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**66° CONGRESSO NAZIONALE** 



**Società Italiana di Neurofisiologia Clinica**

**PROGRAMMA FINALE**

**Palermo**  
**18-21 Maggio 2022**  
**Hotel San Paolo Palace**

# La fatica nella sclerosi multipla: la terapia

***L.M.E. Grimaldi***

**66° CONGRESSO NAZIONALE SINC**  
**Palermo 18-21 maggio 2022**

# Multiple sclerosis-related fatigue lacks a unified definition: A narrative review

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Fatigue is the most common symptom in multiple sclerosis (MS). Although MS-related fatigue (MS-F) strongly affects quality of life and social performance of patients, there is currently a lack of knowledge about its pathophysiology, which in turns leads to poor objective diagnosis and management. Recent studies have shown that MS-F is a complex phenomenon. However, it seems that without a consensus on its nature, it is difficult to study this Article, we review definitions, epidemiology, risk factors, neuroimaging findings, and pharmacological and nonpharmacological interventions for MS-F, which could result in more accurate diagnosis and management.


**Key words:** Diagnosis, epidemiology, etiology, fatigue, management, therapy

**How to cite this article:** Adibi I, Sanayei M, Tabibian F, Ramezani N, Pourmohammadi A, Azimzadeh K. Multiple sclerosis-related fatigue lacks a unified definition: A narrative review. J Res Med Sci 2022;27:24.

Neurol Ther (2021) 10:75–98  
<https://doi.org/10.1007/s40120-021-00239-2>

## REVIEW

# Comprehensive Approach to Management of Multiple Sclerosis: Addressing Invisible Symptoms—A Narrative Review

Lynsey Lakin · Bryan E. Davis · Cherie C. Binns · Keisha M. Currie ·  
 Mary R. Rensel 

MULTIPLE  
 SCLEROSIS  
 JOURNAL

MSJ

*Topical Review*

## What's in a name? That which we call *Multiple Sclerosis Fatigue*

Amy Lynn Hubbard , Heidrun Golla and Hedda Lausberg

*Multiple Sclerosis Journal*

2021, Vol. 27(7) 983–988

DOI: 10.1177/  
 1352458520941481

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La «fatigue» è il più comune e disabilitante singolo sintomo della SM, presente tra il 52% delle CIS e l'88% dei progressivi (75% media di tutti i pazienti con SM).

È anche uno dei più difficili da trattare proprio per la sua natura soggettiva, complessa patofisiologia e varietà che richiede spesso un approccio multidisciplinare.

**What are the invisible symptoms of MS?**  
People living with MS often experience 'invisible symptoms' – symptoms which are not easily visible to others. These most frequently include:

						
Fatigue	Mood changes	Cognitive changes	Physical & emotional pain	Bowel & bladder problems	Sexual dysfunction	Vision changes

Tipiche descrizioni dei pazienti :

1. «apatia incontrollata»
2. «senso di esaurimento»
3. «mancanza di energia»
4. «senso di distacco dalla realtà»
5. «stanchezza immotivata»

«Una soggettiva mancanza di energia fisica e/o mentale che è percepita dal paziente o dal caregiver come interferente con le attività quotidiane usuali o desiderate».

Multiple Sclerosis Council for Clinical Practice Guidelines, 1998

## There are two types of fatigue: primary and secondary fatigue

- (●) **Primary fatigue:** A direct result of damage to the central nervous system by the disease. There are different types of primary fatigue:
  - **Lassitude:** is excessive tiredness that is not directly related to participation in any activity or exercise.
  - **“Neuromuscular fatigue”:** occurs in specific groups of muscles (for example, in the hand after writing).
  - **Fatigue due to heat sensitivity:** an increase in body temperature can cause the appearance of fatigue. This kind of fatigue can result from seasonal weather changes, but can also appear for other reasons (e.g., bathing with hot water or eating hot foods).
- (●) **Secondary fatigue:** may appear as a consequence of factors that are not directly related to MS, like changes in sleep patterns, infections, exercise, medications, etc.



**TABLE 1:** Possible causes of secondary fatigue associated with MS.

Possible causes	Symptoms
Infections	Cold, flu, urinary infections
Medications	Side effects of certain medications, including non-prescription medications and “alternative” products. Interactions between certain medications.
Sleep disorders	Difficulty falling asleep Disrupted sleep from having to get up frequently to urinate or because of spasms and pain Waking up tired or with a headache
Depression	Feeling down and irritable Lack of interest in the people or topics that used to interest you before Feelings of incompetency or failure
Disabilities	Decreased physical fitness of your muscles, heart and/or lungs
Pain	Backache, arthritis pain, headache
Stress	Difficulties at work, family stress, financial worries, issues related to your MS
Respiratory problems	Asthma, respiratory failure

> J Neurol Sci. 2021 Jul 15;426:117437. doi: 10.1016/j.jns.2021.117437. Epub 2021 Apr 9.

## Quality of life in multiple sclerosis is dominated by fatigue, disability and self-efficacy

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Affiliations + expand

PMID: 33991718 DOI: [10.1016/j.jns.2021.117437](https://doi.org/10.1016/j.jns.2021.117437)

### Abstract

**Background and objective:** Quality of life in multiple sclerosis (MS) reflects complex relationships between symptoms (fatigue, spasticity pain, and bladder or vision dysfunction), disability, health perceptions, and self-efficacy.

**Methods:** In this cross-sectional study, a self-report questionnaire pack of patient reported outcome measures was collected from 5695 people with MS (pwMS) alongside clinical data from their neurologists. Each patient reported outcome measure was converted to interval-scaled estimates following fit to the Rasch model. The patient reported outcome measures, as well as perceived health, age, disease subtype and gender, were then subject to path analysis to analyse their relationships with quality of life (QoL), guided by the Wilson and Clearly conceptual framework.

**Results:** The final model explains 81.2% of the variance of QoL. Fatigue is clearly dominant, suggesting a means to intervene and improve QoL. The next most influential factors were disability and self-efficacy, which have similar effect levels. The model can be replicated for pwMS on disease modifying therapy and is largely invariant for gender and disease subtype. Age had an insignificant effect.

**Conclusions:** In order to promote better QoL, MS care should include management of fatigue, interventions to ameliorate disability, and support to enhance self-efficacy. The range of skills needed for these treatments will require input from medical, nursing, therapy and psychology staff, so these findings provide evidence substantiating the need for pwMS to be provided with care by comprehensive multidisciplinary teams.

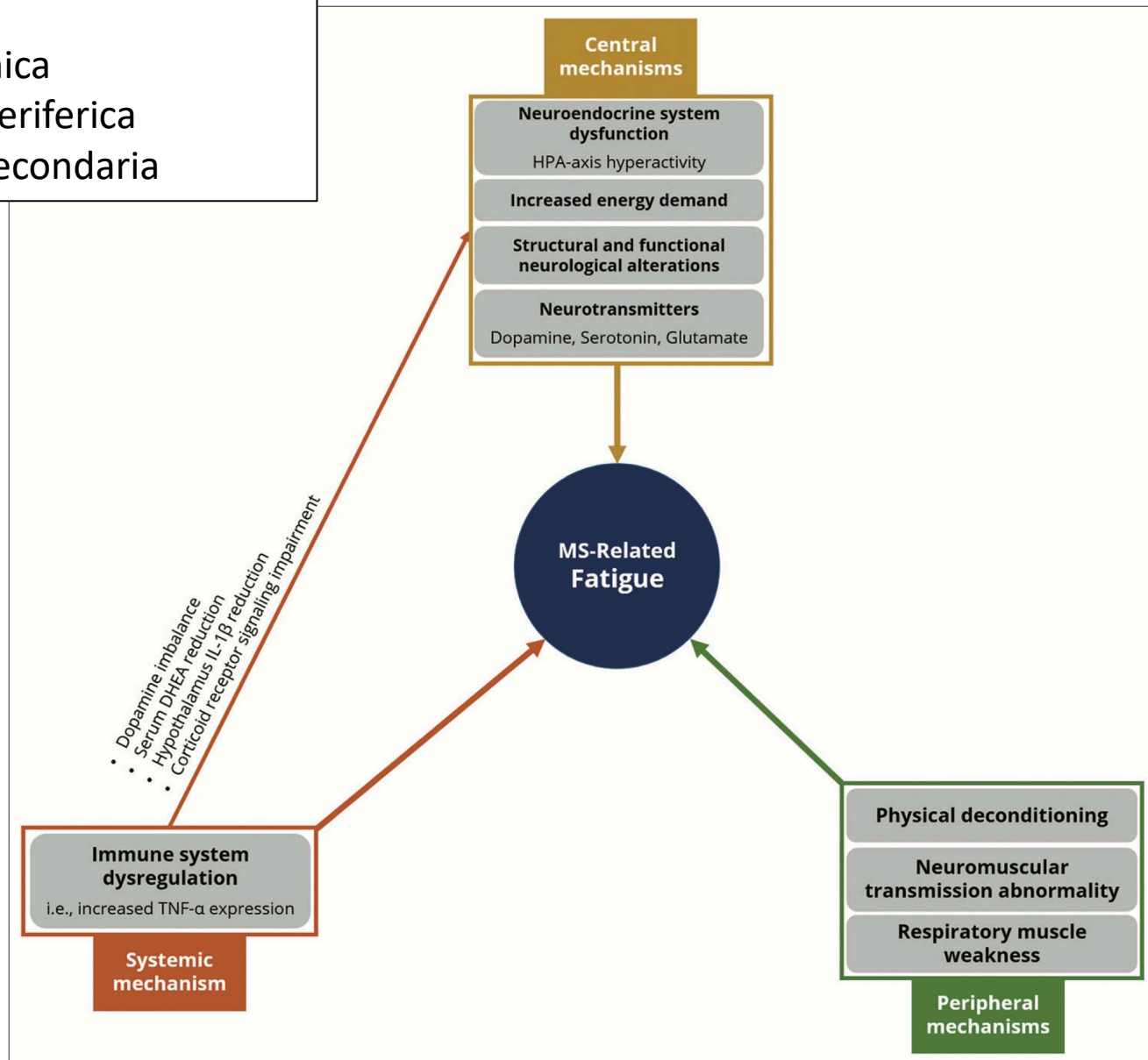


### Fattori di rischio per la fatigue associata alla SM:

1. PP/SP SM > RR SM
2. Età (avanzata > giovanile)
3. Scolarità (minore > maggiore)
4. Status familiare (separati > sposati)
5. Stato psicologico
6. Parasonnie
7. BMI (alto > normale)
8. Attività fisica (poca > molta)
9. Eemicrania

## Tipi di fatigue associata alla SM:

1. Acuta/cronica
2. Centrale/periferica
3. Primaria/secondaria

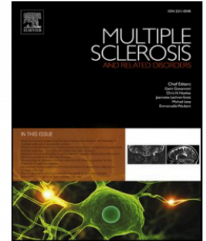




Contents lists available at [ScienceDirect](#)

## Multiple Sclerosis and Related Disorders

journal homepage: [www.elsevier.com/locate/msard](http://www.elsevier.com/locate/msard)



### Experience with the COVID-19 AstraZeneca vaccination in people with multiple sclerosis

#### ARTICLE INFO

##### Keywords

SARS-CoV2

COVID-19

Vaccination

Multiple sclerosis

#### ABSTRACT

**Background:** Some people with multiple sclerosis (pwMS) are at increased risk of severe Coronavirus disease 19 (COVID-19) and should be rapidly vaccinated. However, vaccine supplies are limited, and there are concerns about side-effects, particularly with the ChAdOx1nCoV-19 (AstraZeneca) vaccine.

