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ADVANCES IN MULTIPLE SCLEROSIS

ADVANCES IN MULTIPLE SCLEROSIS PRIMER

AUTHORS

Guy J. Buckle, MD, MPH
June Halper, MSN, APN-C, MSCN, FAAN
David J. Rintell, EdD

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SPONSOR

This activity is sponsored through an educational collaboration by the CMSC, NPA, and The France Foundation.

TARGET AUDIENCE

This activity is intended for neurologists, nurse practitioners, physician assistants, nurses, and other health care providers involved in the management of MS.

STATEMENT OF NEED

This education is designed to support optimal diagnosis, treatment, and management of patients with multiple sclerosis.

EDUCATIONAL ACTIVITY LEARNING OBJECTIVES

Upon completion of this course, the participants should be able to:

- Discuss how new information on the immunopathology of MS affects understanding of the disease process
- Employ current information on the use of MRI to improve diagnosis, treatment, and monitoring of patients with MS
- Apply information on new and emerging therapies to the development of individualized management strategies for patients with MS
- Examine the safety, efficacy, and tolerability of new and emerging therapies for the treatment of MS
- Implement strategies for the identification of barriers to patient adherence and develop management strategies that incorporate patient and family education to address these barriers and improve adherence
- Discuss strategies to address common adverse events and injection-related concerns associated with disease modifying therapies in order to improve patient adherence

ACCREDITATION/DESIGNATION STATEMENT

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FACULTY

Guy J. Buckle, MD
Assistant Professor in Neurology
Harvard Medical School
Director of Clinical Care
Brigham & Women's Hospital
Boston, Massachusetts

David J. Rintell, EdD
Clinical Instructor in Psychiatry
Harvard Medical School
Adjunct Professor of the Practice
Brandeis University
Boston, Massachusetts

June Halper, MSN, APN-C, MSCN, FAAN
Chief Executive Officer
Consortium of Multiple Sclerosis Centers and the International Organization of Multiple Sclerosis Nurses
Hackensack, New Jersey

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CHAPTER 1:
What is MS?

EPIDEMIOLOGY AND DEMOGRAPHICS

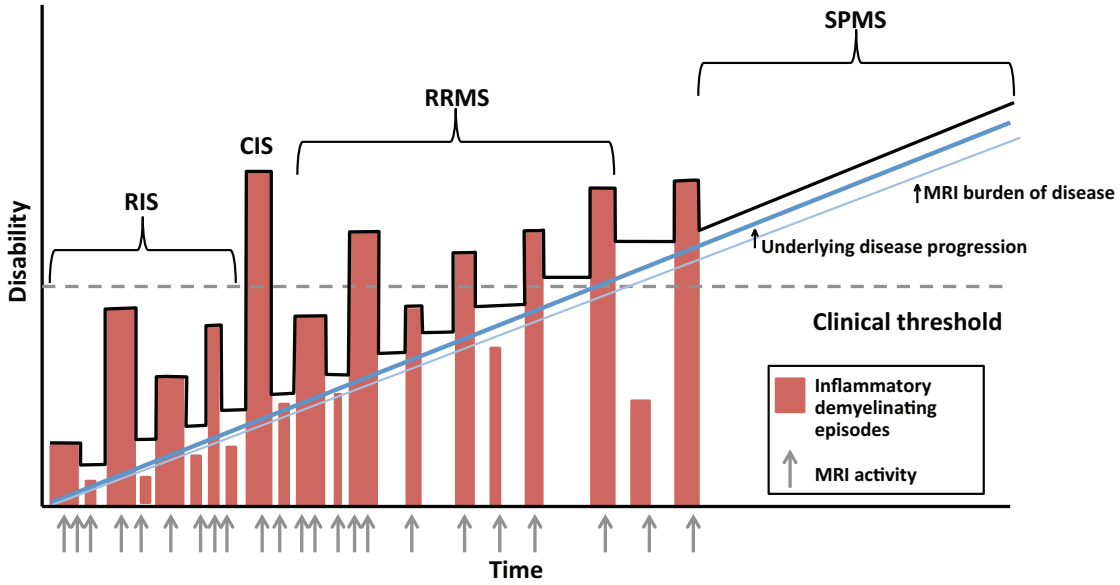
According to the National Multiple Sclerosis Society, more than 2.1 million people worldwide have multiple sclerosis (MS), with over 400,000 persons in the United States affected by this central nervous system (CNS) disorder.[1] MS is typically diagnosed between the ages of 20 and 50; however it can present in children and older adults. More women are affected by MS than men, with a ratio of 2.3 to greater than 3.0, depending on the analysis.[2,3] Susceptibility to MS cannot be attributed to any one specific factor; rather it is likely caused by the interplay of multifactorial elements. There is evidence that environmental and genetic factors influence risk for MS. The incidence and prevalence of MS vary geographically. Higher frequency areas around the globe include Europe, North America, New Zealand, and southeastern Australia; persons of northern European descent have higher risk for MS compared with those of Asian, American Indian, or African heritage. Sunlight exposure, vitamin D, and smoking are additional factors that may impact risk for MS.[4] Risk for the development of MS in first degree relatives is estimated to be one in 40 (compared with one in 750 for an average person in the US).[1] Data from Danish twin studies have shown that the risk for MS in monozygotic twins is 24% compared to 3% for dizygotic twins.[5] Genetic studies have shown an association of MS with major histocompatibility alleles and other non-HLA variants.[6] Many candidate genes thought to affect MS risk are immunologically relevant, related to lymphocyte activation and proliferation, cytokine pathways, co-stimulatory molecules, and signal transduction.[1]

DISEASE COURSE

Inflammation, demyelination, and axonal degeneration contribute to the clinical and imaging features of this chronic, progressive, and disabling disorder. The disease course of MS is quite variable, and is typically categorized as relapsing-remitting, secondary progressive, primary progressive, or progressive-relapsing MS (Figure 1).[8]

superimposed relapses. An initial neurological disturbance lasting more than 24 hours with signs and symptoms consistent with an inflammatory demyelinating disorder (in the absence of fever or infection) is known as a clinically isolated syndrome (CIS).[10] Optic neuritis, a brainstem syndrome, or incomplete transverse myelitis are CIS features typical for MS.[11] The long-term risk

Figure 1: MS Disease Course (adapted from Stys et al)[9]



RIS: radiologically isolated syndrome; CIS: clinically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

The majority of patients with MS (~85%) initially have relapsing-remitting MS (RRMS), which is characterized by distinct relapses followed by periods of remission with no disability progression between attacks. Over time, many patients with RRMS (~50% of those untreated) transition to secondary progressive MS (SPMS) with progressive disability with or without distinct relapses. Approximately 10% of patients with MS have primary progressive (PPMS) disease from the onset, in which functional decline is steady, without acute attacks or periods of remission. Progressive-relapsing MS (PRMS) occurs in a small group of patients (5%), and is characterized by progressive disease from the beginning, with

for conversion to clinically definite MS (CDMS) is higher for those with CIS and abnormal brain MRI findings vs individuals with normal scans. Miller et al defined 5 classes of CIS: 1) clinically monofocal with at least 1 asymptomatic MRI lesion; 2) clinically multifocal with at least 1 asymptomatic MRI lesion; 3) clinically monofocal with normal appearing MRI; 4) clinically multifocal with normal appearing MRI; and the fifth type is now referred to as radiologically isolated syndrome (RIS), in which incidental findings on MRI are suggestive of MS in patients *without* MS symptoms.[12,13] Additional information on CIS and RIS is included in the section on diagnosis and MRI.

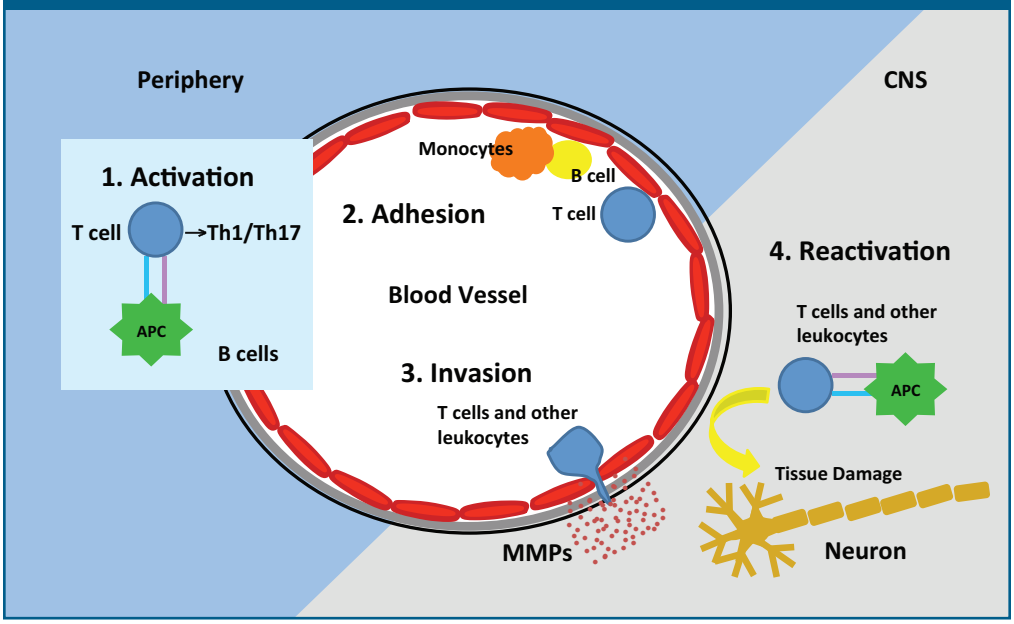
IMPACT ON QUALITY OF LIFE AND ECONOMIC BURDEN OF MS

Not surprisingly, the personal and financial impact of MS is considerable. A recent survey of over 4,500 MS patients conducted in the UK utilized the EQ-5D, a quality of life measure with 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[14] Each of the domains of the EQ-5D has 3 levels, and weighted health indices can be calculated from data collected. Compared with the mean health state of the UK population (82.48), the mean value for MS patients was significantly lower at 59.73.[14] Over 80% of MS patients surveyed indicated that they had difficulty with usual activities, and 76% reported pain/discomfort and mobility problems. Problems in the mobility, self-care, usual activities and pain/discomfort domains were more frequently reported by patients with progressive forms of MS compared with RRMS. The economic burden of MS in the US was estimated in a recent systematic review by Adleman et al.[15] According to their analysis, direct all-cause medical costs for MS ranked second among other chronic conditions; only congestive heart failure was higher. Annual direct costs per patient ranged from ~$16,000-$34,000, with annual indirect costs less than $20,000 (in 2011 dollars).[15] The largest cost drivers were prescription drug costs and indirect costs.

PATHOPHYSIOLOGY

Demyelination, oligodendrocyte loss and axonal/neuronal injury and loss are key features of MS pathology; however the initiating/causative event is unclear. An unresolved question is whether inflammation is initiated in the peripheral immune system ***prior*** to damage in the CNS, or if cytodegeneration occurs first, resulting in the release of highly antigenic myelin debris, and an ensuing inflammatory response follows. In either case, immune cells and inflammatory mediators play a central role in the ongoing damage to CNS structures in MS **(Figure 2)**.

Figure 2: Immunopathogenesis of MS (Adapted from Koch et al)[4]



While this figure is an oversimplified representation, there are a number of key steps thought to be involved in the development of MS lesions. In the periphery (such as in lymph nodes), naïve T cells are activated through interaction with antigen presenting cells in the presence of costimulatory molecules. The proteins that set off this activation sequence may be cross reactive self-antigens, CNS proteins that have been released into the periphery following primary neurodegeneration, or proteins from an infectious agent. These aberrantly reactive T cells differentiate into proinflammatory Th1 and Th17 cells and proliferate; in contrast, numbers of regulatory, anti-inflammatory T cell subsets such as Th2 cells are decreased or have decreased function in MS. Activated T cells, B cells, and monocytes migrate into the CNS through interactions with adhesion molecules on endothelial cells and in the presence of chemokines at the blood brain barrier. Matrix metalloproteinases (MMPs) are up-regulated in MS, which also facilitate transmigration of these inflammatory cells into the CNS. The interaction of myelin-reactive T-cells with antigen presenting cells such as microglia or other inflammatory cells recruited into the CNS such as macrophages, dendritic cells and B cells results in reactivation of T cells. Within the CNS, B cells mature into plasma cells, with local antibody production targeting CNS structures. Damage to myelin, axons, and oligodendrocytes occurs through cell-mediated cytotoxic mechanisms and the release of inflammatory products (oxygen free radicals, nitric oxide, vasoactive amines, complement, proteases, and cytokines).

Disease modifying therapies (DMTs) target various steps of this inflammatory/neurodegenerative process. For example, beta interferons have effects that modulate pro-inflammatory cytokine production and reduce lymphocyte trafficking into the CNS[16]; glatiramer acetate is thought to induce and activate antigen-specific suppressor-type T-cells in the periphery[17]; natalizumab inhibits α4β1-integrin mediated adhesion of leukocytes to VCAM-1 on vascular endothelial cells, preventing migration through the blood brain barrier[18]; fingolimod reduces egress of T-cells from lymph nodes[19]; teriflunomide blocks a key enzyme required for the proliferation of lymphocytes[20]; and dimethyl fumarate appears to induce a Th1 to Th2 shift with a reduction in pro-inflammatory mediators.[21]

DIAGNOSIS

There is no single evaluation or test result that in and of itself can confirm or exclude a diagnosis of MS. MS is a clinical diagnosis, typically supported by MRI findings and additional assessments, and involves exclusion of other conditions/diseases. Typical features of MS and "red flags" ***not*** consistent with a diagnosis of MS are shown in **Table 1**.

