# The Use of Disease-Modifying Therapies in Multiple Sclerosis:

## Principles and Current Evidence

A Consensus Paper by the Multiple Sclerosis Coalition

MS Coalition®

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# DISCLOSURES

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# THE USE OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS

## Principles and Current Evidence

*A Consensus Paper by the Multiple Sclerosis Coalition*


## ABSTRACT

**Purpose**: The purpose of this paper, which was developed by the member organizations of the Multiple Sclerosis Coalition*, is to summarize current evidence about disease modification in multiple sclerosis (MS) and provide support for broad access to U.S. Food and Drug Administration (FDA)-approved MS disease-modifying therapies for people with MS in the United States.

**Development Process**: A writing and development team comprised of professional staff representing the Coalition organizations (Rosalind Kalb, PhD, Kathleen Costello, MS, ANP, June Halper, MSN, APN-C, Lisa Skutnik, PT, MA, MA, Robert Rapp) developed a draft for review and input by nine external reviewers (Brenda Banwell, MD, Aliza Ben-Zachariah, DrNP, ANP, MSCN, James Bowen, MD, Bruce Cohen, MD, Bruce Cree, MD, Suhayl Dhib-Jalbut, MD, Daniel Kantor, MD, Flavia Nelson, MD, and Nancy Sicotte, MD). The reviewers, selected for their experience and expertise in MS clinical care and research, were charged with ensuring the accuracy, completeness and fair balance of the content. The revised paper was then submitted for review by the medical advisors of the member organizations (see p. 33).

The final paper, incorporating feedback from these advisors, was endorsed by all eight Coalition members, and subsequently by Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

**Conclusions**: Based on a comprehensive review of the current evidence, the Multiple Sclerosis Coalition concluded the following:

## TREATMENT CONSIDERATIONS:

- Initiation of treatment with an FDA-approved disease-modifying treatment is recommended:
  - As soon as possible following a diagnosis of relapsing MS
  - For individuals with a first clinical event and MRI features consistent with MS, in whom other possible causes have been excluded
  - For individuals with secondary-progressive multiple sclerosis who continue to demonstrate clinical relapses and/or demonstrate inflammatory changes on MRI
- Treatment with any given disease-modifying medication should be continued indefinitely unless any of the following occur:
  - Sub-optimal treatment response as determined by the individual and his or her treating clinician
  - Intolerable side effects
  - Inadequate adherence to the treatment regimen
  - Availability of a more appropriate treatment
- Movement from one disease-modifying treatment to another should occur only for medically appropriate reasons.
- When evidence of additional clinical or MRI activity while on treatment suggests suboptimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.
- The factors affecting choice of treatment at any point in the disease course are complex and most appropriately analyzed and addressed collaboratively by the individual and his or her treating clinician.

## ACCESS CONSIDERATIONS:

- Due to significant variability in the MS population, people with MS and their treating clinicians require full access to a range of treatment options:
  - Different mechanisms of action allow for treatment change in the event of sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, gender or ethnicity.
- Absence of relapses while on treatment should not be considered a justification for discontinuation of treatment.
- Treatment should not be discontinued to allow for determination of coverage by payers as this puts the patient at risk for recurrent disease activity.

*The Multiple Sclerosis Coalition (see p. 32), which was founded in 2005 to increase opportunities for cooperation and provide greater opportunity to leverage the effective use of resources for the benefit of the MS community, includes Accelerated Cure Project for Multiple Sclerosis, Can Do Multiple Sclerosis, Consortium of Multiple Sclerosis Centers, International Organization of Multiple Sclerosis Nurses, Multiple Sclerosis Association of America, Multiple Sclerosis Foundation, National Multiple Sclerosis Society, United Spinal Association

# CONTENTS

# INTRODUCTION

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by inflammation, demyelination and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation.[1-3] Gradual worsening independent of acute attacks of inflammation, known as progressive or degenerative changes, may take place early, but more so over time.[4] While traditionally viewed as a disease of only white matter, more advanced imaging techniques have demonstrated significant early and ongoing gray matter damage.[5-7]

Those diagnosed with MS may have many fluctuating and disabling symptoms (including fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances and elimination dysfunction) with a significant impact on quality of life for patients and their families. As the most common non-traumatic, disabling neurologic disorder of young adults – a group not typically faced with a chronic disease – MS threatens personal autonomy, independence, dignity and life planning,[8] potentially limiting the achievement of life goals. The free-spirit spontaneity so highly valued by young adults needs to shift to deliberative planning in light of the challenges posed by functional fluctuations and an uncertain future. The patient's self-definition, roles and relationships may be co-opted by the need to adapt to an illness life style with frequent healthcare visits, testing and costly medications.

Compared to patients with other chronic diseases, those diagnosed with MS have diminished ratings in health, vitality and physical functions, and experience limitations in social roles.[9] Productivity and participation are affected for many by early departure from the workforce and inability to fulfill household responsibilities.[10] The lifetime financial cost of MS, including both direct and indirect costs of the disease, has been estimated at $1.2 million.[11] In addition, registry studies specific to MS and large population cohort studies of patients untreated with a disease-modifying therapy, have demonstrated a reduction in survival of 8-12 years.[12]

## Epidemiology, Demographics, Disease Course

It is estimated that there are more than two million people with MS worldwide with approximately 450,000 in the United States.[13-16] Women are affected at least 2-3 times more than men and Caucasians are affected more than other racial groups.[17] However, a recent study[18] suggested that African-American women have a higher than previously reported risk of developing MS. MS is typically diagnosed in early adulthood, but the age range for disease onset is wide with both pediatric cases and new onset of disease in older adults. Historically, a geographic gradient has been observed with a higher incidence of MS with increased distance from the equator.[19,20] However, some recent studies have not demonstrated the same north-south gradient,[21,22] suggesting either a change in regional risk determinants for MS or a broadening of the prevalence and recognition of MS worldwide.

The course of MS varies with 85-90 percent of individuals demonstrating a relapsing-remitting pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses (secondary-progressive MS). Approximately 10-15 percent of those diagnosed never have clinical symptoms consistent with a relapse; rather they demonstrate a steady progression of symptoms over time.[1,23] This primary progressive disease pattern of the disease is generally diagnosed at an older age and is distributed more equally in men and women.

## Inflammation and CNS Damage

At present, much of the CNS damage in MS is believed to result from an immune-mediated process. This process includes components of the innate immune system (including macrophages, natural killer cells and others) as well as adaptive immune system activation of certain lymphocyte populations in peripheral lymphoid organs.[24] CD4+ lymphocytes and CD8+ lymphocytes are activated in the peripheral lymph tissues. Antigen presentation to naïve CD4+ lymphocytes causes differentiation into various T lymphocyte cell populations, depending on the antigen presented, the cytokine environment and the presence of co-stimulatory molecules. The T lymphocyte cell populations include Th1 and Th17 lymphocytes (which are associated with a repertoire of inflammatory cytokines that activate macrophages and opsonizing antibodies) and Th2 lymphocytes and T regulatory cells (which drive humoral immunity or secrete anti-inflammatory cytokines).[24-26]

In people with MS, there is a bias towards a Th1 and Th17 environment with T regulatory dysfunction that allows inflammation to predominate.[27] Secreted cytokines and matrix metalloproteinases disrupt the blood brain barrier.[28] This disruption, along with up-regulation of adhesion molecules on blood vessel endothelium and activated T cells, allows T cells to gain entry into the CNS, where additional activation takes place that initiates an inflammatory and damaging cascade of events within the CNS (see Fig. 1). Multiple inflammatory cells become involved, including microglial cells and macrophages. In addition to CD4+ activation, CD8+ T lymphocytes have also been identified as important contributors to damaging CNS inflammation, and have been identified by numerous researchers as the predominant T cell present in active MS lesions.[29]

Further contributions to CNS damage in MS are associated with B cell activation. B cells function as antigen presenting cells and also produce antibodies that have damaging effects on myelin, oligodendrocytes and other neuronal structures.[30] Recent studies have also revealed that mitochondrial damage (possibly as a result of free radical, reactive oxygen species and nitrous oxide (NO) activity associated with activated microglia) and iron deposition occur in MS and make a significant contribution to demyelination and oligodendrocyte damage.[31-33]

Immune-mediated responses leading to inflammation, with secretion of inflammatory cytokines, activation of microglia, T and B cell activity, mitochondrial damage and inadequate regulatory function, are believed to be at least partially responsible for demyelination, oligodendrocyte loss and axonal damage. Axonal loss, which correlates best with disability, occurs early in the disease process as evidenced by identified pathological changes as well as imaging studies.[34,35]

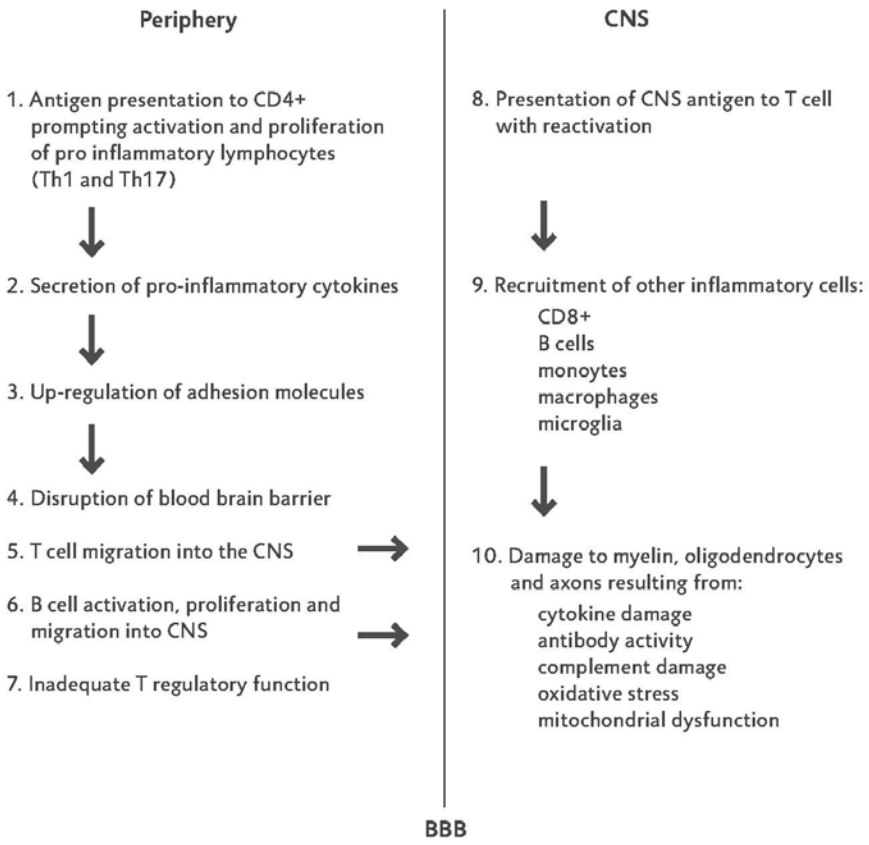


Figure 1: Inflammatory cascade in multiple sclerosis

# OVERVIEW OF APPROVED DISEASE-MODIFYING AGENTS IN MS

To date, 10 disease-modifying agents have been approved by the U.S. Food and Drug Administration (FDA):

