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REVIEW ARTICLE

Advances in disease-modifying therapies for multiple sclerosis: global updates and a regional comparison between the Republic of Moldova and Romania

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ABSTRACT

Introduction. The therapeutic landscape of multiple sclerosis has undergone a remarkable transformation over the past two decades. The paradigm has shifted from reliance on moderate-efficacy, first-generation injectable therapies toward earlier adoption of high-efficacy disease-modifying treatments, particularly in relapsing forms of MS. This evolution reflects an increasing focus on early intensive treatment strategies aimed at preserving long-term neurological function and brain health.

Materials and methods. This narrative review synthesizes recent global evidence on progress in disease-modifying treatments across all multiple sclerosis phenotypes, drawing from randomized controlled trials, real-world studies, and expert consensus guidelines. In addition, it includes a comparative health policy analysis assessing DMT availability, access, and implementation in Romania and the Republic of Moldova, based on national formularies, reimbursement frameworks, and care delivery models.

Results. Globally, the MS treatment algorithm has been reoriented toward early intensive treatment, supported by emerging evidence favoring high-efficacy therapies in the early disease course. While many countries have aligned their protocols accordingly, regional discrepancies persist. Romania, as an EU member, has expanded patient access to 16 reimbursed therapies and biomarker-driven monitoring, and has developed a network of specialized Multiple Sclerosis centers. Conversely, the Republic of Moldova faces structural and economic barriers that restrict access to high-efficacy treatments, advanced diagnostics, and multidisciplinary care – factors contributing to delayed treatment and suboptimal outcomes.

Conclusions. Understanding both global innovations and regional realities is necessary to place current Multiple Sclerosis care in context. Further advancements in science, health policy, and infrastructure will ultimately determine how effectively different nations can convert therapeutic progress into actual improvements in patient outcomes.

Keywords: multiple sclerosis, disease-modifying therapies, Republic of Moldova, Romania.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Despite progress in multiple sclerosis disease-modifying therapies, few studies synthesize global advances with regional comparisons in Eastern Europe or assess how health system disparities affect access and early treatment, particularly in Moldova's underreported multiple sclerosis program.

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The research hypothesis

This review hypothesizes that, despite global consensus on early high-efficacy disease-modifying therapies, disparities in access and clinical practices between Romania and Moldova may contribute to unequal long-term outcomes in multiple sclerosis care.

The novelty added by the manuscript to the already published scientific literature

This manuscript presents a comprehensive synthesis of recent therapeutic advancements in multiple sclerosis, integrating global developments with a unique comparative analysis of treatment access and policy implementation in Romania and Moldova, thereby exposing the contrast between international clinical guidelines and regional healthcare limitations.

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system (CNS) characterized by inflammation, demyelination, axonal loss, and progressive neurological dysfunction. Affecting more than 2.8 million individuals globally as of 2020, MS represents a leading cause of non-traumatic neurological disability among young adults [1]. Although the disease is classically described as relapsing-remitting MS (RRMS), with alternating episodes of neurologic worsening and recovery, it is now recognized that progressive phenotypes – namely, secondary progressive MS (SPMS) and primary progressive MS (PPMS) – account for a significant burden of irreversible disability. These forms are particularly challenging to manage due to their relative resistance to conventional anti-inflammatory treatments.

Over the past decade, the therapeutic landscape for MS has expanded dramatically. The once-limited options – restricted primarily to injectable interferons and glatiramer acetate – have given way to a diverse arsenal of oral agents, monoclonal antibodies, and small-molecule inhibitors targeting specific immunological pathways. The availability of more than 20 disease-modifying therapies (DMTs) recognized by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) has reshaped expectations regarding long-term disease control and quality of life for patients living with MS [2]. This progress has been paralleled by an increasingly nuanced understanding of MS pathophysiology, including the recognition of progression independent of relapse activity (PIRA), which emphasizes the need for early intervention with high-efficacy therapies rather than delayed escalation [2].

Despite these global advances, regional disparities in access to diagnosis, treatment, and monitoring persist. Western Europe and North America benefit from a full-spectrum therapies, comprehensive care models, broad DMT reimbursement, and access to advanced biomarker technologies. In contrast, many Eastern European nations face infrastructural and economic constraints that hinder the implementation of modern MS care standards.

