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Diagnosis and Treatment of Multiple Sclerosis
A Review

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IMPORTANCE Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease of the central nervous system characterized by inflammatory demyelination with axonal transection. MS affects an estimated 900 000 people in the US. MS typically presents in young adults (mean age of onset, 20-30 years) and can lead to physical disability, cognitive impairment, and decreased quality of life. This review summarizes current evidence regarding diagnosis and treatment of MS.

OBSERVATIONS MS typically presents in young adults aged 20 to 30 years with unilateral optic neuritis, partial myelitis, sensory disturbances, or brainstem syndromes such as internuclear ophthalmoplegia developing over several days. The prevalence of MS worldwide ranges from 5 to 300 per 100 000 people and increases at higher latitudes. Overall life expectancy is less than in the general population (75.9 vs 83.4 years), and MS more commonly affects women (female to male sex distribution of nearly 3:1). Diagnosis is made based on a combination of signs and symptoms, radiographic findings (eg, magnetic resonance imaging [MRI] T2 lesions), and laboratory findings (eg, cerebrospinal fluid–specific oligoclonal bands), which are components of the 2017 McDonald Criteria. Nine classes of disease-modifying therapies (DMTs), with varying mechanisms of action and routes of administration, are available for relapsing-remitting MS, defined as relapses at onset with stable neurologic disability between episodes, and secondary progressive MS with activity, defined as steadily increasing neurologic disability following a relapsing course with evidence of ongoing inflammatory activity. These drugs include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and 3 types of monoclonal antibodies. One additional DMT, ocrelizumab, is approved for primary progressive MS. These DMTs reduce clinical relapses and MRI lesions (new T2 lesions, gadolinium-enhancing lesions). Efficacy rates of current DMTs, defined by reduction in annualized relapse rates compared with placebo or active comparators, range from 29%-68%. Adverse effects include infections, bradycardia, heart blocks, macular edema, infusion reactions, injection-site reactions, and secondary autoimmune adverse effects, such as autoimmune thyroid disease.

CONCLUSIONS AND RELEVANCE MS is characterized by physical disability, cognitive impairment, and other symptoms that affect quality of life. Treatment with DMT can reduce the annual relapse rate by 29% to 68% compared with placebo or active comparator.

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Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) disorder characterized by inflammatory demyelination and axonal transection, defined as severed terminal axonal structures representing the pathological correlate of irreversible neurologic damage. MS affects approximately 900 000 people in the US.[1-3] MS is typically diagnosed in adults aged 20 to 30 years and often affects physical functioning, cognition, quality of life, and employment. The cause of MS is unclear, but many genetic (eg, major histocompatibility complex *HLA-DRB1* locus) and environmental factors, such as vitamin D levels (increased risk at levels <100 nmol/L [40 ng/mL; reference range, 40-60 ng/mL]), ambient UV radiation, Epstein-Barr virus infection, and tobacco smoking, are associated with MS.[4-9]

Current treatment for MS consists of a multidisciplinary approach including disease-modifying therapies (DMTs), symptomatic treatment, lifestyle modifications, psychological support, and rehabilitation interventions. The first DMT, interferon beta-1b, was approved by the US Food and Drug Administration (FDA) in 1993. As of July 2020 there were 9 classes of DMTs approved for the treatment of MS (interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate [S1P] receptor modulators, fumarates, cladribine, natalizumab, ocrelizumab, alemtuzumab).

Methods

MEDLINE was searched for articles from January 1, 2008, to October 27, 2020. Keywords and MeSH subject headings related to multiple sclerosis and treatment were used to search for randomized clinical trials and review articles. Articles describing pediatric patients or animal subjects were excluded. Non–English-language articles were excluded. Additional articles were identified by the authors based on their knowledge of literature predating 2008 and review of citations in retrieved articles. A total of 2129 articles were identified. Randomized clinical trials, large observational studies, and meta-analysis were selected for review. A total of 108 articles were included, of which 21 were meta-analyses or reviews, 2 were guideline documents, 34 were randomized clinical trials, and 51 were other article types.

Epidemiology

MS presents in young adults (mean age of onset, 20-30 years). The etiology of MS is unknown, but environmental, lifestyle, and genetic factors may contribute to development and outcomes. The prevalence of MS worldwide ranges from 5 to 300 per 100 000 people and increases at higher latitudes.[10] Latitude effects may be explained by greater sun exposure and higher vitamin D levels, which are associated with a lower prevalence of MS.[6,8] The increased prevalence of MS within families also supports genetic factors. The HLA-DR1*15:01 allele is the most frequent genetic factor associated with MS. HLA-DR1*15:01 carriers have an increased risk of developing MS (odds ratio, 2.92; $P = 1.4 \times 10^{-234}$; absolute data not available).[9] Childhood obesity (age 13 years, body mass index >95th percentile) (hazard ratio, 1.58 [51/378 618 for >95th percentile vs 583/7 012 473 for <85th percentile]) is associated with an increased risk.[7] Meta-analyses primarily composed of case-control studies also indicate that cigarette smoking (relative risk, 1.48 for meta-analysis; cohort study absolute risk difference, 3.1 per 100 000 person-years comparing ever smokers with nonsmokers) and Epstein-Barr virus infection are associated with an increased risk of developing MS (relative risk, 2.17 [95% CI, 1.97-2.39] for meta analysis; cohort study absolute risk difference, 9.1 per 100 000 person-years).[4,5]

Pathophysiology

MS is an autoimmune CNS disorder with lesions (discrete brain areas affected by MS) throughout the CNS. The most characteristic lesions are focal areas of demyelination and inflammation in the white matter identified on magnetic resonance imaging (MRI). Grey matter and cortical lesions are also common on pathologic tissue but may not be reliably visualized with current imaging modalities.[11] After the acute inflammatory phase, MS lesions may enter a chronic state that can include remyelination, inflammation resolution without repair, or a "smoldering" state in which inflammation and myelin degeneration coexist.[12] Early research demonstrated the role of T cells in development of inflammation and demyelination in MS. More recent studies and the effectiveness of B-cell–depleting treatments such as ocrelizumab also support a pathogenic role of B cells most likely through regulation of T cells.[13] Inflammation and neurodegeneration are identified in varying degrees in individuals with MS at disease onset and can change within an individual over time.

