinded. Four studies reported withdrawals (14,17,19,23), but only 1 reported a dropout rate higher than 20 percent before completion of the study (23). Intent-to-treat analysis was performed in 3 of those studies (14,21,23).

Samples sizes were small in most studies (14,16–20); only 1 study calculated the sample size (13).

Results for fatigue. Table 3 summarizes the interventions of included studies and their effects on fatigue. All assessed interventions produced statistically significant reductions in fatigue using at least 1 measurement instrument.

Exercise. All 5 included studies tested the effect of aerobic exercise (15,19–22) and a range of strengthening exercises on fatigue (19). In 4 studies, exercise programs were supervised by health professionals or physiotherapists (15,19,21,22). Most interventions were totally or partially home based (19–22).

The duration of exercise programs ranged from 8 weeks to 8 months, with most of them taking place 3 times weekly for 30–60 minutes. The exercise programs included a warm-up initial phase (5–10 minutes) followed by aerobic activity, such as walking, cycling, swimming, or strengthening (10–40 minutes), and an ending cool-down phase (5–10 minutes).

Fatigue decreased significantly in all studies after the intervention, with moderate to high effect sizes. However, the results were not always consistent across the different instruments used to quantify fatigue (15,19–22).

Behavioral/psychological intervention. Five different intervention types, such as cognitive–behavior therapy (16), psychoeducational intervention (23), relaxation (21), self-management (24), and counseling (13) were assessed in the selected studies. All studies found statistically significant reductions in fatigue using at least 1 measurement instrument. All these results reached moderate to high effect sizes.

The number of sessions in the psychological approaches varied widely, from 1 to 36. Session duration was more homogeneous: 2 studies used 2-hour sessions, and 2 studies used a format ranging between 30- and 45-minute sessions. One study did not report details on the number or the duration of sessions (13).

Goodman et al (16) and Sohng (24) used group sessions. Austin et al (13) used phone-guided sessions, and 1 intervention was done at home (21). In 1 study the intervention was carried out with patients and their partners (23). The intervention provider varied among studies, i.e., a counselor (13), an educator (23), a psychologist (16), and a nurse (24). Intervention was not provided by a professional (21) in only 1 study, in that patients were asked to listen to a 30-minute relaxation audiotape at home and were then seen every 2 weeks for a supervised relaxation session (21).

Regarding the content and the complexity of the interventions, Austin et al (13) and Sohng (24) focused on an overview of pharmacologic therapy; exercise and physical function; interpersonal relationships, social activity and support from family; coping with flares, healthy lifestyles, self-care activities; and management of common SLE-related health problems (fatigue, flares, joint pain, mood, and distress). In the study by Tench et al (21), patients received a low complexity intervention. Patients were instructed to listen to relaxation audiotapes in a darkened, warm, and quiet room. In the cognitive–behavior therapy assessed by Goodman et al (16), the treatment guideline included several components, such as a cognitive model approach (understanding the role of depression, anxiety, and stress in chronic disease; identifying, recording, and challenging negative automatic thoughts; thinking about mistakes, assumptions, and core beliefs; cognitive restructuring; and symptom management techniques), a behavioral approach (behavioral experiments, controlled breathing, progressive muscle relaxation, action plans, goal setting, and problem solving), and illness representations (psychoeducation regarding illness identity, consequences, personal consequences, emotional representations, and timeline). Finally, the focus of the Karlson et al study (23) was self-efficacy for SLE management, couples communication about SLE, social support, and problem solving.