Romania, as a member state of the European Union, has made substantial progress in aligning with international guidelines. The country offers a wide range of reimbursed DMTs, including high-efficacy monoclonal antibodies, and supports specialized MS centers capable of MRI-based monitoring and multidisciplinary management [3]. However, significant urban-rural disparities persist, and access to novel biomarkers such as neurofilament light chain remains limited to research or academic centers.

The Republic of Moldova, by contrast, lags behind, remaining at an earlier stage of systemic MS care development. Although MS prevalence in Moldova is lower than the EU average, estimated at approximately 34 per 100,000, the actual burden may be underestimated due to diagnostic delays and underreporting [4, 5]. National medical insurance covers only a limited range of DMTs, and high-efficacy options, such as ocrelizumab, are available at a single national institution, with restricted patient access. Biomarker testing is unavailable, and longitudinal disease monitoring remains largely clinical, limiting timely therapeutic adjustments.

This article aims to provide a comprehensive review of recent advances in MS disease-modifying therapies and to highlight how these developments are reflected – or remain inaccessible – in two geographically close but systemically divergent countries: Moldova and Romania. By examining their respective challenges and capacities, we aim to identify gaps and evaluate opportunities for alignment with global standards to ensure equitable and effective MS care delivery in resource-limited settings.

Materials and methods

This review is based on a structured analysis of recently published peer-reviewed literature, including randomized controlled trials, network meta-analyses, consensus guidelines, and health policy reports published between 2020 and 2025. Databases such as PubMed and ClinicalTrials.gov were used to identify relevant studies on disease-modifying therapies (DMTs) in multiple sclerosis. The search strategy combined the terms "multiple sclerosis" and "disease-modifying therapies". From a total of 196 articles initially re-

trieved, we excluded articles available only as abstracts, narrative reviews providing only general information about treatments, and studies containing duplicate data. Regarding the situation in Romania and the Republic of Moldova, peer-reviewed literature is scarce. Therefore, the analysis was supplemented with official governmental sources and national reports to ensure a comprehensive overview of treatment access, policy implementation, and health system disparities between the two countries. A qualitative thematic analysis was performed to identify key patterns related to treatment updates and the implementation of early high-efficacy therapy strategies. No specialized software was used for data extraction or analysis. The collected data were synthesized to provide both global updates and regional health system perspectives.

Results and discussions

Contemporary DMT landscape: treatment paradigm shift

Since the approval of interferon-beta in 1993, the DMT landscape has expanded to include over 20 therapies with diverse mechanisms of action [6]. The therapeutic goals of DMTs are to reduce relapse frequency, delay disability progression, and limit radiological activity.

Historically, DMT usage has followed a conservative escalation model: starting with injectables (interferons, glatiramer acetate), escalating to orals (fumarates, teriflunomide), and reserving high-efficacy therapies (HETs) for refractory cases.

Table 1. Classification of DMT's by route of administration

Injectables	Interferons and glatiramer acetate
Oral DMTs	Fumarates, Teriflunomide, Cladribine, and Sphingosine-1phosphate modulators (e.g., Fingolimod, Ozanimod)
Infuzional therapies	Ocrelizumab, Ublituximab, Natalizumab, and Alemtuzumab

First-generation therapies, such as interferon beta (IFN-β) and glatiramer acetate (GA), have demonstrated modest efficacy [1]. Despite their widespread use, these agents exhibit limited capacity to prevent long-term disability, particularly in progressive forms [7].

HETs include monoclonal antibodies (e.g., natalizumab, alemtuzumab, ocrelizumab, ofatumumab, ublituximab) and sphingosine-1-phosphate receptor modulators (e.g., fingolimod, ozanimod, ponesimod) [1, 2]. These drugs target B-cell and T-cell pathways, CNS lymphocyte trafficking, and inflammation more effectively. Network meta-analyses reveal monoclonal antibodies, such as alemtuzumab, ofatumumab, and ocrelizumab, as the most efficacious options for reducing relapses and disability progression [8].

The initial classification of disease-modifying therapies based on treatment lines is now considered outdated. It has been largely replaced in modern practice by efficacy-based, administration-based (Table 1), or mechanism-based categorization (Table 2), which supports earlier use of high-efficacy DMTs for appropriate patients.

Table 2. The latest classification of DMT, based on their mechanisms of action

DMT Class	Examples
Monoclonal antibodies	Ocrelizumab, Ofatumumab, Alemtuzumab, Natalizumab, Ublituximab
Sphingosine-1-phosphate receptor modulators	Fingolimod, Siponimod, Ozanimod, Ponesimod
Anti-proliferative agents	Cladribine, Teriflunomide
Immunomodulators with unknown mechanism	Dimethyl fumarate (DMF), Glatiramer acetate, Interferons

The traditional stepwise escalation model – starting with low-efficacy DMTs – has been increasingly replaced by early intensive therapy (EIT). This shift is reflected in national and international guidelines [2].