Clinical Presentation

The classic presentations of MS include unilateral optic neuritis (blurred vision with associated pain), partial myelitis (extremity and torso impaired sensation, weakness, and/or ataxia), focal sensory disturbance (limb paresthesias, abdominal or chest banding [dysesthesia]), or brainstem syndromes (intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance) (**Table 1**). Objective findings that may be present on neurologic examination include afferent pupillary defect, impaired sensation, motor weakness, ataxia, and gait impairment often in the context of hyperreflexia. A clinical attack or relapse in MS is defined as a single clinical episode with symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection.

Diagnosis

The diagnosis of MS is based on a combination of clinical findings, imaging, and laboratory data using the current diagnostic criteria known as the Revised McDonald Criteria (**Table 2**; **Box**).[14] The diagnosis of MS is defined by the demonstration of dissemination of MS disease characteristics in space and time. Dissemination in space refers to the presence of lesions in distinct CNS anatomical locations including infratentorial, juxtacortical, cortical, periventricular, and spinal cord. These lesions can be identified either through multiple clinical events implicating different areas in the CNS, multiple T2-hyperintense lesions on MRI, or both. Dissemination in time refers to the development of new lesions over time. MRI can demonstrate dissemination in time through the simultaneous presence of gadolinium-enhancing (acute) and nonenhancing lesions (chronic) at one time or development of a new T2 lesion on follow-up MRI. Dissemination in time can also be defined by multiple distinct clinical attacks. In patients with a single clinical attack, the presence of cerebrospinal fluid–specific oligoclonal bands can also fulfill the criterion of dissemination in time, because it reliably indicates intrathecal antibody synthesis and is associated with higher risk of a second attack.[14] In a prospective cohort of patients (N = 251) with a first classic clinical attack, the sensitivity of the 2017 diagnostic criteria for a clinically definite MS diagnosis was 68% and specificity 61%.[15] In addition to meeting these criteria, alternative diagnoses must be excluded, including other CNS inflammatory conditions (eg, neuromyelitis optica spectrum disorder), systemic inflammatory conditions (eg, sarcoidosis), hereditary disorders (eg, Fabry disease), infections (eg, syphilis), toxic and nutritional disorders (eg, B_{12} deficiency), neoplastic diseases (eg, glioblastoma), and vascular diseases (eg, cerebral infarction). Criteria for primary progressive MS (PPMS) are outlined in Table 2.[14]

Table 1. Multiple Sclerosis Terms and Definitions

Term	Definition	Pathology
Optic neuritis	Characterized by pain with eye movements, decreased color vision, and decreased visual acuity evolving over hours to days	Inflammatory demyelination of the optic nerve
Partial myelitis	Variable presentation depending on area of involvement but can include weakness, extremity and torso impaired sensation, hyperreflexia, and/or ataxia evolving over hours to days	Inflammatory demyelination of a portion of the spinal cord
Brainstem syndrome	Variable presentation depending on area of involvement but can include impaired eye movements (internuclear ophthalmoplegia, sixth nerve palsy), facial sensory loss, vertigo, hearing loss, weakness, impaired sensation evolving over hours to days	Inflammatory demyelination in the brainstem
Lhermitte phenomenon	An acute electric shock sensation that radiates from the neck down the spine or extremities, usually triggered by neck flexion	Demyelination in the dorsal column of the spinal cord
Axonal transection	Severed terminal axonal structures representing the pathologic correlate of irreversible neurologic damage	Occurs in lesions both early and late in the disease
"Pseudo relapse"	Transient worsening or reoccurrence of neurologic symptoms secondary to concomitant medical conditions or environmental factors not representing new disease activity	Not applicable
Attack, relapse, or event	A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h with or without recovery and in the absence of fever or infection	Inflammatory demyelinating lesion occurring in eloquent areas of the CNS
Lesion	An area of hyperintensity on a T2-weighted or proton-density-weighted MRI scan that is at least 3 mm in long axis	Focal area of demyelination and inflammation in the CNS
Dissemination in space	Development of lesions in distinct anatomical locations within the CNS	Not applicable
Dissemination in time	Development or appearance of new CNS lesions over time	Not applicable

Abbreviation: CNS, central nervous system.

Natural History

MS is a chronic condition with a variable course. Relapsing-remitting MS (RRMS) starts with clinical relapses with near or complete recovery, but over time recovery may be incomplete, and disability often accumulates. Approximately 20% of patients with RRMS develop progressive neurologic decline later in the disease and transition to secondary progressive MS (SPMS).[16] A small proportion of individuals (15%) have progression from onset defined as PPMS. Prior to the availability of current DMTs, natural history cohort studies of people with RRMS and PPMS reported a median time from onset to requiring a walking aid of 20 and 7 years, respectively.[17,18] In untreated RRMS, a second clinical attack typically occurs within the first 2 years, and the median time to conversion to SPMS from onset is 15 years.[19] In a recent cohort of 517 individuals treated with DMTs, 10.7% (95% CI, 7.2%-14%) of individuals with RRMS needed a walking aid and 18.1% (95% CI, 13.5%-22.5%) of individuals with RRMS transitioned to SPMS after a median of 16.8 years from disease onset.[16] Life expectancy was estimated to be 75.9 years in an MS population vs 83.4 years in a matched population.[20]

Disease Outcomes

Disease activity and progression are typically measured by relapses, MRI activity, and short-term progression of disability. A relapse is defined as new or worsening neurologic symptoms such as weakness, sensory disturbances, and gait impairment persisting 24 hours or longer in the absence of fever or infection to rule out "pseudo relapses." Disability progression is measured by the Expanded Disability Status Scale and components of the Multiple Sclerosis Functional Composite (timed 25-foot walk, 9-hole peg test, low-contrast visual acuity, symbol digit modalities test).[21,22] In addition to clinical measures, radiographic measures of disease progression include the development of new T2 lesions, enlarging T2 lesions, or both. An analysis of 31 randomized clinical trials for treatment in RRMS showed a relation between treatment effects on MRI lesions and relapses (slope = 0.52; R^2 = 0.71), indicating that the effect of treatment on relapses was associated with changes in MRI lesions.[23] In clinical practice, MRIs are important for identifying subclinical disease activity and monitoring the efficacy of DMTs.[23]

Table 2. 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis[a]

No. of clinical attacks	No. of MRI lesions with objective clinical evidence[a]	Additional data needed for diagnosis of multiple sclerosis
Relapsing-remitting multiple sclerosis		
≥2	≥2	None[b]
≥2	1[c]	None
≥2	1	DIS demonstrated by an additional clinical attack implicating a different CNS Site or by MRI
1	≥2	DIT demonstrated by additional clinical attack, MRI, or CSF-specific oligoclonal bands
1	1	DIS demonstrated by additional clinical attack implicating a different CNS site or by MRI *and* DIT demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands
Primary progressive multiple sclerosis		
Required: 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse Plus 2 of the following: 1 or more T2-hyperintense lesions characteristic of multiple sclerosis in 1 or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial; 2 or more T2-hyperintense lesions in the spinal cord; presence of CSF-specific oligoclonal bands		

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; MRI, magnetic resonance imaging.

