fortune Journals

Research Article

ARCHIVES OF INTERNAL MEDICINE RESEARCH

ISSN: 2688-5654

Linking Pathogenesis to Fall Risk in Multiple Sclerosis

Jaylan Patel[1], Marcel P. Fraix[1], and Devendra K. Agrawal[1]*

Abstract

Multiple Sclerosis is a chronic neurological disorder characterized by progressive disability, with falls being a significant consequence of its physical and cognitive impairments. This review explores the major contributors to fall risk in individuals with multiple sclerosis and explores the broader implications of these factors, such as the fear of falling. The primary factors associated with fall risk include gait abnormalities, cognitive dysfunction, and fatigue. These factors often interact, leading to mobility limitations and diminishing overall quality of life. Interventions to mitigate fall risk in multiple sclerosis have shown varying degrees of success. Exercise and rehabilitation strategies improve physical function and balance, while cognitive-behavioral therapy addresses fatigue and associated symptoms. Self-management programs empower patients to take an active role in symptom management, though their effectiveness varies. Disease-modifying therapies are the primary treatment for slowing disease progression, indirectly reducing fall risk. Emerging technologies show promise in enhancing mobility and safety, while machine learning algorithms offer the potential for predicting fall risk in multiple sclerosis populations. This review underscores the need for a comprehensive approach to fall prevention in multiple sclerosis. Healthcare providers can develop personalized strategies to improve mobility, reduce fall incidence, and enhance the quality of life for individuals with multiple sclerosis. Further research is essential to refine these interventions and optimize long-term outcomes.

Keywords: Cognition; Falls; Fall risk; Fatigue; Gait; Multiple sclerosis

Introduction

Multiple Sclerosis (MS) is a chronic, progressive neurological disorder that affects the central nervous system, resulting in various symptoms that can impair mobility, cognition, and overall quality of life. The disease involves autoimmune-mediated demyelination and neurodegeneration, disrupting neural signaling and leading to neurological deficits. MS is more common in women and individuals of White race, with prevalence increasing globally due to several factors. Clinically, MS presents with a wide range of symptoms, including fatigue, cognitive dysfunction, and gait abnormalities. The disease presentation can vary, with there being different sub-types of MS depending on progression and remission. Risk factors are often genetic, environmental, and lifestyle based where each can play a large role in the development or progression of MS.

One of the major concerns for individuals living with MS is the increased risks of falls and their associated injuries, which are more

Affiliation:

[1]Department of Translational Research, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California 91766 USA.

***Corresponding author:**

Devendra K. Agrawal, MSc, Ph.D. (Biochem), Ph.D. (Med Sci), MBA, MS (ITM), FAAAAI, FAHA, FAPS, FIACS Professor and Director, Department of Translational Research Western University of Health Sciences 309 E. Second Street Pomona, California 91766-1854, USA.

Citation: Jaylan Patel, Marcel P. Fraix, and Devendra K. Agrawal. Linking Pathogenesis to Fall Risk in Multiple Sclerosis. Archives of Internal Medicine Research. 8 (2025): 36-47.

Received: January 21, 2025
Accepted: January 27, 2025
Published: January 30, 2025

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

common and worse due to the degenerative nature of the disease [3]. Mobility dysfunction in MS patients is frequently accompanied by gait instability, muscle weakness, and a loss of coordination, significantly hindering daily activities and reducing independence [4, 5]. This literature review will explore the complex relationship between MS-related mobility dysfunction and fall risk, examining the role of various factors such as cognitive impairment, fatigue, and the effectiveness of management strategies, including exercise, self-management programs, and pharmacological interventions.

Pathophysiology, Epidemiology and Clinical Characteristics

Pathophysiology

Multiple Sclerosis is an autoimmune disease where the immune system attacks myelin, the protective covering of nerve fibers, causing inflammation and nerve damage. This process begins by disrupting the blood-brain barrier, which normally prevents leukocytes from entering the brain and then triggers inflammation. Leukocytes, including T cells that produce cytokines and B cells that generate antibodies, are primarily responsible for demyelination, along with microglia, which contribute to inflammation [1]. These cytokines and antibodies attack oligodendrocytes, the cells responsible for producing myelin, ultimately damaging myelin and reducing nerve conduction [2]. This process is illustrated in Figure 1. The disease itself is primarily characterized by episodes of relapse and remission, with varying forms. The diverse nature of MS results in a broad spectrum of symptoms, including mobility impairments, cognitive dysfunction, and fatigue, all of which contribute significantly to the overall burden of the disease.

Epidemiology

It is important to identify the current prevalence of Multiple Sclerosis in today's population and its change over time to determine the scope of healthcare needs and resource allocation. In a study estimating the prevalence of MS in the United States based on administrative health claims, data indicated that the prevalence of MS in adults has been steadily increasing, with 2010 marking an all-time high. Predictions for future trends of MS prevalence also suggest a continued increase [8]. This dataset was limited, as it did not include data from several U.S. communities, possibly indicating that the actual prevalence of MS could be higher than reported. This conclusion aligns with findings from studies in other countries that also show a rising prevalence of MS, potentially due to the aging population and increased incidence rates [17, 18]. Improved diagnostic techniques and heightened awareness among healthcare professionals may also contribute to the observed increase in reported cases. Additionally, changes in environmental and lifestyle factors,

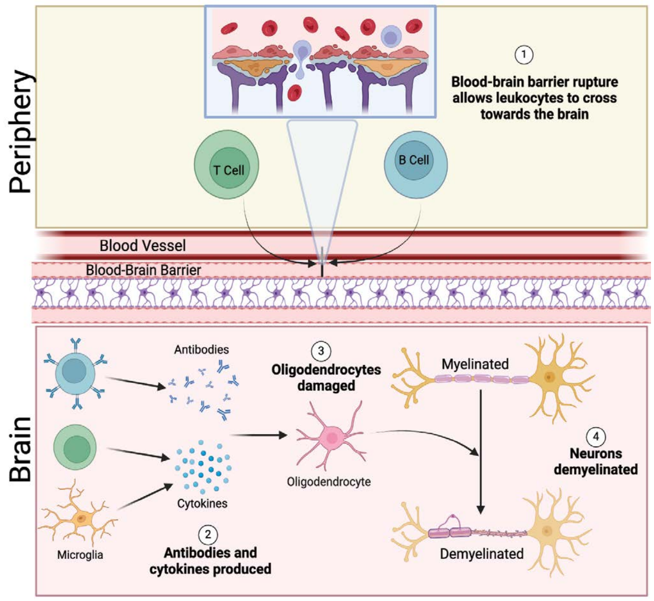

Figure 1: Schematic diagram showing the underlying cellular and molecular mechanisms in the pathogenesis of multiple sclerosis.

such as reduced physical activity and higher rates of obesity, might play a role in this trend. Recognizing these influences is essential for developing public health strategies and ensuring that medical infrastructure and resources are prepared to meet the growing demand for MS care. Understanding the factors contributing to increased prevalence will support better patient outcomes and more effective long-term management of the disease.

