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TARGET AUDIENCE
This activity is intended for neurologists, nurses, nurse practitioners, physician assistants, rehabilitation professionals, case managers, mental health professionals, social workers and others involved in the management of patients with MS.

STATEMENT OF NEED
The number of FDA-approved disease modifying therapies (DMTs) for patients with MS has grown considerably over the last 2 decades. These agents vary by mechanism of action, mode of administration, dosing frequency, side effect profiles and monitoring recommendations. The increasing range of treatment options allows for individualized treatment selection for this patient population and it is critical that clinicians managing patients with MS are familiar with current evidence to support optimal treatment decisions over the disease course. In addition, a multi-dimensional, comprehensive care approach is advocated to promote positive outcomes for individuals with MS. All members of the MS health care team need awareness of how to incorporate the principles of comprehensive care in clinical practice.

LEARNING OBJECTIVES
Upon completion of the activity, participants should be able to:

• Summarize new developments among platform therapies for MS, as well as recent, relevant data regarding their effectiveness and safety
• Differentiate between key characteristics of newer (non-platform) MS therapies that should be considered when starting or switching treatment
• Review recommendations and expert opinion regarding timely and effective monitoring of MS activity and progression
• Evaluate criteria that can support the decision to initiate or switch treatment

• Improve communication and coordination among multidisciplinary clinicians who manage patients with MS
• Apply components of the comprehensive care model into the management of patients with MS
• Identify the dimensions of wellness as it relates to MS

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Estimated Time to Complete Activity: 160 minutes

METHOD OF PARTICIPATION/
HOW TO RECEIVE CREDIT
1. There are no fees for participating in and receiving credit for this activity.
2. Review the activity objectives and CME/CNE information.
3. Complete the CME/CNE activity.
4. Go to www.cmeAIMS.org/AIMS-primer and complete the posttest. A score of at least 75% is required to successfully complete this activity. The participant may take the test until successfully passed.
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6. Your CME/CNE certificate will be available for download.

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This activity is awarded 2.0 contact hour(s) of continuing nursing education for RNs and APRNs.

Laurie Scudder, DNP, NP, has served as Nurse Planner for this activity. She has declared that she has no relevant financial relationships to disclose.

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- **Daniel Ontaneda, MD, MSc** has received grants/research support from Genzyme, National Institutes of Health, NMSS, and
Novartis. He has served as a consultant for Genzyme, Mallinckrodt, and Novartis.

- **Marie Namey, APRN, MSN**, has served as a consultant for Biogen Idec, Genentech, Genzyme, Mallinckrodt, Novartis and Teva Neuroscience. She has received honoraria from Acorus Therapeutics, Biogen Idec, Genentech, Genzyme, Mallinckrodt, Novartis, and Teva Neuroscience.

- **Jacqueline A. Nicholas, MD, MPH** has received grants/research support from Biogen Idec, Genzyme, Novartis, and Teva Pharmaceuticals. She has also served as a consultant for Biogen Idec, Genzyme, Medtronic, Novartis, Teva Pharmaceuticals and has received honoraria from Biogen Idec, Genzyme, Novartis, and Teva Pharmaceuticals.

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**COMMERCIAl SUPPORT**
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MS Pathophysiology and Disease Course

PATHOPHYSIOLOGY
Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). MS is characterized by both inflammatory and neurodegenerative features and affects both the white and grey matter of the brain. Pathological studies demonstrate demyelination, axonal loss, neuronal injury, oligodendrocyte damage, microglial activation, and inflammatory infiltrates. Although once considered a disease that produces demyelination in the white matter alone, we now understand MS may cause axonal loss and affects the grey matter as extensively as the white matter. The exact cause of MS is still unknown and it is not entirely clear if inflammation occurs as a secondary or primary phenomenon.

Perhaps the most commonly proposed hypothesis for the development of MS is one of peripheral autoimmune activation, where T cells are primed against myelin antigens and demyelination occurs as a consequence of immune mediated mechanisms. This hypothesis is supported by the effect of immune modulating therapies in modifying the disease course. There is also clear evidence of clonal expansion of both T and B cells in MS lesions suggesting both humoral and cell mediated immunity play cardinal roles in disease pathology. An alternate hypothesis suggests that a primary event occurring in the CNS may trigger a secondary immune activation response and the resulting injury of grey and white matter. However, what this primary inciting event would be has yet to be discovered. Several factors have been studied and are known to produce an increased risk of MS and may help us understand some clues regarding the etiology of the disease (Table 1).

Table 1: Factors Associated with Increased Risk for MS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relationship to Risk for MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>Insufficiency is a risk factor for MS</td>
</tr>
<tr>
<td>Sunlight exposure</td>
<td>Decreased exposure may relate to vitamin D or other primary process</td>
</tr>
<tr>
<td>Geographic location</td>
<td>Latitude effect, geographic prevalence of disease with decreasing exposure to sunlight; may be mediated by vitamin D, genetics, or infection</td>
</tr>
<tr>
<td>Epstein Barr Virus (EBV)</td>
<td>MS risk increases several fold following EBV infection</td>
</tr>
<tr>
<td>Hygiene (viruses, parasites, bacteria)</td>
<td>Parasites and microbiome may be protective; dysbiotic gut microbiota associated with inflammation and autoimmune diseases</td>
</tr>
<tr>
<td>Genetics</td>
<td>20% of MS risk; susceptibility related to HLA- and immune function-associated genes</td>
</tr>
<tr>
<td>Tobacco exposure</td>
<td>Early tobacco exposure increases risk</td>
</tr>
<tr>
<td>Diet; salt intake</td>
<td>High salt diets may be a risk for MS, hormone and antigen loading</td>
</tr>
</tbody>
</table>
**Inflammation**

An early step in the inflammatory process associated with MS is activation of T cells directed at a CNS antigen through specific antigen presenting cells. Activated T cells induce a shift in immunity towards a Th1-type inflammatory response that causes activation of other immune cells including B lymphocytes and monocytes (Figure 1).

These cells enter the CNS and further the inflammatory process by ongoing activation of immune cells within the CNS and by further disruption of the blood brain barrier and subsequent entry of additional peripheral immune cells. Within the CNS microglial activation occurs and inflammatory cells create direct injury to axons, myelin, and oligodendrocytes causing the pathological changes mentioned above.

**Neurodegeneration**

Significant advances have been made in the concepts that help to explain the progressive worsening of neurological function, most evidently seen in progressive forms of MS. Understanding these mechanisms is of importance if we are to develop therapies that might provide neuroprotective effects in progressive stages of the disease (Figure 2).

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**Figure 1: Proposed Inflammatory Events that Contribute to Demyelination and Axonal Damage in MS**

![Diagram showing proposed inflammatory events in MS]
Several neurodegenerative mechanisms have been identified in MS and include:\textsuperscript{19,20}
- Chronic smoldering inflammation
- Microglia activation and oxidative burst
- Ion channel dysfunction and energetic failure in demyelinated axons
- Hypoxic injury
- Glutamate excitotoxicity
- Changes in mitochondrial function and mitochondrial DNA

- Iron accumulation and oxidative injury
- Final pathway of neuronal loss by apoptosis and necrosis

**DISEASE COURSE**
The disease course of MS is quite variable and likely represents the clinical manifestations from a spectrum of inflammatory and neurodegenerative pathology components. On one end of the spectrum are patients with...
frequent relapses and numerous new focal brain lesions. Patients in this relapsing form of the disease have a significant inflammatory component, conferring a good response to immunomodulating therapies. On the other end of the spectrum are patients with progressive accrual of disability independent of relapses, with little accumulation of new lesions, but significant brain tissue loss (Figure 3).