Table 1: FDA-approved disease-modifying agents in MS (in alphabetical order by route of administration)

*Refer to the full FDA prescribing information for each medication for contraindications and additional details about side effects, warnings and precautions*

| Agent - Self-Injected | Proposed MoA | Side Effects | Warnings/Precautions |
|---|---|---|---|
| **glatiramer acetate**[36] (Copaxone®)<br><br>20 mg SC daily or 40 mg SC three times weekly<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: B** | -promotes differentiation to Th2 and T-reg cells, leading to bystander suppression in CNS[46]<br>-increased release of neurotrophic factors from immune cells[46]<br>-deletion of myelin-reactive T cells[46] | -injection site reactions<br>-lipoatrophy<br>-vasodilation, rash, dyspnea<br>-chest pain[36] | -immediate transient post-injection reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria),<br>-lipoatrophy and skin necrosis<br>-potential effects on immune response |
| **interferon beta 1a**[37,38] (Avonex®) (Rebif®)<br><br>IM 30 mcg weekly; SC 22 mcg or 44 mcg three times weekly<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: C** | -promotes shift from Th1-Th2<br>-reduces trafficking across BBB[47,48]<br>-restores T-reg cells[46]<br>-inhibits antigen presentation[46]<br>-enhances apoptosis of autoreactive T-cells[46] | -flu-like symptoms<br>-injection site reactions<br>-elevated hepatic enzymes<br>-decreased WBC<br>-see warnings[37,38] | -depression, suicide, psychosis<br>-hepatic injury<br>-anaphylaxis and other allergic reactions<br>-CHF<br>-decreased peripheral blood counts<br>-seizures<br>-other autoimmune disorders |
| **interferon beta 1b**[39,40] (Betaseron®) (Extavia®)<br><br>0.25 mg SC every other day<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: C** | -promotes shift from Th1-Th2<br>-reduces trafficking across BBB[47,48]<br>-restores T-reg cells[46]<br>-inhibits antigen presentation[46]<br>-enhances apoptosis of autoreactive T-cells[46] | -flu-like symptoms<br>-injection site reactions<br>-elevated hepatic enzymes<br>-decreased WBC<br>-see warnings[39,40] | -hepatic injury<br>-anaphylaxis and other allergic reactions<br>-depression and suicide<br>-CHF<br>-injection site necrosis<br>-decreased WBC<br>-flu-like symptoms<br>-seizures |
| **dimethyl fumarate**[41] (Tecfidera®)<br><br>240 mg PO twice daily<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: C** | -promotes anti-inflammatory and cytoprotective activities mediated by Nrf2 pathway | -flushing<br>-GI symptoms (abdominal pain, diarrhea, and nausea)[41]<br>-pruritis<br>-rash<br>-erythema | -lymphopenia<br>-opportunistic infection (PML) reported in rare patients taking oral fumarate for psoriasis[49] |

| Agent - Self-Injected | Proposed MoA | Side Effects | Warnings/Precautions |
|---|---|---|---|
| **fingolimod**[42] (Gilenya®)<br><br>0.5 mg PO daily<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: C** | -blocks S1P receptor on lymphocytes preventing egress from secondary lymph organs[47] | -headache<br>-influenza<br>-diarrhea<br>-back pain<br>-elevated hepatic enzymes<br>-cough<br>-bradycardia during first dose<br>-macular edema<br>-lymphopenia<br>-bronchitis/pneumonia (8% vs 4% placebo) | -bradyarrhythmia and/or atrioventricular blocks following first dose – extreme caution during treatment initiation in patients concurrently taking beta blockers or heart-rate-lowering calcium channel blockers<br>-risk of infections<br>-macular edema – posterior reversible encephalopathy syndrome (PRES)<br>-decrease in pulmonary function tests (*FEV*1)<br>-hepatic effects<br>-elevated BP<br>-women should avoid conception for 2 mos. after treatment d/c<br>-decreased lymphocyte counts for 2 months after drug d/c |
| **teriflunomide**[43] (Aubagio®)<br><br>7 mg or 14 mg PO daily<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: X** | -cytostatic effect on rapidly dividing T- and B-lymphocytes in the periphery<br>-inhibition of de novo pyrimidine synthesis<br>-metabolite of leflunomide (used in rheumatoid arthritis (RA) | -ALT increased<br>-alopecia<br>-diarrhea<br>-influenza<br>-nausea<br>-paresthesia<br>-requires cholestyramine or activated charcoal washout for accelerated elimination | -hepatotoxicity<br>-risk of teratogenicity<br>-decreased neutrophils, lymphocytes and platelets<br>-risk of infection, including tuberculosis<br>-no live virus vaccines<br>-potential increased risk of malignancy<br>-peripheral neuropathy<br>-acute renal failure<br>-treatment-emergent hyperkalemia<br>-increased renal uric acid clearance<br>-interstitial lung disease<br>-Stevens-Johnson syndrome and toxic epidermal necrolysis<br>-elevated BP<br>Note: some of these were carried over from leflunomide use in RA |
| **mitoxantrone**[44] (Novantrone®)<br><br>12 mg/m$^2$ IV every 3 months; maximum cumulative dose: 140 mg/m$^2$<br><br>Indication: worsening relapsing remitting, progressive-relapsing, secondary progressive MS<br><br>**Pregnancy Cat: D** | -disrupts DNA synthesis and repair; inhibits B cell, T cell, and macrophage proliferation; impairs antigen presentation, as well as the secretion of interferon gamma, TNFα and IL-2. | -temporary blue discoloration of sclera and urine<br>-nausea<br>-alopecia<br>-menstrual disorders including amenorrhea and infertility<br>-infections (URI, UTI, stomatitis)<br>-cardiac toxicity (arrhythmia, abnormal EKG, congestive heart failure) | -severe local tissue damage if there is extravasation<br>-cardiotoxicity<br>-acute myelogenous leukemia<br>-myelosuppression |
| **natalizumab**[45] (Tysabri®)<br><br>300 mg IV every 28 days<br><br>Indication: relapsing forms of MS<br><br>**Pregnancy Cat: C** | -blocks α4integrin on lymphocytes, thus reducing trafficking of lymphocytes into the CNS[47] | -headache<br>-fatigue<br>-urinary tract infection<br>-lower respiratory tract infection<br>-arthralgia<br>-urticaria<br>-gastroenteritis<br>-vaginitis<br>-depression<br>-diarrhea[45] | -progressive multifocal leukoencephalopathy (PML)<br>-hepatic injury<br>-herpes encephalitis and meningitis<br>-hypersensitivities |

Adapted from Oh J and Calabresi P in Multiple Sclerosis and Related Disorders Clinical Guide to Diagnosis, Medical Management and Rehabilitation 2013,[47] with supplemental data from the Full Prescribing Information for each agent: Copaxone (2014), Avonex (2012), Rebif (2014), Betaseron (2014), Extavia (2012), Gilenya (2014), Aubagio (2012), Tecfidera (2013), Novantrone (2008), Tysabri (2013); Graber et al, 2010.[36-46] BBB = blood-brain-barrier

# DISEASE-MODIFYING THERAPY CONSIDERATIONS

Several important themes emerge from the growing body of evidence in MS therapeutics: 1) Early successful control of disease activity – including the reduction of clinical and sub-clinical attacks and the delay of the progressive phase of the disease – appears to play a key role in preventing accumulation of disability, prolonging the ability of people with MS to remain active and engaged, and protecting quality of life. 2) Physical impairments comprise only one aspect of disability that results from early disease activity and disease progression. 3) Prognosis at the individual level remains highly variable and unpredictable. 4) Adherence to treatment is important to efficacy and may be impacted by a wide range of factors requiring early identification and intervention.

## Disease Factors Highlighting the Importance of Early Treatment

The goal of disease-modifying treatment is to reduce the early clinical and sub-clinical disease activity that is thought to contribute to long-term disability.[50,51]

The following points highlight the importance of early treatment:

### Neuroinflammation and neurodegeneration occur early in the disease course

It has long been thought that in early MS, inflammatory damage with associated demyelination and some axonal damage is the first of a two-stage disease process. In this initial stage, clinical relapses come and go as do focal areas of CNS inflammation with good recovery from neurologic symptoms. As the disease progresses, the second stage is characterized by degenerative changes, including more axonal and oligodendrocyte destruction with irreversible tissue damage and associated progressive clinical symptoms, which are thought to be a consequence of repeated, early inflammatory changes.[2] More recent studies suggest that rather than two distinct stages that occur in sequence, both neuroinflammation and neurodegeneration may occur simultaneously and perhaps independently:

- Early in MS, new MRI activity, evidenced by gadolinium enhancement, occurs approximately 7-10 times more frequently than clinical activity.[52]
- Inflammatory activity has been observed in patients with both relapsing and progressive forms of the disease.[2]
- Abnormalities are evident in normal appearing white matter as well as gray matter in the absence of focal inflammation and are seen early in the disease process.[6]
- Brain atrophy has been identified in early MS, even at the time of the first clinical attack.[53]
- Atrophy has been seen in radiographically isolated syndrome, a "pre-MS" condition with MRI abnormalities in the absence of clinical symptoms.[54]
- Inflammatory changes continue to be seen in secondary-progressive and primary-progressive MS.[2]
- Once a threshold is reached, disability progression continues at a rate that is unrelated to the prior relapse history.[55]

Whether neuroinflammation and neurodegeneration are determined to be independent or interrelated, prompt initiation and optimization of treatment is designed to minimize early inflammation and axonal damage.

### Individuals with a first clinical event accompanied by MRI findings consistent with MS, who do not receive treatment, have a high probability of experiencing further clinical disease activity

The term "clinically-isolated syndrome" (CIS) has been used to describe a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation and demyelination in one or more sites in the central nervous system (CNS).

Eighty percent of the placebo-treated patients in the four published phase III CIS trials had subsequent clinical events, which was defined at the time as conversion to clinically-definite MS (CDMS).[56-59] Follow-up data for these patients indicated a variable disease course, with approximately one-third having minimal clinical relapses and physical disability after 15-20 years but 42-50 percent converting to secondary-progressive (SPMS) with increasing disability.[60,61] Furthermore, baseline MRI findings in CIS predicted the development of definite MS as defined at the time. Lesion volume and the rate of lesion development earlier in the disease course were found to correlate with disability after 20 years.[61]

Subsequent to these trials, the 2010 revision of the McDonald diagnostic criteria facilitated an earlier diagnosis of MS based on a first clinical event and MRI findings demonstrating dissemination in space and time.[62] Using these newer criteria, many individuals in the early CIS trials would already have been diagnosed with MS. Although the term "CIS" may be nearly obsolete today, the importance of delaying and limiting additional relapses early in the disease process remains clear. Based on data from the published CIS trials, prompt identification of early relapsing patients with little or no disability is essential in order to achieve the best possible short- and long-term outcomes.[51]

### Early disease activity and disease course appear to impact long-term disability

Debate is ongoing about the ways and extent to which early disease activity impacts long-term disability.

