Assessment of Unmet Needs in Progressive Multiple Sclerosis

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS), with a highly variable clinical presentation across individuals. Globally, the prevalence of SPMS varies, with reported rates of 57.8/100,000 in the UK, 37.1/100,000 in the USA, and 33.3/100,000 in Germany.[1] The most common initial form, relapsing-remitting MS (RRMS), affects 85–90% of patients and is characterized by episodic relapses followed by partial or full recovery. Most individuals with RRMS transition to secondary progressive MS (SPMS)—a phase defined by a gradual neurological decline, with or without further relapses. This particular stage distinguishes SPMS from primary progressive MS (PPMS), which is progressive from onset.[1]

Over the past few decades, the development of highly effective and well-tolerated disease-modifying therapies (DMTs) have represented a significant advancement in the treatment of relapsing forms of MS.[2] However, substantial unmet needs persist, particularly for individuals affected by progressive forms of MS, characterized by limited and less effective options especially for nonactive SPMS. Recent clinical trials [3] offer a new perspective and new potential treatment options for non-relapsing forms of MS. Despite this, strategies aimed at neurorepair remain limited, and information on these approaches is often incomplete. The underlying causes of MS—particularly the mechanisms driving disease progression—remain unclear, revealing the complex and multifaceted nature of the disease.[2] Continued research and innovation are essential to address these gaps and improve outcomes for all individuals living with MS.

Methodology

This needs assessment is based on a targeted literature review using PubMed and other scientific sources, focusing on studies published between 2017 and 2025. Key clinical trials and expert reviews were selected to identify treatment gaps and unmet needs in progressive multiple sclerosis.

Key Findings

Treatment of RRMS has advanced significantly, offering patients an expanding variety of DMTs. Current treatment options include interferons, monoclonal antibodies such as ocrelizumab and natalizumab, and oral agents like dimethyl fumarate and teriflunomide, which have improved disease control for many individuals living with RRMS. Early initiation of high-efficacy treatments is also recognized as a key strategy to delaying long-term disability.[2,4,5]

In contrast, therapeutic options for progressive MS (PMS) remain limited. While siponimod is approved for active SPMS and ocrelizumab for PPMS, their effectiveness is modest and they are not suitable for all patients.[6,7] There are no approved DMTs for nonrelapsing SPMS, and this represents a significant unmet need.[8]

Bruton's tyrosine kinase inhibitors (BTKIs) are a promising new class of oral therapies, several currently in late stage of clinical trials. Tolebrutinib has shown the first phase 3 evidence of benefit in nonrelapsing SPMS, significantly reducing confirmed disability progression (CDP) and improving

disability outcomes.[8] However, safety concerns—such as risk of liver toxicity—may limit its clinical use if approved.

While symptomatic treatments and relapse management options contribute to improved quality of life for people with MS, significant therapeutic gaps persist—most notably in disease-modifying therapies for progressive forms of MS. Furthermore, access to and evidence for supportive interventions such as physical therapy, nutritional strategies, and complementary approaches varies, reinforcing the necessity for a more comprehensive and customized care model.[9]
These findings highlight the growing need for effective and safe approaches for progressive MS where treatment options remain limited and disability accumulation continues unchecked.

Root causes

Beside The understanding of different forms of MS has evolved significantly over the past decade, there is still a significant lack in terms of diagnostic approaches and therapies especially for progressive forms.
Neurodegenerative processes within the CNS begin in the asymptomatic phase of MS. During this stage, patients may remain unaware of disease progression due to the brain's ability to compensate for neuronal loss. These compensatory mechanisms may include an increased extra-region neural recruitment, activation of homologous areas, and local neuronal plasticity. Once these mechanisms are exhausted, clinical symptoms emerge, ultimately revealing the progression to SPMS. A continuous increase in neurological disability is a key indicator of transition from RRMS to a progressive disease course. This compensation mechanism can delay the diagnosis of SPMS in clinical practice.[1]

