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Review

Fatigue in multiple sclerosis: A scoping review of pharmacological and nonpharmacological interventions

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Abstract

Introduction: Fatigue is a highly prevalent symptom in people with multiple sclerosis. It demands careful assessment and prompt intervention to improve their quality of life and overall burden of disease. This scoping review aims to provide a comprehensive synthesis and update of the existing evidence on the effectiveness of different pharmacological and nonpharmacological interventions for multiple sclerosis (MS)-related fatigue.

Methods: To ensure the transparency and quality of the articles chosen for this scoping review, the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols extension for Scoping Reviews was used. Exclusively randomized controlled trials published between 2016 and 2023 were included.

Results: Twenty-eight articles were analyzed. We found that pharmacological interventions are few and have included the use of Amantadine, Ondansetron, Methylphenidate, and Modafinil, with little effects on fatigue. Nonpharmacological interventions are diverse and include cognitive behavioral therapy, guided imagery, phototherapy, exercise, brain stimulation, and lavender administration with evidence of a statistically significant decrease in fatigue.

Conclusions and Discussion: Current evidence on the effectiveness of pharmacological and nonpharmacological interventions is inconclusive. Lack of knowledge of the pathophysiology of fatigue limits its prevention, control, and management recommendations. A comprehensive and interdisciplinary approach is required to manage this symptom in patients with MS.

Keywords: Fatigue, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is an autoimmune-mediated, chronic, neurodegenerative disease of the central nervous system.[1,2] It affects 2.8 million people worldwide, mainly young adults between the ages of 20 and 40 years. It manifests with focal neurological signs and symptoms that compromise locomotion, vision, sensory perception, cognition, gait, coordination, among others.[3] Fatigue, defined as "*a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities*,"[4] is one of the most prevalent symptoms in patients with MS.[5] It has been reported to have a prevalence in this population of 36.5%–97%.[6] It generates a negative impact on the quality of life of patients[7] compromising their physical, psychosocial, and cognitive domains, leading to high costs for the health system.[8]

The physiopathology associated with fatigue in MS can be divided into primary and secondary. Regarding primary fatigue, different theories have been proposed. There are immune mechanisms mediated by cytokines (especially IL-6 and TNF-alpha), monocytes, and

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microglia. These alterations in cytokines impact neuronal signaling, monoaminergic pathways, and neuronal metabolism. Furthermore, cytokines can alter the neuroendocrine system in the hypothalamic–pituitary–adrenal axis, stimulating cortisol production.[9] Additionally, typical white matter lesions in MS can lead to impaired nerve conduction, reduced axonal transmission, and disruption of communication between centers related to planning, execution, and motivation. Also, gray matter lesions that affect connections and neural circuits result in a loss of the ability to perform precise movements, thus requiring greater energy expenditure and consequently increasing fatigue. Moreover, lesions in the brainstem nuclei can lead to a reduction in neurotransmitters, particularly dopaminergic, serotonergic, and noradrenergic, which contributes to decreased motivation and mood, further exacerbating fatigue.[9] In contrast, the secondary mechanism is associated with concomitant circumstances or diseases, such as anemia, thyroid disturbances, sleep disorders, and poor physical fitness.[10] The poorly understood and heterogeneous pathophysiology has been a barrier to the development of effective treatments for managing fatigue. Currently, pharmacological and non-pharmacological strategies have been developed that aim to impact the mechanisms associated with primary fatigue. The results of these studies are controversial, making the management of fatigue one of the most complex and challenging issues. Pharmacological strategies, such as amantadine, modafinil, and methylphenidate, have been used to manage fatigue, based on their effects on the dopaminergic and noradrenergic systems[9]; however, some studies have documented that these molecules are not superior to placebo in improving fatigue.[11] These medications only address one cause of fatigue, and additional alterations associated with fatigue remain unaddressed. Other nonpharmacological interventions, such as transcranial direct current stimulation (tDCS), have been investigated and show a recommendation level between high and moderate for managing fatigue in MS, impacting cortical excitability.[12]

Miller and Soundy conducted a systematic review up to 2016 to provide evidence-based recommendations for the treatment of fatigue in people with MS. They found that nonpharmacological interventions, such as energy conservation techniques and exercise, could improve fatigue in the context of MS. Moreover, psychobehavioral interventions demonstrated potential effectiveness, although the available information remains limited. Conflicting evidence was found regarding pharmacological treatments, particularly with amantadine and Prokarin; however, modafinil showed potential benefits.[13] This article highlights the potential benefits of both pharmacological and nonpharmacological interventions, though stronger evidence is still needed to make more robust clinical recommendations. Therefore, the purpose of this review is to update the findings from 2016 to 2023, aiming to assess whether other pharmacological and nonpharmacological strategies and additional evidence have emerged that could lead to new recommendations and changes in clinical practice.

Methods

To synthesize the published evidence on the pharmacological and nonpharmacological interventions for MS-related fatigue, an initial Systematic Review was proposed for the development of this study. However, due to the heterogeneity of the interventions, methods to study fatigue, and results, the research team decided to conduct a scoping review. This type of review leads to identifying knowledge gaps and types of available data on a specific topic[14] which were aligned with the intended purpose of this study. This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols extension for Scoping Reviews (PRISMA-ScR) methodology[15] in order to facilitate the transparent reporting of the available data.

The protocol of the study was registered in the Open Science Framework registries for Scoping Reviews under the registration DOI: https://doi.org/10.17605/OSF.IO/EUCJA.

Eligibility criteria

The researchers conducted independent searches covering two time periods as follows: from the deadline of the Miller and Soundy review (May 2016) until December 2023. Search strategies (Table 1) were established by an experienced researcher and discussed with the team for additional refinement. Search was performed on three databases containing medical and psychological information: PubMed, Academic Search Complete/EBSCO, and ScienceDirect. Articles based on clinical trials (CT), randomized controlled trials (RCTs), and experiments written in English and Spanish were included. The selection of the articles was based on the title and abstract. Pilot studies were excluded as well as gray literature. Studies that involved adult patients diagnosed with MS, with the presence of fatigue, independent of gender, type of sclerosis, stage of disease, and degree of disability were included. For

Table 1. Search strategies.

