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PHYSICAL ACTIVITY AS A NON-PHARMACOLOGICAL ADJUNCT THERAPY IN THE MANAGEMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS: A NARRATIVE REVIEW OF CURRENT EVIDENCE

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ABSTRACT

Background: Historically, patients with Relapsing-Remitting Multiple Sclerosis (RRMS) were advised to avoid physical exertion to prevent symptom exacerbation. However, recent evidence has catalyzed a paradigm shift, positioning physical activity as a critical disease-modifying intervention.
Objective: This narrative review aims to summarize the current state of knowledge regarding the role of physical activity as a non-pharmacological adjunct therapy in RRMS, focusing on its biological mechanisms, symptomatic impact, and clinical safety.
Methods: An analysis of contemporary literature was conducted, focusing on the molecular, structural, and psychosocial effects of exercise in individuals with RRMS.
Results: Physical activity modulates the central nervous system by upregulating neurotrophic factors, such as Brain-Derived Neurotrophic Factor (BDNF), which support synaptic plasticity and axonal survival. It induces a favorable systemic cytokine shift, reducing pro-inflammatory markers (TNF-α, IL-17). Clinically, structured exercise—comprising aerobic training, progressive resistance training, and mind-body interventions—effectively mitigates pathological fatigue, improves mobility, and supports cognitive processing speed. High-intensity protocols and task-oriented circuit training have shown potential neuroprotective effects, including the preservation of gray matter volume. Modern management of thermal sensitivity (Uhthoff's phenomenon) and personalized intensity based on the Expanded Disability Status Scale (EDSS) ensure a high safety profile.
Conclusion: Physical activity acts in synergy with Disease-Modifying Therapies (DMTs), creating a "dual-track" strategy that addresses both inflammatory activity and neurodegenerative decline. Initiating exercise within the "Window of Opportunity" early after diagnosis is essential to maximize the preservation of neurological reserve. Physical activity should be considered a fundamental pillar of multidisciplinary MS care, vital for functional independence and improved quality of life.

KEYWORDS

Multiple Sclerosis; RRMS; Physical Activity; BDNF; Neuroprotection; DMT Adjunct; Exercise Rehabilitation

CITATION

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1. Introduction

Multiple Sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system and remains one of the primary causes of non-traumatic disability in young adults (1). The Relapsing-Remitting subtype (RRMS) is the most frequently diagnosed clinical course, characterized by acute relapses—periods of new or worsening neurological symptoms—followed by phases of partial or complete remission. The pathophysiology of RRMS involves a complex cascade of inflammatory and neurodegenerative processes, including focal lymphocytic infiltration and myelin sheath destruction, which eventually lead to progressive axonal loss and the accumulation of functional deficits (2).

For decades, the medical approach to physical activity in MS was clinically conservative. Patients were routinely advised to avoid exertion due to fears of exacerbating fatigue and triggering Uhthoff's phenomenon—a temporary worsening of neurological symptoms caused by an increase in core body temperature (3,4). However, the last two decades have witnessed a radical paradigm shift. Contemporary scientific evidence has not only debunked the myth that exercise is harmful but has positioned physical activity as a cornerstone adjunct therapy with significant neuroprotective and anti-inflammatory potential (5).

The objective of this narrative review is to summarize the current state of knowledge regarding the role of physical activity as a non-pharmacological adjunct in the management of RRMS. This review focuses on the multidimensional impact of exercise: from molecular mechanisms that stimulate brain neuroplasticity to the mitigation of core symptoms such as pathological fatigue and cognitive impairment, and ultimately, the improvement of overall quality of life. This analysis aims to demonstrate that appropriately programmed training is not merely a rehabilitative tool but a vital disease-modifying intervention that serves as an essential pillar of modern, interdisciplinary MS care.

2. Materials and Methods

This study is a narrative review of the current literature regarding the role of physical activity in the management of multiple sclerosis. A comprehensive search was conducted in electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library, to identify relevant studies published primarily between 2014 and 2026.