Acupuncture. Greco et al (17) assessed the effects of a standardized 10-session acupuncture protocol plus usual medical care designed to reduce pain and fatigue in patients with SLE. In this 3-armed RCT, participants were

Table 2. Main characteristics of selected studies*

Author, year (ref.)	Country	Design	Evidence level†	Followup, weeks	No.	Inclusion criteria	Intervention	
							Experimental	Control
Robb-Nicholson et al, 1989 (20)	US	RCT	+	8	20	Women with fatigue	Aerobic exercise 30 mins, 3 times/wk for 8 wks	Nonaerobic stretching exercises 30 mins, 3 times/wk for 8 wks
Ramsey-Goldman et al, 2000 (19)	US	RCT	+	35	10	Women	Aerobic exercise 50 mins, 3 times/wk, phase 1: 8 wks (with supervision) and phase 2: 28 wks (patients' homes/telephone supervision)	Range of motion/muscle strengthening 50 mins, 3 times/wk, phase 1: 8 wks (with supervision) and phase 2: 28 wks (patients' homes/telephone supervision)
Tench et al, 2003 (21)	UK	RCT	+	12	93	Women age 16–55 years	Aerobic exercise or relaxation 3 times/wk for 12 wks	No training/no relaxation
De Carvalho et al, 2005 (15)	Brazil	Non-RCT	+	12	60	Women age 18–55 years	Supervised cardiovascular training program for 60 mins, 3 times/wk for 12 wks	No training
Yuen et al, 2011 (22)	US	PCS	−	10	50	Sedentary African American women age 18–65 years with moderate fatigue	Home exercise program using the Wii Fit 3 days/wk for 30 minutes for 10 wks	
Austin et al, 1996 (13)	US	RCT	++	26	58	Patients age >21 years with moderate to severe fatigue	Telephone intervention strategies (treatment counseling) for 6 months	Symptom monitoring strategy
Karlson et al, 2004 (23)	US	RCT	+	52	122	Patients age >18 years (plus their partners)	Psychoeducational intervention: a 1-hour session with a nurse educator with subsequent monthly telephone counseling for 6 months	Attention intervention
Sohng, 2003 (24)	Korea	PCS	+	12	41	Patients age >18 years	Self-management 2 hours for 6 wks	No intervention
Goodman et al, 2005 (16)	Australia	PCS	+	12	33	Patients with SLE	Cognitive–behavior therapy for 2 1-hour sessions separated by 20 mins rest break	Usual medical care
Greco et al, 2008 (17)	US	RCT	+	5	24	Patients age >18 years with pain	Standardized acupuncture protocol, 10 sessions over 5 wks	Minimal needling control (plus usual medical care) or control group (usual medical care)
Davies et al, 2012 (14)	UK	RCT	+	6	23	Women age 18–65 years with BMI >25 kg/m^2	Low glycemic index diet (carbohydrate limited to 45 gm/day)	Calorie restricted diet (max 2,000 kcal/day) for 6 wks
McGrath et al, 1994 (18)	US	PCS	−	3	15	Patients taking no known photosensitizers	UVA radiation therapy: 65 kJ/m^2/day for 15 days over 3 consecutive wks	

* RCT = randomized controlled trial; non-RCT = nonrandomized controlled trial; PCS = prospective cohort study; SLE = systemic lupus erythematosus; BMI = body mass index; UVA = ultraviolet A light.
† Scottish Intercollegiate Guidelines Network criteria: + = well-conducted study with a low risk of bias; ++ = high-quality study with a very low risk of bias; and − = study with a high risk of bias.