	Multiple sclerosis	Fatigue	Intervention
Controlled Vocabulary	"Multiple sclerosis" [Mesh] "Multiple Sclerosis, Relapsing-Remitting" [Mesh] "Multiple Sclerosis, Chronic Progressive" [Mesh]	"Fatigue" [Mesh]	"Psychosocial intervention" [Mesh] "Drug therapy" [Mesh] "Complementary therapies" [Mesh] "Controlled Clinical Trial" [Mesh] "Randomized Controlled Trial" [Mesh]
Free text	Multiple sclerosis	Fatigue	Pharmacologic intervention Nonpharmacologic intervention
Filters	**Multiple Sclerosis:** (Multiple Sclerosis OR Multiple Sclerosis relapsing-remitting OR Multiple Sclerosis Chronic Progressive)	**Fatigue:** Fatigue	**Pharmacologic Intervention:** (Drug Therapy [MeSH] OR pharmacologic intervention OR Controlled Clinical Trial [Mesh] OR Randomized Controlled Trial [Mesh]) **Nonpharmacologic intervention:** (Psychosocial intervention [MeSH] OR Complementary therapies [MeSH] OR Non-pharmacologic intervention OR Controlled Clinical Trial [Mesh] OR Randomized Controlled Trial [Mesh])

the methodological quality, three researchers simultaneously evaluated the full text using the Joanna Briggs Institute guidelines. The PRISMA diagram illustrated in Figure 1 exhibits the process used to initially identify 5389 records to finally include 26 RCT studies in this review. Table 2 details the inclusion and exclusion criteria for the selection of articles.

The database search yielded 5389 records. Of these, 5248 were excluded due to duplication or failure to meet the inclusion criteria based on the title and abstract. Out of the 87 eligible articles, 59 had research designs that did not meet the inclusion criteria, including pilot studies, observational studies, studies without a control group, without sample randomization, or with low-quality randomization processes. In one study, fatigue was not assessed, and in another, the patients had tuberous sclerosis.

Data extraction

The careful reading of each of the articles included in this scoping review allowed us to extract relevant data that provided insights into both pharmacological and nonpharmacological interventions for managing fatigue associated with MS. As a result, the researchers created an analysis matrix (Table 2) where the following information was recorded: authors, year of publication, journal, study objective, study design, population and sample, MS type, country of the sample's origin or where the study was conducted, instruments used to measure fatigue, fatigue treatment or interventions utilized, and intervention outcomes on fatigue: fatigue behavior (increase, decrease, or no change), previous and posterior score, and p value. Each of the articles was read, and data were extracted and charted by two researchers to ensure the reliability of the recorded information.

Results

Demographic characteristics

A total of 1819 participants were included in the studies reviewed, with the majority of the reported being female (73.99%; $n = 1346$). Most of the studies' mean age ranged between 40 and 50 years. Fifteen of the studies included patients with Relapsing-Remitting MS (RRMS), seven studies included both phenotypes (RRMS and progressive forms). All the studies were RCTs.

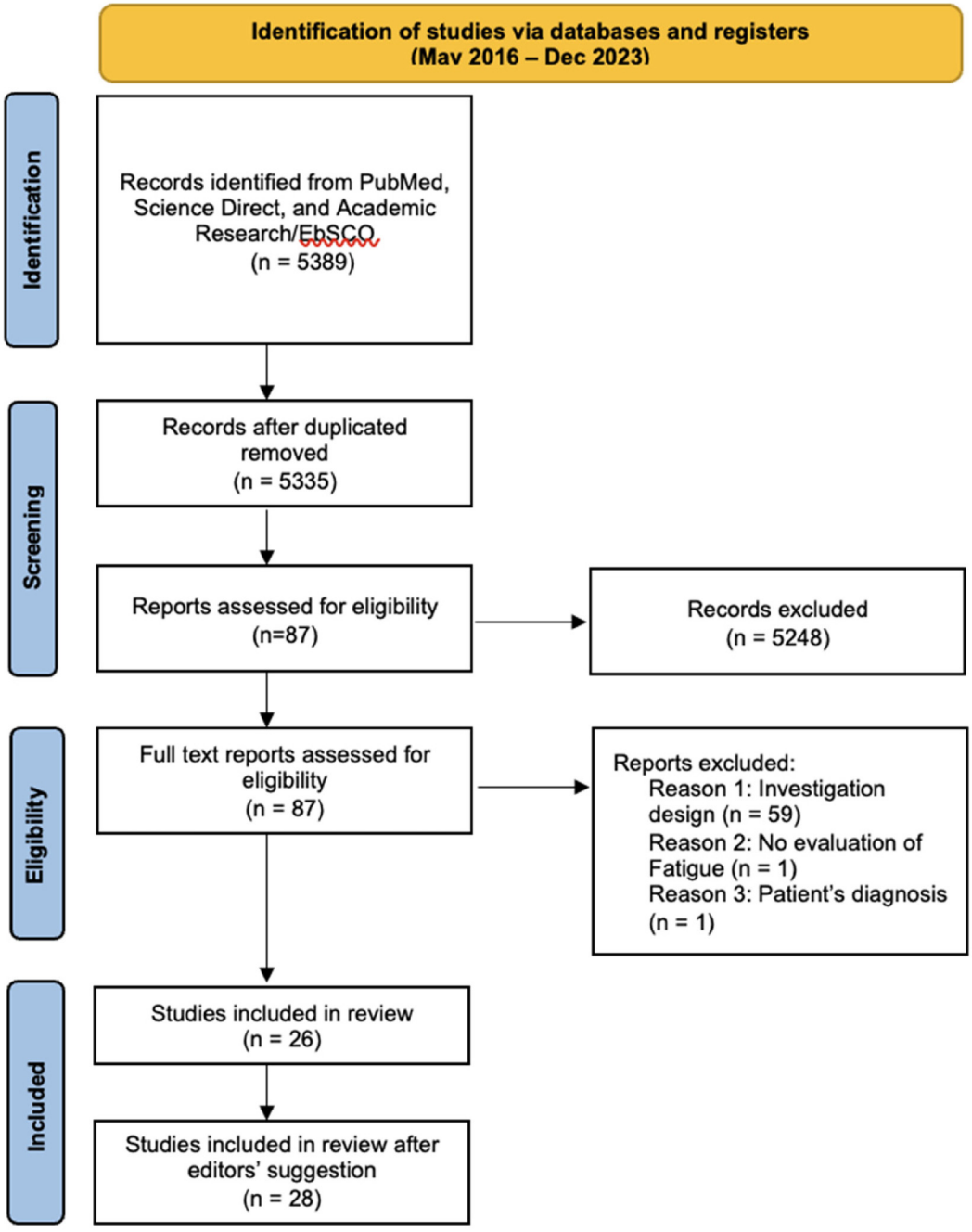

Figure 1. PRISMA flowchart.

Fatigue measures

The most predominantly used measure for Fatigue in the studies was the Fatigue Severity Scale (FSS) (17 studies), followed by the Modified Fatigue Impact Scale (MFIS) (12 studies). Other measurements used were the Visual Analogue Fatigue Scale (VAFS), followed by the Fatigue Scale for Motor and Cognitive Function (FSMC), Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue short form, Fatigue Impact Scale (FIS), and the Fatigue Assessment Scale and the Checklist individual strength (CIS20r) subscale for fatigue severity.

Checklist Individual Strength subscale fatigue severity is a self-report instrument that measures four dimensions of fatigue (severity, decrease in motivation, concentration, and activity) to report the

Table 2. Inclusion and exclusion criteria considered for the selection of articles.