- Some evidence suggests that early disability progression as measured by the Expanded Disability Status Scale (EDSS)[63] is the result of residual impairments from partially-resolved relapses.[50,64-66] Natural history studies suggest that relapses in the first two years of disease impact early progression,[67] with the impact of early relapses diminishing later in the disease course.[68]
- The onset and evolution of secondary-progressive MS (SPMS) – in which inflammatory attacks decrease – also appear to have an important association with long-term disability.[69] From this perspective, earlier SPMS onset is a primary predictor of disability, which means that a person's prognosis is essentially determined before progressive symptoms become predominant.
- Data from both early and late in the disease course highlight the impact of early disease activity on long-term outcomes. In patients identified as having CIS, Brex and colleagues[70] found that increases in lesion volume on MRI in the first five years of the disease correlate with the degree of long-term disability. And data from the 16-year cohort study follow-up of the pivotal trial of interferon beta-1b suggest that long-term physical and cognitive outcomes may be determined early in the disease.[71]

Given the medications that are currently available – all of which primarily target inflammation – the optimal window for impacting long-term disability is during the early relapsing phase of the disease, with the goal being to slow the accumulation of lesion volume, decrease the number of relapses and prevent disability from both unresolved relapses and disease progression.[50]

### Cognitive changes, depression and fatigue occur very early in the disease process

It is currently recognized that approximately 60 percent of people with MS will experience cognitive impairment;[72] 36-54 percent will experience a major depressive disorder;[73] and up to 92 percent will experience significant fatigue,[74] contributing to increased disability and reduction in quality of life.

- Evidence is accumulating that approximately 20-30 percent of people with a first clinical event have already experienced cognitive changes.[75-81]
- Some studies suggest that cognitive deficits may precede the onset of MS by as much as 1.2 years.[75] More specifically, verbal deficits have been shown to occur early and may predict the presence of cognitive impairment in people with a first clinical event.[77]

- Early cognitive changes are also known to progress, even in people with little or no physical changes,[80] and deterioration can be expected over a three-year period in approximately one-third of people with short disease duration.[82]
- Cognitive deficits are detected in approximately 30 percent of pediatric MS patients.[83-85]
- Depression and fatigue have been found along with cognitive deficits in early MS, with each having a significant impact on quality of life, employment and other important activities of daily life[86,87] – findings that highlight the importance of early treatment to help preserve people's ability to remain optimally engaged in everyday activities, including employment, and social interactions.[51,80]

### So-called "benign MS" may not be benign for many people

The most common working definition of "benign MS" – an Expanded Disability Status Score (EDSS) $\leq$3 at 10 years[88] – is highly weighted for patients' motor abilities and fails to capture non-motor components of the disease, particularly mood, cognition and fatigue.

- Cognitive, psychological and social changes and challenges were found in one cohort of individuals with "benign MS."[89]
- In another cohort of people with benign MS followed for 10.9 additional years, many developed higher EDSS scores, cognitive impairment, pain and depression, as well as a significant increase in new or enlarging T2 lesions and gadolinium (Gd)-enhancing lesions over time.[90]
- Sayao and colleagues evaluated disease status in a "benign MS" cohort after 20 years and found that while 51 percent remained benign, 21 percent had progressed to EDSS $\geq$6 and 23 percent had converted to SPMS. The authors concluded that appropriate criteria for determining which individuals will have a truly benign course of the disease have not yet been identified.[91]

Because truly benign MS can only be diagnosed retrospectively, after a minimum of 20 years, any decision to delay treatment for a given individual needs to take into account all of these important variables.[92]

## Evidence Demonstrating the Impact of Treatment Following a First Clinical Event

Although none of the available treatments are fully effective in stopping MS disease activity or disease progression, evidence points to the impact of early treatment on a range of disease factors:

### Delaying conversion to clinically-definite MS (CDMS)

Each of the four published placebo-controlled phase III trials in patients with clinically-isolated syndrome (CIS)[56-59] demonstrated that early treatment successfully delayed conversion to CDMS (as defined at the time of these trials) by about 45 percent at two to three years compared with placebo. Data have also been presented but not yet published demonstrating a delay of conversion to CDMS with teriflunomide.[93]

The eight-year, open-label follow-up of the early intervention study with interferon beta-1b, which compared the immediate treatment group with the delayed treatment (placebo) group, further demonstrated a reduced risk of CDMS and longer median time to CDMS in the early treatment group,[94] although the greatest differences occurred in the first year of treatment. A follow-up open-label phase of the early intervention study with glatiramer acetate demonstrated a reduced risk of CDMS and a delay in conversion to CDMS in the immediate treatment group as compared with the delayed treatment (placebo) group.[95]

## Evidence Demonstrating the Impact of Treatment on Relapsing MS

Although none of the available disease-modifying therapies are fully effective in controlling the disease, each has been shown to provide significant benefits in relapsing forms of MS. *Due to differences in patient cohorts, trial designs and outcome measures, as well as changes in diagnostic criteria, these data should not be used to compare efficacy of specific agents across trials.*

### Impact on clinical outcomes (relapse rates and disability progression)

Table 2: Disease-modifying therapies: pivotal trial data on relapse rate and disability progression (in alphabetical order within route of administration)*

| Agent | Effect on Annualized Relapse Rate Compared to Placebo* | Effect on Disability Progression Compared to Placebo |
|---|---|---|
| **Self-Injected Agents** | | |
| glatiramer acetate[96] | 29% | 12% decrease (N.S.)<br>progression free: 75.4 placebo; 78.4% treated |
| interferon beta 1-a subcutaneous[97] | 32% | 30% decrease in proportion with sustained disability progression |
| interferon beta 1-a intramuscular[98] | 18%[47] | 37% decrease in time to sustained disability progression |
| interferon beta 1-b[99] | 34% | 29% decrease (N.S.)<br>insignificant change from baseline EDSS |
| **Oral Agents** | | |
| dimethyl fumarate[100,101] | 53%[100]<br>44%[101] | 38% decrease in risk of disability progression[100]<br>N.S.[101] |
| fingolimod[102] | 54% | 30% decrease in risk of disability progression |
| teriflunomide[103] | 31% | 23.7% 7mg; 29.8% 14mg |
| **Intravenous agents** | | |
| mitoxantrone[104] | 67% | placebo: increased 0.23 EDSS over 24 mos; 12 mg/m2: decreased 0.13 EDSS over 24 mos [absolute and relative risks not reported] |
| natalizumab[105] | 68% | 42% decrease in risk of confirmed disability progression |

Adapted from Oh & Calabresi in Rae-Grant, et al, 2013;[47] Johnson et al, 1995;[96] PRISMS Study Group 1998;[97] Jacobs et al, 1996;[98] IFNB MS Study Group, 1993;[99] Gold et al, 2012;[100] Fox et al, 2012;[101] Kappos et al, 2010;[102] O'Connor et al, 2011;[103] Hartung et al, 2002;[104] Polman et al, 2006.[105] N.S.=not significant.

* Comparison across clinical trials is impossible due to differences in patient populations, diagnostic definitions, primary and secondary endpoints and outcome metrics.

While it remains unclear the extent to which reducing relapses impacts long-term disability levels, it is evident that relapse reduction translates into increased comfort and quality of life, fewer days lost from work and other essential activities of daily life, and reduces the risk of residual deficits.

## Impact on MRI parameters

Table 3: Disease-modifying therapies: pivotal trial data on MRI parameters (listed alphabetically within route of administration)*

| Agent | Effect on GD+ lesions | Effect on new or enlarging T2 lesions |
|---|---|---|
| **Self-injected Agents** | | |
| glatiramer acetate | cumulative # Gd lesions at 9 months: 17 placebo; 11 treated | not reported in PI |
| interferon beta 1-a subcutaneous | median # of active lesions per patient per scan: 2.25 placebo; 0.5 44 mcg | median percent (%) change of MRI PD-T2 lesion area at 2 years: 11% placebo; -3.8% 44 mcg |
| interferon beta 1-a intramuscular | mean # at 2 years: placebo 1.6; treated 0.8 | % change study entry to year 2: 6.55% placebo;13.2% treated |
| interferon beta 1-b | no Gd outcomes from phase 3 pivotal trial | median percent change in MRI area (n=52, scans q6wks): 16.5% placebo; 1.1% 0.25 mg |
| **Oral Agents** | | |
| dimethyl fumarate | mean # Gd+ lesions at 2 years: placebo 1.8; 240 mg bid 0.1 | mean # new or newly enlarging T2 lesions over 2 years: 17 placebo; 2.6 240 mg bid |
| fingolimod | mean # T1 Gd-enhancing lesions at month 24: placebo 1.1; 0.5mg 0.2 | mean # new or newly enlarging T2 lesions over 24 month: 9.8 placebo; 2.5 0.5 mg |
| teriflunomide | mean # Gd-enhancing lesions per scan: placebo 1.331; 14 mg 0.261 | median change from baseline in total lesion volume (T1 +T2) (mL) at week 108: 1.127 placebo; 0.345 14 mg |
| **Intravenous Agents** | | |
| mitoxantrone | # of patients with new Gd-enhancing lesions: placebo 5/32 (16%); 5 mg/m$^2$ 4/37 (11%); 12 mg/m$^2$ 0/31 | change in # of T2-weighted lesions, mean Month 24-baseline: placebo 1.94; 5mg/m$^2$ 0.68; 12 mg/m$^2$ 0.29 |
| natalizumab | median # Gd lesions at 2 years: placebo 0; treated 0% with 2 or more enhancing lesions: placebo 16%; treated 1% | median # new or enlarging T2 lesions at 2 years: placebo 5; treated 0 |

Full Prescribing Information for each agent: Copaxone (2014),[36] Avonex (2012),[37] Rebif (2014),[38] Betaseron (2014)[39], Extavia (2012),[40] Tecfidera (2013),[41] Gilenya (2014),[42] Aubagio (2012),[43] Novantrone (2008),[44] Tysabri (2013).[45]

*Comparison across clinical trials is impossible due to differences in patient populations, diagnostic definitions, primary and secondary endpoints and outcome metrics.