Table 1: Features of MS[1,22]

Typical Features of MS	Atypical "Red Flags" for MS
• Relapses and remissions at the outset (in RRMS) • Onset between ages 15 and 50 • Early signs and symptoms of multifocal disease (dissemination in space), such as: – Optic neuritis – Internuclear ophthalmoplegia – Lhermitte's sign – Sensory level (paresthesias, numbness) – Pyramidal tract signs: weakness, spasticity, Babinski sign – Neurogenic bladder • Abnormal brain and/or spinal MRI • Abnormal spinal fluid	• Steady progression at outset (except in PPMS) • Onset before age 10 or after age 50 • Lack of typical symptoms: no problems with vision, bladder, sensation, etc • Abnormality in a single location: no dissemination in space (except in CIS) • Deficit developing within minutes • Gray matter symptoms: dementia, seizures, aphasia • Peripheral CNS symptoms: neuropathy, myopathy, fasciculations • Other diseases present: genetic, systemic • Normal MRI of the brain and spine • Normal spinal fluid

A mnemonic to aid in the differential diagnosis of MS is shown in **Table 2.**

Table 2: Mnemonic for the Differential Diagnosis of MS ('VITAMINS')[1]

V	Vascular	Multiple lacunar infarcts; Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL); spinal arteriovenous malformation
I	Infectious	Lyme disease; syphilis; HIV myelopathy; progressive multifocal Leukoencephalopathy (PML); HTLV-1 myelopathy
T	Traumatic	Spondylotic myelopathy
A	Autoimmune	Neuromyelitis optica; acute disseminated encephalomyelitis; CNS vasculitis; Behcet syndrome; sarcoidosis; systemic lupus erythematosus
M	Metabolic/Toxic	Central pontine myelinolysis; vitamin B12 deficiency; vitamin B6 deficiency; radiation; hypoxia
I	Idiopathic/Genetic	Spinocerebellar degeneration; Friedreich ataxia; Arnold-Chiari malformation; adrenoleukodystrophy; metachromatic dystrophy
N	Neoplastic	CNS lymphoma; glioma; paraneoplastic encephalomyelitis; metastatic cord compression
S	Psychiatric	Somatization disorder

A diagnosis of MS requires clinical evidence of lesions or damage in at least 2 distinct areas of the CNS ('dissemination in space'), evidence that the damage occurred at least 1 month apart ('dissemination in time'), and elimination of other potential diagnoses. Current (2010) McDonald diagnostic criteria for MS are summarized in **Table 3**.

Table 3: 2010 McDonald Diagnostic Criteria for MS[10]

Clinical Presentation		Additional Data Needed for MS Diagnosis
Attacks*	CNS Clinical Lesions	
≥ 2	Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
≥ 2	Objective clinical evidence of 1 lesion	Dissemination in **space**, demonstrated by: • Baseline MRI with ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); OR • Await a further clinical attack implicating a different CNS site
1	Objective clinical evidence of ≥ 2 lesions	Dissemination in **time**, demonstrated by: • Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time on brain MRI; OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; OR • Await a second clinical attack
1	Objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in **space and time**, demonstrated by: ***For DIS:*** • Baseline MRI with ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); OR • Await a second clinical attack implicating a different CNS site; and ***For DIT:*** • Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time on brain MRI; OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; OR • Await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)		1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: • MRI evidence for DIS in the brain based on ≥ 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions • MRI evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

*An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection.

As reflected in the McDonald criteria, MRI is usually critically important in the diagnosis of MS (lesion dissemination in time and space), as well as in ruling out other conditions that may mimic MS. A few basics related to MRI and MS are included in **Table 4**.

Table 4: MRI and MS[1,22]

MRI Image	Description
T1 Weighted images	• MS plaques or lesions appear dark (hypointense) or are not visible (isointense) acutely on non-contrast scans • IV administration of gadolinium (Gd+; MRI contrast agent) allows visualization of areas of acute inflammation in the brain parenchyma resulting from breakdown of the blood-brain barrier; enhancement usually resolves within 2-6 weeks • Gd+ enhancing lesions are a marker of acute inflammatory MS disease activity, even in clinically asymptomatic patients • Persistent (> 6 months) T1 'black holes' are markers of demyelination and significant axonal loss/transection and have better correlation with progressive disability
T2 Weighted/FLAIR* images	• T2 lesions (hyperintense) are a marker of MS disease burden and accumulate over time • T2 images alone do not allow discrimination between new lesions and older plaques on a single scan and must be compared to prior images to assess disease activity over time • T2 lesions alone are pathologically non-specific and are frequently found in a variety of other conditions

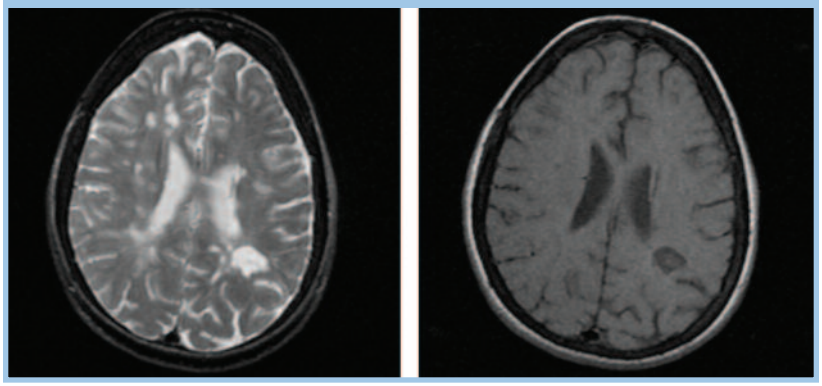
*FLAIR: fluid-attenuated inversion recovery

Table 5 and Figures 3-8 illustrate MRI findings and associated relevance in MS diagnosis and management.

Table 5: Helpful MRI Findings in MS Diagnosis and Management

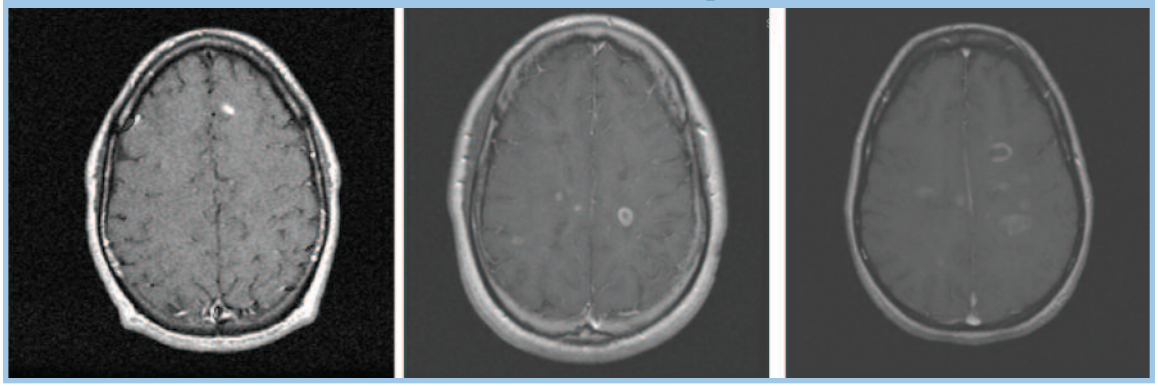
Technique–Feature	Relevance
T1 Persistent 'Black Hole'	Tissue destruction/axonal transection **(Figure 3)**
T1 Gd+ Various Patterns	Active inflammation/blood brain barrier disruption **(Figure 4)**
FLAIR Hyperintensity	Juxtaventricular/juxtacortical sensitivity **(Figure 5)**
T2/Proton Density Hyperintensity	Infratentorial sensitivity/specificity **(Figure 6)**
T2 Spinal Cord Hyperintensity	Increased diagnostic specificity **(Figure 7)**
Atrophy–Volume Loss	Correlation with disability **(Figure 8)**

Figure 3: T1 Persistent 'Black Hole'–Tissue Destruction



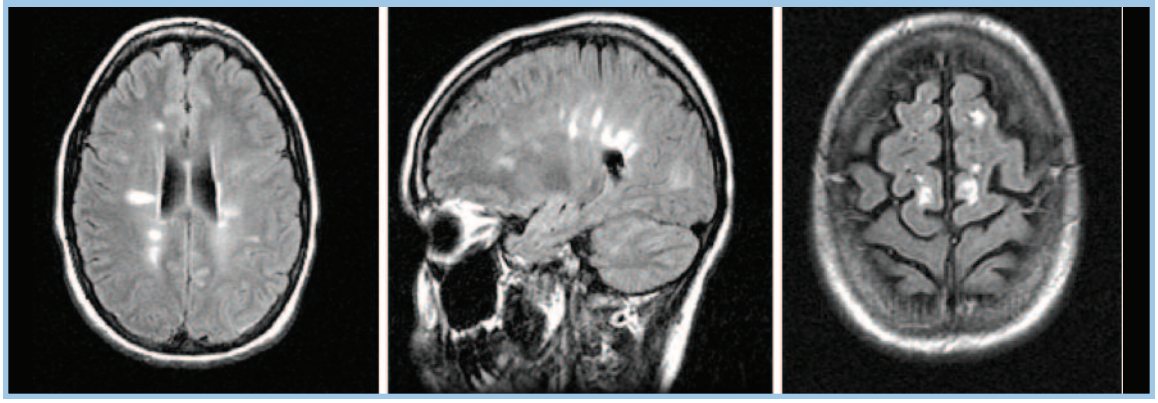
Legend: T2 (left) and corresponding T1 (right) images showing a chronic hypointensity (black hole) in the left periventricular white matter. Note other areas of T2 signal abnormality without corresponding T1 hypointensity.

Figure 4: T1 Gadolinium Enhancing—Sign of Active Inflammation/ Blood Brain Barrier Disruption



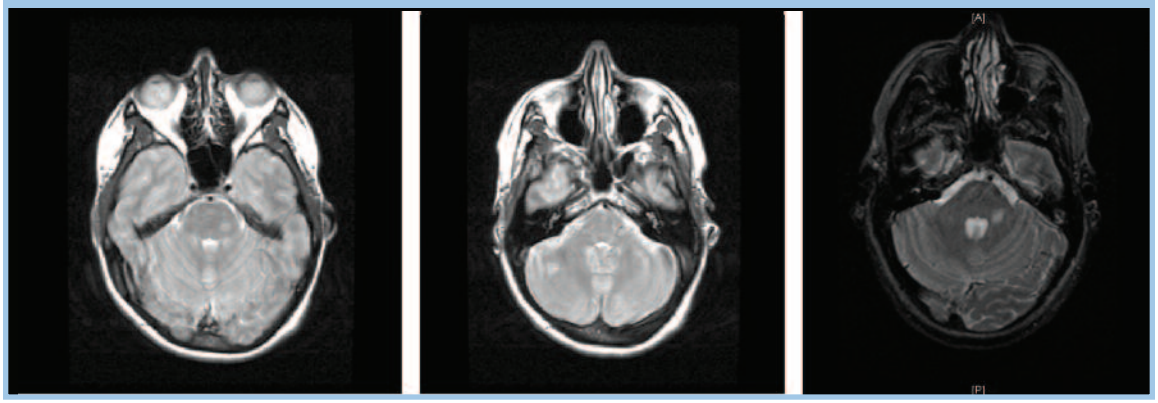
Legend: Characteristic patterns of T1 post-contrast enhancement in MS: Left, homogeneous; Middle, punctate and ring-enhancing; Right, Open ring sign

Figure 5: FLAIR Hyperintensity—Juxtaventricular/Juxtacortical Sensitivity



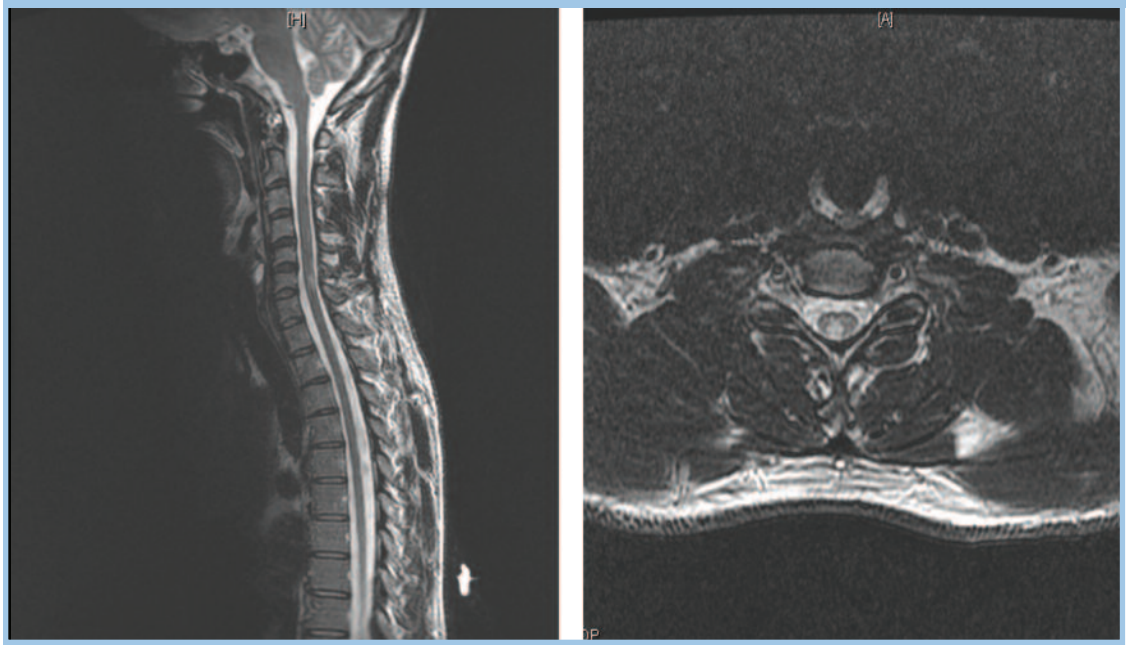
Legend: Axial and sagittal FLAIR images revealing typical rounded or oval hyperintensities in the periventricular white matter and corpus collosum (left and middle), oriented perpendicularly to the ventricles (Dawson's fingers); and cortical lesions (right), all typical for MS

Figure 6: T2 Proton Density Hyperintensity–Infratentorial Sensitivity/Specificity



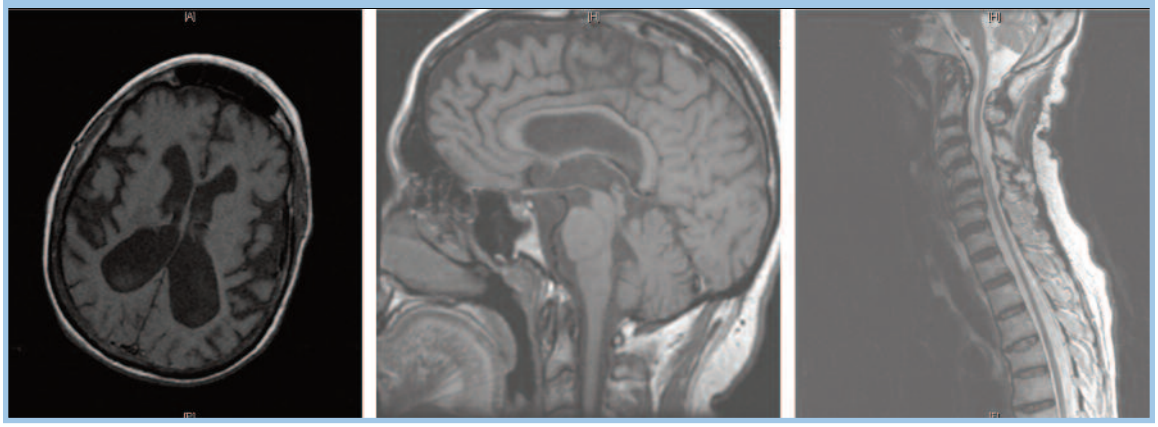
Legend: Proton Density and T2-weighted scans showing common sites of MS involvement in the posterior fossa: Pons (left); cerebellar white matter (middle); and middle cerebellar peduncle (right)

Figure 7: T2 Spinal Cord Hyperintensity–Increased Diagnostic Specificity



Legend: T2 sagittal (left) and axial (right) MRI showing typical spinal cord findings in CIS or early MS. Lesions occupy 1-2 vertebral levels on sagittal scans and less than half the diameter of the cord on the corresponding axial view.