Inclusion criteria	Exclusion criteria
Adults patients	
Multiple sclerosis diagnosis	Physical or psychiatric comorbidities that may exacerbate the experience of fatigue
All multiple sclerosis phenotypes	
Any stage of disability	
Presence of fatigue assessed as a research outcome	Presence of fatigue related to other diseases or treatments (e.g., fatigue related to cancer or its treatments).
Use of pharmacological interventions for fatigue management	Use of pharmacological interventions for purposes other than treatment of fatigue.
Use of nonpharmacological interventions for fatigue management	Use of nonpharmacological interventions for purposes other than treatment of fatigue.
Study design: clinical trials (CT); randomized controlled trials (RCT); experimental studies	Pilot studies
Language: English and Spanish	

perception of fatigue intensity. Fatigue Impact Scale is a three-dimensional (cognitive, physical, social) self-report instrument designed by Fisk et al.[16] to measure the extent to which fatigue has caused problems for people with MS, through 40 items. Modified FIS is a 21-item version of the FIS developed to be used when responding to the full version may be exhausting for patients.[17,18] Patient-Reported Outcomes Measurement Information System fatigue short form is a multidimensional (fatigue, physical functioning, pain, emotional distress, social role participation) self-report instrument that enhances communication between patients and healthcare professionals, designed for researching the impact of variables such as fatigue on the quality of life of people with chronic illnesses, so that the measurement of reports and quantification of changes in this variable can be optimized.[19] Specifically, it differentiates two dimensions of fatigue: experience measured through the topography of the response (intensity, frequency, and duration) and its impact on social, physical, and mental activities.[20] Fatigue Severity Scale is an unidimensional brief self-report instrument, created by Krupp et al. to measure fatigue in people diagnosed with MS or systemic lupus erythematosus and to measure the impact of fatigue by identifying the degree of its severity.[21]

Intervention categories

After careful review, interventions were grouped into two broad categories: (1) Pharmacological ($n = 2$) and (2) Nonpharmacological ($n = 26$). Pharmacological interventions (Table 2) included the use of amantadine, modafinil, methylphenidate, and ondansetron. Due to the heterogeneity of the studies in the Nonpharmacological category, three subgroups were established to classify the interventions as follows (a) psychological, (b) exercise and other interventions, and (c) brain stimulation.

Psychological interventions ($n = 5$) (Table 3) included those based on psychological intervention approaches, exercise, and other interventions ($n = 17$) (Table 4) used diverse therapeutic methods ranging from exercise to the use of lavender. The last category was the use of brain stimulation interventions ($n = 4$) (Table 5), including pulsed electromagnetic field, and transcranial direct current stimulation.

Pharmacological interventions

Characteristics. Two published articles were found to evaluate the use of pharmacological interventions to treat fatigue in MS patients (Table 6). A total of 194 individuals were included in these studies, with one involving patients with RRMS. These randomized crossover CTs assessed treatment sequences of 4–6 weeks with a washout period of two weeks, alternating the use of the following interventions: amantadine, modafinil, methylphenidate, ondansetron, and placebo.

Measurements and findings. One of the studies[22] assessed fatigue through the FSS evaluating the score before and four weeks after each treatment. Significant results were found for the use of

Table 3. Psychological interventions.

Author	Year of publication	Journal	Study objective	Study Design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
van den Akker et al.[15]	2018	*Journal of Psychosomatic Research*	To investigate which psychological factors mediate change in fatigue during and after CBT	RCT	91(70 female / 21 male) Age: 50.6 (8.3) years (CBT) Age: 46.4 (11.6)(control)	RRMS PPMS SPMS	Netherlands	CIS20r	Cognitive Behavioral Therapy	CBT improved fatigue perceptions, increased physical activity, less sleepiness, less helplessness, and improved physical functioning.	42.86	T8: 33.50 (10.39) T16 (Post Intervention): 33.97 (11.20) T26: 36.90 (12.13) T52: 38.92 (9.69)
Hugos et al.[17]	2019	*Multiple Sclerosis Journal*	To evaluate the long-term effect of Fatigue Take Control on MS-associated fatigue.	RCT	74 77% female Age: 53 years	NR	United States	MFIS	Self-Management Program, FTC vs control group	Participation in FTC improved self-reported fatigue for up to six months. These improvements were not statistically different between groups ($p = 0.64$, 0.92, and 0.82, respectively)	FTC 47.5 (13.1) Control: 46.2 (11.6)	Program completion: FTC: 43.3 (16.6) Control: 45.3 (12.1) Follow-up three months FTC: 42.2 (17.5) Control 43.3 (13.1) Follow-up six months FTC: 41 (19.2) Control: 43 (13.2) Follow-up 12 months FTC: 38.6 (18.4) Control: 43.7 (12.8)
Case et al.[19]	2018	*Journal of Evidence-Based Integrative Medicine*	Examine the potential of HLGI to enhance self-reported quality of life	RCT	17 No information on gender Age: 50.8 ± 11.5	RRMS	United States	FSS	Healing Light Guided Imagery	Patients who completed HLGI showed significant reductions in fatigue ($p < 0.01$). 24% decrease in fatigue scores (95% CI, 27.6–43.1)	41.9 (12.7)	24% decrease
Beitollahi et al.[18]	2022	*BMC Neurology*	Determining the effect of guided imagery on fatigue, stigma and mood in MS patients	RCT	60 patients 53 female / 7 male Age: 38.40 ± 10.29 (Intervention group) Age: 39.73 ± 9.45 (Control group)	RRMS and progressive phenotypes	Iran	FSS	Guided Imagery	In the intervention group, the mean score of fatigue decreased from 59.72 ± 18.32 to 35.8 ± 16.15, significant reduction in the levels of fatigue ($p < 0.0001$) compared to before intervention	59.72 ± 18.32	35.8 ± 16.15

(continued)

Table 3. Continued.