Subsequent to the pivotal trials, several investigations have demonstrated an impact of treatment on the evolution of persistent T1 hypointensities (known as "black holes"), which are thought to be indicative of tissue damage, and on atrophy:

- Glatiramer acetate was shown to limit the evolution of newly formed lesions into chronic black holes.[106]
- In a phase 2 study comparing dimethyl fumarate with placebo, new Gd-enhancing lesions had a lower probability of evolving into T1-hypointense lesions in the 240 mg tid treatment group versus the placebo group.[107]
- Treatment-naïve patients randomized to two doses of interferon beta or glatiramer acetate experienced no additional brain atrophy in years two and three – with overall median increases in brain volume from baseline to year three being similar across all groups – demonstrating the neuroprotective effects of treatment.[108]
- Several studies utilizing differing designs have demonstrated the ability of intramuscular interferon beta-1a, alone or in combination with other medications, to reduce the progression of whole-brain or cortical-brain atrophy versus placebo or no treatment.[109-111]
- A study evaluating the effects of glatiramer acetate, intramuscular and subcutaneous interferon beta-1a, and interferon beta-1b on brain volume loss in relapsing-remitting MS over a five-year period found that all of the medications significantly reduced brain volume loss compared to no treatment.[112]

- In a phase 3 fingolimod study, fingolimod reduced brain volume loss over 12 months compared with intramuscular interferon beta-1a in all patient subgroups.[113]
- In the two-year, placebo-controlled trial (the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis [AFFIRM] study), involving 942 patients with relapsing multiple sclerosis (MS), brain atrophy was greater in year 1 and less in year 2 in natalizumab-treated patients.[114]

### Impact on long-term clinical outcomes

Following a cohort of people over an extended period of time has many limitations, including uncontrolled design, poor accounting for drop-outs and retrospective assessments in most cases. However, some important data have emerged:

- Most of the extension studies from the pivotal trials indicated a positive impact on conversion to clinically definite MS, relapse rates and disease progression,[71,94,115-116] although much of the impact may take place early in the disease course.[71]
- The 10-year follow-up of the early intervention trial with interferon beta-1a (intramuscular) found a delayed conversion to clinically definite MS and reduced relapse rates in the early treated group compared to the delayed treatment group, but no difference in disability outcomes, most likely because both groups received treatment relatively early in the disease course.[117]
- Approximately 90 percent of untreated RRMS patients will have SPMS after 20-25 years.[118] Evidence from several studies now indicates that disease-modifying therapies have an impact on the conversion from relapsing to progressive MS:
  - In a study comparing the time interval from disease onset to secondary progression in relapsing-remitting patients treated with disease-modifying therapy and patients receiving no treatment, a significantly longer time to secondary-progression was seen in the treated group.[119]
  - A study comparing treated and untreated patients over a 10-year period, prior to the endpoint of conversion to secondary-progressive MS, found that treatment with a disease-modifying therapy significantly reduced the risk of disease progression in patients considered high- or low-risk at disease onset.[120]
  - In a study comparing patients treated with interferon beta for up to seven years with untreated patients, the treated group had a significant reduction in the incidence of secondary progression as well as in the incidence of EDSS progression.[121]
- The impact of early treatment on other clinical outcomes is also important. Extension study data from the early treatment trial with interferon beta-1b suggest that early treatment helps to preserve cognitive function compared to delayed treatment,115,122 with evidence suggesting that long-term (physical and cognitive) outcomes may largely be determined early in the disease course.71 A recent study demonstrated decreased mortality in patients treated early in the course of their disease compared with those treated somewhat later,12 a finding that needs to be confirmed with the newer agents in long-term studies.

### Improving quality of life

Clinical and MRI outcomes do not fully capture the impact of MS disease-modifying therapies for people with MS. Unfortunately, efforts to assess the impact of treatment on quality of life have been limited. Not being on a disease-modifying therapy was one of the factors identified as contributing to a decrease in health-related quality of life in the NARCOMS database, although quality of life generally remained generally stable for most people over the five years of the study.[123] Health-related quality of life scores on physical and mental components of the Short form (36) Health Survey (SF-36 – a patient-reported survey of health outcomes) improved in the pivotal trials of natalizumab.[124] In the pivotal trial of dimethyl fumarate, patients on treatment evidenced a significantly greater

change in SF-36 physical component summary scores compared with those in the placebo arm and similar benefits were seen in other measures of functioning and general well-being as early as Week 24.[125]

Early treatment to reduce loss of mobility has been shown to help preserve people's ability to carry out instrumental activities of daily living,[126] and the ability to work was found to improve after one year of treatment with natalizumab.[127]

### Benefits gained through early treatment may never be equaled in those whose treatment is delayed

Data suggesting that benefits gained through early treatment – including delayed conversion to clinically definite MS, reduced relapse rates and slowed progression of disability – may not be equaled in those who start treatment later in the disease course,[56,58,117,128-130] suggesting that people who start treatment later may not "catch up" with those who start treatment immediately.

As stated earlier, however, the 10-year follow-up to the early intervention trial with interferon beta-1a (intramuscular) found no difference in disability outcomes between the early- and delayed-treatment groups, indicating that the delayed treatment group did appear to experience a "catch up" in this particular outcome. It remains to be determined the extent to which the older medications – and the newer medications for which we do not yet have any long-term data – impact longer-term disability outcomes for people with MS.

## Evidence Supporting the Need for Treatment to be Ongoing

Once a disease-modifying treatment is initiated, evidence suggests that treatment needs to be ongoing for benefits to persist. Cessation of treatment has been shown to negatively impact clinical and MRI outcomes.

- Non-adherence and gaps in treatment are associated with increased rate of relapses and progression of disability.[131-132]
- In a review of the adherence literature, relapse rate and progression were greater in those who stopped injectable disease-modifying treatment and several reviewed trials showed an increase in emergency department utilization by patients who had stopped treatment.[133]
- In one study, relapses and MRI activity returned to baseline following cessation of interferon therapy, although there was a several month refractory period before activity resumed.[134] In another study, active patients treated with interferon beta promptly returned to pre-treatment levels of disease activity following discontinuation of treatment,[135] leading the authors to recommend that treatment not be stopped in patients who are responding to treatment. A similar return to baseline disease activity in interferon-treated patients was observed in secondary-progressive MS, with an increase in EDSS scores and MRI activity in the year after discontinuation of treatment.[136]
- Relapse rates returned to baseline following interruption of natalizumab treatment,[137] and in a partially placebo-controlled exploratory study of disease activity during an interruption of natalizumab therapy, patients whose treatment was interrupted had an increased risk of disease and MRI activity compared with those on continuous treatment.[138] In a retrospective study of patients refractory to interferon or glatiramer who had been switched to natalizumab and then stopped it, some patients had significant relapses – indicating that simple withdrawal of this medication without an exit strategy may risk return of disease activity or rebound, typically beginning within one-to-six months.[139-142]
- Cessation of fingolimod after a period of stability was followed by clinical relapse and multiple enhancing lesions on MRI in two patients,[143] and both patients had a significant worsening in EDSS score associated with their clinical activity. In another report of six cases of fingolimod discontinuation, five patients returned to pre-treatment disease activity within three months and one patient had both clinical and MRI rebound activity.[144]

These studies and case reports illustrate the need for ongoing disease-modifying treatment in MS. Regardless of the reason for the discontinuation of treatment – a decision by the treating clinician, patient non-adherence, cost or insurance coverage issues – these findings indicate that discontinuation or interruption of treatment will provoke a return of disease activity in many people.

## Use of Disease-Modifying Therapies in Pediatric MS

Studies have estimated the incidence of pediatric MS to be between 0.18 and 0.51/100,000 children per year.[145-146] Three percent of adult patients retrospectively report a possible first attack prior to age 18 in childhood.[147] More than 97 percent of children and adolescents experience a relapsing-remitting disease course,[145] with annualized relapse rates 2 to 3 times that of adults with MS during the first three years of disease.[148] In addition to motor and other physical symptoms, 30-40 percent of children with MS demonstrate cognitive impairment early in the disease course.[83-85]

The interferon beta medications and glatiramer acetate are generally considered the initial treatment options for children with MS.[145,149] As in adults, however, evidence of ongoing relapses, MRI activity, and increasing disability indicate the need to change treatment, and some children and teens experience particularly active disease that does not respond to the first treatment used, or even subsequent options.[149] In one study involving 258 children over a mean observation period of 3.9 years, a little more than half were successfully managed on the first medication they were given, while 25.2 percent were switched once, 11.2 percent were switched twice, and 7.8 percent required three changes in medication. While some were switched from one injectable medication to another, others required more aggressive treatment in order to control their disease.[149] Several retrospective analyses regarding safety and tolerability of natalizumab support the use of natalizumab in pediatric MS patients with active disease.[150-152]

The importance of evaluating therapies in the MS pediatric population has been emphasized[145] and pediatric clinical trials of all new agents are now mandated by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), opening the door for clinical trials that will inform the use of agents in children and teens with very active disease.[153-154] Such trials are critical not only to provide patients and clinicians with efficacious treatments, but also to ensure safety, tolerability and appropriate dosing.

## Rationale for Access to Full Range of Treatment Options

At the present time, 10 medications are FDA-approved to treat MS (See Table 1), with seven different mechanisms of action that are thought to address distinct components of the immune-mediated disease process. These medications also differ in their route and frequency of delivery as well as their side effect and risk profiles. *None of these medications are completely effective and the effectiveness of any given medication varies considerably from one individual to another and for any given individual at different points in time*. In addition, people with MS differ in their tolerance for different delivery mechanisms and side effects, and clinicians and patients vary in their tolerance for risk, with risk tolerance likely undergoing shifts as the disease progresses. For all of the following reasons, access to the full range of options is essential in order to optimize the ability of people with MS and their clinicians to make optimal treatment decision.