**Objectives:** To report our first experience of pwMS receiving the AstraZeneca vaccine.

**Methods:** Service evaluation. pwMS using the MS service at Barts Health NHS Trust were sent questionnaires to report symptoms following vaccination.

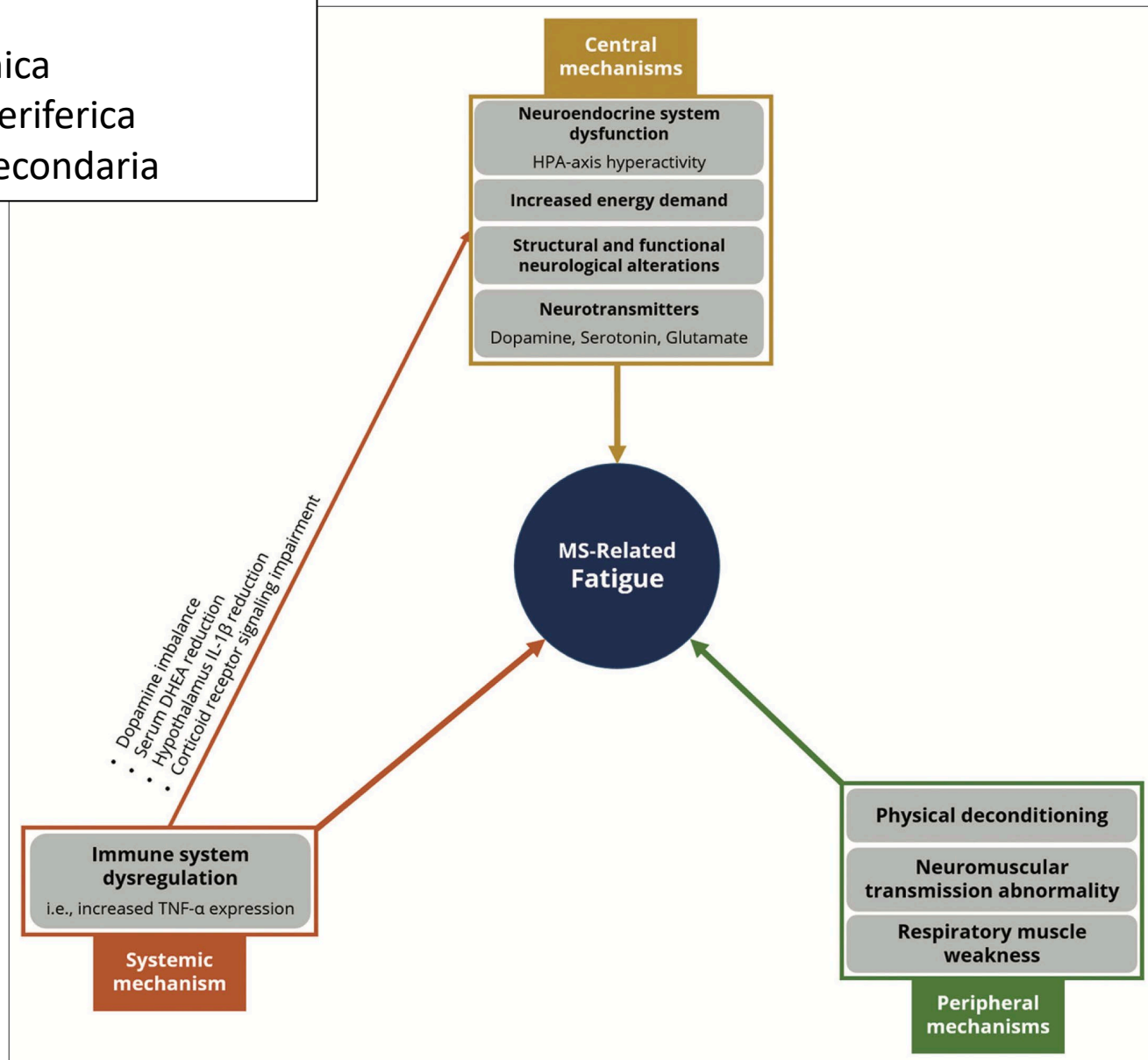
**Results:** Thirty-three responses were returned, 29/33 pwMS received a first dose of AstraZeneca vaccine, the remaining four received a first dose of BioNTech/Pfizer vaccine.

All but two patients (94%) reported any symptoms including a sore arm (70%), flu-like symptoms (64%), fever (21%), fatigue (27%), and headache (21%). In more than 2/3 patients, symptoms lasted up to 48 hours, and with the exception of two pwMS reporting symptom duration of 10 and 12 days, respectively, symptoms in the remainder resolved within seven days. No severe adverse effects occurred.

**Conclusions:** pwMS report transient symptoms following AstraZeneca vaccination, characteristics of which were similar to those reported in the non-MS population. Symptoms may be more pronounced in pwMS due to the temperature-dependent delay in impulse propagation (Uhthoff's phenomenon) due to demyelination.

## Tipi di fatigue associata alla SM:

1. Acuta/cronica
2. Centrale/periferica
3. Primaria/secondaria





## Correlation between fatigue and brain atrophy and lesion load in multiple sclerosis patients independent of disability

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Received 5 March 2007; received in revised form 1 June 2007; accepted 3 July 2007

Available online 1 August 2007

### Abstract

**Background:** Fatigue is a major problem in multiple sclerosis (MS), and its association with MRI features is debated.

**Objective:** To study the correlation between fatigue and lesion load, white matter (WM), and grey matter (GM), in MS patients independent of disability.

**Methods:** We studied 222 relapsing remitting MS patients with low disability (scores  $\leq 2$  at the Kurtzke Expanded Disability Status Scale). Lesion load, WM and GM were measured by fully automated, operator-independent, multi-parametric segmentation method. T1 and T2 lesion volume were also measured by a semi-automated method. Fatigue was assessed by the Fatigue Severity Scale (FSS), and patients divided in high-fatigue (FSS  $\geq 5$ ;  $n=197$ ) and low-fatigue groups (FSS  $\leq 4$ ;  $n=25$ ).

**Results:** High-fatigue patients showed significantly higher abnormal white matter fraction (AWM-f), T1 and T2 lesion loads, and significant lower WM-f, and GM-f. Multivariate analysis showed that high FSS was significantly associated with lower WM-f, and GM-f. Females and highly educated patients were significantly less fatigued.





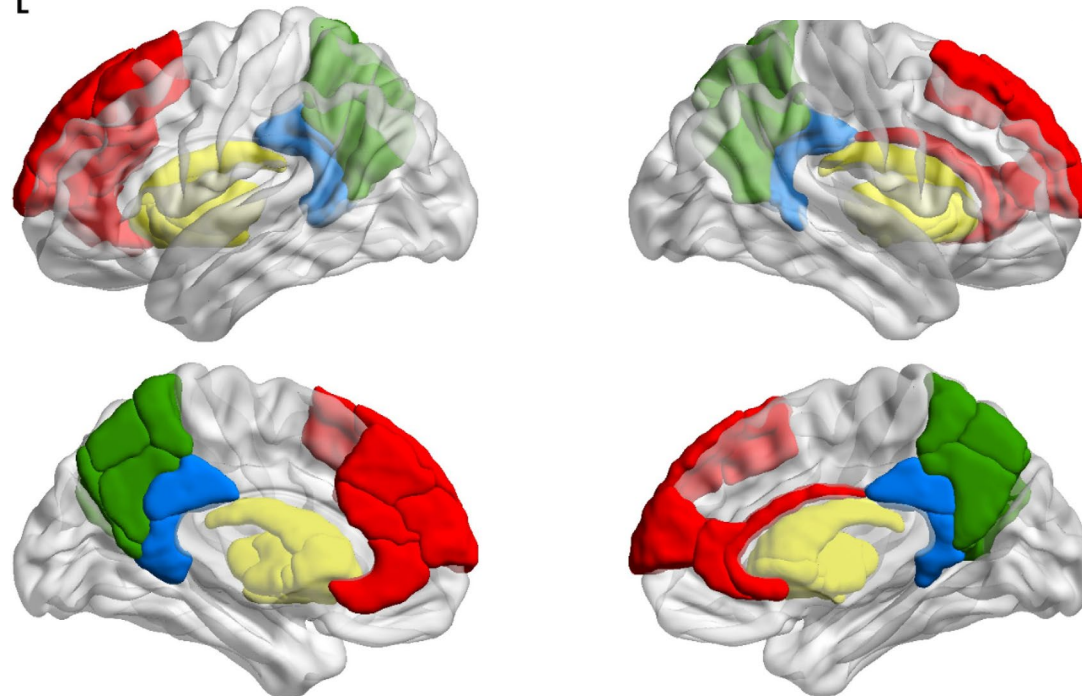
## Dynamic functional connectivity as a neural correlate of fatigue in multiple sclerosis

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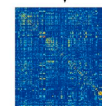
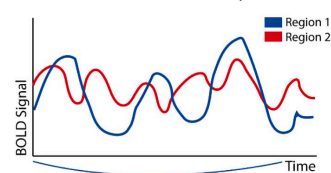
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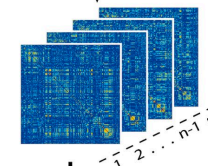
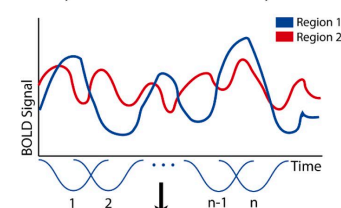


### A. Static functional connectivity



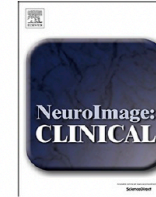
sFC\*

### B. Dynamic functional connectivity



dFC - summed difference  
dFC - coefficient of variation\*

**Conclusions:** Less dynamic connectivity between the basal ganglia and the cortex is associated with greater fatigue in MS patients, independent of disability status. Within patients, lower dynamics of these connections could relate to lower efficiency and increased fatigue. Increased dynamics in non-fatigued patients compared to healthy controls might represent a network organization that protects against fatigue or signal early network dysfunction.



