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FATIGUE IN MULTIPLE SCLEROSIS – MECHANISMS, DIAGNOSIS, AND TREATMENT OPTIONS

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ABSTRACT

Fatigue is one of the most prevalent and debilitating symptoms of multiple sclerosis (MS), affecting up to 95% of patients and significantly impairing quality of life. This review synthesizes current knowledge on the pathophysiology, diagnosis, and treatment of MS-related fatigue. Fatigue in MS is a multidimensional phenomenon that includes physical, cognitive, and central components, stemming from both primary neurological mechanisms and secondary comorbidities. The underlying pathophysiological contributors include demyelination, dopaminergic dysregulation, pro-inflammatory cytokine activity, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, and mitochondrial impairment. Diagnosis primarily relies on subjective self-report scales such as the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), and Fatigue Scale for Motor and Cognitive Functions (FSMC), though overlapping symptoms like depression and sleep disorders complicate clinical assessment. Treatment remains challenging: while pharmacological options—such as amantadine, modafinil, and ponesimod—offer limited and inconsistent benefits, non-pharmacological strategies, particularly physical activity and cognitive-behavioural therapy (CBT), show stronger evidence for improving fatigue and patient well-being. The paper emphasizes the necessity of an individualized, multidimensional treatment approach to effectively manage fatigue and mitigate its impact on the physical, social, and occupational functioning of individuals with MS.

KEYWORDS

Multiple Sclerosis, Fatigue, MS-Related Fatigue, Cognitive Dysfunction

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Introduction

Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS) that leads to demyelination and neurodegeneration. It is also considered the most common potential cause of neurological disability in young adults. [1]

In 2023, nearly 3 million people worldwide were living with multiple sclerosis. [2]

The highest incidence of MS is observed in European and American countries, ranging from 111 to 300 cases per 100,000 inhabitants. In Asia, the incidence is approximately 30 cases per 100,000 inhabitants, while the lowest rates are reported in African countries and the Western Pacific region, which is around 5 cases per 100,000 people. [3]

MS is characterized by recurrent relapses that contribute to the accumulation of neurological deficits. Each relapse may result in permanent damage to nervous system function, manifesting as a wide spectrum of impairments. The most common symptoms include muscle weakness, spasticity, tremor, ataxia, chronic fatigue, and sensory disturbances. Additionally, patients often experience autonomic dysfunction (e.g., bowel and bladder problems), pain, sexual dysfunction, as well as speech (dysarthria), swallowing (dysphagia), cognitive, and psychiatric disturbances. Progressing deficits lead to gradual limitations in mobility and independence in daily activities, significantly affecting patients' quality of life. [4]

Fatigue is one of the most burdensome symptoms for individuals with MS, occurring in up to 80% of patients and markedly impairing daily functioning. [5]

Due to its high prevalence, nonspecific nature, and diagnostic and therapeutic challenges, MS-related fatigue remains a significant clinical issue. [6]

The aim of this thesis is to review current data on the mechanisms underlying fatigue in MS, its diagnosis, and the available therapeutic options.

The Concept of Fatigue in MS

Fatigue is defined as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.” [7]

From an etiological perspective, fatigue is categorized as primary or secondary. Primary fatigue results directly from the pathophysiology of MS, i.e., demyelination, axonal damage, activation of pro-inflammatory cytokines, and dysfunction of the central nervous system. It is considered an inherent effect of the disease itself, independent of other symptoms or complications. Secondary fatigue, on the other hand, arises from factors associated with MS, such as sleep disturbances, chronic pain, infections, adverse effects of treatment, or depression. [8]

Based on its manifestation and the localization of underlying mechanisms, fatigue in multiple sclerosis can be classified into three main types: physical, cognitive, and central.

Physical fatigue manifests as muscle weakness and rapid exhaustion during physical activity. Patients often describe it as a feeling of “heavy legs” or “lack of strength in the limbs.”