## Non-responders need access to other options

The goal of treatment is to control disease activity and prevent irreversible damage as quickly and effectively as possible. When a person's medication does not provide sufficient benefit or provides initial benefit and then ceases to do so – as determined by the individual and his or her clinician in light of continued clinical and/or MRI disease activity – the reasons for lack of efficacy need to be explored[155] and alternative options need to be tried.[50] It is known, for example, that disease activity that occurs in spite of treatment with IFN beta is associated with unfavorable long-term outcomes.[156-157] Furthermore, MRI activity as well as relapses are key indicators of progression[158-159] and the presence of Gd enhancing lesions has been shown to correlate strongly with severe disability 15 years later.[156]

## Treatment with interferon beta is frequently associated with the development of neutralizing antibodies (NAbs)

Although comparisons are challenged by the lack of standardization in assays and lack of consensus concerning the relevant threshold of NAb concentration,[160] the phase III trials of the interferon beta medications,[97-99] as well as subsequent direct comparison studies,[161-162] have demonstrated that NAbs are a common occurrence with these medications and that there is significant variability between the medications in terms of their occurrence. Furthermore, the studies suggest that the presence of NAbs reduces the clinical efficacy of interferon beta – although the impact may not be clear for some time.[160] Determining the impact of NAbs for any given individual is further challenged by the fact that NAb-positive patients may revert to NAb-negative status or fluctuate between positive and negative NAb status.[161] However, the fact remains that a person who has persistent disease activity on interferons, regardless of whether this is due to Nabs or not, needs access to additional non-interferon treatment options.[163-164]

## Individuals with contraindications need access to suitable options

For a variety of reasons (cited as contraindications in medication labeling[36-40,42-43,45]), individuals may not be suitable candidates for one or another of the available disease-modifying therapies:

- Hypersensitivity to natural or recombinant interferon beta, albumin or other component of the formulation, precluding the use of interferon medications
- Hypersensitivity to glatiramer acetate or mannitol
- Cardiac or macular conditions precluding the use of fingolimod
- Current or past diagnosis of progressive multifocal leukoencephalopathy (PML), precluding the use of natalizumab
- Severe hepatic impairment, precluding the use of fingolimod, interferons, natalizumab and teriflunomide
- Current use of leflunomide, precluding the use of teriflunomide

  In addition to these contraindications, post-marketing data (Avonex; Rebif; Betaseron; Extavia)[37-40] have led many clinicians to avoid the use of interferon beta medications in individuals who are depressed or have a history of significant depression. Though several studies have found no relationship between these medications and depression in people with MS the package labels carry a warning regarding this.[165-168]

**Because severity of disease varies at onset – with some individuals experiencing early aggressive disease – patients and their treating clinicians need access to all available options**

- **Adults with very active disease from onset**
  Although MS remains a highly unpredictable disease, some effort has been made to identify patients at high risk of disease progression:
  - Scalfari and colleagues found that time to Expanded Disability Status Scale (EDSS) 3 highly and independently predicted time to EDSS 6, 8 and 10. The same group found that higher early relapse frequencies and shorter first inter-attack intervals increased the probability of – and hastened conversion to – secondary progression, and that although long-term outcomes were highly variable, some individuals who experienced frequent relapses and/or accumulated a large number of focal lesions on T2 MRI within the first five years were at greater risk of disability.[67]
  - Fisniku and colleagues[61] found lesion volume and its change at earlier time points to be correlated with disability after 20 years. In their study lesion volume increased for at least 20 years in relapse-onset multiple sclerosis and the rate of lesion growth was three times higher in those who developed secondary progression than in those who remained relapsing-remitting.
  - A prospective study in British Columbia that utilized three possible criteria for aggressive MS – confirmed Expanded Disability Status Scale (EDSS) ≥6 within five years of MS onset; confirmed EDSS ≥ 6 by age 40; and secondary progressive MS within three years of a relapsing-onset course – identified aggressive MS in 4-14% of people depending on the definition used.[169] Although the majority were men and those with PPMS, there were also a significant number of female patients and patients with RRMS.

  Given these findings, patients with highly inflammatory and potentially aggressive disease may determine with their treating clinician that the benefit-to-risk ratio may warrant starting a therapy with potentially greater risks.[170]

  In addition, there is evidence to suggest the use of natalizumab[171] or mitoxantrone[172-175] as induction therapy for people with early aggressive disease characterized by frequent relapses with incomplete recovery and the accumulation of focal lesions in MRI.[176]

- **African-Americans appear to have more active disease**
  Several studies have now pointed to a more active disease course in African-Americans with MS. In one cohort, primary-progressive MS was more common in African-American patients, as was cerebellar dysfunction and a more rapid progression of disability.[177] Compared to Caucasians, African-American patients have also been found to have a greater likelihood of developing opticospinal MS and transverse myelitis and to have a more aggressive course.[178] Increased tissue damage and lesion volumes have also been found in African-Americans.[179] Given that there are also preliminary indications that African-Americans may not respond as well to the available disease-modifying therapies,[180-181] it is essential for African-American patients and their clinicians to have access to the full range of treatment options in the event that one or another does not provide sufficient benefit.

- **Children with aggressive disease**
  As mentioned above (see p. 17), some children may experience very active disease that does not respond to the medications generally considered to be first-line treatment options for pediatric-onset MS.

**People who for one reason or another are not adhering to a treatment regimen need access to treatment options that increase their likelihood of adherence.**

People who do not adhere to or persist with their treatment regimen are unlikely to receive the full benefit the treatment.[182-183] Fortunately, the available data – which thus far includes only the injectable medications – suggest that adherence is relatively high.[184]

Factors associated with poorer adherence include:

- Perceived lack of efficacy in relation to expectations[183,185]
- Route of administration[186-187]
- Perceived risks[185,188-189] [injectables only]
- Tolerability issues with injectables, including flu-like symptoms and injection-site reactions[190-193]
- Length of time on treatment[189]
- Costs[194]
- Psychosocial factors, including coping style,[195] mood,[139,196] and "forgetting."[189,192-193]

Addressing adherence issues begins with identifying the non-adherent patient so that the cause(s) can be identified and addressed. In some instances, this may include an alternative treatment option that is likely to enhance the person's ability to adhere to the treatment plan.

# CONCLUSIONS REGARDING THE NEEDS OF PEOPLE WITH MS

Although there is still much that we do not fully understand about the pathophysiology of MS, the last 20 years have provided a significant number of treatment options that improve prognosis and quality of life for people with MS. Furthermore, the growing body of evidence highlights the importance of early and ongoing access to disease-modifying therapies.

## Treatment Considerations

- Initiation of treatment with an FDA-approved disease-modifying treatment is recommended:
  - As soon as possible following a diagnosis of relapsing MS
  - For individuals with a first clinical event and MRI features consistent with MS, in whom other possible causes have been excluded
  - For individuals with secondary-progressive multiple sclerosis who continue to demonstrate clinical relapses and/or demonstrate inflammatory changes on MRI
- Treatment with a given medication should be continued indefinitely unless any of the following occur:
  - Sub-optimal treatment response as determined by the individual and his or her treating clinician
  - Intolerable side effects
  - Inadequate adherence to the treatment regimen
  - Availability of a more appropriate treatment
- Movement from one disease-modifying treatment to another should occur only for medically appropriate reasons.
- When evidence of additional clinical or MRI activity while on treatment suggests suboptimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.
- The factors affecting choice of treatment at any point in the disease course are complex and most appropriately analyzed and addressed collaboratively by the individual and his or her treating clinician.

## Access Considerations

- Due to significant variability in the MS population, people with MS and their treating clinicians require full access to a range of treatment options:
  - Different mechanisms of action allow for treatment change in the event of sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, gender or ethnicity.
- Absence of relapses while on treatment should not be considered a justification for discontinuation of treatment.
- Treatment should not be discontinued to allow for determination of coverage by payers as this puts the patient at risk for recurrent disease activity.

# REFERENCES


1. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996; 46:907–911.
2. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009; 132(Pt 5):1175-89.
3. Charil A, Filippi M. Inflammatory demyelination and neurodegeneration in early multiple sclerosis. J Neurol Sci. 2007;259(1-2):7-15.
4. Lassmann H, Van Horssen J, Mahad D. Progressive multiple sclerosis: Pathology and pathogenesis. Nat Rev Neurol. 2012; 8:647–656.
5. Simon JH. MRI outcomes in the diagnosis and disease course of multiple sclerosis. In Goodin D (Ed) Handb Clin Neurol. 2014;122:405-25.
6. Lucchinetti CF, Popescu BFG, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. N Engl J Med. 2011;365(23):2188–2197.
7. Klaver R, De Vries HE, Schenk GJ, Geurts JJ. Grey matter damage in multiple sclerosis: a pathology perspective. Prion. 2013 Jan-Feb;7(1):66-75.
8. Boeije HR, Duijnstee MS, Grypdonck MH, Pool A. Encountering the downward phase: biographical work in people with multiple sclerosis living at home. Soc Sci Med 2002; 55: 881-93.
9. Sprangers MAG, de Regt EB, Andries F, et al. Which chronic conditions are associated with better or poorer quality of life? J Clin Epidemiol 2000; 53: 895-907.
10. Julian LJ, Vella L. Vollmer, T. Hadjimichael O. Employment in multiple sclerosis. Exiting and re-entering the work force. J. Neurol. 2008; 255:1354-1360.
11. Trisolini M, Honeycutt A, Wiener J. Lesesne S. Global economic impact of multiple sclerosis. Multiple Sclerosis International Federation 2010.
12. Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNB-1b trial. Neurology. 2012 Apr 24;78(17):1315-22.
13. Giesser BS. Diagnosis of multiple sclerosis. Neurol Clin. 2011 May;29(2):381-8.
14. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000 Sep 28;343(13):938-52.
15. Weinshenker BG. The natural history of multiple sclerosis. Neurol Clin. 1995 Feb;13(1):119-46.
16. Weinshenker BG. The natural history of multiple sclerosis: update 1998. Semin Neurol. 1998;18(3):301-7.
17. Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, et al. Incidence and prevalence of multiple sclerosis in the Americas: A systematic review. Neuroepidemiology 2013;40(3):195-210.
18. Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. Neurology. 2013 May 7;80(19):1734-9.
19. Alla S, Mason DF Multiple sclerosis in New Zealand. J Clin Neurosci. 2013 Nov 4. pii: S0967-5868(13)00591-2.
20. Simpson S Jr, Blizzard L, Otahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry. 2011 Oct;82(10):1132-41.
21. Berg-Hansen P, Moen S, Harbo H, Celius E. High prevalence and no latitude gradient of multiple sclerosis in Norway. Mult Scler. 2014 Mar 6.
22. Aguirre-Cruz L, Flores-Rivera J, De La Cruz-Aguilera DL, Rangel-López E, Corona T. Multiple sclerosis in Caucasians and Latino Americans. Autoimmunity. 2011 Nov;44(7):571-5.

23. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Neurology 2014 May 28 [Epub ahead of print].
24. Koch MW, Metz LM, Agrawal SM, Yong VW. Environmental factors and their regulation of immunity in multiple sclerosis. J Neurol Sci. 2013 Jan 15;324(1-2):10-6.
25. Lubetzki C, Stankoff B. Demyelination in multiple sclerosis Handb Clin Neurol. 2014;122:89-99.
26. Durelli L, Conti L, Clerico M, Boselli D, Contessa G, Ripellino P, et al. T-helper 17 cells expand in multiple sclerosis and are inhibited by interferon-beta. Ann Neurol. 2009;65:499–509.
27. Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA. Loss of functional suppression by CD4þCD25þ regulatory T cells in patients with multiple sclerosis. J Exp Med. 2004 Apr 5;199(7):971-9.
28. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. Nat Med. 2013 Dec;19(12):1584-96.
29. Babbe H, Roers A, Waisman A, Lassmann H, Goebels N, Hohlfeld R, et al. Clonal expansions of Cd8+ T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. J. Exp Med. 2000; 192,393-404.
30. Disanto G, Hall C, Lucas R, Ponsonby AL, Berlanga-Taylor AJ, Giovannoni G, Ramagopalan SV; Ausimmune Investigator Group. Assessing interactions between HLA-DRB1*15 and infectious mononucleosis on the risk of multiple sclerosis. Mult Scler. 2013 Sep;19(10):1355-8.
31. Haider L, Fischer MT, Frischer JM, Bauer J, Höftberger R, et al. Oxidative damage in multiple sclerosis lesions. Brain. 2011 Jul;134(Pt 7):1914-24.
32. Witte ME, Mahad DJ, Lassmann H, van Horssen J. Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis. Trends Mol Med. 2013 Dec 23. pii: S1471-4914(13)00210-4.
33. Trapp BD, Stys PK. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. Lancet Neurol. 2009 Mar;8(3):280-91.
34. Ellwardt E, Zipp F. Molecular mechanisms linking neuroinflammation and neurodegeneration in MS. Exp Neurol. 2014 Feb 14. [Epub ahead of print].
35. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998 Jan 29;338(5):278-85.
36. Copaxone® (glatiramer acetate) [prescribing information]. Overland Park, KS: Teva Neuroscience, Inc.; 2014.
37. Avonex® (interferon beta-1a) [prescribing information]. Cambridge, MA: Biogen Idec, Inc.; 1996–2012.
38. Rebif® (interferon beta-1a) [medication guide]. Rockland, MA: EMD Serono, Inc.; New York, NY: Pfizer, Inc.; 2014.
39. Betaseron® (interferon beta-1b) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2014.
40. Extavia® (interferon beta-1b) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
41. Tecfidera® (dimethyl fumarate ) [prescribing information]. Cambridge, MA: Biogen Idec, Inc.; 2013.
42. Gilenya® (fingolimod) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2014.
43. Aubagio® (teriflunomide) [prescribing information]. Cambridge, MA: Genzyme Corporation; 2012.
44. Novantrone® (mitoxantrone) [package insert]. Rockland, MA: EMD Serono, Inc.; 2008.
45. Tysabri® (natalizumab) [medication guide]. Cambridge, MA: Biogen Idec, Inc.; 2013.
46. Graber JJ, McGraw CA, Kimbrough D, Dhib-Jalbut S. Overlapping and distinct mechanisms of action of multiple sclerosis therapies. Clin Neurol Neurosurg. 2010 Sep;12(7):583-91.
47. Oh J & Calabresi PA. Disease Modifying Therapies in Relapsing Multiple Sclerosis in Rae-Grant, Fox & Bethoux Multiple Sclerosis and Related Disorders Clinical Guide to Diagnosis, Medical Management and Rehabilitation. 2013. New York: Demos Health.

48. Korporal M, Haas J, Balint B, Fritzsching B, Schwarz A, Moeller S, et al. Interferon beta-induced restoration of regulatory T-cell function in multiple sclerosis is prompted by an increase in newly generated naive regulatory T cells. Arch Neurol. 2008 Nov;65(11):1434-9.
49. van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. N Engl J Med. 2013 Apr 25;368(17):1658-9.
50. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, et al. Canadian Multiple Sclerosis Working Group. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013 May;40(3):307-23.
51. Gold R, Wolinsky JS, Amato MP, Comi G. Evolving expectations around early management of multiple sclerosis. Ther Adv Neurol Disord. 2010;3(6):351-367.
52. Kappos L, Moeri D, Radue EW, Schoetzau A, Schweikert K, Barkhof F, et al. Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Gadolinium MRI Meta-analysis Group. Lancet. 1999 Mar 20;353(9157):964-9.
53. Dalton CM, Chard DT, Davies GR, Miszkiel KA, Altmann DR, Fernando K, et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. Brain. 2004 May;127(Pt 5):1101-7.
54. Stromillo ML, Giorgio A, Rossi F, Battaglini M, Hakiki B, Malentacchi G, et al. Brain metabolic changes suggestive of axonal damage in radiologically isolated syndrome. Neurology. 2013 Jun 4;80(23):2090-4.
55. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000 Nov 16;343(20):1430-8.
56. Comi G, Martinelli V, Rodegher M, Moiola L, Bajenaru O, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374(9700):1503-1511.
57. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006;67(7):1242-1249.
58. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet. 2001;357(9268):1576-1582.
59. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis: CHAMPS Study Group. N Engl J Med. 2000 Sep 28;343(13):898-904.
60. Miller DH, Chart DT, Ciccarelli O. Clinically isolated syndromes. Lancet Neurol. 2012 Feb;11(2):157-69.
61. Fisniku KL, Brex PA, Altmann DR, Miszkiel KA, Benton CE, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain. 2008 Mar;131(Pt 3):808-17. Epub 2008 Jan 29.
62. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292-302.
63. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;Nov 33(11):1444-52.
64. Vercellino M, Romagnolo A, Mattioda A, Masera S, Piacentino C, et al. Multiple sclerosis relapses: a multivariate analysis of residual disability determinants. Acta Neurol Scand. 2009 Feb;119(2):126-30.
65. Hirst C, Ingram G, Pearson O, Pickersgill T, Scolding N, Robertson N. Contribution of relapses to disability in multiple sclerosis. J Neurol. 2008 Feb;255(2):280-7.
66. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003 Dec 9;61(11):1528-32.

67. Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis, a geographically based study. 10. Relapses and long-term disability. Brain. 2010 Jul;133(Pt 7):1914-29.
68. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, UBC Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. Neurology. 2009 Nov 17;73(20):1616-23.
69. Scalfari A, Neuhaus A, Daumer M, Deluca GC, Muraro PA, Ebers GC. Early relapses, onset of progression, and late outcome in multiple sclerosis. JAMA Neurol. 2013 Feb;70(2):214-22.
70. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med. 2002 Jan 17;346(3):158-64.
71. Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon beta-1b trial in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012;83(3):282-287.
72. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012 Jun;18(6):891-8.
73. Minden S, Turner A, Kalb R, Burke D. Emotional disorders in multiple sclerosis. National MS Society 2014.
74. Minden SL, Frankel D, Hadden L, Perloffp J, Srinath KP, Hoaglin DC. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. Mult Scler. 2006 Feb;12(1):24-38.
75. Achiron A, Chapman J, Magalashvili D, Dolev M, Lavie J, et al. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PLoS One. 2013 Aug 1;8(8):e71058.
76. Anhoque CF, Biccas-Neto L, Dominques SC, Teixeira AL, Domingues RB. Cognitive impairment and optic nerve axonal loss in patients with clinically isolated syndrome. Clin Neurol Neurosurg. 2013 Jul;115(7):1032-5.
77. Viterbo RG, Iaffaldano P, Trojano M. Verbal deficits in clinically isolated syndrome suggestive of multiple sclerosis. J Neurol Sci. 2013 Jul 15;330(1-2):56-60.
78. Reuter F, Zaaraoui W, Crespy L, et al. Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2011;82(10):1157-1159.
79. Zipoli V, Goretti B, Hakiti B, Siracusa G, Sorbi S, Portaccio E, et al. Cognitive impairment predicts conversation to multiple sclerosis in clinically isolated syndromes. Mult Scler. 2010 Jan;16(1):62-7.
80. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol. 2008 Dec;7(12):1139-51.
81. Glanz BI, Healy BC, Hviid LE, Chitnis T, Weiner HL. Cognitive deterioration in patients with early multiple sclerosis: a 5-year study. J Neurol Neurosurg Psychiatry. 2012;83(1):38-43.
82. Amato MP, Portaccio E, Goretti B, Zipoli V, Iudice A, et al. Relevance of cognitive deterioration in early relapsing-remitting MS: 3-year follow-up study. Mult Scler. 2010 Dec;16(12):1474-82. doi: 10.1177/1352458510380089. Epub 2010 Aug 20.
83. Julian L, Serafin D, Charvet L, Ackerson J, Benedict R, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. J Child Neurol. 2013 Jan;28(1):102-7.
84. Till C, Ghassemi R, Aubert-Broche B, Kerbrat A, Collins DL, et al. MRI correlates of cognitive impairment in childhood-onset multiple sclerosis. Neuropsychology 2011 May;25(3):319-32.
85. Amato MP, Goretti B, Ghezzi A, Lori S, Zipoli V, et al. Cognitive and psychosocial features of childhood and juvenile MS. Neurology. 2008 May 13;70(20):1891-7.
86. Langdon D, Benedict R, Wicklein EM, Fredrikson S. Report of cognitive difficulties by clinically isolated syndrome patients and carers: the multiple sclerosis neuropsychological questionnaire data from the CogniCIS baseline cohort. *25th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS)*. 2009; Dusseldorf, Abstract P406.

87. Langdon D, Benedict R, Wicklein EM, Fredrikson S. Report of cognitive difficulties by clinically isolated syndrome patients and carers: the multiple sclerosis neuropsychological questionnaire data from the CogniCIS baseline cohort. *25th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS)*. 2009; Dusseldorf, Abstract P407.
88. Ramsaransing GS, De Keyser J. Predictive value of clinical characteristics for 'benign' multiple sclerosis. Eur J Neurol. 2007 Aug;14(8):885-9.
89. Amato MP, Zipoli V, Goretti B, Portaccio E, De Caro MF, et al. Benign multiple sclerosis: cognitive, psychological and social aspects in a clinical cohort. J Neurol. 2006 Aug;253(8):1054-9. Epub 2006 Apr 11.
90. Correale J, Peirano I, Romano L. Benign multiple sclerosis: a new definition of this entity is needed. Mult Scler. 2012 Feb;18(2):210-8. .
91. Sayao AL, Devonshire V, Tremlett H. Longitudinal follow-up of 'benign' multiple sclerosis at 20 years. Neurology. 2007 Feb 13;68(7):496-500.
92. Sayao AL, Bueno AM, Devonshire V, Tremlett H. The psychosocial and cognitive impact of longstanding 'benign' multiple sclerosis. Mult Scler. 2011 Nov;17(11):1375-83.
93. Miller A, Wolinsky J, Kappos L, Comi G, Freedman MS, et al. TOPIC main outcomes: efficacy and safety of once-daily oral teriflunomide in patients with clinically isolated syndrome. Platform presentation at ECTRIMS: Window of opportunity in MS; October 3, 2013.
94. Edan G, Kappos L, Montalban X, Polman CH, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. J Neurol Neurosurg Psychiatry. 2013 Nov 11.
95. Comi G, Martinelli V, Rodegher M, Moiola L, Leocani L et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. Mult Scler. 2013 Jul;19(8):1074-83.
96. Johnson KP, Brooks, BR, Cohen JA, Ford CC, Goldstein J, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology. 1995 Jul;45(7):1268-76.
97. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998 Nov 7;352(9139):1498-504.
98. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996 Mar;39(3):285-94.
99. IFNB Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993 Apr;43(4):655-61.
100. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, et al. DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1098-107.
101. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, et al. CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1087-97.
102. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. . N Engl J Med. 2010 Feb 4;362(5):387-401.
103. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al; TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011 Oct 6;365(14):1293-303.
104. Hartung HP, Gonsette R, König N, Kwiecinski H, Guseo A, et al. Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet. 2002 Dec 21-28;360(9350):2018-25.