# Motor fatigue is associated with asymmetric connectivity properties of the corticospinal tract in multiple sclerosis

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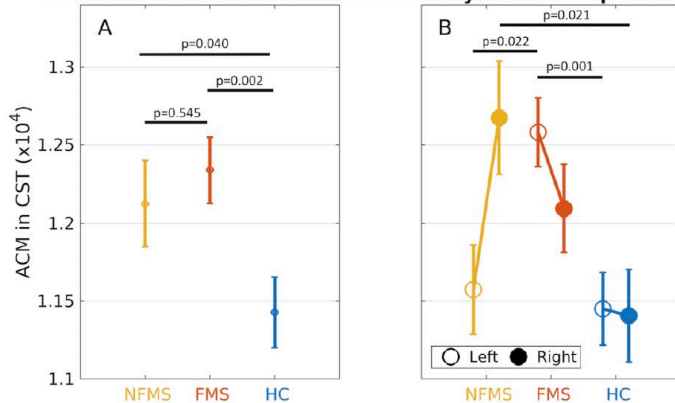
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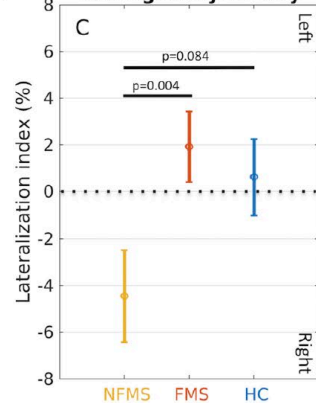
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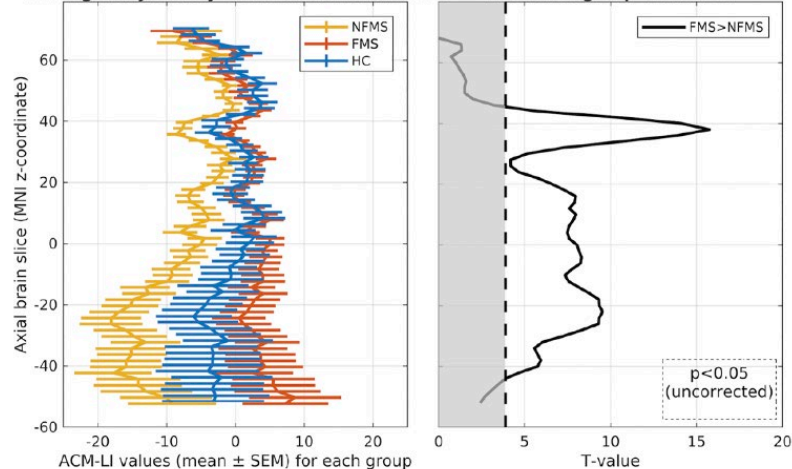
**Mean voxel-wise anatomical connectivity of cortico-spinal tract**



**Left-right asymmetry**



**Left-Right asymmetry in ACM values within CST** **Slice-wise group-difference**



**TABLE 2 |** Commonly used pharmacological treatments for MS symptoms [adapted from (31, 32)].

Symptom	Pharmacological treatment
<b>MOBILITY-RELATED SYMPTOMS</b>	
Spasticity	Baclofen, tizanidine, nabiximols (THC:CBD), benzodiazepines (diazepam, clonazepam), gabapentin, dantrolene, botulinum toxin A (local treatment), intrathecal baclofen
Ataxia and tremor	Propranolol, clonazepam, levetiracetam, isoniazid, carbamazepine, ondansetron, dolasetron, cannabinoids, glutethimide
Impaired ambulation	Aminopyridines (fampridine)
<b>BLADDER, BOWEL, AND SEXUAL DYSFUNCTION</b>	
Urinary dysfunction	<i>Bladder inefficiency:</i> $\alpha$ 1-blockers (indoramin) <i>Bladder overactivity:</i> antimuscarinics, intravesical botulinum toxin A, desmopressin, cannabinoids, intravesical vanilloids
Bowel dysfunction	Bulking agents, Laxatives
Sexual dysfunction	Sildenafil, tadalafil, vardenafil
<b>FATIGUE, COGNITIVE IMPAIRMENT, AND MOOD DISTURBANCE</b>	
Fatigue	Amantadine, modafinil, pemoline, aminopyridine, carnitine
Cognitive dysfunction	Acetylcholinesterase inhibitors, memantine, amantadine, pemoline, ginkgo biloba, L-amphetamine sulfate
Mood disturbance	Fluoxetine, sertraline, moclobemide
<b>PAIN</b>	
Paroxysmal pain	Carbamazepine, oxcarbazepine, lamotrigine, gabapentin, topiramate, misoprostol
Persistent pain	Amitriptyline, pregabalin, gabapentin, lamotrigine, levetiracetam, cannabinoids
<b>VISUAL AND BRAINSTEM SYMPTOMS</b>	
Visual dysfunction	Memantine, gabapentin
Brainstem-related symptoms	Antiepileptic drugs
<b>SLEEP DISORDERS</b>	
Excessive sleepiness	Modafinil
Restless legs syndrome	Dopaminergic agonists



## The Broad Concept of “Spasticity-Plus Syndrome” in Multiple Sclerosis: A Possible New Concept in the Management of Multiple Sclerosis Symptoms

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**TABLE 4 |** Adverse sexual function effects of drugs used in the symptomatic treatment of MS [adapted from (33)].

Symptoms of MS	Treatment	Adverse sexual function effects associated with treatment
Cognitive dysfunction	Donepezil	N/A
Spasticity	Baclofen Tizanidine Dantrolene Clonidine Benzodiazepines	ED, inability to ejaculate (rare) Urinary frequency, urgency, incontinence, urinary retention Decreased libido, ED, retrograde ejaculation N/A N/A
Fatigue	Amantadine Modafinil Methylphenidate Amphetamine/dextroamphetamine	Decreased libido N/A N/A ED, changes in libido (dose dependent)
Pain	Tricyclic antidepressants  Valproic acid Carbamazepine Oxcarbazepine Lamotrigine Gabapentin Duloxetine	ED, ejaculatory impairment, anorgasmia, decreased libido ED ED N/A ED N/A Decreased libido, ED, ejaculation dysfunction and anorgasmia
Bladder and bowel dysfunction	Anticholinergic medication	Dry mouth, vaginal dryness, constipation
Depression	SSRIs  Bupropion Venlafaxine	Decreased libido, anorgasmia, delayed ejaculation N/A ED, anorgasmia

ED, erectile dysfunction; MS, multiple sclerosis; N/A, not applicable; SSRIs, selective serotonin reuptake inhibitors.

# Summary of evidence-based guideline: Complementary and alternative medicine in multiple sclerosis

Report of the Guideline Development Subcommittee of the American Academy of Neurology



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## ABSTRACT

**Objective:** To develop evidence-based recommendations for complementary and alternative medicine (CAM) in multiple sclerosis (MS).

**Methods:** We searched the literature (1970–March 2011; March 2011–September 2013 MEDLINE search), classified articles, and linked recommendations to evidence.

**Results and recommendations:** Clinicians might offer oral cannabis extract for spasticity symptoms and pain (excluding central neuropathic pain) (Level A). Clinicians might offer tetrahydrocannabinol for spasticity symptoms and pain (excluding central neuropathic pain) (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity (short-term)/tremor (Level B) and possibly effective for spasticity and pain (long-term) (Level C). Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols) for spasticity symptoms, pain, and urinary frequency (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity/urinary incontinence (Level B). Clinicians might choose not to offer these agents for tremor (Level C). Clinicians might counsel patients that magnetic therapy is probably effective for fatigue and probably ineffective for depression (Level B); fish oil is probably ineffective for relapses, disability, fatigue, MRI lesions, and quality of life (QOL) (Level B); ginkgo biloba is ineffective for cognition (Level A) and possibly effective for fatigue (Level C); reflexology is possibly effective for paresthesia (Level C); Cari Loder regimen is possibly ineffective for disability, symptoms, depression, and fatigue (Level C); and bee sting therapy is possibly ineffective for relapses, disability, fatigue, lesion burden/volume, and health-related QOL (Level C). Cannabinoids may cause adverse effects. Clinicians should exercise caution regarding standardized vs non-standardized cannabis extracts and overall CAM quality control/nonregulation. Safety/efficacy of other CAM/CAM interaction with MS disease-modifying therapies is unknown.