Cognitive fatigue concerns cognitive functions and presents as reduced concentration, diminished intellectual performance, and a sensation of “slowed thinking.” These symptoms may appear even without prior physical exertion.

Central fatigue is considered the most challenging to capture clinically. It may occur immediately upon waking, regardless of sleep duration or activity level, and its mechanisms are linked to damage within brain structures responsible for regulating central nervous system activity—particularly the basal ganglia, thalamus, and brainstem. [8]

Population data indicate that fatigue occurs in 80–95% of patients with MS, and as many as 55% consider it the most debilitating symptom of the disease. [9] It is important to note that there is no single “typical” pattern of fatigue—patients often experience a mixed presentation in which physical, cognitive, and central elements overlap and fluctuate over time. [10]

Understanding this classification is crucial, as different types of fatigue may require distinct therapeutic interventions.

Table 1. Classification of Fatigue in Multiple Sclerosis

Type of fatigue	Characteristics	Main symptoms	Possible mechanisms
Physical	Decreased muscle strength and endurance during physical activity.	<ul style="list-style-type: none"> – feeling of heaviness in the limbs – rapid exhaustion with exertion – difficulty performing movements 	<ul style="list-style-type: none"> – damage to pyramidal tracts – muscle deconditioning – spasticity
Cognitive (mental)	Reduced efficiency of cognitive and motivational functions.	<ul style="list-style-type: none"> – concentration difficulties – slowed thinking (“brain fog”) 	<ul style="list-style-type: none"> – alterations in the frontal cortex – co-occurring depression – sleep disturbances
Central (neurological)	General, hard-to-define sense of exhaustion, independent of activity level.	<ul style="list-style-type: none"> – lack of energy from the morning – fatigue disproportionate to effort – unexplained weakness 	<ul style="list-style-type: none"> – demyelination of brain structures – impaired dopaminergic transmission

Source: Bakshi R. *Fatigue associated with multiple sclerosis: diagnosis, impact and management.* Multiple Sclerosis Journal. 2003;9(3):219–27.

Pathophysiological Mechanisms of Fatigue in MS

Fatigue in multiple sclerosis is a multifactorial phenomenon that does not arise solely from neurological damage but also involves immunological, hormonal, and metabolic alterations. It is believed that both mechanisms directly related to MS pathophysiology—central mechanisms—as well as indirect factors can contribute to and exacerbate fatigue symptoms. [11]

Damage to central nervous system structures

Demyelinating and neurodegenerative changes characteristic of MS lead to disturbances within structures responsible for regulating motor activity, attention, and arousal, such as the basal ganglia, thalamus, brainstem, and prefrontal cortex. [12]

A study by Genova et al. using fMRI demonstrated that patients with high levels of fatigue exhibit reduced activation in the prefrontal cortex and caudate nucleus during a cognitive task. In contrast, individuals with lower fatigue showed greater activation of compensatory structures, suggesting the existence of adaptive mechanisms that may protect against cognitive decline. [13]

These findings support the view that fatigue has a measurable neurological basis associated with the dysfunction of specific brain regions.

Dysregulation of dopaminergic neurotransmission

Dysfunction of the dopaminergic system plays a significant role in the development of fatigue. Dopamine, a neurotransmitter responsible for motivation, attention, and drive regulation, is essential for the subjective sense of energy. Neuroimaging studies have demonstrated reduced activity in the mesolimbic and mesocortical pathways in MS patients experiencing fatigue. [14]

The involvement of dopaminergic mechanisms is also supported by clinical improvement observed following pharmacological interventions such as modafinil or bupropion. [15]

The role of cytokines and inflammation

Several studies have investigated the impact of chronic inflammation on fatigue symptoms in MS. Hanken et al. (2020) reported that elevated serum IL-6 levels significantly correlate with higher levels of cognitive fatigue. [16]

