# Pharmacological management of progressive multiple sclerosis

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# PHARMACOLOGICAL MANAGEMENT OF PROGRESSIVE MULTIPLE SCLEROSIS

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# Abbreviations

**AHSCT** Autologous hematopoietic stem cell transplantation
**ARR** Annualized relapse rate
**BBB** Blood-brain barrier
**CIS** Clinically isolated syndrome
**CMV** Cytomegalovirus
**CNS** Central nervous system
**CSF** Cerebrospinal fluid
**DMT** Disease-modifying therapy
**DNA** Deoxyribonucleic acid
**EBV** Epstein Barr virus
**EDSS** Expanded disability status scale
**GA** Glatiramer acetate
**HBV** Hepatitis B virus
**HLA** Human leukocyte antigen
**HSC** Hematopoietic stem cell
**HSV** Herpes simplex virus
**IFN** Interferon
**IL- 10** Interleukin-10
**IL-4** Interleukin-4
**LUT** Lower urinary tract
**MHC** Major histocompatibility complex
**MMP** Metalloproteinases
**MOA** Mechanism of action
**MRI** Magnetic resonance imaging
**MS** Multiple sclerosis
**OCB** Oligoclonal band
**PPMS** Primary progressive multiple sclerosis
**RRMS** Relapsing-Remitting Multiple Sclerosis
**S1P** Sphingosine 1-phosphate
**S1PR** Sphingosine 1-phosphate receptor
**SNRI** Serotonin and norepinephrine reuptake inhibitors
**SPMS** Secondary progressive multiple sclerosis
**TCA** Tricyclic antidepressants
**TEAE** Treatment-emergent adverse event
**VLA** Very late antigen

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# Abstract

**Title**: Pharmacological management of progressive multiple sclerosis

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Multiple sclerosis (MS) is a chronic neurological disorder that affects the central nervous system (CNS), which includes the brain and spinal cord. It is categorized as an autoimmune condition in which the immune system mistakenly targets the CNS protective myelin sheath. It is divided into relapsing-remitting, primary progressive, and secondary progressive MS.

Progressive form is one of the most incapacitating and disabling varieties of MS, however, it can take many various forms.

Progressive MS is a chronic, degenerative neurological disorder that, unlike relapsing-remitting (RR) MS, where symptoms come and go is characterized by a steady and progressive worsening of neurological function over time.

There are two types of progressive MS: primary progressive MS (PPMS) and secondary progressive MS (SPMS). PPMS is characterized by a gradual and steady decline in neurological function from the onset of the disease, while SPMS develops after an initial period of RR MS, with symptoms becoming steadily worse over time.

The symptoms of progressive MS vary widely and can include mobility issues, spasticity, fatigue, vision problems, and cognitive impairment. There is no cure for progressive MS, but there are treatments that can help manage symptoms and slow the progression of the disease.

Pharmacological treatments currently available for progressive MS are intended to reduce the disease's development and enhance patients' quality of life. The most used medications for progressive MS include immunomodulatory and immunosuppressive drugs, as well as monoclonal antibodies and stem cell transplants. These medications target different aspects of the immune system and can help reduce inflammation, demyelination, and neurodegeneration. However, their efficacy varies from patient to patient, and they can also cause significant side effects. Newer therapies are being developed that target specific molecules and pathways involved in MS pathogenesis, with the goal of achieving greater efficacy and fewer side effects.



**Keywords**: progressive multiple sclerosis, neurodegeneration, immune system

# Sažetak

Naslov rada: Farmakološko liječenje progresivne multiple skleroze
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Multipla skleroza (MS) je kronični neurološki poremećaj koji zahvaća središnji živčani sustav(CNS), koji uključuje mozak i kralježničku moždinu. Kategorizira se kao autoimuno stanje u kojem imunološki sustav pogrešno oštećuje zaštitnu mijelinsku ovojnicu CNS-a.

Dijeli se na relapsno-remitentnu (RR), primarno progresivnu i sekundarno progresivnu MS.

Progresivna MS jedna je od varijanti MS-a koja najviše onesposobljava i dovodi do invalidnosti, međutim, može poprimiti mnogo različitih oblika.

Progresivna MS je kronični, degenerativni neurološki poremećaj koji za razliku od RR MS, gdje simptomi dolaze i nestaju, karakterizira postojano i progresivno pogoršanje neurološke funkcije tijekom vremena.

Postoje dvije vrste progresivne MS: primarno progresivna MS (PPMS) i sekundarno progresivna MS (SPMS). PPMS karakterizira postupno i postojano opadanje neurološke funkcije od početka bolesti, dok se SPMS razvija nakon početnog razdoblja RRMS, sa simptomima koji se s vremenom stalno pogoršavaju. Simptomi progresivne MS uvelike variraju i mogu uključivati probleme s pokretljivošću, spastičnost, umor, probleme s vidom i kognitivno oštećenje. Ne postoji lijek za progresivnu MS, ali postoje lijekovi koji mogu pomoći u upravljanju simptomima i usporiti napredovanje bolesti.

Farmakološki modaliteti liječenja koji su trenutno dostupni za progresivnu MS namijenjeni su smanjenju razvoja bolesti i poboljšanju kvalitete života bolesnika. Najčešće korišteni lijekovi za progresivnu MS uključuju imunomodulatorne i imunosupresivne lijekove, kao i monoklonska antitijela i transplantacije matičnih stanica. Ovi lijekovi djeluju na različite aspekte imunološkog sustava i mogu pomoći u smanjenju upale, demijelinizacije i neurodegeneracije. Međutim, njihova učinkovitost razlikuje se od bolesnika do bolesnika a terapije mogu uzrokovati i značajne nuspojave. Razvijaju se novije terapije koje ciljaju na specifične molekule i putove uključene u patogenezu MS-a, s ciljem postizanja veće učinkovitosti i manje nuspojava.

**Ključne riječi**: progresivna multipla skleroza, neurodegeneracija, imunološki sustav

# Introduction

An autoimmune reaction to self-antigens results in multiple sclerosis (MS), a multifocal demyelinating disease with progressive neurodegeneration. Clinical symptoms differ depending on the location of the neurologic lesions and frequently coincide with inflammatory cell invasion across the blood-brain barrier (BBB), which leads to demyelination and edema.

Even though DMTs have become more widely available in recent years MS is still a serious and debilitating disorder because none of the known treatments cease or cure the illness. Many neurological processes, including bladder control, bowel and sexual function, cognition, coordination, and balance, as well as vision, gait, and motor function, may be damaged during the course of MS.

This overview goal is to present a known pathophysiology of MS and the latest trends in the investigation and treatment of the condition with a focus on progressive MS.

# Literature review

## 1 Multiple Sclerosis – phenotype

MS is a chronic inflammatory condition of the central nervous system (CNS), that primarily affects patients between the ages of 20 and 40. It is characterized by demyelination, followed by degeneration that causes axonal loss and neuronal injury. Although the precise cause of MS is still unknown, our current knowledge of the disease's immunopathogenesis and natural history indicates an immune dysregulation brought on by a combination of genetic predispositions and environmental variables (1).

### 1.1 Epidemiology

MS impacts young adults and affects about 2.8 million people globally (2).
MS has the highest prevalence in North America (140 per 100,000 inhabitants) and Europe (108 per 100,000) and the lowest in East Asia (2.2 per 100,000 inhabitants) and sub-Saharan Africa (2.1 per 100,000 inhabitants) (2).
The mean age at diagnosis is 32 years, and the combined incidence rate among the 75 reporting nations is 2.1 per 100,000 people/year. MS is twice as common in women as it is in men (2). The etiology of MS is not fully understood; however, environmental, genetic, and epigenetic factors all contribute to the pathogenesis of MS and may combine with modifiable risk factors (3).
At higher latitudes, the prevalence of MS rises, ranging from 5 to 300 per 100,000 people worldwide (4).Too much sun exposure and increased vitamin D levels, which are linked to a lesser prevalence of MS, may explain latitude effects(5,6).
Genetic factors are also confirmed by the rising prevalence of MS within families. The genetic variant most strongly associated to MS is the HLA-DR1*15:01 allele. Individuals with HLA-DR1*15:01 carriers are more susceptible to developing MS(7). In addition, symptomatic Epstein-Barr virus(EBV) infection and cigarette smoking are linked to an increased risk of developing MS (8,9).

### 1.2 Pathogenesis

The myelin and other CNS antigens are assumed to be the source of the immunopathogenesis of MS, which results in persistent peripheral activation of autoreactive T cells(10). This loss of self-tolerance in genetically sensitive people

may be brought on by an environmental antigen, most often an infectious agent like a virus. A molecular mimicry process known as cross-reactivity between an endogenous protein (such as myelin basic protein) and the pathogenic exogenous protein (viral or bacterial antigen) can cause the infection to result in bystander activation of T cells or the release of autoantigens as a result of cellular damage (11).