Figure 8: Atrophy/Volume Loss—Correlation with Disability



Legend: CNS atrophy in MS. Note marked atrophy of periventricular and subcortical white matter (left), corpus callosum (middle), and spinal cord (right)

Analysis of cerebrospinal fluid (CSF) may be part of diagnostic assessments for MS, as CSF IgG oligoclonal bands may be present in ~90% (or more) of patients with MS at some point in the disease course, and are a reflection of a humoral immune response within the CNS.[22] A meta-analysis by Dobson et al reported that patients with CIS with oligoclonal bands had an odds ratio of 9.9 for conversion to MS, but CSF may be negative early in the disease course and does not rule out a diagnosis of MS.[23] Visual or somatosensory evoked potentials may also be part of the diagnostic workup for patients with suspected demyelinating disease.[1,22]

CLINICALLY ISOLATED SYNDROME (CIS)

The majority of patients with MS present with a stereotypical constellation of symptoms and signs constituting a first clinical "attack" of demyelination, often referred to as a clinically isolated syndrome (CIS). CIS typically comprises unilateral optic neuritis, partial transverse myelitis, or a brainstem-cerebellar syndrome (see below). The majority of patients presenting with CIS will also have characteristic lesions on brain MRI not accounting for their clinical presentation and indicative of prior asymptomatic episodes of inflammatory demyelination. These patients should be managed based on their risk of having a second attack and thus converting to relapsing remitting MS (RRMS), also known as clinically definite MS (CDMS).

In the Optic Neuritis Treatment Trial (ONTT), the cumulative probability of developing MS by 15 years after onset of optic neuritis was 50% (95% confidence interval, 44-56%) and risk was strongly related to presence of lesions on the baseline non–contrast-enhanced brain MRI.[24] Twenty-five percent of patients with no lesions on baseline brain MRI developed MS during follow-up compared with 72% of patients with ≥ 1 lesions. Within a 5-year time window the risk of conversion was 51% in patients with 3 or more MRI lesions, with patients generally experiencing only mild disability.[25]

Morrissey et al found that at five years, 72% of patients presenting with a clinically isolated syndrome involving the optic nerve, brainstem, or spinal cord experienced a second attack.[26] They also found that 13% of patients with 1-3 MRI lesions at presentation achieved an EDSS of at least 3, while 45% of patients with ≥ 4 lesions reached this endpoint. A follow-up study after a mean of 20.2 years demonstrated that 82% of

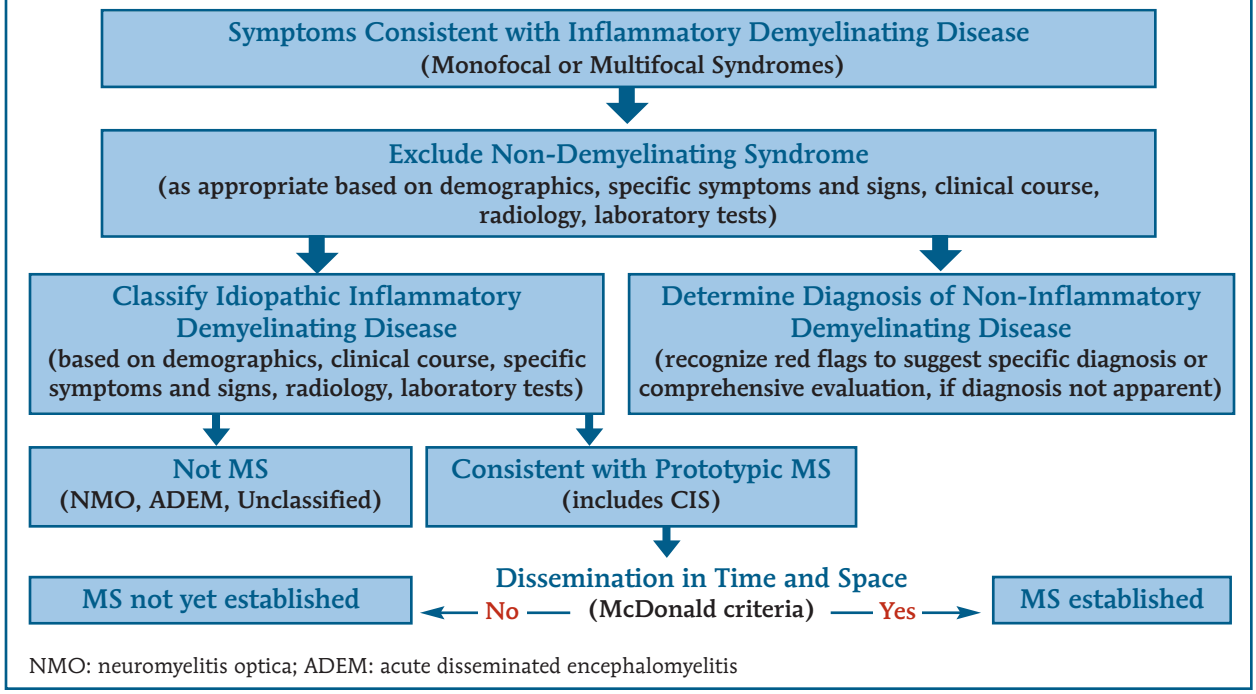
patients with abnormal MRI eventually converted to MS, and 21% of patients with baseline normal MRIs converted.[27] At 20 years 58% were classified as relapsing-remitting (39% benign, EDSS ≤ 3), and 42% were secondary progressive. Patients with secondary progression had a threefold faster growth rate of T2 MRI lesions.[27] Using modern imaging criteria, it is now also possible to make a diagnosis of MS prior to a second clinical attack by demonstrating new asymptomatic lesions on MRI (ie, dissemination in time) **[Table 3, page 14]**, and most disease modifying therapies (DMTs) are utilized in both RRMS and CIS with characteristic abnormal MRI findings.

RADIOGRAPHICALLY ISOLATED SYNDROME (RIS)

Recently several groups of patients scanned for unrelated reasons (with no suspicion of a demyelinating event) but found to have MRIs that look radiologically like MS have been identified and followed. Lebrun et al reported that when a repeat brain MRI was obtained (mean time 6 months, range = 3-30 months), 73% of this group developed new lesions.[28] A clinical event occurred in 33% of patients with a time from initial MRI to event of 2.3 years (range = 0.8-5 years). Okuda et al reported radiologic progression in 59% of patients with a median follow-up of 2.7 years (range 0.1-26 years), and clinical progression in 30% with a median follow-up of 5.4 years (range 1.1-9.8 years).[13] Gadolinium enhancement was also predictive of a follow-up event. A review of RIS studies by Granberg et al reported that two-thirds of the patients with RIS progressed radiologically with new lesions and/or Gd enhancement on MRI, and one-third of the patients with RIS developed symptoms characteristic of MS during 2-5 years of follow-up.[29] Cervical spinal cord lesions were associated with increased risk of clinical progression in the RIS patient cohorts. The management of patients with RIS is an unresolved issue; ie, whether to wait and follow clinically as well as with MRI, or whether to treat with disease modifying therapies, and additional studies are needed to inform clinical practice.[29]

As a result of an international consensus conference of MS experts in 2006, an algorithm for the differential diagnosis of MS was developed **(Figure 9)**.

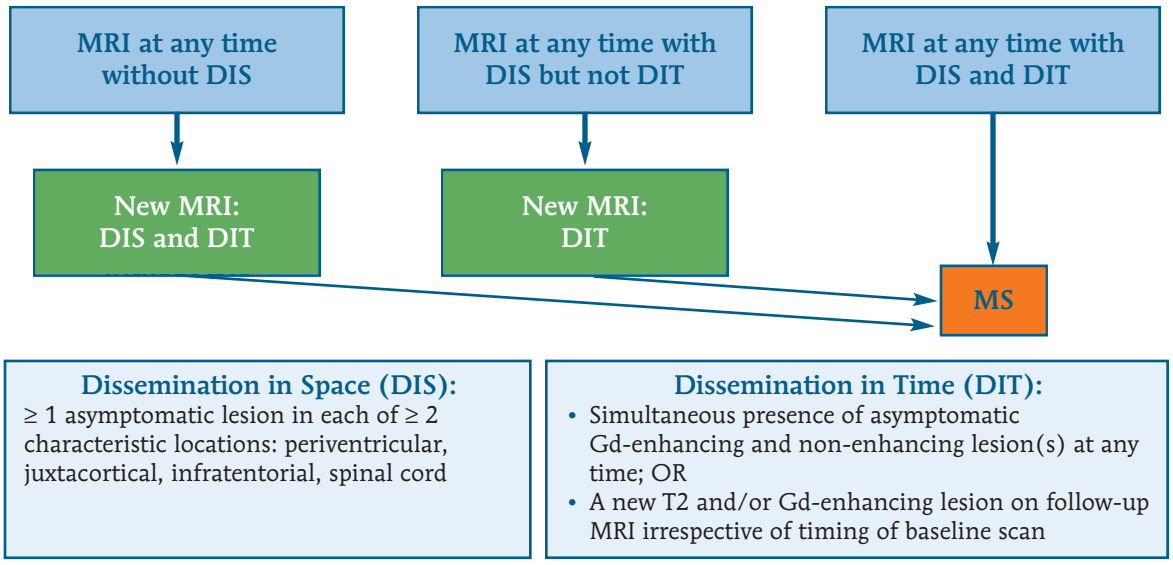
Figure 9: Steps in MS Differential Diagnosis (adapted from Miller et al)[12]



NMO: neuromyelitis optica; ADEM: acute disseminated encephalomyelitis

Guidance on the incorporation of MRI data into the work up of patients with CIS (such as optic neuritis, a brainstem syndrome, or partial myelitis) has been published by the MAGNIMS group.[30] An algorithm from this publication is shown in **Figure 10**.

Figure 10: Diagnostic Algorithm in Patients with Clinically Isolated Syndromes (CIS)*



*Algorithm only applies to patients with typical CIS, aged 14 to 50 years and after having performed a complete diagnostic workup

In 2009, the Consortium of Multiple Sclerosis Centers updated protocols for the use of MRI in both diagnosis and follow-up of patients with MS **(Tables 6 and 7)**.[31]

Table 6: MRI Evaluation: Patients with Clinically Isolated Syndrome and Suspected MS[31]

Timing	Evaluation
Baseline	• Brain MRI with gadolinium • Spinal cord MRI, if there is persisting uncertainty about the diagnosis and/or the findings on brain MRI are equivocal • Spinal cord MRI, if presenting symptoms or signs are at the level of the spinal cord
Follow-up	• Brain MRI with gadolinium to demonstrate new disease activity

Table 7: MRI Evaluation: Patients with an Established Diagnosis of MS[31]

Timing	Evaluation
Baseline	• Brain MRI with gadolinium
Follow-up	A brain MRI with gadolinium is recommended: • To evaluate an unexpected clinical worsening concerning for a secondary diagnosis • For the reassessment of the original diagnosis • For reassessment before starting or modifying therapy • To assess subclinical disease activity should be CONSIDERED every 1-2 years. The exact frequency may vary depending on clinical course and other clinical features

Ford et al have pointed out limitations associated with conventional MRI in clinical practice, including the inability to identify lesion type; poor characterization of the degree of injury within a demyelinated lesion; abnormalities in normal-appearing white matter, gray matter, and 'diffusely abnormal white matter' may be missed; variations in results occur due to interpreter skill, equipment settings and field strength of the MRI; and quantitative analysis of lesion load and comparison between serial MRI scans are challenging in the clinical setting.[32] Other imaging techniques have advantages that may be useful for MS, as summarized in **Table 8**.

Table 8: Alternative Imaging Platforms with Benefits for MS[32]

Imaging Approach	Benefits in MS
Magnetization transfer imaging (MTI) and Magnetization transfer ratio (MTR)	• Sensitivity for myelin and axonal integrity • Show structural integrity of tissues
Proton magnetic resonance spectroscopy (^{1}H-MRS)	• Measure and quantify metabolic biomarkers such as glutamate and N-acetylaspartate involved in MS pathology • Determine changes in biomarkers in relation to MS treatments
Diffusion tensor imaging (DTI)	• Predict lesions that may evolve into black holes • Identifies neural tracts within the CNS and how lesions may interrupt specific tracts
Functional MRI (fMRI)	• Measure compensatory process that may evolve due to brain plasticity
Myelin water imaging	• Measure myelin density

CHAPTER 2:
Treatment of MS

DISEASE MODIFYING THERAPIES–Current Therapies

The number of DMTs available for patients with MS has changed dramatically over the last 20 years. As of this writing (November 2013), there are 10 DMTs approved by the US FDA for RRMS, including 3 oral agents **(Table 9)**.[33]

Table 9: Disease-Modifying Therapies for the Management of MS[33]

Agent	US FDA Approval	Dose	Route	Schedule
Interferon (IFN) β-1b (Betaseron®)	1993	250 mcg	SC	QOD
IFNβ-1a (Avonex®)	1996	30 mcg	IM	QW
Glatiramer acetate (Copaxone®)	1996	20 mg	SC	QD
Mitoxantrone (Novantrone®)	2000	12 mg/m^2	IV	Q3M
IFNβ-1a (Rebif®)	2002	22 mcg or 44 mcg	SC	TIW
Natalizumab (Tysabri®)	2004	300 mg	IV	Q4W
IFNβ-1b (Extavia®)	2009	250 mcg	SC	QOD
Fingolimod (Gilenya®)	2010	0.5 mg	PO	QD
Teriflunomide (Aubagio®)	2012	7 mg or 14 mg	PO	QD
Dimethyl fumarate (Tecfidera®)	2013	240 mg	PO	BID

