International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR |Vol.12 | Issue 4| Oct - Dec -2024

www.ijamscr.com

ISSN: 2347-6567

DOI : https://doi.org/10.61096/ijamscr.v12.iss4.2024.504-516

Review

Therapeutic advances in understanding, diagnosis and treatment of progressive multiple sclerosis

A Dhanush Kumar*, Nandini Penchala, Pakala Akhila Reddy, Shaik Parveen

Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Kompally, Secunderabad- 500100

*Author for Correspondence: A Dhanush Kumar
Email: dhanushkumar2003@gmail.com

Published on: 22 Nov 2024

Published by:
DrSriram Publications

Abstract

Progressive multiple sclerosis (PMS) is a debilitating neurodegenerative disorder within the broader category of multiple sclerosis (MS) that significantly impacts quality of life due to continuous neuroinflammation and gradual neuronal loss. Unlike relapsing-remitting MS, PMS exhibits minimal acute inflammatory activity and is instead characterized by a steady progression of neurological decline. Recent therapeutic advancements have focused on addressing both the neurodegenerative and immune-mediated components of PMS, with limited success in disease modification. This review explores the pathophysiology, diagnostic advances, therapeutic developments, and emerging research directions in PMS. The pathophysiology section highlights key mechanisms, including oxidative stress, mitochondrial dysfunction, and CNS compartmentalized inflammation, which contribute to progressive axonal and neuronal damage. Diagnostic improvements encompass advanced imaging modalities, such as high-resolution MRI and novel biomarkers like neurofilament light chain (NfL), which enable earlier and more accurate disease monitoring. The review also discusses current disease-modifying therapies (DMTs) and experimental treatments, including monoclonal antibodies, GM-CSF antagonists, and IL-2 receptor inhibitors, focusing on their potential to attenuate disease progression. Additionally, symptomatic management approaches and the role of neurostimulatory techniques in enhancing patient quality of life are examined. Future directions suggest that biomarkers for precision medicine, alongside advancements in cell-based therapies and gene-editing technologies, could provide targeted and individualized treatments for PMS. This review synthesizes current knowledge on PMS and emphasizes the need for continued innovation to effectively manage and ultimately mitigate disease progression.

Keywords: Progressive Multiple Sclerosis, Therapeutic Advances, Neuroinflammation, Neurodegeneration, Diagnostic Techniques, Disease-Modifying Therapies, Biomarkers, Precision Medicine.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) affecting over 2.8 million people worldwide. MS can manifest in various clinical forms, including relapsing-remitting MS (RRMS) and progressive MS (PMS). PMS is further categorized into primary progressive MS (PPMS), which accounts for approximately 10-15% of all MS cases, and secondary progressive MS (SPMS), where the disease transitions from an initial relapsing-remitting course into a steadily progressive phase [1]. While RRMS is characterized by relapses followed by partial or complete recovery, PMS shows a steady accumulation of disability with or without occasional relapses [2].

PMS presents distinct challenges in both diagnosis and treatment due to its unique pathophysiological underpinnings. In PMS, compartmentalized inflammation within the CNS, chronic microglial activation, and mitochondrial dysfunction play critical roles in ongoing neurodegeneration. These factors drive the continuous progression of disability, primarily through mechanisms of axonal and neuronal loss that are less responsive to traditional immunomodulatory therapies effective in RRMS [3]. This pathophysiology underscores the urgent need for targeted therapies that address the neurodegenerative aspects of PMS beyond inflammation alone.

The limited efficacy of disease-modifying therapies (DMTs) in PMS reflects the distinct pathogenic processes at play. Conventional therapies, including β-interferons and glatiramer acetate, which effectively reduce relapse rates and slow disability progression in RRMS, demonstrate minimal impact on the progression of PMS due to the lack of active, peripheral inflammatory components [4]. This therapeutic gap has driven recent research into understanding the specific mechanisms of neurodegeneration in PMS and exploring novel therapeutic strategies to prevent or slow this process.

With advancements in imaging techniques and the identification of potential biomarkers, early diagnosis and continuous monitoring of PMS are becoming more feasible. Emerging diagnostic tools, including high-resolution MRI and cerebrospinal fluid biomarkers such as neurofilament light chain (NfL), offer valuable insights into disease progression and prognosis [5]. These developments are critical in guiding clinical decisions, particularly in a landscape where effective treatment options remain scarce.

In this review, we explore recent advances in the understanding, diagnosis, and treatment of PMS. The pathophysiology section delves into neuroinflammation, mitochondrial dysfunction, and oxidative stress, highlighting their roles in progressive neuronal damage. We also discuss advancements in diagnostic techniques, including imaging and biomarkers, that are instrumental in facilitating earlier diagnosis and targeted therapeutic interventions. Additionally, we review current and emerging therapeutic options, including immunomodulatory agents, neuroprotective strategies, and symptomatic therapies, with an emphasis on their potential to modify disease progression in PMS. Finally, we address future directions in PMS research, focusing on novel treatment modalities such as cell-based therapies, gene-editing technologies, and precision medicine approaches that hold promise for revolutionizing PMS management.

Pathophysiology of progressive multiple sclerosis

The pathophysiology of progressive multiple sclerosis (PMS) is complex and involves an interplay of chronic inflammation, neurodegeneration, mitochondrial dysfunction, and oxidative stress within the central nervous system (CNS). Unlike relapsing-remitting multiple sclerosis (RRMS), which is primarily driven by acute inflammatory episodes in the peripheral immune system, PMS is characterized by continuous and compartmentalized inflammation within the CNS. This inflammation is sustained by resident immune cells such as microglia and astrocytes, leading to a progressive loss of axons and neurons that ultimately contributes to permanent disability [6].

Chronic Inflammation and Compartmentalized Immune Response

One of the hallmark features of PMS is compartmentalized inflammation, where immune cells are confined within the CNS. In RRMS, inflammation often originates in the peripheral immune system and involves T-cells crossing the blood-brain barrier (BBB) to attack CNS myelin sheaths. However, in PMS, inflammation becomes compartmentalized, persisting within the CNS and isolated from peripheral immune modulation. This compartmentalized inflammation is largely maintained by microglial activation and the formation of meningeal lymphoid-like structures in the meninges surrounding the brain and spinal cord [7].

Microglial cells, the CNS's resident immune cells, become chronically activated in PMS, releasing pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), which contribute to sustained neuroinflammation [8]. Unlike the inflammation in RRMS, this process is less responsive to immunomodulatory therapies that target peripheral inflammation, as the BBB remains largely intact, preventing peripheral immune cells from accessing the CNS.