Similarly, Gilio et al. (2022) found that lower concentrations of anti-inflammatory cytokines in cerebrospinal fluid correlate with increased fatigue severity, indicating the important role of cytokine imbalance in the pathogenesis of this symptom. [17]

This is further supported by findings from Damato et al. (2022), who observed elevated levels of proinflammatory cytokines in the serum of patients experiencing moderate to severe fatigue. [18]

Hypothalamic–pituitary–adrenal (HPA) axis dysregulation

Growing evidence suggests that dysregulation of the hypothalamic–pituitary–adrenal axis occurs in individuals with MS and may contribute to chronic fatigue. Studies have reported both a flattened diurnal cortisol rhythm and a blunted stress response. [19]

Mokary et al. (2024) demonstrated that lower salivary cortisol levels correlate with increased fatigue severity and mood disturbances in MS patients, which may indicate reduced HPA axis activity in this population. [20]

However, a 2023 systematic review showed inconsistencies in findings on HPA axis involvement, as not all studies confirmed a link between cortisol levels and fatigue intensity. This suggests a complex mechanism potentially influenced by additional factors such as depression or sleep disorders. [21]

Mitochondrial dysfunction and oxidative stress

Mitochondrial abnormalities are increasingly recognized as a key mechanism underlying fatigue in MS. Studies have shown reduced activity of respiratory chain complexes I and IV in glial cells and neurons derived from MS patients, resulting in decreased ATP production and increased oxidative stress. [22]

The severity of these disturbances has been linked to the intensity of fatigue symptoms reported in clinical cohorts.

Diagnosis of Fatigue in MS

Tools for assessing fatigue

In the diagnostic evaluation of fatigue in patients with multiple sclerosis, self-report instruments are commonly used to assess the subjective experience of fatigue and its impact on daily functioning. The most widely used scales include the Fatigue Severity Scale (FSS), the Modified Fatigue Impact Scale (MFIS), and the Fatigue Scale for Motor and Cognitive Functions (FSMC).

Table 2. Comparison of fatigue assessment scales in multiple sclerosis

Scale	Full name	Number of items	Scoring range	Administration time	Assessment scope (descriptive)	Pathological threshold	Advantages	Disadvantages
FSS	Fatigue Severity Scale	9	1–7	~5 min	Overall level of fatigue	≥ 4 (mean score across 9 items)	Quick, well-validated, widely used	Does not differentiate fatigue types
MFIS	Modified Fatigue Impact Scale	21	0–4	~10–15 min	Impact of fatigue on physical, cognitive, and psychosocial functioning	≥ 38 (total score)	More comprehensive; widely used in clinical research	Longer completion time
FSMC	Fatigue Scale for Motor and Cognitive Functions	20	1–5	~10 min	Differentiates motor and cognitive fatigue	≥ 43 (for each domain separately)	Precise differentiation of fatigue types; good validity	Less commonly used in routine clinical practice

Differential Diagnosis of Fatigue

The diagnostic assessment of fatigue in multiple sclerosis should take into account its potential coexistence with other symptoms, particularly depression and sleep disturbances. Studies have shown that depression may significantly influence scores on the MFIS and FSS scales, potentially leading to an overestimation of fatigue severity. [23]

Therefore, it is recommended to use parallel screening tools such as the Beck Depression Inventory (BDI) or the Hospital Anxiety and Depression Scale (HADS).

Sleep disorders, including insomnia and excessive daytime sleepiness, may also contribute to secondary fatigue. To assess these conditions, tools such as the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale are used. Multicenter studies indicate that as many as 60–70% of MS patients experiencing fatigue also present symptoms of sleep disturbances. [24]

Diagnostic challenges

Fatigue, despite being one of the most common and disabling symptoms of multiple sclerosis, is difficult to diagnose and classify due to the absence of objective biological markers. As a result, all assessment instruments rely on patients' subjective reporting. [25]

Additionally, fatigue in MS may fluctuate significantly throughout the day and can be modified by external factors. [26]

In clinical practice, fatigue often overlaps with other symptoms such as pain, cognitive dysfunction, or spasticity, which complicates the interpretation of scale results. [27]

Therefore, the use of multiple assessment tools and interpretation of outcomes within the context of the patient's overall clinical picture is essential.