The search strategy focused on identifying high-quality evidence addressing the following thematic areas:

1. Biological and molecular mechanisms: The impact of exercise on neurotrophic factors (e.g., BDNF, CNTF), cytokine shifts, and the stabilization of the blood-brain barrier.
2. Clinical symptom management: The efficacy of various training modalities in mitigating pathological fatigue, cognitive impairment, and mobility deficits.
3. Modern intervention strategies: The application of High-Intensity Interval Training (HIIT), task-oriented circuit training, and technology-driven approaches such as Virtual Reality (VR) and robotic-assisted gait training.
4. Safety and Clinical Guidelines: Evidence-based recommendations for exercise prescription across different levels of the Expanded Disability Status Scale (EDSS), management of thermosensitivity (Uhthoff's phenomenon), and the integration of physical activity into the DMT (Disease-Modifying Therapy) regimen.

Keywords used in the search included: "multiple sclerosis", "RRMS", "physical activity", "exercise therapy", "neuroprotection", "BDNF", "fatigue", and "rehabilitation".

Articles were selected based on their relevance to the topic, methodological rigor (with a priority on meta-analyses and randomized controlled trials), and contribution to the current paradigm shift in MS care. Both experimental and clinical studies, as well as authoritative systematic reviews and global consensus guidelines, were included to provide a holistic perspective on the disease-modifying potential of exercise.

3. Biological Mechanisms

The therapeutic efficacy of physical activity in RRMS is primarily driven by its ability to modulate the central nervous system's molecular environment through the upregulation of neurotrophic factors, most notably Brain-Derived Neurotrophic Factor (BDNF) (6,7). These signaling proteins, including BDNF, CNTF, and IGF-1, act as "neuro-fertilizers" that promote synaptogenesis and axonal survival, thereby enhancing the "neurological reserve" against demyelination (8). While aerobic and resistance training elicit significant immediate neurotrophic spikes, the integration of cognitive-aerobic dual-tasking has been shown to yield superior sustained increases in BDNF levels (9). Furthermore, recent evidence suggests that the specific exercise modality and associated cognitive load are more critical predictors of this neurotrophic response than simple dose-related parameters like session duration (10).

Regular physical activity induces a targeted cytokine shift by significantly reducing key pro-inflammatory markers, such as TNF-α, IFN-γ, and IL-17, while having no significant effect on anti-inflammatory cytokines, including IL-10 and IL-4 (11). This creates a less hostile immune environment, potentially moderating the autoimmune response. Emerging evidence also suggests that exercise may stabilize the blood-brain barrier (BBB) by strengthening tight junctions, thereby limiting the infiltration of peripheral immune cells into the CNS (12). Collectively, these mechanisms suggest that exercise provides a neuroprotective shield, slowing the progression of atrophy and functional decline.

4. Impact on Symptoms

The clinical translation of exercise-induced neuroprotection is most evident in the management of MS-related fatigue, which affects up to 80% of patients (13). Contrary to historical fears that exertion would exacerbate exhaustion, contemporary evidence shows that structured aerobic and resistance training significantly reduces fatigue levels. This is likely achieve by improving metabolic efficiency and reducing the systemic inflammatory "noise" that contributes to pathological tiredness (14).

Furthermore, physical activity is a critical intervention for mobility and postural control. Progressive resistance training (PRT) targets muscle paresis and spasticity, directly improving gait speed and reducing the risk of falls (15). In RRMS, where disability is often episodic, maintaining a high functional reserve through exercise can shorten the recovery time after a relapse (16).

Recent studies also highlight the neurocognitive benefits of exercise. By stimulating BDNF-mediated plasticity, physical activity supports executive functions and information processing speed, which are often compromised early in the disease course (17). Finally, the psychosocial impact cannot be overlooked; regular movement significantly alleviates depressive symptoms and anxiety, which are frequent comorbidities in RRMS (18). Thus, exercise acts as a multifunctional tool, addressing both the physical and neuropsychiatric dimensions of the disease.

5. Types of Interventions

The design of exercise programs for patients with Relapsing-Remitting Multiple Sclerosis (RRMS) has evolved significantly from historical caution toward a multi-modal rehabilitative approach. While earlier interventions were often fragmented due to concerns regarding symptom exacerbation, contemporary evidence emphasizes the efficacy of diverse physical activities, including aerobic, resistance, and mind-body exercises such as yoga (19). Recent meta-analyses indicate that while aerobic training demonstrates a particularly robust effect on the physical domain of health-related quality of life (HRQOL), the clinical success of these interventions is heavily contingent upon specific training parameters, such as professional supervision and a program duration of at least three months (20).