The limited effectiveness of current DMTs for progressive forms of MS, represents another critical gap. The reason lies in the main target of this treatment, the inflammatory activity —such as relapses or new MRI lesions—. These therapies primarily target peripheral immune mechanisms and have limited ability to cross the blood–brain barrier, which may explain their reduced efficacy in non-active progressive MS, where CNS-resident inflammation and neurodegeneration are the dominant pathological processes.[10,11] As a result, patients with active forms of MS may benefit from treatment due to reduced relapse rates and lesion development. On the contrary, patients with non-active progressive disease respond less effectively to DMTs, as ongoing neurodegeneration, rather than inflammation, becomes the primary driver of disability. Only two DMTs have demonstrated significant benefits in reducing disability progression specifically in active SPMS: Siponimod, as shown in the EXPAND study,[6] and interferon-beta-1b, demonstrated in the European Study in patients with early active SPMS.[3,12]

Recommendations

To prevent progression and avoid or control the transition from RRMS to progressive forms, is essential the early treatment with highly effective therapies. Inflammation drives neurological

damage early in MS; early intervention can prevent the accumulation of irreversible neuronal damage, reducing relapses and long-term disability.[3]
Just a few therapies show efficacy in active forms of progressive MS, such as siponimod and interferon-beta-1b. Other treatment options remain inadequate—particularly for patients with non-active disease, where chronic neurodegeneration and compartmentalized CNS inflammation are key drivers of disability. It is essential to prioritize the continued investigation of therapeutic candidates that target these mechanisms more directly.
Some agents are currently in clinical development: BTK inhibitors (e.g., tolebrutinib, fenebrutinib), masitinib, ibudilast, foralumab, frexalimab, and vidofludimus calcium. Many of these compounds are able to cross the blood–brain barrier and modulate CNS-resident immune responses, offering a promising approach for progressive MS. However, further research is needed to establish their long-term efficacy and safety, and to determine their place in the therapeutic landscape.[3,8]
There is a significant unmet need for disease-modifying therapies targeting progressive forms of MS. While RRMS has seen therapeutic advances, progressive MS remains under-addressed, warranting increased investment in research to explore novel targets and mechanisms.

Another important gap to address is the repair of damage myelin sheaths. Autologous hematopoietic stem cell transplantation (aHSCT) may offer a promising approach by depleting autoreactive immune cells and supporting regeneration of oligodendrocyte producing myelin. While early trials show potential, more research is needed to explore its long-term benefits and viability as a therapeutic target.[3]

Another key gap lies in the need for more tailored, patient-centered treatment approaches that go beyond standard clinical measures. People with MS—especially those with progressive forms—often experience persistent symptoms not captured by MRI findings or relapse rates. This shows the importance of integrating patient-reported outcomes and focusing on quality of life in treatment planning.

There is a growing need for medical education and training to prepare physicians with the required knowledge to recognize and address even the most challenging and invisible aspects of MS. This includes fostering stronger communication with patients and working in close collaboration with other specialists—such as physiotherapists, pain specialists, and psychologists—to build a coordinated, multidisciplinary care network. Supporting the appropriate use of complementary therapies (e.g. physiotherapy, acupuncture, massage, dietary interventions) in addition to the medical treatment, can further improve patient well-being, and it should always be guided by clinicians who understand and fully know the patient's medical history and their evolving challenges. It is essential to monitor patient-reported outcomes and deliver truly personalized care.[13,14]

Desired outcomes

- Promote early intervention in relapsing-remitting MS (RRMS) to prevent progression and long-term neurological damage.
- Incentive research and clinical trial of innovative therapies that specifically target mechanisms of progression in non-active and active progressive MS.

- Advance neuroprotective and neurorepair strategies, such as remyelination therapies and promising approaches like autologous hematopoietic stem cell transplantation (aHSCT).
- Promote patient-centered, individualized care by integrating clinical measures with patient-reported outcomes, enhancing interdisciplinary collaboration, and expanding access to supportive therapies tailored to each patient's evolving needs.

Conclusion

Addressing these needs requires a multidimensional approach that combines early intervention by well-prepared medical professionals, ongoing scientific research and clinical trials to develop innovative therapies across all forms of MS, and the implementation of personalized care models tailored to each patient’s clinical presentation and biological profile.