In recent years, high-efficacy therapies (HETs) have gained traction as the favored strategy in MS treatment for treatment-naïve patients with active disease. The existing evidence suggests that it is desirable to start HET as early as possible to achieve maximum neuroprotection. Randomized clinical trials and observational studies have demonstrated lower relapse rates, reduced MRI activity, and decreased long-term disability when HETs are initiated within the first five years following the onset of symptoms [2]. Prospective research has repeatedly demonstrated that both early relapse and MRI lesion activity predict, to a large extent, disability accumulation in the years to come. Therefore, interventions at these levels are crucial for modifying the course of the disease.

High-efficacy DMTs, including ocrelizumab, alemtuzumab, cladribine, natalizumab, and ofatumumab, have shown substantial efficacy, with annualized relapse rates (ARR) reduced by up to 70%, which is well beyond the efficacy of traditional injectable therapies, such as interferon-beta or glatiramer acetate [9]. Apart from relapse control, HETs are also more efficient in preventing PIRA, a phenomenon that is now clearly recognized. The ASCLEPIOS studies have shown that ofatumumab robustly delayed PIRA compared to teriflunomide [10]. Additionally, the effect of HETs on preserving brain volume is relatively significant. Brain atrophy (a neurodegeneration marker strongly correlated with cognitive and physical decline) develops at a slower pace in those treated with high-efficacy drugs, with annual rates of brain volume loss reduced to ~0.2% [11]. Most critically, real-world data now indicate that starting with HETs early in the disease is more effective than proceeding stepwise in a classic escalation approach. A retrospective cohort study by Harding et al. reported that patients initiated on HETs had a 47% reduction in the hazard of developing significant disability compared to those started on moderate-efficacy drugs [12]. This evidence has contributed to a treatment paradigm that emphasizes aggressive therapy with high-efficacy treatments as early as possible to achieve optimal long-term functional outcomes for individuals with MS.

A recent network meta-analysis by Samjoo et al. (2023) offers valuable insights into the comparative effectiveness of current HETs [8]. In terms of reducing the ARR, alemtuzumab, ofatumumab, and ublituximab emerged as the most

effective agents. For delaying three-month confirmed disability progression (CDP), the highest efficacy was observed with alemtuzumab, ocrelizumab, and ofatumumab. Similarly, in the context of a six-month CDP, alemtuzumab, natalizumab, and ocrelizumab demonstrated superior outcomes. The safety profiles of these high-efficacy therapies, especially when administered early in the disease course, have been reported in multiple trials to be similar to those of moderate-efficacy DMTs, providing data relevant to considerations around timing and selection of treatment strategies [2].

Special considerations in progressive MS treatment

Progressive MS patients exhibit poor response to traditional anti-inflammatory therapies. Smoldering lesions, PIRA, and oxidative stress contribute to relentless disability accumulation [13]. Therapeutic strategies targeting microglia, mitochondrial protection, and remyelination are gaining interest.

PPMS remains challenging due to its insidious onset and lack of relapses. Ocrelizumab is the only FDA-approved agent for PPMS, based on the ORATORIO trial, which demonstrated reduced disability progression over 120 weeks [13].

Historically, the treatment of SPMS has been hindered by the limited efficacy of traditional DMTs. However, recent trials have demonstrated benefits with newer agents. Siponimod, a selective S1P1/5 modulator, showed a significant reduction in 3-month CDP in the EXPAND trial, particularly in active SPMS [14, 15]. Ocrelizumab has also shown promise in reducing PIRA in SPMS subpopulations [13].

Novel and investigational therapies

Recent advances in molecular immunology and neuroinflammation have led to the development of a new generation of DMTs that target pathways previously difficult to access in MS pathogenesis. Among these, Bruton's tyrosine kinase (BTK) inhibitors, Janus kinase (JAK) inhibitors, and other kinase-targeting molecules represent some of the most promising drug classes currently in development [16]. A common advantage of many of these agents is their ability to penetrate the CNS, enabling modulation of immune activity both systemically and within the CNS – a critical step in addressing progressive and treatment-refractory disease phenotypes.