Myelin-reactive T lymphocytes can pass the (BBB) after becoming activated in the peripheral area. Very late antigen-4(VLA-4 )on T lymphocytes interact with vascular cell adhesion molecule-1 on capillary endothelial cells during the transmigration process, which is aided by the production and overexpression of several adhesion molecules, chemokines, and MMPs (12).

EBV, cytomegalovirus (CMV), Hepatitis B virus (HBV), Herpes simplex virus (HSV), human herpetic viruses 6, 7 (HHV6, HHV7), measles viruses, coronaviruses, and other infectious agents are just a few of the infectious agents that contribute to MS in some combination of genetic, environmental, and infectious factors. Observations that viral infections usually precede MS episodes are consistent with a link between viruses and the disease. IFN, which is created during the infection, may trigger immunopathological processes which contribute to demyelination. Environmental factors, such as a lack of vitamin D, may also contribute to the development of MS (13). A role of obesity in the development of MS is increasingly being shown by studies over the last seven years. Teenage obesity is linked to a higher chance of developing MS in women, according to large cohort studies (14). Although being more moderately overweight is also linked to an elevated risk of MS, the association is highest for those with a BMI >27. Additionally, obesity raises the chance of pediatric-onset MS (15).

### 1.3 Role of B cells and antibodies in multiple sclerosis

Although it is generally accepted that T cells play a large part in the inflammatory demyelination of MS, mounting evidence points to a significant involvement for B cells in the pathophysiology of the illness. There are both independent and antibody-dependent processes and its thought that the MS- CNS damage is caused by B-cells. In addition to the release of antibodies by B-cell functions involved in pathogenesis include : (i) antigen presentation to T cells and promoting the antiproliferation of brain-homing T cells (possibly by memory B cells), (ii) Production of soluble toxic

factors that cause oligodendrocyte and neuronal injury, (iii) production of pro-inflammatory cytokines and chemokines that spread inflammation, (iv) production of soluble toxic factors that contribute to the development of ectopic lymphoid aggregates in the meninges, (v) and production that serves as a reservoir for EBV infection are among the other effects. These B cell behaviors could contribute to the development and recurrence of MS (16).

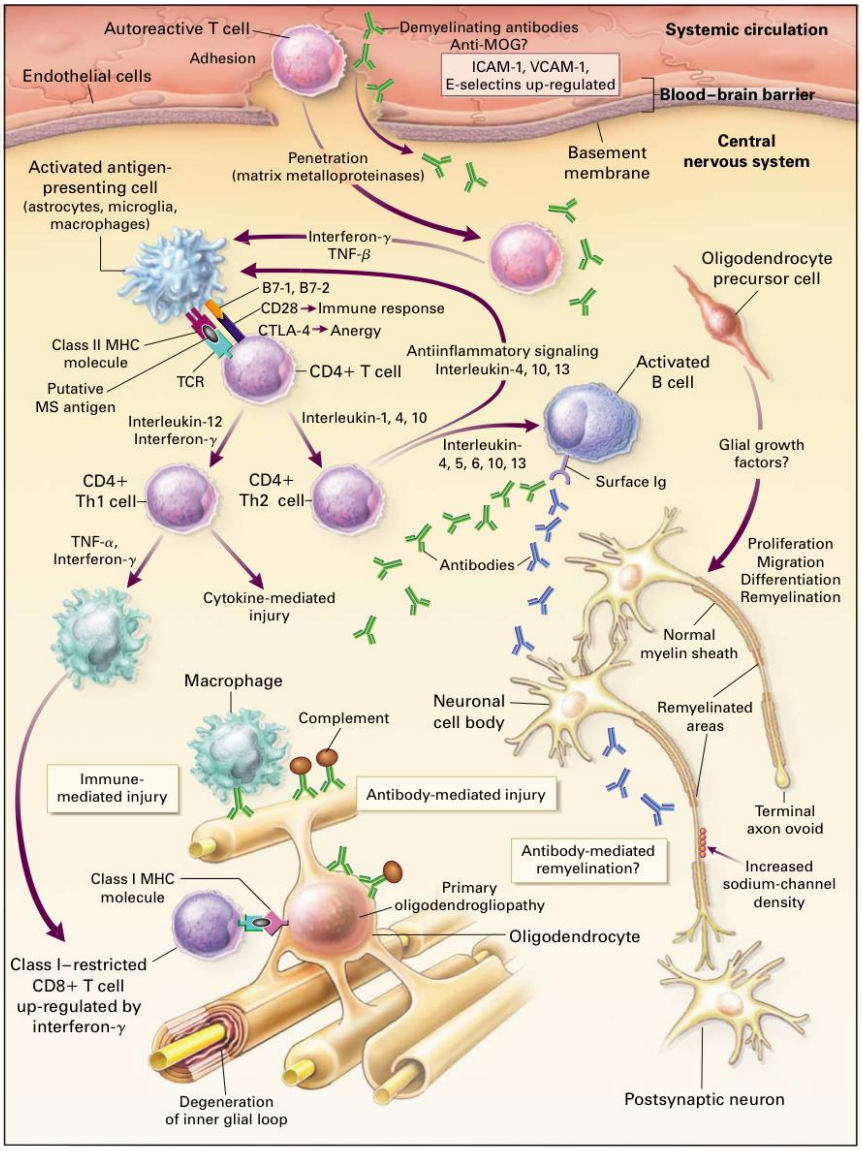



**Figure 1.** Possible mechanisms of injury and repair in multiple sclerosis according to Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000 Sep

## 2. Clinical features of multiple sclerosis

A journey through the asymptomatic, prodromal, and symptomatic phases MS is required to understand the condition. According to the updated 2017 McDonald Criteria for dissemination in space (DIS), a radiologically isolated syndrome (RIS) is a condition in which brain or spine MR imaging, or both, shows incidental white matter lesions that are typical in morphology and location of a demyelinating disease but without a documented history of demyelinating episodes, persistent neurologic decline, or any other potential causes of the white matter lesions, such as those resulting from vascular, infectious, toxic, or drug-related disease (17,18). When a patient manifests with a clinically isolated syndrome (CIS), MS is often assumed. The location of the eloquent lesion will determine whether this is monosymptomatic or polysymptomatic. Clinical signs typical of a demyelinating event describe the patient's initial presentation in CIS. When there is clinical proof of a single exacerbation and the magnetic resonance imaging( MRI) does not entirely match RRMS criteria, a patient is diagnosed with CIS (19,20). Several recent studies have proposed additional potential CSF biomarkers as predictors of conversion from CIS to RRMS in addition to the idea that the presence of oligoclonal bands(OCB) is crucial prognostically (21).

Optic neuritis, brainstem, and spinal cord syndromes are the most often observed presentations; nevertheless, a wide range of less common presentations exist, including cortical presentations such as dominant parietal lobe syndromes (22).

**Table 1.** Common presenting symptoms of multiple sclerosis according to Oh J, Vidal-Jordana A, Montalban X Opin Neurol. 2018 Dec (23).

| **Topography** | **Symptoms** |
|---|---|
| Optic nerve | Mononuclear painful vision loss |
| Spinal cord | Hemiparesis, mono/paraparesis<br>Hypoesthesia, dysesthesia, paresthesia<br>Urinary and/or fecal sphincter dysfunction |
| Brainstem and cerebellum | Diplopia, oscillopsia<br>Vertigo gait ataxia, dysmetria |

| | |
|---|---|
| | Intentional/postural tremor Facial paresis and/or hypoesthesia |
| Cerebral hemisphere | Faciobrachial–crural hemiparesis Faciobrachial–crural hemi hypoesthesia |

Several phenotypes have been described in the clinical feature of MS which includes RRMS being the most prevalent phenotype, with relapses occurring in 85% of patients followed by periods of stability. A relapse is characterized by new or returning neurologic symptoms that are unrelated to fever or illness and persist for at least 24 hours, as well as new neurologic findings that are validated by the examining neurologist. Relapses are directly tied to the development of the disease progression in the first five years, especially for those who are developing persistent disability (24,25).

PPMS is a disease phenotype that progresses from the time of beginning while allowing for brief slight improvements and sporadic plateaus.

PPMS affects between 10% and 15% of MS patients.

SPMS phenotype develops after an initial phase of RR disease, with or without sporadic relapses, modest remissions, and plateaus. After 10 years, 50% of untreated RRMS patients and 90% after 25 years will transit to SPMS, respectively (26).

SPMS is always diagnosed retrospectively by the subjective judgment of the clinician, after evidence of irreversible disability accrual on the Expanded Disability Status Scale (EDSS) becomes markedly apparent, a process that can take up to 3 or more years. The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. This is true even though the onset of SPMS is identified as a "key turning point" in the MS disease continuum (27). Relapsing MS patients' underlying concern over whether their disability is permanent or will improve causes a time of diagnostic doubt known as the "transition phase," which postpones the diagnosis of SPMS (28).

Either clinical relapses or changes in neuroimaging (new/enlarging T2 lesions or gadolinium-enhancing lesions) are used to indicate disease activity. Several clinical

and imaging characteristics that PPMS and SPMS share have led to their inclusion in the progressive illness spectrum.