[a] Adapted with permission from *Lancet Neurology*.[14]

[b] Although no MRI is required for the diagnosis, an MRI scan of the brain should be obtained in all patients with a suspected diagnosis of MS unless not possible.

[c] One lesion as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location.

Box. Common Questions Regarding Diagnosis and Treatment of Multiple Sclerosis (MS)

How Is Multiple Sclerosis Diagnosed?

The diagnosis of MS is based on a combination of clinical findings, imaging, and laboratory data using the current diagnostic criteria known as the Revised McDonald Criteria.[14] The diagnosis of MS is defined by the demonstration of dissemination of MS disease characteristics in space and time. Dissemination in space refers to the presence of lesions in distinct CNS anatomical locations including infratentorial, juxtacortical, cortical, periventricular, and spinal cord. Dissemination in time refers to the development of new lesions over time. MRI can demonstrate dissemination in time through the simultaneous presence of gadolinium-enhancing (acute) and nonenhancing lesions (chronic) or development of a new T2 lesion on follow-up MRI. Dissemination in time can also be defined by multiple distinct clinical attacks. In patients with a single clinical attack, the presence of CSF-specific oligoclonal bands can also fulfill the criterion of dissemination in time.

How Should an Initial Disease-Modifying Therapy Be Selected for Relapsing-Remitting Multiple Sclerosis?

Disease-modifying therapies available for relapsing-remitting multiple sclerosis have varying mechanisms of action and routes of administration. These drugs include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and 3 types of monoclonal antibodies. There are 2 main treatment approaches for relapsing-remitting MS that are based on evaluating the risks and efficacy of the disease-modifying therapies. The escalation approach starts with the least-potent medications with relatively few adverse effects, such as interferons or fumarates, and if there is evidence of disease activity the treatment is escalated to a more potent medication. An alternative option is to initiate a medication with greater efficacy, such as ocrelizumab or natalizumab, at the time of diagnosis. Observational data suggest that initial treatment with a higher efficacy medication may be associated with a lower risk of conversion to secondary progressive MS; ongoing randomized trials will provide more definitive data to inform treatment choices.

How Should Patients With Multiple Sclerosis Be Monitored?

People with MS are monitored with neurologic examinations and brain MRI scans, evaluating for new T2 or enhancing lesions. Laboratory monitoring is individualized based on the disease-modifying therapies, symptomatic medications, or both.

Abbreviation: CNS, central nervous system; MRI, magnetic resonance imaging.

Treatment

Overview of Treatment

Treatment of MS includes DMTs, acute relapse treatment, comorbidity management, symptom control, psychological support, rehabilitative strategies, and lifestyle modifications.

Disease-Modifying Therapies

DMTs for MS decrease the frequency of relapses and reduce short-term disability. The first DMT, interferon beta-1b, was approved by the FDA in 1993. Prior to approval of interferon beta-1b, several broad-spectrum immunosuppressive options were used including azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and corticosteroids. Effectiveness of these older therapies was based on studies that were not definitive because of small sample sizes. Currently, these therapies are less frequently prescribed now that DMTs are available.

Mitoxantrone, a type II topoisomerase inhibitor, was approved in 2000 for RRMS and SPMS but causes a dose-dependent cardiac toxicity (congestive heart failure). Mitoxantrone has been largely replaced by DMTs with similar efficacy, such as natalizumab, with better safety profiles. Currently available DMTs have a range of mechanism of actions, administration routes, and degrees of efficacy. All DMTs modulate the immune system through mechanisms that include sequestration of lymphocytes, T_H1/T_H2 shift, interference with DNA synthesis in lymphocytes, depletion of immune cells, and/or changes in cytokine secretion pattern (**Figure**). Although some medications such as the monoclonal antibodies and S1P receptor modulators have a well-defined mechanism of action, for others, the mechanism remains poorly defined. S1P modulators bind 1 of the 5 subtypes of S1P receptors resulting in internalization of the receptor and sequestration of lymphocytes in lymph nodes. Cladribine is a purine analogue taken up into rapidly proliferating cells such as lymphocytes and incorporated into DNA, leading to cell death. CD20 monoclonal antibodies (ocrelizumab) selectively bind B cells that express the CD20 antigen, leading to cell destruction by complement dependent cytotoxicity as well as antibody-dependent, cell-mediated cytotoxicity. Natalizumab is a monoclonal antibody that selectively binds α_4 integrin subunit expressed on the surface of lymphocytes, preventing the entry of lymphocytes into the CNS. Alemtuzumab is a monoclonal antibody that selectively binds CD52 antigen on lymphocytes, leading to lymphocyte depletion.