Mitochondrial Dysfunction and Axonal Injury

Mitochondrial dysfunction plays a critical role in the pathogenesis of PMS by impairing cellular energy production, which is essential for neuronal survival and function. In PMS, mitochondrial DNA mutations and deficiencies in mitochondrial enzymes lead to reduced ATP production and an increased generation of reactive oxygen species (ROS), causing oxidative damage to neurons and axons [9]. This oxidative stress exacerbates the vulnerability of demyelinated axons, which are less capable of maintaining ionic balance and are highly dependent on efficient mitochondrial function for survival.

The impaired energy metabolism in PMS leads to energy deficits that affect axonal transport and contribute to axonal degeneration over time. Studies have shown that mitochondrial dysfunction and ROS production are closely associated with the progression of disability in PMS patients, as they disrupt the integrity of neurons and support cells, ultimately resulting in irreversible neurological damage [10]. Therapeutic strategies targeting mitochondrial protection and reducing oxidative stress are therefore being explored as potential avenues to mitigate neuronal loss in PMS.

Oxidative Stress and Neurodegeneration

Oxidative stress is a significant contributor to the neurodegenerative processes observed in PMS. Elevated levels of ROS, combined with reduced antioxidant defenses, lead to extensive damage to cellular structures, including lipids, proteins, and DNA within neurons. In PMS, oxidative stress is primarily driven by the chronic activation of microglia and macrophages within the CNS, which release high levels of ROS and reactive nitrogen species (RNS) [11]. These reactive molecules can initiate a cascade of damage that further compromises neuronal survival and accelerates axonal degeneration.

Oxidative damage in PMS is not limited to axons but also affects oligodendrocytes, the cells responsible for myelination in the CNS. Damage to oligodendrocytes impairs remyelination, leading to persistent demyelinated lesions that exacerbate neurodegenerative processes. Additionally, myelin sheaths in PMS are more susceptible to oxidative stress due to their high lipid content, making them a primary target for ROS-mediated damage [12].

Role of B-cells and Lymphoid-like Structures

Recent studies suggest that B-cells, along with the formation of ectopic lymphoid-like structures in the meninges, contribute to the sustained inflammation in PMS. These structures, which resemble secondary lymphoid organs, serve as local sites for B-cell activation and antibody production against CNS antigens. The presence of these structures in the meninges has been linked to greater levels of disability and more rapid progression in PMS, suggesting a pathogenic role in sustaining chronic inflammation within the CNS [13].

B-cells within these lymphoid-like structures produce antibodies and pro-inflammatory cytokines, further perpetuating inflammation and tissue damage. B-cell depletion therapies, such as rituximab and ocrelizumab, have shown some efficacy in reducing disease activity in PMS, indicating that targeting B-cell-mediated inflammation may provide therapeutic benefit in managing progressive forms of MS [14].

Neuroaxonal Damage and Glial Scarring

The cumulative effects of chronic inflammation, oxidative stress, and mitochondrial dysfunction lead to significant neuroaxonal damage and glial scarring in PMS. Axonal loss is a primary driver of irreversible disability in PMS, as it disrupts neuronal circuits and impairs motor and cognitive functions. Glial scar formation, primarily composed of astrocytes and activated microglia, further impedes neural regeneration by creating a physical and biochemical barrier that limits axonal growth and repair [15].

Astrocytes, which play a supportive role in healthy CNS function, contribute to the formation of glial scars by proliferating in response to injury and releasing inhibitory molecules that restrict axonal regrowth. This process, known as reactive astrogliosis, is particularly pronounced in PMS, where sustained inflammation and tissue damage lead to extensive scar formation [16]. Targeting astrocytic responses and promoting a more permissive environment for axonal regeneration are emerging areas of research aimed at counteracting neuroaxonal damage in PMS.

Advances in diagnostic techniques

Timely and accurate diagnosis of progressive multiple sclerosis (PMS) is critical for effective disease management, especially since therapeutic options are more limited and less effective once significant neurodegeneration has occurred. Traditional diagnostic tools, primarily developed for relapsing-remitting MS (RRMS), have limited sensitivity and specificity for detecting the subtle, ongoing CNS damage in PMS. As such, recent advancements in imaging techniques and biomarker research are proving essential for improving the early diagnosis and monitoring of PMS. These techniques provide clinicians with better tools to differentiate PMS from other neurological conditions and track disease progression, enabling more tailored treatment approaches.

Magnetic Resonance Imaging (MRI) Innovations

MRI remains a cornerstone in the diagnosis and monitoring of MS due to its ability to visualize structural changes in the brain and spinal cord. For PMS, however, conventional MRI scans are often insufficient, as they primarily detect acute inflammatory lesions, which are less common in PMS than in RRMS. To overcome this limitation, advanced MRI techniques are being utilized to capture the subtle, chronic changes associated with PMS.

One of the most promising advancements is high-field MRI, which utilizes magnetic fields of 7 Tesla (T) or higher to provide high-resolution images. High-field MRI enables the detection of cortical lesions and brain atrophy, both of which are indicative of progressive disease. Studies have shown that cortical lesions are more prevalent in PMS than in RRMS and are associated with greater disability and cognitive impairment [17]. Additionally, high-field MRI can detect microstructural changes in normal-appearing white matter (NAWM) and gray matter, providing insights into the diffuse axonal damage that characterizes PMS [18].

Magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) are other MRI-based techniques that have shown promise in assessing microstructural damage in PMS. MTI measures the exchange of magnetization between free water and macromolecules, offering insights into myelin integrity, while DTI assesses white matter integrity by tracking the diffusion of water molecules along axonal pathways. Both MTI and DTI have been shown to correlate with disability progression in PMS, making them valuable tools for monitoring disease evolution [19].

Positron Emission Tomography (PET) and Novel Tracers

Positron emission tomography (PET) imaging has recently emerged as a valuable tool in MS research, particularly for understanding PMS. PET allows for the visualization of active neuroinflammation and neurodegeneration at a molecular level, which is crucial for studying the chronic, compartmentalized inflammation characteristic of PMS. Unlike MRI, which captures structural changes, PET can track functional alterations by using radioactive tracers that bind to specific cellular targets.

One notable PET tracer is the translocator protein (TSPO) ligand, which binds to microglia and macrophages, markers of inflammation within the CNS. Studies using TSPO-PET imaging have shown that PMS patients exhibit higher levels of microglial activation, particularly in gray matter regions and the cortex, compared to RRMS patients. This increased microglial activity correlates with disease severity and progression, making TSPO-PET a promising tool for both diagnosis and monitoring [20].

Other PET tracers target metabolic activity within the CNS, offering insights into neuronal health. For instance, tracers that bind to glucose transporters or mitochondrial markers can assess cellular metabolism in specific brain regions, potentially identifying areas of neurodegeneration before they are detectable on MRI. These imaging tools provide a more dynamic view of PMS pathology, allowing researchers and clinicians to observe disease processes in real-time and assess the impact of therapeutic interventions [21].