Pharmacological Treatment of Fatigue in MS

Despite the significant impact of MS-related fatigue on quality of life, pharmacological treatment options remain limited. The symptomatic management of fatigue primarily includes amantadine, modafinil, fampridine, and more recently investigated immunomodulatory agents such as ponesimod.

Amantadine, originally used for the treatment of Parkinsonian symptoms and influenza, exerts its effect in MS by modulating dopaminergic and glutamatergic neurotransmission, leading to improved motor activity and reduced subjective fatigue.

In a randomized clinical trial comparing amantadine with acupuncture, patients receiving 100 mg of amantadine twice daily for 8 weeks demonstrated a reduction in fatigue as measured by the FSS scale. The effect was most pronounced during the first 4 weeks of treatment and persisted throughout the observation period. [28]

Modafinil, initially approved for narcolepsy, acts as an adrenergic and dopaminergic agonist. Although early studies suggested promising outcomes in alleviating MS-related fatigue, systematic reviews and meta-analyses have not provided conclusive evidence supporting its efficacy. Consequently, many experts recommend that modafinil be considered only in cases of fatigue that are resistant to other interventions. [29]

Fampridine, a potassium channel blocker primarily used to improve gait in MS patients, may also influence subjective fatigue by enhancing conduction in demyelinated axons.

A systematic review of studies reported that fampridine may reduce fatigue in some patients, particularly those with motor deficits, although this effect was not consistently observed across all trials. The drug's effectiveness appears to be limited to a subgroup of patients with significant motor pathway involvement. [30]

Ponesimod, a selective sphingosine-1-phosphate receptor modulator (S1P1), is approved as a disease-modifying therapy for relapsing-remitting MS. Studies have shown that patients treated with ponesimod reported reduced fatigue as measured by the FSIQ-RMS questionnaire. This effect is attributed to reduced inflammatory activity and improvement of overall neurological function. [31]

Pharmacological management of fatigue in MS remains a clinical challenge, and the effectiveness of available treatments is often moderate. Among current options, amantadine is the most frequently used and demonstrates modest but consistent benefits in recent studies. Modafinil and fampridine may be helpful in selected cases, although their efficacy is less predictable. Given the limited success of pharmacological therapies, ruling out secondary causes and implementing non-pharmacological interventions remain essential components of managing fatigue in MS.

Non-pharmacological Treatment of Fatigue in MS

Given the limited effectiveness of pharmacotherapy in managing fatigue in multiple sclerosis, interest in non-pharmacological therapeutic strategies has been steadily increasing. The best-documented interventions include physical activity, cognitive-behavioural therapy (CBT), and digital or telemedicine tools supporting self-regulation and symptom monitoring.

Physical exercise and movement-based interventions

Regular physical activity plays a key role in reducing fatigue. A systematic review encompassing over 150 randomized trials demonstrated that the most effective interventions include balance and postural training, mind-body exercises such as yoga or tai chi, as well as resistance and endurance training. [32]

Cognitive-behavioural therapy (CBT)

Cognitive-behavioural therapy has long been used in the treatment of depression and anxiety, but its application in MS-related fatigue has shown increasing effectiveness. In a review by Masoud et al., fatigue-focused CBT was found to produce a moderate therapeutic effect ($SMD \approx 0.60$) and significantly improved subjective ratings of energy and perceived agency. [32]

The beneficial impact of CBT may be linked to modulation of the immune and neuroinflammatory systems. Chronic inflammation has been associated with increased fatigue and the exacerbation of depressive symptoms. Psychotherapy has been shown to reduce the expression of inflammatory markers and improve psychological well-being, which indirectly contributes to reduced fatigue. [33]

Non-pharmacological interventions represent an important component of fatigue management in MS. The strongest evidence supports the effectiveness of physical exercise and cognitive-behavioural therapy. Given the limitations of pharmacological treatments, a comprehensive therapeutic approach incorporating lifestyle modification, psychological support, and patient activation appears most promising.