*Neurology*® 2014;82:1083–1092

**Table 2 CAM therapies with sufficient evidence to support practice recommendations in multiple sclerosis**

CAM intervention	Number and class of studies	MS types studied	Outcome	Recommendation level
<b>Cannabinoids</b>				
<b>OCE</b>	2 Class I, <sup>13,14</sup> 1 Class II, <sup>17</sup> 1 Class III <sup>18</sup>	RRMS, SPMS, PPMS, MSU	Symptoms of spasticity, pain	A Effective
	1 Class I <sup>13</sup>	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II <sup>17</sup>	MSU	Signs and symptoms of spasticity (long-term)	C Effective
	2 Class I, <sup>13</sup> 1 Class II <sup>16</sup>	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence	U
<b>Synthetic THC</b>	1 Class I, <sup>13</sup> 1 Class II <sup>17</sup>	RRMS, SPMS, PPMS	Symptoms of spasticity, pain	B Effective
	1 Class I <sup>13</sup>	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II <sup>17</sup>	MSU	Signs and symptoms of spasticity (long-term)	C Effective
	1 Class I, <sup>13</sup> 1 Class II, <sup>16</sup> 1 Class III <sup>19</sup>	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence, central neuropathic pain	U
<b>Sativex oromucosal spray</b>	3 Class I, <sup>23–25</sup> 2 Class II, <sup>26,27</sup> 3 Class III <sup>28–30</sup>	MSU	Symptoms of spasticity, pain, urinary frequency	B Effective
			Signs of spasticity, incontinence episodes	B Ineffective
			Tremor	C Ineffective
			Anxiety/sleep, cognition, QOL, fatigue	U
<b>Smoked cannabis</b>	2 Class III <sup>31,32</sup>	RRMS, SPMS, MSU	Spasticity, pain, balance and posture, cognition	U

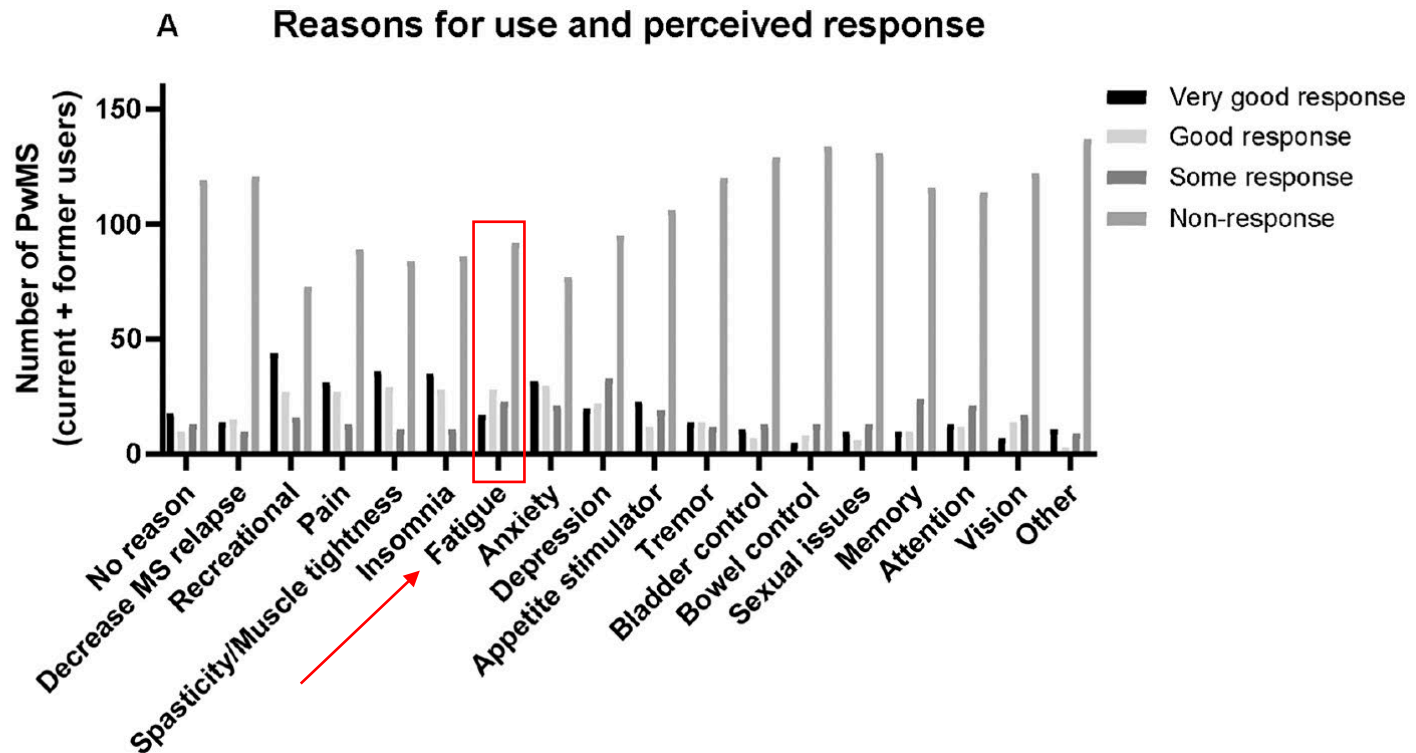




Original article

## Use of cannabis in patients with multiple sclerosis from Argentina

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 Alejandro Caride<sup>a</sup>, Juan I. Rojas<sup>h,i</sup>, Ricardo Alonso<sup>g</sup>



# Fatigue in MS e sostanze psicoattive.....

Randomized Controlled Trial > Mult Scler Relat Disord. 2021 Nov;56:103273.

doi: 10.1016/j.msard.2021.103273. Epub 2021 Sep 20.

## Methylphenidate may improve mental fatigue in individuals with multiple sclerosis: A pilot clinical trial

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Affiliations + expand

PMID: 34564057 DOI: [10.1016/j.msard.2021.103273](https://doi.org/10.1016/j.msard.2021.103273)

### Abstract

**Background:** Fatigue is the most common symptom in multiple sclerosis (MS), previously attributed to dopamine imbalance. Evidence suggests that methylphenidate, a psychostimulant that increases striatal and prefrontal dopamine levels, is effective in reducing fatigue in various disorders. However, its effect on state vs. trait mental fatigue in MS is yet to be examined.

**Methods:** This pilot study investigates the efficacy of methylphenidate on decreasing self-reported mental fatigue in 12 individuals with MS in a double-blind, placebo-controlled, cross-over randomized clinical trial.

**Results:** Our results show that "state", but not "trait" MS-related fatigue, was reduced after 4 weeks of methylphenidate administration as compared to placebo.

Review > Exp Neurol. 2022 Jan;347:113906. doi: 10.1016/j.expneurol.2021.113906.

Epub 2021 Oct 26.

## Treatment of multiple sclerosis fatigue with the synthetic psychoactive drug modafinil

Eleonora Cocco<sup>1</sup>, Paola Fadda<sup>2</sup>

Affiliations + expand

PMID: 34710403 DOI: [10.1016/j.expneurol.2021.113906](https://doi.org/10.1016/j.expneurol.2021.113906)

### Abstract

Multiple sclerosis (MS) is a complex disorder characterized by a broad spectrum of symptoms that evolve throughout the disease. Symptoms can be categorized as visible and invisible based on external sight recognition. However, although others poorly recognize it, invisible symptoms such as mood dysfunction, neuropathic pain, or fatigue can significantly affect activities of daily living and the quality of life of people with MS (PwMS). PwMS frequently complain of fatigue, which has physical or cognitive manifestations. Fatigue in MS does not improve or resolve with rest, and it is disproportionate with respect to the exerted effort. Fatigue management in MS is challenging, and a few pharmacological approaches have been successfully proposed. Among them, the drug modafinil has attracted attention because of its properties as a synthetic psychoactive drug. In this review, we focus on the evidence available to date, supporting the use of modafinil in MS fatigue. However, despite the availability of some trials evaluating the effects of modafinil on fatigue, their contrasting results failed to support its usefulness in fatigue management in MS.



## **Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomized, crossover, double-blind trial**

**Bardia Nourbakhsh, M.D.<sup>1</sup>, Nisha Revirajan, M.B.B.S.<sup>2</sup>, Bridget Morris, M.S.N.<sup>1</sup>, Christian Cordano, M.D.<sup>2</sup>, Jennifer Creasman, M.S.P.H.<sup>3</sup>, Michael Manguinao, B.S.<sup>2</sup>, Kristen Krysko, M.D.<sup>2</sup>, Alice Rutatangwa, D.O.<sup>2</sup>, Caroline Auvray, M.D.<sup>2</sup>, Salman Aljarallah, M.B.B.S.<sup>1</sup>, Chengshi Jin, Ph.D.<sup>3</sup>, Prof Ellen Mowry, M.D.<sup>1,4</sup>, Prof Charles McCulloch, Ph.D.<sup>3</sup>, Prof Emmanuelle Waubant, M.D.<sup>2</sup>**