This progressive form of the disease is characterized by mechanisms of neurodegeneration without focal inflammation and poor response to immunomodulating medications.

To facilitate diagnosis, classification, and clinical care, disease categories have been developed that classify the disorder in relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive MS (PPMS) disease courses. Most patients (~85%) begin with a relapsing remitting (RRMS) form of the disease, and may then develop gradual accumulation of disability independent of relapses (SPMS). A minority of patients begin the disease with a progressive course from the onset with no clinical relapses (PPMS).

*Activity: clinical relapses and/or MRI (Gd-enhancing MRI lesions; new/enlarging T2 lesions)
Refined descriptors for MS disease course have recently been published, where an effort was made to better describe the disease process in conjunction with the broad classification scheme (Figures 4 and 5).

The updated disease course descriptors include qualifiers of clinical relapse rate, imaging findings, and disease progression to describe overall MS activity. The core phenotypes of relapsing-remitting and progressive disease have been retained. Clinically isolated syndrome (CIS), an initial neurological disturbance lasting more than 24 hours with signs and symptoms consistent with an inflammatory demyelinating disorder (that could be MS), is now included in the 2013 phenotypes. CIS and RRMS are further classified as ‘active’ or ‘not active,’ with ‘active’ indicating clinical and/or radiological activity (relapses, gadolinium-enhancing MRI lesions, new or enlarging T2 lesions). Progressive disease (primary or secondary) is now sub-classified as ‘active with progression,’ ‘active but without progression,’ ‘not active but with progression,’ and ‘not active and without progression.’

‘Progression’ in this context refers to gradual accumulation of disability.
Neuromyelitis optica (NMO) is an autoimmune, inflammatory disorder of the CNS that primarily targets the optic nerves and spinal cord causing optic neuritis and transverse myelitis. The pathogenic antibody aquaporin 4 IgG (AQP4, also known as NMO-IgG), was discovered in 2004 and is highly specific for the disease. Prior to the discovery of this antibody, the disease was initially named Devic’s disease and was believed to be a monophasic condition, which caused concomitant bilateral optic neuritis and transverse myelitis. Eventually, relapsing cases were reported.

In 2006, the AQP4 autoantibody test was included in the diagnostic criteria for NMO. These diagnostic criteria included two major criteria,

Table 2: NMO Spectrum Disorders (NMOSD) Diagnostic Criteria for Adult Patients

<table>
<thead>
<tr>
<th>Diagnostic Criteria for NMOSD with AQP4 IgG</th>
<th>Diagnostic Criteria for NMOSD without AQP4 IgG or NMOSD with unknown AQP4 IgG Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. At least 1 core clinical characteristic</td>
<td>1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:</td>
</tr>
<tr>
<td>2. Positive test for AQP4 IgG using best available detection method (cell-based assay strongly recommended)</td>
<td>a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses</td>
<td>b. Dissemination in space (2 or more different core clinical characteristics)</td>
</tr>
<tr>
<td></td>
<td>c. Fulfillment of additional MRI requirements, as applicable</td>
</tr>
<tr>
<td></td>
<td>2. Negative tests for AQP4 IgG using best available detection method, or testing unavailable</td>
</tr>
<tr>
<td></td>
<td>3. Exclusion of alternative diagnoses</td>
</tr>
</tbody>
</table>

Core Clinical Characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI Requirements for NMOSD without AQP4 IgG and NMOSD with Unknown AQP4 IgG Status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted Gd-enhancing lesion extending over ½ optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) OR ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions
history of optic neuritis and transverse myelitis, along with at least two of three supportive criteria: AQP4 seropositivity; myelitis extending over ≥ 3 vertebral bodies in length termed longitudinally extensive transverse myelitis (LETM); and/or brain MRI not meeting diagnostic criteria for MS. These criteria were more relaxed and allowed the diagnosis to be made even if patients were found to have lesions within the brain outside of optic nerve and spinal cord or if they had unilateral optic neuritis. Later, NMO Spectrum Disorders (NMOSD) were identified to include individuals with AQP4 seropositivity who presented with an initial attack and/or patients not yet meeting full NMO criteria, but who were identified to be at risk for further attacks. The NMOSD also included patients with other presentations localizing to the cerebrum, diencephalic and brainstem regions. In addition, patients with co-existent autoimmune diseases such as systemic lupus or Sjogren’s syndrome who were found to also be seropositive for AQP4 IgG were included under the NMOSD category.

Making the proper diagnosis of NMO/NMOSD versus MS as early as possible is important as some MS disease modifying therapies appear to worsen disease activity in NMO. Furthermore, disability in NMO is dependent upon relapses, which are often more severe with less recovery than those occurring in MS.

In 2015, the International Panel for NMO Diagnosis (INPD) was formed and revised NMO diagnostic criteria were developed to incorporate new knowledge and to help aid in earlier diagnosis of this disorder (Table 2). In the new criteria the terms NMO and NMOSD have been unified to NMOSD with AQP4 IgG Positivity and NMOSD without AQP4 IgG Positivity or unknown AQP4 IgG status.

Currently there are no FDA-approved treatments for NMOSD, but off-label oral immunosuppressants (mycophenolate, azathioprine, prednisone) and off label-intravenous rituximab (a chimeric monoclonal antibody resulting in B cell depletion) have all shown benefit in case series and observational studies. Phase 3 clinical trials are currently underway to study treatment options for NMOSD. These placebo-controlled studies are separately evaluating eculizumab, a terminal complement inhibitor, in the PREVENT trial; MEDI-551, a humanized monoclonal antibody targeting CD19 resulting in B cell depletion; and SA237, an anti-IL-6 receptor antibody.
General Framework for the Management of MS

A multidimensional, comprehensive care approach is advocated to optimize outcomes for patients with MS. Comprehensive care is patient-centered, multidisciplinary care provided by a team that adopts a whole-person orientation. The patient is viewed as an integral team member, and is empowered to actively participate in care planning and self-care actions. Comprehensive care encompasses relapse management, disease modifying therapies (DMTs), symptom management, psychosocial support, and rehabilitation.

Currently approved DMTs for MS are summarized in Table 3.