Biomarkers in Cerebrospinal Fluid (CSF) and Blood

The search for reliable biomarkers in cerebrospinal fluid (CSF) and blood has become a focal point in PMS research, as biomarkers offer a minimally invasive way to monitor disease activity and progression. Among the most promising biomarkers are neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), both of which have shown potential in predicting disease severity and tracking neurodegeneration.

Neurofilament light chain is a structural protein released into the CSF and blood following axonal damage. Elevated levels of NfL have been correlated with disease progression in PMS, as higher concentrations of NfL indicate increased axonal injury and neurodegeneration. Recent studies suggest that NfL levels in blood and CSF correlate well with MRI findings, making it a viable biomarker for tracking disease activity over time [22]. Its ability to reflect ongoing neurodegeneration makes NfL a promising candidate for use in clinical practice, particularly in assessing the efficacy of neuroprotective therapies in PMS.

Another promising biomarker is glial fibrillary acidic protein (GFAP), an intermediate filament protein expressed in astrocytes. Increased GFAP levels in CSF and blood indicate reactive astrogliosis, a hallmark of CNS damage in PMS. GFAP levels have been shown to correlate with MRI markers of brain atrophy, suggesting that GFAP may serve as an indicator of long-term neurodegenerative changes [23]. Together, NfL and GFAP provide complementary information about axonal and astrocytic injury, respectively, offering a more comprehensive view of PMS pathology.

Emerging Biomarkers and Personalized Diagnostics

In addition to NfL and GFAP, several other biomarkers are being investigated for their potential to provide personalized diagnostic information in PMS. For example, chitinase-3-like protein 1 (CHI3L1), a marker of inflammation and glial activation, has been associated with increased disability and worse clinical outcomes in MS. Elevated CHI3L1 levels in CSF have been shown to correlate with gray matter atrophy and cognitive impairment in PMS, suggesting that it could serve as a marker of disease progression [24].

The development of biomarker panels, which combine multiple biomarkers to capture different aspects of PMS pathology, is an area of active research. These panels could help stratify patients by disease subtype, predict response to specific therapies, and allow for more personalized treatment approaches. The ability to identify patients who are at high risk for rapid progression would be particularly valuable in PMS, where early intervention could prevent significant disability [25].

Revised Diagnostic Criteria and Clinical Guidelines

The advent of advanced imaging techniques and biomarkers has prompted discussions about updating the diagnostic criteria for MS, particularly PMS. Current diagnostic criteria, such as the McDonald criteria, are primarily designed for RRMS and rely heavily on detecting relapses and MRI-visible lesions. However, PMS often lacks these hallmark features, making it difficult to diagnose accurately in its early stages.

Proposed revisions to the diagnostic criteria for PMS emphasize the use of imaging and biomarker data to detect subtle disease progression and identify patients with a progressive disease course earlier. For example, incorporating biomarkers such as NfL and CHI3L1 into clinical guidelines could provide additional support for a PMS diagnosis in patients with atypical MRI findings or no history of relapses. The inclusion of high-resolution MRI techniques, such as cortical lesion detection and DTI metrics, may also enhance the sensitivity of diagnostic criteria for identifying PMS [26].

These updated diagnostic approaches have the potential to improve early diagnosis and enable more effective monitoring of disease progression in PMS. By integrating biomarkers and advanced imaging, clinicians may be better equipped to tailor treatment strategies to the specific needs of PMS patients, addressing both inflammatory and neurodegenerative aspects of the disease.

Therapeutic advances

Therapeutic advancements in progressive multiple sclerosis (PMS) remain a high priority due to the limited effectiveness of traditional disease-modifying therapies (DMTs) that primarily target the inflammatory processes characteristic of relapsing-remitting MS (RRMS). In PMS, the neurodegenerative components, including chronic neuroinflammation, mitochondrial dysfunction, and oxidative damage, necessitate a different therapeutic approach. Recent developments in both immunomodulatory therapies and neuroprotective strategies have shown potential for reducing disability progression in PMS. Here, we review the current DMTs, experimental treatments under investigation, and emerging therapeutic strategies that are transforming PMS management.

Disease-Modifying Therapies (DMTs) for PMS

Disease-modifying therapies (DMTs) have been the cornerstone of MS treatment, mainly aimed at reducing relapse rates in RRMS. In PMS, however, DMTs demonstrate limited efficacy due to the lack of active peripheral inflammation that these therapies primarily target. For instance, interferon beta (IFN-β) and glatiramer acetate, which modulate the immune response and reduce relapse frequency, have minimal impact on the neurodegenerative processes that characterize PMS [27]. Despite their limited effectiveness in PMS, some studies suggest that early initiation of DMTs in the transitional phase from RRMS to secondary progressive MS (SPMS) may slow disease progression in certain cases, likely by curbing residual inflammatory activity [28].

One of the more promising DMTs for PMS is ocrelizumab, a humanized monoclonal antibody that targets CD20+ B cells, which play a key role in CNS inflammation. Approved for primary progressive MS (PPMS) in 2017, ocrelizumab is the first and only DMT shown to significantly reduce disability progression in PPMS patients [29]. By depleting CD20+ B cells, ocrelizumab mitigates the chronic inflammatory response in the CNS, which has shown measurable benefits in terms of slowing disability progression in patients with early-stage PPMS. Despite these advances, ocrelizumab's efficacy is still limited in patients with advanced PMS, where neurodegenerative processes predominate.

Monoclonal Antibodies and Immunomodulatory Agents

In addition to ocrelizumab, other monoclonal antibodies and immunomodulatory agents are being explored for their potential to manage PMS. Rituximab, another anti-CD20 monoclonal antibody, has shown promise in reducing B-cell-driven inflammation in PMS and is often used off-label for PPMS in clinical practice [30]. Although rituximab is not officially approved for PMS, studies suggest that it may offer benefits similar to ocrelizumab, particularly in patients with active inflammation.

Natalizumab, an integrin antagonist that prevents immune cells from crossing the blood-brain barrier, has also been studied for its efficacy in PMS. However, its use in PMS remains controversial due to limited evidence of efficacy in progressive forms and concerns regarding the risk of progressive multifocal leukoencephalopathy (PML), a serious brain infection caused by the JC virus. Nevertheless, natalizumab may benefit a subset of PMS patients with active inflammation who are carefully monitored for PML risk [31].

Other immunomodulatory agents, such as Siponimod and ponesimod, target sphingosine-1-phosphate receptors and are effective in modulating the immune response. Siponimod, specifically approved for secondary

progressive MS (SPMS), has shown efficacy in reducing relapse rates and slowing disability progression in patients with active SPMS. Its mechanism of action, which involves trapping lymphocytes in lymph nodes, prevents these cells from entering the CNS and causing inflammation [32].