MS treatment should be individualized, with consideration of multiple factors, including clinical course of disease, efficacy and safety of each therapeutic agent, dosage and frequency of administration, presence of medical or psychiatric comorbidities, and patient preference. With increasing options available, some clinicians may choose the use of more aggressive treatments early in disease course while others may reserve these as second-line options. However, determining which patients are likely to benefit most from which approach may be challenging, and few carefully controlled studies are available for guidance. Glatiramer acetate and the IFNβs have well-established safety and tolerability profiles, whereas long-term safety data for the newer oral agents are more limited. Patient education and counseling regarding risks and benefits of DMTs and realistic treatment expectations are necessary. For all treatment options, routine follow-up care is essential to continually monitor patient response to therapy and evaluate treatment adherence. In **Tables 10 to 15**, information is provided on the currently approved DMTs, with the exception of mitoxantrone, which is not routinely used in the US and Canada due to safety concerns. Mitoxantrone is an antineoplastic agent that carries a black box warning due to cardiotoxicity risk (cardiomyopathy, reduced left ventricular ejection fraction, and congestive heart failure) that increases with cumulative exposure, and risk for the development of secondary acute myeloid leukemia.[33]

Table 10: Interferonβ[34,35,36,37,38,39,40]

Interferonβ-1a/b Betaseron®, Avonex®, Rebif®, Extavia®	
Mechanism of Action	Enhancement of suppressor T-cell activity, reduction of proinflammatory cytokine production, down regulation of antigen presentation, inhibition of lymphocyte trafficking into the CNS
Dosing/Administration	• IFNβ-1a: 30 mcg IM, once weekly • IFNβ-1a: 22 or 44 mcg SC, 3 times weekly • IFNβ-1b: 250 mcg SC, every other day
Efficacy	• IFNβ-1b – Reduction in annualized relapse rate (ARR) by 34% vs placebo – Decreased accumulation of T2-hyperintense lesions on MRI vs placebo – 21 year study showing survival benefit vs placebo • IFNβ-1a (IM) – Reduction in ARR vs placebo – Decreased disability progression at 2 years vs placebo – Decreased accumulation of T2-hyperintense lesions on MRI vs placebo • IFNβ-1a (SC) – Reduction in ARR by ~30% vs placebo – Decreased disability progression at 2 years vs placebo • IFNβ-1b or IFNβ-1a: Delayed conversion of CIS to CDMS
Safety	• Flu-like symptoms often with mild elevation in body temperature • Injection-site reactions, especially with SC administration • Laboratory abnormalities (liver enzymes, white blood cell count, platelets, thyroid function) • May exacerbate depression • Pregnancy Category C
Comments	Long-term safety and efficacy generally well established. Head to head trials show superior efficacy of high-dose, high-frequency administration over low-dose weekly administration. Interferons are often poorly tolerated, and neutralizing antibodies may develop over time, which may impact efficacy

Table 11: Glatiramer Acetate[17,41,42,43,44,45]

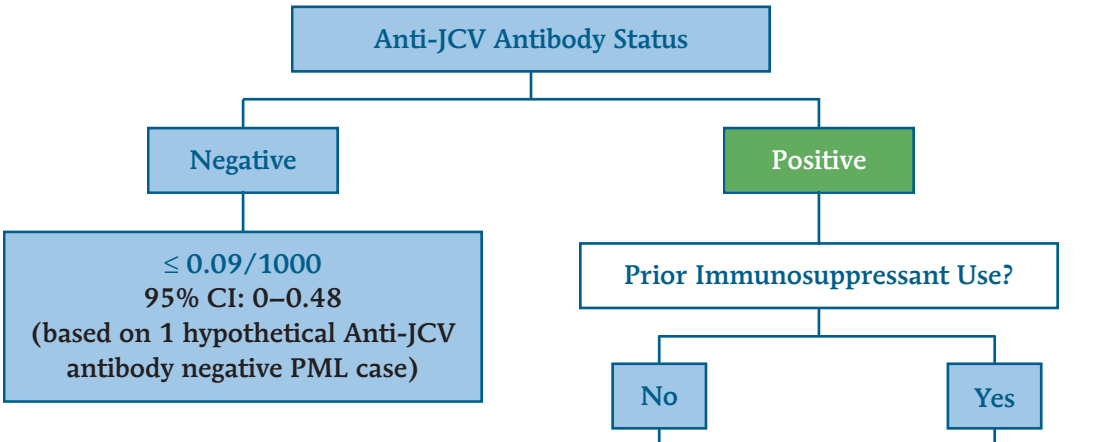
Glatiramer Acetate–Copaxone®	
Mechanism of Action	Copolymer composed of 4 amino acids (L-glutamic acid, L-lysine, L-alanine, L-tyrosine) Immunomodulatory; preferential differentiation of Th2 cells; and inhibition of antigen-specific T-cell activation
Dosing/Administration	20 mg SC, every day
Efficacy	• Pivotal trial in RRMS, GA vs placebo for 2 years – 29% reduction in relapse rate – Mean change in EDSS significantly lower in treated group • PreCISe Trial in CIS (GA vs. Placebo) – 45% decreased risk in developing CDMS – 58% decrease in number of T2 lesions – Trial halted at interim analysis because of positive results • Early vs delayed GA in CIS reduced CDMS conversion risk by 41% • US GA Trial (open-label) 15 year analysis – Low relapse rates – 57% stable/improved EDSS scores – 65% had not transitioned to SPMS – No long-term safety issues
Safety	• No systemic side effects • No medication interactions • Injection site redness, swelling or itching • Lipoatrophy at injection sites may worsen over time • Pregnancy category B • "Post-injection systemic reaction" – Variable combination of flushing, chest tightness, shortness of breath, palpitations, anxiety – Transient (15-30 minutes), self-limited, sporadic, unpredictable – Not an allergic response
Comments	Long-term safety and efficacy generally well established. Generally well tolerated and effective for most patients. Head to head trials show equivalent efficacy to high-dose, high-frequency interferons. Long-term use may be limited by lipoatrophy from daily injections. Recent GALA trial shows positive results with 40 mg dose given thrice weekly (see Emerging Therapies section)

Table 12: Natalizumab[18,46,47,48]

Natalizumab–Tysabri®	
Mechanism of Action	Humanized monoclonal antibody Inhibition of α4β1-integrin mediated adhesion of leukocytes to VCAM-1 on vascular endothelial cells at the blood brain barrier, which prevents leukocyte migration into the brain
Dosing/Administration	300 mg IV, every 4 weeks
Efficacy	• AFFIRM Trial–Phase 3 – 68% reduction in ARR vs placebo – 42% reduction in disability progression – 92% reduction in Gd+ lesions vs placebo • SENTINEL Study–Phase 3 – Natalizumab added to IFNβ-1a 30 mcg IM, once weekly reduced relapse rates and fewer new or enlarging T2 lesions vs IFNβ-1a alone
Safety	• Increased risk for UTI or other common infections • Hypersensitivity and neutralizing antibodies • Infusion-related reactions • Pregnancy Category C • Progressive Multifocal Leukoencephalopathy (PML)* – Demyelinating CNS infection caused by the JC virus – Previously known risk factors were HIV/AIDS and other forms of immunosuppression – Risk increases with presence of antibodies to JC virus, prior immunosuppressant use, and length of exposure to natalizumab – Common symptoms include cognitive decline, visual symptoms and severe, focal neurologic deficit – Often results in severe neurologic impairment or death • TOUCH® Prescribing Program (REMS)** – Prescriber and patient must be enrolled – Pharmacies and infusion centers must be specially certified
Comments	Generally well tolerated and felt by many clinicians to be the most effective FDA-approved DMT. Use is primarily limited by risk for PML, and patients should be tested for anti-JCV antibodies for risk stratification and must be followed closely while on treatment **(see Figure 11)**

*A PML risk stratification algorithm is shown in Figure 11.
**TOUCH program is unique to the United States.

Figure 11: Estimated Incidence of Natalizumab-Associated PML Stratified by Risk Factors[49]



Natalizumab Exposure	No Prior IS Use	Prior IS Use
1–24 months	0.56/1000 95% CI: 0.36–0.83	1.6/1000 95% CI: 0.91–2.6
25–48 months	4.6/1000 95% CI: 3.7–5.6	11.1/1000 95% CI: 8.3–14.5

Table 13: Fingolimod[19,50,51]

Fingolimod–Gilenya®	
Mechanism of Action	Sphingosine1-phosphate receptor modulator; prevents egress of lymphocytes from lymphoid tissues into the periphery
Dosing/Administration	0.5 mg oral, once daily
Efficacy	• FREEDOMS-Phase 3 – Fingolimod 1.25, 0.5 mg vs placebo – Reduced ARR vs placebo (60% and 54% for 1.25 and 0.5 mg doses, respectively – Reduced risk of disability progression for both doses vs placebo – Both doses superior to placebo for Gd+ enhancing lesions at 24 months • TRANSFORMS-Phase 3 – Fingolimod 1.25, 0.5 mg vs IFNβ-1a (IM) – Reduced ARR vs IFNβ-1a (38% and 52% for 1.25 and 0.5 mg doses, respectively) – Fingolimod superior on MRI endpoints
Safety	• Bradycardia and prolongation of QTc interval – First dose monitoring; must be conducted in an approved center; observe for signs/symptoms of bradycardia for ≥ 6hrs; ECG prior to dosing and at the end of the observation period – Multiple interactions with other QTc-prolonging agents, and risk of cardiac arrhythmias, eg, AV block; Torsades de Pointes • Liver enzyme elevations (monitor regularly) • Lymphocytopenia (monitor regularly) does not generally require discontinuation • Macular edema – Ophthalmologic exam at baseline and at 3-4 months • Pulmonary effects (bronchospasm) • Increased infection risk – CBC prior to treatment initiation – Varicella zoster vaccination if antibody negative – Avoid live attenuated vaccines while on treatment • Pregnancy Category C • If treatment is stopped for more than 12-14 days, first dose monitoring should be repeated
Comments	First-in-class compound with limited long-term safety/efficacy data. Generally well tolerated and effective. Use may be limited by REMS program and multiple medication interactions. Clinical trials of lower doses and more selective S1P receptor modulators are underway

Table 14: Teriflunomide[20,52,53]

Teriflunomide–Aubagio®	
Mechanism of Action	Inhibition of dihydroorotate dehydrogenase, a key enzyme in de novo pyrimidine synthesis required by rapidly dividing lymphocytes; diminishes the numbers of activated T- and B-cells available to migrate to the CNS
Dosing/Administration	7 or 14 mg oral, once daily
Efficacy	• TEMSO-Phase 3 – Teriflunomide 7 or 14 mg vs placebo – Relative risk reduction of ARR ~31% for both doses vs placebo – Significant reduction in disability progression at 2 yrs for 14 mg dose vs placebo – Superior on MRI endpoints vs placebo • TOWER-Phase 3 – Teriflunomide 7 or 14 mg vs placebo – Reduction in ARR, 22 and 36% for 7 and 14 mg doses vs placebo – 12-week sustained disability progression reduced by 32% with 14 mg teriflunomide vs placebo
Safety	• Hair thinning • Gastrointestinal (nausea, diarrhea) are generally mild • Elevation in liver enzymes (check monthly for first 6 months) • Neutropenia, leukopenia, lymphocytopenia (generally mild) • PPD or T-spot assay (check prior to initiation) • Pregnancy Category X • Accelerated teriflunomide elimination procedure with cholestyramine or activated charcoal if needed due to unexpected pregnancy or other adverse event
Comments	Generally well tolerated and moderately effective. Use may be limited by pregnancy Category X, although long-term safety data available for parent compound (leflunomide) in rheumatoid arthritis are reassuring

Table 15: Dimethyl Fumarate/BG-12[21,54,55]

Dimethyl Fumarate/BG-12–Tecfidera®	
Mechanism of Action	Anti-inflammatory properties via effects on the Nrf2 pathway; Th1 to Th2 shift, anti-oxidant properties, potential neuroprotective effects
Dosing/Administration	240 mg oral, twice daily
Efficacy	• DEFINE-Phase 3 – BG-12 240 mg BID or TID vs placebo – 53% and 48% reduction in ARR for 240 mg BID and TID vs placebo, respectively – 90% (BID) and 73% (TID) reduction in Gd+ enhancing lesions at 2 years vs placebo – 85% (BID) and 74% (TID) reductions in new or enlarging T2 lesions vs placebo • CONFIRM-Phase 3 – BG-12 240 mg BID or TID vs placebo; glatiramer acetate active control – 44% and 51% reduction in ARR for 240 mg BID and TID vs placebo, respectively (29% for GA vs placebo) – Superior MRI outcomes for BG-12 and GA vs placebo
Safety	• Flushing (not an allergic response) common • Diarrhea, nausea, abdominal cramps common • Generally started at ½ dose (120 mg, BID) for first week • Flushing and GI symptoms decrease after first 2-4 weeks of treatment • Elevation of liver enzymes (rare) • Leukopenia, lymphocytopenia (rare) • Pregnancy Category C
Comments	Side effects (flushing and GI) are common with treatment initiation and may require extended titration and/or symptomatic medications to address side effects. Short half-life and BID dosing is critical for efficacy. Limited long-term safety/efficacy data in MS, though other fumarate preparations have extensive use for treatment of psoriasis outside of the US

DISEASE MODIFYING THERAPIES– Emerging Therapies

Therapeutic options for MS are rapidly increasing, adding to the complexity of patient care. A variety of agents are currently in clinical development; many differ in mechanism of action, route of administration, and efficacy and safety profiles. Different preparations of two long established therapies (glatiramer acetate and IFNβ-1a) with less frequent dosing schedules are being evaluated in patients with RRMS.[56,57] The 12-month GALA trial is an international randomized, placebo-controlled, phase 3 trial with glatiramer acetate given at 40 mg SC, three times a week (in contrast to the currently approved 20 mg SC daily dose schedule).[56] This less frequent dosing schedule was associated with significant improvements in ARR (34% reduction) and MRI endpoints (45% reduction in Gd+ enhancing lesions; 35% reduction in new/enlarging T2 lesions) compared with placebo.[56] Injection site reactions were the most common adverse events associated with glatiramer acetate treatment. Pegylated (PEG) IFNβ-1a is being evaluated in the phase 3 ADVANCE study.[57] Results show that PEG IFNβ-1a (125 mcg SC) either every 2 weeks or every 4 weeks is superior to placebo, with significant reductions in ARR (28-36%), 12-week confirmed disability progression (38%), and the number of new/enlarging T2 lesions (28-67%).[58] The most commonly reported adverse events with PEG IFNβ-1a were redness at the injection site and flu-like symptoms.[58]

Alemtuzumab is a humanized monoclonal antibody that recognizes and binds to CD52 on T cells and B cells; infusion of alemtuzumab results in depletion and repopulation of these cell populations, with sustained changes in adaptive immunity.[59] Data from 2 phase 3 trials of alemtuzumab in patients with MS have been published. In the CARE-MS I trial, recently diagnosed RRMS patients were randomized to alemtuzumab IV, 12 mg/day or 24 mg/day for 5 days at baseline and 3 days at 12 months, or IFNβ-1a 44 mcg three times per week; and in the CARE-MS II trial, patients with RRMS and at least 1 relapse on IFNβ or glatiramer acetate were randomized to either dose of alemtuzumab or IFNβ-1a.[60,61] In both trials, both doses of alemtuzumab were shown to be more effective than high-dose, high-frequency interferon, although the incidence of adverse reactions, including autoimmune complications, was higher for the 24 mg/day group, and the 12 mg/day dose is likely to be approved both in Europe and the US with an extensive REMS program. Results for the 12 mg/day dosing regimen from CARE-MS I and CARE-MS II are summarized in **Table 16**.