Table 3: Disease Modifying Therapies for MS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Approval</th>
<th>Dose and Route of Administration</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon (IFN) β-1b (Betaseron®)</td>
<td>1993</td>
<td>250 mcg, SC, QOD</td>
<td>Enhancement of suppressor T-cell activity, reduction of proinflammatory cytokine production, down regulation of antigen presentation, inhibition of lymphocyte trafficking into the CNS</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex®)</td>
<td>1996</td>
<td>30 mcg, IM, QW</td>
<td></td>
</tr>
<tr>
<td>IFNβ-1a (Rebif®)</td>
<td>2002</td>
<td>22 mcg or 44 mcg, SC, TIW</td>
<td></td>
</tr>
<tr>
<td>IFNβ-1b (Extavia®)</td>
<td>2009</td>
<td>250 mcg, SC, QOD</td>
<td></td>
</tr>
<tr>
<td>Pegylated IFNβ-1a (Plegridy™)</td>
<td>2014</td>
<td>125 mcg SC every 14 days</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone®)</td>
<td>1996</td>
<td>20 mg, SC, QD</td>
<td>Immunomodulatory; preferential differentiation of Th2 cells; and inhibition of antigen-specific T-cell activation</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone®)</td>
<td>2014</td>
<td>40 mg, SC, TIW</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate (Glatopa™)</td>
<td>2015</td>
<td>20 mg, SC QD</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone®)</td>
<td>2000</td>
<td>12 mg/m², IV, every 3 months</td>
<td>DNA topoisomerase II inhibitor suppresses proliferation of T and B cells, macrophages</td>
</tr>
<tr>
<td>Natalizumab (Tysabri®)</td>
<td>2004</td>
<td>300 mg, IV, every 4 weeks</td>
<td>Inhibition of α4β1-integrin mediated adhesion of leukocytes to VCAM-1 on vascular endothelial cells at the blood brain barrier, which prevents leukocyte migration into the brain</td>
</tr>
<tr>
<td>Alemtuzumab (Lemtrada™)</td>
<td>2014</td>
<td>12 mg/day, IV for 5 days; then 12 mg/day for 3 days 12 months after the 1st treatment course</td>
<td>Humanized monoclonal antibody, anti-CD52; T and B cell depletion</td>
</tr>
</tbody>
</table>
PRIMER

ADVANCES IN MULTIPLE SCLEROSIS

Table 3: Disease Modifying Therapies for MS (cont)\textsuperscript{35}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Approval</th>
<th>Dose and Route of Administration</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod (Gilenya\textsuperscript{®})</td>
<td>2010</td>
<td>0.5 mg, PO, QD</td>
<td>Sphingosine1-phosphate receptor modulator; prevents egress of lymphocytes from lymphoid tissues into the periphery</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio\textsuperscript{®})</td>
<td>2012</td>
<td>7 mg or 14 mg, PO, QD</td>
<td>Inhibition of dihydro-orotate dehydrogenase, a key enzyme in de novo pyrimidine synthesis required by rapidly dividing lymphocytes; diminishes the numbers of activated T- and B-cells available to migrate to the CNS</td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera\textsuperscript{®})</td>
<td>2013</td>
<td>240 mg, PO, BID</td>
<td>Anti-inflammatory properties via effects on the Nrf2 pathway; Th1 to Th2 shift, anti-oxidant properties, potential neuroprotective effects</td>
</tr>
</tbody>
</table>

With an ever increasing array of therapeutic agents available for the management of MS, DMT selection must be individualized to each patient’s disease course and severity with consideration of prognostic factors. Currently, there is no expert consensus on DMT selection. Following a treatment algorithm is not recommended as each individual patient’s disease course, severity, medical and/or psychiatric comorbidities, preferences, safety and tolerability concerns, and lifestyle should be considered (Figure 6).

Figure 6: Considerations for Individualized Treatment Decisions in MS

- Disease Course
- Symptom Severity
- Insurance Coverage/Cost
- Medical and/or Psychiatric Comorbidities
- Mode of Administration; Dosing Frequency
- DMT Safety Tolerability
- Patient Preferences
- Lifestyle Treatment Adherence
Patients with MS should be monitored while on DMTs for treatment efficacy by MRI, clinical history and neurologic examination to detect relapses and disease progression, and for safety and tolerability. Recent studies have also demonstrated the importance of quality of life metrics for patients on MS DMTs.

**MRI:** The formal recommendation of the CMSC MRI Task Force is to obtain an MRI of the brain with and without gadolinium at baseline, prior to starting or switching MS DMTs, and at least once every 1-2 years while on an MS DMT to assess for subclinical disease activity.\(^3\) In clinical practice, MRI every 6 or 12 months may be needed for selected patients. It is also recommended to obtain an MRI of the brain 6 months after starting an MS DMT to establish a new baseline. Routine spinal cord monitoring MRIs are not recommended unless the presentation is mostly recurrent TM. There may now be a trend to monitor the spinal cord for asymptomatic lesions, particularly in patients with radiologically isolated syndrome (RIS).\(^3\) It is useful to obtain a spine MRI at baseline if relapse history is consistent with spinal cord localization.

**MS Relapses:** Generally an MS relapse is defined as a new neurologic symptom with onset in the absence of fever or infection lasting longer than 24 hours.

**Safety:** Depends on specific DMT and standard monitoring guidelines should be followed.

**Side Effects & Tolerability:** If the DMT is causing a patient side effects and/or lowering their quality of life, the neurologist/care team should consider alternative DMT options that may be better tolerated (for example, if a patient experiences significant pain and injection site reactions on interferon, a switch to an oral DMT may be considered).

**Adherence:** If a patient is unable to take their DMT regularly as directed, it will not be as effective and thus, strategies for improving adherence on their current therapy may be explored (examples include use of a pill box, setting alarms, or a calendar). In addition, one may consider switching to an alternate DMT in which the patient may have improved adherence. For example, for a patient who cannot remember to take a pill twice daily (dimethyl fumarate), they may have improved adherence on a once daily therapy (fingolimod).

Disease-free status or no evidence of disease activity (NEDA) has become a therapeutic goal for the treatment of patients with MS ([Figure 7](#)). NEDA has been defined as the absence of new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on MRI, and no sustained EDSS score progression or clinical relapse.\(^3\) Some authors have also suggested inclusion of brain atrophy measures and patient-related outcome measures in NEDA.\(^3\)

Treatment switches may be considered for a number of reasons including lack of efficacy (breakthrough disease), safety concerns, tolerability and difficulty with adherence. For example: if a patient is on an injectable therapy and has evidence of disease activity based on MRI, neurologic examination or MS relapses, neurologists should consider advancing the patient’s therapy to an oral therapy (teriflunomide, DMF or fingolimod) or an infusion (natalizumab, alemtuzumab). There is no universal treatment algorithm as each patient's disease course is unique. Patients on natalizumab may need to switch to alternative MS therapies due to increased risk of PML with time on treatment or many other reasons. Natalizumab treated patients often have a more aggressive MS phenotype as they may have had a suboptimal response to alternative MS DMTs and thus, are at higher risk of recurrence of MS disease activity with treatment interruption. The RESTORE trial demonstrated an increased risk of disease activity with treatment interruption up to 24 weeks in patients who had been stable for at least one year.
on natalizumab. A washout (time off DMT) is often considered in between therapies to ensure that there are not overlapping effects with immunomodulatory therapy that could potentially result in increased risk of infection. This must be carefully balanced as washing out may lead to increased risk of MS relapse or new MRI disease activity. Clinicians may consider limiting time off treatment during a washout as the RESTORE trial demonstrated that clinical activity/relapses occurred as early as 4-8 weeks and radiographic disease activity as early as 12 weeks. The therapy selected to switch onto after natalizumab depends on reasons for discontinuation and each individual patient’s disease course. Studies have evaluated the switch from natalizumab to fingolimod and demonstrated that limiting the length of washout is beneficial in preventing new MS disease activity. An observational comparative effectiveness study showed that patients switching to fingolimod vs. interferon beta or glatiramer acetate after natalizumab suspension were less likely to suffer a relapse.
Updates on the Treatment of RRMS