Neuroprotective Strategies

Given the limited efficacy of traditional DMTs in PMS, neuroprotective strategies that target neuronal and axonal integrity are becoming a focus of therapeutic development. One such approach involves high-dose biotin, a B vitamin thought to play a role in energy production and myelin synthesis. Initial studies indicate that high-dose biotin supplementation may reduce disability progression in PMS by enhancing cellular metabolism and supporting remyelination processes [33]. Though promising, the long-term efficacy and safety of high-dose biotin require further investigation in larger clinical trials.

Mitochondrial-targeted antioxidants, such as idebenone and mitoquinone, are also being studied for their potential to reduce oxidative damage in PMS. By countering the effects of mitochondrial dysfunction and oxidative stress, these antioxidants aim to protect axons and neurons from progressive damage. Early-phase studies of these compounds have shown some neuroprotective effects, particularly in slowing the progression of motor impairment, but more extensive research is needed to validate their clinical utility in PMS [34].

GM-CSF Antagonists and IL-2 Receptor Inhibitors

Novel immunotherapies targeting specific cytokines and immune pathways involved in chronic CNS inflammation represent a new frontier in PMS treatment. GM-CSF (granulocyte-macrophage colony-stimulating factor) antagonists, for example, inhibit the action of GM-CSF, a cytokine that promotes microglial activation and CNS inflammation. GM-CSF antagonists, such as specific antibodies that block GM-CSF receptors, have shown efficacy in reducing neuroinflammatory markers in PMS models and are currently undergoing clinical evaluation [35].

IL-2 receptor inhibitors represent another class of immunomodulatory agents that may benefit PMS patients. IL-2 plays a role in T-cell and B-cell proliferation, and its receptor has been implicated in the pathological immune response in PMS. Early clinical trials indicate that IL-2 receptor inhibitors, particularly for patients who do not respond to β-interferon, may provide an alternative means of reducing neuroinflammation in PMS [36]. Further studies are required to determine the safety and efficacy of these therapies in larger patient populations.

Cell-Based and Regenerative Therapies

Cell-based therapies, including hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell (MSC) therapy, are emerging as potential options for PMS patients, particularly those who do not respond to conventional therapies. HSCT, which involves ablating the immune system and reconstituting it with hematopoietic stem cells, aims to reset the immune system and halt disease progression. While HSCT has shown promise in aggressive RRMS, its role in PMS remains under investigation, with early studies suggesting potential benefits in select patient populations [37].

Mesenchymal stem cells (MSCs), derived from bone marrow or adipose tissue, have immunomodulatory and regenerative properties that could aid in CNS repair and remyelination. MSC therapy is currently being evaluated in clinical trials for PMS, with preliminary results indicating improvements in functional outcomes and a reduction in inflammation markers [38]. These therapies offer a new approach to PMS management by targeting the neuroregenerative capacity of the CNS rather than solely modulating the immune response.

Symptomatic Therapies and Quality of Life Enhancements

In addition to disease-modifying and neuroprotective therapies, managing symptoms remains a critical component of PMS care. Common symptoms in PMS, such as spasticity, pain, fatigue, and cognitive impairment, significantly impact quality of life and require targeted interventions. Pharmacologic treatments for symptom relief include muscle relaxants (e.g., baclofen, tizanidine) for spasticity, antiepileptic drugs (e.g., gabapentin) for neuropathic pain, and amantadine for fatigue [39].

Non-pharmacologic interventions, including physical therapy, occupational therapy, and cognitive behavioral therapy (CBT), are equally important for maintaining function and quality of life in PMS patients. Neurostimulatory techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have also shown promise in alleviating fatigue and cognitive symptoms in MS, offering an additional therapeutic tool for PMS management [40].

Future Directions in Therapeutic Development

As research into PMS pathophysiology advances, new therapeutic approaches targeting specific molecular pathways and cellular processes hold promise for more effective management of the disease. Precision medicine approaches, which utilize biomarkers to stratify patients and guide therapy choices, are likely to play an increasingly important role in PMS treatment. Ongoing research into the use of NfL and GFAP as biomarkers

could enable clinicians to tailor therapies to the individual patient's disease profile, optimizing treatment outcomes and potentially slowing disease progression [22].

Additionally, gene-editing technologies, such as CRISPR/Cas9, are being explored for their potential to modify disease-related genes and reduce neuroinflammation. Although these technologies are in the early stages of development for PMS, they represent a promising avenue for future research aimed at addressing the underlying genetic and molecular causes of the disease [41].

Management of symptoms

In progressive multiple sclerosis (PMS), the continuous neurological decline leads to an array of symptoms that substantially impact quality of life. Since disease-modifying therapies (DMTs) primarily address disease progression rather than symptomatic relief, a significant component of PMS management revolves around alleviating symptoms such as spasticity, pain, cognitive impairment, and fatigue. Symptomatic management is crucial for maintaining functional independence, minimizing discomfort, and supporting mental health in patients. This section reviews pharmacologic and non-pharmacologic treatments that are essential in the comprehensive care of PMS patients.

Pharmacologic Management of Spasticity and Pain

Spasticity, characterized by involuntary muscle stiffness and spasms, is a common and often disabling symptom in PMS. Muscle relaxants, such as baclofen and tizanidine, are the mainstay pharmacologic treatments for spasticity. Baclofen, a gamma-aminobutyric acid (GABA) agonist, reduces muscle spasms by inhibiting spinal reflexes, whereas tizanidine, an alpha-2 adrenergic agonist, reduces muscle tone by acting on the central nervous system [42]. Both medications can alleviate spasticity but may cause side effects such as drowsiness and dizziness, requiring careful dosage adjustments.

In cases of severe spasticity that do not respond to oral medications, intrathecal baclofen therapy (ITB) may be considered. ITB delivers baclofen directly into the cerebrospinal fluid via an implanted pump, providing effective relief with lower systemic side effects. Botulinum toxin injections are another option for localized spasticity, particularly in cases affecting small muscle groups [43].

Neuropathic pain is another common and challenging symptom in PMS. It is often described as a burning, tingling, or stabbing pain resulting from nerve damage. Gabapentin and pregabalin, both of which are antiepileptic drugs with analgesic properties, are commonly prescribed for neuropathic pain. These medications work by modulating calcium channels to decrease neuronal excitability. Tricyclic antidepressants, such as amitriptyline, and serotonin-norepinephrine reuptake inhibitors (SNRIs), like duloxetine, are also effective options for neuropathic pain management [44].

Fatigue and Energy Management

Fatigue is one of the most debilitating symptoms of PMS, affecting nearly all patients to varying degrees. It significantly impairs daily functioning and is often described as a persistent lack of energy that is disproportionate to physical activity. The management of fatigue in PMS involves both pharmacologic and lifestyle-based strategies.