Clinical Presentation

Multiple Sclerosis is characterized by the destruction of myelin sheaths along neurons, which disrupts nerve signal transmission [4]. This progressive condition typically begins with neurological dysfunction and can evolve into chronic neurodegeneration, resulting in permanent neurological deficits. Clinically, MS manifests with a wide array of symptoms that vary based on the regions affected and the stage of the disease. Common symptoms include cognitive impairment, vision disturbances, sensory deficits, muscle weakness, and motor dysfunction [6, 7]. Certain populations are at a higher risk of developing MS, with studies indicating an increased prevalence among women and White individuals in the U.S. [8, 9]. Unique clinical features of MS include Lhermitte's sign, an electric shock-like sensation triggered by neck flexion, and the Uhthoff phenomenon, where symptoms will worsen with elevated core body temperature [5, 6]. These diverse clinical presentations can lead to significant disability over time, affecting mobility, coordination, and the ability to perform daily activities. The variability and unpredictability of symptom progression make MS a challenging disease to manage, contributing to a heightened risk of falls and related complications.

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

Disease Progression

Multiple Sclerosis can be categorized into several types based on disease characteristics and progression. The most common form is Relapsing-Remitting Multiple Sclerosis (RRMS), which is characterized by episodes of neurological decline followed by complete or partial recovery, without continuous disease progression [10, 11]. This type is typically diagnosed in young adults and is influenced by factors such as relapse rates and environmental triggers. Over time, many individuals with RRMS transition to Secondary Progressive Multiple Sclerosis (SPMS) [11, 12]. SPMS follows the relapsing-remitting phase, especially in cases of inadequate treatment, and is marked by a progressive decline in neurological function, often leading to significant disability [10-12]. Primary Progressive Multiple Sclerosis (PPMS) is another major type, defined by a steady decline in neurological function from the onset, with no distinct relapses or remissions [10, 11]. Additionally, there is Clinically Isolated Syndrome (CIS), which refers to a single neurological episode suggestive of MS that does not yet meet diagnostic criteria. CIS often progresses to MS after subsequent episodes, with risk factors for conversion including neuronal demyelination and patient-specific factors such as body mass index (BMI) [13, 14]. However, further research is needed to clarify the mechanisms and predictors of CIS progression to MS. Each MS type can also be categorized as active or non-active, reflecting the presence or absence of ongoing relapses or disease progression. Active disease is associated with current relapses or new lesion formation, while non-active disease indicates a stable state. Despite this classification, progression independent of relapse activity has been identified as a major factor contributing to disability development across MS types [15, 16]. These classifications (Table 1) provide a framework for understanding the diversity of MS, encompassing its primary forms and clinical presentations within the disease spectrum.

Risk Factors

The exact cause of Multiple Sclerosis remains unknown, but it is widely believed to arise from a combination of genetic and environmental factors. Genetic predisposition plays a significant role in MS risk, as evidenced by studies examining familial and broader population-based heritability. A study involving 25,186 MS patients of Nordic ancestry assessed the heritability between PPMS and relapsing-onset MS. Results indicated a clear familial risk of developing MS. Although, no significant differences were found between the phenotypes, suggesting that similar mechanisms underlie different MS types. The highest risk was observed in full siblings, followed by parents and offspring [19, 20]. Further supporting this genetic association, a meta-analysis of genetic variants analyzed 32,367 MS cases alongside controls. This study identified a significant link between MS diagnosis and seven low-coding variants, emphasizing that low-frequency genetic variation contributes to MS heritability [21]. Understanding these genetic risk factors is crucial for determining the pathogenesis of MS and could guide the development of targeted therapies in the future.

Environmental and lifestyle factors also contribute to the development of MS. A case-control study found that adolescent smoking was linked to a significant increase in MS risk. The study also showed that a history of measles infection and a larger body size were associated with higher MS risk. At the same time, fish consumption and sunlight exposure have a protective effect [22]. This research underscores how complex the web of risk factors can be, touching on everything from infections to diet and lifestyle habits. However, the relatively small sample size means more extensive research is needed to confirm these findings and better understand their implications. In a genome-wide association study with 377,234 participants, physical activity was analyzed alongside the risk of Multiple Sclerosis.

Table 1: Subtypes of Multiple Sclerosis and their associated features.

Subtype	Characteristics	Disease Progression	Additional Notes
Clinically Isolated Syndrome	A single episode of MS-like symptoms that does not meet the criteria for an MS diagnosis.	May progress to MS after further episodes.	BMI and demyelination are risk factors for progression to MS
Primary Progressive	Consistent decline in neurological function from the onset, with no relapses or improvement.	Continuous progression from onset.	
Relapsing-Remitting	Episodes of neurological degradation followed by complete or partial recovery	No continuous progression during remission.	Most common form, frequently diagnosed in women and individuals of White race.
Secondary Progressive	Follows RRMS, marked by a progressive decline in neurological function, often resulting in disability.	Gradual worsening over time.	Transition often occurs when treatment during RRMS is insufficient.

BMI, body mass index; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

The results showed a statistically significant, negative correlation between physical activity and the risk of MS [23]. Intense physical activity during adolescence was associated with a decreased likelihood of developing MS, particularly when considering late-onset development. On the other hand, light physical activity did not demonstrate a significant association with MS risk in the same way as vigorous exercise [24]. This relationship is further supported by findings on obesity, which indicate a positive association between childhood obesity and an increased risk of developing MS later in life [25]. These studies highlight the importance of maintaining an active lifestyle and a healthy body weight from a young age to mitigate the risk of MS. Further studies would be useful to increase our understanding and strengthen these associations for possible preventative measures.

Smoking, in particular, stands out as a major risk factor not just for developing MS but also for increasing the chances of relapse. In a study of 355 MS patients undergoing treatment with natalizumab, those who smoked a pack a day had significantly higher relapse rates [26]. A similar study involving 834 patients treated with interferon-gamma found comparable results, showing an increased relapse rate among smokers, particularly those with relapsing-remitting MS [27]. These findings make it clear that lifestyle choices can have a real impact on disease progression. Encouraging smoking cessation could be a crucial part of managing MS and preventing relapses. It's a reminder that while we often focus on treatments and medications, simple lifestyle changes can make a meaningful difference. Public health campaigns and support programs could play a vital role in helping MS patients make these changes and potentially improve their long-term health.