The primary mechanism of action for all DMTs is thought to be diminishing neuroinflammation. Some DMTs may also slow the underlying neurodegenerative process (eg, brain atrophy), but data are limited and the effect is not as robust as the effect on neuroinflammation. For these reasons, all of the discussed DMTs are approved to treat RRMS or active SPMS, which are thought to have more inflammatory disease activity. PPMS has less neuroinflammation and more neurodegeneration. The only DMT approved for treatment of PPMS is ocrelizumab. Ocrelizumab is hypothesized to treat progressive disease by reducing B-cell–mediated inflammation that may lead to neurodegeneration. The recent discovery of meningeal B-cell follicles in SPMS suggests that B cells may play a more significant role in progressive disease, potentially explaining the benefit seen with B-cell–depleting treatments.[24]

Efficacy, Safety Profile, and Adverse Effects

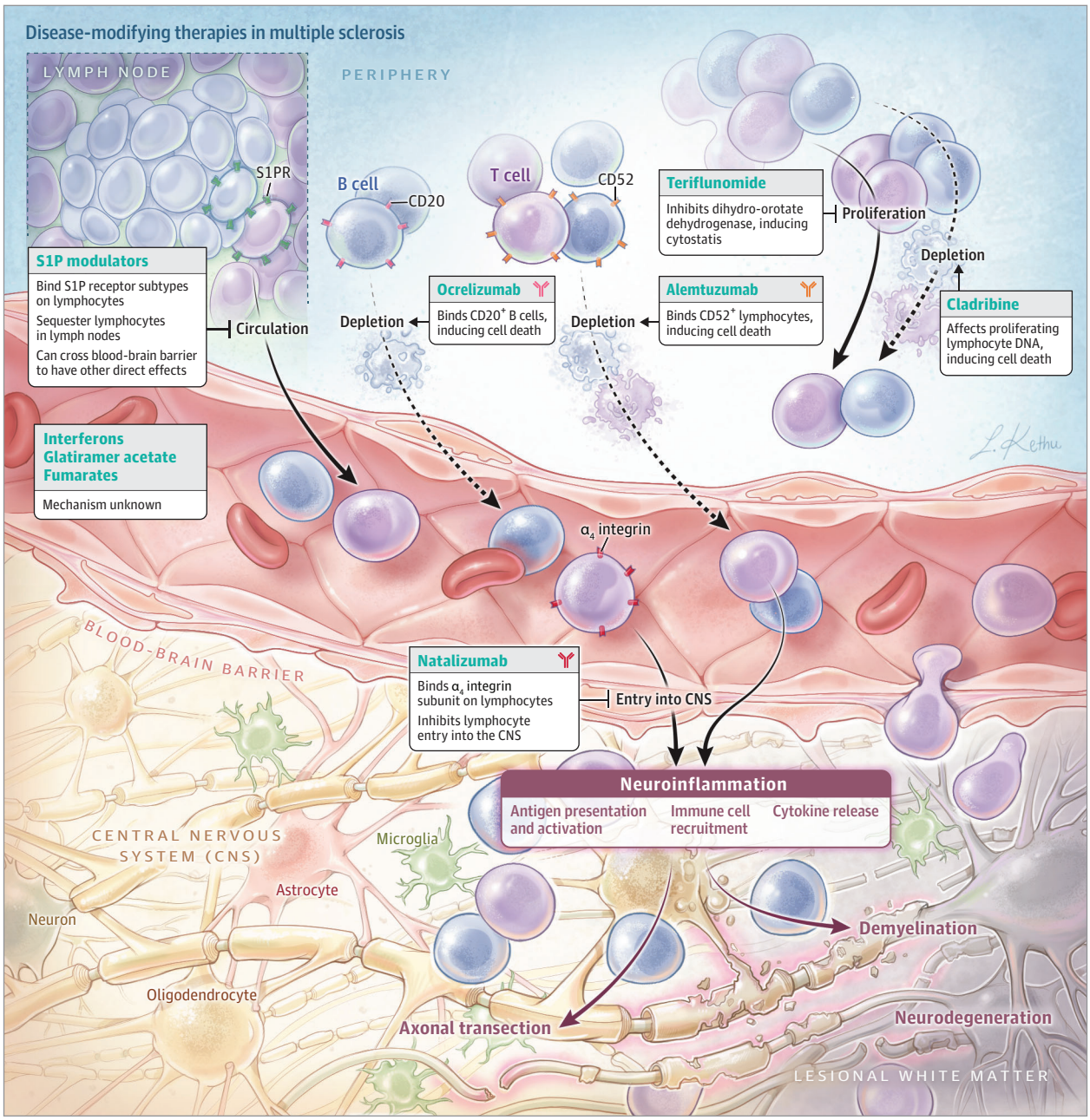
The primary outcome for all phase 3 clinical trials of DMTs was the annualized relapse rate of MS. However, relapse rates varied by the population studied and the period when trials were conducted; therefore, absolute relapse rates should be interpreted with caution.[25]

Adverse effects of DMTs are listed in **Table 3**. Monitoring for adverse effects is needed for DMTs. Some (natalizumab and alemtuzumab) require a specific risk evaluation mitigation strategy (see below). Because of their effects on the immune system, most DMTs are associated with an increased risk for infection, typically urinary tract infections, upper respiratory tract infections, and pneumonias (Table 3).

Injectable DMTs

Injectable medications (interferons, glatiramer acetate) reduce the relapse rate by 29% to 34% compared with placebo.[26-29,31] They are

Figure. Treatment Targets of Disease-Modifying Therapies Currently Approved for Multiple Sclerosis



Ocrelizumab selectively bind B cells that express the CD20 antigen and alemtuzumab selectively binds CD52 antigen on lymphocytes, leading to cell death. Natalizumab selectively binds α_4 integrin subunit on lymphocytes, preventing entry into the central nervous system (CNS). Sphingosine 1-phosphate (S1P) modulators selectively bind S1P receptor (S1PR) subtypes, resulting in internalization of the receptor and leading to sequestration of the lymphocytes in the lymph nodes. S1P modulators are also able to cross the blood-brain barrier, where they may have other direct effects. Teriflunomide inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase, impairing pyrimidine synthesis, resulting in a cytostatic effect on proliferating lymphocytes. Caldribine is a purine analogue that is taken up into rapidly proliferating cells such as lymphocytes and incorporated into DNA, leading to cell death. Several classes of disease-modifying therapies (fumarates, glatiramer acetate, interferons) have less well-understood mechanisms.

generally considered to be safer than alternative therapies, owing to a lower incidence rate of infections compared with oral and infusion therapies (8.9 per 1000 person-years for injectables, vs 14.3 for fingolimod vs 11.4 for natalizumab vs 19.7 for rituximab),[47] but have limitations of frequent injections (daily to every 2 weeks) and adverse effects of injection site reactions and flu-like symptoms.