5.1. Aerobic Training (AT)

Aerobic training, often performed on stationary bicycles, treadmills, or through aquatic exercises, remains the gold standard for addressing cardiovascular fitness and pathological fatigue (21,22). While moderate-intensity continuous training (MICT), typically performed at 40–85% of maximal intensity, remains the traditional prescription for cardiovascular fitness in RRMS, evidence suggests that higher-intensity aerobic protocols are more efficient in stimulating the release of brain-derived neurotrophic factor (BDNF) and promoting systemic anti-inflammatory effects (23). Recently, High-Intensity Interval Training (HIIT) has gained traction as a time-efficient alternative. Studies suggest that HIIT may be superior to steady-state exercise in improving peak oxygen uptake (VO2max) and could potentially have a stronger impact on neuroplasticity, provided that thermal sensitivity is managed through appropriate cooling strategies (24).

5.2. Progressive Resistance Training (PRT)

Resistance training is essential for addressing skeletal muscle weakness and spasticity, which are hallmarks of RRMS progression. Unlike aerobic exercise, progressive resistance training (PRT) focuses on both muscle hypertrophy—specifically increasing the cross-sectional area of type II fibers—and critical neural adaptations, such as enhanced motor unit recruitment and increased rate of force development (25). By using free weights, resistance bands, or pneumatic machines, patients can build a "functional reserve" that compensates for demyelination-induced conduction blocks. PRT has been shown to improve gait kinematics and balance, directly reducing the risk of falls (26). Emerging evidence from randomized controlled trials suggests that progressive resistance training (PRT) may exert a significant neuroprotective, and potentially neuroregenerative, effect in RRMS. Longitudinal MRI data indicate that 24 weeks of supervised PRT can induce a significant increase in cortical thickness across multiple brain regions and show a trend toward reducing the rate of whole-brain atrophy (PBVC) compared to non-exercising controls. These structural improvements in gray matter correlate with enhanced neuromuscular function, positioning PRT as a cornerstone of disease-modifying lifestyle interventions (27).

5.3. Mind-Body and Neuromotor Interventions

In recent years, "alternative" modalities such as Yoga, Pilates, and Tai Chi have been integrated into standard MS care. These interventions prioritize proprioception, core stability, and the mind-muscle connection (28). For patients with RRMS, these methods are particularly effective in managing sensory deficits and improving the quality of life. Yoga, in particular, integrates specific physical postures (*asana*) with regulated breathing (*pranayama*), which effectively modulate physiological functions such as blood pressure and lung capacity. Evidence-based reviews suggest that this multidimensional approach serves as a crucial adjunct therapy for managing psychosocial stress and systemic MS symptoms (29).

5.4. Task-Oriented and Aquatic Therapy

Task-oriented circuit training (TOCT), which mimics activities of daily living (ADL) such as stair climbing, sit-to-stand transitions, and manual tasks (e.g., dressing or writing), is highly effective for patients across a broad disability spectrum (EDSS 2.0–5.5). Evidence indicates that TOCT not only improves objective measures of balance and walking endurance but also significantly enhances patients' perceived confidence during daily activities (30). Furthermore, intensive functional repetitions in TOCT may harness experience-dependent neuroplasticity, leading to improvements in long-term verbal memory, thereby addressing both motor and cognitive decline in RRMS (31). Similarly, aquatic therapy offers a unique environment where the buoyancy of water supports weak limbs and the hydrostatic pressure aids circulation. Most importantly, the cooling effect of water minimizes the risk of Uhthoff's phenomenon, allowing patients to exercise at higher intensities without the transient worsening of neurological symptoms (32,33).

6. Safety and Barriers

Despite the clear benefits of physical activity, several barriers often prevent patients with RRMS from engaging in regular exercise. The most prominent physiological hurdle is thermosensitivity, historically known as Uhthoff's phenomenon. This involves a transient worsening of neurological symptoms—such as blurred vision or increased paresthesia—triggered by a rise in core body temperature during exertion (34). Modern management strategies, however, mitigate this risk through pre-cooling and mid-cooling techniques, such as using cooling vests, ingesting cold fluids, or performing exercises in temperature-controlled aquatic environments (35). It is crucial to emphasize that these symptoms are temporary and do not indicate new demyelinating activity or a clinical relapse.

Beyond thermal issues, pathological fatigue acts as a paradoxical barrier; many patients avoid exercise because they feel too exhausted to begin, unaware that structured movement is one of the few evidence-based treatments for MS-related fatigue (36). Additionally, fear of falling and balance instability can lead to a cycle of inactivity, resulting in secondary deconditioning (37).