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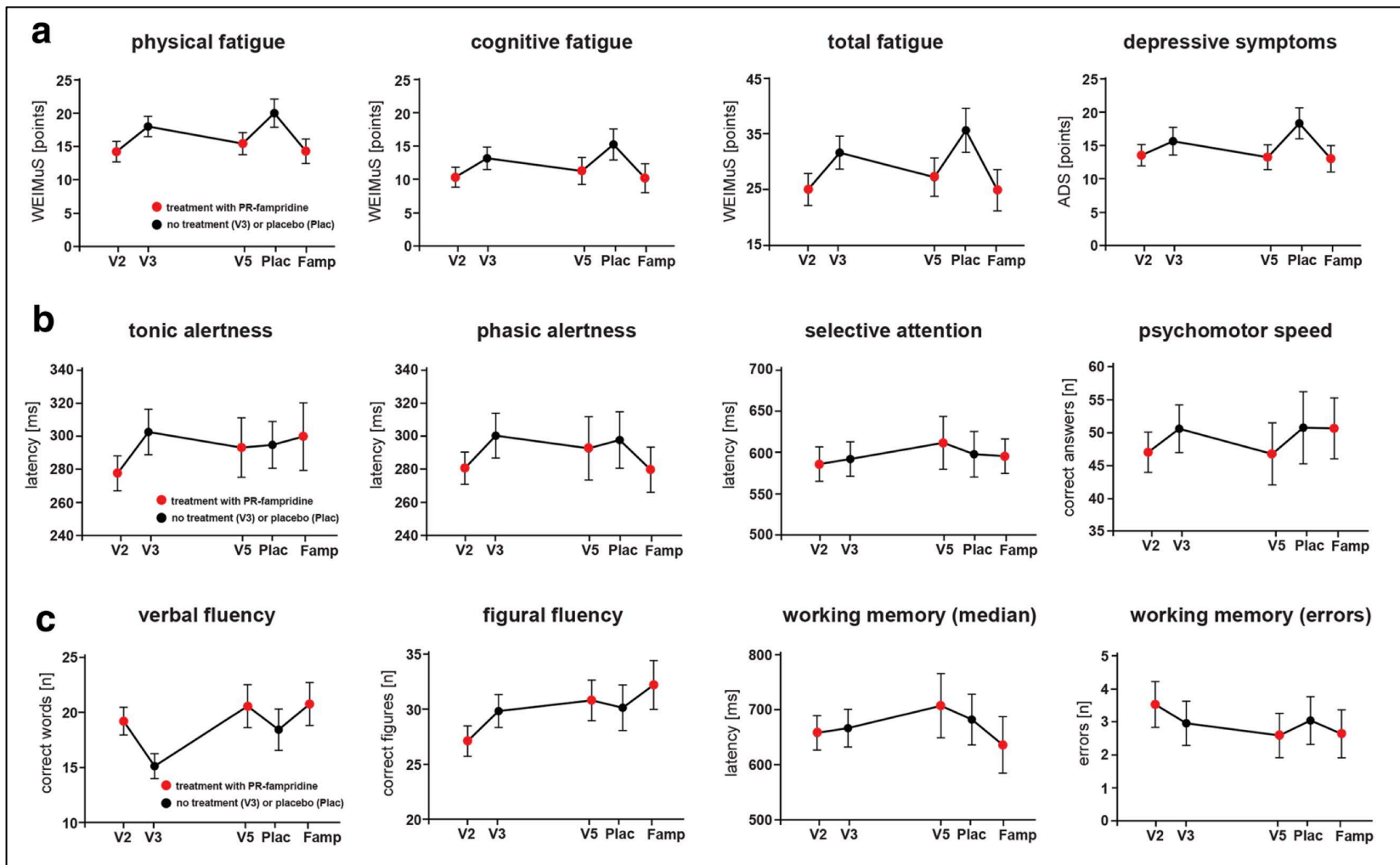
**Interpretation**—Amantadine, modafinil, and methylphenidate were not superior to placebo in improving MS-related fatigue and caused more frequent adverse events. The results of this study do not support an indiscriminate use of amantadine, modafinil, and methylphenidate for the treatment of fatigue in MS.



## Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years

Sarah D. Broicher<sup>1</sup> · Linard Filli<sup>1</sup> · Olivia Geisseler<sup>1</sup> · Nicole Germann<sup>1</sup> · Björn Zörner<sup>2</sup> · P. Brugger<sup>1</sup> · M. Linnebank<sup>3</sup>

Received: 29 November 2017 / Accepted: 12 February 2018  
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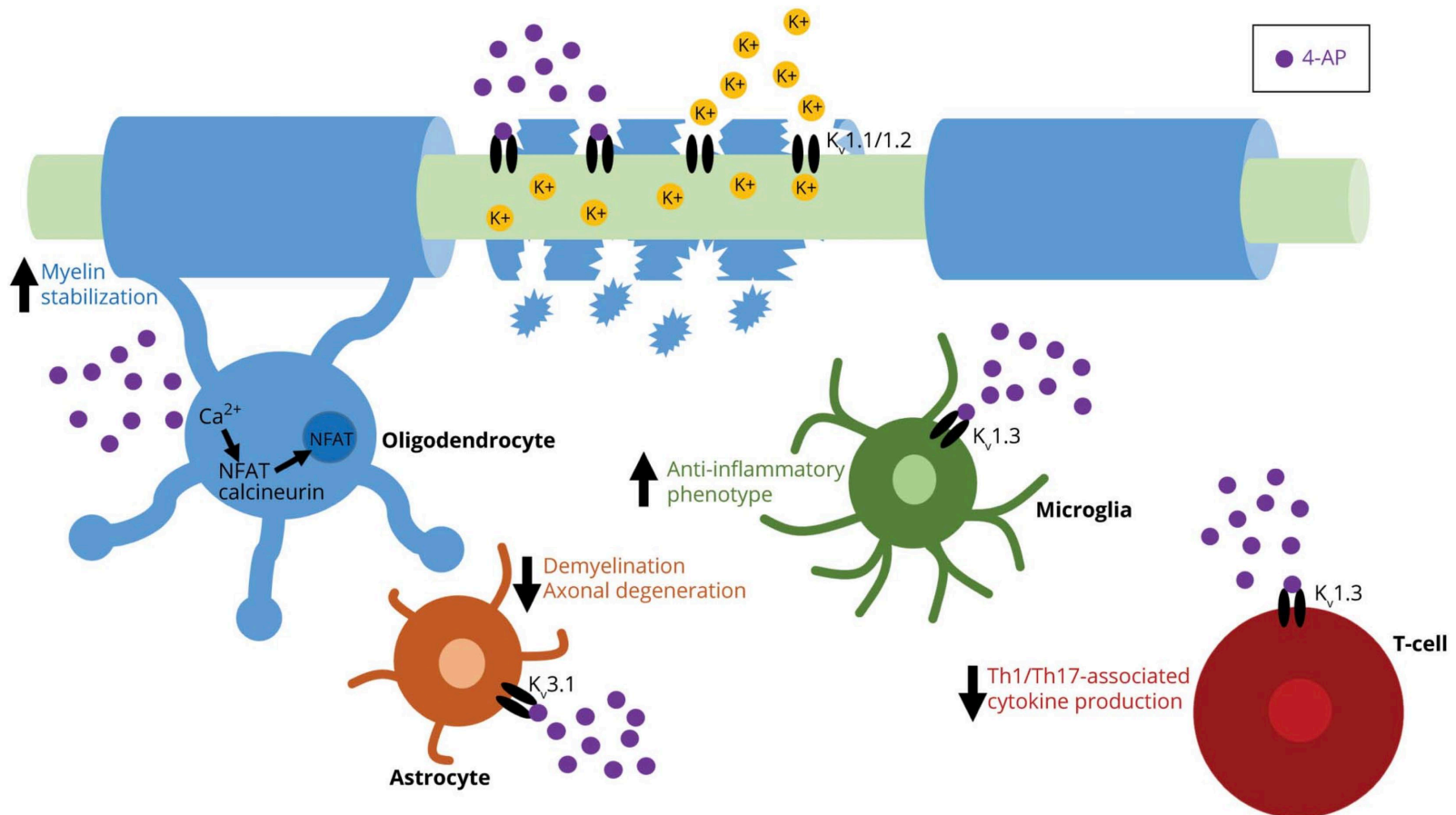


# Neuroprotective Properties of 4-Aminopyridine

Michael Dietrich, PhD, Hans-Peter Hartung, MD, PhD, FRCP, and Philipp Albrecht, MD  
*Neurol Neuroimmunol Neuroinflamm* 2021;8:e976. doi:10.1212/NXI.0000000000000976

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**Figure** Presumed Mode of Action and Additional Potential Effects of 4-AP in Demyelinating Disease



4-AP blocks potassium channels and therefore enhances signal transduction of the axon.<sup>9,10</sup> Potential immunomodulatory effects may be exerted by Kv1.3 channels expressed by microglia<sup>25</sup> and T-cells.<sup>35</sup> The Kv3.1 channel on astrocytes might be targeted by 4-AP to suppress demyelination and axonal degenerating.<sup>34</sup> In another preclinical study, 4-AP stabilized myelin via the NFAT pathway.<sup>37</sup> 4-AP = 4-aminopyridine; NFAT = nuclear factor of activated T-cells.

## Early Treatment Improvements in Depression Are Associated With Overall Improvements in Fatigue Impact and Pain Interference in Adults With Multiple Sclerosis

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· Kevin N. Alschuler, PhD<sup>1,5</sup> · Dawn M. Ehde, PhD<sup>1</sup>

Published online: 16 November 2020

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### Abstract

**Background** Depression, fatigue, and pain commonly co-occur in multiple sclerosis (MS) and are positively associated with one another. However, it is unclear whether treatment-related improvement in one of these symptoms is associated with improvements in the other two symptoms.

**Purpose** This study examined whether early improvements in depressive symptoms, fatigue impact, and pain interference during a multisymptom intervention in persons with MS were associated with overall improvements in the other two symptoms.

**Methods** Secondary analysis of a randomized controlled trial in which both treatments improved depressive symptoms, fatigue, and pain interference. Adults with MS experiencing chronic pain, chronic fatigue, and/or moderate depressive symptoms ( $N = 154$ , 86% women) participated in an 8-week, telephone-delivered intervention: self-management ( $n = 69$ ) or education ( $n = 85$ ); intervention groups were combined for the current study. Outcome measures were depressive symptoms (PHQ-9), fatigue impact (Modified Fatigue Impact Scale), and pain interference (Brief Pain Inventory). Path analysis

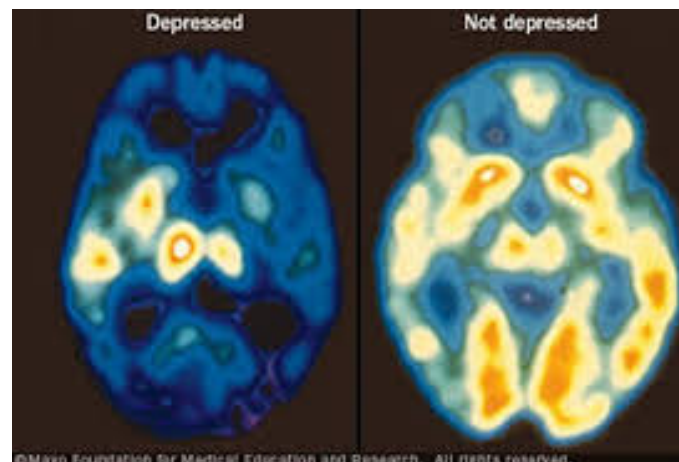
examined associations between pre-to-mid intervention improvement in one symptom (i.e., depression, fatigue, pain interference) and pre-to-post (overall) improvement in the other two symptoms.