Oral DMTs

Oral medications (S1P modulators, fumarates, teriflunomide) vary in their effects on relapse reduction from 36% to 58% over 2 years.[32,34,36-39,48] The S1P receptor modulators (fingolimod, siponimod, ozanimod) are administered once daily, and their main adverse effects such as bradycardia and heart block are a result of initial

Table 3. Disease-Modifying Therapies for Multiple Sclerosis

Medication category, medication	Reduction of annualized relapse rate, % (sample size)	Absolute relapse rate reduction difference[a]	Route and frequency of administration	Required baseline testing	Required monitoring	Recommended additional testing	Common adverse effects	Rare serious adverse effects
Interferons								
Interferon beta[26-29b]	34% (n = 372)[26] 32% (n = 172)[30] 28% (n = 1516)[28] 32% (n = 560)[27]	0.41 0.15 0.141 0.83	Subcutaneously every other day or ×3/wk; intramuscularly once a wk or every 2 wk[c]	CBC with differential and liver function	CBC with differential and liver function every 6 mo	None	Headache (44%-65%) Flu-like symptoms (47%-57%) Injection site reaction (8%-89%) Leukopenia (7%-28%)	Liver toxicity
Amino acid copolymer								
Glatiramer acetate[31]	29% (n = 251)	0.25	Subcutaneously daily or ×3/d	None	None	CBC with differential and liver function	Injection site reaction (8%) Immediate postinjection reaction (2%-16%)	Skin necrosis
S1P receptor modulators								
Fingolimod[32]	54% (n = 1272)[32] 52%[d] (n = 1153)[33]	0.22 0.17	Oral once daily	CBC with differential, liver function, VZV antibodies, fundus examination, ECG, FDO[e]	Fundus examination 3-4 mo after initiation, CBC with differential and liver function every 6 mo	Skin examinations[f]	Headache (25%) Liver enzyme elevation (15%) Back pain (10%) Hypertension (8%)	Infections, PML, macular edema, liver toxicity, PRES, hypertension, bradyarrhythmia, heart block, respiratory effects
Siponimod[34]	55% (n = 1651)	0.09	Oral once daily[g]	*CYP2C9* genotype, CBC with differential, liver function, VZV antibodies, fundus examination, ECG, FDO[h]	None	CBC with differential and liver function every 6 mo	Headache (15%) Hypertension (13%) Liver enzyme elevation (11%)	Bradycardia, heart block, liver toxicity, macular edema, respiratory effects
Ozanimod[35]	48% (n = 1346)[35] 38% (n = 1313)[48]	0.18 0.17	Oral	None	None	CBC with differential and liver function every 6 mo	Upper respiratory tract infection (26%) Liver enzyme elevation (10%) Orthostatic hypotension (4%) UTI (4%) Back pain (4%) Hypertension (4%)	Bradycardia, heart block, liver toxicity, macular edema, respiratory effects
Fumarates								
Dimethyl fumarate[36,37] Diroximel fumarate[38]	44%[d] (n = 1417)[36] 53% (n = 1234)[37]	0.18 0.19	Oral twice daily	CBC with differential, liver function	CBC with differential every 6 mo	Liver function annually	Skin flushing (40%) Diarrhea (14%) Nausea (12%) Abdominal pain (18%) Vomiting (9%)	Infections, liver toxicity, lymphopenia, PML

(continued)

Table 3. Disease-Modifying Therapies for Multiple Sclerosis (continued)

Medication category, medication	Reduction of annualized relapse rate, % (sample size)	Absolute relapse rate reduction difference[a]	Route and frequency of administration	Required baseline testing	Required monitoring	Recommended additional testing	Common adverse effects	Rare serious adverse effects
Pyrimidine synthesis inhibitor								
Teriflunomide[39,40]	31% (n = 1088)[39]	0.17	Oral once daily	CBC with differential, liver function, PPD or QFT, blood pressure	Liver function monthly for first 6 mo then every 6 mo	CBC with differential every 6 mo	Headache (16%) Increased liver enzymes (15%) Diarrhea (14%) Nausea (11%) Alopecia (13%)	Hepatotoxicity, teratogenicity
Purine analogue								
Cladribine[41]	58% (n = 1326)	0.19	Two oral treatment courses 12 mo apart	CBC with differential, liver function, VZV antibodies, HIV, PPD and QFT, hepatitis panel, age-appropriate cancer screening	Age-appropriate cancer screenings, CBC with differential 2 and 6 mo after starting each course; if lymphocyte count <200/μL, monitor monthly until month 6	None	Upper respiratory tract infection (38%) Headache (25%) Lymphopenia (24%) Nausea (10%) Back pain (8%)	Malignancy, teratogenicity, pulmonary tuberculosis, herpes infections, PML
Anti-α_4 integrin receptor monoclonal antibody								
Natalizumab[42]	68% (n = 942)[42]	0.5	Intravenously once every 4 wk	CBC with differential, liver function, JCV serology, brain MRI	JCV serology every 3-6 mo, brain MRI every 6-12 mo for JCV-seronegative patients	CBC with differential and liver function every 6 mo; antinatalizumab neutralizing antibodies at 6 mo	Headache (38%) Fatigue (27%) Arthralgia (19%) Abdominal discomfort (11%) UTI (21%) Lower respiratory tract infection (17%)	PML, hepatotoxicity, herpes infections, hypersensitivity reactions
Anti-CD20 monoclonal antibodies								
Ocrelizumab[43]	46% (n = 821) 47%[d] (n = 835)	0.13 0.13	Intravenously once every 6 mo	CBC with differential, liver function, hepatitis panel	None	PPD or QFT at baseline, CBC with differential and liver function annually	Infusion reactions (34%) Upper respiratory tract infections (40%) Herpes infections (6%)	Hepatitis B reactivation, PML, malignancy risk potential
Ofatumumab[44]	51% (n = 927) 59% (n = 955)	0.11 0.15	Subcutaneously monthly after initial load	Hepatitis panel, serum immunoglobulins	None	PPD or QFT at baseline, CBC with differential and liver function annually	Infections (51.6%) Injection reaction (20.2%) Headache (13.3%)	Hepatitis B reactivation, PML, reduction in immunoglobulins

(continued)

Table 3. Disease-Modifying Therapies for Multiple Sclerosis (continued)