Impact of fatigue on daily functioning and quality of life

Fatigue in MS is a symptom that significantly affects daily functioning and often has a greater impact on life than motor symptoms. It limits physical, social, and occupational activity, thereby reducing quality of life.

As demonstrated in a 2025 study by Ravazoula and Koutsojannis, patients experiencing severe fatigue are less likely to engage in social activities, show reduced motivation, and more frequently encounter difficulties maintaining occupational stability. [34]

Chronic fatigue often co-occurs with sleep and mood disturbances. Interventions aimed at improving sleep quality can reduce fatigue and enhance overall functioning. This is supported by evidence from a study in which a telerehabilitation programme improved sleep, reduced fatigue, and increased quality of life among MS patients. [35]

Conclusions

Fatigue is one of the most common and burdensome symptoms of multiple sclerosis (MS), affecting as many as 80–95% of patients. This paper examined fatigue in MS as a complex phenomenon with both primary and secondary components. Three main types of fatigue were identified, along with their clinical characteristics and underlying pathophysiological mechanisms, including neurotransmitter dysfunction, inflammatory and immunological processes, dysregulation of the HPA axis, as well as mitochondrial deficits and oxidative stress.

The diagnosis of fatigue relies primarily on self-report scales; however, the absence of objective biological markers remains a significant limitation. Differential diagnosis must also consider coexisting symptoms, especially depression and sleep disturbances.

Both pharmacological and non-pharmacological treatment options were discussed, including physical rehabilitation and cognitive-behavioural therapy (CBT). Particular emphasis was placed on the importance of a holistic therapeutic approach.

The paper highlights that fatigue in MS substantially reduces quality of life and negatively affects patients' social, occupational, and emotional functioning. Effective management of this symptom requires an individualized and multidimensional therapeutic strategy.

REFERENCES

1. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2002;359(9313):1221-1231. doi:10.1016/S0140-6736(02)08220-X
2. Mohammed EMA. Understanding Multiple Sclerosis Pathophysiology and Current Disease-Modifying Therapies: A Review of Unaddressed Aspects. *Front Biosci (Landmark Ed)*. 2024;29(11):386. doi:10.31083/j.fbl2911386
3. Lorenzut S, Negro ID, Pauletto G, et al. Exploring the Pathophysiology, Diagnosis, and Treatment Options of Multiple Sclerosis. *J Integr Neurosci*. 2025;24(1):25081. doi:10.31083/JIN25081
4. Duan H, Jing Y, Li Y, Lian Y, Li J, Li Z. Rehabilitation treatment of multiple sclerosis. *Front Immunol*. 2023;14:1168821. Published 2023 Apr 6. doi:10.3389/fimmu.2023.1168821
5. Yeni K, Terzi M. Multiple Sclerosis-related Fatigue: An Updated Review of Pathophysiology and Associated Variables Contributing Factors. *J Mult Scler Res*. 2025;5(2):33-42. doi:10.4274/jmsr.galenos.2025.2025-4-4
6. Abdelfattah, E., Rehab, N., Fahmy, E., Alsaid, H. Relationship Between Fatigue And Balance In Patients With Multiple Sclerosis. *Benha International Journal of Physical Therapy*, 2025; 3(2): 41-48. doi: 10.21608/bijpt.2025.388175.1092
7. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis. Washington DC: Paralyzed Veterans of America; (1998).
8. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Multiple Sclerosis Journal*. 2003;9(3):219-227. doi:10.1191/1352458503ms904oa
9. R.J. Mills, C.A. Young, A medical definition of fatigue in multiple sclerosis, *QJM: An International Journal of Medicine*, Volume 101, Issue 1, January 2008, Pages 49–60, <https://doi.org/10.1093/qjmed/hcm122>
10. Penner, IK., Paul, F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol* 13, 662–675 (2017). <https://doi.org/10.1038/nrneurol.2017.117>
11. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*. 2013;80(4):409-416. doi:10.1212/WNL.0b013e31827f07be
12. Kos D, Kerckhofs E, Nagels G, D'hooghe MB, Ilsbrouckx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair*. 2008;22(1):91-100. doi:10.1177/1545968306298934
13. Deluca, John & Genova, Helen & Hillary, Frank & Wylie, Glenn. (2008). Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *Journal of the neurological sciences*. 270. 28-39. 10.1016/j.jns.2008.01.018.
14. Dobryakova E, Genova HM, DeLuca J, Wylie GR. The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders. *Front Neurol*. 2015;6:52. Published 2015 Mar 12. doi:10.3389/fneur.2015.00052