Bruton's tyrosine kinase (BTK) inhibitors

BTK inhibitors are small-molecule oral agents designed to interfere with B-cell receptor signaling, ultimately modulating B-cell activation, survival, and antigen presentation. In the context of MS, these effects extend beyond peripheral immune suppression; many BTK inhibitors have demonstrated the capacity to cross the blood-brain barrier (BBB), targeting B-cell populations within the CNS. This is particularly important given the increasing recognition of CNS-compartmentalized inflammation, including meningeal B-cell follicles and smoldering lesions, as key drivers of disease progression in MS [6].

Among the BTK inhibitors under investigation, evobrutinib and tolebrutinib have progressed furthest in clinical development [16, 17]. Tolebrutinib, for instance, has shown efficacy in reducing the formation of new T2 lesions and has demonstrated potential in addressing non-relapsing secondary progressive MS in Phase III studies. In addition, tolebrutinib has recently shown a 31% reduction in disability progression in non-relapsing secondary progressive MS, earning breakthrough status from the FDA [18]. BTK inhibitors may offer a therapeutic advantage in patients with progressive disease forms, for whom current therapies offer limited benefit.

JAK inhibitors and kinase-targeting molecules

Janus kinase (JAK) inhibitors constitute another novel therapeutic class under evaluation for MS. By modulating the JAK-STAT signaling pathway – a key regulator of cytokine-mediated immune responses – these agents may suppress pro-inflammatory cascades in both adaptive and innate immune cells. While already approved for other autoimmune conditions such as rheumatoid arthritis and ulcerative colitis, their role in MS remains investigational. JAK inhibitors may be beneficial in MS subtypes with overlapping autoimmune features or treatment-resistant inflammation.

Researchers are also exploring other intracellular signaling targets, including the PI3K/Akt/mTOR and MAPK pathways, which regulate cell survival, proliferation, and metabolism. Modulators of these pathways may influence not only immune cell function but also glial responses and neurodegeneration, making them appealing candidates for progressive MS and neuroprotective therapy strategies [6].

Novel immunotherapies and viral-targeted approaches

Beyond kinase inhibition, entirely new immunological strategies are being developed. One of the most revolutionary concepts involves chimeric antigen receptor (CAR) T-cell therapy, an approach adapted from oncology. In MS, CAR-T cells are engineered to target and selectively eliminate autoreactive B or T lymphocytes [19]. These therapies remain in preclinical and early-phase trials but show promise in creating long-term immune tolerance and could benefit patients with aggressive or refractory disease.

The investigation of the Epstein-Barr virus (EBV) role in MS development represents a separate research direction. The available epidemiological and experimental data indicate that EBV infection serves as a necessary, although not sufficient, condition for MS development. The development of vaccine candidates targeting EBV proteins including gp350 has reached early-phase clinical testing [1]. This vaccine strategy focuses on preventing EBV infection or reducing its impact in individuals already infected. If proven effective, EBV vaccination could serve as a primary prevention method for at-risk groups or as an adjunct treatment for patients in the early stages of MS.

Comparative analysis: disease-modifying therapies in the Republic of Moldova and Romania

While global therapeutic advancements in MS have reshaped disease management paradigms, access to these therapies varies considerably across countries. This is especially evident in Eastern Europe, where health system resources, regulatory policies, and socioeconomic factors influence the availability and implementation of DMTs. A comparative overview of the Republic of Moldova and Romania provides critical insights into disparities in MS care within the region.

Romania, a European Union (EU) member state, has de-

veloped a national MS treatment program supported by the National Health Insurance House, enabling broad access to EMA-approved DMTs. In contrast, the Republic of Moldova – a non-EU country with limited healthcare funding – faces substantial barriers to ensuring comprehensive DMT coverage. Both countries report an increasing prevalence of MS, with Romania estimating 12,500-13,000 patients and Moldova approximately 2,000, although registry data in Moldova remain incomplete.

Availability of DMTs

As of 2025, Romania offers an extensive portfolio of 16 EMA-approved DMTs through its national program, including both moderate- and high-efficacy agents. Romanian patients typically have access to DMTs across all disease stages, including those with SPMS and PPMS, with established pharmacovigilance and MRI monitoring frameworks integrated into their clinical care (Tables 3 and 4).