Table 16: Alemtuzumab in RRMS: CARE-MS I and CARE-MS II[60,61]

Outcomes	CARE-MS I Treatment Naive		CARE-MS II Treatment Experienced	
	IFN β-1a (n = 187)	Alemtuzumab (n = 376)	IFN β-1a (n = 202)	Alemtuzumab (n = 426)
ARR	0.39	0.18*	0.52	0.26*
Sustained disability accumulation over 6 mo (% pts)	11%	8%	20%	13%‡
New/enlarging T2 lesions (% pts)	58%	48%†	68%	46%*
T1-GdE lesions at 24 mo (% pts)	19%	7%*	23%	9%*
Median Δ in brain parenchymal fraction	−1.488%	−0.867%*	−0.810%	−0.615%‡
Thyroid-associated AEs (% pts)	6%	18%	5%	16%
ITP (% pts)	0%	1%	0%	1%

Alemtuzumab IV, 12 mg/day for 5 days at baseline, 3 days at 12 months
IFNβ-1a 44 mcg SC 3X per week
*$P < 0.0001$; †$P < 0.05$; ‡$P < 0.01$

Based on the results of the CARE-MS studies, alemtuzumab was recently approved for MS by the European Medicines Agency in September 2013, and is currently under US FDA review.[62]

A summary of therapies currently in late-stage development for MS is shown in Table 17.

Table 17: Emerging Therapies for MS[60,61,63,64,65,66,67,68,69]

Treatment	Mechanism of Action	Route of Administration	Status
Alemtuzumab	Humanized monoclonal antibody, anti-CD52; T cell depletion	IV	Under FDA review
Ocrelizumab	Humanized monoclonal antibody, anti-CD20; B cell depletion	IV	Phase 3
Daclizumab	Humanized monoclonal antibody, anti-CD25, subunit of IL-2 receptor	SC	Phase 3
Laquinimod	Immunomodulatory, anti-inflammatory; potentially neuroprotective	Oral	Phase 3 studies BRAVO and ALLEGRO complete; CONCERTO recruiting
Siponimod	Sphingosine-1-phosphate receptor modulator	Oral	Phase 3 (SPMS)

TREATMENT OF PROGRESSIVE FORMS OF MS

Despite the virtual explosion of treatment options for early MS (CIS and early RRMS/CDMS) in the past two decades, no universally recognized or approved safe and effective treatment options for established progressive disability in MS are currently available, and many practitioners regard this as the greatest unmet need in MS therapeutics. Although mitoxantrone has been approved for over a decade for rapidly worsening and progressive forms of MS, its use has been severely limited by its toxicity, including cardiac toxicity and treatment-related leukemia. Many different combinations of the agents outlined above with various immunosuppressive agents and/or corticosteroids have been advocated anecdotally over the years, and there is no consensus on when or how to discontinue immune-based therapy entirely in advanced progressive disease. Many of the currently available therapies for RRMS have been tried and found to be ineffective, or at most minimally effective in progressive MS, but several trials of newer therapies (some with putative "neuroprotective" effects) are currently underway for both primary and secondary progressive MS and hold out hope for potentially slowing disease progression.

RELAPSE MANAGEMENT

While DMTs are effective in reducing the risk of relapse and disease progression, acute exacerbations that produce neurologic dysfunction may still occur. An MS relapse (attack or exacerbation) is a new or worsening neurological deficit consistent with inflammation and demyelination that lasts longer than 24 hours, is separated by at least 30 days from the last relapse, is not related to infection, fever or other stresses, and has no other explanation.[1] Treatment of relapses is recommended, particularly when activities of daily living are impacted; therapeutic options are summarized in **Table 18.**

Table 18: Treatment of Acute Relapses in Patients with RRMS[1,22,70]

Treatment	Potential Side Effects	Comments
IV methylprednisolone (1 gram/day for 3 to 5 days)	Gastritis, insomnia, irritability/mood changes, flushing, hypertension, acne, transient elevation in blood glucose	Most commonly used therapy; need to evaluate comorbid conditions that may be exacerbated by corticosteroid therapy
Oral prednisone (1250 mg/day for 3 to 5 days)	Gastritis, insomnia, irritability/mood changes, flushing, hypertension, acne, transient elevation in blood glucose, avascular necrosis of the hip (rare)	Bioequivalent to 1 gram of IV methylprednisolone; need to evaluate comorbid conditions that may be exacerbated by corticosteroid therapy
Adrenocorticotrophic Hormone (ACTH) (80-120 units IM or SQ for 2 to 3 weeks)	Fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, weight gain	An option in patients who are not responsive to or are unable to tolerate corticosteroids; cost may limit use
Plasmapheresis	Infection, metabolic acidosis, hypocalcemia, hypotension, and catheter related complications	Second-line treatment for steroid-resistant relapses
Intravenous immunoglobulin (0.4 g/kg/day for 5 days)	Headache, fever, myalgia, hypercoagulability	May be considered in patients unresponsive to steroids, or during pregnancy; not FDA approved for MS

SYMPTOM MANAGEMENT

While DMTs help to reduce relapse frequency and minimize MRI-associated disease activity, other approaches are needed for the management of the myriad MS symptoms. Axonal injury and loss contribute to symptomatic burden, with lesions in specific brain/spinal cord regions associated with symptom presentation. MS symptoms are summarized in Table 19.

Table 19: MS Symptoms

Common	Less Common	Rare
• Fatigue • Focal muscle weakness • Gait problems • Spasticity • Neuropathic pain • Paresthesias • Visual changes • Bowel, bladder, and sexual dysfunction • Depression • Disordered sleep	• Dysarthria, scanning speech, and dysphagia • Lhermitte's sign • Ataxia • Vertigo • Cognitive dysfunction • Tremor, incoordination	• Decreased hearing • Seizures • Tinnitus • Paralysis

MS symptoms may stabilize, fluctuate, or progress with time. Left untreated, primary symptoms may worsen or precipitate other symptoms. For example, patients with bladder dysfunction may be at increased risk for urinary tract infections; patients with limited mobility may be at risk for skin breakdown; weakness and numbness in lower extremities may contribute to risk for falls. Multiple dimensions of everyday life are ultimately impacted by primary and secondary symptoms associated with MS. There is inter-relatedness with MS symptoms; for example, depression may increase fatigue, a depressed and fatigued patient may be reluctant to exercise, reduced exercise may lead to spasticity or constipation, spasticity may interfere with quality sleep, sleeplessness may contribute to fatigue, etc. Symptom management is extremely important for optimizing function and quality of life for patients with MS. Due to the diverse nature of symptoms, a multidisciplinary, collaborative approach is necessary to meet patients' varied needs. Nonpharmacological and pharmacological treatment approaches for common MS symptoms are summarized in Table 20 (use of many pharmacological agents included are off-label). Note that depression is addressed in greater detail in the chapter on Comprehensive Care.

Table 20: Treatment of MS Symptoms[1,22,71]

MS Symptom	Management Approach	
	Nonpharmacological	Pharmacological
Fatigue • Most common MS symptom (experienced by 75-95% of patients) • 50-60% of patients identify fatigue as one of their most troubling symptoms	• Manage/eliminate secondary causes of fatigue (eg, medications, coexisting conditions, disrupted sleep, etc.) • Exercise, PT, OT; (to increase stamina) • Energy saving techniques; effective energy expenditure • Cooling strategies/devices	• Amantadine • Modafinil • Armodafinil • Methylphenidate
Spasticity • Occurs in ~80% of patients • Highly variable, mild to quite severe • Most frequently in muscles of upper and lower extremities	• Stretching and range of motion exercises • Timing exercises • Strengthening exercises • Relaxation techniques • Positioning • PT, OT • Surgical procedures in rare cases of intractable spasticity	• Baclofen (oral or intrathecal) • Tizanidine • OnabotulinumtoxinA • Diazepam • Dantrolene • Clonazepam • Gabapentin • Phenol
Gait problems • ~50% of patients with RRMS will need walking assistance within 15 yrs of diagnosis • Weakness, impaired balance, numbness, spasticity are contributing factors	• Mobility aids • Exercise • PT • Ankle foot orthotics • Functional electrical stimulation devices	• Dalfampridine (only approved to improve walking speed)
Pain • Common symptom, prevalence ~64% • One of the most bothersome symptoms • Continuous or intermittent neuropathic pain, such as dysesthesias, trigeminal neuralgia, Lhermitte's sign; musculoskeletal pain	• Meditation, mindfulness, relaxation techniques • PT • Acupuncture • Coping strategies • Hypnosis	• Gabapentin • Pregabalin • Nortriptyline • Desipramine • Carbamazepine • Oxcarbazepine • Amitriptyline • Lamotrigine • Topiramate • Venlafaxine • Duloxetine • Baclofen • Common analgesics • Opioids (rarely) • Topical agents (capsaicin, lidocaine)

Table 20: Treatment of MS Symptoms[1,22,71] *(cont.)*

MS Symptom	Management Approach	
	Nonpharmacological	Pharmacological
Visual changes • Broad and varied, affecting up to 80% of patients • Optic neuritis: frequently the initial clinical manifestation of MS	• Training in visual compensation • Environmental modifications • Adaptive equipment, as needed	• Optic neuritis – High dose corticosteroids • Nystagmus – Baclofen – Clonazepam – Gabapentin – Memantine
Bladder dysfunction • Urinary symptoms occur in 50-80% of MS patients • Failure to store; failure to empty; or a combination	• Check for UTI • Bladder diary • Timed voiding • Dietary/fluid intake adjustments • Sacral neuromodulation • Intermittent self-catheterization • Indwelling catheter • Suprapubic catheter	• Storage dysfunction – Oxybutynin (oral, transdermal) – Tolterodine – Fesoterodine – Solifenacin – Darifenacin – Trospium – Desmopressin – Intravesical onabotulinumtoxinA • Emptying dysfunction – Tamsulosin
Bowel symptoms • Bowel dysfunction reported by ~60% of MS patients • Constipation (most common); also involuntary bowel movements	• Medication review • Exercise • Dietary measures • Timed evacuations • Manual stimulation • Enemas	• Constipation – Psyllium – Calcium polycarbophil – Magnesium oxide – Polyethylene glycol – Lactulose – Senna – Docusate sodium – Lubiprostone – Bisacodyl, glycerin suppositories • Bowel incontinence – Loperamide

Table 20: Treatment of MS Symptoms[1,22,71] *(cont.)*

MS Symptom	Management Approach	
	Nonpharmacological	Pharmacological
Sexual dysfunction • 40-80% of women with MS – Decreased genital sensation, libido and vaginal lubrication; difficulties with orgasm • 25-75% of men with MS – Erectile dysfunction; decreased genital sensation; difficulty with ejaculation; reduced libido	• Medication review • Adequately treat underlying neuropathic or visceral pain, spasticity • Counseling • Psychotherapy, sex therapy • Lubricants	• Sildenafil (♂) • Vardenafil (♂) • Tadalafil (♂)
Depression • Lifetime risk between 40-60%	• Psychotherapy (group or individual), CBT • Exercise • Helping others	• Selective serotonin reuptake inhibitors (SSRIs) • Serotonin norepinephrine reuptake inhibitors (SNRIs) • Bupropion

REHABILITATION

As part of comprehensive care, a plan of exercise, functional training, and activities that address specific individual needs can help to improve mobility, activities of daily living (ADLs), and overall quality of life. According to the Medical Advisory Board of the National Multiple Sclerosis Society,

> "Rehabilitation is a process that helps a person achieve and maintain maximal physical, psychological, social and vocational potential, and quality of life consistent with physiologic impairment, environment, and life goals."[1]

In a 2004 Expert Opinion Paper, the National Clinical Advisory Board of the National Multiple Sclerosis Society provided the following rehabilitation recommendations[1]:

- Individuals with MS should be referred for assessment by rehabilitation professionals when there is abrupt or gradual worsening of function or increase in impairment that has a significant impact on an individual's mobility, safety, independence, and/or quality of life
- Patients who present with any functional limitation should have an initial evaluation and appropriate management
- Assessment for rehabilitation services should be considered early in the disease when behavioral and lifestyle changes may be easier to implement
- The complex interaction of motor, sensory, cognitive, functional and affective impairments in an unpredictable, progressive, and fluctuating disease such as MS requires periodic reassessment, monitoring, and rehabilitative interventions
- The frequency, intensity and setting of the rehabilitative intervention must be based on individual needs. Needs may be best met in an interdisciplinary, inpatient setting; others are best met at home, or in an outpatient setting
- Research and professional experience support the use of rehabilitative interventions in concert with other medical interventions for the following impairments:
  - Mobility impairments (strength, gait, balance, range of motion, coordination, tone, and endurance)
  - Fatigue
  - Pain
  - Dysphagia
  - Bladder/bowel dysfunction
  - Decreased independence in ADLs
  - Impaired communication
  - Diminished quality of life
  - Depression and other affective disorders
  - Cognitive dysfunction
- Appropriate assessments and outcome measures must be applied periodically to establish and revise goals, identify the need for treatment modification, and measure results of the intervention
- Known complications of MS (contractures, disuse atrophy, decubiti, and risk of falls) may be reduced or prevented by specific rehabilitative interventions
- Maintenance of function, optimal participation, and quality of life are essential outcomes
- Maintenance therapy includes rehabilitation interventions designed to preserve current status of ADLs, safety, mobility, and quality of life, and to reduce the rate of deterioration and development of complications
- A thorough assessment for wheelchairs, positioning devices, other durable medical equipment, and environmental modifications by rehabilitation professionals is recommended and will result in the use of the most appropriate equipment
- Regular and systematic communication between the referring health care provider and rehabilitation professionals will facilitate comprehensive, quality care

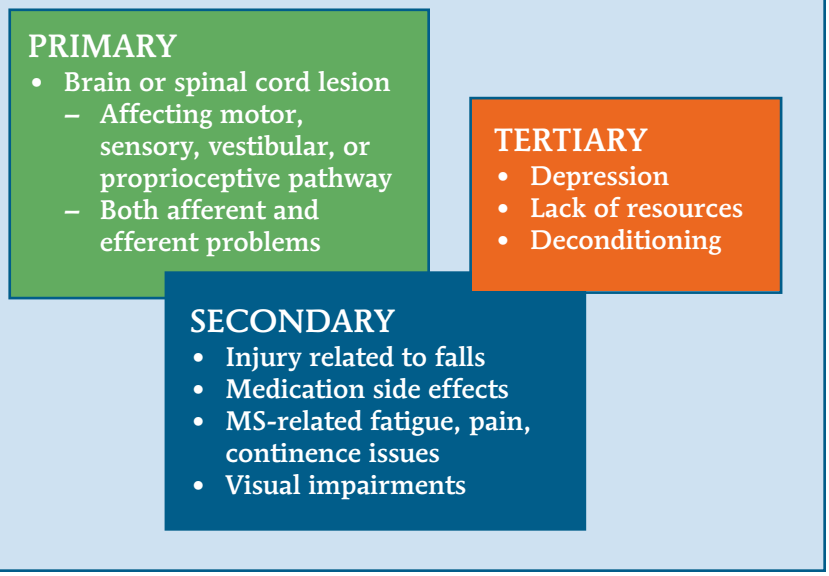
- Third party payers should cover appropriate and individualized restorative and maintenance rehabilitation services for people with MS

Rehabilitation for patients with MS is valuable early in the disease process and through advanced stages of disease. Rehabilitation strategies can be restorative in order to reestablish function that has been lost with an exacerbation or preventive for patients with stable neurological impairment.[72] Due to the progressive and varied nature of MS, rehabilitation needs to be dynamic and individualized to meet each patient's ongoing needs. Consideration should be given to the patient's cognitive status, family/support network, and history of adherence to prescribed therapies. Depending on the individual, rehabilitation may be on an inpatient or outpatient basis, involving home care and/or access to community support or fitness and wellness programs.