PLATFORM THERAPIES

Glatiramer Acetate

Glatiramer acetate (GA) is a random polymer of amino acids made to appear similar to myelin basic protein. GA was approved in 1996 as a 20 mg once daily subcutaneous injection for RRMS and in 2009 the label was expanded to include CIS. A new preparation of GA with less frequent dosing was approved in 2014 based on the results of the GALA trial. The GALA trial studied GA at 40 mg subcutaneous injection three times weekly vs. placebo. The new formulation demonstrated 34% reduction in risk of relapse, 45% reduction in gadolinium enhancing lesions and 35% reduction in new or enlarging T2 lesions as compared to placebo. An open-label, randomized, multicenter study (GLACIER) was conducted to evaluate the safety and tolerability of GA 40 mg three times weekly compared with GA 20 mg daily in patients with RRMS. GLACIER demonstrated that GA 40 mg three times weekly was well tolerated with a favorable side effect profile as compared to 20 mg once daily (50% reduction in annualized rate of injection-related adverse events). A generic version of GA 20 mg (daily subcutaneous injection) received FDA approval in April of 2015.

Interferon

Interferon beta therapies have remained a standard of care treatment for RRMS for over 20 years, but these agents vary in the frequency of administration and type of injection (subcutaneous vs. intramuscular). Pegylated interferon beta-1a (PEG IFNβ-1a) was developed by attaching a polyethylene glycol side-chain to the interferon molecule via pegylation. This modification confers prolonged half-life allowing for less frequent administration. FDA-approved in 2014, PEG IFNβ-1a is a subcutaneous injection (125 µg) administered every two weeks for RRMS. The ADVANCE trial demonstrated significant reduction in annualized relapse rate (36%), disability progression (38% reduction) and MRI outcomes (67% reduction in new or enlarging T2 lesions and 86% reduction in gadolinium enhancing lesions) for PEG IFNβ-1a as compared to placebo. The reported side effect profile for PEG IFNβ-1a is similar to that of other interferons.

ORAL THERAPY UPDATES AND NEW SAFETY CONCERNS

Dimethyl Fumarate

Dimethyl fumarate (DMF) is a twice daily oral therapy for RRMS. Anti-inflammatory and cytoprotective effects of DMF are proposed to be mediated via the Nrf2 pathway, and a shift from Th1 to Th2 cytokine response. There is a rare risk of progressive multifocal leukoencephalopathy (PML) in patients on DMF. Rare cases of PML have been reported in patients on DMF associated with lymphopenia. In three patients, the absolute lymphocyte count was less than 500 cells/µL for 1-4 years and in one patient the absolute lymphocyte count was 600 cells/µL for greater than 6 months. According to the label, a baseline CBC with differential should be checked and once DMF is initiated, it should be checked every 6–12 months thereafter. If the absolute lymphocyte count drops below 500 cells/µL for greater than 6 months, treatment interruption should be considered.

Fingolimod

Fingolimod, the first oral-therapy approved for RRMS (FDA approved in 2010), is a sphingosine-1-phosphate receptor modulator that prevents lymphocyte egress from lymph nodes into the periphery. In phase 3 clinical trials, treatment with fingolimod was associated with ~50% reduction in ARR compared with placebo or IFNβ-1a. This therapy requires intensive first dose monitoring due to risk of first-dose bradycardia. Data from clinical trials indicate that
A PRACTICAL GUIDE TO IDIOPATHIC

Updates on the Treatment of RRMS

Primers in Multiple
treatment with fingolimod is associated with first-degree AV block in 4.7% of patients and second-degree AV block in 4% (either Mobitz I or II:I) (placebo rates are 1.6% and 2%, respectively). Due to a rare risk of macular edema, a fundoscopic exam including macular evaluation is recommended prior to treatment initiation and 3-4 months after treatment initiation. Infectious risks remain a concern on fingolimod due to rare reports of fingolimod-associated zoster virus infections, PML, and cryptococcal infections (cutaneous, pulmonary and meningitis). Rare cases of PML have been reported with fingolimod. The mechanism of PML associated with fingolimod remains unclear.

Teriflunomide
Teriflunomide is a once daily oral therapy FDA approved in 2012 for RRMS (available in 14 mg and 7 mg doses). The exact mechanism of action for teriflunomide is unknown, but likely involves reduction in the number of lymphocytes entering the CNS by inhibiting dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis in rapidly proliferating cells. Teriflunomide is pregnancy category X and both women and men planning to conceive should undergo a rapid elimination procedure utilizing activated charcoal or cholestyramine (teriflunomide is slowly eliminated from the plasma). Teriflunomide carries a black box warning for hepatotoxicity. No cases of PML have been reported with teriflunomide. At ECTRIMS 2015, Kappos et al reported on 2.5 year follow-up of the TOWER extension study in patients with RRMS. These authors reported no new safety signals with teriflunomide treatment in the extension study, and an adverse event profile consistent with that seen in core studies, supporting a positive benefit vs. risk ratio for patients with RRMS.

INFUSION THERAPIES
Natalizumab
Natalizumab is a humanized, monoclonal antibody which inhibits α4β1-integrin mediated adhesion of leukocytes to VCAM-1 on vascular endothelial cells at the blood brain barrier, thus preventing leukocyte migration into the brain and is administered IV once every 28 days. The Tysabri Observational Program (TOP) is an open-label, international, phase IV, prospective observational study designed to evaluate the long-term safety and impact on disease activity and progression of natalizumab monotherapy in patients with RRMS. Interim results from TOP have demonstrated that annualized relapse rates remain low, EDSS remains stable, and no change in known safety concerns have occurred for up to 5 years following natalizumab treatment initiation. A nine-year post-marketing surveillance study demonstrated no increased risk of malignancy with natalizumab treatment as compared to the general population.

The rare risk of PML should continue to be closely monitored in patients on natalizumab using a JCV serum antibody test prior to treatment initiation and periodically while on treatment (Table 4).

Table 4: Estimated US Incidence of PML Stratified by Risk Factor

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Negative</th>
<th>Natalizumab Exposure</th>
<th>Anti-JCV Antibody Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-24 months</td>
<td>&lt; 1/1,000</td>
</tr>
<tr>
<td>Anti-JCV Antibody Positive</td>
<td>No Prior Immunosuppressant Use</td>
<td>1/1,000</td>
</tr>
<tr>
<td>Prior Immunosuppressant Use</td>
<td>3/1,000</td>
<td>12/1,000</td>
</tr>
<tr>
<td></td>
<td>49-72 months</td>
<td>6/1,000</td>
</tr>
<tr>
<td></td>
<td>1/1,000</td>
<td>13/1,000</td>
</tr>
</tbody>
</table>
For patients who are JCV positive, the patient’s JCV serum antibody index value may be taken into account to further clarify risk of PML (Table 5). Natalizumab use in patients with history of prior immunosuppressant therapy is not recommended in patients who are JCV serum Ab positive due to increased risk of PML. PML risk increases beyond 24 doses. All patients on natalizumab must be enrolled in TOUCH, an observational risk monitoring program.