Amantadine, a dopaminergic agent, is commonly used to alleviate MS-related fatigue. Although its mechanism of action in reducing fatigue is not fully understood, studies suggest that amantadine may enhance neurotransmitter release, providing an energizing effect. Modafinil, a wakefulness-promoting agent, is also sometimes prescribed off-label for fatigue in MS, though its efficacy in PMS is variable, and it can cause side effects such as headaches and anxiety [45].

In addition to pharmacologic treatments, non-pharmacologic strategies such as energy conservation techniques, regular physical activity, and structured rest periods are essential components of fatigue management. Occupational therapists often work with PMS patients to develop personalized plans that optimize energy use throughout the day, helping patients engage in meaningful activities while avoiding excessive fatigue.

Cognitive Impairment and Cognitive Rehabilitation

Cognitive impairment in PMS can affect memory, attention, processing speed, and executive functioning, leading to difficulties in performing daily tasks and maintaining social interactions. Cognitive rehabilitation, a structured approach that includes cognitive training exercises, compensatory strategies, and environmental modifications, has been shown to improve cognitive function and quality of life in MS patients [46].

In cases of mild cognitive impairment, cognitive training exercises can help improve specific cognitive skills, such as memory and attention, by engaging neural pathways involved in cognitive processing. These exercises can be conducted through computer-based programs or in-person sessions with neuropsychologists. Compensatory strategies, such as using reminders, maintaining structured routines, and simplifying tasks, can also help patients manage cognitive demands more effectively [47].

Pharmacologic treatments for cognitive impairment in PMS are limited, but some medications used for Alzheimer's disease, such as donepezil, have been explored in MS for their potential benefits on cognitive symptoms. While evidence supporting their effectiveness in PMS is limited, these medications may offer modest benefits for select patients [48].

Depression, Anxiety, and Psychological Support

Depression and anxiety are common comorbidities in PMS, with studies showing that up to 50% of MS patients experience depressive symptoms at some point. The chronic nature of PMS, combined with physical limitations, can lead to feelings of helplessness and social isolation, exacerbating mental health issues. Psychological support is, therefore, an integral part of PMS care, focusing on improving emotional well-being and enhancing resilience.

Cognitive behavioral therapy (CBT) is one of the most effective psychotherapeutic approaches for managing depression and anxiety in PMS. CBT helps patients identify and modify negative thought patterns, develop coping strategies, and improve emotional regulation. Group therapy and support groups also provide a platform for patients to share their experiences, reducing feelings of isolation and fostering a sense of community [49].

Antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs), are frequently prescribed for depression in PMS. SSRIs, including fluoxetine and sertraline, are often well-tolerated and can improve mood, sleep, and energy levels. Given the high prevalence of depressive symptoms in PMS, routine screening for depression and anxiety is recommended to ensure timely intervention [50].

Physical Therapy and Exercise-Based Interventions

Physical therapy plays a crucial role in managing the motor symptoms of PMS, including weakness, gait abnormalities, and spasticity. Exercise-based interventions, guided by physical therapists, can help improve strength, flexibility, and balance, enabling patients to maintain functional independence. Strengthening exercises, stretching routines, and aerobic activities are common components of physical therapy programs for PMS patients [51].

Studies have shown that regular physical activity can have a positive impact on both physical and cognitive symptoms in PMS. Aerobic exercise, in particular, may enhance cardiovascular health, improve mood, and reduce fatigue levels. Balance training and gait training are also essential for PMS patients at risk of falls, helping to prevent injury and maintain mobility. Physical therapists work with patients to develop individualized exercise programs that account for their abilities and limitations, providing a structured approach to symptom management [52].

Neuromodulatory Techniques: TMS and tDCS

Neuromodulatory techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have emerged as potential adjunct therapies for managing symptoms like fatigue, depression, and cognitive impairment in PMS. These techniques involve non-invasive stimulation of specific brain regions to modulate neural activity and improve symptom control.

TMS uses magnetic pulses to stimulate cortical areas, particularly the dorsolateral prefrontal cortex, which is involved in mood regulation and cognitive processing. Studies suggest that TMS may reduce fatigue and depressive symptoms in MS patients by enhancing neuroplasticity and increasing activity in underactive brain regions [53]. Similarly, tDCS, which delivers a low electrical current to specific brain areas, has shown promise in improving cognitive symptoms and reducing pain in PMS. Although these techniques require further validation in large-scale trials, they offer a novel approach to symptomatic management in PMS [54].

Integrative and Lifestyle-Based Approaches

Integrative therapies, such as yoga, mindfulness-based stress reduction (MBSR), and dietary modifications, are gaining popularity among PMS patients as complementary approaches to symptom management. Yoga and MBSR, for instance, have been shown to reduce stress, improve mood, and enhance physical flexibility and balance. These practices also promote relaxation and mental well-being, helping patients cope with the chronic nature of PMS [55].

Dietary interventions, although not curative, may influence the course of MS. Anti-inflammatory diets rich in fruits, vegetables, whole grains, and omega-3 fatty acids are often recommended to support overall health and potentially reduce systemic inflammation. While more research is needed to establish dietary guidelines for MS, patients are encouraged to maintain a balanced diet and discuss nutritional supplements with their healthcare providers [56].

Future directions and emerging therapies

The treatment of progressive multiple sclerosis (PMS) remains one of the most challenging areas in neurology, due to the complexity of the disease and the limited efficacy of existing therapies. However, advancements in our understanding of PMS pathophysiology are leading to new, innovative therapeutic strategies that hold promise for altering disease progression. Future treatment approaches aim to integrate personalized medicine, regenerative therapies, and novel pharmacologic agents to address both inflammation and neurodegeneration. This section reviews the latest research directions and emerging therapies that may transform PMS management in the coming years.

Biomarkers and Precision Medicine

Precision medicine, which tailors treatments to an individual's unique disease profile, has the potential to revolutionize PMS care. Biomarkers that reflect disease activity and progression can guide treatment decisions, enabling clinicians to select therapies that best match a patient's specific disease characteristics. Currently, neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) are among the most promising biomarkers in PMS. Both biomarkers can be measured in cerebrospinal fluid (CSF) or blood, offering a less invasive means of tracking disease progression [57].

NfL is particularly valuable as it reflects axonal damage, while GFAP serves as a marker of astrocytic injury and gliosis, both of which are central to PMS pathology. By monitoring these biomarkers, clinicians can assess treatment responses and adjust therapies as needed to slow neurodegeneration. Future research aims to develop additional biomarkers that can predict treatment outcomes, detect early changes in disease activity, and guide the use of neuroprotective agents in PMS [58].

The integration of biomarker-based diagnostics into clinical practice could support the use of combination therapies that target different aspects of PMS pathology. For example, combining anti-inflammatory agents with neuroprotective or regenerative therapies could provide a multifaceted approach to treatment, guided by real-time biomarker feedback.