**Results** Early reduction in depressive symptoms was associated with an overall reduction in pain interference and fatigue impact ( $p$ 's  $< .01$ ). Early reduction in fatigue impact was associated with an overall reduction in depressive symptom severity ( $p = .04$ ) but not pain interference. Early reduction in pain interference was not associated with reductions in fatigue impact or depressive symptoms.

**Conclusions** These findings suggest the potential importance of reducing depressive symptoms to overall improvement in fatigue and pain interference in persons with MS.

**Clinical Trial Registrations** NCT00944190.

**Keywords:** Pain · Fatigue · Depression · Multiple sclerosis · Symptom management





# Three-Day Dietary Manipulation in Multiple Sclerosis

## Exercise and Fatigue Outcomes

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Bianca Weinstock-Guttman, MD; Todd C. Rideout, PhD; Richard W. Browne, PhD; Andrew D. Ray, PhD

**Background:** In persons with multiple sclerosis (MS), the effect of nutrition on exercise performance and fatigue remains unknown. The objective was to determine whether a 3-day diet high in triglycerides (FAT) compared with a 3-day diet high in carbohydrates (CARB) would improve fatigue and exercise performance in persons with MS.

**Methods:** A randomized controlled crossover design was incorporated to study FAT versus CARB on submaximal cycling endurance (60% of peak oxygen consumption), substrate utilization, and fatigue in 12 persons with mild-to-moderate MS (Expanded Disability Status Scale score, 2.0-5.0) and 12 age- and sex-matched controls.

**Results:** There were no differences in cycling time between diets in either group ( $P = .29$ ). The MS group had no changes in fatigue between diets ( $P = .64$ ); the control group demonstrated increased total mental fatigue after FAT ( $P = .05$ ). The control group increased carbohydrate oxidation by 24% at rest and 13% during exercise after CARB. Similarly, the control group significantly increased fat oxidation after FAT by 22% at rest and 68% during exercise ( $P = .01$ ). These changes were not seen in the MS group. Compared with controls, persons with MS oxidized approximately 50% less fat during exercise after FAT ( $P = .05$ ).

**Conclusions:** Neither CARB nor FAT altered submaximal exercise performance or baseline fatigue in the MS group. The results suggest that persons with MS are unable to adapt to dietary changes and oxidize fatty acids as efficiently as controls. *Int J MS Care.* 2021;23:199-205.

Received: 2018.01.26

Accepted: 2018.04.18

Published: 2018.08.18

# Effect of Rehabilitation on Fatigue Level in Patients with Multiple Sclerosis

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Source of support:** Departmental sources

**Background:** The objective of this study was to evaluate the effect of a rehabilitation program in changing the perception of fatigue in patients with multiple sclerosis.

**Material/Methods:** The study involved 65 respondents/patients with clinically confirmed multiple sclerosis (54 women, 11 men, average age 46.49 years). The evaluation of the effects of fatigue on the physical, psychological, and psychosocial aspects of life was assessed using the Modified Fatigue Impact Scale (MFIS). To test the effectiveness of the neurorehabilitation program, we enrolled 2 groups: the experimental group (EG, n=32, 29 women, 3 men, Expanded Disability Status Scale (EDSS) 4.8 average, SD±1.77, min. 1.5 max 8.0) participated in the intervention and rehabilitation program over a period of 12 weeks and the control group (CG, n=33, 25 women, 8 men. EDSS average 5.12±1.74 SD, min. 2.0 max. 8.0). Each group of patients was divided into 3 sub-groups according to the severity of EDSS: a) 1–3.5, b) 4–6, and c) 6.5–8. For the statistical evaluation of the significance of the observed changes, the MANOVA/ANOVA model was used.

**Results:** Between the input and output assessment of the MFIS individual areas questionnaire between the EG and the CG, there existed a statistically significant in the physical area ( $p<0.000$ ), psychological area ( $p<0.000$ ), and psychosocial area ( $p=0.002$ ).

**Conclusions:** Our results support the importance of an active approach in patients with multiple sclerosis using individualized rehabilitation intervention programs.

## Conclusions

For many years, people with MS have limited their physical activity because of the fear of increased disability. Fatigue is a major symptom affecting the normal daily activities of these patients. This study shows that an individualized rehabilitation program can improve fatigue level in patients with multiple sclerosis, regardless of the disability level. These benefits, although clinically significant, are short-lived; therefore, ongoing physiotherapy might be necessary for sustained benefit, whether this is defined as improvement in mobility or prevention of deterioration. It is thus necessary to ensure the availability of comprehensive outpatient rehabilitation for all MS patients.





## Effects of normobaric hypoxic endurance training on fatigue in patients with multiple sclerosis: a randomized prospective pilot study

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Received: 29 January 2021 / Revised: 1 May 2021 / Accepted: 4 May 2021 / Published online: 18 May 2021  
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### Abstract

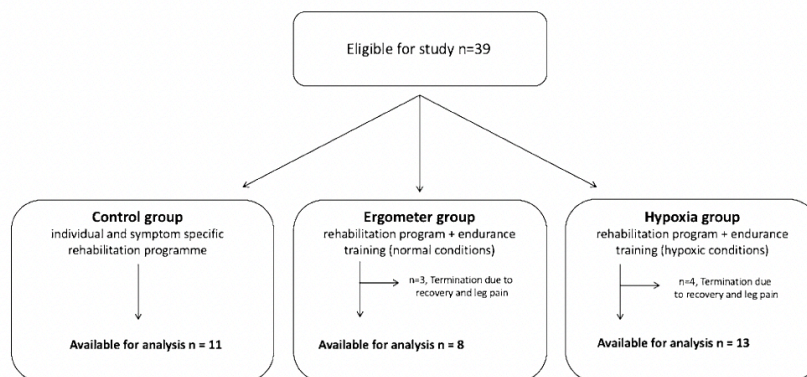
**Background** Fatigue is one of the most frequent symptoms in patients with multiple sclerosis (MS), causing a major impact on quality-of-life. Non-pharmacological intervention strategies involve physical activity, which has been shown to reduce fatigue. Training under normobaric hypoxic conditions is thought to improve the response to endurance training and may, therefore, have an additional benefit over normoxic training conditions in MS patients.

**Objective** To compare the effects of endurance training under hypoxic and normoxic conditions on fatigue, mobility and spasticity in patients with MS during inpatient rehabilitation.

**Methods** Thirty-nine patients with MS were assigned within a randomized prospective longitudinal pilot study to (1) a routine clinical rehabilitation program, (2) a routine clinical rehabilitation program + normoxic endurance training and (3) a routine clinical rehabilitation program + hypoxic endurance training for 14 days. Fatigue (WEIMuS and MFIS), spasticity (MSSS-88) and walking endurance (6MinWT) were assessed at days 0, 7 and 14.

**Results** Fatigue scores improved significantly in all groups, but these improvements were reached faster in the groups which additionally received endurance training (normoxic  $p=0.004$ ; hypoxic  $p=0.002$ ). Spasticity scores were significantly lower in endurance training groups at the end of the study compared to baseline (normoxic  $p=0.048$ , hypoxic  $p=0.012$ ), while only the hypoxic group increased significantly in 6MinWT ( $p=0.001$ ).

**Conclusions** Our findings demonstrate that endurance training provides substantial benefit to neurological rehabilitation programs. Endurance training under hypoxic conditions could positively influence walking endurance within a 2-week training intervention and warrants further investigations.



Review

# Therapeutic Effects of the Pilates Method in Patients with Multiple Sclerosis: A Systematic Review

Gustavo Rodríguez-Fuentes <sup>1,\*</sup>, Lucía Silveira-Pereira <sup>2</sup>, Pedro Ferradáns-Rodríguez <sup>2</sup> and Pablo Campo-Prieto <sup>1</sup>

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**Abstract:** The Pilates Method is a rehabilitation tool with verified benefits in pain management, physical function, and quality of life in many different physiotherapy areas. It could be beneficial for patients with multiple sclerosis (pwMS). The aim of the study was to summarize current evidence for the effectiveness of Pilates in pwMS. A comprehensive search of Cinahl, Scopus, Web of Science, PEDro, and PubMed (including PubMed Central and Medline) was conducted to examine randomized controlled trials (RCT) that included Pilates intervention in multiple sclerosis. The PEDro scale and the Cochrane risk-of-bias tool, RoB-2, were used to evaluate risk of bias for RCT. Twenty RCT (999 patients) were included. Ten were of good quality (PEDro), and seven had low risk of bias (RoB-2). Pilates improves balance, gait, physical-functional conditions (muscular strength, core stability, aerobic capacity, and body composition), and cognitive functions. Fatigue, quality of life, and psychological function did not show clear improvement. There was good adherence to Pilates intervention (average adherence  $\geq 80\%$ ). Cumulative data suggest that Pilates can be a rehabilitation tool for pwMS. High adherence and few adverse effects were reported. Future research is needed to develop clinical protocols that could maximize therapeutic effects of Pilates for pwMS.



Citation: Rodríguez-Fuentes, G.; Silveira-Pereira, L.; Ferradáns-Rodríguez, P.



	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Güngör et al. [27] 2021	+	×	-	+	+	×
Fleming et al. [28] 2021	-	+	+	+	+	-
Gheitasi et al. [29] 2021	+	+	+	+	+	+
Arntzen et al. [30] 2020	+	+	+	+	+	+
Ozkul et al. [31] 2020	+	+	+	+	+	+
Banitalebi et al. [32] 2020	×	+	+	+	+	×
Abasiyanik et al. [33] 2020	×	×	+	+	+	×
Fleming et al. [34] 2019	+	×	×	+	+	×
Eftekhari and Etemadifar [35] 2018	×	-	×	+	+	×
Ozkul et al. [36] 2018	+	+	+	+	+	+
Duff et al. [37] 2018	+	+	+	+	+	+
Eftekhari and Etemadifar [38] 2018	×	-	+	+	+	×
Kalron et al. [39] 2017	+	+	+	+	+	+
Bulguroglu et al. [40] 2017	×	×	-	+	+	×
Kara et al. [41] 2017	×	×	×	+	+	×
Fox et al. [42] 2016	+	+	+	+	+	+
Küçük et al. [43] 2016	×	+	+	-	+	×
Hosseini Sisi et al. [44] 2014	×	×	×	×	+	×
Guclu-Cunduz et al. [45] 2014	×	+	+	+	+	×
Marandi et al. [46] 2013	×	×	×	×	+	×

Domains:  
D1: Bias arising from the randomization process.  
D2: Bias due to deviations from intended intervention.  
D3: Bias due to missing outcome data.  
D4: Bias in measurement of the outcome.  
D5: Bias in selection of the reported result.