Alemtuzumab
Alemtuzumab is a humanized anti-CD52 monoclonal antibody FDA approved in 2014 for RRMS in individuals who have failed prior disease modifying therapies. It is an intravenous infusion administered in two courses; once daily (12 mg/day) for 5 days in year 1 and once daily for 3 days 12 months following the first treatment course. The therapy is not recommended for re-dosing unless the patient experiences new evidence of disease activity.

Alemtuzumab was FDA approved based on clinical efficacy results from the CARE MS I (treatment naive RRMS) and CARE MS II (RRMS with 1 or more relapses on prior DMT) phase 3 clinical trials comparing alemtuzumab vs. IFNβ-1a 44 mcg three times weekly. Results from the CARE MS I and II extension trials have recently been reported, and demonstrate continued clinical efficacy in patients treated with alemtuzumab. During the extension studies, as-needed retreatment with alemtuzumab was available ≥ 1 year apart based on evidence of disease activity (MRI activity or relapse). In CARE MS I, 5-year extension results showed that 68% of subjects were not re-dosed after month 12 and 69-72% of patients were free of new MRI disease activity at year 3, 4 and 5. In CARE MS II, 5-year extension results demonstrated that 60% of patients were not re-dosed after month 12, 75% were free of sustained disability accumulation and 68-70% were free from new MRI disease activity in years 3, 4 and 5.

Due to serious risks associated with alemtuzumab, there is a REMS program in place for all patients treated with alemtuzumab with serum and urine test monitoring once monthly for 48 months after their last infusion (Table 6). According to the label, risks associated with alemtuzumab include: ITP (2%), glomerular nephropathies (0.3%), autoimmune thyroid disease (34%), infections (herpes viral infections 16%, HPV 2%, active and latent TB 0.3%, listeria monocytogenes within first month of treatment, pneumonitis (0.5%), rare cases of thyroid cancer, and infusion reactions (92% total; 3% rated as severe infusion reactions).

Table 5: JCV Serum Antibody Index May Further Clarify Natalizumab Associated PML Risk

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Index</th>
<th>PML Risk Estimate per 1,000 Anti-JCV Antibody-Positive Patients by Natalizumab Treatment Duration (No Prior IS Use)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-24 months (99% CI)</td>
</tr>
<tr>
<td>≤ 0.9</td>
<td>0.1 (0–0.15)</td>
</tr>
<tr>
<td>≤ 1.1</td>
<td>0.1 (0–0.23)</td>
</tr>
<tr>
<td>≤ 1.3</td>
<td>0.1 (0–0.28)</td>
</tr>
<tr>
<td>≤ 1.5</td>
<td>0.1 (0–0.3)</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>1.0 (0.84–1.07)</td>
</tr>
</tbody>
</table>
Table 6: Notable Recommended Safety Monitoring for MS DMTs

<table>
<thead>
<tr>
<th>Disease Modifying Therapy</th>
<th>Prior to Treatment Initiation</th>
<th>Following Treatment Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>• CBC with differential</td>
<td>• Monthly CBC with differential</td>
</tr>
<tr>
<td></td>
<td>• Serum creatinine</td>
<td>• Monthly serum creatinine</td>
</tr>
<tr>
<td></td>
<td>• Thyroid function tests</td>
<td>• Urinalysis with cell counts</td>
</tr>
<tr>
<td></td>
<td>• TB test</td>
<td>(for 48 months after last dose)</td>
</tr>
<tr>
<td></td>
<td>• Urinalysis with urine cell</td>
<td>• TSH every 3 months (for 48</td>
</tr>
<tr>
<td></td>
<td>counts</td>
<td>months after last dose)</td>
</tr>
<tr>
<td></td>
<td>• Dermatologic exam</td>
<td>• Dermatologic exam once annually</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy test</td>
<td>• HPV test once annually in females</td>
</tr>
<tr>
<td></td>
<td>• VZV titer (if negative, immunize and wait 6 weeks post vaccination to initiate)</td>
<td></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>• CBC with differential</td>
<td>• CBC with differential</td>
</tr>
<tr>
<td></td>
<td>• LFTs</td>
<td>• LFTs</td>
</tr>
<tr>
<td></td>
<td>• JCV serum antibody test</td>
<td>• JCV serum antibody test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>periodically</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>• CBC with differential</td>
<td>• CBC with differential every 6 months</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>• CBC with differential</td>
<td>• CBC with differential</td>
</tr>
<tr>
<td></td>
<td>• LFTs</td>
<td>• LFTs every 6 months</td>
</tr>
<tr>
<td></td>
<td>• VZV titer</td>
<td>• Fundoscopic evaluation; screening for macular edema 3-4 months after treatment initiation</td>
</tr>
<tr>
<td></td>
<td>• Fundoscopic exam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• EKG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1st dose observation: 6 hour observation with hourly heart rate and blood pressure; EKG at end of monitoring]</td>
<td></td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>• CBC with differential</td>
<td>• LFTs once monthly for 6 months</td>
</tr>
<tr>
<td></td>
<td>• LFTs</td>
<td>• Blood pressure periodically</td>
</tr>
<tr>
<td></td>
<td>• Bilirubin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pregnancy test and confirm use of reliable contraception</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• TB test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Blood pressure</td>
<td></td>
</tr>
</tbody>
</table>

Disease Modifying Therapy Prior to Treatment Initiation

- Monthly CBC with differential
- Monthly serum creatinine
- Urinalysis with cell counts (for 48 months after last dose)
- TSH every 3 months (for 48 months after last dose)
- Dermatologic exam once annually
- HPV test once annually in females

Disease Modifying Therapy Following Treatment Initiation

- CBC with differential
- LFTs
- JCV serum antibody test periodically
EMERGING THERAPIES IN RELAPSING MULTIPLE SCLEROSIS

Daclizumab
Daclizumab high-yield process (HYP) is a humanized monoclonal antibody targeting CD25, the alpha subunit of the IL-2 receptor.\textsuperscript{77} Recently published results of DECIDE, a phase 3 clinical trial, demonstrated that daclizumab HYP 150 mg subcutaneous every 4 weeks met the study primary endpoint with a 45% reduction in ARR as compared to IFNβ-1a intramuscular (30 µg) once weekly.\textsuperscript{77} Additionally, treatment with daclizumab was associated with a 54% reduction in new or enlarging T2 lesions on MRI. There was no difference in disability progression between the two treatment arms. Notable adverse events associated with daclizumab were cutaneous events including rash and eczema, and elevation of liver enzymes up to 5x the upper limit of normal.\textsuperscript{77}

Ocrelizumab
Ocrelizumab (OCR) a humanized monoclonal antibody targeting CD20, is being studied in two identical double-blind, double-dummy phase 3 clinical trials (OPERA I and OPERA II) in patients with RRMS.\textsuperscript{78,79} Recently presented primary outcome results demonstrated that treatment with OCR 600 mg intravenous administered every 6 months was associated a 46-47% reduction in ARR compared to IFNβ-1a 44 mcg subcutaneous three times weekly.\textsuperscript{80} Confirmed disability progression was reduced by 43% and 37% in the OCR arms in the two studies. Furthermore, a 94-95% reduction in number of T1 gadolinium enhancing lesions and a 77-83% reduction in new or enlarging T2 lesions on MRI was associated with OCR treatment as compared to interferon beta-1a.\textsuperscript{80} Infusion related reactions were more common in the OCR arms and serious infections were similar for the OCR and interferon treatment arms.