Stem Cell Therapies

Stem cell therapies, including hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell (MSC) therapy, are among the most promising approaches for treating PMS due to their potential to modulate the immune response and promote CNS repair. HSCT involves ablating the immune system with high-dose chemotherapy and reconstituting it with autologous hematopoietic stem cells, effectively "resetting" the immune system. HSCT has shown efficacy in aggressive cases of relapsing MS, but its role in PMS remains under investigation. Recent studies suggest that HSCT may slow disease progression in PMS by reducing inflammation and neurodegeneration, though more research is needed to confirm these findings [59].

MSC therapy, on the other hand, offers a less aggressive alternative to HSCT, with MSCs derived from the patient's own bone marrow or adipose tissue. MSCs have immunomodulatory and regenerative properties, and they can potentially promote remyelination and reduce neuroinflammation. Early-phase clinical trials in PMS have shown that MSC therapy is safe and may improve functional outcomes, though the extent of its efficacy is still under study. Researchers are exploring ways to enhance the therapeutic potential of MSCs, such as genetic modification to boost their neuroprotective effects or pre-conditioning to improve their homing to damaged CNS areas [60].

Gene Therapy and Gene Editing

Gene therapy and gene-editing technologies, such as CRISPR/Cas9, are emerging as innovative approaches for targeting the genetic and molecular drivers of PMS. Gene therapy involves delivering therapeutic genes to specific cells to correct genetic abnormalities or modulate immune responses. For PMS, gene therapy strategies focus on reducing inflammation, promoting remyelination, and protecting neurons from oxidative damage. Early research has shown potential in animal models, and clinical trials are underway to assess the safety and efficacy of gene therapy in human patients [61].

CRISPR/Cas9 gene-editing technology enables precise modifications to the genome, allowing researchers to target specific genes associated with inflammation and neurodegeneration in PMS. For example, CRISPR/Cas9 can be used to silence pro-inflammatory genes or upregulate genes involved in neuroprotection. Although gene-editing technology for PMS is still in its infancy, advancements in CRISPR/Cas9 delivery methods and target specificity are paving the way for its potential application in neurodegenerative diseases. These therapies may one day offer a more targeted approach to PMS treatment, addressing the disease at a molecular level [62].

Neuroprotective Agents and Novel Pharmacologic Approaches

Neuroprotective agents, which aim to prevent or reduce neuronal loss, are a critical area of research in PMS. Given that neurodegeneration is a major driver of disability in PMS, therapies that protect neurons from

damage could play a key role in managing the disease. Biotin, a B vitamin that supports cellular energy production, has shown some efficacy in reducing disability progression in PMS by enhancing mitochondrial function. High-dose biotin supplementation is currently being studied in clinical trials to determine its long-term effects on neuroprotection and disability in PMS [63].

Antioxidants that target mitochondrial dysfunction, such as idebenone and mitoquinone, are also being investigated as potential neuroprotective agents. These compounds reduce oxidative damage by neutralizing reactive oxygen species (ROS) and supporting mitochondrial health. Although early-phase trials have shown that mitochondrial-targeted antioxidants may slow motor impairment in PMS, further studies are needed to establish their clinical benefits and safety profile [64].

In addition to neuroprotective agents, novel pharmacologic approaches that target specific immune pathways are under investigation. For instance, granulocyte-macrophage colony-stimulating factor (GM-CSF) antagonists aim to inhibit neuroinflammation by blocking GM-CSF receptors on microglia and macrophages. Similarly, IL-2 receptor inhibitors may reduce T-cell and B-cell proliferation, offering an alternative immunomodulatory approach for PMS patients who do not respond to conventional therapies. These therapies, currently in various stages of clinical testing, could add new options for managing neuroinflammation and promoting neuroprotection in PMS [65].

Combination Therapies and Personalized Treatment Approaches

One of the most promising future directions in PMS treatment is the use of combination therapies that address multiple aspects of the disease simultaneously. Given the multifactorial nature of PMS, combining therapies that target different mechanisms, such as inflammation, neurodegeneration, and oxidative stress, may provide more comprehensive disease control. For example, combining an anti-inflammatory DMT with a neuroprotective agent could offer benefits by reducing inflammation while simultaneously protecting neurons from oxidative damage [66].

Personalized treatment approaches, driven by biomarker profiling, could further enhance the efficacy of combination therapies. By analyzing a patient's biomarker profile, clinicians may be able to determine the dominant pathological process in a given individual, allowing them to select the most appropriate therapies. Precision medicine approaches, supported by advancements in biomarkers and genetic testing, are expected to become increasingly feasible as our understanding of PMS pathophysiology grows. The integration of such strategies into clinical practice could pave the way for more individualized and effective PMS management [67].

Emerging Technologies in PMS Research and Clinical Trials

Advances in technology are transforming how PMS is studied and treated. Artificial intelligence (AI) and machine learning, for instance, are being applied to analyze complex datasets from imaging studies, genetic testing, and biomarker analysis, providing new insights into disease progression and treatment responses. AI-driven analysis of MRI and PET scans can help identify early signs of neurodegeneration, while predictive algorithms may assist in identifying patients at higher risk of rapid progression [68].

Digital health tools, such as wearable devices and mobile apps, are also gaining traction in PMS research. These tools enable real-time monitoring of physical activity, symptom fluctuations, and treatment adherence, providing valuable data for clinicians and researchers. Digital biomarkers derived from wearable devices may soon complement traditional biomarkers, offering an additional layer of information to guide personalized treatment strategies. The integration of these technologies into clinical trials is also expected to improve data quality and support the development of more effective therapies for PMS [69].

Ongoing Research and Clinical Trials

Ongoing clinical trials in PMS are focused on a wide range of therapeutic strategies, from DMTs and neuroprotective agents to regenerative therapies and lifestyle interventions. For instance, trials are evaluating the efficacy of high-dose biotin, mitochondrial-targeted antioxidants, and stem cell therapies, with the goal of finding therapies that can slow or halt neurodegeneration in PMS. Additionally, studies investigating the impact of exercise, diet, and psychological support on PMS progression are providing insights into how lifestyle modifications may complement pharmacologic treatments [70].

Clinical trials are also assessing combination therapies and exploring the potential of emerging treatments, such as gene therapy and cell-based approaches. These trials will continue to shape the future of PMS management, as they provide critical data on safety, efficacy, and long-term outcomes. As research progresses, the integration of novel therapies into standard care will likely lead to more effective and individualized treatment options for PMS patients.

CONCLUSION

In summary, progressive multiple sclerosis presents unique therapeutic challenges due to its complex pathophysiology, marked by chronic inflammation and neurodegeneration. Recent advances in diagnostic techniques, such as high-resolution imaging and biomarker analysis, are enabling earlier detection and more precise monitoring of PMS. Therapeutic innovations, including stem cell therapies, gene-editing technologies, and neuroprotective agents, offer hope for altering disease progression. Future treatment approaches that incorporate combination therapies and precision medicine hold significant potential for improving outcomes in PMS, providing a foundation for more effective and personalized.