The person with MS and the family/support system should be an integral part of the interdisciplinary rehabilitation team. Other key members of this team include:

- Neurologist/Physiatrist
- Nurse/NP/PA
- Physical therapist
- Occupational therapist
- Speech-language pathologist
- Social worker/Case manager
- Psychologist/Psychiatrist/Neuropsychologist
- Vocational rehabilitation counselor
- Recreational therapist

Figure 12: Factors Impacting Mobility in Patients with MS



Mobility issues are an important focus of rehabilitation efforts. Multiple factors can negatively impact mobility in patients with MS as shown in **Figure 12**.

Improvement in strength, mobility, and fitness through rehabilitation can translate into improved ADLs, improved quality of life, fewer complications, reduced health care utilization, and improved safety. There is evidence that physical activity is associated with lower depression, fatigue, and pain, and higher levels of social support and self-efficacy in persons with MS; such effects are expected to have quality of life benefits as well.[73] The effectiveness of the rehabilitation team is contingent on open communication, sharing of information, and a clear understanding of the patient's needs, challenges and goals. Evaluation of patients for rehabilitation can include a variety of assessments as shown in **Table 21.**

Table 21: Rehabilitation Evaluation

- Ambulation/mobility
- Posture
- Balance
- Transfers
- Bed mobility
- Range of motion
- Strength
- Tone
- Coordination
- Sensation
- Proprioception
- Speech/swallowing
- Cognitive function
- Pain
- Vocational
- Homemaking/self-care
- Driving
- Home assessment
- Leisure skills
- Safety
- Equipment
- Endurance
- Communication

Additional considerations: fatigue, bladder/bowel disturbances, visual deficits, emotional concerns/depression, social support, environmental factors, other medical problems/diagnoses, medications and possible side effects, time of day for evaluation

The rehabilitation team may engage the patient in a range of interventions, such as:

- Functional skills training
- Therapeutic exercise with emphasis on home exercise program or referral to community based program
- Balance activities
- Coordination activities
- Gait skills
- Postural exercises
- Respiratory exercises
- Relaxation exercises
- Equipment recommendations/procurement
- Education/support/referral

Beneficial outcomes associated with various interventions for patients with MS as reported by Beer et al are summarized in **Table 22**.

Table 22: Rehabilitation Interventions for Patients with MS (adapted from Beer et al)[74]

Intervention	MS Patient Group/Symptoms	Beneficial Effects
Inpatient multidisciplinary rehabilitation	Moderate-severe disability	Improvement in disability, participation, QOL
Outpatient multidisciplinary rehabilitation	Low-moderate disability	Improvement in disability, participation, QOL
Exercise therapy	Impairments of motor functions and mobility, spasticity	Improvement in muscle power function, exercise tolerance functions, and mobility-related activities
Endurance training, aerobic training	Low-moderate motor impairments, reduced physical fitness	Improvement of aerobic capacity, muscle strength, fatigue
Resistance training	Low-moderate motor impairments, reduced muscle strength	Improvement of muscle strength, mobility
Treadmill training	Low-moderate walking disabilities	Improvement of endurance, walking speed, reduced oxygen consumption, cardiovascular reconditioning
Robot-assisted gait training	Severe walking disabilities	Improvement of walking speed and distance, strength
Hippotherapy (horseback riding)	Spasticity of lower limbs, impaired trunk control	Improvement of trunk control, reduced spasticity
Hydrotherapy (cool water no higher than 82 degrees)	All types of MS	Improvement of motor functions
Cooling therapy	Uhthoff's phenomenon, increased fatigue during exercise	Improvement of motor functions, reduced fatigability during training
Transcutaneous electric nerve stimulation	Spasticity/muscle spasm	Improvement in symptoms
Occupational therapy, educational programs	Limitations in ADLs, fatigue	Improvement of muscle function, ADL, reduction of fatigue impact, increased self-efficacy
Respiratory training	Severely disabled, with insufficient respiratory functions	Improvement in respiratory function, reduced risk for pulmonary infection
Bladder rehabilitation program	Urinary symptoms	Reduction in incontinence, urgency, frequency
Neuropsychological training-computerized[75]	Cognitive deficits	Improvement of attentional deficits, communication, memory

A variety of tools may be employed to help patients with mobility, such as orthotics, functional electrical stimulators, canes, crutches, walkers, and wheelchairs. The rehabilitation team can support patients not only in the identification of appropriate mobility devices for individual needs, but also in acceptance of the need for assistive devices.

Successful rehabilitation includes evaluation and identification of problem areas, development of an individualized treatment plan with active participation of a motivated, engaged patient, establishment of attainable goals, a team effort, and ongoing emotional support.[76] Periodic assessments should be conducted to monitor progress toward goals, with adjustments as needed to match changing patient needs. Many scales and outcomes measures are utilized for the ongoing monitoring of patients with MS. The Expanded Disability Status Scale (EDSS), Modified Ashworth Scale, the Spasm Frequency Scale, and the Multiple Sclerosis Functional Composite (MSFC) are included in **Tables 23-26**.

A variety of additional outcomes measures for MS, including those used in clinical trials are available on the National Multiple Sclerosis Web site **(http://www.nationalmssociety.org/ms-clinical-care-network/researchers/clinical-study-measures/index.aspx)**; and videos of several outcomes measures are available on the International Organization of MS Rehabilitation Therapists Web page on the Consortium of Multiple Sclerosis Centers Web site (**http://iomsrt.mscare.org/clinical-page/videos**).

Table 23: Expanded Disability Status Scale (EDSS)[77]

Score	Description
0	Normal neurologic exam
0.1	No disability, minimal signs in one functional system (FS)
1.5	No disability, minimal signs in more than one FS (more than one grade 1)
2.0	Minimal disability in one FS (one grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (eg, to work a full day without special provisions); (usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (usual FS equivalents are combinations with more than two FS grade 3+)
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (usual FS equivalents are combinations with more than two FS grade 3+)
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4+)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4+ in several systems)
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations, generally 4+ in several systems)
9.0	Helpless bed patient; can communicate and eat; (usual FS equivalents are combinations, mostly grade 4+)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4+)
10.0	Death due to MS

Table 24: Modified Ashworth Scale[78]

Score	Criteria
0	No increase in muscle tone
1	Slight increase in muscle tone (catch and release at the end of range of motion)
1+	Slight increase in muscle tone manifested by a catch followed by minimal resistance throughout the remainder of the ROM (less than half the ROM)
2	More marked increase in muscle tone through most of ROM but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Table 25: Spasm Frequency Scale[79]

Score	Criteria
0	No spasms
1	No spontaneous spasms except with vigorous stimulation
2	Occasional spontaneous spasms and easily induced spasms
3	More than 1, but less than 10 spontaneous spasms per hour
4	More than 10 spontaneous spasms per hour

Table 26: Multiple Sclerosis Functional Composite (MSFC)[80]

Component	Description
1. Timed 25-Foot Walk	• Quantitative measure of lower extremity function • First component of MSFC administered at each visit • A patient completes 2 trials of the 25-foot walk, walking as quickly as possible, safely • Assistive devices may be used • 3-minute time limit per trial
2. 9-Hole Peg Test	• Quantitative measure of upper extremity [arm and hand] function • Second component of the MSFC to be administered • Dominant and non-dominant hands are tested twice • 5-minute time limit per trial
3. Paced Auditory Serial Addition Test (PASAT)	• Measure of cognitive function that assesses auditory information processing speed and flexibility, and calculation ability • Last measure of the MSFC • Single digits are presented either every 2 or 3 seconds, and the patient is asked to add each new digit to the one immediately prior to it

CHAPTER 3:
Comprehensive Care

PSYCHOSOCIAL ISSUES

The chronic, unpredictable, and potentially disabling nature of MS and overall impact on quality of life undoubtedly contribute to psychosocial problems for patients with MS. A survey of patients from 4 university-affiliated MS centers revealed that 60% of MS patients were found to have mental health problems, yet only 46% of these patients had received treatment of any type.[81] Although the values vary depending on the rating scale/screening measures used, patients with MS have a high rate of depression compared with individuals with other neurological and chronic illnesses, and the general population.[82,73] Point prevalence rates of depression in patients with MS range from 26-57%, and the lifetime risk for depression in MS ranges from 40-60%.[83,73] While some studies find that more advanced illness has been shown to be a risk factor for depression in MS, this is not supported in other studies.[84]

The link between MS and depression includes[83]:

- The psychosocial effects of MS disability
  - Loss of vocational status, social roles, sense of control, participation abilities
  - Perceptions related to uncertainty in disease, lack of hope
- Direct effect of lesions on brain structures that are involved in regulating and maintaining mood state
- Effects of interferonβ and intravenous methylprednisolone, which may be associated with mood changes

Depression carries a high morbidity and can be life threatening, so assessment and treatment are highly important in managing patients with MS. Compared with patients with MS who do ***not*** have depression, depressed patients[85]:

- Perform poorly on cognitive function tests
- Have lower quality of life by standardized measures
- Have increased time lost from work
- Greater disruption of social support and family systems
- Reduced medication adherence

The high prevalence of depression, the negative impact of depression on patients with MS, and the associated risk for suicide are compelling reasons to screen patients with MS for depression. Two commonly used screening tools for the MS population include the Beck Depression Inventory (BDI) and the Center for Epidemiologic Studies Depression Scale (CES-D).[86,87] These tools have 21 and 20 questions, respectively. It is important for clinicians to recognize that some symptoms among DSM-5 criteria for major depressive disorder are also common MS symptoms, namely fatigue, insomnia, and difficulty concentrating and thinking.[88] Some researchers prefer the CES-D due to concern that the items relating to somatic symptoms on the BDI may overlap with symptoms of MS, however the BDI has been determined to be reliable and valid for this population.[89] A short-form of the BDI (BDI-FS) has 7 items, and does not confound MS-related neurological symptoms.[90,91] Rapid screening may also be accomplished with simply 2 questions, as reported by Mohr et al.[92]

Screening for Depression: 2-items

1. During the past 2 weeks, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past 2 weeks, have you often been bothered by little interest or pleasure in doing things?

The Patient Health Questionnaire (PHQ-9) is a 9-item depression scale based on *DSM-IV*.[93] This can be filled out by patients while in the waiting room, and then scored by the clinician. This tool can be used to make a tentative criteria-based

diagnosis of depression, and obtain a severity score that can be used to guide treatment and monitor treatment response. However, two of the nine items on the PHQ-9 refer to somatic symptoms which can occur in MS without the presence of depression, making its use questionable in an MS treatment environment.

Clinicians should consider screening patients with MS for anxiety and other mental disorders as well. Anxiety has recently been identified as having a similar prevalence in MS as depression, yet we know little about when and why it occurs.[94,95]

Depression can be found in very early MS. In two separate studies, it has been reported that 30-32% of patients with CIS were found to experience depression.[96,97]

Depression that does not meet the criteria for Major Depressive Disorder can still impose functional limitations and disability on the patient. If the criteria for 'Mood Disorder due to a General Medical Condition' were utilized, depression rates in the MS population would be much higher.[88] This diagnosis requires a depressed mood or diminished interest or pleasure that causes distress and impairment. In Minden's 1987 sample, where one-third of the MS patients met the criteria for major depression, 64% were reported to have low mood.[98] Subsyndromal symptoms of depression can be associated with a great deal of distress, can be debilitating, and are responsive to therapy.[83]

Depression in MS often goes unrecognized and untreated. In one study, for example, 25% of patients with depression were unaware that they were depressed, and received no treatment.[99] In a second study, over 16% of patients had CES-D scores ≥ 21 without awareness or treatment for a measured serious depression.[100]

Effective treatments are available for patients with MS and depression. The Goldman Consensus Statement on depression in MS (published in 2005) recommends a combination of psychotherapy and pharmacotherapy for such patients.[85] Psychotherapeutic interventions such as cognitive behavioral therapy (CBT), either group or individual-based (and even conducted over the phone), can be beneficial for patients with MS and depression.[73] Psychotherapy with a focus on specific coping skills and MS symptom management are particularly useful for this patient population.[83] Exercise and helping others are behavioral modifications that are also linked with reduced depression in patients with chronic conditions such as MS. Commonly used pharmacologic agents for the treatment of depression in patients with MS are shown in **Table 27**.