Fall Risk and Contributing Factors in Multiple Sclerosis

Falls are a major concern for individuals with Multiple Sclerosis, posing an increased risk of injury and disability. Studies have consistently shown that those with MS experience a significantly higher incidence of falls compared to healthy controls, even after accounting for variables such as age and gender [28, 29]. This emphasizes the direct link between fall risk and the disease itself rather than external confounding factors. Figure 2 illustrates the major symptoms associated with increased fall risk in MS patients, which will be elaborated on in subsequent sections. Falls are particularly common among individuals with progressive MS, higher levels of disability, or impaired motor function [30]. While some falls may result in minor injuries, others can have severe consequences, especially for older adults, leading to serious injuries, disability, or loss of independence in activities of daily living [3]. Understanding the risk factors associated with falls in MS is essential for developing targeted preventive strategies to minimize injury and improve patient outcomes.

Along with disability, a significant consequence of falls in MS is the risk of fractures. Low bone mineral density would increase the chances of fractures or breaks upon falling. Research indicates that individuals with MS frequently have reduced bone density and a higher prevalence of osteoporosis [31]. Alarmingly, population studies, such as one conducted in Canada, highlight low screening rates for bone density among individuals with MS, leaving many unaware of their elevated risk for fractures [32]. These findings demonstrate the importance of proactive bone health assessments and fall prevention measures in the MS population.

Predicting fall risk in individuals with Multiple Sclerosis is essential for preventing injuries. A study that utilized a machine learning algorithm to identify fall risk factors revealed several key contributors. The primary risk factors included the status of MS disease progression and the presence of disability. Smoking and exercise habits were identified as other influences of fall risk [33]. Monitoring the progression of MS in patients and assessing their level of disability are critical steps for physicians to evaluate the relative risk of falling. While interventions targeting disease progression and disability could have the greatest impact, these factors are largely beyond the patient's immediate control. Therefore, promoting changes in smoking and exercise habits presents the most practical approach to reducing fall risk in individuals with MS.

Machine learning algorithms have been increasingly utilized to analyze gait data and assess fall risk in individuals with Multiple Sclerosis [34]. One study employed such algorithms to evaluate 11 different gait data sources, including gait analysis systems, walk tests, scales, and self-reported questionnaires. Among these, self-reported data emerged as the most reliable indicator of an individual's health status. Self-reports of falls were shown to be strong predictors of future fall risk and the likelihood of injurious falls [34, 35]. However, this approach is limited by its retrospective nature, as it relies on a prior fall to generate predictions. It is difficult to integrate preventive interventions with this method. Furthermore, self-reports also possess other limitations. A study investigating their accuracy found discrepancies between actual and reported falls among individuals with MS, emphasizing the need for more reliable fall detection methods [36]. Larger studies are necessary to accurately evaluate the reliability of self-reports, in this context. Additionally, other machine learning algorithms have demonstrated high predictive accuracy by incorporating factors such as disability status, years since MS diagnosis, and demographic data [37]. An algorithm utilizing postural sway as a predictive measure has also shown promise in accurately assessing fall risk [38]. The variety of components contributing to fall risk has led to the development of numerous predictive models, making it challenging to determine which is most reliable. Enhancing

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

these algorithms by integrating additional predictive factors could further improve their accuracy and support the development of more effective fall-prevention strategies for individuals with MS.

Gait

Gait, or walking pattern, plays a critical role in evaluating an individual's movement and fall risk. Abnormal gait is often associated with reduced motor function, making its assessment essential for understanding fall risk. Neurological disorders, such as Multiple Sclerosis, commonly lead to gait impairments [39], with severity influenced by various factors. A study on gait pathology in individuals with MS identified common deficits, such as reduced knee and ankle excursions [40]. Among these, impaired knee flexion has been highlighted as a significant dysfunction associated with MS, as noted in multiple studies [40, 41]. These gait abnormalities reflect the underlying pathology of MS, characterized by demyelination in the central nervous system, which results in muscle weakness and impaired motor control. Consequently, reduced motor function contributes to an increased risk of falls. Additionally, balance is often impaired in MS as well and is a critical factor in maintaining a stable gait. Its decline typically contributes to gait dysfunction and a heightened risk of falls [42].

An observational study investigated the relationship between spatio-temporal gait parameters and falls in individuals with Multiple Sclerosis [43]. Participants identified as "fallers" exhibited greater gait variability compared to the "non-faller" group, with step length variability showing the strongest correlation with fall risk, which is also supported by separate studies [43-45]. Further research found that fallers and near-fallers shared similar motor profiles, which differed from those of non-fallers [46]. These findings highlight the potential of gait analysis as a valuable tool for identifying individuals at higher risk of falls. Moreover, gait variability may represent a promising target for interventions aimed at reducing fall incidence in individuals with MS.

Cognition

Cognitive impairment is a common and significant concern for individuals with Multiple Sclerosis, affecting various aspects of mental functioning and in turn affecting daily life. Studies have consistently shown that individuals with MS are at a significantly higher risk of cognitive impairment [47–49]. The most common deficits include reduced processing speed and difficulties with word finding [47, 48]. While these impairments are often less pronounced in younger individuals with MS, similar cognitive profiles observed in both younger and older populations suggest that these deficits are primarily a consequence of MS rather than age-related disorders [49]. Furthermore, the onset age of MS plays a role in the prevalence of cognitive impairment. Individuals with pediatric-onset MS are more likely to experience a rapid cognitive decline and a higher prevalence of cognitive impairment compared to those with adult-onset MS [50, 51].

Additionally, cognitive dysfunction is often associated with fall risk. It can negatively affect gait and balance, leading to an increased likelihood of falls. This relationship was demonstrated through self-reported falls and scales in individuals with MS, showing a clear correlation [52, 53]. Cognitive impairment in MS varies across disease stages [54] and is strongly linked to the mobility challenges associated with the condition. Therefore, monitoring cognitive function is crucial for accurately assessing fall risk. Proper evaluation of cognitive impairment enables physicians to identify patients at heightened risk, allowing them to provide targeted education and implement preventative strategies to reduce the likelihood of falls.

Fatigue

Fatigue is a common and debilitating symptom associated with Multiple Sclerosis, significantly impacting daily activities and overall quality of life. Studies have consistently shown a strong association between fatigue and MS [55, 56]. Among the various forms of MS, progressive types are linked with higher levels of fatigue compared to non-progressive forms [57], and no significant difference in fatigue levels has been observed between the different subtypes of progressive MS [58]. Fatigue in MS is often made worse by comorbid conditions, which are prevalent in this population and contribute to worse clinical outcomes [59–61]. Depression and insomnia are among the most common comorbidities linked to fatigue [61, 62]. Research has shown that alleviating depression in individuals with MS leads to significant reductions in physical fatigue [63, 64]. Similarly, insomnia has been identified as a primary factor associated with fatigue in MS [65, 66]. Therefore, effective management of sleep disturbances and other comorbidities could substantially improve fatigue levels.