Anti-LINGO
A different therapeutic strategy being explored for MS involves anti-LINGO-1 (BIIB033), a humanized monoclonal antibody that antagonizes LINGO-1. In animal models blockade of LINGO-1 has been shown to promote myelin repair.\textsuperscript{81} RENEW is a phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy of anti-LINGO in individuals experiencing their first acute optic neuritis.\textsuperscript{82} Patients treated with high dose corticosteroids were randomized to anti-LINGO 100 mg/kg IV every 4 weeks (6 doses) or placebo. Treatment with anti-LINGO was associated with improvement in optic nerve latency, as measured by full field visual evoked potential, consistent with remyelination in this patient population.\textsuperscript{83} The results of the RENEW trial provide support for further evaluation of anti-LINGO in patients with RRMS.
Treatment of Progressive MS

There are currently no therapies approved to treat purely progressive forms of MS (SPMS, PPMS) and trial results have been mostly disappointing. However, recognition of this significant unmet need has provided impetus for a new wave of clinical research to find effective therapies for this stage of the disease. Several international efforts including the International Progressive MS Alliance and the Multiple Sclerosis Outcomes Assessments Consortium (MSOAC) have been formed to accelerate drug development in progressive MS. In the last 2-3 years, several clinical trials in progressive MS have been completed or are currently underway some of which hold great promise as effective treatment options. Although some recent negative clinical trial results have been disappointing, they have provided valuable lessons regarding trial design and the difficulty translating results from relapsing into progressive MS.

Current treatment of progressive MS is mainly focused on symptomatic management, rehabilitation and control of complications. Effective treatment is paramount to maintain the quality of life for progressive MS patients; however the current need is for disease modifying neuroprotective, neuro-restorative therapies. We will review selected completed and ongoing trials of significance in progressive MS.

Fingolimod
Fingolimod, a sphingosine-1-phosphate receptor modulator, is an FDA-approved once-daily oral medication for relapsing forms of multiple sclerosis. Data from phase 3 trials in patients with RRMS demonstrated a significant effect of fingolimod on brain atrophy in this patient population. INFORMS was a three year, phase 3, double-blind, randomized multicenter, placebo controlled trial examining the effect of fingolimod 0.5 mg daily versus placebo in patients with PPMS. Eligibility criteria were clinical diagnosis of PPMS, 2-10 year disease duration, and evidence of disability progression in the previous 2 years. The primary endpoint was 3-month confirmed disability progression, based on a composite of change from baseline in EDSS, 25-foot Timed Walk Test, or 9-Hole Peg Test. The study randomized 970 subjects from 158 different sites. The primary endpoint was not met, and percent brain volume change was also not different between the fingolimod and placebo groups.

Ocrelizumab
In recognition of the role of B cells in the pathophysiology of MS, targeting this cell population has been investigated as a disease modifying strategy. Monoclonal antibodies that target CD20 such as rituximab, ocrelizumab, and ofatumumab produce prolonged depletion of B lymphocytes through complement-dependent cytotoxicity, stimulation of apoptosis, and/or antibody-dependent cytotoxicity. Hawker et al evaluated rituximab (a chimeric anti-CD20 monoclonal antibody) in a phase 3 trial of patients with PPMS. Treatment with rituximab was not associated with a significant difference in time to confirmed disease progression relative to placebo in this study; however these authors reported a benefit in subgroup analysis of patients younger than 51 years and those with gadolinium enhancing lesions at baseline. A newer humanized anti-CD20 monoclonal antibody, ocrelizumab, has been studied in both RRMS and PPMS. Positive results were recently reported with ocrelizumab in the OPERA I and OPERA II trials in patients with RRMS. A phase 3 randomized parallel group double blind placebo controlled study of ocrelizumab versus placebo (ORATORIO) in PPMS has completed enrollment of over 700 subjects with results expected in 2017. Patients were randomized to 2:1 to receive either
ocrelizumab (300 mg IV, two infusions, 14 days apart) or placebo every 24 weeks for at least 120 weeks. Eligible patients were 18-55 years of age, with a diagnosis of PPMS, EDSS score 3.0 to 6.5 at screening, and disease duration < 15 years for EDSS > 5.0 and < 10 years for EDSS ≤ 5.0. The primary endpoint for the ORATORIO trial is time to onset of confirmed disability progression (≥ 12-week sustained increase in EDSS scores). At ECTRIMS, Montalban et al reported that ocrelizumab treatment was associated with a 24% reduction in clinical disability progression at 12 weeks vs placebo.92 Demonstrated benefits in MRI endpoints and whole brain volume loss were also demonstrated for ocrelizumab treatment compared with placebo.92

HIGH DOSE BIOTIN
Biotin (vitamin H, vitamin B7) is a vitamin coenzyme for carboxylases involved in key steps in energy metabolism and fatty acid synthesis.93 In addition, biotin activates an enzyme involved in myelin synthesis. In a non-controlled pilot study of patients with primary or secondary progressive MS, high dose biotin (100-600 mg/day) was associated with improvement or normalization of both clinical and paraclinical measures (visual evoked potentials, proton magnetic spectroscopy).94 This proof of concept study led to an ongoing phase 3 clinical trial in patients with primary or secondary progressive MS.95 Eligible patients met diagnostic criteria for secondary or primary MS with EDSS between 4.5 and 7.0 and evidence of EDSS progression within the last two years. Patients were randomized to high dose biotin (300 mg daily) or placebo for 24 months. The primary endpoint was defined as the proportion of patients who improved at 9 months, with confirmation at 12 months. Improvement was defined as either a decrease in EDSS or improvement in T25FW of ≥ 20%.
Tourbah et al recently reported preliminary results from this study.96 Approximately 13% of patients in the biotin arm had an improvement in EDSS while none in the placebo arm had improvement.96 Although the differences were statistically significant, the low proportion of responders, and lack of imaging data (atrophy) make the results unclear. Further results of this study are expected to be published soon. Whether the effect seen was a purely symptomatic improvement versus actual disease modifying activity also is still not known.

IBUDILAST
Ibudilast is a phosphodiesterase inhibitor that was studied in a phase 2 study in patients with RRMS.97 Barkhof et al reported that in this patient population, ibudilast (30 or 60 mg/day orally) demonstrated no significant effect on lesions or relapses; however a significant benefit was noted with the 60 mg dose in protective effects on brain atrophy.97 The authors interpreted these data as potential neuroprotective properties associated with ibudilast.97 Ibudilast is currently being investigated in a multi-center, placebo controlled, double blind, Phase 2 study in patients with progressive MS (SPRINT-MS).98 Eligible patients are randomized to ibudilast (up to 100 mg/day) or placebo for 96 weeks. The primary outcome measures are adjusted mean rate of change in brain atrophy over 96 weeks as measured by brain parenchymal fraction and safety. A total of 255 patients have been recruited into the trial, and results are expected in 2017.