105. Polman CH, O'Conner PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.
106. Filippi M, Rovaris M, Rocca MA, Sormani MP,Wolinsky JS, et al. Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes". Neurology 2001 Aug 28;57(4):731-3.
107. MacManus DG, Miller DH, Kappos L, Gold R, Havrdova E et al. BG-12 reduces evolution of new enhancing lesions to T1-hypointense lesions in patients with multiple sclerosis. J Neurol. 2011 Mar;258(3):449-56.
108. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis; a prospective, randomized, multicenter study. Lancet Neurol. 2009 Oct;8(10):889-97.
109. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012 Apr;18(4):418-24.
110. Radue EW, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, et al. Natalizumab plus interferon beta-1a reduces lesion formation in relapsing multiple sclerosis. J Neurol Sci. 2010 May 15;292(1-2):28-35.
111. Zivadinov R, Locatelli L, Cookfair D, Srinivasaraghavan B, Bertolotto A, Ukmar M, et al. Interferon beta-1a slows progression of brain atrophy in relapsing-remitting multiple sclerosis predominantly by reducing gray matter atrophy. Mult Scler. 2007 May;13(4):490-501.
112. Khan O, Bao F, Shah M, Caon C, Tselis A, Bailey R, et al. Effect of disease-modifying therapies on brain volume in relapsing-remitting multiple sclerosis: results of a five-year brain MRI study. J Neurol Sci. 2012 Jan 15;312(1-2):7-12.
113. Barkhof F, de Jong R, Sfikas N, de Vera A, Francis G, Cohen J. The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis. Mult Scler. 2014 May 8 [epub ahead of print].
114. Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology 2007;Apr 24;68(17):11390-401.
115. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, et al; BENEFIT Study Group. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet Neurol. 2009 Nov;8(11):987-97.
116. Rovaris M, Comi G, Rocca MA, Valsasina P, Ladkani D, Pieri E, Weiss S, Shifroni G, Wolinsky JS, Filippi M; European/Canadian Glatiramer Acetate Study Group. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. Mult Scler. 2007 May;13(4):502-8.
117. Kinkel RP, Dontchev M, Kollman C, Skaramagas TT, O'Connor PW, et al. Association between immediate initiation of intramuscular interferon beta-1a at the time of a clinically isolated syndrome and long-term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. Arch Neurol. 2012;69(2):183-190.
118. Trojano M, Paolicelli D, Bellacosa A, Cataldo S. The transition from relapsing-remitting MS to irreversible disability: clinical evaluation. Neurol Sci. 2003 Dec;24 Suppl 5:S268-70.
119. Tedeholm H, Lycke J, Skoog B, Lisovskaja V, Hillert J, et al. Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs. Mult Scler. 2013 May;19(6):765-74.
120. Bergamaschi R, Quaglini S, Tavazzi E, Amato MP, Paolicelli D, et al. Immunomodulatory therapies delay progression in multiple sclerosis. Mult Scler. 2012 May 31. [epub ahead of print].
121. Trojano M, Pellegrini F, Fuiani A, Paolicelli D, Zipoli V, et al. New natural history of interferon-beta treated relapsing multiple sclerosis. Ann Neurol. 2007 Apr;61(4):300-6.

122. Penner IK, Stemper B, Calabrese P, Freedman MS, Polman CH, et al. Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis. Mult Scler. 2012 Oct;18(10):1466-71.
123. Janzen W, Turpin KV, Warren SA, Marrie RA, Warren KG. Change in the health-related quality of life of multiple sclerosis patients over 5 years. Int J MS Care. 2013 Spring;15(1):46-53.
124. Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. Ann Neurol. 2007 Oct;62(4):335-46.
125. Kappos L, Gold R, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Quality of life outcomes with BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: The DEFINE study. Mult Scler. 2014 Feb;20(2):243-52.
126. Salter AR, Cutter GR, Tyry T, Marrie RA, Vollmer T. Impact of loss of mobility on instrumental activities of daily living and socioeconomic status in patients with MS. Curr Med Res Opin. 2010 Feb;26(2):493-500.
127. Wickstrom A, Nystrom J, Svenningsson A. Improved ability to work after one year of natalizumab treatment in multiple sclerosis: Analysis of disease-specific and work-related factors that influence the effect of treatment. Mult Scler. 2013 Apr;19(5):622-30.
128. Clerico M, Faggiano F, Palace J, Rice G, Tintorè M, Durelli L. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005278. doi: 10.1002/14651858.CD005278.pub3.
129. PRISMS Study Group and University of British Columbia MS/MRI Analysis Group. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology. 2001 Jun 26;56(12):1628-36.
130. Schwid SR, Bever CT, Jr. the cost of delaying treatment in multiple sclerosis: what is lost is not regained. Neurology. 2001 Jun 26;56(12):1620.
131. Cohen B, Leist T, Coyle P, Zwibel H, Markowitz C, Tullman M. MS therapy adherence and relapse risk. Neurology 2013; 80 (Meeting Abstracts 1): PO1. 193.
132. Burks J, Malangone M, Jhaveri S, Zhou L, Stern S, et al. The clinical outcomes associated with adherence to and discontinuation of disease-modifying treatments. Mult. Scler 2012;18(Suppl 4):279-508; Poster 716.
133. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. J Manag Care Pharm. 2013 Jan-Feb;19(1 Suppl A):S24-40.
134. Richert ND, Zierak MC, Bash CN, Lewis BK, McFarland HF, Frank JA. MRI and clinical activity in MS patients after terminating treatment with interferon beta-1b. Mult Scler. 2000;2:86–90.
135. Siger M, Durko A, Nicpan A, Konarska M, Grudziecka M, Selmaj K. Discontinuation of interferon beta therapy in multiple sclerosis patients with high pre-treatment disease activity leads to prompt return to previous disease activity. J Neurol Sci. 2011 Apr 15;303(1-2):50-2.
136. Wu X, Dastidar P, Kuusisto P, Ukkonen M, Huhtala H, Elovaara I. Increased disability and MRI lesions after discontinuation of IFN-beta-1a in secondary progressive MS. Acta Neurol Scand 2005;112:242–7.
137. O'Connor PW, Goodman A, Kappos L, Lublin FD, Miller DH, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology. 2011 May 31;76(22):1858-65.
138. Fox RJ, Campbell Cree, BA, De Seze J, Gold R, Hartung HP, et al. MS disease activity in RESTORE: A randomized 24-week natalizumab treatment interruption study. Neurology. 2014 Mar 28. [Epub ahead of print]
139. Fragoso YD, Adoni T, Anacleto A, de Gama PD, Goncalves MV, Matta AP, Parolin MF. Recommendations on diagnosis and treatment of depression in patients with multiple sclerosis. Pract Neurol. 2014 Feb 5. [Epub ahead of print]

140. Salhofer-Polanyi S, Baumgartner A, Kraus J, Maida E, Schmied M, Leutmezer F. What to expect after natalizumab cessation in a real-life setting. Acta Neurol Scand. 2014 April 10. [Epub ahead of print].
141. Sorensen PS, Koch-Henriksen N, Petersen T, Ravnborg M, Oturai A, Sellebjerg F. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS. J Neurol. 2014 April 12 [Epub ahead of print].
142. West TW, Cree BA. Natalizumab dosage suspension: are we helping or hurting? Ann Neurol. 2010; Sep 68(3):395-99.
143. Ghezzi A, Rocca MA, Baroncini D, Annovazzi P, Zaffaroni M, Minonzio G, et al. Disease reactivation after fingolimod discontinuation in two multiple sclerosis patients. J Neurol. 2013 Jan;260(1):327-9.
144. Hakiki B, Portaccio E, Giannini M, Razzolini L, Pastò L, Amato MP. Withdrawal of fingolimod treatment for relapsing-remitting multiple sclerosis: report of six cases. Mult Scler. 2012 Nov;18(11):1636-9.
145. Chitnis T, Tardieu M, Amato MP, Banwell B, Bar-Or A, Ghezzi A, et al. International Pediatric MS Study Group Clinical Trials Summit: meeting report. Neurology. 2013 Mar 19;80(12):1161-8.
146. Absoud M, Lim MJ, Chong WK, De Goede CG, Foster K, et al. Paediatric acquired demyelinating syndromes: incidence, clinical and magnetic resonance imaging features. Mult Scler. 2013 Jan;19(1):76-86.
147. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult Scler. 2009 May;15(5):627-31.
148. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009 Jan;66(1):54-9.
149. Yeh EA, Waubant E, Krupp LB, Ness J, Chitnis T, Kuntz N, et al; National Network of Pediatric MS Centers of Excellence. Multiple sclerosis therapies in pediatric patients with refractory multiple sclerosis. Arch Neurol. 2011 Apr;68(4):437-44.
150. Arnal-Garcia C, Garcia-Montero MR, Malaga I, Millan-Pascual J, Oliva-Nacarino P et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. Eur J Paediatr Neurol. 2013 Jan;17(1):50-4.
151. Ghezzi A, Possilli C, Grimaldi LM, Moiola L, Brescia-Morra V, et al. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. Mult Scler. 2013 Jul;19(8):1106-12.
152. Kornek B, Aboul-Enein F, Rostasy K, Milos RI, Steiner I, et al. Natalizumab therapy for highly active pediatric multiple sclerosis. JAMA Neurol. 2013 Apr;70(4):469-75.
153. Chitnis T. Pediatric demyelinating diseases. Continuum (Minneap Minn). 2013 Aug;19(4 Multiple Sclerosis):1023-45.
154. Chitnis T, Tenenbaum S, Banwell B, Krupp L, Pohl D. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler. 2012 Jan;18(1):116-27.
155. Freedman MS, Cohen B, Dhib-Jalbut S, Jeffery D, Reder AT, et al. Recognizing and treating suboptimally controlled multiple sclerosis: steps toward regaining command. Curr Med Res Opin. 2009 Oct;25(10):2459-70.
156. Bermel RA, You X, Foulds P, Hyde R, Simon JH, Fisher E, Rudick RA. Predictors of long-term outcome in multiple sclerosis patients treated with interferon β. Ann Neurol. 2013 Jan;73(1):95103.
157. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. Eur J Neurol. 2009 Nov;16(11):1202-9.
158. Rudick RA, Lee JC, Simon J, Ransohoff RM, Fisher E. Defining interferon beta response status in multiple sclerosis patients. Ann Neurol. 2004 Oct;56(4):548-55.
159. Sormani MP, Li DK, Bruzzi P, Stubinski B, Cornelisse P, et al. Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. Neurology. 2011 Nov 1;77(18):1684-90.
160. O'Connor PW, Oh J. Disease-modifying agents in multiple sclerosis. Handb Clin Neurol. 2014;122:465-501.