Fatigue is a critical factor in determining fall risk in individuals with MS. Utilizing self-reporting and fatigue scales, several studies have demonstrated a clear association between fatigue levels and fall risk among individuals with MS [67–70]. These findings emphasize the importance of identifying and addressing fatigue in this population to mitigate fall risk. Since fatigue contributes significantly to fall risk, managing comorbidities such as depression and insomnia not only improves fatigue but also reduces the likelihood of falls. Accurate assessment and targeted interventions for fatigue in individuals with MS can enhance safety, functional independence, and quality of life.

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

Fear of Falling

Educating individuals with Multiple Sclerosis about their increased risk of falling and its potential consequences is crucial. However, this education can inadvertently contribute to a fear of falling, where individuals become overly cautious, limit movement, and adopt sedentary behaviors. A study employing a machine learning algorithm found that approximately 37% of individuals with MS experience a fear of falling, highlighting its relevance and prevalence within this population [71]. This fear often leads to reduced physical activity, which is associated with numerous adverse health outcomes, including an elevated risk of cardiovascular disease and diabetes [72, 73]. For patients with MS, maintaining adequate physical activity can be particularly challenging when their fear of falling is present.

Studies have shown individuals with a fear of falling often experience decreased physical activity, increased fatigue, and greater walking difficulties. Despite these challenges, there was no significant difference in fall incidence between individuals with a fear of falling and control groups [74, 75]. This highlights the negative impact of the fear of falling on overall well-being without a corresponding reduction in fall risk. Similarly, studies comparing fall incidence in active versus sedentary individuals with MS have found no significant difference between the two groups [76, 77]. This suggests that staying active and engaging in regular exercise does not increase the risk of falling for individuals with MS. On the contrary, maintaining an active lifestyle is essential for overall health. Current evidence does not support the notion that a sedentary lifestyle reduces fall risk, highlighting the need to encourage physical activity in individuals with MS. Therefore, patient education should emphasize both the risks of falling and the importance of staying active.

Strategies to Reduce Fall Risk in Multiple Sclerosis

Exercise

As previously established, mobility impairment is a common issue for individuals with Multiple Sclerosis and can significantly impact daily activities. Therefore, managing this dysfunction alongside the progression of MS is crucial. Consistent exercise has been explored as a potential treatment for mobility impairments in MS patients. Several randomized controlled trials have evaluated various exercise methods, including high-velocity resistance training, intense aerobics, progressive resistance training, and cycling. Some of these studies reported statistically significant improvements in balance, walking ability, muscle strength, and fatigue [78-80]. These findings suggest that exercise may be an effective treatment for mobility dysfunction in MS. Studies also show evidence of increased cognitive processing speed, potentially due to improved cardiorespiratory fitness [81]. This cognitive improvement may contribute to a reduced risk of falls. However, other studies have found no significant evidence of walking improvement among individuals actively exercising compared to control groups. Instead, the most consistent benefits observed were enhanced muscle performance and reduced fatigue in the exercise group [82–86]. Despite mixed results regarding walking improvements, most studies reported a correlated increase in the quality of life for participants [78-80, 82-84]. Additional research is needed to further explore the exact effects of exercise on mobility dysfunction in individuals with MS. Notably, innovative interventions like exoskeleton-assisted walking have shown promising results. One study demonstrated a significant improvement in functional mobility with exoskeleton-assisted walking compared to conventional gait training [87]. This method holds potential for individuals with mobility and cognitive impairments contributing to gait dysfunction. Improving gait through such interventions could reduce fall incidence in individuals with MS, offering a meaningful approach to enhancing both mobility and overall quality of life.

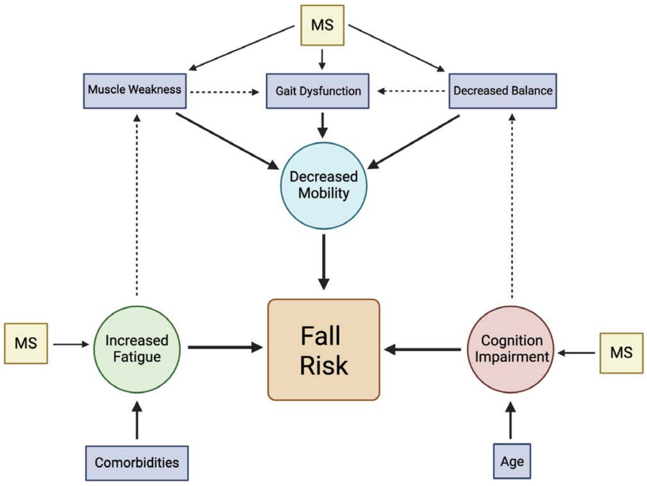

Figure 2: Flow chart illustrating the interconnected symptoms contributing to fall risk in patients with Multiple Sclerosis (MS).

Self-Management Programs

Self-management programs are another approach being explored as a treatment for mobility dysfunction in individuals with Multiple Sclerosis. These programs are designed to educate participants and empower them to achieve specific health outcomes. Some self-management programs focus on reducing fall incidence in individuals with MS by combining education and exercise over a set period. One such program, "Free from Falls", demonstrated a relative decrease in fall incidence among participants compared to those who received only a brochure. However, the reduction in falls was only slightly better than the control group [88]. A similar study testing the same program found no significant difference in fall incidence between participants and those

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

receiving neurologist-initiated interventions and education [89]. These findings suggest that the efficacy of the "Free from Falls" program is comparable to standard physician-led education, highlighting the need for further evaluation. Another program, Balance Right in MS, focuses on improving balance as a means of reducing fall incidence and is currently undergoing testing to determine its effectiveness [90]. Additional research is required to refine existing programs or develop new ones to achieve the desired outcome of reducing falls among individuals with MS.

Various programs have been developed to assist in managing the diverse symptoms associated with Multiple Sclerosis, including fatigue. Self-management programs that combine education and symptom management strategies have demonstrated effectiveness in reducing fatigue in individuals with MS [91–93]. However, like the fall prevention program, studies indicate that these programs may not consistently outperform general patient education in achieving desired outcomes [94]. While fatigue reductions were reported, the differences between the program and general advice were not statistically significant. Despite this, self-management programs may still hold value, particularly in cases where patient education is insufficient or inaccessible. They offer structured guidance that could benefit individuals who require additional support in managing their symptoms.