Based on clinical and radiological characteristics, progressive MS that has just begun or that has transitioned from relapse forms can also be categorized as active or inactive. Independent of relapses, clinical evidence of disease progression in patients with progressive disease has the potential to alter the path of their illness (29).

**Table 2.** Definitions of active and progressive forms of the disease and relevant time frames for assessments according to Ziemssen Bhan V, Chataway J, Chitnis T, Campbell Cree BA, Havrdova EK, et al Neuroinflamm. 2023 Jan (30).

| Term | Definition by Lublin et al. | Recommended time frame. for assessments |
|---|---|---|
| Active disease | Clinical parameters: relapses, acute/subacute episodes of new or increasing neurologic dysfunction, followed by full or partial recovery in the absence of fever or infection and/or Imaging parameters: Gd+ T1 lesions or new or unequivocally enlarging T2 lesions | Yearly or another time frame (if specified) |
| Disease progression | Disability accrual independent of relapse activity during progressive phase of MS (PPMS or SPMS) | Yearly by clinical assessment or another time frame (if specified) |
| Worsening disease | Any increase in impairment/disability irrespective of resulting from residual deficits post relapse or (increasing) progressive disability during the progressive phase of the illness | Not required |

**3. Diagnosis**

The primary criteria for the diagnosis of MS are clinical, and they include the elimination of other conditions that may mimic MS, as well as the presentation of

symptoms and signs associated with white matter lesions that are disseminated in both time and space. There is not a single laboratory test that can detect MS, although a number of assays can help to confirm the clinical diagnosis: In more than 90% of patients, CSF study reveals increased immunoglobulin concentrations and 2 or more OCBs.

Neurophysiological measurements that show delayed latencies of the auditory, visual, and somatosensory evoked potentials as well as longer central motor conduction delays are indicative of demyelination and may indicate clinically silent lesions. Blood tests are frequently done to rule out conditions that can mimic MS (31).

### 3.1 Magnetic resonance imaging

Each patient should have MRI imaging performed, which should be performed at least on the brain and, if the presentation is spinal, also on the spinal cord (22). In MS patients, an MRI of the brain reveals ovoid, well-circumscribed, perpendicular to the ventricle's lesions in periventricular, juxtacortical, and infratentorial regions, among others. MRI scans of the spinal cord frequently show involvement of the spinal cord and are well-defined, tiny lesions in lateral or posterior part of the spinal cord (32). Sagittal 3D fluid-attenuated inversion recovery (FLAIR) collection is regarded as the essential procedure for diagnosing and monitoring MS due to its great sensitivity. However, high quality two-dimensional (2D) pulse-sequences (i.e., 3 mm slice thickness and no gap between slices) can offer an adequate alternative in centers that are unable to capture sufficiently high-quality 3D FLAIR images. Precontrast images barely help with the interpretation of postcontrast hyperintensities, hence precontrast T1-weighted sequences are rarely necessary. There is no proof that 3 T MRI results in an earlier diagnosis of MS, even though 3 T scanners offer a greater detection rate for MS lesions and potentially faster acquisition times than lower magnetic field strengths. As long as scans are of high quality and have a suitable signal-to-noise ratio and spatial resolution (i.e., 1 mm 1 mm pixel in-plane resolution), they can still be used to detect brain lesions at the time of diagnosis (33).

Imaging has two purposes: when interpreted by a skilled neuroradiologist, it can exclude out MS mimics and help to confirm the diagnosis by displaying dispersion in both time and space. Incidental findings, such as pituitary adenomas, pineal cysts, vascular malformations, benign meningiomas, and prolapsed intervertebral discs,

make for about 2% of non-MS-related abnormalities found during an MRI. While these unanticipated findings may clinically complicate matters, they shouldn't detract from the MS diagnosis (22).

According to the clinical presentation of the disease, McDonald's criteria describe the diagnosis of MS phenotypes.

**Table 3.** Diagnostic criteria for RR MS according to Dobson R, Giovannoni G. Neurol. 2019 (22)

| McDonald 2017 (relapsing–remitting MS) |
|---|
| Either<br>(i) Objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack involving a different CNS site or<br>(ii) ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical/cortical, infratentorial, spinal cord) |
| Either<br>(i) ≥2 attacks separated by at least 1 month or<br>(ii) (ii) simultaneous presence of asymptomatic gadolinium enhancing and non-enhancing lesions at any time or<br>(iii) a new T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of its timing with reference to a baseline scan or<br>(iv) demonstration of CSF-specific OCBs (as a substitute for DIT) |

Diagnostic criteria for PPMS according to Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al Lancet Neurol. 2018 (17).

Patients with the following criteria can be diagnosed with primary progressive multiple sclerosis:

| 1 year of disability progression (evaluated either retrospectively or prospectively), regardless of clinical relapse. |
|---|
| Plus, two of the following criteria: |
| • One or more T2-hyperintense lesions characteristic of |

| |
|---|
| multiple sclerosis in one or more of the following brain |
| regions: periventricular, cortical or juxtacortical, or infratentorial |
| • Two or more T2-hyperintense lesions in the spinal cord |
| • Presence of CSF-specific oligoclonal bands |

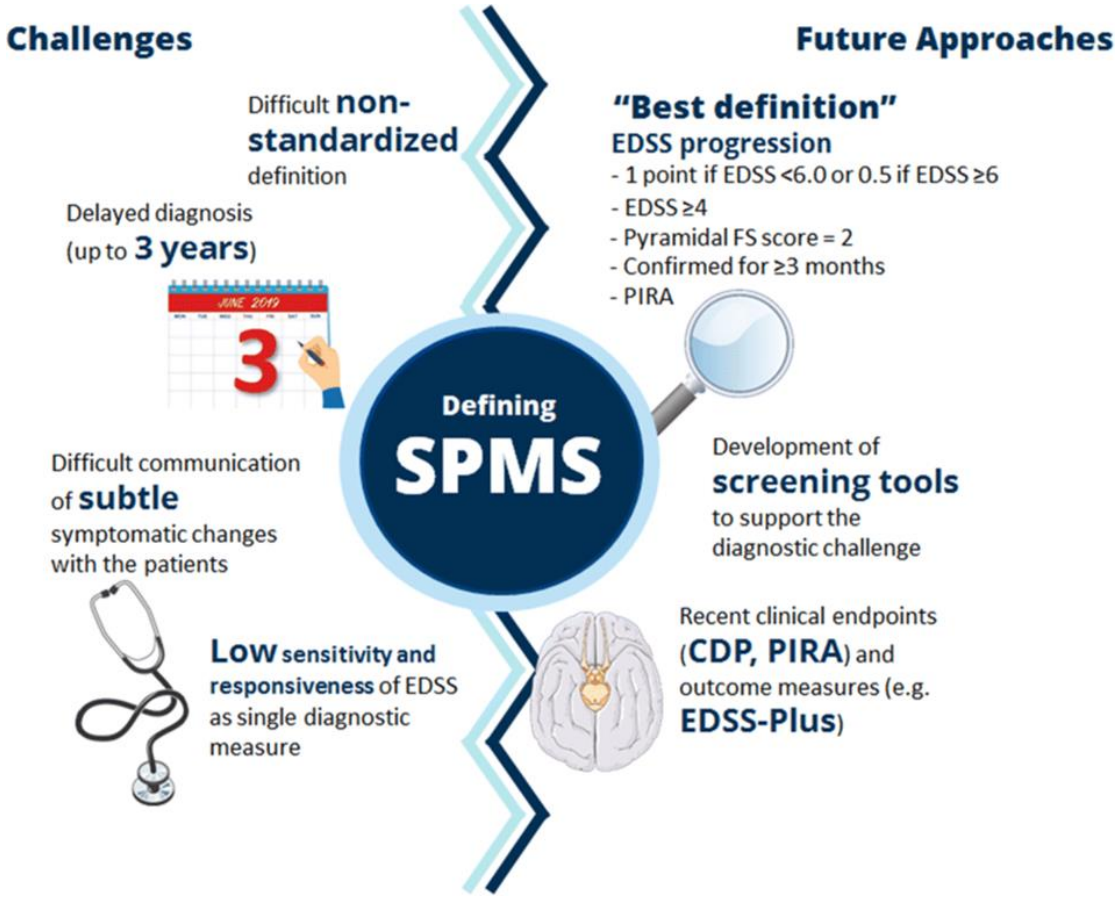
The second most prevalent type of MS is SPMS. Within 15 years, one in two people with untreated RRMS may develop SPMS, and up to two-thirds will develop it by 30 years, which will impair everyday activities and cause a progressive decline in neurological function. Both the patient and the doctor find the diagnosis of SPMS difficult, and it is frequently made retrospectively and delayed up to 3 years (34).There are no precise clinical, radiological, immunological, or pathological criteria that define the beginning of SPMS or transition to the progressive phase of the disease (29,35). The doctors tend to be more cautious than the patients regarding disease progression to avoid categorization on a final phase of the disease, sometimes also with an emotional component and limited treatment options, in addition to this uncertainty recognizing the transition to SPMS and the lack of objective tests (36,37). A "best definition" was produced based on a large cohort study (MSBase), a retrospective review of data from 17.356 MS patients and after consideration of 576 potential SPMS definitions, to enable comparison of future research investigations. It is based on regularly EDSS evaluations and suggests SPMS when the EDSS step becomes worse (35).

| | |
|---|---|
| EDSS progression: 1 point if EDSS <6 or 0.5 if EDSS ≥ 6.0 | EDSS ≥ 4 |
| | Pyramidal functional system (FS) score = 2 |
| | Confirmed for ≥ 3 months |
| | PIRA- progression independent of relapse activity |

There have been reports of changes in a few biochemical markers in patients with SPMS compared to RRMS, although there is still no clear standard use for them. High levels of the proteins 14-3-3, tau, neurofilaments, chi-tinase 3-like 1, and cystatin C are associated with the advancement of MS patients' disabilities (38). There are significant connections between EDSS, disease duration, and MRI measurements for up to 19 metabolites from the tryptophan and phenylalanine metabolisms that exhibit distinctive changes to the SPMS phenotype (39).