Judgement  
High  
Some concerns  
Low



# Home-based Pilates for symptoms of anxiety, depression and fatigue among persons with multiple sclerosis: An 8-week randomized controlled trial

Karl M Fleming , Susan B Coote and Matthew P Herring 

## Abstract

**Background:** Symptoms of anxiety, depression and fatigue are common comorbidities among persons with multiple sclerosis (PwMS). A previous pilot study supported Pilates as a feasible exercise modality that may improve these outcomes among PwMS.

**Objective:** To quantify the effects of 8 weeks of home-based Pilates on symptoms of anxiety, depression and fatigue among PwMS.

**Methods:** A total of 80 PwMS (69 female) were randomized to twice-weekly home-based Pilates guided by a DVD) or wait-list control. Validated questionnaires assessed anxiety, depressive and fatigue symptoms at baseline, weeks 2, 4, 6 and 8. Using intention to treat, repeated measures analysis of covariance (RM-ANCOVA) adjusted for baseline physical activity examined between-group differences across time. Hedges'  $d$  quantified the magnitude of differences in outcome change. Sensitivity analyses examined female-only samples.

**Results:** Group  $\times$  time interactions were statistically significant for all outcomes (all  $p \leq 0.005$ ). Pilates significantly reduced (all  $p \leq 0.03$ ) depressive symptoms (Quick Inventory of Depressive Symptomatology,  $d = 0.70$ ; Hospital Anxiety and Depression Scale-Depression,  $d = 0.74$ ), anxiety (State-Trait Anxiety Inventory,  $d = 0.30$ ; Hospital Anxiety and Depression Scale-Anxiety,  $d = 0.49$ ), cognitive ( $d = 0.44$ ), physical ( $d = 0.78$ ), psychosocial ( $d = 0.56$ ) and total fatigue ( $d = 0.76$ ). Female-only results were materially the same.

**Conclusion:** Home-based Pilates significantly improved anxiety, depressive and fatigue symptoms among PwMS with minimal-to-mild mobility disability, including moderate-to-large, clinically meaningful improvements in depressive and fatigue symptoms.

Trial Registration: ClinicalTrials.gov (NCT04120207)

Multiple Sclerosis Journal

2021, Vol. 27(14) 2267–2279

DOI: 10.1177/  
13524585211009216

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# Acupuncture for multiple sclerosis: A literature review

Faezeh Khodaie <sup>1</sup>, Naghmeh Abbasi <sup>2</sup>, Amir Hooman Kazemi Motlagh <sup>3</sup>, Baixiao Zhao <sup>4</sup>, Abdorreza Naser Moghadasi <sup>5</sup>

Affiliations + expand

PMID: 35259684 DOI: [10.1016/j.msard.2022.103715](https://doi.org/10.1016/j.msard.2022.103715)

## Abstract

**Background:** Acupuncture as a complementary and alternative medicine (CAM) modality appears to be a helpful integrative therapy for multiple sclerosis (MS). Due to the chronicity of the disease and persistent symptoms, a large number of patients seek to use CAM for the MS treatment. Therefore, the present review aimed to determine the effectiveness of acupuncture in the treatment of multiple sclerosis.

**Methods:** PUBMED database was searched for English articles (at least English abstracts) in September 2021, including all articles published since the earliest literature until September 2021. Review articles were searched for relevant data. The searched keywords in titles and abstracts included ((acupuncture) OR (electroacupuncture)) AND (multiple sclerosis).

**Results:** Totally, out of 75 studied articles, 31 were included in this research. The advantages of acupuncture are mainly reflected in regulating neuro-immune system, improving the quality of life, reducing fatigue, improving the bladder function, reducing the spasm and pain of the limbs, delaying the progression of the disease, and reducing relapses.

**Conclusions:** According to the review of the recent articles, traditional Chinese acupuncture and scalp acupuncture appear to help improve the symptoms of multiple sclerosis (including fatigue, neural functional deficits, pain, gait impairments, and bladder dysfunction) and reduce relapses. Therefore, acupuncture could be used as an integrative therapy in patients with MS.



# Effects of Reflexology on Pain, Fatigue, and Quality of Life in Multiple Sclerosis Patients: A Clinical Study

Hatice Dilek Doğan, Mehtap Tan

PMID: 33789252

## Abstract

**Context:** Multiple Sclerosis (MS), occupies the first row among the diseases which leads to loss of neurological ability without depending on a trauma in the adults. Reflexology is one of complementary therapies based on activating a body's power to recover itself by special hand techniques applied to feet and hands. Positive changes in spasticity, pain, fatigue, depression, cortisol levels, anxiety, and blood pressure levels have been observed in MS patients after reflexology.

**Objectives:** This study was conducted to determine the effect of reflexology on pain, fatigue and quality of life in MS patients.

**Design:** The study was conducted experimentally by taking pretest and repeated measurements on reflexology and control groups determined by simple randomization.

**Setting:** The study took place in the neurology clinics at two university hospitals in Turkey.

**Participants:** Potential participants were 685 patients at the clinics who had been diagnosed with MS 6 months at least prior to the study. Of that group, 66 patients were included in the study, 33 in the intervention group and 33 in the control group.

**Intervention:** Reflexology was applied on each patient in the intervention group for 3 sessions a week for 12 weeks, and weekly pain and fatigue and monthly quality of life were evaluated. No intervention was made to the control group. Both groups received routine treatment.

**Outcome measures:** Measurements occurred at baseline, weekly and monthly throughout the trial, and postintervention. Pain and fatigue were evaluated weekly using a Visual Analogue Scale (VAS) and the Fatigue Severity Scale (FSS), respectively and quality of life was evaluated monthly using the Multiple Sclerosis Quality of Life-54 (MSQOL-54) scale.

**Results:** In the intervention group, significant decreases were observed in the pain scores from the seventh week and in the fatigue scores from the fifth week ( $P < .001$ ). In the assessment of quality of life, the combined physical health and combined mental health scores were found to be higher in the intervention group than in the control group ( $P < .001$ ).

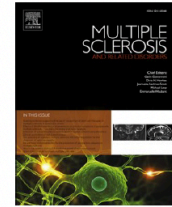
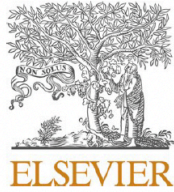
**Conclusion:** The study indicates that reflexology can be used as a complementary and alternative therapy to reduce pain and fatigue and enhance quality of life in MS patients.



## Foot Reflexology Chart







## Effects of hippotherapy on postural balance, functional mobility, self-perceived fatigue, and quality of life in people with relapsing-remitting multiple sclerosis: Secondary results of an exploratory clinical trial

Andréa Gomes Moraes<sup>a,\*</sup>, Silvia G.R. Neri<sup>a,b</sup>, Robert W. Motl<sup>c</sup>, Carlos Bernardo Tauil<sup>d</sup>, Felipe von Glehn<sup>e</sup>, Éber Castro Corrêa<sup>f</sup>, Ana Cristina de David<sup>a</sup>



Findings from this clinical trial provide exploratory evidence that hippotherapy improves postural balance, functional mobility, self-perceived fatigue, and quality of life of people with MS. Given the benefits of this intervention on these disabling symptoms, hippotherapy may be a useful approach for therapists to offer as a complementary treatment for people with MS.



# Personalized, bilateral whole-body somatosensory cortex stimulation to relieve fatigue in multiple sclerosis

Andrea Cancelli, Carlo Cottone, Alessandro Giordani, Simone Migliore, Domenico Lupoi, Camillo Porcaro, Massimiliano Mirabella, Paolo Maria Rossini, Maria Maddalena Filippi and Franca Tecchio

Multiple Sclerosis Journal

1–9

DOI: 10.1177/

1352458517720528

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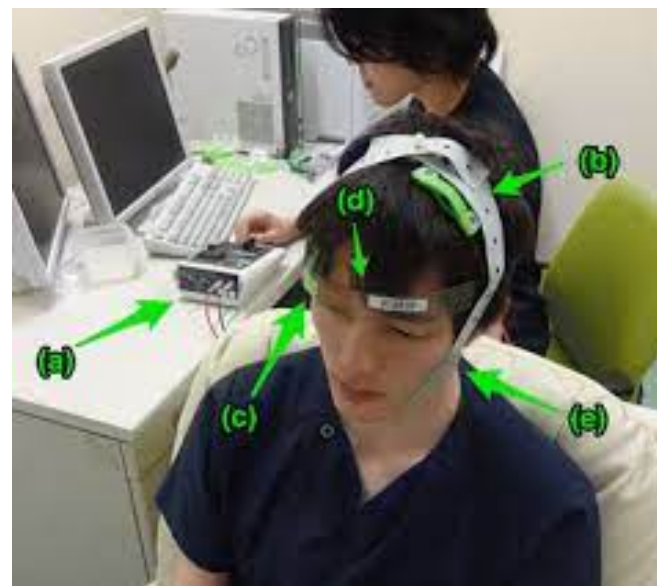
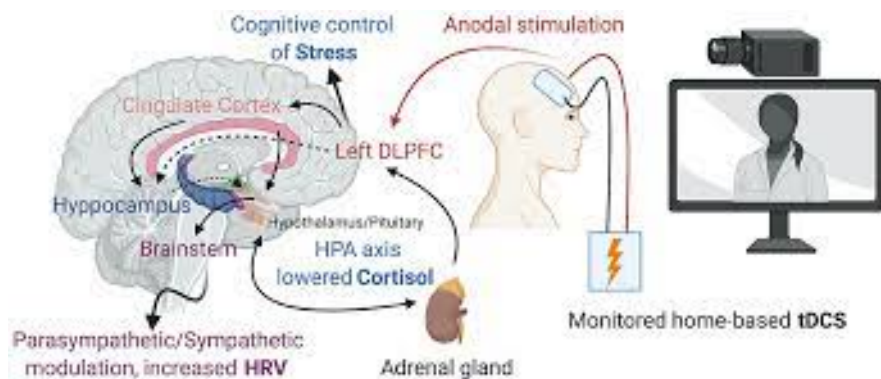
**Table 3.** Fatigue levels.