Neurologists often prescribe pharmacologic treatment and provide counseling to their MS patients who are experiencing depression. In fact medical providers, including neurologists and primary care clinicians, provided half of the mental health care to people with MS treated at four academic MS Centers in a recent study.[101] Although neurologists may not have expected treatment of mental health disorders to be part of their professional role, they are often the first line of treatment, and can be quite effective. However, effective psychopharmacologic treatment of depression requires frequent office visits to monitor for effectiveness during the first months of treatment, as a dosage increase is often indicated in MS.[102] This may not be feasible for many neurologists. Establishing a consultative relationship with a psychopharmacologist, as well as a strong referral network to mental health professions is advised. Co-location of mental health professionals at clinics and offices that treat MS patients is obviously desirable, both for patient convenience and communication between providers.[101]

Table 27: Pharmacologic Agents for Depression in Patients with MS

Drug	Daily Dose	Common Side Effects
Selective Serotonin Reuptake Inhibitors		
Fluoxetine (Prozac®)	20-80 mg	Nausea, diarrhea, anorexia, sexual dysfunction, anxiety, insomnia, asthenia
Sertraline (Zoloft®)	50-200 mg	
Fluvoxamine (Luvox®)	100-300 mg	
Paroxetine (Paxil®)	20-50 mg	
Citalopram (Celexa®)	20-40 mg	
Escitalopram (Lexapro®)	10-20 mg	
Serotonin Norepinephrine Reuptake Inhibitors		
Duloxetine (Cymbalta®)	40-120 mg	Nausea, dry mouth, constipation, dizziness, insomnia, decreased appetite, asthenia, headache
Desvenlafaxine (Pristiq®)	50-100 mg	
Venlafaxine (Effexor®)	75-225 mg	
Other		
Bupropion (Wellbutrin®)	150-450 mg	Headache, dry mouth, nausea, insomnia

Considerations for the treatment of depression:

- Treatment plans should be individualized
- Allow at least 6-12 weeks for a stable dose trial for a given antidepressant medication
- Monitor response to treatment using a depression scale such as the BDI, BDI-FS, or PHQ-9
  - A positive response is considered a 50% reduction from baseline (pre-treatment); nonresponse would be considered no net change from pre-treatment values

COGNITIVE DYSFUNCTION IN MS

Reports of the prevalence of cognitive impairment in patients with MS range from 35-60% (depending on the study, patient sample population, and neuropsychological measures utilized).[103] A cohort study by Amato et al with MS patients recruited before DMT availability reported cognitive impairment in 26% of patients at baseline, and in 56% 10 years later.[104] The National MS society estimates that only about 10% of MS patients have moderate to severe cognitive impairment.[1]

Typical cognitive deficits in patients with MS include[105]:

- Slowed speed of information processing
- Verbal fluency
- Attention and concentration
- Working memory
- Recent memory
- Visual/spatial perception
- Executive functioning

General intelligence, language, and long-term memory are generally not affected by MS.

Cognitive problems can impact activities of daily living, individual sense of self, role and responsibilities in the family, friendships and social connections, vocational capacity, and overall quality of life.

Risk factors for cognitive deterioration in patients with MS include:

- Increasing age
- Early age of MS onset
- Male sex
- Secondary progressive stage of disease
- Extent of gray matter atrophy
- Lower premorbid IQ (high premorbid intelligence appears to be protective against the progression of cognitive decline)

Depression, sleep difficulties and fatigue can all negatively impact cognitive abilities. In addition, some medications used for symptomatic treatment of MS have side effects that may contribute to (or appear to be) cognitive problems. Examples include amantadine (for fatigue); antimuscarinics, anticholinergics and antispasmodics (for bladder management); anticonvulsants such as topiramate (for neurogenic pain); baclofen and benzodiazepines (for muscle spasticity).[106]

A number of studies have reported associations between MRI findings and cognitive dysfunction, such as:

- A correlation between area of white matter lesions and cognitive impairment[103]
- Significant correlation between diffusion MRI metrics and neuropsychological testing[107]
- Correlation between brain: intracranial volume ratio and neuropsychological tests of nonverbal memory and mental processing speed[108]
- Third ventricle volume as a predictor of cognitive dysfunction (normalized thalamic volume lower in MS patients vs. healthy controls)[109]
- Cortical atrophy correlated with deficits in multiple measures of memory and executive function[110]
- Independent associations have been demonstrated between subcortical volume loss, and/or cortical atrophy, and MS-associated cognitive dysfunction[103]

Cognitive dysfunction has been reported early in the disease course (including in patients with CIS), and may be present even when physical disability is minimal.[111] A recent cross-sectional study of 1500 MS patients included 200 CIS, 1173 RRMS, 100 SPMS, and 27 patients with PPMS. Each of these groups scored below matched healthy controls on a computerized Global

Assessment Battery (which includes information processing speed, attention, verbal function, visual spatial perception, executive function, memory, and motor skills domains).[112] Patients with SPMS in this study had significantly lower global cognitive scores compared with CIS, RRMS and PPMS groups, and also had longer mean disease duration (20.5 vs 3.2, 9.8, and 8.9 years, respectively).[112] When the authors analyzed cognitive performance in patients with disease durations of 1, 5, 10, 15, 20, 25, and 30 years, they noted a significant decline in cognitive domains after 5 years from disease onset. While this result suggests that there may be a therapeutic window for intervention, limited data exist on the effect of DMTs on cognition in patients with MS. Patients with RRMS who were part of an open-label extension study of glatiramer acetate had stable cognitive performance over 10 years of prospective follow-up, which may be a reflection of effects of glatiramer acetate on disease burden or progression.[113] Fischer et al reported effects of IFNβ-1a (30 mcg IM weekly) vs placebo on cognitive function over 2 years.[114] In this study, patients with RRMS treated with IFNβ-1a had improved performance compared with placebo on measures of information processing and learning/memory. Recently, 5-year follow-up results of the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study have been published.[115] In this prospective, observational, cohort study, patients with RRMS were treated with either 22 or 44 mcg IFNβ-1a (SC, 3 times weekly); the primary endpoint of the extension study was the proportion of patients with cognitive impairment at year 5. Between baseline and 5 years, only small non-significant increases were observed in the proportion of patients with cognitive impairment in the two treatment groups, suggesting relative stability in cognitive function over this time frame.[115]

Even mild impairments in cognitive functioning may have a significant impact on daily life for patients with MS and their loved ones. Subtle changes in cognitive function such as deficits in information processing speed may not be readily apparent during routine health care visits. The National Clinical Advisory Board of the National Multiple Sclerosis Society has advised periodic screening and assessment for cognitive deficits in patients with MS, utilizing both patient and family queries for such assessment. Neuropsychological tests used for patients with MS include the Brief Repeatable Battery (BRB)[116] (40-45 minutes to administer), the Symbol Digit Modalities Test (SDMT)[117] (a brief test that can be repeated at monthly intervals), and the Minimal Assessment of Cognitive Function in MS (MACFIMS)[118] (requires ~90 minutes to complete). **(Table 28)**

Table 28: Neuropsychological Tests for Patients with MS

Cognitive Domain	MACFIMS[118]	BRB[116]
Auditory processing speed and working memory	Paced Auditory Serial Addition Test	Paced Auditory Serial Addition Test
Visual processing speed and working memory	Symbol Digit Modalities Test	Symbol Digit Modalities Test
Auditory or verbal episodic memory	California Verbal Learning Test–2nd Edition	Selective Reminding Test
Visual or spatial episodic memory	Brief Visuospatial Memory Test-Revised	10/36 Spatial Recall Test
Expressive language	Controlled Oral Word Association Test	Controlled Oral Word Association Test
Spatial processing	Judgment of Line Orientation	---
Executive function	Delis-Kaplan Executive Function System Sorting	---

Some clinicians order full neuropsychological examinations to determine a base-line early in MS. Others utilize neuropsychological examinations to answer specific questions relating to a patient's employment, ability to care for others, drive, etc. A neuropsychological exam may be costly and time consuming, but it can be a useful tool in following MS. In the pediatric MS context, where cognitive deficits are common and affect school performance, neuropsychological batteries are performed about every two years.

For patients identified with cognitive deficits, rehabilitation may be facilitated by speech and language therapists and/or occupational therapists. Solution-focused, practical training and compensatory strategies designed to maximize function in the presence of specific deficits are utilized. Examples are included in **Table 29**. Safety considerations related to ability to perform normal roles should also be addressed for patients with cognitive impairment, such as driving, cooking, and child care.

Table 29: Strategies for Helping Patients with Cognitive Dysfunction

Problem	Strategies
Processing speed	Take time; ask a speaker to slow down; use a recording device to review
Short-term memory	Make lists/notes; mnemonics; navigation system; smart phone reminders; key organizer
Attention and concentration	Minimize distractions; create a structured environment; avoid multi-tasking; work in a quiet area
Executive functioning	Make organized lists; prioritization; check things off, use organization aids (PDA, planner); templates for repeated tasks
Verbal fluency	Word games, on-line games and activities
Visual/spatial functioning	GPS, note to self, phone camera

In some cases, medication might be helpful for cognitive problems. Pharmacological therapies evaluated for MS-associated cognitive deficits include acetylcholinesterase inhibitors, stimulants, potassium channel blockers, and fatigue medications, although results to date do not support specific pharmacological treatment recommendations.[103]

FAMILY ISSUES

Several publications refer to the impact of MS on family life as "an uninvited guest" who moves in and never leaves. Guilt, anger, grief, sadness, and a sense of burden can complicate family dynamics and introduce communication barriers that were not present prior to a MS diagnosis.[119] MS onset typically occurs during productive years (between 20 and 50); a time associated with educational pursuits, career development, marriage, and having and raising children. The unpredictable nature and progressive course of MS impact the patient's role within the family structure, and may influence family planning, relationships with spouses/significant others and children, and have short and long-term financial consequences.[120,121] While it is the purpose of this section to identify family concerns to alert clinicians of their existence, it should also be noted that most families are able to negotiate the changes that accompany MS and continue to achieve a healthy functional level. Examples of family issues related to MS are included in **Table 30.**

Clinicians who care for patients with MS should be vigilant for any signs of difficulty or dysfunction within the family. Connecting patients and their families with mental health professionals, community resources, services, and support can help with the many challenges associated with MS.

- Mental health professionals can help to facilitate conversations to meet social and emotional needs of all family members
- Counseling can provide support for couples struggling with relationship issues
- Rehabilitation specialists can provide strategies to manage fatigue and enhance the patient's ability to function within the family, and engage in enjoyable family recreation
- The multidisciplinary care team can help with planning and problem solving for the changing needs of the patient, possible future disability, and help to minimize stress and anxiety associated with the future
- Parents should be encouraged to provide age appropriate information and education about MS for children, and provide opportunities for children to voice questions or concerns. Children may benefit from coming to occasional health care appointments to ask questions. As children grow and develop cognitively, more basic explanations about MS need to be expanded to match their increased capacity to understand the illness.
- Financial advisor(s) can provide consultation to understand how best to manage health care and other expenses
- The National MS Society and local chapters, the Multiple Sclerosis Association of America, and the MS Foundation provide educational materials, information on camps, programs, support groups, and a variety of services to support the needs of families with MS

Table 30: MS and Family Issues

Who/What Within the Family Is Impacted?	Examples of Issues
Patient	• Limitations to participation in parenting activities either during relapses or with progressive disease • Shifting of parental responsibilities • Guilt over letting the family down; not fulfilling obligations • Loss of identity due to changes in employment status or familial roles • Changes in the ability to participate in family activities and events • Loss of independence; dependence on caregivers and others • Embarrassment needing help with self-care • Sexual dysfunction • Family planning decisions, pregnancy, childbirth
Spouse/significant other/caregiver	• Caregiver burden • Sudden need to change roles and responsibilities • Distress, depression, and anxiety in part due to uncertainty and unpredictability of the disease • MS patient's cognitive and mood changes can be particularly challenging • Negative impact on caregiver's health • Influence on the caregiver's ability to pursue their own professional/career aspirations • Changes in intimacy due to partner's sexual dysfunction, physical limitations
Children	• Difficulty understanding a complex disease • Worry that behavior somehow contributed to Mom or Dad developing MS • Concern that a child's behavior may make a parent's MS worse • Difficulty understanding 'invisible symptoms,' fatigue, weakness, etc. that limit their parent's ability to participate/perform normal activities • Changes to social and educational plans • Limitations to participation in extracurricular activities • Social isolation • Taking on too much caregiver burden
Family financial situation	• Loss of income, potentially the "bread winner" in the family • Direct and indirect health care expenses • Costs associated with future disability and associated care

PSYCHOSOCIAL ADAPTATION TO MS

In order to fully support the psychosocial functioning of the patient with MS (and his or her family/care network), it is important to be mindful of the adaptation process that occurs following an MS diagnosis. Adaptation refers to the "continuous process by which an individual makes substantive changes over time, to accommodate for changing life circumstances and to maintain maximal functioning."[122] The health care team can play a role in helping to facilitate this process for patients with MS. The ultimate goal of the adaptation process is successful adjustment, individual and family growth, and accommodation to life with a chronic illness. The phases of adaptation to MS are summarized in **Table 31.**

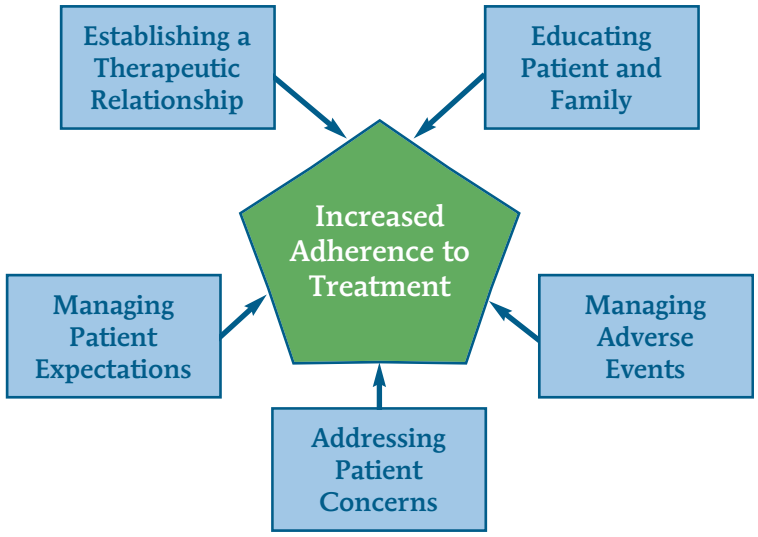
Table 31: Psychosocial Adaptation to MS

Phase of Adaptation	Considerations
Pre-symptomatic Phase	• Precedes awareness of neurological deficits • Serves as a reference point for what follows • Learning about this phase provides information about a patient's level of premorbid functioning, skills, interests, and hopes for the future
Symptomatic Phase	• Period between the onset of symptoms and the confirmation of the diagnosis
Crisis Phase	• Following the diagnosis, a time of struggling to understand the diagnosis, and the short and long term implications • Large volume of information to process and comprehend • Patient's partner experiences the life changing implications of the diagnosis and sense of loss • Both the patient and partner need: – Education – Hope – Help addressing fears, dealing with the experience of grief • Time to consider disclosure of illness to family members, friends, and employers • Defenses and coping mechanisms kick in • Social support may or may not be welcome at this time
Interim/Transitional Phase	• Period of stabilization • Patient is physically much like before • Reassuring for patients • Patients and families "get back on their feet" • Hopefulness emerges • "Naïve optimism" • Important to emphasize the need for treatment during remissions and periods of low disease activity
Chronic Phase	• "MS is here to stay" • A fuller experience of loss and better understanding and acceptance of the unpredictability of the illness • Much of the adaptation to MS takes place, effectively addressing challenges – Identity – Social isolation and social support – Couples issues – Personality issues and personal history • Important to normalize disease progression when it occurs (this is not a 'failure') • With increasing disability, the patient will need to accept care/assistance from others
Accommodation Phase	• Patients and families have adjusted to life with MS • Patients have become comfortable receiving personal care • Post-traumatic growth; benefit finding (positive growth in the midst of adversity) • Important for patients to maintain contact with neurologist during this phase