The neurofilaments, especially the neurofilament light chain (NfL), are currently promising biomarkers. These days, they can even be detected at extremely low blood concentrations when compared to CSF levels. This is a sensitive (albeit non-specific) and clinically significant biomarker that is extremely helpful in the diagnosis of a number of neurological illnesses, including MS to track MS tissue damage (40,41).

**Figure 2.** Challenges and future approaches on the definition of SPMS according to Inojosa H, Proschmann U, Akgün K, Ziemssen T. Neurol. 2021 (34).



## 4.Multiple Sclerosis Treatment

### 4.1 Interferons and Glatiramer Acetate

To be able to change the course of the disease, disease-modifying medicines restrict or regulate immune function.

They predominantly exert anti-inflammatory activity during the relapsing phase of MS; they lessen the frequency of relapses, decrease the buildup of MRI lesions, stabilize, delay, and in some cases somewhat improve disability.

Interferons (INF) and glatiramer acetate (GA), the first permitted treatments are well-tolerated medications that quickly became widely used. These drugs modestly lower the frequency of MS relapses and number of new T2 and Gadolinium positive lesions (42).The recognized antiviral properties of IFNs were the primary reason for the first interest in IFN as a potential therapy option for MS. IFNs' immunomodulatory and antiproliferative effects were later identified.

It is unclear what is the mechanism of action (MOA) of IFN- treatments in MS. Their beneficial therapeutic effect is thought to be mediated by a number of interconnected mechanisms, including down-regulation of MHC class II expression on antigen-presenting cells (dendritic cells, Langerhans cells, and B-cell lymphocytes), induction of interleukin 10 (IL-10) production on T cells, which changes the balance in favor of anti-inflammatory T helper (Th)-2 cells, and inhibition of T-cell migration as a result (43).The MOA of GA and beta-IFNs are completely different. A synthetic four amino acid copolymer called GA is used to mimic myelin basic protein. GA results in a shift from Th1 towards Th2 cytokines (e.g. IL-4, IL-10 and transforming growth factor-beta), which may contribute to disease amelioration (44).

### 4.2 Teriflunomide

In August 2013, the European Union approved the once-daily oral medication teriflunomide for the treatment of adult patients with RRMS. The influence teriflunomide has on lymphocytes that divide quickly is thought to be the basis for its proposed MOA. Dihydroorotate dehydrogenase, a crucial mitochondrial enzyme necessary for de novo pyrimidine production, is inhibited by teriflunomide in a selective and reversible manner. Teriflunomide decreases the proliferation of activated T and B cells, which are believed to take part in the inflammatory process in the CMS, as a result of reduced de novo pyrimidine synthesis (45). 1088 patients with MS, aged 18 to 55, participated in a randomized trial. Teriflunomide doses of 7 mg or

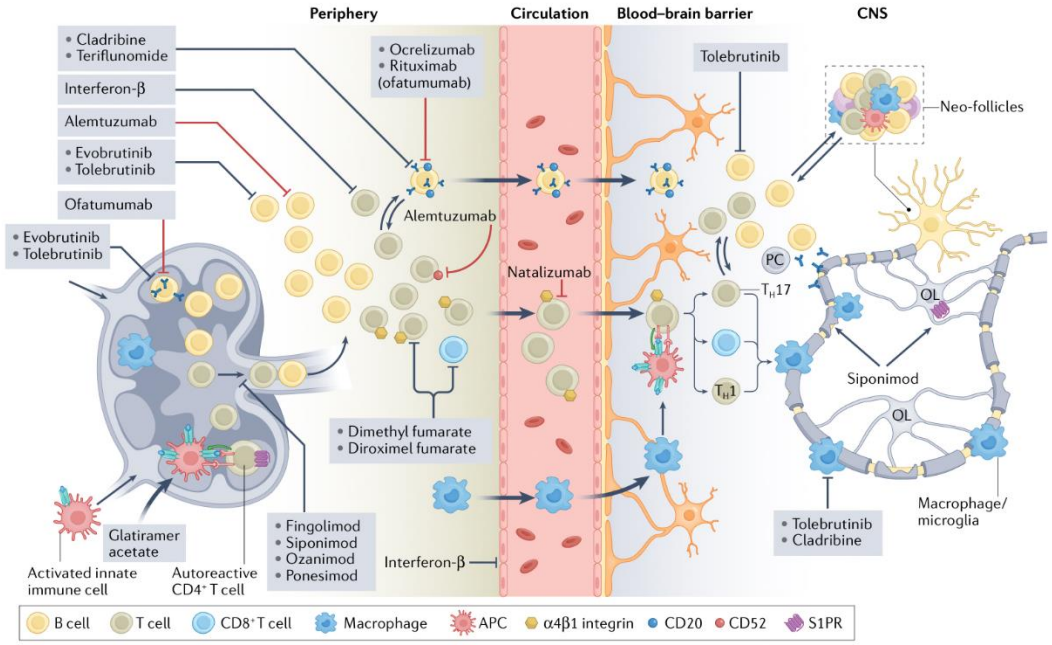
14 mg were given to patients at random (in a 1:1:1 ratio) once daily for 108 weeks. It has been concluded that teriflunomide significantly decreased recurrence rates, disability progression (at the higher dose), and MRI indications of disease activity when compared to placebo, according to the findings. Teriflunomide frequently causes the following adverse effects: nausea, diarrhea, loss or thinning of hair, elevated liver enzyme levels, white blood cell count decline and infections. An increased risk of infections, such as respiratory and urinary tract infections, has been reported (46).

The process of normal cell division necessary for placental and fetal growth and development may be disrupted by teriflunomide because it prevents the synthesis of pyrimidine. Teriflunomide may raise the risk of birth abnormalities since leflunomide, a chemically related substance to teriflunomide, has also been reported to be embryolethal and to increase the risk of malformations (such as cranial, axial skeletal, and major vascular) in the offspring of exposed pregnant mice (47).

### 4.3 Dimethyl Fumarate

Dimethyl fumarate (DMF) and its metabolite, monomethyl fumarate, are thought to cause T and B lymphocytes to undergo apoptosis and elevate type 2 helper T-cell (i.e. anti-inflammatory) cytokine levels. The precise mechanism by which DMF exerts its therapeutic effect in MS is unknown (48,49)**.** One proposed mechanism is the activation of the nuclear factor (erythroid-derived 2)-like 2 (NRF2) pathways. NRF2 is a protein involved in the cellular defense against oxidative stress. By activating NRF2, DMF can help protect cells from damage caused by oxidative stress(50). DMF significantly decreased the rate of recurrence in patients with RRMS in two randomized controlled phase III trials when compared to placebo. DMF effectiveness is further supported by additional favorable impacts on MRI measurements as substitute disease activity markers (51). Regarding pregnancy, it should only be thought for administration during pregnancy if the possible benefits outweigh the fetal danger (47). In the phase II and phase III trials, DMF was generally well tolerated and safe. Most notably, during any of the trials, no rise in malignancies was seen in patients treated with DMF. No opportunistic infections were detected in MS patients receiving DMF, and infection rates were comparable between patients receiving a placebo and those receiving the medication. Flushing and gastrointestinal side effects made up the majority of the phase II and phase III studies' adverse events (51).