Medication category, medication	Reduction of annualized relapse rate, % (sample size)	Absolute relapse rate reduction difference[a]	Route and frequency of administration	Required baseline testing	Required monitoring	Recommended additional testing	Common adverse effects	Rare serious adverse effects
Anti-CD52 monoclonal antibody								
Alemtuzumab[45,46]	55%[d] (n = 563)[45] 49% (n = 628)[46]	0.21 0.26	Intravenously, 2 courses 12 mo apart	CBC with differential, creatinine, thyrotropin, ALT, AST, hepatitis panel, VZV antibodies, PPD or QFT, urinalysis	CBC with differential, creatinine, and urinalysis every mo until 48 mo after last drug dose; thyrotropin every 3 mo until 48 mo after last drug dose, skin examination annually	HIV at baseline, liver function, gynecologic examination/HPV screening annually	Rash (53%) Headache (52%) Infusion reactions (92%) Thyroid disorder (34%) Infection (71%) Herpes infection (16%)	Autoimmune conditions (ITP, antiglomerular basement membrane disease, hepatitis), HPV infection, stroke, TB, PML, malignancy risk potential

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood cell count; ECG, electrocardiogram; FDO, first-dose observation; HPV, human papillomavirus; ITP, immune thrombocytopenia; JCV, John Cunningham virus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; PPD, purified protein derivative; PRES, posterior reversible encephalopathy syndrome; QFT, QuantiFERON-TB Gold; S1P, sphingosine 1-phosphate; TB, tuberculosis; UTI, urinary tract infection; VZV, varicella zoster virus.

[a] Absolute relapse reduction value, along with a number-needed-to-treat analysis, should be interpreted with caution because of the variable of relapses.

[b] Includes interferon beta-1a, interferon beta-1b, peginterferon beta-1a.

[c] Frequency and route of administration dependent on interferon.

[d] Trial had an active comparator.

[e] All patients must have an FDO that includes observation after taking the first dose for at least 6 hours, with pulse and blood pressure assessment hourly and ECG prior to dosing and at end of observational period.

[f] Increased risk of basal cell carcinoma and melanoma.

[g] Target dose and titration depends on *CYP2C9* genotype.

[h] FDO only required in patients with a cardiac history.

[i] Fundus examination only required for patients with a history of diabetes mellitus and uveitis that increase the risk of macular edema.

activation of the S1P receptor. In subsequent dosing, the S1P modulator acts as a functional antagonist, leading to downregulation of the receptors.[32,34,35] Each S1P modulator selectively binds the 5 S1P receptor subtypes with varying affinity. Interaction with the subtype 1 receptor on cardiac myocytes may result in first-dose bradycardia (0.5%-4%) and heart block (1.2%-3%). S1P modulators are associated with an increased risk of herpetic infections (2.1%-8.7%), increased liver enzyme levels (10%-15%), and macular edema (1.6%-2%) due to increased vascular permeability (1.6%-2%). Therefore, ophthalmologic examination of the fundus for macular edema is required before initiating fingolimod. Disseminated varicella infection has been documented (1 death in a phase 3 trial of disseminated varicella).[33] Patients treated with S1P modulators should undergo monitoring with a complete blood cell count; measurement of serum transaminase (alanine aminotransferase and aspartate aminotransferase) and total bilirubin levels; testing for varicella zoster virus (VZV) antibodies; and electrocardiogram prior to initiation. If a patient tests negative for VZV antibodies, it is recommended to delay start until the patient receives vaccination against VZV.

For fingolimod, all patients require first-dose observation, typically in an outpatient clinic or the patient's home for at least 6 hours with pulse and blood pressure assessment hourly to detect severe bradycardia and heart block. For siponimod, a first-dose observation is recommended for patients with a cardiac history (sinus bradycardia, first- or second-degree atrioventricular block, or a history of myocardial infarction or heart failure) and an ophthalmologic examination is required for macular edema. *CYP2C9* genotype testing is required prior to initiation to determine titration and dosing schedule based on the patient's ability to metabolize the medication. For ozanimod, an ophthalmologic assessment is recommended for individuals with a history of uveitis or macular edema.

The most common adverse effects associated with the fumarates (dimethyl fumarate and diroximel fumarate) are skin flushing and gastrointestinal disturbances. Monitoring is required for lymphopenia less than 0.5×10^9/L (6%). An adverse effect with teriflunomide is hepatotoxicity (ALT level >3 times upper limit of normal [6%]); therefore monthly hepatic testing for the first 6 months is required.[40] Tuberculosis has occurred during treatment with teriflunomide; therefore tuberculosis screening is required prior to initiation. Cladribine has several common adverse effects, primarily infections, and may increase risk of malignancy (pancreatic carcinoma, malignant melanoma, ovarian cancer). Therapy initiation should begin with two 4- to 5-day consecutive day treatment courses.[41] Cladribine should not be started in patients with hepatitis B because of risk of hepatitis B reactivation (occurred in 1 of 806 clinical trials participants [0.2%]). Tuberculosis testing is required because of rare pulmonary tuberculosis.

Progressive multifocal leukoencephalopathy (PML) may occur because of reactivation of the John Cunningham virus (JCV) that can lead to CNS infection due to decreased immune surveillance in immunocompromised states. PML can present with a variety of progressive symptoms over days to weeks, including weakness, vision changes, impaired

memory, confusion, and personality changes and corresponding T2/fluid-attenuated inversion recovery lesions on MRI scan. Fingolimod and dimethyl fumarate have been rarely associated with PML in MS. Cases of PML have been reported among patients receiving cladribine for oncologic indications.