OPTIMIZING TREATMENT ADHERENCE

According to a 2003 World Health Organization report, adherence to long-term therapies in developed countries is approximately 50%.[123] The National Association of Chain Drug Stores reports that only 25-30% of prescriptions are taken properly, and 15-20% of prescriptions are refilled as prescribed.[124] Similar to other chronic conditions, adherence to DMTs for patients with MS can be challenging. Menzin et al recently reported a review of the literature on adherence to DMTs among patients with MS, based on studies published between 2001 and 2011.[125] This analysis, which included 16 prospective and 8 retrospective studies, showed that adherence to injectable DMTs for patients with MS ranged from 41 to 88%. Weighted mean adherence varied by DMT agent; 69.4% for IM IFNβ-1a; 63.8% for SC IFNβ-1a; 58.4% for SC IFNβ-1b; and 56.8% for SC GA.[125] The benefits of improved patient adherence to DMTs are clear: reduced risk for relapse, reduced MS disease progression, and lower medical resource utilization and costs.[125,126]

Figure 13: Strategies to Enhance Adherence to DMTs*



*Adapted from Brandes et al[129]

Predictors of adherence for patients with MS include:

- Self-efficacy
- Hope
- Perceived health care provider support
- No previous use of DMTs
- Spousal/family support
- Perceived benefits of adherence
- Use of an injection device for parenteral medications
- Positive patient education by health care providers

In several studies, the most frequently identified reason for treatment nonadherence identified by MS patients was simply forgetting to take medication (cited by 58% of patients, in a study by Treadaway et al).[127] Barriers to adherence to DMTs for patients with MS include:

- Injection-related reasons (anxiety, skin reaction, pain)
- Forgetting to take the medication
- Disease symptoms
  - Impaired visual function
  - Lack of manual dexterity
  - Spasticity
- Cognitive impairment
- Depression and anxiety
- Perceived lack of efficacy of medication
- Coping with adverse events
- Complacency
- Treatment fatigue

The MS health care team can play a significant role in helping patients optimize use of medication, and minimize missed doses of DMTs. Indeed, a high-quality patient clinician relationship can positively impact treatment adherence.[128] A generalized approach is summarized in **Figure 13**.

Suggested interventions to address specific barriers to treatment adherence for patients with MS are presented in **Table 32**.

Table 32: Interventions to Promote Treatment Adherence for Patients with MS (adapted[128])

Barrier	Interventions
Forgetting medication dose(s)	• Assess patient response to specialized requirements associated with medication • Perform cognitive assessment, including assessment for memory impairment • Evaluate/facilitate adjustment of frequency and complexity of regimen • Arrange for telephone and/or text messaging support/reminders • Incorporate family (eg, spouse and older children) into treatment plan • Use pill organizer, pill box • Consider switching to a DMT with less frequent dosing • Pairing administration of medication to a usual, repetitive daily activity
Side Effects	• Educate on expected symptoms, including pattern/duration (symptoms likely to diminish over time) • Consider change of dosing times • Provide recommendations for management of anticipated treatment-specific side effects (such as nausea, diarrhea, headache, flushing, flu-like symptoms, etc) • Employ dose titration or dose reduction if appropriate
Injection-site reactions	• Use site rotation; consider site mapping • Warm medication to room temperature • Allow alcohol to dry fully before injection • Consider avoiding alcohol swab and replacing with soap/water • Avoid vigorous rubbing of site pre- or post-injection • Use ethyl chloride spray, EMLA cream, or topical analgesics to site • Enlist support of injection-training nurses • Evaluate formulation and regimen: consider albumin-free formulations, the use of autoinjectors, and oral treatment options • Pretreat with ice for 1 minute; apply ice or cold compress after treatment to reduce swelling • Use hydrocortisone cream for swelling/rash relief
Fear or anxiety related to treatment	• Assess patient self-efficacy • Enlist support of patient family, significant others • Apply motivational interviewing techniques • Consider mindfulness training and guided imagery • For injectable medications, consider thinner gauge/shorter needle, or switch to a therapy that incorporates an autoinjector
Fatigue/tiring of treatment regimen	• Consider mindfulness training for fatigue • Evaluate/facilitate adjustment of frequency and complexity of regimen • Consider switch to a DMT with less frequent dosing • Evaluate/facilitate treatment for depression, other psychosocial factors
Economic/financial challenges	• Enlist support of social worker for help navigating system/finances • Facilitate contact with medication assistance programs for DMTs

Atreja et al have provided a mnemonic ("SIMPLE") to help clinicians remember categories of efforts to improve adherence:[130]

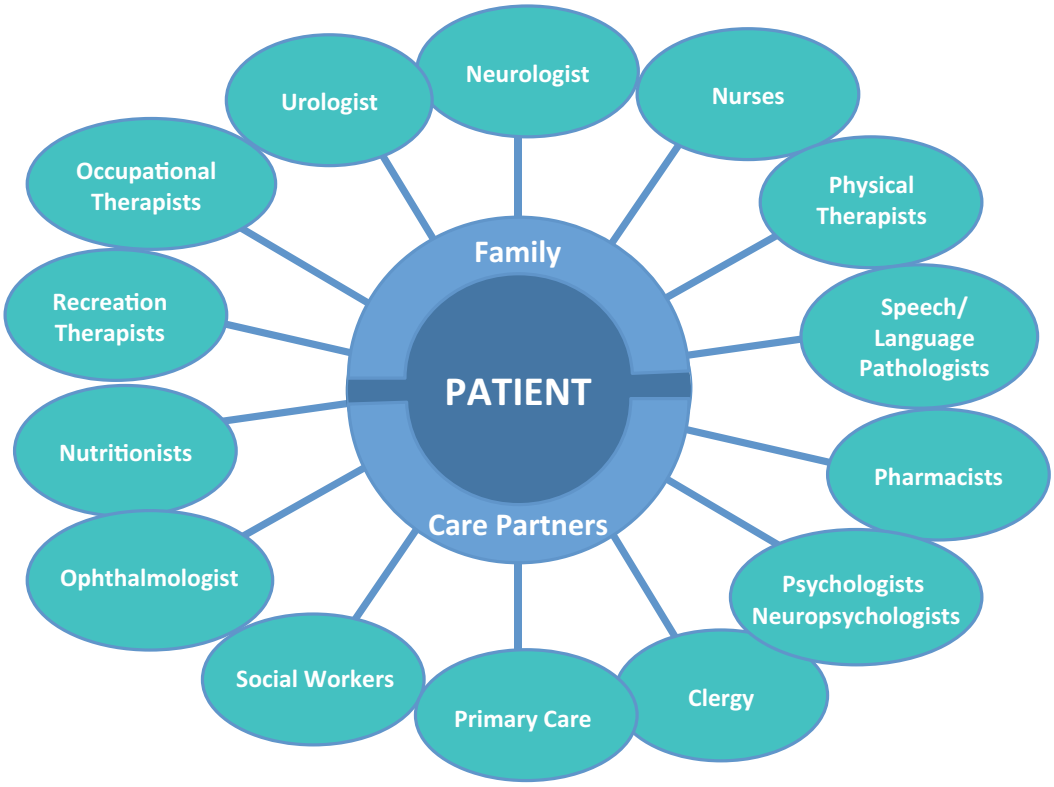
Simplify regimen
Impart knowledge
Modify patient beliefs and human behavior
Provide communication and trust
Leave the bias
Evaluate adherence

Effective communication and patient-provider shared decision making are pivotal to such efforts. The approach should be individualized to the patient, taking into consideration whether the individual is newly diagnosed/new to treatment vs. a long treatment history; the patient's attitude about taking medication; and what motivates the patient. With increasing use of oral therapies for MS, adherence-related issues may be different than with injectable DMTs. Independent of treatment approach, realistic expectations of treatment are essential. Patients may need to be reminded of the necessity of ongoing treatment even during periods of remission, and that relapses can occur in spite of treatment. The importance of treatment adherence cannot be understated. As Haynes et al noted in their 2009 review, "… effective ways to help people follow medical treatments could have far greater effects on health than any treatment itself."[131]

MULTIDISCIPLINARY, COLLABORATIVE CARE

The needs of patients with MS change over the course of the disease, and a multidisciplinary team approach is considered the most effective means of providing continuity of care. From adjusting to a MS diagnosis, to managing DMTs, symptom management, and dealing with accumulating disability, professionals from various disciplines can help support patients in order to maximize functioning and quality of life. The patient is at the center of the collaborative care team, as illustrated in **Figure 14**.

Figure 14: Collaborative, Multidisciplinary Care for MS



Consistent with the principles of the chronic care model, the MS team can help patients be informed, activated and engaged in the management of their condition. In a 2010 white paper, the CMSC provided the following objectives of comprehensive MS care[132]:

- Diagnose and/or confirm the diagnosis of MS
- Treat both acute episodes and modify the long-term disease course
- Provide medical treatment and management of MS symptoms
- Promote mobility for persons with physical impairments
- Minimize secondary and tertiary symptoms
- Help patients to maximize functional abilities, independence, safety measures, and productivity
- Assist patients and their families to cope with the psychological implications of MS
- Encourage patients and their families to become part of the rehabilitation process
- Provide education and information to patients, their families, health care professionals and the community
- Network with other community resources to obtain appropriate services
- Design, conduct, and participate in research studies in multiple sclerosis

Coordination of care for patients with MS is dependent on shared information amongst the multidisciplinary team: medication changes, test results (labs, ECGs, CXR, MRI, etc), concerns about safety/potential medication side effects, changes in cognitive functioning, psychiatric issues, etc. Electronic medical records and email can facilitate information sharing. Active communication and collaboration among clinicians (either within a community or in an MS comprehensive care center) is vital to support the changing needs of patients with MS and their families, and is consistent with quality indicators for MS.[133]

Comprehensive care is patient-centered, multidisciplinary care provided by a team that adopts a whole-person orientation. The patient is viewed as an integral team member, and is empowered to actively participate in care planning and self-care actions. This approach employs a balanced, rational, and dynamic methodology of treatment and care goals. It also avoids duplication or fragmented services through communication among team members, coordination and continuity of care. At different points along the disease continuum, care for a person with MS might include neurological, nursing, individual and family education and support, psychological and psycho-social services, physical, occupational, and speech therapies, and routine primary care and screening. The goal is to stabilize function, avoid or delay further deterioration, and minimize any comorbidities or complications that may occur during the disease course. Outcome focus is on approaches that sustain independence, educated decision-making, and realistic planning over the long course of the disease.

CHAPTER 4:
Patient Education, Tools, and Resources

PATIENT EDUCATION, TOOLS, AND RESOURCES

DIAGNOSIS

About MS. http://www.nationalmssociety.org/about-multiple-sclerosis/index.aspx

For People Newly Diagnosed
http://www.nationalmssociety.org/about-multiple-sclerosis/newly-diagnosed/index.aspx

About MS. http://mymsaa.org/about-ms/overview/#

National Institute of Neurological Disorders and Stroke Multiple Sclerosis Information Page
http://www.ninds.nih.gov/disorders/multiple_sclerosis/multiple_sclerosis.htm

Related Conditions
http://www.nationalmssociety.org/about-multiple-sclerosis/related-conditions/index.aspx

Diagnostic Workup for Patients with Suspected Demyelinating Disease: Testing Options
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/diagnosing-multiple-sclerosis/diagnostic-workup/index.aspx

Diagnostic Criteria
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/diagnosing-multiple-sclerosis/diagnostic-criteria/index.aspx

Differential Diagnosis
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/diagnosing-multiple-sclerosis/differential-diagnosis/index.aspx

Consortium of MS Centers MRI Protocol for the Diagnosis and Follow-up of MS
http://www.mscare.org/?page=MRI_protocol

TREATMENT

Treatments
http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx

Disease Modification
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/managing-ms/comprehensive-care/disease-modification/index.aspx

Emerging Therapies Collaborative. http://ms-coalition.org/emergingtherapies/

Symptom Management
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/managing-ms/comprehensive-care/symptom-management/index.aspx

Brochures on Managing Specific Issues
http://www.nationalmssociety.org/multimedia-library/brochures/managing-specific-issues/index.aspx

Brochures on Staying Well
http://www.nationalmssociety.org/multimedia-library/brochures/staying-well/index.aspx

Rehabilitation
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/managing-ms/comprehensive-care/rehabilitation-/index.aspx

International Organization of Multiple Sclerosis Rehabilitation Therapists
http://iomsrt.mscare.org/

Clinical Study Measures
http://www.nationalmssociety.org/ms-clinical-care-network/researchers/clinical-study-measures/index.aspx

Can Do Multiple Sclerosis. http://www.mscando.org/

Abledata (assistive technology information and resources). http://www.abledata.com/

American Occupational Therapy Association. http://www.aota.org/

American Speech-Language-Hearing Association. http://www.asha.org/

PSYCHOSOCIAL ISSUES

Psychosocial Support
http://www.nationalmssociety.org/ms-clinical-care-network/clinical-resources-and-tools/core-curriculum/managing-ms/comprehensive-care/psychosocial-support/index.aspx

Brochures on Managing Major Changes
http://www.nationalmssociety.org/multimedia-library/brochures/managing-major-changes/index.aspx

MS Connection. http://www.msconnection.org/

People Helping People: Peer Connection Programs
http://nationalmssociety.org/living-with-multiple-sclerosis/connection-programs/index.aspx/PeerToPeer

American Psychological Association Division 22: Rehabilitation Psychology
http://www.apa.org/about/division/div22.aspx

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