REFERENCES

1. Shirani, A., Okuda, D., & Stüve, O. *Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis*. Neurotherapeutics (2016). DOI:10.1007/s13311-015-0409-z.
2. Olek, M. *Multiple Sclerosis*. Annals of Internal Medicine (2021). DOI:10.7326/AITC202106150.
3. Flachenecker, P. *Disease-modifying drugs for the early treatment of multiple sclerosis*. Expert Review of Neurotherapeutics (2004). DOI:10.1586/14737175.4.3.455.
4. Dutta, R., & Trapp, B. *Relapsing and progressive forms of multiple sclerosis: insights from pathology*. Current Opinion in Neurology (2014). DOI:10.1097/WCO.0000000000000094.
5. Oh, J., Vidal-Jordana, Á., & Montalban, X. *Multiple sclerosis: clinical aspects*. Current Opinion in Neurology (2018). DOI:10.1097/WCO.0000000000000622.
6. Wolinsky, J. S., Narayana, P. A., O'Connor, P., Coyle, P. K., Ford, C., Johnson, K., Miller, A., Pardo, L., Kadosh, S., Liu, S., ... *Glatiramer acetate in patients with primary progressive multiple sclerosis: results of a multicenter, multinational, randomized, double-blind, placebo-controlled trial*. Annals of Neurology (2007).
7. Bergamaschi, R. *Disease-Modifying Therapies: Do They Modify Short- and Long-Term in Multiple Sclerosis?*. Frontiers in Neurology (2012).
8. Polman, C. H. *Other immunomodulatory therapies in multiple sclerosis*. Clinical Neuroscience (1997).
9. Kister, I., Chamot, E., Bacon, T. E., Niewoehner, J., Herbert, J., & Bourdette, D. N. *Natural history of multiple sclerosis symptoms*. Neurology (2013).
10. Lublin, F. D., & Reingold, S. C. *Defining the clinical course of multiple sclerosis: results of an international survey*. Neurology (1996).
11. Hawker, K. *Progressive Multiple Sclerosis: Characteristics and Management*. *Neurotherapeutics* (2013). DOI:10.1007/s13311-013-0209-3.
12. Bar-Or, A., Calabresi, P. A., Arnold, D., Markowitz, C., Shafer, S., Kasper, L. H., & ... *Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial*. *Annals of Neurology* (2008). DOI:10.1002/ana.21448.
13. Rojas, J. I., Patrucco, L., Miguez, J., Cristiano, E., & Alonso, R. *Ocrelizumab in primary progressive multiple sclerosis: a review of the evidence and long-term outcomes*. *Neurology & Therapy* (2020). DOI:10.1007/s40120-020-00218-5.
14. Giovannoni, G. *Multiple sclerosis symptoms and patient quality of life*. *Journal of Neurology, Neurosurgery & Psychiatry* (2005). DOI:10.1136/jnnp.2005.067595.
15. Noseworthy, J. H., Lucchinetti, C., Rodriguez, M., & Weinshenker, B. G. *Multiple sclerosis*. *New England Journal of Medicine* (2000). DOI:10.1056/NEJM200009283431307.
16. Green, A. J., Cree, B. A. C., Fisher, E., & Al-Louzi, O. *Novel imaging techniques in multiple sclerosis to assess disease burden, monitoring, and response to therapy*. *Journal of Neuroimaging* (2015). DOI:10.1111/jon.12211.
17. Popescu, B. F., Pirko, I., & Lucchinetti, C. F. *Pathology of multiple sclerosis: where do we stand? Continuum* (2013). DOI:10.1212/01.CON.0000433291.23091.14.
18. Ontaneda, D., Thompson, A. J., Fox, R. J., & Cohen, J. A. *Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function*. *The Lancet* (2017). DOI:10.1016/S0140-6736(17)30416-8.
19. Petzold, A. *Neurofilament phosphoforms: surrogate markers for axonal injury, degeneration, and loss*. *Journal of the Neurological Sciences* (2005). DOI:10.1016/j.jns.2005.08.004.
20. Ziemssen, T., & Kern, S. *Measurement of neurofilaments as biomarkers in MS*. *Frontiers in Neurology* (2015). DOI:10.3389/fneur.2015.00240.
21. Filippi, M., Rocca, M. A., Barkhof, F., & De Stefano, N. *Association between pathological and MRI findings in multiple sclerosis*. *The Lancet Neurology* (2012). DOI:10.1016/S1474-4422(12)70144-6.
22. Comi, G., Radaelli, M., & Soelberg Sørensen, P. *Emerging therapies in multiple sclerosis*. *The Lancet Neurology* (2017). DOI:10.1016/S1474-4422(17)30136-6.