Author	Year of publication	Journal	Study objective	Study Design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
Motl et al.[16]	2023	*Contemporary Clinical Trials*	Investigated the effectiveness of a theory-based, Internet-delivered, behavioral intervention focusing on physical activity promotion for immediate and sustained improvements in secondary, PROs of function, symptoms, and QOL in MS	RCT	237 female / 32 male Age: 48.8 (9.4) Age: 48.8 (9.4) (Intervention group: BIPAMS) Age: 48.8 (9.5) (Control group: (Wellness for MS; WellMS)	RRMS	United States	FSS MFIS	Behavioral intervention based on Social Cognitive Theory	A sustained reduction in overall fatigue severity ($p < 0.01$) and the physical impact of fatigue ($p < 0.05$) was reported in the BIPAMS condition, but not in the WellMS condition.	BIPAMS: FSS:5.0 (0.1) MFIS-Cognitive (0–40): 17.2 (0.8) —— WellMS: FSS: 4.9 (0.1) MFIS-Cognitive (0–40): 17.0 (0.8)	BIPAMS: Immediate follow up FSS: 4.6 (0.1) MFIS-Cognitive (0–40): 15.6 (0.8) six-month follow up: 4.7 (0.1) MFIS-Cognitive (0–40): 15.3 (0.9) WellMS: Immediate follow-up FSS: 4.9 (0.1) MFIS-Cognitive (0–40): 16.4 (0.8) six-month follow-up: FSS: 4.9 (0.1) MFIS-Cognitive (0–40): 18.3 (0.8)

Table 4. Exercise and other interventions.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
Kargarfard et al.[26]	2018	*Archives of Physical Medicine and Rehabilitation*	"To assess the effects of an eight-week aquatic exercise training program on functional capacity, balance, and perceptions of fatigue in women with MS"	RCT	32 female Age: 36.4 ± 8.2 years old Age: 36.59.0 (intervention group) Age: 36.27.4 (Control group)	RRMS	Iran	MFIS	Aquatic exercise training	Total MFIS score improved in the experimental group ($p < 0.001$)	43.1 ± 14.6	32.8 ± 5.9
Negaresh et al.[29]	2019	*Explore*	"Investigate the effects of exercise training on fatigue and depression in normal and overweight individuals with MS"	RCT	61 Normal weight group = 31 11 females and 6 males (intervention group, $n = 17$) Age: 31.2 ± 3.1 years 9 female / 5 male Overweight group = 30 11 female / 6 males (intervention group, $n = 17$) Age: 32.1 ± 3.3 years 9 females and 4 males	RRMS	Iran	FSS	Exercise training	The exercise conditions had statistically significant improvements for fatigue whereas the control showed no significant changes ($F = 12.7$, $p = 0.00$)	Normal weight: 3.2 ± 0.7 Overweight: 3.6 ± 0.8	-
Callesen et al.[24]	2020	*Multiple Sclerosis Journal*	"To investigate the effects of Progressive Resistance Training and Balance and Motor Control Training on gait performance and impact on fatigue in people with multiple sclerosis"	RCT	71 patients (55 female / 16 male) Age: 52 [30; 46; 58; 75] years BMCT group = 28 23 female / 5 male Age: 51 [31; 43; 56; 75] years PRT Group = 23 16 female / 7	RRMS; PPMS; SPMS	Denmark	MFIS	PRT BMCT	A significant adjusted between-group difference in both BMCT and PRT was seen in fatigue reduction compared to control	BMCT: 40.8 (11.1) PRT: 43.9 (15.8)	BMCT: −11.1 [−15.3; −6.9]* PRT: −12.8 [−17.7; −7.8]*

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Table 4. Continued.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
					male Age: 52 [38; 47; 59; 64] years							
Abonie and Hettinga[21]	2020	*International Journal of Environmental Research and Public Health*	Evaluate the effect of a tailored activity pacing intervention on fatigue and physical activity behaviors in adults with MS.	RCT	21 Intervention group = 11 3 female / 8 male Age: 57.9 ± 8.0 years old Control group = 10 3 female / 7 male Age: 60.9 ± 9.5 years old	RRMS; PPMS; SPMS	United Kingdom	FSS	Tailored Activity Pacing	No significant effect were detected in fatigue severity (Mean difference = −0.36; 95% CI (−1.02–0.30); $p = 0.27$)	4.7 ± 2.0	4.6 ± 1.9
Bilek et al.[30]	2022	*Multiple Sclerosis and Related Disorders*	"Investigate the effect of a regular aerobic exercise program on irisin serum level, depression, fatigue, and cognitive performance in patients with MS"	RCT	32 female Intervention group: 16 Age: 28.31 ± 5.89 years Control group: 16 Age: 32.5 ± 8.75 years	RRMS	Turkey	FIS	Aerobic exercise	A significant improvement was observed in FIS in the Study Group compared to pretreatment ($p < 0.05$)	FIS: 41.00 ± 33.71	FIS: 27.75 ± 27.72
Englund et al.[28]	2022	*Multiple Sclerosis and Related Disorder*	Evaluate the effects of high-intensity resistance training on self-reported fatigue in people with MS.	RCT	71 (62 female / 9 male) Age: 42.1 (9.7) years Group A = 35 28 female / 7 males Age: 40.5 (9.7) years Group B = 36 34 female / 2 males Age: 43.6 (9.6) years Control group = 69 53 female and 16 male	RRMS	Sweden	FSS	HIRT	HIRT leads to clinically relevant reductions in self-reported fatigue	Group A: FSMC: 78.1 (9.4) FSS: 5.6 (0.8) Group B: FSMC: 76.4 (9.7) FSS: 5.3 (0.9)	Group A: FSMC: 67.2 (16.0) FSS: 4.7 (1.3) Group B: FSMC: 66.6 (10.7) FSS: 4.3 (1.2)

(continued)

Table 4. Continued.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
					Age: 43.6 (10.3) years							
Bahmani et al.[27]	2022	*Science & Sports*	"Investigate the effect of home-based aerobic training and vitamin D supplementation on fatigue and QoL in patients with MS during the COVID-19 outbreak."	RCT	38 female Group AT + VitD = 10 Age: 27.7 ± 2.68 years AT group = 9 Age: 26.77 ± 2.27 years Group VitD = 9 Age: 25.44 ± 2.29 years Group C = 10 Age: 28.11 ± 3.62 years	NR	Iran	MFIS (Persian version)	Aerobic Training Diet Vitamin D	After eight weeks, scores of MFIS significantly decreased in all intervention groups ($p = 0.001$)	AT + Vit D: 35.57 ± 4.20 AT: 35.96 ± 4.05 Vit D: 35.20 ± 3.64	AT + Vit D: 29.69 ± 5.46 AT: 30.61 ± 4.35 Vit D: 33.31 ± 2.37
Fleming et al.[23]	2021	*Multiple Sclerosis Journal*	"To quantify the effects of eight weeks of home-based Pilates on symptoms of anxiety, depression, and fatigue among PwMS"	RCT	80 (69 female/ 11 male) Intervention group: 39 36 female and 3 male Age: 46.7 (10.0) years Control group: 41 33 female and 8 male Age: 47.4 (10.2) years	NR	Ireland	MFIS	Home-based pilates	Compared to control, total fatigue was lower for Pilates at week 8 (Mdiff = −10.60, $p \leq 0.007$, $d = 0.81$, 95% CI: 0.32, 1.30). The mean reduction in total fatigue resulted in NNT = 3 (95% CI: 2, 6)	Intervention group: 43.6 ± 9.8	Follow-up week 2: 38.6 ± 11.9 Follow-up week 4: 36.5 ± 14.5 Follow-up six week: 33.3 ± 13.6 Follow-up eight week: 31.0 ± 13.5
Moraes et al.[25]	2021	*Multiple Sclerosis and Related Disorders*	"Examine the effects of hippotherapy on postural balance, functional mobility, self-perceived fatigue and quality of life in people with Multiple Sclerosis"	RCT	33 Intervention group = 17 Control group = 16 No gender or age data were reported	RRMS	Brazil	FSS MFIS	Hippotherapy	Significant improvement in the intervention group (Cohens' $d = 0.57$ to 0.83, all $p < 0.05$), but not in the control group (all $p > 0.05$)	FSS: 5.0 ± 1.6 MFIS: 44.2 ± 19.0	FSS: 4.0 ± 1.7 MFIS: 32.3 ± 18.5
Lysogorskaia et al.[22]	2023	*Annals of Neurosciences*	Examine the effect of yoga on symptoms and quality of life in patients with MS vs physical therapy	RCT	36 (30 female/ 6 male) Age: Yoga group: 39 ± 10.4	RRMS PMS, SPMS	Russia	FAS	Yoga Exercise	No statistically significant difference between the groups in terms of improvement in MS fatigue	Yoga: 31.7 ± 6.6 Exercise: 29.0 ± 6.8	Yoga: 28.4 ± 4.9 Exercise: 27.1 ± 6.2