SIMVASTATIN
Although statins have been studied in relapsing forms of MS with un-convincing results, a large phase 2 study in SPMS demonstrated a beneficial effect of simvastatin (80 mg daily) on brain atrophy.99 Simvastatin reduced annualized atrophy by 43% compared to placebo. The possibility of a phase 3 trial however is unclear given the medication is off patent.100

NATALIZUMAB
The safety and efficacy of natalizumab to slow the accumulation of disability progression in patients with secondary progressive MS was evaluated in
the phase 3, placebo-controlled ASCEND trial. The trial completed enrollment of 889 patients, however, top-line results indicate that the study did not achieve significance on primary or secondary endpoints and the study has been terminated.

**MS-SMART TRIAL**

MS-SMART is a phase 2b multicenter trial being conducted in the United Kingdom designed to evaluate 3 different agents have shown promise in MS, particularly SPMS. Eligible patients with SPMS and EDSS 4.0-6.5 are being randomized to one of four different treatment arms; placebo, amiloride (5 mg BID), riluzole (50 mg BID), or fluoxetine (20 mg BID) for 96 weeks of treatment. The primary endpoint is MRI-derived percentage brain volume change over 96 weeks. The study is of considerable interest as it is using several potential neuroprotective agents (rather than immunomodulators), and it involves a smart clinical trial design aimed at minimizing exposure to placebo. MS-SMART has a target enrollment of 440 with estimated study completion in 2017.
Pediatric MS

Accumulating data over recent years have provided new insights into MS in children. A recent review reported that the overall incidence of acquired demyelinating syndromes ranges from 0.6 to 1.66 per 100,000 children and adolescents per year. The incidence of pediatric MS varies worldwide (Table 7).

The current clinical definition of pediatric MS includes the following:

1. Two clinical events (without encephalopathy) both consistent with attacks typical of MS, separated by more than 30 days, and affecting more than one area of the brain, optic nerves, or spinal cord
2. A first clinical event consistent with MS in a patient between 12-18 years who fulfills the 2010 McDonald MRI dissemination in space (≥ 1 T2 lesion in two of the four following locations: periventricular, juxtacortical, infratentorial, or spinal cord), and dissemination in time (clinically-silent enhancing or non-enhancing on T1-weighted images) criteria on baseline MRI
3. One clinical event (without encephalopathy) typical of MS and MRI demonstrating at least one new T2 lesion on a scan more than 30 days after the incident attack
4. An event that fulfills criteria initially for acute disseminated encephalomyelitis, followed by a second non-acute disseminated encephalomyelitis event (> 3 months from symptom onset) associated with new MRI lesions demonstrating 2010 McDonald dissemination in space criteria

MRI features of pediatric MS and several mimics are summarized in Table 8.

According to recent reports, 2-10% of all patients with MS have clinical onset before the age of 18 years. Female gender, BMI, exposure to second-hand smoke, ≥ 1 HLA-DRB3 alleles, and remote EBV infection are risk factors for pediatric MS susceptibility or disease activity. Primary progressive MS is extremely rare in children; 97% of those with disease onset prior to age 18 have relapsing-remitting disease. Compared to adult-onset MS, childhood onset-MS is associated with increased T2 MRI burden at disease onset, and frequent cognitive deficits, yet slower EDSS-related disability progression. In addition, relapse frequency is higher in children within the initial 2-5 years of MS disease onset compared with adults with MS. Aubert-Broche et al evaluated age-expected brain growth in patients with MS onset prior to age 18 compared with age- and sex-matched controls. These authors reported that MS onset during childhood and adolescence is associated with abnormally small brain volumes, and in particular, reduction of age-expected thalamic volume—evidence of neurodegeneration early in the disease (even in children).

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of Pediatric MS per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>0.13/100,000</td>
</tr>
<tr>
<td>Canada</td>
<td>0.18/100,000</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.66/100,000</td>
</tr>
<tr>
<td>Germany</td>
<td>0.3/100,000</td>
</tr>
<tr>
<td>United States</td>
<td>0.51/100,000</td>
</tr>
</tbody>
</table>
The lack of FDA-approved disease modifying therapies for pediatric MS is currently an unmet need. While DMTs are used off-label in the pediatric MS population, clinical trials in these patients are needed to better inform treatment decisions. The International Pediatric Multiple Sclerosis Study Group (IPMSSG) advocates offering therapy to all patients diagnosed with MS, recognizing that there is not a method to prospectively identify patients who will have few

### Table 8: MRI Features of Pediatric MS and Mimics (adapted from 103)

<table>
<thead>
<tr>
<th>Neurologic Disorder</th>
<th>Frequent MRI Findings</th>
<th>Common MRI Features</th>
<th>Features Suggestive of Alternative Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>• &gt; 1 periventricular T2 lesion(s)</td>
<td>• Juxtacortical lesions</td>
<td>• Absence of T2 lesions at baseline</td>
</tr>
<tr>
<td></td>
<td>• Periventricular lesions oriented perpendicular to corpus callosum</td>
<td>• Brainstem or cerebellar lesions</td>
<td>• Failure to document T2 lesion accrual</td>
</tr>
<tr>
<td></td>
<td>• &gt; 1 T1 hypointense lesion</td>
<td>• Low global brain volume</td>
<td>• Meningeal Gd-positive</td>
</tr>
<tr>
<td></td>
<td>• Gd-positive and Gd-negative lesions</td>
<td></td>
<td>• Visible cortical lesions on T2 at 1.5 or 3T</td>
</tr>
<tr>
<td></td>
<td>• Low thalamic volume</td>
<td></td>
<td>• Focal cortical volume loss</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>• &lt; 2 periventricular lesions</td>
<td>• Diffuse ill-defined multifocal bilateral lesions</td>
<td></td>
</tr>
<tr>
<td>(ADEM)</td>
<td>• Absence of non-enhancing T1 hypointense lesions</td>
<td>• LETM (when cord involvement in present)</td>
<td></td>
</tr>
<tr>
<td>Neuromyelitis optica (NMO)</td>
<td>• LETM</td>
<td>• Absence of optic nerve or spinal cord involvement over time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Long optic nerve lesions</td>
<td>• Well-defined lesions</td>
<td>• Sole presence of well-defined lesions</td>
</tr>
<tr>
<td></td>
<td>• Diencephalic lesions</td>
<td>• Expansive lesions of the optic nerve</td>
<td>• Focal spinal cord lesions</td>
</tr>
<tr>
<td></td>
<td>• Periaqueductal lesions</td>
<td>• Absence of cortical lesions</td>
<td></td>
</tr>
<tr>
<td>Chronic relapsing inflammatory</td>
<td>• Absence of brain or spine involvement</td>
<td>• Gd-positive optic nerve lesions</td>
<td></td>
</tr>
<tr>
<td>optic neuropathy (CRION)</td>
<td>• Unilateral or bilateral optic nerve involvement</td>
<td>• Chiasmal lesions</td>
<td></td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>• Meningeal Gd-positive</td>
<td>• Multifocal T2 lesions</td>
<td>• Absence of cortical lesions</td>
</tr>
<tr>
<td></td>
<td>• Focal cortical T2 lesions</td>
<td>• Optic neuritis and cord lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Magnetic resonance angiography lesions</td>
<td>• Normal or near-normal brain MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Angiographic evidence of vascular beading</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gd: gadolinium; LETM: longitudinally extensive transverse myelitis; MRS: magnetic resonance spectroscopy
Considerations related to the conduct of clinical trials in pediatric patients with MS were summarized following the International Pediatric MS Study Group Clinical Trials Summit (Table 9).