Monoclonal Antibody DMTs

Monoclonal antibody infusions (natalizumab, ocrelizumab, ofatumumab, alemtuzumab) have higher efficacy than injectable and oral DMTs and reduce relapse rate by 68% (absolute reduction, 0.5) compared with placebo and by 46% to 59% (absolute reduction, 0.11-0.26) compared with active comparators (interferon beta-1a).[43,45,46] All of these therapies can cause infusion reactions characterized by headache, nausea, urticaria, pruritus, and flushing, which can be mitigated by premedications including antihistamines, antipyretics, and steroids. Infusion reactions are less common for natalizumab (24%) compared with ocrelizumab (34%-40%) and alemtuzumab (92%). Alemtuzumab is associated with autoimmune adverse effects.[45,46,49] These include frequent (40%) thyroid conditions (hypothyroidism and hyperthyroidism) and more serious rare conditions including immune thrombocytopenia (3.2%) and antiglomerular basement membrane disease (0.2%).[49] There has been postmarking reports of cerebrovascular events (13 reported to the FDA since 2014). Because of these potential adverse effects, there is a Risk Evaluation and Mitigation Strategy (REMS) program for alemtuzumab, with monthly laboratory monitoring required until 48 months after the last drug dose to facilitate timely detection of autoimmune conditions.[50] A REMS is a drug safety program required by the FDA to ensure the benefits from a drug outweigh the risks. The most serious risk for treatment with natalizumab is PML. Among patients who take the drug for longer than 24 months, the risk is estimated to be 0.09 cases per 1000 in JCV-seronegative patients and 2 per 1000 among JCV-seropositive patients.[51] The risk can be further stratified based on the index level of JCV, prior immunosuppressant use, and number of years receiving treatment. Natalizumab has a REMS program that includes every 6-month JCV serology testing and monitoring for signs and symptoms of PML. There have also been reports of PML with alemtuzumab.[52] Herpetic infections are common (16%)[45,46] with alemtuzumab; therefore, herpetic prophylaxis with acyclovir (200 mg twice daily) is required starting on the first day of dosing and continuing for a minimum of 2 months after therapy completion or until the $CD4^+$ lymphocyte count is more than 200/μL.[45,46] Ocrelizumab and natalizumab are associated with less than a 10% risk of herpetic infection; prophylaxis is not required but under certain circumstances may be offered (eg, lymphocyte count <0.5/μL). Hepatitis B reactivation has occurred with other CD20 monoclonal antibodies, alemtuzumab, and in 1 participant in a cladribine clinical trial of 806 participants. Therefore ocrelizumab and alemtuzumab are not prescribed for individuals with hepatitis B.[43,45,46] Pulmonary tuberculosis is a rare infection with alemtuzumab (0.3%). Tuberculosis testing prior to initiation is recommended.

Treatment Strategy

There are 2 main treatment approaches for RRMS that are based on evaluating the risks and efficacy of the DMTs. Historically, the most common treatment approach was escalation, starting with the least potent medications with relatively few adverse effects. People with MS are monitored with neurologic examinations and MRIs; if there is evidence of disease activity with treatment or breakthrough disease (eg, relapse or MRI activity), treatments are escalated to a more potent medication. This approach minimizes risks but may result in undertreatment, defined as breakthrough disease and accumulated disability. An alternative option is to initiate a medication with greater efficacy at the time of diagnosis. The rationale for this treatment approach is to provide better relapse control and delay accumulation of disability. However, a limitation of this approach is that patients are exposed to higher risks of adverse events and some patients may not require such intensive treatment. Observational data suggest that initial treatment with a higher-efficacy medication may be associated with a lower risk of conversion to SPMS; ongoing randomized trials will provide more definitive data to inform treatment choices.[53]

Relapse Treatment

The primary role of DMTs is to prevent relapses and future disability. However, none of the DMTs suppress all relapses. If relapse symptoms are mild and do not impair function, treatment not be necessary. For moderate or severe relapses, first-line treatment is typically high-dose systemic steroids (intravenous methylprednisolone [500 mg-1000 mg]) for 3 to 5 days to accelerate relapse recovery. A randomized noninferiority trial concluded that oral therapies were noninferior to intravenous steroids for clinical improvement of MS and had a similar safety profile for relapse treatment.[54] If relapses are severe and refractory to steroids, treatment with plasma exchange may be warranted.[55]

DMT Treatment Duration

Once an individual has started a DMT, the treatment is lifelong unless breakthrough disease or adverse effects occur that require a medication switch. Several observational studies have suggested that older individuals receiving injectable or oral DMTs who have been stable clinically and radiographically for an extended period (≥4 years) have a low reoccurrence of disease activity and may benefit from treatment discontinuation.[56,57] An ongoing randomized trial (DISCO-MS [NCT03073603]) is evaluating whether discontinuing therapy in patients with "nonactive" disease is beneficial.

Pregnancy and Breastfeeding

Women are often diagnosed with MS during childbearing years; therefore, pregnancy and breastfeeding are important considerations regarding treatment. In a prospective study that followed up 254 women with MS through pregnancy, mean relapse rates (not receiving DMT) were significantly lower during the first and third trimesters of pregnancy compared with the year prior to pregnancy (0.7 [SD, 0.9] per woman per year in the year before pregnancy vs 0.5 [SD, 1.3] during the first trimester [$P = .03$] and 0.2 [SD, 1.0] during the third trimester [$P < .001$]).[58] The mean rate was not significantly different, compared with prior to pregnancy, in the second trimester (0.6 [SD, 1.6], $P = .17$). The mean rate of relapse increased during the first 2 months postpartum to 1.2 (SD, 2.0) ($P < .001$); however, only 28% of participants experienced a relapse.

Several studies have suggested that prepregnancy DMT use may decrease postpartum relapse rates.[59] A recent meta-analysis that

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 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.

included 7034 pregnancies in 6430 women showed a similar association. Prepregnancy DMT use was associated with annualized relapse rate decreasing from 0.57 (95% CI, 0.45-0.70) before pregnancy to 0.36 (95% CI, 0.28-0.44) during the first trimester, 0.29 (95% CI, 0.21-0.36) during the second trimester, and 0.16 (95% CI, 0.11-0.21) during the third trimester, with a postpartum rebound to 0.85 (95% CI, 0.70-1.00).[60] All DMTs except glatiramer acetate should be discontinued at least 4 months prior to conception (this duration depends on the medication). Birth control should be used during receipt of DMT.[59] It is imperative to discuss pregnancy planning early in the treatment course. When relapse occurs during pregnancy, steroids should be avoided during the first trimester because of the potential risk of cleft palate.[61]

The effect of breastfeeding on relapse rate is not well-defined, but available evidence from 1 meta-analysis found that breastfeeding was associated with lower risk of a postpartum relapse (odds ratio, 0.63 [95% CI, 0.45-0.88]; $P = .006$).[62] Breastfeeding is not recommended while receiving DMTs, with the possible exception of the injectable therapies, as many DMTs are found in breast milk and are potentially harmful to infants.[63] Gadolinium contrast should be avoided during pregnancy.