**Figure 3.** Targets of current disease-modifying therapies in MS according to Bierhansl L, Hartung HP, Aktas O, Ruck T, Roden M, Meuth SG Nat Rev Drug Discov. 2022 Aug;21 (52)**.**




### 4.4 Natalizumab

The first infusion DMT for RRMS to receive approval was natalizumab in 2004. It is a monoclonal antibody against integrin 1 beta 4 alpha that is administered via monthly infusion or subcutaneous injection and is a selective adhesion molecule inhibitor. The binding to a protein called integrin 1 beta 4 alpha on the surface of immune cells known as lymphocytes prevents the lymphocytes from entering the bloodstream and crossing the blood-brain barrier into the CNS. By blocking the entry of lymphocytes into the CNS, natalizumab reduces the infiltration of immune cells into the brain and spinal cord, where they contribute to the inflammation and damage seen in MS. This helps to decrease the frequency and severity of relapses in patients with relapsing forms of MS (53)**.**

This therapy significantly changed the course of treatment because of its powerful efficacy in reducing relapses and MRI activity, in addition to its route and frequency of administration. Due to the possible danger of developing progressive multifocal leukoencephalopathy, it is necessary to obtain serological and MRI protocols. John Cunningham virus (JC) status and index level performed every six months, can be

used to categorize risk, although for seropositive patients using the medicine for longer than 2 years, the risk rises to 3 per 1000. Due to this, seropositive patients are typically not advised to continue taking this medicine for longer than two years. This medication is therefore primarily used in JCV seronegative patients or those with JCV index less than 1.5 (54).

### 4.5 Anti-CD20 (rituximab, ocrelizumab, ofatumumab)

Anti-CD20 antibodies use for B-cell depleting therapy have produced evidence that B cells are involved in the pathophysiology of MS. The concept that B cells and their autoantibodies contribute to MS pathophysiology led researchers to target B cells using the depleting antibody rituximab, a chimeric anti-CD20 monoclonal antibody (55)**.**

Rituximab was designed and approved for the treatment of rheumatoid arthritis and B-cell malignancies. It significantly reduced inflammatory activity in RRMS and largely used complement-mediated lysis to eliminate CD20-expressing B cells (55).

With the probable existence of ectopic lymphoid follicles harboring B-lymphocytes in the CNS thought to contribute to MS pathology, particularly that of progressive MS, studies have also explored at intrathecal rituximab in the treatment of progressive MS(56). Rituximab is administered intravenously, and the dosing regimen can vary, but it commonly involves two infusions of 1,000 mg each, given two weeks apart. Maintenance infusions are usually given every six to twelve months (55).

In contrast to rituximab and ocrelizumab, ofatumumab is an anti-CD20 human monoclonal IgG1 antibody that binds tightly to a specific membrane epitope. Ofatumumab, is the first entirely human type 1 immunoglobulin G1 kappa (IgG1) monoclonal antibody that is now approved for the treatment of chronic lymphocytic leukemia. However, it has also recently undergone evaluation for usage in RRMS (57). Ofatumumab has the advantage of being administered subcutaneously by patients or caretakers using an auto-injector pen, which is done every four weeks. In contrast to standard antibody therapies, which require a day to be set aside in a clinic for the infusion, this may offer greater access to therapy in the case of a chronic disease requiring regular treatment delivery. Ofatumumab was given Food and Drug (FDA) Administration approval in August 2020 as an auto-injector pen treatment for all types of relapsing MS, including CIS, secondary progressive MS, and RRMS. It was approved by EMA for RRMS in 2021 (57). Infusion-related responses occur

when rituximab and ocrelizumab are administered as a side effect. The responses most usually occurred after the first infusion and frequently included moderate flu-like symptoms, lightheadedness, or pruritus. In addition, anti-CD 20 therapy could contribute to infections more likely. This is because these drugs work by targeting B-cells, which are involved in the immunological response. Having fewer B-cells could make the immune system less effective at warding off diseases. Upper respiratory infections, urinary tract infections, and herpes virus reactivation are examples of common infections (58).

### 4.6 Cladribine

Cladribine, a synthetic purine nucleoside analog, is a prodrug, that cannot be deaminated by the enzyme adenosine deaminase, yet this prodrug is phosphorylated by deoxycytidine kinase inside of the cell. Cladribine triphosphate, its active metabolite, builds up inside the cell and disrupts cellular metabolism, damages DNA, and causes apoptosis as a result (59,60). In addition, an injection of cladribine causes a quick, severe, and long-lasting lymphocyte depletion, according to the results of the immunophenotyping of 309 CLARITY participants. Cladribine selectively depletes lymphocytes and has a predilection for B lymphocytes. Memory B lymphocytes appear particularly vulnerable to this depletion. Cladribine improves immunological tolerance and lowers immune cell infiltration into the CNS in addition to its pro-apoptotic effects (61). Hematopoietic stem cell transplantation, the oral formulation cladribine and the monoclonal antibody alemtuzumab are categorized as immune reconstitution therapies (IRTs). The goal of IRTs is to reestablish durable immunological tolerance by eradicating a pathogenic immune repertoire through a brief period of acute immunosuppression and then rebuilding a new and healthy immune system. It has been demonstrated that when given intermittently, it can cause a long-lasting remission of MS that is sustained over ensuing treatment-free intervals. Clinical or radiological response is unrelated to immune depletion, but when the immune system is restored, the lymphocyte repertoire undergoes significant changes that allow the immune system to once again respond to infections (62).
Cladribine is able to pass the blood-brain barrier in the context of MS, reaching a concentration in the cerebrospinal fluid that is roughly 25% lower than that in the peripheral. This should enable the reduction of lymphocyte numbers at regions of

focal inflammation and spinal cord. Cladribine has a 40% estimated bioavailability, therefore it can be taken orally or parenterally. The dosage regimen comprises of two treatment courses, each of which has two treatment weeks. These courses are at least four weeks apart (63). Myelosuppression and secondary neoplasia are two of the most severe possible adverse reactions to cladribine therapy. The most frequent side effects in the CLARITY research were lymphocytopenia, headaches, nasopharyngitis, and upper respiratory tract infections and three of the patients developed herpes zoster. Regarding neoplasms leiomyomas, ovarian and pancreatic cancer were reported (64). Before starting therapy in years 1 and 2, both females who are or may get pregnant and males who might become fathers should be counseled about the possibility of substantial danger to the fetus and the requirement for reliable contraception. Effective contraception must be used in both sexes of reproductive potential while receiving therapy with cladribine and for at least 6 months after the last dosage. The excretion of cladribine in human milk is unknown. Breastfeeding is prohibited during treatment with cladribine and for 1 week following the last dosage due to the risk of serious adverse effects in infants who are breastfed (65).

**4.7 Alemtuzumab**

A humanized monoclonal antibody called alemtuzumab is designed against the cell surface protein CD52(66). CD52 is present mainly on the cell surface of lymphocytes but also at lower concentrations on NK cells, monocytes, macrophages and eosinophils (67). Due to antibody-dependent cell-mediated cytotoxicity, alemtuzumab therapy causes a fast and significant decrease in peripheral lymphocytes, (68) complement-dependent cytolysis and induction of apoptosis (69), followed by a favorable immune system reconstruction (70).

Alemtuzumab is thought to have an initial anti-inflammatory effect by lowering the level of circulating T and B lymphocytes, which is followed by a distinct temporal (early B-cell and monocyte recovery, delayed T-cell recovery) and qualitative pattern of repopulation, which minimizes the chance of future relapse and disease progression (71). Alemtuzumab should be taken at a dose of 12 mg per day by intravenous infusion (each infusion will continue for around 4 hours), for two initial treatment courses and maybe up to two more if necessary. Alemtuzumab is given for 5 consecutive days during the first cycle and for 3 consecutive days during the second course 12 months later. When taking a second course, the first one should have been

completed 12 months prior, and the medicine is taken for three consecutive days . Patients should receive pre-treatment with corticosteroids for the first three days of any therapy course, right before each alemtuzumab infusion. All patients should get oral prophylaxis for herpes infection on the first day of each treatment course and continuing for at least a month after treatment. Patients must avoid from eating raw or undercooked meats, soft cheeses, and unpasteurized dairy products for at least two weeks before, during, and after receiving an infusion of alemtuzumab to lower their chance of contracting listeriosis or Listeria meningitis (72).

It has been demonstrated that receiving alemtuzumab increases the likelihood of developing autoimmune-mediated diseases such thyroid problems, Immune thrombocytopenia purpura (ITP), or, very infrequently, nephropathies like Goodpasture disease with anti-glomerular basement membrane antibodies. One possible explanation for this could be a connection between lymphopenia-related autoimmunity and homeostatic T-cell proliferation after alemtuzumab-mediated lymphocyte reduction (47,48).

### 4.8 Autologous hematopoietic transplantation

A well-known, multi-step technique called a hematopoietic stem cell transplant (HSCT) replaces a patient's blood and lymphatic systems with new ones made of HSCs. HSCs can be obtained from either the healthy donor (allogeneic transplantation) or from the patient (autologous transplantation) (75).