In contrast, Moldova currently reimburses only three DMTs through its national insurance company. Two additional therapies, glatiramer acetate and cladribine, are included in the expanded list approved by the Ministry of Health and are expected to become available by the end of 2025 as part of a national MS initiative (Table 4). However, access remains dependent on centralized hospital supply, and high-efficacy agents are unavailable outside of clinical trials and private purchases abroad. This limited repertoire constrains physicians' ability to individualize therapy or apply early high-efficacy treatment strategies advocated by current international guidelines [2].

Table 3. DMT's availability in Romania and Republic of Moldova

Romania	Republic of Moldova
Interferon beta-1a	Interferon beta-1a
Interferon beta-1b	Interferon beta-1b
Glatiramer acetate	*Glatiramer acetate (approved in 2025)*
Dimethyl fumarate	n/a
Diroximel fumarate	n/a
Teriflunomide	n/a
Fingolimod,	n/a
Ozanimod	n/a
Ponesimod	n/a
Siponimod	n/a
Natalizumab	n/a
Alemtuzumab	n/a
Ocrelizumab	Ocrelizumab (introduced in 2023)
Cladribine	*Cladribine (approved in 2025)*
Ofatumumab	n/a
Ublituximab (approved in 2024, pending reimbursement listing)	n/a

Treatment guidelines and practice patterns

Romania adheres to international best practices and has developed national MS management protocols aligned with the recommendations of the European Committee for Treatment and Research in MS (ECTRIMS). Romanian neurologists frequently adopt the early use of high-efficacy therapies, especially in patients with poor prognostic indicators.

In Moldova, treatment often follows an escalation-based approach due to the limited therapeutic options available. Therapy initiation is frequently delayed because of diagnostic lags, out-of-pocket imaging costs, and the centralization of care at tertiary centers. The national protocol has not yet incorporated recommendations regarding HETs, and MS is not recognized as a priority condition under Moldova's chronic disease funding mechanisms.

Moldova's planned expansion of the DMT list marks a step forward. However, systemic challenges – including regulatory approval timelines, cost constraints, a limited neurologist workforce, and the absence of MS-specific rehabilitation services – continue to hinder equitable care. Collaborative efforts, including regional partnerships, telemedicine, and integration with EU-funded health programs, could help bridge this therapeutic divide.

Table 4. Comparative analysis of national MS peculiarities

Factor	Romania	Republic of Moldova
Number of reimbursed DMTs	15 (soon to be 16)	3 (soon to be 5)
Access to high-efficacy DMTs	Broad (ocrelizumab, alemtuzumab, natalizumab, ofatumumab etc.)	Limited (ocrelizumab)
Reimbursement system	National insurance with broad DMT coverage	Coverage via centralized procurement
Number of MS centers	20	1
Monitoring infrastructure	MRI every 6–12 months; registry-based	Irregular MRI access; limited registry
Protocol adherence	ECTRIMS-aligned, EIT-supported	Outdated, escalation-based
Pediatric MS therapies	available	limited to second-line therapy with interferons

Conclusions

The management of multiple sclerosis has undergone significant evolution in recent years, driven by a growing understanding of disease mechanisms and the long-term consequences of early inflammatory activity. According to current international standards and clinical guidelines, early initiation of HETs is now considered the preferred strategy for patients with active MS, offering better long-term outcomes in terms of relapse reduction, disability progression, and preservation of brain volume, across all disease phenotypes. In contrast, the traditional escalation model, once widely adopted, has been largely abandoned due to its inherent delays in achieving optimal disease control, or, in some cases, is reserved for a modest subgroup of patients.

Although the global landscape of MS treatment has evolved significantly, regional inequalities remain considerable. MS management practice in Romania has advanced to a modern standard, with unrestricted access to all available DMTs and adequate infrastructural resources for biomarker-guided treatment. Moldova, however, continues to grapple with systemic challenges and limited access to high-efficacy therapies, despite the availability of ocrelizumab for the past

2 years. Addressing these disparities requires not only increased resource allocation but also the adoption of current, evidence-based treatment paradigms that prioritize early, effective disease control in all individuals with MS.

Competing interests

None declared.

Authors' contributions

AB conceived the study, contributed to the design, and drafted the manuscript. OO participated in the literature review and contributed to data synthesis. EM assisted in the analysis of clinical data and contributed to manuscript writing. MS contributed to the organization of data and formatting of the manuscript. CAS provided critical input on the Romanian healthcare system and contributed to the regional policy analysis section. VL supervised the study, provided expert guidance throughout, and critically revised the final manuscript. All authors reviewed the work critically and approved the final version of the manuscript

Ethics approval

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