15. Zifko UA. Management of fatigue in patients with multiple sclerosis. *Drugs*. 2004;64(12):1295-1304. doi:10.2165/00003495-200464120-00003
16. Yeni K, Terzi M. Multiple Sclerosis-related Fatigue: An Updated Review of Pathophysiology and Associated Variables Contributing Factors. *J Mult Scler Res*. 2025 Aug 29;5(2):33-42. doi: 10.4274/jmsr.galenos.2025.2025-4-4. Epub 2025 Jun 25.
17. Gilio L, Buttari F, Pavone L, et al. Fatigue in Multiple Sclerosis Is Associated with Reduced Expression of Interleukin-10 and Worse Prospective Disease Activity. *Biomedicines*. 2022;10(9):2058. Published 2022 Aug 23. doi:10.3390/biomedicines10092058
18. Damato EG, Fillioe SJ, Margevicius SP, et al. Increased Serum Levels of Proinflammatory Cytokines Are Accompanied by Fatigue in Military T-6A Texan II Instructor Pilots. *Front Physiol*. 2022;13:876750. Published 2022 Apr 28. doi:10.3389/fphys.2022.876750
19. Mordillo-Mateos L, Soto-Leon V, Torres-Pareja M, et al. Fatigue in Multiple Sclerosis: General and Perceived Fatigue Does Not Depend on Corticospinal Tract Dysfunction. *Front Neurol*. 2019;10:339. Published 2019 Apr 9. doi:10.3389/fneur.2019.00339
20. Mokary, Yousef & Vaheb, Saeed & Yazdan Panah, Mohammad & Afshari-Safavi, Alireza & Moases Ghaffary, Elham & Barzegar, Mahdi & Shirbacheh, Ali & Shaygannejad, Vahid & Mirmosayyeb, Omid. (2024). The Association of Salivary Cortisol Levels With Depression, Anxiety, and Quality of Life in Male Relapsing-Remitting Multiple Sclerosis Patients: A Case-Control Study. *Acta Neurologica Scandinavica*. 2024. 10.1155/2024/8728071.
21. Pereira GM, Soares NM, Souza AR, Becker J, Finkelsztejn A, Almeida RMM. Basal cortisol levels and the relationship with clinical symptoms in multiple sclerosis: a systematic review. *Arq Neuropsiquiatr*. 2018;76(9):622-634. doi:10.1590/0004-282X20180091
22. Campbell G, Mahad DJ. Mitochondrial dysfunction and axon degeneration in progressive multiple sclerosis. *FEBS Lett*. 2018;592(7):1113-1121. doi:10.1002/1873-3468.13013
23. Tarasiuk J, Kapica-Topczewska K, Czarnowska A, Choraży M, Kochanowicz J, Kułakowska A. Co-occurrence of Fatigue and Depression in People With Multiple Sclerosis: A Mini-Review. *Front Neurol*. 2022;12:817256. Published 2022 Feb 15. doi:10.3389/fneur.2021.817256
24. Yi X, Zhang Y, Du Q, et al. Global prevalence of fatigue in patients with multiple sclerosis: a systematic review and meta-analysis. *Front Neurol*. 2024;15:1457788. Published 2024 Oct 2. doi:10.3389/fneur.2024.1457788
25. Penner, IK. (2023). Clinical Assessment Tools for Fatigue. In: Penner, IK. (eds) *Fatigue in Multiple Sclerosis*. Springer, Cham. https://doi.org/10.1007/978-3-031-13498-2_10