Table 3. Interventions and their effects on fatigue*

Author, year (ref.)	Interventions	Instrument	Fatigue reduction	Fatigue results	*P*	Cohen's *d*	Effect size
Exercise							
Robb-Nicholson et al, 1989 (20)	Aerobic exercise	POMS fatigue		No significant differences			
		VAS	✓	Significant reduction in exercise group (vs. control)	≤ 0.01	0.83–1.68†	0.37–0.63†
Ramsey-Goldman et al, 2000 (19)	Aerobic exercise/range of motion/muscle	FSS	✓	Significant reduction in both groups, but no significant differences between groups	NR		
Tench et al, 2003 (21)	Aerobic exercise	FSS		No significant differences			
		CFS	✓	Significant reduction in exercise group (vs. control)	0.04	3.87†	0.89†
		VAS	✓	Significant reduction in exercise group (vs. control)	0.05	3.03†	0.83†
De Carvalho et al, 2005 (15)	Cardiovascular training program	FSS	✓	Significant reduction in intervention group, but no significant differences between groups	< 0.001	0.63†	0.30†
Yuen et al, 2011 (22)	Home exercise program (Wii Fit)	FSS	✓	Significant reduction, 18.4% reduction from baseline	0.002	1.05†	0.47†
Psychological interventions							
Austin, 1996 (13)	Treatment counseling and/or symptom monitoring strategy	FSS	✓	Significant reduction for the combined treatment counseling and symptom monitoring strategy groups	0.001	0.64†	0.30†
Tench, 2003 (21)	Relaxation	FSS		No significant differences			
		CFS		No significant differences			
		VAS	✓	Significant reduction in relaxation group (vs. control)	0.05	3.06†	0.84†
Karlson et al, 2004 (23)	Psychoeducational intervention	VAS	✓	Significant reduction in psychoeducational group (vs. control)	0.02	0.5†	0.24†
Sohng, 2003 (24)	Self-management	MAF	✓	Significant reduction in self-management group (vs. control)	0.049		
Goodman et al, 2005 (16)	Cognitive–behavior therapy	FIS	✓	Significant reduction	< 0.02		0.27
Acupuncture							
Greco et al, 2008 (17)	Standardized acupuncture protocol	FSS	✓	Significant reduction in acupuncture and minimal needling groups (vs. control)	NR		
Diet							
Davies et al, 2012 (14)	Low glycemic index diet or calorie restricted diet	FSS	✓	Significant reduction in both groups, but no significant differences between groups	< 0.03	0.47–0.18†	0.23–0.09†
Phototherapy							
McGrath et al, 1994 (18)	UVA radiation therapy	Likert scale, 0–3	✓	Significant reduction	< 0.005	4.02†	0.90†

* POMS fatigue = Profile of Mood States, subscale for fatigue; VAS = visual analog scale; FSS = Fatigue Severity Scale; NR = not reported; CFS = Chalder Fatigue Scale; MAF = Multidimensional Assessment of Fatigue; FIS = Fatigue Intensity Scale; UVA = ultraviolet A light.
† Values were calculated according to the data available.

randomly assigned to receive acupuncture, minimal needling (which involves shallow insertion of needles on body areas that are not known to correspond to acupuncture), or usual care.

A statistically significant improvement of fatigue was obtained in both the acupuncture and minimal needling groups, with comparable effect sizes and clinical benefits (defined as 30% or greater reduction in symptoms). Also, an enhancement of vitality was obtained in the minimal needling group according to the Short Form 36 health survey.

Diet. One small RCT (n = 23) assessed the effectiveness of 2 different diets, a low glycemic index (GI) diet and a calorie-restricted diet, to reduce the fatigue in patients with SLE and explored the potential benefit of weight loss on this symptom (14).

In the low GI diet, the carbohydrate intake was limited to 45 gm per day of low GI food, without restricting the consumption of fat and protein. There was no calorie restriction and the estimated composition of the diet was 10–15% of daily calories from carbohydrates, 25% from proteins, and 60% from both saturated and unsaturated fats. The control group received a conventional low-calorie diet with a restriction of 2,000 kcal per day, approximately 50% of calories from carbohydrates, 15% from proteins, and 30% from fats.

Both diets reached statistically significant reduction in fatigue (mean ± SD 4.9 ± 0.9 to 4.4 ± 1.2 in the low GI diet group and 4.7 ± 1.5 to 4.4 ± 1.7 in the low-calorie diet group) from baseline, with a moderate effect size for low GI diet and a low effect size for low-calorie diet. Also, significant weight loss occurred in both diet groups (low GI diet group mean ± SD 3.9 ± 0.9 kg, and low-calorie diet group 2.4 ± 2.2 kg) (14).