(continued)

Table 4. Continued.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
			(exercise therapy) and no exercise.		Exercise group: 46.1 ± 11.3 Control group: 46.2 ± 10.4							
Rezaeizadeh et al.[33]	2022	*Multiple Sclerosis and Related Disorders*	"Evaluate the effect of MS14 on the physical activity of MS patients."	RCT	80 (73 female / 7 male) Intervention group: 40.49 ± 9.13 years Control group: 38.47 ± 10.21	NR	Iran	FSS	MS14® Persian-medicine derived natural product	Changes of Fatigue Severity Scale ($p = 0.001$) was significant for the MS14 group	46.00 ± 11.69	40.44 ± 13.21
Tramontano et al.[34]	2018	*Restorative Neurology and Neuroscience*	"To investigate the clinical effects of vestibular rehabilitation on balance skills and secondly on fatigue and activity of daily living in highly disabled multiple sclerosis people."	RCT	30 (17 female / 13 male) Age: 50.64 ± 11.73 years (vestibular rehabilitation) Age: 45.77 ± 10.91 years (control)	NR	Italy	FSS	Vestibular rehabilitation (VR)	A significant performance increase in the vestibular rehabilitation group but not in the control group in FSS ($p = 0.007$)	54.6 ± 8	49.2 ± 7.6
Yeni et al.[35]	2022	*Complementary Therapies in Clinical Practice*	"Evaluate the effect of self-acupressure on fatigue in patients with Multiple Sclerosis"	RCT	123 (83 female and 40 male) Age: 41.18 ± 10.72 years old. Acupressure group = 41 26 female and 15 male Age: 40.56 ± 10.83 years Sham group = 40 29 female and 11 male Age: 42.07 ± 10.18 years old Control group = 42 28 female and 14 male Age: 40.95 ± 11.30 years old	RRMS	Turkey	FSS	Self-acupressure	In the 4th week: significant decrease in the mean score of fatigue of the experimental group vs the other two groups (Acupressure:4.15 ± 1.09, Control:5.47 ± 1.11, Sham:5.34 ± 1.14, $p < 0.0001$).	5.54 ± 0.87	Follow-up two week: 4.64 ± 1.03 Follow-up four week: 4.15 ± 1.09

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Table 4. Continued.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
Asghari et al.[32]	2023	*Scientific reports - Nature*	Impact of probiotic SB on inflammatory indexes and oxidative stress indicators and mental health, fatigue, pain, and quality of life in patients with MS	RCT	50(15 male / 35 female) Intervention group 7 male 18 female Age Range: 18–29: 9 30–39: 13 ≥40: 3 Control group 8 male 17 female Age range: 18–29: 9 30–39: 13 ≥40: 3	RRMS	Iran	FSS	Probiotic SB	FSS decreased in the probiotic group after four months of supplementation vs the placebo group after (probiotic: −5.55 ± 5.59 vs. placebo: −2.35 ± 4.92, $p = 0.01$)	28.50 ± 14.29	22.95 ± 10.86
Moravejolahkami et al.[31]	2020	*International Journal of Food Properties*	"Investigate the effects of a modified form of Mediterranean Diet (mMeD), instead of the previously tested multimodal interventions, on QOL and fatigue severity in MS volunteers."	RCT	147 Diet group = 68 57 female and 11 male Age: 38.6 ± 8.6 years old Control Group = 79 65 female and 14 male Age: 40 ± 9.6 years	RRMS	Iran	FSS VAS	Mediterranean Diet	The mean difference for chronic fatigue (measured by FSS) was Significant decreased ($p < 0.001$) in the mMed group after six-month follow up.	VAFS: 5.1 ± 2.2	Three-month VAFS: 5.0 ± 1.0 End of trial VAFS: 5.4 ± 0.5 six month: FSS: decrease 9.8 ± 11.5
Motaghi et al.[36]	2022	*Multiple Sclerosis and Related Disorder*	"Investigate the efficacy of lavender capsule on improving fatigue symptoms in MS patients."	RCT	48 (41 female and 7 male) Intervention group = 24 20 female and 4 male Age: 36 ± 8.10 years Control group = 24 21 female and 3 male Age: 37.91 ± 7.36 years old	RRMS	Iran	MFIS	Lavender	Significant reduction ($p < 0.001$) in the intervention group compared to the control group after the intervention	Lavender group: 40.56 (7.63) Control group:41.43 (7.89)	Lavender group:7.04 (4.91) Control group:38.17 (9.78)

(continued)

Table 4. Continued.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
Mateen et al.[20]	2020	*Journal of Neurology*	"Determine whether bright white LT was feasible and tolerable as an intervention in people with moderate to severe MS-associated fatigue"	RCT	35 (28 female / 7 male) Group BWLT = 20 16 female / 4 male Age: 47.2 years (32–64) Dim red LT group=15 12 female / 3 male Age: 43 years (35–49.5)	RRMS	United States	FSS	Bright White Light Therapy	The BWLT arm, the mean FSS score was reduced to 45.8 after four weeks ($p = 0.04$) of LT and to 44.9 after the washout period ($p = 0.02$, vs baseline. No statistically significant difference between the two study arms ($p = 0.8$)	BWLT:52.600 DLRT:52.867	Six week follow-up: BWLT: 45.8 DRLT 46.7 10 week follow-up: BWLT: 44.933 DRLT: 43.917