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) is a type of psychotherapy widely utilized for managing symptoms associated with Multiple Sclerosis. Fatigue is a significant contributor to fall risk in MS, and several studies have demonstrated that CBT is effective in reducing MS-related fatigue [95–98]. Notably, evidence suggests a stronger association between fatigue reduction and CBT than with exercise interventions in MS patients [98]. By alleviating fatigue, CBT may contribute to a reduction in fall risk among individuals with MS. CBT also addresses other common MS symptoms, such as pain and insomnia, which can indirectly influence fall risk. Pain, often debilitating in MS patients, may be mitigated with CBT, though further research is required to confirm its efficacy in this context [99]. Insomnia, another prevalent symptom of MS, has been shown to improve significantly with CBT in the general population [100–102], with similar benefits observed in MS patients [103]. Improved sleep quality from CBT could lead to reduced fatigue, thereby decreasing fall risk. Overall, CBT presents a versatile treatment strategy for managing multiple MS symptoms, highlighting its potential role in comprehensive fall risk management. Further research is needed to explore its broader applications in MS care.

Medication

Medication is often the primary form of treatment for Multiple Sclerosis, with disease-modifying therapies (DMT) playing an important role in reducing disease activity and slowing progression. Fumarate, an oral DMT, is commonly prescribed for active RRMS and has demonstrated efficacy in reducing relapse rates. However, gastrointestinal side effects are frequently reported [104, 105]. Interferon beta, an injectable DMT, is also effective in managing relapsing forms of MS by reducing relapse frequency and severity. It also can cause side effects, including flu-like symptoms and injection site reactions [106]. Early initiation of DMTs before an MS diagnosis has been shown to lower the risk of a first clinical episode, emphasizing the importance of timely diagnosis and intervention [107]. Additional research is required on the treatment's effect in the context of early application. Despite their effectiveness, DMTs are not targeted for the later, progressive forms of MS, such as PPMS and SPMS, where limited and conflicting research highlights the need for further investigation.

A significant challenge to DMT efficacy is patient compliance, with studies showing that approximately 31% of patients fail to adhere to prescribed treatments due to personal beliefs or outlooks [108]. Addressing noncompliance through targeted interventions and identifying contributing factors is essential for maximizing the benefits of DMTs. By slowing disease progression and preserving motor function, these therapies can inherently reduce fall risk in individuals with MS. A study assessing fall risk in patients with MS found that the group receiving DMT treatment had a 48% decreased incidence of falling compared to those not receiving treatment [109]. This suggests that DMTs may not only indirectly impact fall risk by slowing disease progression but can also directly influence fall incidence. The benefits of these therapies are maximized when patients begin treatment early and follow prescribed regimens consistently. Further research is essential to evaluate the long-term impact of DMTs on fall risk, particularly in patients with advanced MS, and to identify strategies that can enhance patient compliance and optimize therapeutic outcomes.

Key Points

- Multiple sclerosis can result in a range of physical and cognitive impairments, contributing to mobility dysfunction, cognitive deficits, fatigue, and an increased risk of falls.
- Gait dysfunction in multiple sclerosis is a significant factor contributing to fall risk, with impairments often resulting from a combination of factors, such as muscle weakness, cognitive dysfunction, and fatigue.
- Cognitive impairments in MS are associated with both disease progression and fall risk, affecting gait and balance, and increasing fall likelihood in patients.
- Fatigue is a prevalent symptom in MS, increasing mobility dysfunction and contributing to fall risk, especially when

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

combined with comorbidities, such as insomnia, where effective treatment of these comorbidities can help alleviate fatigue and reduce fall risk.

- Exercise interventions have shown benefits in improving muscle performance, balance, and reducing fatigue, though the direct impact on mobility in MS patients remains mixed.
- Self-management programs, particularly those focusing on fall prevention and combining education with exercise, have demonstrated some success, but their efficacy is often like physician-led approaches.
- Cognitive behavioral therapy has proven effective in reducing MS-related fatigue, pain, and insomnia, indirectly reducing fall risk through their alleviation.
- Disease-modifying therapies slow disease progression and reduce fall risk by preserving motor function, but patient noncompliance remains a significant challenge to their efficacy.

Funding

The research work of DKA is supported by the R25AI179582 and R01 HL147662 grants from the National Institutes of Health, USA. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Competing interests

All authors have read the manuscript and declare no conflict of interest. No writing assistance was utilized in the production of this manuscript.

Consent for publication

All authors have read the manuscript and consented for publication.

References

1. Høglund RA, Maghazachi AA. Multiple sclerosis and the role of immune cells. World J Exp Med 4 (2014): 27-37.
2. Zhao X, Jacob C. Mechanisms of Demyelination and Remyelination Strategies for Multiple Sclerosis. Int J Mol Sci 24 (2023): 6373.
3. Adam CE, Fitzpatrick AL, Leary CS, et al. The impact of falls on activities of daily living in older adults: A retrospective cohort analysis. PLoS One 19 (2024): e0294017.
4. Filippi, M., Bar-Or, A., Piehl, F. et al. Multiple sclerosis. Nat Rev Dis Primers 43 (2018).
5. Compston A, Coles A. Multiple sclerosis. Lancet 372 (2008): 1502-1517.
6. Tafti D, Ehsan M, Xixis KL. Multiple Sclerosis. [Updated 2024 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
7. Ford H. Clinical presentation and diagnosis of multiple sclerosis. Clin Med (Lond) 20 (2020): 380-383.
8. Wallin MT, Culpepper WJ, Campbell JD, et al; US Multiple Sclerosis Prevalence Workgroup. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 92 (2019): e1029-e1040.
9. Hittle M, Culpepper WJ, Langer-Gould A, et al. Population-Based Estimates for the Prevalence of Multiple Sclerosis in the United States by Race, Ethnicity, Age, Sex, and Geographic Region. JAMA Neurol 80 (2023): 693-701.
10. Tafti D, Ehsan M, Xixis KL. Multiple Sclerosis. 2024 Mar 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; (2024).
11. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med 8 (2018): a028928.
12. Cunill V, Massot M, Clemente A, et al. Relapsing-Remitting Multiple Sclerosis Is Characterized by a T Follicular Cell Pro-Inflammatory Shift, Reverted by Dimethyl Fumarate Treatment. Front Immunol 9 (2018): 1097.
13. Kolčava J, Kočica J, Hulová M, et al. Conversion of clinically isolated syndrome to multiple sclerosis: a prospective study. Mult Scler Relat Disord 44 (2020): 102262.
14. Ro LS, Yang CC, Lyu RK, et al. A prospective, observational study on conversion of clinically isolated syndrome to multiple sclerosis during 4-year period (MS NEO study) in Taiwan. PLoS One 14 (2019): e0202453.
15. Chisari CG, Amato MP, Di Sapio A, et al. Active and non-active secondary progressive multiple sclerosis patients exhibit similar disability progression: results of an Italian MS registry study (ASPERA). J Neurol 271 (2024): 6801-6810.
16. Portaccio E, Betti M, De Meo E, et al; Italian Multiple Sclerosis Register. Progression independent of relapse activity in relapsing multiple sclerosis: impact and relationship with secondary progression. J Neurol 271 (2024): 5074-5082.
17. Campbell JA, Simpson S Jr, Ahmad H, et al. Change in multiple sclerosis prevalence over time in Australia 2010-2017 utilising disease-modifying therapy prescription data. Mult Scler. 26 (2020): 1315-1328.
18. Yamout BI, Assaad W, Tamim H, et al. Epidemiology

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

and phenotypes of multiple sclerosis in the Middle East North Africa (MENA) region. Mult Scler J Exp Transl Clin 6 (2020): 2055217319841881.