Comorbidities

In people with MS, comorbidities (eg, psychiatric and cardiovascular) and other health behaviors (eg, tobacco use) are associated with increased disability, MRI changes such as lower brain volume, increased mortality, and decreased quality of life.[64,65] These may be due to direct biological effects such as accelerated neurodegeneration, decreased neuronal repair, and increased peripheral immune activation, or to indirect effects such as delay in diagnosis, added morbidity, and altered treatment responses.[64,66] Therefore, specific interventions such as smoking cessation, hypertension management, and overall health maintenance are important (**Table 4**).

Psychiatric disorders (depression and anxiety) are more common in people with MS (21%-50%), and prevalence estimates are 2 to 3 times higher than the general population.[67] Despite the high prevalence of these psychiatric disorders, these patients are still at risk for underdiagnosis and undertreatment.[68] Treatment is associated with improved mood and quality of life in people with MS and may improve DMT adherence.[91]

Vascular comorbidities such as hyperlipidemia, hypertension, heart disease, diabetes, and peripheral artery disease can lead to worse outcomes in MS. In 1 study (N = 8983), 1 or more vascular comorbidities at the time of diagnosis was associated with an increased risk of ambulation disability (hazard ratio, 1.51 [95% CI, 1.41-1.61]; absolute data not reported). In the same study, the median time between diagnosis and need for ambulatory assistance was 18.8 years in patients without and 12.8 years for those with vascular comorbidities.[64] The mechanism of vascular comorbidities accelerating disability is likely multifactorial because of increased peripheral inflammation, increased inflammatory responses in the brain, increased abundance of oxidative stress, disruption of cerebral endothelial cells, hypoperfusion/ischemia, and blood brain barrier dysfunction.[64,92] Treatment of these comorbidities has not extensively been tested in MS with regard to improving MS disease outcomes.

Lifestyle Modifications

Lifestyle modifications may reduce comorbidities and improve outcomes. Based on observational data and a small pilot study,

physical activity is associated with improved symptoms and anti-inflammatory effects and may be associated with larger brain volume.[65,93] In 1 randomized clinical pilot exercise intervention study (N = 42), significant improvements in fitness as measured by peak oxygen consumption and 6-minute walk distance, as well as improvements in depression symptoms, fatigue, and tested verbal learning and memory, were observed.[93] While the evidence for physical activity improving outcomes in MS is currently based on small trials and observational data, there is little risk to the patient and physical activity can add a nonpharmacologic approach to a patient's treatment regimen. Currently there is no high-quality evidence to support dietary modification to improve MS outcomes. Likewise, vitamin D supplementation is often recommended, but there are no clinical trials to support improved MS outcomes with supplementation.

People with MS should be encouraged to remain active in intellectually challenging activities, since these activities are associated with improved cognitive function.[94] Cigarette smoking cessation is important in people with MS because smoking may be associated with a worse prognosis.[95]

Symptomatic Treatment

Management of symptoms including spasticity, pain, fatigue, cognitive impairment, bladder and bowel issues, gait dysfunction, mood dysregulation, and sleep disturbance is integral in treatment (Table 4). Treating these symptoms should include a combination of pharmacological and nonpharmacological treatments. Spasticity is a commonly reported symptom in MS, defined as a velocity-dependent increase in muscle tone.[77] Like spasticity, chronic pain including dysesthesias, back pain, tonic spasms, Lhermitte phenomenon (an acute electric shock sensation that radiates from the neck down the spine or extremities, usually triggered by neck flexion), visceral pain, and trigeminal neuralgia are common.[96] The pathophysiology of pain is multifactorial, including disease-related central pain from corticospinal disinhibition, activation of nociceptive afferents, and consequences of the disease, such as spasticity.[96]

Fatigue and cognitive dysfunction can be a direct effect of MS or due to secondary causes such as depression or sleep-related disorders. Fatigue is often considered the most debilitating symptom, leading to loss of employment and impairment of activities of daily living.[97] Fatigue primarily due to MS can persist or be sporadic and tends to worsen with heat.[97] Cognitive dysfunction in MS often affects verbal memory, recall, and abstract reasoning and can include impaired linguistic functioning.[83] In 1 cohort study of early-onset MS (N = 45), 56% of patients with MS were cognitively impaired after 10 years.[83] Neurogenic lower urinary tract dysfunction presenting as urgency, incontinence, and frequency is common, and pharmacologic therapies target detrusor overactivity. However, these medications should be prescribed cautiously in patients with cognitive dysfunction, as they can exacerbate confusion and somnolence. People with MS often experience worsening of symptoms when exposed to heat; thus, temperature control—including ensuring access to air conditioning; avoiding hot tubs, saunas, and hot showers; and the use of cooling vests during warmer weather—may be an important aspect in improving MS-related symptoms.[98]

Because of the broad and complex nature of comorbidities and symptoms related to MS, the authors recommended that patients with MS be followed up by a team of health care providers to achieve comprehensive care, including a neurologist; primary care physician; physical, occupational, and speech therapists; psychologist; urologist; and specialists in physical medicine and rehabilitation, pain management, and infectious diseases, as needed. No large randomized trials have comprehensively evaluated multidisciplinary care on MS outcomes.

Future Directions

New therapies under evaluation include cell-based (hematopoietic and mesenchymal stem cells) and remyelination therapies with the potential to further improve MS treatment. High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation is not part of routine practice, but there is evidence it may have therapeutic effects. An ongoing clinical trial (BEAT-MS [NCT04047628]) will evaluate the efficacy and safety of this treatment.[99-101] Therapies promoting remyelination have potential to slow or reverse disability. There have been several studies with a variety of compounds (eg, biotin, clemastine, and opicinumab, mesenchymal stem cells) evaluating remyelination potential, but data are limited.[102-106]

Limitations

This review has some limitations. First, some aspects of therapy were not included. Second, few trials have directly compared DMTs. Third, data regarding many aspects of MS care, including management of comorbidities and symptoms, were limited to studies that were not randomized clinical trials.

Conclusions

MS is characterized by physical disability, cognitive impairment, and other symptoms that affect quality of life. Treatment with DMT can reduce the annualized relapse rate by 29% to 68% compared with placebo or active comparator.

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Concept and design: All authors.
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