Table 5. Brain stimulation interventions.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
Charvet et al.[37]	2018	*Multiple Sclerosis Journal*	To evaluate the effect of tDCS in reducing MS-associated fatigue.	RCT	Study 1: 35 10 females and 5 males (intervention group) Age: 53.4 ± 8.0 years old 13 female and 7 male (control group) Age: 51.0 ± 12.7 years Study 2: 27 8 females and 7 males (intervention group) Age: 44.8 ± 16.2 years 8 females and 4 males (sham group) Age: 43.4 ± 16.2 years	RRMS and progressive (not specified primary or secondary)	United States	FSS PROMIS VAS	RS-tDCS	Study 1: delivered 10 open-label tDCS treatments (1.5 mA; $n = 15$) compared to a cognitive training only condition ($n = 20$). There was modest fatigue reduction in the active group (−2.5 ± 7.4 vs −0.2 ± 5.3, $p = 0.30$, Cohen's $d = -0.35$), Study 2: a randomized trial of active (2.0 mA, $n = 15$) or sham ($n = 12$) delivered for 20 sessions. There was statistically significant reduction for the active group (−5.6 ± 8.9 vs 0.9 ± 1.9, $p = 0.02$, Cohen's $d = -0.71$)	Study 1: PROMIS 26.9 ± 7.6 Study 2: PROMIS 26.6 ± 9.2	Study 1: PROMIS 24.4 ± 6.3 Study 2: PROMIS 21.0 ± 6.4
Granja-Domínguez, et al.[38]	2022	*Brazilian Journal of Physical Therapy*	Determine the effect of low-frequency pulsed electromagnetic field therapy, compared to placebo, on fatigue level, walking performance, depressive symptoms, and quality of life in patients with relapsing-remitting MS.	RCT	44 (38 female and 6 male) Intervention group = 22 19 female and 3 male Age: 40.8 ± 9.1 years Placebo group = 22 19 female and 3 male Age: 42.2 ± 10.9 years	RRMS	Spain	FSS MFIS	Pulsed electromagnetic field therapy	No differences between groups for changes in fatigue symptoms from baseline to end of intervention (mean and 95% confidence interval FSS: −0.6, 95%CI: −1.3, 0.1; MFIS: −5.4, 95% CI: −15.1, 4.4) or at follow-up (FSS: −0.6, 95% CI: −1.4, 0.2; MFIS: −2.1, 95% CI: −10.9, 6.8).	FSS: 5.7 ± 1.1 MFIS: 51.7 ± 15.8	Post intervention FSS: 4.8 ± 1.5 MFIS: 39.9 ± 19.9 three-month postintervention: FSS:4.8 ± 1.6 MFIS: 44.1 ± 19.7
Cancelli et al[65]	2017	*Multiple sclerosis Journal*	To strengthening the reliability of the five-day transcranial direct current stimulation	RCT	Total 10 (8 Female, 2 male) Mean age: 43.2	RRMS	Italy	mFIS	Five-day tDCS in the bilateral whole-body somatosensory cortex	The amelioration of fatigue symptoms after Real stimulation (40% of baseline)	Stimulation: mFIS pre 52.3. Sham:51.3	Stimulation: mFIS post 27.6 Sham:46.0

(continued)

Table 5. Continued.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
			in a randomized, double-blind, Sham-controlled, crossover study, with modified Fatigue Impact Scale (mFIS) score reduction at the end of the treatment as primary outcome							was significantly larger than after Sham stimulation (14%, $p = 0.012$).		
Chalah et al.[68]	2017	*Journal of the Neurological Sciences*	To evaluate the effects of anodal tDCS over the left DLPFC and the right PPC on MS fatigue.	RCT	Total: 10 (6 male, 4 female) mean age: 40.50 ± 11.18 years, age range: 26–63 years.	RRMS (N:9) SPMS (N:1)	France	MFIS VAS FSS	Three anodal tDCS blocks: active stimulation over the left DLPFC active stimulation over the right posterior parietal cortex, and sham stimulation over either cortical site. The blocks consisted of five consecutive daily sessions and were held apart by a washout interval of three weeks.	Active tDCS over the left DLPFC resulted in a significant improvement in FSS	FSS mean score before: 5.1 ± 0.5 MFIS global scores mean score before: 43.6 ± 5.1, MFISphysical (mean score before: 21.6 ± 2.3, MFISpsychosocial subscales (mean score before: 4.1 ± 0.7)	FSS mean score after: 3.3 ± 0.4, $p < 0.01$), MFIS global scores after: 22.4 ± 4.2, $p < 0.05$), MFISphysical, after: 11.6 ± 2.2, $p < 0.01$) and MFISpsychosocial after 0.8 ± 0.3, $p < 0.01$)

Table 6. Pharmacological interventions.

Author	Year of publication	Journal	Study objective	Study design	Population and sample	MS type	Country	Instrument used to measure fatigue	Fatigue intervention	Main outcomes	Pre-Score	Post-Score
Khazaei et al.[13]	2019	*Clinical and Translational Medicine*	Evaluation of the effects of amantadine and ondansetron in Iranian MS patients and comparison between these drugs by using the Persian version of FSS	RCT	53 patients (45 female / 8 male) Age: 54 ± 7.88 years	NR	Iran	FSS (Persian version)	Amantadine Ondansetron	Significant decrease in fatigue severity in amantadine group ($p = 0.002$) and ondansetron group ($p < 0.001$). A significant difference was found between two groups after treatments ($p = 0.026$), amantadine decreased severity of fatigue more than ondansetron	Amantadine: 43.07 ± 10.36 Ondansetron: 43.22 ± 9.67	Amantadine: 37.36 ± 7.87 Ondansetron: 40.00 ± 8.94
Nourbakhsh, et al.[14]	2021	*The Lancet Neurology*	Compare the efficacy of Modafinil, Amantadine, and Methylphenidate with each other and placebo in patients with multiple sclerosis fatigue.	RCT	141 (109 female / 32 male) Age: 46.8 ± 10.7 years	RRMS	United States	MFIS	Amantadine Modafinil Methylphenidate	Nonsignificant effect with any of the treatments were found ($p = 0.20$)	51.3 (49.0–53.6)	Placebo: 40.6 (38.2–43.1) Amantadine: 41.3 (38.8–43.7) Modafinil 39.0 (36.6–41.4) Methylphenidate: 38.6 (36.2–41.0)

RCT: randomized controlled trial; NR: not reported; FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale; RRMS: Relapsing-Remitting Multiple Sclerosis; PPMS: Primary Progressive Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; FIS: Fatigue Impact Scale; FSMC: Fatigue Scale for Motor and Cognitive Functions; FAS: Fatigue Assessment Scale; PROMIS: Patient-Reported Outcomes Measurement Information System; VAS: visual analog fatigue ratings; CIS20r: Checklist Individual Strength subscale fatigue severity; CBT: Cognitive Behavioral Therapy; FTC: Fatigue Take Control; HLGI: Healing Light Guided Imagery; PROs: patient-reported outcomes; QOL: quality of life; BIPAMS: Behavioral Intervention for Physical Activity in MS; PRT: Progressive Resistance Training; BMCT: Balance and Motor Control Training; AT: Aerobic Training; SB: *Saccharomyces boulardii*; BWLT: Bright White Light Therapy; DRLT: Dim red LT; RS-tDCS: Remotely supervised transcranial direct current stimulation; tDCS: transcranial direct current stimulation; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; VAFS: Visual Analogue Fatigue Scale; HIRT: high-intensity resistance training.

amantadine and ondansetron to decrease fatigue; however, Amantadine decreased severity more than ondansetron (43.07 (±10.36) before to 37.36 (±7.87) after treatment vs. 43.22 (±9.67) before and 40.00 (±8.94) after, respectively).