In the relapsing forms of the disease, the approved MS treatments are effective in reducing clinical and radiological inflammation. Unfortunately, no medication can halt disability progression. Moreover, the progression of MS may be quite aggressive and show resistance to traditional disease-modifying medications. AHSCT may be a viable treatment option in such circumstances (76). A task force was recently established by the American Society for Blood and Bone Marrow Transplantation to examine the available data and make recommendations regarding the use of AHSCT for treatment-refractory MS. At five years after transplantion, their assessment of retrospective data revealed an overall rate of relapse-free survival of 80–87%, with many trials demonstrating EDSS stability or improvement (77). In a retrospective cohort research on 120 MS patients who received HSCT revealed a markedly lower recurrence rate at 2 and 4 years of follow-up as well as a decline in T2 lesions on MRI. According to the study, 87% of patients at 4 years and 93% at 2 years had not

experienced a relapse. According to the study's findings, AHSCT was able to stop the EDSS ratings from rising (78).

Given that it is frequently selected as a last resort and that many failed DMTs have been tried before, AHSCT appears to have greater potential for treating MS patients with various disease courses. AHSCT has evolved into a more solid method of treating MS because of gaining knowledge and experience in the field of stem-cell therapy (79).

## 5. Progressive multiple sclerosis treatment

### 5.1 Mitoxantrone

Crosslinks and strand breaks are brought on by mitoxantrone, a deoxyribonucleic acid (DNA)-reactive substance that intercalates into DNA by hydrogen bonding. In addition to interfering with DNA, topoisomerase II, an enzyme that unravels and repairs damaged DNA, is also severely inhibited by mitoxantrone. This prevents DNA strand ligation and delays the continuation of the cell cycle. Similarly, to a number of other anti-cancer medications, mitoxantrone also has immunomodulatory effects that reduce humoral immunity (80). In vitro and in vivo anticancer experiments, mitoxantrone promoted macrophage-mediated inhibition of B-cell, T-helper, and T-cytotoxic lymphocyte activity, notably in the spleen and draining lymph nodes (81)**.**

For the treatment of RRMS, SPMS, and progressive-relapsing MS, mitoxantrone is approved for use as either first-line therapy or in cases of failure or intolerance to prior immunomodulatory therapy (82).

Due to the possibility of heart toxicity, treatment is limited to a cumulative total life dose of 140 mg/m 2 body surface. There is a 0.21% relative risk of developing acute leukemia associated to therapy. Safety evaluations, such as routine blood tests and echocardiography, are therefore required both during and after therapy (83).

### 5.2 Siponimod

For the treatment of SPMS, oral siponimod, a next-generation, selective sphingosine 1-phosphate receptor (S1PR)1 and 5 modulator, has received approval in a number of nations, with different countries having different indications (84)**.** S1P plays a crucial role in several physiological processes, such as immunological, cardiovascular, and brain functions. S1P does this by acting on five G protein-coupled receptors called S1P receptors (S1PR1-5) that are expressed differently in different cell types and

organs (85,86)**.** The S1PR axis has been associated with a variety of immune-mediated diseases, including MS, because of S1P's critical role in mediating several pathways, including lymphocyte trafficking, vascular homeostasis, microglial activation, neuronal interactions, axonal growth, oligodendrocyte survival, myelination, and integrity of the blood-brain barrier (86,87). Its primary mode of action in MS is the reduction of circulating lymphocytes, which stops the CNS from being infiltrated. Because it can pass through the blood brain barrier (BBB) very easily, it may directly encourage neuronal repair via regulating S1P1 on astrocytes and S1P5 on oligodendrocytes. The data from a Phase I study show that the siponimod-induced decrease in lymphocyte counts in peripheral blood starts happening right away after the first dosage, peaks after 4-6 hours, and persists all the way through treatment.

Naive and central memory T cells (CCR7+) are preferentially affected by the peripheral blood alterations compared to peripheral effectors memory T cells, and CD4 + T cells exhibit more dramatic peripheral blood changes than CD8 + T cells (88). According to the EDSS, SPMS is linked to the progressive accumulation of physical disability, which may be visible in patients with EDSS scores as low as 2.0 (26,29). In EXPAND, a phase 3 research of patients with SPMS, over 50% of whom required walking aids (EDSS 6.0) at study entry, the effectiveness and safety of siponimod were examined. Siponimod demonstrated superiority over placebo in terms of slowing the development of physical disability and cognitive impairment, with significantly greater decreases in annualized relapse rate (ARR), MRI lesion activity, and brain volume loss (total and grey matter), as well as a safety profile like other S1P receptor modulators. The key element of EXPAND trial was a pivotal double-blind, randomized, placebo-controlled, event- and exposure-driven phase 3 research that lasted up to 3 years (median exposure time: 18 months) and focused at the effectiveness, safety, and tolerability of siponimod in SPMS patients (89).

In the crucial EXPAND trial, which included 1099 siponimod users and 546 placebo users, oral siponimod was usually well tolerated by SPMS patients (median exposure to study drug was 18 months). With siponimod compared to placebo, the EXPAND study found a significant 21% lower risk of 3-month CDP (the primary efficacy outcome, defined as a 1-point increase in EDSS if baseline score was 3.0-5.0 and a 0.5-point increase if baseline EDSS was 5.5-6.5 confirmed 3 months later). Despite a tendency towards a more favorable response in younger patients, such improvements

were observed in all patient categories based on age, gender, relapse history, Gd+ T1 lesion burden, prior therapies, and MS severity (90).

Treatment with siponimod was linked to improvements in cognitive processing speed as measured by symbol digit modalities test (SDMT) scores (a change of 4 points or more is regarded as clinically significant). Between baseline and month 24, the average SDMT score changed by 0.79 with siponimod and by 1.55 with a placebo (89). A retrospective, multicenter, non-interventional study evaluating siponimod's effectiveness and safety in 227 SPMS patients under practical circumstances. Data were collected at predetermined time points in accordance with the protocol for the retrospective investigation. Each quarter, clinical readouts were evaluated. Radiological progression, an increase in the EDSS, or the development of recent relapses while receiving treatment were used to measure disease progression. The study evaluated siponimod's efficacy, adverse event profile, and discontinuation rate as a therapy for SPMS in a real-world sample. Treatment with siponimod exhibited an overall stabilizing effect regarding clinical and radiological outcome measurements during this brief observation, with only a small number of patients engaging in follow-ups after 12 months. However, a significant fraction of patients stopped taking siponimod as a result of disease activity and adverse events (AE). As therapy discontinuation was more common in our sample than in the EXPAND study, AE provide a significant challenge to treatment adherence and management in the real-world scenario. It's important to note that in the three months that followed treatment withdrawal, 11.9% of patients showed relapse activity, and 28.4% of patients showed new T2 lesions. These findings support the possibility that people using siponimod had a higher risk of illness progression after stopping their medication (91).

Most treatment-emergent adverse events (TEAEs; 89 vs. 82%) in the siponimod and placebo groups were mild to moderate in intensity, and only a small number of patients terminated treatment as a result. In both the siponimod and placebo groups, the most frequent TEAEs were headache, fall, hypertension, dizziness, nausea, diarrhea, elevated alanine aminotransferase levels, and pain in an extremity (92).

Another UK NICE appraisal of using siponimod is currently being recommended for the treatment of adult SPMS patients with active disease demonstrated by relapses or imaging-features of inflammatory disease. In the end, a variety of factors, such as patient desire, disease features, and pharmacoeconomic considerations, will determine the therapy option (84). For patients using siponimod, a first-dose observation is

advised if they have a history of heart disease (sinus bradycardia, first- or second-degree atrioventricular block, or a history of myocardial infarction or heart failure), and an eye exam is necessary to check for macular edema. To determine titration and dose schedule based on the patient's capacity to metabolize the medicine, CYP2C9 genotype testing is necessary before treatment can start (93). Siponimod may harm fetuses according to tests done on animals. Women of reproductive potential should use reliable contraception to prevent conception both during and for 10 days after stopping siponimod treatment since it takes the body around 10 days to clear siponimod from the body. Additionally, people who have already experienced some severe infections (such as progressive multifocal leukoencephalopathy or cryptococcal meningitis) should not use the medication. Because siponimod affects the immune system, it should not be administered to patients who have cancer or certain immunological disorders (94).