From a clinical safety perspective, exercise is considered highly safe for RRMS patients when properly dosed. Systematic reviews consistently show that the relapse rate is not increased by exercise; in fact, it may even be reduced (38,39). The primary safety requirement is the personalization of intensity based on the patient's current EDSS score and the avoidance of high-intensity training during an active relapse (40). By addressing these barriers through patient education and professional supervision, physical activity can be safely integrated as a permanent pillar of MS management.

7. Adjunct Therapy

The modern management of Relapsing-Remitting Multiple Sclerosis (RRMS) has evolved into a dual-track strategy where pharmacological interventions and lifestyle modifications, specifically physical activity, work in synergy. While Disease-Modifying Therapies (DMTs)—ranging from interferon-beta to high-efficacy monoclonal antibodies—are essential for reducing relapse rates and focal lesion accumulation, they often fall short in addressing the progressive neurodegenerative aspects and the symptomatic burden of the disease. This is where physical activity acts as a critical non-pharmacological adjunct, bridging the gap between biological stability and functional recovery (5).

The integration of exercise into the DMT regimen creates a robust 'neuroprotective shield.' While pharmacotherapy primarily targets peripheral immune dysregulation to prevent new inflammatory attacks, physical activity enhances the brain's internal resilience by acting as a synaptic protector. Evidence suggests that exercise directly counters inflammatory synaptopathy and promotes the creation of new dendritic spines—neuroregenerative processes that remain largely unaddressed by current pharmacological agents (41). By increasing the levels of neurotrophic factors such as BDNF, exercise may support neuroprotective mechanisms, including synaptic plasticity. These pathways complement the primary action of current DMTs, which focus predominantly on modulating inflammatory activity rather than directly stimulating neural repair (42). Therefore, a patient who is pharmacologically stable but physically inactive remains at a higher risk of "silent" progression and accelerated brain atrophy (43).

Furthermore, physical activity addresses the secondary complications of RRMS that drugs cannot fix. Issues such as deconditioning, metabolic syndrome, and cardiovascular comorbidities—which are more prevalent in MS populations due to sedentary behavior—can exacerbate disability (44). Regular exercise improves metabolic health, thereby optimizing the environment in which DMTs operate.

The concept of the "Window of Opportunity" is particularly relevant here. Initiating high-intensity rehabilitation alongside the start of DMT treatment can maximize the preservation of the neurological reserve (7). Clinicians should view exercise not as an optional "wellness" addition, but as a physiological necessity. For an adjunct therapy to be effective, it must be personalized and integrated into the multidisciplinary care plan, ensuring that the patient is not just "relapse-free," but functionally optimized for long-term independence (45). The practical stratification of exercise modalities relative to the patient's neurological status, as measured by the EDSS, is visualized in Figure 1.

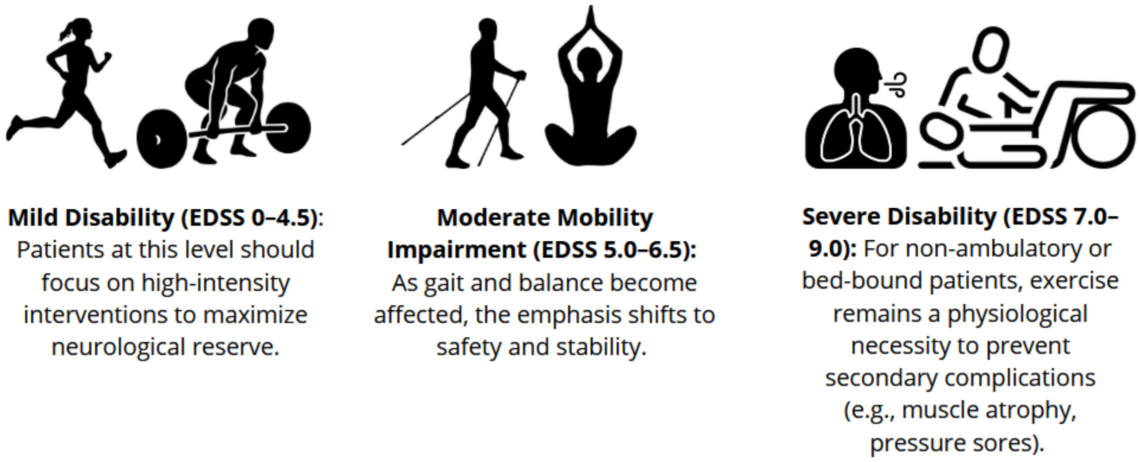

Fig. 1. *Personalized exercise prescription framework based on the Expanded Disability Status Scale (EDSS) for patients with Multiple Sclerosis.*

This infographic provides a clinical decision-making tool for tailoring physical activity to the functional capacity of patients with RRMS.