Stimulation	Real		Sham	
Time	Pre	Post	Pre	Post
Mean	52.5	27.6	51.3	46.0
SD	9.8	19.4	12.2	18.6
ES*	1.1		0.6	



## Fatigue in Multiple Sclerosis: A Review of the Exploratory and Therapeutic Potential of Non-Invasive Brain Stimulation

OPEN ACCESS

*Samar S. Ayache<sup>1,2\*</sup>, Nicolas Serratrice<sup>3,4</sup>, Georges N. Abi Lahoud<sup>3,4</sup> and Moussa A. Chalah<sup>1,2\*</sup>*

Second, in terms of tDCS, the data altogether suggest promising tDCS effects obtained on MS fatigue. The current challenge remains to find the best parameters to optimize treatment effects (e.g., applying a higher number of sessions, selecting the best cortical target, selecting the best return electrode location, designing patient-tailored electrodes, increasing the current intensity up to 4 mA) (56, 57, 68, 69, 78).

Review

# Virtual Reality-Based Therapy Improves Fatigue, Impact, and Quality of Life in Patients with Multiple Sclerosis. A Systematic Review with a Meta-Analysis

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**Citation:** Cortés-Pérez, I.; Sánchez-Alcalá, M.; Nieto-Escámez, F.A.; Castellote-Caballero, Y.; Obrero-Gaitán, E.; Osuna-Pérez, M.C. Virtual Reality-Based Therapy Improves Fatigue, Impact, and Quality of Life in Patients with Multiple Sclerosis. A Systematic Review with a Meta-Analysis. *Sensors* **2021**, *21*, 7389. <https://doi.org/10.3390/s21217389>

Academic Editor: Marco Carratù

Received: 13 September 2021  
Accepted: 4 November 2021  
Published: 6 November 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Abstract:** Patients with multiple sclerosis (PwMS) have a high level of fatigue and a reduced quality of life (QoL) due to the impact of multiple sclerosis (MS). Virtual reality-based therapy (VRBT) is being used to reduce disability in PwMS. The aim of this study was to assess the effect of VRBT on fatigue, the impact of MS, and QoL in PwMS. Methods: A systematic review with meta-analysis was conducted through a bibliographic search on PubMed, Scopus, Web of Science, and PEDro up to April 2021. We included randomized controlled trials (RCTs) with PwMS that received VRBT in comparison to conventional therapy (CT) including physiotherapy, balance and strength exercises, and stretching or physical activity, among others; or in comparison to simple observation; in order to assess fatigue, MS-impact, and QoL. The effect size was calculated using Cohen's standardized mean difference with a 95% confidence interval (95% CI). Results: Twelve RCTs that provided data from 606 PwMS (42.83 ± 6.86 years old and 70% women) were included. The methodological quality mean, according to the PEDro Scale, was 5.83 ± 0.83 points. Our global findings showed that VRBT is effective at reducing fatigue (SMD −0.33; 95% CI −0.61, −0.06), lowering the impact of MS (SMD −0.3; 95% CI −0.55, −0.04), and increasing overall QoL (0.5; 95% CI 0.23, 0.76). Subgroup analysis showed the following: (1) VRBT is better than CT at reducing fatigue (SMD −0.4; 95% CI −0.7, −0.11), as

well as in improving the mental dimension of QoL simple observation at reducing the impact of MS overall QoL (SMD 0.79; 95% CI 0.3, 1.28); and (2) than CT in improving the global (SMD 0.6, 95% CI 0.3, 0.9) and mental dimensions (SMD 0.6; 95% CI 0.08, 1.1). Subgroup analysis showed the following: (1) VRBT is better than CT at reducing fatigue (SMD −0.4; 95% CI −0.7, −0.11), as

**Keywords:** multiple sclerosis; virtual reality; virtual reality-based therapy

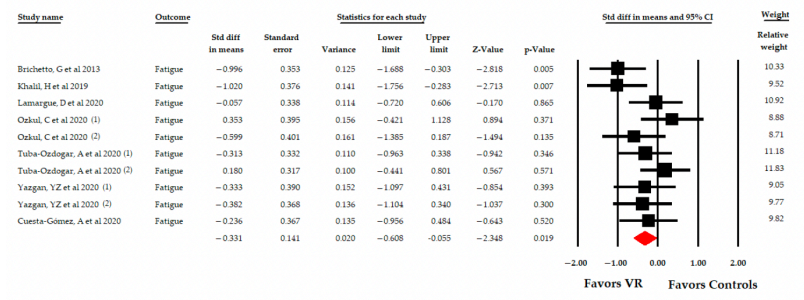


Figure 2. Forest Plot of the Effect of Virtual Reality on Fatigue.

## 5. Conclusions

Our results showed that VR-based therapy is effective in reducing fatigue and the impact of MS, as well as increasing QoL in PwMS. Specifically, to reduce fatigue, VR-based intervention is better than CT. In terms of the impact of MS, VR-based intervention was better than simple observation. To increase overall QoL, VR-based therapy is better than simple observation and the combined use of VR-based intervention with CT is better than CT alone. Finally, VR-based intervention also showed a positive effect on the physical and mental dimensions of QoL, demonstrating a significant increase in both dimensions when the VR-based intervention was used in combination with CT, compared to CT alone. Nevertheless, further research is needed to assess the effect of VR-based intervention, both alone and when combined with other therapies.



Review

# New Strategies for Rehabilitation and Pharmacological Treatment of Fatigue Syndrome in Multiple Sclerosis

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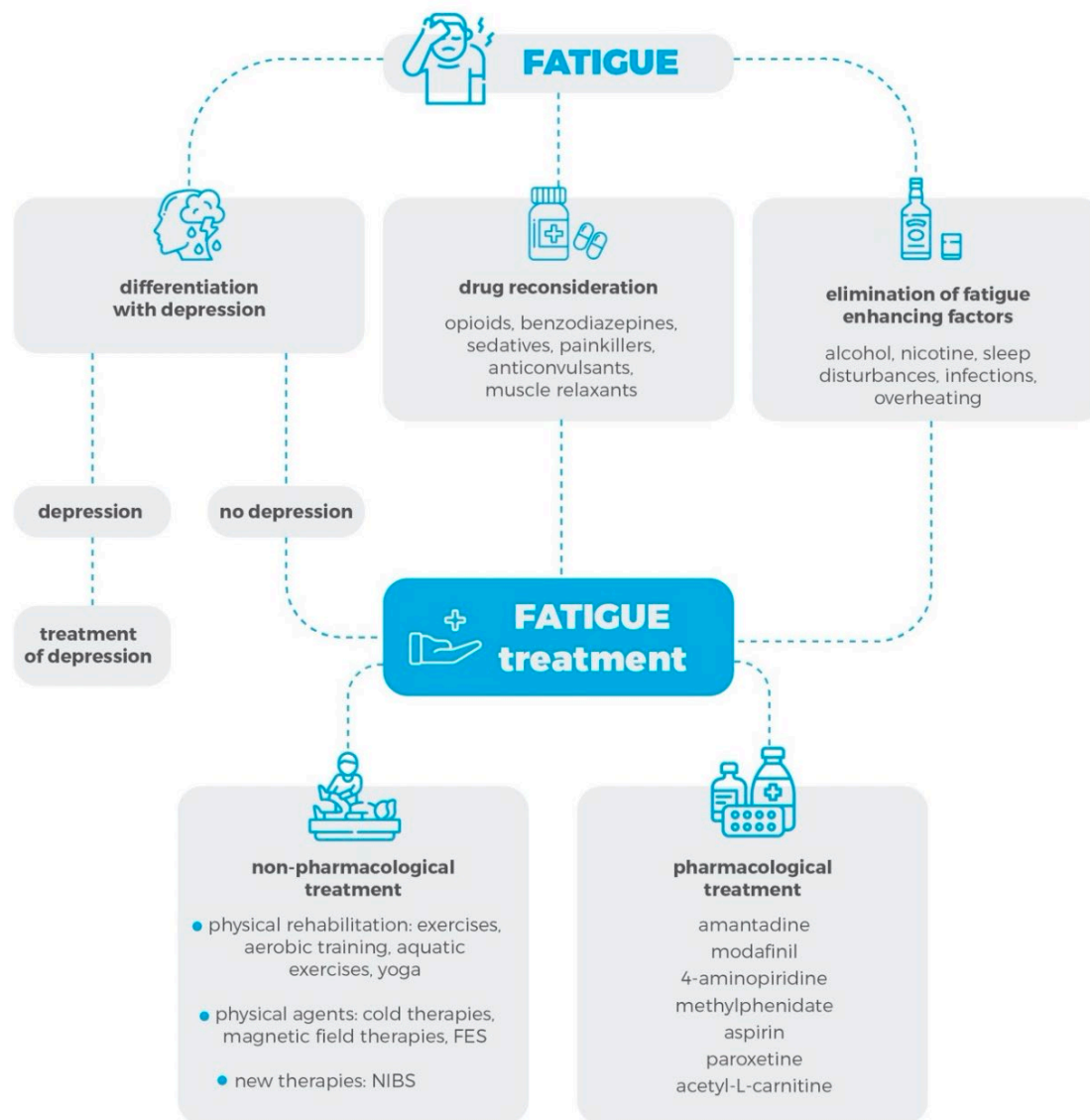
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Received: 27 September 2020; Accepted: 5 November 2020; Published: 7 November 2020







# Fatigue

## 10 ways to manage MS fatigue

- ⊕ 1. Keep a fatigue diary
- ⊕ 2. Take rest when you need it
- ⊕ 3. Prioritise tasks
- ⊕ 4. Improve your posture
- ⊕ 5. Organise your living and work spaces
- ⊕ 6. Healthy eating
- ⊕ 7. Any kind of exercise could help
- ⊕ 8. Fatigue management programmes
- ⊕ 9. What drug treatments might help with MS fatigue?
- ⊕ 10. Finding help and taking help that's offered



«Che fatica essere uomini...»