### 5.3 Ocrelizumab

The activation of pro-inflammatory T cells, the release of pro-inflammatory cytokines, and the generation of autoantibodies that target myelin all play crucial roles in the pathogenesis of MS. .Hence, the use of B cell-depleting monoclonal antibodies as a kind of treatment for autoimmune illnesses, such as MS, has grown recently (95)**.** The discovery of a particular IgG fraction in the CSF provided the first indication of B-cell participation in MS. The activity of clonally expanded B lymphocytes is visible in these fractions, which are referred to as OCB in the intrathecal space. According to the 2017 MS diagnostic criteria, OCB can eventually replace dissemination in over 90% of people with MS (17,96). In 2004, ectopic lymphoid follicle-like structures comprising CD20 + B cells as well as CD138 + plasma cells and follicular dendritic cells were detected in the leptomeninges of SPMS patients. This finding made a significant addition to the evidence supporting the presence of B cells in the CNS (56). Ocrelizumab is recommended for the treatment of adult patients with primary progressive or relapsing types of MS. In secondary progressive types of MS, B cell-rich meningeal aggregates with subpial cortical lesions are reportedly more common (56)**.** Ocrelizumab is an anti-CD20 antibody that spares CD20-negative plasma cells while eradicating circulating immature and mature B cells. Complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity are the anti-CD20

antibodies' effector mechanisms (97)**.** In two phase III investigations of patients with RRMS, OPERA I and OPERA II ocrelizumab totally reduced the CD19+ B-cell count in blood (CD19+ cells function as a measure of B-cell counts in patients treated with anti-CD20) (98). In a phase II study of patients with RRMS, the median time to B-cell replenishment was 72 weeks following the final ocrelizumab infusion (99)**.** In vitro, ocrelizumab is linked to higher antibody-dependent, cell-mediated cytotoxic effects compared to rituximab and lowered complement-dependent cytotoxic effects. In addition ocrelizumab, a humanized molecule, may provide a better benefit-risk profile than rituximab since it is believed to be less immunogenic with repeated infusions (100). Earlier and ongoing ocrelizumab treatment up to 5 years is shown to give persistent benefit on clinical and MRI indices of inflammatory disease activity in long-term data from open label ocrelizumab extension in RRMS patients. Additionally, a reduced proportion of patients with illness progression and a slower pace of brain volume loss were both signs of the favorable effect (101).

Participants in the ORATORIO study were given the option to continue taking ocrelizumab or switch from taking a placebo to ocrelizumab after the double-blind phase was complete. Over the course of at least 6.5 research years, of which 3.5 study years were under the open-label extension, all participating patients were monitored. 451 people were enrolled in the open-label extension out of the 732 subjects in the ORATORIO research. MRI parameters (percentage change from baseline for T2 lesion volume and T1 hypointense lesion volume) and disability measures (24-week confirmed disability progression, 9HPT, composite progression, and confirmed time to requiring a wheelchair) were in favor of patients who were treated from the start in the ocrelizumab arm at the time of the most recent analysis (102).

One of the advantages of ocrelizumab over other MS treatments is that it has a favorable safety profile. The most common side effects are infusion-related reactions, which can include fever, chills, and fatigue. However, these reactions are typically mild and can be managed with premedication such as antihistamines and corticosteroids, and by slowing down the infusion rate. In rare cases, severe infusion-related reactions may occur, which can include anaphylaxis, a severe allergic reaction that can be life-threatening (95).

Ocrelizumab may also cause infections like upper respiratory tract infections, urinary tract infections, and herpes infections in addition to infusion-related events. Patients using ocrelizumab may experience these infections more frequently, therefore it is

important to monitor patients for any infection symptoms while they are being treated (95). Four neoplasms (0.5% of patients) occurred in the ocrelizumab group in the OPERA trials—two cases of invasive ductal breast carcinoma, one case each of renal cell carcinoma and malignant melanoma—and two (0.2%) in the INF group—mantle-cell lymphoma and squamous-cell carcinoma in the chest. Two cases of breast cancer, two cases of basal-cell skin cancer, and one case of malignant melanoma were among the five additional cases of neoplasm that were reported in the open-label extension study, in which all patients received ocrelizumab (98). Ocrelizumab's real-world efficacy data were consistently positive, showing decreases in relapse rates and rates of disease progression comparable to those reported in the OPERA I/OPERA II and ORATORIO clinical trials, as well as in studies with more diverse patient populations that were underrepresented in the pivotal trials. The provided results indicate that ocrelizumab has a similar or higher efficacy than alternative medication options, despite the fact that direct comparisons are complicated by the lack of treatment randomization (103). Additional significant real-world ocrelizumab use in RRMS and PPMS patients in addition to demonstrating favorable real-world effectiveness that appears to be consistent with clinical trial data; three studies report stable or improving health related quality of life (HRQoL) after up to one year of ocrelizumab treatment. Five studies examined the clinical effectiveness of switching from natalizumab to ocrelizumab and three additional studies examined the clinical effectiveness and safety of switching from other DMTs to ocrelizumab (103). Rituximab and ocrelizumab belong to the IgG1 antibody family, and they are transported via the placenta in a linear pattern, with minimal transport happening during the first trimester and maximal transport occurring in the third. Therefore, early in pregnancy there should be minimum fetal exposure, but in the third trimester there may be greater exposure (104,105). There is little information available on the use of B cell therapy during pregnancy, but several publications have examined the safety and efficacy of rituximab administration in patients with neuromyelitis optica spectrum disorder (NMOSD) and MS as well as other immunological, rheumatological, and hematooncological diagnoses both before and during pregnancy. The findings of these research showed no significant safety indications (106,107). Studies evaluating ocrelizumab exposure and pregnancy outcomes were few in number. A German cohort research examined the effects of ocrelizumab or rituximab treatment on pregnancy outcomes and disease activity in women with NMOSD and

MS. The cohort for the study consisted of 68 known outcomes from 88 pregnancies in 81 women. In women exposed during pregnancy, there were significantly more preterm deliveries, and two significant congenital anomalies were seen in the same group of treated patients. Other pregnancy outcomes that had been assessed were comparable between groups. Three women in the entire group experienced serious infection (SI) during pregnancy, and three of the neonates had SI that required hospitalization. Pregnant women with MS did not experience any relapses; however, one relapse did occur in the NMOSD group (108). However, female patients of childbearing age are advised to use effective birth control while receiving ocrelizumab up to 12 months (an EMA recommendation) or for at least 6 months (an FDA recommendation) after the last infusion (109,116).

## 6. Symptomatic treatment

Table 4. Comorbidity and symptom management in multiple sclerosis according to McGinley MP, Goldschmidt CH, Rae-Grant AD. 2021 Feb (93).

Table 4. Comorbidity and Symptom Management in Multiple Sclerosis

| | Prevalence | Symptom management | | Potential etiologies/risk factors |
|---|---|---|---|---|
| | | Pharmacological | Nonpharmacological | |
| Comorbidities | | | | |
| Depression | 37% (n = 2312)[67] to 45% (n = 8722)[68] | SSRIs and SNRIs (fluoxetine 20-60 mg/d, sertraline 50-200 mg/d, duloxetine 60 mg/d, venlafaxine 75-225 mg/d) | Screened regularly with short questionnaires, psychotherapy | Combination of biological (fatigue, cognitive dysfunction, pain, family history of depression, female sex)[69] and psychosocial factors (lower SES and education levels) |
| Anxiety | 16.5% (n = 8729)[68] to 35.6% (n = 140)[70] | SSRIs and SNRIs (fluoxetine 20-60 mg/d, sertraline 50-200 mg/d, duloxetine 60 mg/d, venlafaxine 75-225 mg/d) | Psychotherapy | Reactive to stress of chronic illness (increased psychosocial stressors, decreased social supports), dysfunction of the frontostriatal circuits[70] |
| Vascular comorbidities (hypercholesterolemia, hypertension, heart disease, diabetes, peripheral artery disease) | 52.8% (n = 8983)[64] Mean age, 52.7 (SD, 10.4) y | Targeted treatment of hyperlipidemia, hypertension, heart disease, diabetes, and peripheral artery disease | Lifestyle modifications (ie, diet and exercise) | Similar to the general population |
| Sleep disorders (restless legs syndrome, obstructive sleep apnea, insomnia) | 51.5% (n = 1063)[71] to 70% (n = 11 400)[72] | Restless legs syndrome: pramipexole (0.125-0.5 mg every night at bedtime), gabapentin (300-2400 mg daily), and benzodiazepines (as low a dose as possible), clonazepam 0.5-2 mg every night at bedtime) | Obstructive sleep apnea: weight loss, positive upper airway pressure, and sometimes surgical interventions Insomnia: education on proper sleep hygiene, stimulus control, sleep restriction, biofeedback, and cognitive behavioral therapy | Pain, depression, spasticity, urinary dysfunction, brainstem dysfunction, hypothalamic dysfunction, medication adverse effect |
| Vitamin D deficiency | 30%[73] | Vitamin D supplementation (1000-4000 IU/d, aiming for blood level >70 nmol/L)[74] | NA | Immunomodulatory and anti-inflammatory effects[8,74] |
| Tobacco use | 45% (n = 1190)[75] | Varenicline (1 mg twice daily after initial titration) | Counseling | |
| Symptoms | | | | |
| Neuropathic pain | 39.8% (n = 428)[76] | Gabapentin (300-2700 mg/d split into 3 doses), pregabalin (300-600 mg/d in 2-3 doses), amitriptyline (25-150 mg/d), duloxetine (30-60 mg/d),carbamazepine (600-800 mg/d), oxcarbazepine (300-1200 mg/d in 2 doses), lamotrigine (50-200 mg/d after slow titration), topiramate (25-200mg/d in 2 doses) | Exercise, physical therapy, psychological treatments (eg, cognitive behavioral therapy), neuromodulation (transcutaneous electrical nerve stimulation, transcranial direct current stimulations, or spinal stimulators), nerve blocks | Demyelinating lesions in the nociceptive pathways |
| Trigeminal neuralgia | 4% (n = 428)[76] | Carbamazepine (600-800 mg/d), oxcarbazepine (300-1800 mg/d in 2 doses): lamotrigine (50-400 mg/d in 2 doses after slow titration), baclofen (60-80 mg/d in divided doses after titration) | Consider surgical or radiation interventions | Lesions in trigeminocervical complex |
| Spasticity | 84% (n = 20 969)[77] | Baclofen (5-80 mg/d in divided doses with titration), tizanidine (2-36 mg/d in divided doses after titration), benzodiazepines at lowest possible dose (diazepam 5-40 mg/d in divided doses), dantrolene (100 mg ×3/d after titration) intrathecal baclofen pump; botulinum toxin injections for focal spasticity | Exercise, physical therapy | Upper motor neuron dysfunction causing combination of central paresis and muscle hyperactivity |
| Fatigue | 78% (n = 656)[78] to 94%(n = 25 728)[79] | Amantadine (100 mg twice daily), modafinil (200 mg daily), armodafinil (150 mg daily) | Cognitive behavioral therapy, relaxation therapy, aerobic exercise, and cooling devices | Hypothalamic-pituitary-adrenal axis dysfunction, monoaminergic system dysfunction, secondary causes from other comorbid conditions (medication adverse effect, sleep-related disorders, depression, thyroid dysfunction)[80,81] |
| Cognitive impairment | 43% (n = 100)[82] to 56% (n = 45)[83] | Can consider donepezil (5-10 mg daily) and memantine (5-20 mg daily), but no strong evidence to support their use | Occupational therapy and cognitive rehabilitation | Grey matter lesions, cerebral atrophy (especially in mesial temporal lobes), and other psychosocial factors and general health-related factors (education level, depression) |