19. Boles GS, Hillert J, Ramanujam R, et al. The familial risk and heritability of multiple sclerosis and its onset phenotypes: A case-control study. Mult Scler 29 (2023): 1209-1215.
20. Song J, Westerlind H, McKay KA, et al. Familial risk of early- and late-onset multiple sclerosis: a Swedish nationwide study. J Neurol 266 (2019): 481-486.
21. International Multiple Sclerosis Genetics Consortium. Electronic address: chris.cotsapas@yale.edu; International Multiple Sclerosis Genetics Consortium. Low-Frequency and Rare-Coding Variation Contributes to Multiple Sclerosis Risk. Cell 175 (2018): 1679-1687.e7.
22. Halawani AT, Zeidan ZA, Kareem AM, Alharthi AA, Almalki HA. Sociodemographic, environmental and lifestyle risk factors for multiple sclerosis development in the Western region of Saudi Arabia. A matched case control study. Saudi Med J 39 (2018): 808-814.
23. Li C, Lin J, Yang T, et al. Physical activity and risk of multiple sclerosis: A Mendelian randomization study. Front Immunol 13 (2022): 872126.
24. Wesnes K, Myhr KM, Riise T, et al. Physical activity is associated with a decreased multiple sclerosis risk: The EnvIMS study. Mult Scler 24 (2018): 150-157.
25. Wesnes K, Riise T, Casetta I, et al. Body size and the risk of multiple sclerosis in Norway and Italy: the EnvIMS study. Mult Scler 21 (2015): 388-395.
26. Petersen ER, Søndergaard HB, Laursen JH, et al. Smoking is associated with increased disease activity during natalizumab treatment in multiple sclerosis. Mult Scler 25 (2019): 1298-1305.
27. Petersen ER, Oturai AB, Koch-Henriksen N, et al. Smoking affects the interferon beta treatment response in multiple sclerosis. Neurology 90 (2018): e593-e600.
28. Mazumder R, Murchison C, Bourdette D, et al. Falls in people with multiple sclerosis compared with falls in healthy controls. PLoS One 9 (2014): e107620.
29. Quinn G, Comber L, McGuigan C, et al. Risk factors for falling for people with Multiple Sclerosis identified in a prospective cohort study. Clin Rehabil 35 (2021): 765-774.
30. Block VJ, Pitsch EA, Gopal A, et al. Identifying falls remotely in people with multiple sclerosis. J Neurol 269 (2022): 1889-1898.
31. Bisson EJ, Finlayson ML, Ekuma O, et al. Multiple sclerosis is associated with low bone mineral density and osteoporosis. Neurol Clin Pract 9 (2019): 391-399.
32. Bisson EJ, Ekuma O, Marrie RA, et al. Factors associated with receiving bone mineral density screening among people with multiple sclerosis. Mult Scler Relat Disord 28 (2019): 305-308.
33. Özgür S, Koçaslan Toran M, Toygar İ, et al. A machine learning approach to determine the risk factors for fall in multiple sclerosis. BMC Med Inform Decis Mak 24 (2024): 215.
34. Schumann P, Scholz M, Trentzsch K, et al. Detection of Fall Risk in Multiple Sclerosis by Gait Analysis-An Innovative Approach Using Feature Selection Ensemble and Machine Learning Algorithms. Brain Sci 12 (2022): 1477.
35. Cameron MH, Thielman E, Mazumder R, et al. Predicting falls in people with multiple sclerosis: fall history is as accurate as more complex measures. Mult Scler Int (2013): 496325.
36. Chowdhury, N.; Hildebrand, A.; Folsom, J.; et al. Are "Gold Standard" Prospective Daily Self-Report Fall Calendars Accurate? A Comparison with a Real-Time Body-Worn Self-Report Device in Multiple Sclerosis (P4.404). Neurology (2018) 90.
37. Piryonesi SM, Rostampour S, Piryonesi SA. Predicting falls and injuries in people with multiple sclerosis using machine learning algorithms. Mult Scler Relat Disord 49 (2021): 102740.
38. Sun R, Hsieh KL, Sosnoff JJ. Fall Risk Prediction in Multiple Sclerosis Using Postural Sway Measures: A Machine Learning Approach. Sci Rep 9 (2019): 16154.
39. Bernhard FP, Sartor J, Bettecken K, et al. Wearables for gait and balance assessment in the neurological ward - study design and first results of a prospective cross-sectional feasibility study with 384 inpatients. BMC Neurol 18 (2018): 114.
40. Filli L, Sutter T, Easthope CS, et al. Profiling walking dysfunction in multiple sclerosis: characterization, classification and progression over time. Sci Rep 8 (2018): 4984.
41. Broekmans T, Gijbels D, Eijnde BO, et al. The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. Mult Scler 19 (2013): 112-119.
42. Brandstadter R, Ayeni O, Krieger SC, et al. Detection of subtle gait disturbance and future fall risk in early multiple sclerosis. Neurology 94 (2020): e1395-e1406.

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

43. Kalron A. Association between gait variability, falls and mobility in people with multiple sclerosis: A specific observation on the EDSS 4.0-4.5 level. NeuroRehabilitation 40 (2017): 579-585.

44. Kalron A, Frid L, Menascu S, et al. The association between gait variability with the energy cost of walking depends on the fall status in people with multiple sclerosis without mobility aids. Gait Posture 74 (2019): 231-235.

45. Kalron A, Allali G, Achiron A. Neural correlates of gait variability in people with multiple sclerosis with fall history. Eur J Neurol 25 (2018): 1243-1249.

46. Fritz NE, Eloyan A, Baynes M, et al. Distinguishing among multiple sclerosis fallers, near-fallers and non-fallers. Mult Scler Relat Disord 19 (2018): 99-104.

47. Jakimovski, D., Roy, S., Jaworski, M., et al. Cognitive Profiles of Aging in Multiple Sclerosis. Frontiers in Aging Neuroscience 11 (2019): 457830.

48. Brandstadter R, Fabian M, Leavitt VM, et al. Word-finding difficulty is a prevalent disease-related deficit in early multiple sclerosis. Multiple Sclerosis Journal 26 (2020): 1752-1764.

49. Branco, M., Ruano, L., Portaccio, E. et al. Aging with multiple sclerosis: prevalence and profile of cognitive impairment. Neurol Sci 40 (2019): 1651–1657.