26. Broch L, Simonsen CS, Flemmen HØ, et al. High prevalence of fatigue in contemporary patients with multiple sclerosis. *Mult Scler J Exp Transl Clin*. 2021;7(1):2055217321999826. Published 2021 Mar 18. doi:10.1177/2055217321999826
27. Heidari, M., Taghizadeh, G., Nabavi, S. M., Penner, I. K., Lajevardi, L., & Akbarfahimi, M. (2025). Reliability and validity of the Persian version of the Fatigue Scale for Motor and Cognitive Functions (P-FSMC) in Iranian people with multiple sclerosis. *Disability and Rehabilitation*, 47(19), 5123–5132. <https://doi.org/10.1080/09638288.2025.2466716>
28. Hadianfard M, Poursadeghfard M, Fazeli N. A Comparative Study of Acupuncture and Oral Amantadine in Relieving Fatigue in Patients with Multiple Sclerosis: A Randomized Clinical Trial. *J Acupunct Res* 2025;42:344-354. <https://doi.org/10.13045/jar.25.0009>
29. Toljan K, Aboseif A, Amin M. Efficacy of pharmacologic treatments for fatigue in multiple sclerosis: A systematic review and meta-analysis. *Mult Scler Relat Disord*. 2025;96:106352. doi:10.1016/j.msard.2025.106352
30. Diaz-Quiroz M, Chicue-Cuervo PC, Garcia-Moreno L, Gaviria-Carrillo M, Talero-Gutierrez C, Palacios-Espinosa X. Fatigue in multiple sclerosis: A scoping review of pharmacological and nonpharmacological interventions. *Mult Scler J Exp Transl Clin*. 2025;11(1):20552173241312527. Published 2025 Feb 13. doi:10.1177/20552173241312527
31. Kappos L, Fox RJ, Burcklen M, et al. Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial. *JAMA Neurol*. 2021;78(5):558–567. doi:10.1001/jamaneurol.2021.0405
32. Masoud, S. A., Karami, F., Noorbakhsh, M., Akbari, H., Masoud, M. S. and Karami, M. (2025). Non-Pharmacological Interventions for Fatigue in Multiple Sclerosis: A Systematic Review. *Studies in Multidisciplinary Medical Research*, 1(5), 25-45. doi: 10.32592/smmr.202501.05.04
33. Vitali E, Cattane N, D'Aprile I, Petrillo G, Cattaneo A. Systemic Inflammation at the Crossroad of Major Depressive Disorder and Comorbidities: A Narrative Review. *International Journal of Molecular Sciences*. 2025; 26(19):9382. <https://doi.org/10.3390/ijms26199382>
34. Ravazoula, C., & Koutsojannis, C. (2025). Beyond Disability Scores: The Provocative Truth of Psychosocial Resilience in Battling MS Quality of Life in Western Greece. Preprints. <https://doi.org/10.20944/preprints202511.0922.v1>
35. Kaya A, Karadağ-Saygı E, Kucukosmanoglu Z, Keniş-Coşkun Ö, Ağan Yıldırım K. Effect of Telerehabilitation Exercise Program on Sleep Quality and Fatigue in Individuals With Multiple Sclerosis. *Ann Rehabil Med*. 2025;49(5):302-309. doi:10.5535/arm.250010