161. Sorensen PS, Koch-Henriksen N, Ross C, Clemmesen KM, Bendtzen K. Danish Multiple Sclerosis Study Group. Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. Neurology. 2005;65(1):33-9.
162. Sorensen PS, Ross C, Clemmesen KM, Bendtzen, Frederiksen JL, et al; Danish Mulitple Sclerosis Study Group. Clinical importance of neutralising antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. Lancet. 2003 Oct 11;362(9391):1184-91.
163. Bertolotto A, Capobianco M, Amato MP, Capello, E, Capra R, et al. Guidelines on the clinical use for the detection of neutralizing antibodies (NAbs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group. Neurol Sci. 2014 Feb;35(2):307-16.
164. Goodin DS, Frohman EM, Hurwitz B, O'Connor PW, Oger JJ, et al. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an incidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2007 Mar 27;68(13:977-84.
165. Kirzinger SS, Jones J, Siegwald A, Crush AB. Relationship between disease-modifying therapy and depression multiple sclerosis. Int J MS Care. 2013 Fall;15(3):107-12.
166. Kim S, Foley FW, Picone MA, Halper J, Zemon V. Depression levels and interferon treatment in people with multiple sclerosis. Int J MS Care. 2012 Spring;14(1):10-6.
167. Patti F, Amato MP, Trojano M, Bastianello S, Tola MR, et al. Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGnitive Impairment in Multiple Sclerosis) Study. Mult Scler. 2011 Aug;17(8):991-1001.
168. Patten SB, Williams JV, Metz LM. Anti-depressant use in association with interferon and glatiramer acetate treatment in multiple sclerosis. Mult Scler. 2008 Apr;14(3):406-11.
169. Menon S, Shirani A, Zhao Y, Oger J, Traboulsee A, Freedman MS, Tremlett H. Characterising aggressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2013 Nov;84(11):1192-8.
170. Cross AH, Naismith RT. Established and novel disease-modifying treatments in multiple sclerosis. J Intern Med. 2014 Jan 20. Epub ahead of print
171. Hutchinson M, Kappos L, Calabresi PA, Confavreux C, Giovannoni G, Galetta SL, et al; AFFIRM and SENTINEL Investigators. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol. 2009 Mar;256(3):405-15.
172. Edan G, Comi G, Le Page E, Leray E, Rocca MA, et al. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial. J Neurol Neurosurg Psychiatry. 2011 Dec;82(12):1344-50.
173. Le Page E, Leray E, Taurin G, Coustan M, Chaperon J, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. J Neurol Neurosurg Psychiatry. 2008 Jan;79(1):52-6.
174. Vollmer T, Panitch H, Bar-Or A, Dunn J, Freedman MS, Gazda SK, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. Mult Scler. 2008 Jun;14(5):663-70.
175. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomized multicenter study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry. 1997 Feb;62(2):112-8.
176. Edan G, LePage E. Induction therapy for patients with multiple sclerosis: why? when? how? CNS Drugs. 2013 Jun;27(6):403-9.
177. Naismith RT, Trinkaus K, Cross AH. Phenotype and prognosis in African-Americans with multiple sclerosis: a retrospective chart review. Mult Scler.2006 Dec; 12(6): 775–781.
178. Cree BA, Khan O, Bourdette D, Goodin DS, Cohen JA, et al. Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. Neurology 2004 Dec 14; 63(11): 2039–2045.

179. Weinstock-Guttman B, Ramanathan M, Hashmi K, Abdelrahman N, Hojnacki D et al. Increased tissue damage and lesion volumes in African Americans with multiple sclerosis. Neurology. 2010 Feb 16;74(7):538-44.
180. Klineova S, Nicholas J, Walker A. Response to disease modifying therapies in African Americans with multiple sclerosis. Ethn Dis. 2012 Spring;22(2):221-5.
181. Cree BA, Al-Sabbagh A, Bennett R, Goodin D. Response to interferon beta-1a treatment in African American multiple sclerosis patients. Arch Neurol 2005 Nov;62(11):1681-3.
182. Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. Patient Prefer Adherence. 2010 Feb 4;4:1-9.
183. Tremlett HL, Oger J. Interrupted therapy: stopping and switching of the beta interferons prescribed for MS. Neurology. 2003 Aug 26;61(4):551-4.
184. Reynolds MW, Stephen R, Seaman C, Rajagopalan K. Persistence and adherence to disease modifying drugs among patients with multiple sclerosis. Curr Med Res Opin. 2010 Mar;26(3):663-74.
185. Fox RJ, Salter AR, Tyry T, Sun J, You X, Laforet G, Campagnolo D. Treatment discontinuation and disease progression with injectable disease-modifying therapies. Int J MS Care. 2013 Winter;15(4):194-201.
186. Saunders C, Caon C, Smrtka J, Shoemaker J. Factors that influence adherence and strategies to maintain adherence to injected therapies for patients with multiple sclerosis. J Neurosci Nurs. 2010 Oct;42(5 Suppl):S10-8.
187. Mohr DC, Cox D, Merluzzi N. Self-injection anxiety training: a treatment for patients unable to self-inject injectable medications. Mult Scler. 2005 Apr;11(2):182-5.
188. Clanet MC, Wolinsky, Ashton RJ, Hartung HP, Reingold SC. Risk evaluation and monitoring in multiple sclerosis therapeutics. Mult Scler. 2013 Nov 30. [Epub ahead of print]
189. Caon C, Saunders C, Smrtka J, Baster N, Shoemaker J. Injectable disease-modifying therapy for relapsing-remitting multiple sclerosis: a review of adherence data. J Neurosci Nurs. 2010 Oct;42(5 Suppl):S5-9.
190. Giovannoni G, Southam E, Waubant E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. Mult Scler. 2012 Jul;18(7):932-46.
191. Beer K, Muller J, Hew-Winzeler AM, Bont A, Maire P, et al. The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. BMC Neurol. 2011 Nov 10;11:144.
192. Devonshire V, Lapierre Y, Macdonell R, Ramo-Tello C, Patti F, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol. 2011 Jan;18(1):69-77.
193. Treadaway K, Cutter G, Salter A, Lynch S, Simsarian J, et al. Factors that influence adherence with disease-modifying therapy in MS. J Neurol. 2009 Apr;256(4):568-76.
194. Dor A, Lage MJ, Tarrants ML, Castelli-Haley J. Cost sharing, benefit design, and adherence: the case of multiple sclerosis. In: Dor A, editor. Pharmaceutical Markets and Insurance Worldwide. Bingley, UK: Emerald Group Publishing Limited; 2010.
195. Grytten N, Aarseth JH, Espeset K, Johnsen GB, Wehus R, et al. Stoppers and non-starters of disease-modifying treatment in multiple sclerosis. Acta Neurol Scand. 2013 Feb;127(2):133-40.
196. Tarrants M, Oleen-Burkey J, Castelli-Haley J, Lage MJ. The impact of comorbid depression on adherence to therapy for multiple sclerosis. Mult Scler Int. 2011;2011:271321.

# THE MULTIPLE SCLEROSIS COALITION

The Multiple Sclerosis Coalition (MSC) was founded in 2005 by three independent multiple sclerosis organizations in an effort to work together to benefit individuals with MS. Since that time, the MSC has grown to eight member organizations, all of whom provide critical MS programs and services.

**Vision:** To improve the quality of life for those affected by MS through a collaborative national network of independent MS organizations.

**Mission:** To increase opportunities for cooperation and provide greater opportunity to leverage the effective use of resources for the benefit of the MS community.

The primary objectives of the MSC are to educate, advocate, collaborate and improve the efficiency of services for individuals with MS and those who are close to them. With so much on the horizon in terms of MS research, treatments, advocacy and symptom management, the MSC provides critical momentum to work together to enhance these exciting MS initiatives and to ensure this collective support continues.

## Member Organizations

### Accelerated Cure Project for Multiple Sclerosis (ACP)

Accelerated Cure Project is a national non-profit dedicated to curing MS by determining its causes. Accelerated Cure has a repository of samples and data from people with MS and other demyelinating diseases. Samples are available to researchers who submit all data they generate back to the repository to be shared with others.

**www.acceleratedcure.org | 781-487-0008**

### Can Do Multiple Sclerosis (Can Do MS)

Can Do MS is a national nonprofit organization and a leading provider of innovative lifestyle empowerment programs that empower people with MS and their support partners to transform and improve their quality of life.

**www.mscando.org | 800-367-3101**

### Consortium of Multiple Sclerosis Centers (CMSC)

The Consortium of Multiple Sclerosis Centers provides leadership in clinical research and education; develops vehicles to share information and knowledge among members; disseminates information to the health care community and to persons affected by multiple sclerosis; and develops and implements mechanisms to influence health care delivery.

**www.mscare.org | 201-487-1050**

### International Organization of Multiple Sclerosis Nurses (IOMSN)

The International Organization of Multiple Sclerosis Nurses is the first and only international organization focuses solely on the needs and goals of professional nurses, anywhere in the world, who care for people with multiple sclerosis. Mentoring, educating, networking, sharing - the IOMSN supports nurses in their continuing effort to offer HOPE.

**www.iomsn.org | 201-487-1050**

### Multiple Sclerosis Association of America (MSAA)

The Multiple Sclerosis Association of America is a leading resource for the entire MS community, improving lives today through vital services and support. MSAA provides free programs and services, such as: a Helpline, award-winning publications; website featuring educations videos and research updates; shared –management tools to assist the MS community in managing their MS; safety and mobility equipment; cooling accessories for heat-sensitive individuals; educational events and activities; RI funding and insurance advocacy; as well as other services.

**www.mymsaa.org | 800-532-7667**

### Multiple Sclerosis Foundation (MSF)

The Multiple Sclerosis Foundation's mission is to provide nationally accessible programs and services, to those affected by MS, which in turn, helps them maintain their health, safety, self-sufficiency, and personal well-being. We strive to heighten public awareness of MS in order to elicit financial support while promoting understanding for those diagnosed.
**www.msfocus.org | 800-225-6495**

### National Multiple Sclerosis Society

The National Multiple Sclerosis Society is a collective of passionate individuals who want to do something about MS NOW - to move together toward a world free of multiple sclerosis. The Society mobilizes people and resources to drive research for a cure and to address the challenges of everyone affected by MS.
**www.nationalMSsociety.org | 800-344-4867**

### United Spinal Association

United Spinal Association is the largest disability-led national non-profit organization founded by paralyzed veterans in 1946 and has since provided service programs and advocacy to improve the quality of life of those across the life span living with spinal cord injuries and disorders such as multiple sclerosis, amyotrophic lateral sclerosis and spina bifida. There are more than a million individuals throughout the country with SCI/D and to whom the Association's work is dedicated. United Spinal has close to 40,000 members, 48 chapters and close to 200 support groups nationwide. Throughout its history, United Spinal Association has devoted its energies, talents and programs to improving the quality of life for these Americans and for advancing their independence. United Spinal Association is also a VA-recognized veterans service organization serving veterans with disabilities of all kinds.
**www.unitedspinal.org | 718-803-3782**

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