The study performed by Nourbakhsh,[11] evaluated fatigue through the MFIS at week 5 of each study period including placebo, amantadine, modafinil, and methylphenidate. No statistically or clinically significant results were obtained for the use of these treatments. However, there was a significant effect of the treatment on the psychosocial subscale of the MFIS.

Nonpharmacological interventions

Psychological interventions

Characteristics. The five psychological interventions included in this review focused on diverse therapeutic methods, including Cognitive Behavioral Therapy (CBT) ($n = 1$), behavioral intervention based on Social Cognitive Theory ($n = 1$), Fatigue Take Control (FTC) ($n = 1$), and Guided Imagery ($n = 2$) (Table 3) 479 patients were included. Two studies included patients with RRMS and two studies included both phenotypes (RRMS and progressives phenotypes). The mean time of intervention for the studies was 12.0 weeks,[4–24] with the majority ($n = 4$) implementing individual interventions vs. small groups ($n = 1$).

Measurements and findings. Four studies assessed fatigue through the FSS, while the others through the MFIS and the CIS20r. Overall, patients reported improvement in fatigue through most of the interventions, being statistically significant; however, one of them did not report p value. Cognitive behavioral therapy reported a considerable decrease in fatigue,[23] evaluated through the CIS20r, during the first eight weeks of intervention (42.86 (8.46) at baseline vs. 33.50 (10.39) at T8), however, when compared to the control group at week 52, there was no significant difference between groups (38.92 (9.69) in CBT vs. 39.54 (9.01) in the control group). The other study[24] that evaluated a behavioral intervention for physical activity focusing on measuring Patient Reported Outcomes showed significant results with a change of the FSS[1–7] from 5.0 (0.1) to 4.6 (0.1) and 4.7 (0.1) in the immediate and six-month follow up, respectively. Another study[25] reported fatigue scores improving significantly between baseline and follow-ups with the greatest mean change in the intervention group (FTC) at 12 months, being significantly greater than the control group, with a mean improvement of 8.9 points on the MFIS. The guided imagery intervention showed improvement with a decrease of up to 23.91 points in the FSS in the guided imagery intervention with audio files,[26] being statistically significant.

Exercise and other interventions

Characteristics. The majority of studies ($n = 10$) in this category used exercise as a therapeutic approach, including: aerobic exercises, tailored activity pacing, interval exercise training, high-intensity resistance training (HIRT), pilates, progressive resistance training (PRT), aquatic exercise training, and hippotherapy (Table 4) Other interventions included in this category involved acupressure, diet, vestibular rehabilitation, probiotic supplementation, natural products, and the use of lavender and Bright White Light Therapy (BWLT). In total, 988 participants were included in these studies, with 10 of these involving patients with RRMS and 3 with both phenotypes (progressives and RRMS). Most of the interventions were supervised ($n = 11$), while the rest ($n = 6$) were self-administered.

Measurements and findings. Several methods were used to evaluate fatigue, with FSS ($n = 10$) and MFIS ($n = 6$) being the most used, followed by FSMC, FIS, FAS, and VAFS. Most of the exercise intervention studies showed statistically significant results when compared to control groups, except for the Tailored Activity Pacing Intervention[27] and yoga intervention,[28] which showed no significant results. Exercise intervention studies that evaluated fatigue through the MFIS demonstrated a decrease in fatigue with the greatest mean decrease in the Home-based pilates intervention[29] 43.6 ± 9.8 at baseline vs. 31.0 ± 13.5 at week 8 of follow-up, followed by the PRT intervention[30] with a decrease of -12.8 [-17.7; -7.8] and the Hippotherapy intervention[31] 44.2 ± 19.0 to 32.3 ± 18.5. Aquatic exercise training[32] showed a decrease from 43.1 ± 14.6 to 32.8 ± 5.9, while the AT + Vitamin D intervention[33] 35.57 ± 4.20 to 29.69 ± 5.46. Those in which exercise interventions were evaluated through the FSS included the HIRT[34] and exercise training[35] which showed a decrease in fatigue mean scores. One article on aerobic exercise[36] was evaluated through the FIS with a change from 41.00 ± 33.71 to 27.75 ± 27.72. The strategies, involving those not-related to exercise, that applied the FSS included the use of Mediterranean Diet[37] with a decrease of 9.8 ± 11.5

at six-month follow-up, the use of *Saccharomyces boulardii* Probiotic[38] from 28.50 ± 14.29 to 22.95 ± 10.86, the use of a Herbal derived product MS14[39] (46.00 ± 11.69 to 40.44 ± 13.21)[40] Vestibular rehabilitation and Self-Accupressure.[41] The use of Lavender[42] showed a statistically and clinically significant decrease in the MFIS from 40.56 (7.63) to 7.04 (4.91). Lastly, the BWLT group reported a reduction in the FSS after four weeks of therapy, but no statistically significant differences were reported between the BWTL and control group study arms ($p = 0.8$).

Brain stimulation interventions

Characteristics. There were four RCTs identified in this category, including 126 patients, based on the use of tDCS ($n = 3$) and the use of pulsed electromagnetic field therapy ($n = 1$) (Table 5). Two studies included RRMS and progressive phenotypes and 2 studies included patients with RRMS. The mean time of intervention was 2.35 weeks.[4,5]

Measurements and findings. Methods used to evaluate fatigue include FSS, PROMIS, mFIS, and VAFS. Fatigue scores evaluated through the FSS showed statistically significant results for intervention with tDCS[43] with a decrease from 26.6 ± 9.2 to 21.0 ± 6.4 between baseline and posttreatment analysis. Moreover, five-day tDCS in the bilateral whole-body somatosensory cortex showed improvement of fatigue symptoms compared to placebo group measured by the mFIS (score preintervention: 52.3, score post intervention: 27.6)[65] and active tDCS over the left DLPFC resulted in a significant improvement in FSS.[68] However, in the pulsed electromagnetic field therapy,[44] there were no differences in changes between the intervention and the placebo group.