Ultraviolet radiation. McGrath et al (18) assessed a daily low dose of dermal ultraviolet A radiation, 5 days a week, for 3 consecutive weeks, in a small sample of patients (n = 15) with SLE, resulting in a significantly decreased score for fatigue after the intervention.

DISCUSSION

The primary goal of this systematic review was to examine the effects of nonpharmacologic therapeutic interventions for decreasing fatigue in adults with SLE. Five categories of interventions were identified among the included studies: exercise, behavioral and psychological approaches, diet, acupuncture, and ultraviolet irradiation therapy.

The analysis of the selected studies revealed that aerobic exercise is an effective procedure to reduce fatigue in patients with SLE. However, although all studies reported data supporting a decrease in fatigue, the results were not always consistent across the different instruments used to quantify the actual reduction. Neill et al (7) suggested that the principles for appropriate exercise programs in cancer-related fatigue (25,26) could be applied to chronic autoimmune conditions, including starting exercise early in the disease course or following disease flare, beginning with low-intensity activities and avoid provoking symptoms, combining aerobic and resistance training whenever possible, progressively increasing intensity, and performing exercise at least 3 times weekly for 15–30 minutes as tolerated. The results of this review support the proposition that a number of exercise-based interventions improve fatigue (15,19–22). Based on such results, a variety of aerobic exercise, such as walking (15,20,21), jogging (20), cycling (20,21), swimming (21) or even using Wii Fit (22), can be recommended on a regular basis in order to reduce fatigue in lupus patients. However, it remains difficult to draw definitive evidence-based conclusions regarding what specific exercise protocol is the most beneficial.

A number of psychological interventions also appeared effective in reducing fatigue in patients with SLE. They included cognitive–behavior therapy, psychoeducational programs, relaxation, and self-management, with most studies concluding that fatigue decreased (16,21,23,24). No differences were observed in 1 study between active counseling and placebo (consisting of symptom monitoring), but lower fatigue scores for both the intervention group and the control group were encountered (13). Therefore, psychological interventions could help SLE patients to improve management capacities, including coping abilities, although the broad variety of psychological interventions makes it difficult to reach definitive conclusions regarding the effectiveness of the therapies and the best approach. This indicates the need for further research to evaluate the effects and cost-effectiveness of the different modalities of psychological interventions.

The results reported with diet (14) and ultraviolet A irradiation (18) are promising. However, it seems premature to confirm their efficacy in improving fatigue. On the other hand, no differences between acupuncture and placebo were observed (17).

In order to avoid selection bias when performing the systematic review, a set of inclusion and exclusion criteria were pre-established. An exhaustive search using multiple databases was followed by an independent evaluation of all retrieved papers by 2 reviewers. However, this systematic review is not free from limitations. First, only a limited number of studies evaluating different nonpharmacologic interventions for decreasing fatigue in adults with SLE were identified. Furthermore, several sources of heterogeneity were present among the included studies. A wide range of intervention procedures, designs, and outcome-measuring instruments, as well as different followup intervals, were found. Other limitations are the small sample sizes of the trials and the lack of controlling for possible co-interventions that could also improve fatigue, such as treatment with vitamin D, iron, or hydroxychloroquine. Finally, this systematic review was limited to studies written in English and Spanish.

In summary, studies on nonpharmacologic interventions suggest at least some effect in reducing fatigue of patients with SLE. However, methodological differences between studies, mainly the diversity of interventions and instruments for quantifying fatigue, make it difficult to draw solid conclusions. Consequently, more studies are needed to verify the promising results shown in this review in order to recommend specific interventions to

treat this frustrating and limiting symptom affecting most patients with SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. del Pino-Sedeño had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Del Pino-Sedeño, Trujillo-Martín, Ruiz-Irastorza, Cuellar-Pompa, Serrano-Aguilar.

Acquisition of data. Del Pino-Sedeño, Trujillo-Martín, Cuellar-Pompa, de Pascual-Medina.

Analysis and interpretation of data. Del Pino-Sedeño, Trujillo-Martín.

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