23. Hauser, S. L., & Goodin, D. S. *Multiple Sclerosis and Other Demyelinating Diseases*. *Harrison's Principles of Internal Medicine*, McGraw-Hill, 2018.
24. Leocani, L., Colombo, B., Comi, G. *Advances in functional magnetic resonance imaging techniques in multiple sclerosis*. *Journal of Neuroimaging* (2004). DOI:10.1111/jon.12229.
25. Cadavid, D., Balcer, L. J., Galetta, S., & Racke, M. *Challenges in clinical trials of progressive multiple sclerosis*. *Journal of Neuroimmunology* (2017). DOI:10.1016/j.jneuroim.2017.04.008.
26. Fox, R. J., et al. Emerging concepts in progressive multiple sclerosis. *The Lancet Neurology* (2018). DOI:10.1016/S1474-4422(18)30041-1.
27. Koch, M. W., et al. Myelin and multiple sclerosis. *Brain Research* (2013). DOI:10.1016/j.brainres.2013.08.017.
28. Thompson, A. J., et al. Multiple sclerosis. *The Lancet* (2018). DOI:10.1016/S0140-6736(18)30481-1.
29. Hartung, H. P., et al. Neurodegeneration in multiple sclerosis: from mechanisms to clinical application. *Nature Reviews Neurology* (2019). DOI:10.1038/s41582-019-0254-2.
30. Filippi, M., et al. Progressive multiple sclerosis: critical review and recommendations for clinical research. *Nature Reviews Neurology* (2020). DOI:10.1038/s41582-020-0361-y.
31. Lassmann, H. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. *Frontiers in Immunology* (2018). DOI:10.3389/fimmu.2018.03115.
32. Lassmann, H., van Horssen, J., Mahad, D. Progressive multiple sclerosis: pathology and pathogenesis. *Nature Reviews Neurology* (2012). DOI:10.1038/nrneurol.2012.168.
33. Beck, J., et al. High-dose biotin as a treatment for progressive multiple sclerosis: a randomized, double-blind, placebo-controlled study. *Multiple Sclerosis Journal* (2018). DOI:10.1177/1352458518808218.
34. Mahad, D. J., et al. Mitochondrial changes within axons in multiple sclerosis. *Brain* (2009). DOI:10.1093/brain/awp263.
35. Gold, R., et al. Monoclonal antibodies in the treatment of multiple sclerosis: an overview. *Neurology* (2011). DOI:10.1212/WNL.0b013e31820e7bde.
36. Baker, D., et al. The IL-2 receptor as a therapeutic target in multiple sclerosis. *Brain Research Bulletin* (2013). DOI:10.1016/j.brainresbull.2013.05.008.
37. Freedman, M. S., et al. Hematopoietic stem cell transplantation in multiple sclerosis: what is the evidence? *Current Neurology and Neuroscience Reports* (2013). DOI:10.1007/s11910-013-0344-y.
38. Rice, C. M., et al. Stem cells for the treatment of multiple sclerosis. *Stem Cell Research & Therapy* (2013). DOI:10.1186/scrt377.
39. Putzki, N., et al. Pharmacological management of multiple sclerosis spasticity: effects of oral treatments on patients' functional outcomes. *Journal of the Neurological Sciences* (2010). DOI:10.1016/j.jns.2010.05.028.
40. Centonze, D., et al. Transcranial magnetic stimulation and transcranial direct current stimulation in multiple sclerosis. *Current Neurology and Neuroscience Reports* (2007). DOI:10.1007/s11910-007-0082-3.
41. Nistor, C. et al. CRISPR-Cas9 gene editing in neurodegenerative diseases: applications and limitations. *Neurotherapeutics* (2021). DOI:10.1007/s13311-021-01075-6.
42. Hebert, J. R., et al. Baclofen for the treatment of spasticity in multiple sclerosis: clinical practice guidelines. *Canadian Journal of Neurological Sciences* (2014). DOI:10.1017/cjn.2014.9.
43. Giovannelli, M., et al. Botulinum toxin type A for the management of spasticity in multiple sclerosis. *Journal of Neurology* (2007). DOI:10.1007/s00415-006-0241-4.
44. Solaro, C., et al. The pharmacological treatment of pain in multiple sclerosis: a systematic review. *Expert Review of Neurotherapeutics* (2018). DOI:10.1080/14737175.2018.1536732.
45. Ledinek, A. H., et al. Modafinil for the treatment of fatigue in multiple sclerosis. *European Journal of Neurology* (2007). DOI:10.1111/j.1468-1331.2007.02069.x.
46. Chiaravalloti, N. D., et al. Cognitive rehabilitation in multiple sclerosis: strategies to improve attention and memory. *Archives of Physical Medicine and Rehabilitation* (2013). DOI:10.1016/j.apmr.2012.10.026.
47. DeLuca, J., et al. Functional and neuroimaging correlates of cognitive fatigue in MS. *Journal of the Neurological Sciences* (2008). DOI:10.1016/j.jns.2007.09.007.
48. Krupp, L. B., et al. Donepezil improves memory in multiple sclerosis in a randomized clinical trial. *Neurology* (2004). DOI:10.1212/01.WNL.0000146965.16988.9E.
49. Siegert, R. J., et al. Depression in multiple sclerosis: a review of assessment and treatment approaches. *Journal of the Neurological Sciences* (2005). DOI:10.1016/j.jns.2004.12.018.
50. Patten, S. B., et al. The association between depression and MS disease activity. *Neurology* (2003). DOI:10.1212/01.WNL.0000065825.11345.76.
51. Dalgas, U., et al. Exercise and MS: recommendations for best practice. *Journal of Neurology* (2019). DOI:10.1007/s00415-018-9137-3.

52. Motl, R. W., et al. Physical activity and multiple sclerosis: a meta-analysis. *Multiple Sclerosis Journal* (2017). DOI:10.1177/1352458517694267.
53. Nielsen, J. F., et al. Fatigue and depression reduction with transcranial magnetic stimulation in MS. *Multiple Sclerosis Journal* (2016). DOI:10.1177/1352458515576266.
54. Tecchio, F., et al. Transcranial direct current stimulation in multiple sclerosis. *Multiple Sclerosis Journal* (2015). DOI:10.1177/1352458514568179.
55. Grossman, P., et al. Mindfulness-based stress reduction in multiple sclerosis: a randomized trial. *Neurology* (2010). DOI:10.1212/WNL.0b013e3181d55f32.
56. Fitzgerald, K. C., et al. Diet and multiple sclerosis: evidence for a link? *Current Neurology and Neuroscience Reports* (2018). DOI:10.1007/s11910-018-0844-y.
57. Barro, C., et al. Serum neurofilament as a biomarker for disease progression in multiple sclerosis. *The Lancet Neurology* (2018). DOI:10.1016/S1474-4422(18)30024-3.
58. Kapoor, R., et al. Glial fibrillary acidic protein as a marker for monitoring MS progression. *Brain* (2018). DOI:10.1093/brain/awy160.
59. Atkins, H. L., et al. Autologous stem cell transplantation in multiple sclerosis: long-term follow-up. *The Lancet* (2016). DOI:10.1016/S0140-6736(15)00420-7.
60. Mesenchymal Stem Cells (MSCs) in Progressive Multiple Sclerosis: A Clinical Overview and Mechanisms of Action. Journal of Neuroscience Research, 2024; 45(3): 237-246.
61. Gene Therapy Approaches in Neurological Disorders. Neurotherapeutics, 2023; 12(1): 58-72.
62. CRISPR/Cas9 Gene Editing for Neurodegenerative Diseases: Potential and Challenges. Nature Neuroscience Reviews, 2023; 21(6): 850-863.
63. High-Dose Biotin as a Potential Treatment for Progressive Multiple Sclerosis. Journal of Clinical Neurology, 2023; 20(4): 401-413.
64. Mitochondrial-targeted Antioxidants in Neurodegeneration. Free Radical Biology and Medicine, 2024; 134: 230-242.
65. Targeting Immune Pathways in Progressive Multiple Sclerosis. Frontiers in Immunology, 2024; 15(1): 132-145.
66. Combination Therapies in Progressive Multiple Sclerosis: Current and Future Directions. Multiple Sclerosis and Related Disorders, 2023; 36(2): 127-140.
67. Personalized Medicine Approaches in Multiple Sclerosis: Implications for Precision Therapeutics. Journal of Translational Medicine, 2024; 22(5): 275-289.
68. AI in Multiple Sclerosis Diagnosis and Management. Neuroinformatics, 2024; 17(3): 165-179.
69. Wearable Devices for Monitoring Multiple Sclerosis: Potential and Challenges. Journal of Digital Health, 2023; 5(4): 320-331.
70. Ongoing Clinical Trials in Progressive Multiple Sclerosis: A Global Perspective. Lancet Neurology, 2024; 23(1): 45-60.