Discussion and conclusions

The findings show that nonpharmacological interventions for MS-related fatigue could be effective in reducing or alleviating fatigue symptoms. Given the heterogeneity of nonpharmacological options and the diversity of possible mechanisms involved in fatigue, psychological aspects must be considered in this experience. Expectations are considered as mediating variables involved in the experience of feeling relieve[45] and, consequently, to the concepts of placebo and placebo effect. Literature refers that about 40% of prescriptions act as placebo.[46] People with MS experience suffering,[47] frustration with therapeutic failure,[48] the unknown etiology of their disease,[49] progression, and general discomfort inherent to the course of the disease or treatment.[50] With these conditions, expectations about a treatment that can alleviate a disabling symptom are desirable and quickly established.[45]

Placebo has nonspecific mechanisms of action, with explanations being broad, including behavior similar to that of conventional drugs (e.g., latency time, maximum effect, dose–response relation, tolerance, addiction, adverse effects, and reinforcing or reducing the effects of other drugs).[51] Mechanisms of brain empathy[52] resulting from the activation of nuclei of the prefrontal cortex, the cerebral amygdala, the limbic system, as well as the increased release of dopamine[53] and oxytocin[54] explain the learning of expectations of healing and pleasurable experiences. In fact, placebo will depend on psychological (individual differences) and brain responses in a therapeutic context, which affects the construction of meanings and the perception of well-being. Oxytocin would have a significant effect on decreasing anxiety and increasing confidence.[55] For example, the study by Motaghi et al. highlights the effect of lavender in decreasing MS-related fatigue and, at the same time, this substance has been described to have an anxiolytic effect,[56] which could be mediating the experience of fatigue relief.

Psychological interventions such as psychoeducation and CBT contribute to acquiring knowledge and developing or optimizing coping skills that modulate stress and fear and increase self-efficacy, which in turn contributes to modifying the interpretation of the experience associated with fatigue.[57] Psychoeducation allows addressing emotional concerns caused by the distress of being overwhelmed or confused[58] due to fatigue, and improves the perception of emotional well-being.[59] Mindfulness is a technique that contributes to reducing anxiety and achieving greater states of relaxation, results that also increase the perception of emotional well-being and quality of life, and can contribute to the transformation of the emotional experience[60] associated with fatigue.

The effects of all nonpharmacological interventions are indirect.[61] That is, they increase the perception of well-being and quality of life through various mechanisms such as the reduction of symptoms and tension, increased perception of control, heightened positive expectations, and even the production of endorphins, as seen with exercise and physical activity, which can also improve endurance and

energy, and whose practice may be associated with better mental health and greater psychological well-being.[62] It is common for people to believe that interventions of this type do not produce side effects, leading to greater acceptance and trust, in contrast to what occurs with pharmacological treatments, which have a clear aversive association with these effects.

Previous studies largely align with our findings. Miller et al.[13] reported that nonpharmacological interventions led to improvements in fatigue, including resistance training, aerobic training, combined exercise training, CBT, energy conservation programs, and acupuncture. However, only yoga showed a significant reduction in this symptom. In fact, Harrison et al.[63] published a meta-analysis based on publications from nine databases up to August 2018, examining the most promising exercise-based and behavioral interventions for treating fatigue in MS. They found that all types of exercise have moderate to high effects in reducing this symptom, with balance exercises being superior. CBT also outperforms energy conservation programs, with strong supporting evidence.

One of the novel nonpharmacological strategies is tDCS**.** Some of the hypotheses for why this intervention may be effective involve their impact on different synaptic pathways and structural levels. In fact, it can modulate different cortical and subcortical networks, glutamatergic neurons and reduce GABA transmission.[64] Moreover, it can modulate the axonal membrane potential, contributing to long-term changes such as alterations in the function and conformation of axonal components such as ion channels and the inflammatory environment.[64]

The results regarding tDCS are heterogeneous, which can be explained by methodological differences among the studies. Firstly, different cortical areas have been targeted, such as bilateral motor or sensory areas,[65] which appear to be effective, whereas stimulation of the right posterior parietal region seems ineffective, and the response to left dorsolateral prefrontal stimulation has been inconsistent. Furthermore, protocols vary in terms of current intensity and session duration; greater positive effects are observed when sessions are repeated.[64] Conducting studies with larger samples and standardized protocols will help determine the optimal approach for tDCS. This field holds significant potential for future research.

Regarding pharmacological interventions, there are few studies published to date, and the results have not documented a clinically significant impact. In addition to pharmacological therapies currently being investigated to treat fatigue, disease-modifying therapy (DMT) could impact fatigue by reducing inflammation, disability, and the number of brain lesions. However, very few RCTs have included fatigue as an outcome of DMT. In fact, fatigue as an outcome of DMT RCTs is underrepresented, there are few studies evaluating it, and the data are suboptimal. Another point to strengthen in research is for RCTs to include fatigue as an outcome.[66]

The evidence so far has shown that the efficacy of pharmacological therapy is heterogeneous. Miller and Soundy[13] found that amantadine, pemoline, and carnitine did not lead to significant improvement in fatigue, although pemoline combined with acetylsalicylic acid showed positive results in one study. Modafinil demonstrated improvement in some studies. In our study, we observed a significant decrease in fatigue severity in both the amantadine-treated group ($p = 0.002$) and the ondansetron-treated group ($p < 0.001$).[22] However, in another RCT, no significant effect was found for modafinil, amantadine, and methylphenidate ($p = 0.20$).[11]

The studies included in this scoping review involve a heterogeneous population in terms of phenotype, disease duration, and DMT use; additionally, various severity scales were employed. Although these are specific instruments for measuring fatigue, they are heterogeneous in their construction, purpose, and outcome, accounting for both the impact and the topography of the response (frequency, duration, or intensity). All the instruments used in the various studies included in this review were brief, self-report measures, and have adequate psychometric properties. With the exception of FSS and VAFS all are multidimensional. Therefore, this may explain the heterogeneity of results.

It is not possible to make a strong recommendation regarding the optimal type of intervention to manage fatigue in patients with MS. The studies published to date have heterogeneous evaluation methods, intervention times, results, and populations.

Conclusion

Fatigue is a secondary symptom that is difficult to manage and the evidence of its impact on the quality of life of patients is sufficient and

growing,[6,67] so that ignoring or undervaluing the symptom results in a decrease in quality of life. Greater attention and commitment from the treating team toward this aspect is recommended. This review highlights the need for a multimodal, interdisciplinary, and comprehensive therapeutic approach to the fatigue experienced by patients with MS. This represents several challenges, such as the conformation of multidisciplinary teams, which maintain a continuous interprofessional dialogue that allows adjustments based on the evolution of this symptom; the design of personalized, contextual, and flexible palliative interventions that address the biological, psychological, and physical dimensions. Moreover, consider the design and implementation of economically viable and sustainable proposals which improve the quality of life and decrease disease burden, ultimately aiming to reduce the costs of healthcare interventions in the long term.

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