(continued)

Table 4. Comorbidity and Symptom Management in Multiple Sclerosis (continued)

| | | Symptom management | | |
|---|---|---|---|---|
| | Prevalence | Pharmacological | Nonpharmacological | Potential etiologies/risk factors |
| Urinary dysfunction | 90% (n = 1882)[84] | Detrusor overactivity: oxybutynin (2.5-20 mg daily), tolterodine (1-4 mg daily), mirabegron (25-50 mg daily), botulinum toxin injections | Pelvic floor exercises and intermittent self-catheterization<br>If intermittent self-catheterization becomes not possible, consider suprapubic catheter | Lesions in the lateral corticospinal tracts and reticulospinal tracts in cervical cord causing detrusor and sphincter dysfunction |
| Gait impairment | 50%-91%, depending on disease duration (n = 25 728)[79] | Dalfampridine (10 mg twice daily) | Physical therapy | Weakness, spasticity |
| Bowel dysfunction | 52%[85] (n = 77) to 68% (n = 280)[86] | Stool softeners, stimulants, laxatives, enema | Timed bowel evacuation, dietary fiber, biofeedback, physical activity, hydration | Combination of cortical dysfunction of the frontal lobe and spinal cord dysfunction, pelvic floor dyssynergia |
| Sexual dysfunction | 73%[87] (n = 99) | Phosphodiesterase-5 inhibitors, intracavernous vasodilator agents | Penile prostheses, vaginal lubricants | Sphincteric dysfunction, psychological factors, medication adverse effects |
| Tremor | 25% (n = 200)[88] - 58% (n = 100)[89] | β-Blockers (propranolol 60-320 mg/d in divided doses), primidone (250-750 mg/d in divided doses after titration), gabapentin (300-2700 mg/d in divided doses) | Joint stabilization maneuvers, limb weights, use of large-handled utensils, deep brain stimulation | Cerebellar and cerebellar connection dysfunction |
| Dysphagia | 38% (n = 103)[90] | Referral to speech and language pathologist for formal evaluation | Diet modification, swallowing exercises, electrical stimulation | Dysfunction of corticobulbar tracts, cerebellum, brainstem, lower cranial nerves |

Abbreviation: NA, not applicable; SES, socioeconomic status; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Management of symptoms such as spasticity, pain, fatigue, cognitive decline, urinary dysfunction, bowel problems, gait instability, emotional dysregulation, and sleep disturbance is essential in the treatment of MS. Nowadays available treatment is a combination of pharmacological and nonpharmacological therapy that is used to manage these symptoms (110). Spasticity, which is characterized as a velocity-dependent rise in muscle tone, is a frequently reported symptom of MS. Symptomatic treatment for spasticity may include medications such as baclofen or tizanidine, or physical therapy and stretching exercises (111).

MS can directly induce fatigue and cognitive dysfunction, or they can result from secondary factors like depression or sleep problems. Fatigue is often considered the most debilitating symptom frequently thought to cause loss of work and affect daily life tasks (112). Fatigue can be managed with lifestyle modifications such as regular exercise, good sleep habits, and energy conservation techniques. Medications such as modafinil or amantadine may also be used to manage fatigue (93).

Patients with MS frequently experience neurogenic lower urinary tract dysfunction, which has a detrimental effect on quality of life. Whether a patient has storage (overactive bladder) or voiding (underactive bladder or detrusor sphincter dyssynergia), the recommendations for pharmaceutical treatment of lower urinary tract (LUT) dysfunction in neurological patients, vary. Antimuscarinics are the first-line treatment for storage issues, and more recently, beta-3-receptor agonists have been commercially accessible and can be effective as a complement or as a stand-

alone therapy. Only alpha-blockers are now considered as a form of medical treatment for voiding difficulties, and in cases where such treatments fail, neuromodulation or catheterization may be recommended (113). Central neuropathic pain, which is caused by demyelinating lesions in the brain and spinal cord as a result of MS, is pain which develops as a direct or indirect result of these lesions (114). Tricyclic antidepressant (TCAs) (such as nortriptyline and amitriptyline), serotonin and norepinephrine reuptake inhibitors (SNRIs) (such as duloxetine and venlafaxine), voltage-gated calcium channel a2-d subunit ligands (such as gabapentin and pregabalin), and topical lignocaine (a Na+ channel blocker) are among the first-line medications being advised.

Botulinum toxin can be used to treat overactive bladder and neuropathic pain, and amantadine injections can be used to alleviate exhaustion (110). THC+CBD can be used as an oromucosal spray to treat MS patients' spasticity symptoms. One trial checked the role of THC: CBD spray for treating central pain in MS patients. In this randomized study, there were two groups, the placebo, and the treatment group. The result of the study showed that THC: CBD spray significantly reduced the pain and improved the sleep quality in MS patients (115).

Nowadays it is proposed that patients with MS be followed up by a team of healthcare professionals to receive comprehensive care due to the wide-ranging and complex nature of comorbidities and symptoms associated with MS. This team should include a neurologist, primary care physician, physical, occupational, and speech therapists, psychologists, urologists, and specialists in physical medicine and rehabilitation, pain management, and infectious diseases, as necessary. Psychologists, urologists, and specialists in physical medicine and rehabilitation, pain management, and infectious diseases, as necessary.

# Conclusion

In conclusion, pharmacological treatment plays an essential role in managing multiple sclerosis. DMTs are the cornerstone of treatment for relapsing-remitting MS, and they can help reduce the frequency and severity of relapses, slow down disease progression, and preserve neurological function.

Monoclonal antibodies have emerged as a promising class of drugs for the treatment of MS. These drugs are designed to target specific immune cells or molecules involved in the pathogenesis of MS, offering a more targeted approach to treatment. In clinical trials, these medications reduced inflammation, slowed the course of the disease, and decreased the number of relapses. Many MS patients will undoubtedly have better prognosis as a result of the increased usage of early, very effective oral medications or monoclonal antibodies due to the new approved medicines and improved knowledge of their risk-benefit profiles.

For progressive MS, DMTs may have limited efficacy, and symptomatic therapies may be used to manage specific symptoms such as spasticity, fatigue, and bladder dysfunction. Both siponimod and ocrelizumab are important advancements in the treatment of MS, providing options for different forms of the disease and have demonstrated efficacy in reducing disease activity and slowing the progression of MS. Autologous stem cell transplantation has emerged as a potential treatment for MS, particularly in cases of aggressive disease that have not responded to other therapies.

Several new treatments are currently being investigated for progressive MS and ultimately, the choice of treatment for progressive MS will depend on several factors, including the individual's age, disease severity, and specific symptoms. A healthcare provider specializing in MS care can help determine the most appropriate treatment plan.

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# Biography

Inbal Abramovich was born in Israel on the 11 of June 1995.
When she moved to the United States in 2006 - 2007, while she was still in middle school, she realized she wanted to be a doctor. Her majors in high school were biology and Science Society.
She finished her two years of required reserve service in the Home Front Command for the Israeli Defense Force (IDF).
She wanted to follow her dream to become a medical doctor!
During 2017-2023, Inbal studied general medicine at the University of Zagreb, School of medicine, Croatia, and finished her degree in the MSE program.
During 2021-2022 Inbal was awarded the Dean’s award for the 4th year.