50. McKay KA, Manouchehrinia A, Berrigan L, et al. Long-term Cognitive Outcomes in Patients With Pediatric-Onset vs Adult-Onset Multiple Sclerosis. JAMA Neurol 76 (2019): 1028-1034.

51. Wallach AI, Waltz M, Casper TC, et al. Cognitive processing speed in pediatric-onset multiple sclerosis: Baseline characteristics of impairment and prediction of decline. Mult Scler 26 (2020): 1938-1947.

52. VanNostrand M, Sogoloff B, Giroux C, et al. Predicting falls in adults with multiple sclerosis using patient-reported measures: Are perceptions of dual-tasking missing? Mult Scler Relat Disord 68 (2022): 104115.

53. Bilgin YOU, Koskderelioglu A, Gedizlioglu M. Fall risk is related to cognitive functioning in ambulatory multiple sclerosis patients. Neurol Sci 44 (2023): 3233-3242.

54. Sumowski JF, Leavitt VM, Rocca MA, et al. Mesial temporal lobe and subcortical grey matter volumes differentially predict memory across stages of multiple sclerosis. Mult Scler 24 (2018): 675-678.

55. Gustavsen S, Olsson A, Søndergaard HB, Andresen SR, Sørensen PS, Sellebjerg F, Oturai A. The association of selected multiple sclerosis symptoms with disability and quality of life: a large Danish self-report survey. BMC Neurol 21 (2021): 317.

56. Le HH, Ken-Opurum J, LaPrade A, et al. Exploring humanistic burden of fatigue in adults with multiple sclerosis: an analysis of US National Health and Wellness Survey data. BMC Neurol 24 (2024): 51.

57. Rooney S, Wood L, Moffat F, et al. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. Mult Scler Relat Disord 28 (2019): 276-282.

58. Herring TE, Alschuler KN, Knowles LM, et al. Differences in correlates of fatigue between relapsing and progressive forms of multiple sclerosis. Mult Scler Relat Disord 54 (2021): 103109.

59. Salter A, Lancia S, Kowalec K, et al. Comorbidity and Disease Activity in Multiple Sclerosis. JAMA Neurol 81 (2024): 1170–1177.

60. Salter A, Kowalec K, Fitzgerald KC, et al. Comorbidity is associated with disease activity in MS: Findings from the CombiRx trial. Neurology 95 (2020): e446-e456.

61. Diržiuvienė B, Mickevičienė D. Comorbidity in multiple sclerosis: Emphasis on patient-reported outcomes. Mult Scler Relat Disord 59 (2022): 103558.

62. Schellaert V, Labauge P, Lebrun C, et al. Psychological processes associated with insomnia in patients with multiple sclerosis. Sleep 41 (2018).

63. Knowles LM, Arewasikporn A, Kratz AL, et al. Early Treatment Improvements in Depression Are Associated With Overall Improvements in Fatigue Impact and Pain Interference in Adults With Multiple Sclerosis. Ann Behav Med 55 (2021): 833-843.

64. Knowles LM, Mistretta EG, Arewasikporn A, et al. Improvement in depressive symptoms is associated with sustained improvement in fatigue impact in adults with multiple sclerosis. Mult Scler Relat Disord 92 (2024): 106158.

65. Johansson K, Wasling P, Axelsson M. Fatigue, insomnia and daytime sleepiness in multiple sclerosis versus narcolepsy. Acta Neurol Scand. 144 (2021): 566-575.

66. Labuz-Roszak B, Kubicka-Bączyk K, Pierzchała K, et al. Fatigue and its association with sleep disorders, depressive symptoms and anxiety in patients with multiple sclerosis. Neurol Neurochir Pol 46 (2012): 309-317.

67. Abou L, Fritz NE, Kratz AL. Self-reported fatigue impact is associated with frequency of falls and injurious falls in people with multiple sclerosis. Mult Scler Relat Disord 78 (2023): 104910.

68. Abou L, McCloskey C, Wernimont C, et al. Examination of Risk Factors Associated With Falls and Injurious Falls in People With Multiple Sclerosis: An Updated

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

Nationwide Study. Arch Phys Med Rehabil. 105 (2024): 717-724.

69. Alzahrani N, Bamutraf O, Mukhtar S, et al. Exploring key factors associated with falls in people with multiple sclerosis: The role of trunk impairment and other contributing factors. Heliyon 10 (2024): e39589.

70. Jawad A, Baattaiah BA, Alharbi MD, et al. Factors contributing to falls in people with multiple sclerosis: The exploration of the moderation and mediation effects. Mult Scler Relat Disord 76 (2023): 104838.

71. Schumann P, Trentzsch K, Stölzer-Hutsch H, et al. Using machine learning algorithms to detect fear of falling in people with multiple sclerosis in standardized gait analysis. Mult Scler Relat Disord 88 (2024): 105721.

72. Boudreaux BD, Romero EK, Diaz KM. Sedentary behavior and risk of cardiovascular disease and all-cause mortality in United States adults with hypertension. J Hypertens.

73. Bellettiere J, Healy GN, LaMonte MJ, et al. Sedentary Behavior and Prevalent Diabetes in 6,166 Older Women: The Objective Physical Activity and Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci 74 (2019): 387-395.

74. Kalron A, Aloni R, Givon U, et al. Fear of falling, not falls, impacts leisure-time physical activity in people with multiple sclerosis. Gait Posture. (2018).

75. Schumann P, Trentzsch K, Stölzer-Hutsch H, et al. Using machine learning algorithms to detect fear of falling in people with multiple sclerosis in standardized gait analysis. Mult Scler Relat Disord 88 (2024): 105721.

76. Farber AE, Menascu S, Kalron A. The association of fear of falling and falls with sedentary behavior in people with multiple sclerosis. J Psychosom Res 181 (2024): 111675.

77. Kalron A, Aloni R, Givon U, et al. Fear of falling, not falls, impacts leisure-time physical activity in people with multiple sclerosis. Gait Posture. 2018 Sep; 65 (2018): 33-38.

78. Andreu-Caravaca L, Ramos-Campo DJ, Chung LH, et al. Effects of fast-velocity concentric resistance training in people with multiple sclerosis: A randomized controlled trial. Acta Neurol Scand 146 (2022): 652-661.

79. Cakt BD, Nacir B, Genç H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. Am J Phys Med Rehabil 89 (2010): 446-457.

80. Feys P, Moumdjian L, Van Halewyck F, et al. Effects of an individual 12-week community-located “start-to-run” program on physical capacity, walking, fatigue, cognitive function, brain volumes, and structures in persons with multiple sclerosis. Multiple Sclerosis Journal 25 (2019): 92-103.