- **At lower disability levels (EDSS 0–4.5)**, the therapeutic goal is neuroprotection and maximization of the neurological reserve through high-intensity interventions (HIIT, vigorous resistance training).
- **In the moderate range (EDSS 5.0–6.5)**, where gait instability becomes more prevalent, the focus shifts to neuromotor training and safety, emphasizing modalities that reduce fall risk, such as Nordic walking and adapted yoga.
- **For individuals with severe disability (EDSS 7.0–9.0)**, exercise remains a physiological necessity. The focus here is on preventing secondary deconditioning, muscle atrophy, and pressure sores through respiratory training, passive range-of-motion (ROM) exercises, and functional electrical stimulation (FES).

This graduated approach ensures that exercise therapy is integrated as a permanent pillar of MS care across the entire disease spectrum(45).

8. Conclusions

The shift in the clinical management of Relapsing-Remitting Multiple Sclerosis (RRMS) from restrictive rest to structured physical activity represents one of the most significant advancements in holistic MS care. As demonstrated in this review, physical activity is no longer merely a supportive measure for symptom relief but a potent non-pharmacological adjunct therapy with the potential to modify the disease course. By modulating the molecular environment of the CNS through the release of neurotrophic factors like BDNF and inducing a favorable systemic cytokine shift, exercise provides a neuroprotective shield that addresses both the inflammatory and neurodegenerative components of the disease.

The integration of various exercise modalities—aerobic, resistance, and mind-body interventions—allows for a personalized approach that mitigates the most debilitating symptoms of RRMS, including pathological fatigue, mobility impairment, and cognitive decline. Furthermore, the strategic use of cooling techniques has successfully addressed historical safety concerns regarding Uhthoff's phenomenon, making exercise accessible even to those with high thermal sensitivity.

Crucially, the synergy between physical activity and Disease-Modifying Therapies (DMTs) offers a dual-track strategy: while DMTs control external immune aggression, exercise builds internal neurological and functional reserves. To maximize clinical outcomes, physical activity should be initiated within the "Window of Opportunity" early after diagnosis, ensuring that patients remain not only relapse-free but functionally resilient. Future MS management must move toward a fully integrated model where the prescription of movement is considered as fundamental as pharmacological intervention, ensuring long-term independence and improved quality of life for individuals living with RRMS.

Abbreviations
- **ADL** – Activities of Daily Living
- **AT** – Aerobic Training
- **BBB** – Blood-Brain Barrier
- **BDNF** – Brain-Derived Neurotrophic Factor
- **CNS** – Central Nervous System
- **CNTF** – Ciliary Neurotrophic Factor
- **DMT** – Disease-Modifying Therapy
- **EDSS** – Expanded Disability Status Scale
- **FES** – Functional Electrical Stimulation
- **HIIT** – High-Intensity Interval Training
- **HRmax** – Maximum Heart Rate
- **HRQOL** – Health-Related Quality of Life
- **IFN-γ** – Interferon gamma
- **IGF-1** – Insulin-like Growth Factor 1
- **IL-4** – Interleukin 4
- **IL-10** – Interleukin 10
- **IL-17** – Interleukin 17
- **LTP** – Long-Term Potentiation
- **MICT** – Moderate-Intensity Continuous Training
- **MRI** – Magnetic Resonance Imaging
- **MS** – Multiple Sclerosis
- **MSSS** – Multiple Sclerosis Severity Score
- **PBVC** – Percentage Brain Volume Change
- **PRT** – Progressive Resistance Training
- **ROM** – Range of Motion
- **RRMS** – Relapsing-Remitting Multiple Sclerosis
- **SMD** – Standardized Mean Difference
- **TNF-α** – Tumor Necrosis Factor alpha
- **TOCT** – Task-Oriented Circuit Training
- **VO$_2$max** – Maximal Oxygen Uptake
- **VR** – Virtual Reality

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