81. Sandroff BM, Bollaert RE, Pilutti LA, et al. Multimodal exercise training in multiple sclerosis: A randomized controlled trial in persons with substantial mobility disability. Contemp Clin Trials 61 (2017): 39-47.

82. Grazioli E, Tranchita E, Borriello G, et al. The Effects of Concurrent Resistance and Aerobic Exercise Training on Functional Status in Patients with Multiple Sclerosis. Curr Sports Med Rep 18 (2019): 452-457.

83. Correale L, Buzzachera CF, Liberali G, et al. Effects of Combined Endurance and Resistance Training in Women With Multiple Sclerosis: A Randomized Controlled Study. Front Neurol 12 (2021): 698460.

84. Dodd KJ, Taylor NF, Shields N, et al. Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: a randomized controlled trial. Mult Scler 17 (2011): 1362-1374.

85. Langeskov-Christensen M, Hvid LG, Jensen HB, et al. Efficacy of high-intensity aerobic exercise on common multiple sclerosis symptoms. Acta Neurol Scand 145 (2): 229-238.

86. Jallouli S, Maaloul R, Ghroubi S, et al. Benefits of self-paced concurrent training on lung function, cardiopulmonary fitness and fatigue perception in patients with multiple sclerosis. Neurodegener Dis Manag 14 (2024): 173-187.

87. Androwis GJ, Sandroff BM, Niewrzol P, et al. A pilot randomized controlled trial of robotic exoskeleton-assisted exercise rehabilitation in multiple sclerosis. Mult Scler Relat Disord 51 (2021): 102936.

88. Kannan M, Hildebrand A, Hugos CL, et al. Evaluation of a web-based fall prevention program among people with multiple sclerosis. Mult Scler Relat Disord 31 (2019): 151-156.

89. Cameron MH, Hildebrand A, Hugos CL, et al. Free From Falls education and exercise program for reducing falls in people with multiple sclerosis: A randomized controlled trial. Mult Scler 28 (2022): 980-988.

90. Gunn H, Stevens KN, Creanor S, et al. Balance Right in Multiple Sclerosis (BRiMS): a feasibility randomized controlled trial of a falls prevention program. Pilot Feasibility Stud. 7 (2021): 2.

91. Hugos CL, Chen Z, Chen Y, et al. A multicenter randomized controlled trial of two group education

Patel J., Arch Intern Med Res 2025
DOI:10.26502/aimr.0194

programs for fatigue in multiple sclerosis: Short- and medium-term benefits. Mult Scler 25 (2019): 275-285.

92. Ehde DM, Arewasikporn A, Alschuler KN, et al. Moderators of Treatment Outcomes After Telehealth Self-Management and Education in Adults With Multiple Sclerosis: A Secondary Analysis of a Randomized Controlled Trial. Arch Phys Med Rehabil 99 (2018): 1265-1272.

93. Plow M, Finlayson M, Liu J, et al. Randomized Controlled Trial of a Telephone-Delivered Physical Activity and Fatigue Self-management Interventions in Adults With Multiple Sclerosis. Arch Phys Med Rehabil. 2019 Nov; 100 (2019): 2006-2014.

94. Thomas S, Thomas PW, Kersten P, et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. J Neurol Neurosurg Psychiatry 84 (2013): 1092-1099.

95. van den Akker LE, Beckerman H, Collette EH, et al. Cognitive behavioural therapy for MS-related fatigue explained: A longitudinal mediation analysis. J Psychosom Res 106 (2018): 13-24.

96. Gay MC, Cassedanne F, Barbot F, et al. Long-term effectiveness of a cognitive behavioural therapy (CBT) in the management of fatigue in patients with relapsing remitting multiple sclerosis (RRMS): a multicentre, randomised, open-label, controlled trial versus standard care. J Neurol Neurosurg Psychiatry 95 (2024): 158-166.

97. Braley TJ, Ehde DM, Alschuler KN, et al. Comparative effectiveness of cognitive behavioural therapy, modafinil, and their combination for treating fatigue in multiple sclerosis (COMBO-MS): a randomised, statistician-blinded, parallel-arm trial. Lancet Neurol 23 (2024): 1108-1118.

98. Harrison AM, Safari R, Mercer T, et al. Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. Mult Scler 27 (2021): 1657-1678.

99. Gromisch ES, Kerns RD, Czlapinski R, et al. Cognitive Behavioral Therapy for the Management of Multiple Sclerosis-Related Pain: A Randomized Clinical Trial. Int J MS Care 22 (2020): 8-14.

100. Jernelöv S, Blom K, Hentati Isacsson N, et al. Very long-term outcome of cognitive behavioral therapy for insomnia: one- and ten-year follow-up of a randomized controlled trial. Cogn Behav Ther 51 (2022): 72-88.

101. Vedaa Ø, Hagatun S, Kallestad H, et al. Long-Term Effects of an Unguided Online Cognitive Behavioral Therapy for Chronic Insomnia. J Clin Sleep Med 15 (2019): 101-110.

102. Hagatun S, Vedaa Ø, Nordgreen T, et al. The Short-Term Efficacy of an Unguided Internet-Based Cognitive-Behavioral Therapy for Insomnia: A Randomized Controlled Trial With a Six-Month Nonrandomized Follow-Up. Behav Sleep Med 17 (2019): 137-155.

103. Siengsukon CF, Beck ES Jr, Drerup M. Feasibility and Treatment Effect of a Web-Based Cognitive Behavioral Therapy for Insomnia Program in Individuals with Multiple Sclerosis: A Pilot Randomized Controlled Trial. Int J MS Care 23 (2021): 107-113.

104. Saida T, Yamamura T, Kondo T, et al. A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries. BMC Neurol 19 (2019): 5.

105. Singer BA, Arnold DL, Drulovic J, et al. Diroximel fumarate in patients with relapsing-remitting multiple sclerosis: Final safety and efficacy results from the phase 3 EVOLVE-MS-1 study. Mult Scler 29 (2023): 1795-1807.

106. Filipi M, Jack S. Interferons in the Treatment of Multiple Sclerosis: A Clinical Efficacy, Safety, and Tolerability Update. Int J MS Care 22 (2020): 165-172.

107. Okuda DT, Kantarci O, Lebrun-Frénay C, et al. Dimethyl Fumarate Delays Multiple Sclerosis in Radiologically Isolated Syndrome. Ann Neurol 93 (2023): 604-614.

108. Stratos K, McGarragle K, Thistle J, et al. Non-compliance with disease modifying therapies in patients with Multiple Sclerosis: A qualitative analysis. Mult Scler Relat Disord 41 (2020): 102016.

109. Cameron MH, Karstens L, Hoang P, et al. Medications Are Associated with Falls in People with Multiple Sclerosis: A Prospective Cohort Study. Int J MS Care 17 (2015): 207-214.