Table 9: Consensus Benefits and Challenges Associated with the Conduct of Clinical Trials in Pediatric MS (adapted\textsuperscript{104})

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Challenges</th>
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<tbody>
<tr>
<td>1. To gain accurate information regarding pharmacokinetics, in particular effective dosing of therapies</td>
<td>1. Pediatric MS is a rare disease with an estimated worldwide prevalence of 2,000 cases in centers affiliated with the IPMSSG (survey, September 2011). Enrollment rate in potential trials is presently unknown</td>
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<tr>
<td>2. To assess short-term and long-term safety of therapies</td>
<td>2. There are limited natural history data in pediatric MS documenting accrual of annualized relapse rate, motor and cognitive disability, and MRI lesions and their correlation with clinical parameters</td>
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<tr>
<td>3. To assess the effect of therapies on normal development</td>
<td>3. First-line agents, interferon β and glatiramer acetate are commonly used; however, there have been no randomized controlled trials conducted with these agents in pediatric MS</td>
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<tr>
<td>4. To confirm whether there is a clinical benefit of specific therapies in children (especially young children) commensurate with that observed in adult patients with MS</td>
<td>4. Some relevant outcome measures in pediatric MS may be different from those traditionally used in adult MS trials, and may require new and currently unvalidated measures</td>
</tr>
<tr>
<td>5. To gain regulatory approval for drugs particularly in countries and regions where insurance coverage and subsequent use relies on approval</td>
<td>5. Frequent sampling may pose significant feasibility challenges when assessing pharmacokinetic parameters, particularly for those who require exposure to varied doses</td>
</tr>
<tr>
<td>6. There is little knowledge regarding the underlying biological similarities and differences between pediatric and adult-onset MS, which may provide insights into the potential effects of various agents</td>
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</tr>
<tr>
<td>7. There are ethical challenges of performing studies in children, such as risk of exposure to novel agents and use of a placebo</td>
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</tr>
<tr>
<td>8. Long-term safety assessments are crucial, but require the identification of appropriate parameters as well as mechanisms to accurately capture this information</td>
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</tr>
<tr>
<td>9. Regulatory requirements may differ across regions, which if not reconciled may result in redundant studies being required</td>
<td>9. There is little knowledge regarding the underlying biological similarities and differences between pediatric and adult-onset MS, which may provide insights into the potential effects of various agents</td>
</tr>
</tbody>
</table>
Health and Wellness

According to the World Health Organization, "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Health is a dynamic and ever-changing condition that enables an individual to function at optimum potential regardless of limitations. Wellness has been defined as an active process of becoming aware of and making choices toward a healthy and fulfilling life. Wellness is multidimensional. A popular model adopted by many university, corporate, and public health programs encompasses 6 dimensions:107

1. Social
2. Occupational
3. Spiritual
4. Physical
5. Intellectual
6. Emotional

The MS care team can support positive, healthy choices to promote an overall balance of physical, social, spiritual, and emotional well-being for individuals with MS throughout the disease course.

General wellness recommendations for people with MS include:

• Regular visits with a primary care provider for age-appropriate screening, prevention and management of comorbidities, and immunizations as appropriate
• Regular exercise (shown to positively affect mood, fatigue, cognition and quality of life in addition to decreasing risk of vascular comorbidities)
• Healthy diet to maintain a healthy weight and reduce risk for comorbidities
• Smoking cessation
• Vitamin D supplementation to maintain 25-OH Vitamin D level in the upper half of normal range
• Stress management
• Moderation of alcohol intake
• Participation in other activities that improve wellness and wellbeing (such as yoga, tai chi, relaxation techniques, gardening)

NUTRITION

Good nutrition is essential for promoting wellness. Research has shown that persistent consumption of diets high in salt, animal fat, red meat, sugary drinks, and low fiber is associated with an upregulation of metabolic pathways characterized by production of proinflammatory molecules, dysbiotic gut microbiota, and low-grade systemic inflammation.108,109 For individuals with a CNS demyelinating disorder such as MS, the potential for negative consequences associated with a ‘proinflammatory diet’ are clear.

Over the years, many foods and diets have been proposed as beneficial for people with MS. Research efforts have been limited, but most diets recommend avoiding highly processed foods, foods with high glycemic index, and food that is high in saturated fat. Most diets also recommend reducing consumption of fatty red meat and increasing consumption of fruits and vegetables.

General dietary recommendations include:110,111

• Eat calcium-rich foods
• Eat foods containing or fortified with vitamin D
• Use low-fat dairy products
• Eat protein daily (meat, poultry, fish, eggs, beans, nuts, etc)
• Choose lean cuts of meat, chicken, poultry and fish
• Increase omega-3 fatty acids in the diet (flaxseed, soy, soybean oil, canola oil, walnuts, fish and fish oils)
• Eat 5-9 servings of fruits and vegetables a day, including dark, green leafy vegetables, and fresh fruit
• Avoid saturated fats
• Avoid trans fats, cholesterol, salt, and added sugars
• Eat whole-grain breads and fiber-rich foods
• Drink at least 8-10 cups of fluid a day
• Grill, bake, steam, or poach foods (instead of frying)
• Use poly- and monounsaturated margarines and oils, such as canola and olive oil
• Avoid mega-doses of vitamin supplements
• Avoid sugar-containing and caffeinated beverages
• Eat no fewer than 3 meals a day, and preferably 5-6 small meals a day, including breakfast
• Monitor portion size
• There have been no recommendations regarding elimination of gluten for persons with MS

BODY MASS INDEX
Maintenance of healthy weight is part of overall wellness for all persons, including those with MS. Hedstrom et al conducted a Swedish population-based case-control study evaluating BMI and risk for MS.112 This study, which included 1571 cases and 3371 controls, showed that subjects with BMI > 27 kg/m² at age 20 had a two-fold increased risk of developing MS compared with normal weight subjects.112 These authors speculate that the obesity epidemic may explain part of the increasing MS incidence as recorded in some countries, and further that measures addressing adolescent obesity may serve as a preventive strategy against MS.112 Ben-Zacharia recently reported results of a 5 year retrospective study evaluating the association between baseline BMI and MS progression.113 This study showed that the odds of having increased EDSS by at least 1 point in obese patients with mild disability were 8 times greater than for those with normal BMI.113 In addition, the odds of having new brain MRI lesions were 6.2 times greater in overweight subjects and 2.6 times greater in obese subjects than in subjects with normal BMI.113 These results highlight the importance of weight control and potential benefits with regard to disease progression in this patient population.

SMOKING
In 1964, the Surgeon General reported the hazards of cigarette smoking.114 In addition to the general health and safety concerns, evidence is mounting on how smoking can affect MS. Cigarette smoking is a known risk factor for MS, and smokers are more likely to be diagnosed with progressive MS than never-smokers.115,116 In addition, Healy et al reported that compared with never-smokers, current smokers had significantly worse disease at baseline (EDSS scores, multiple sclerosis severity score, and brain parenchymal fraction), and converted from RRMS to secondary progressive MS faster than non-smokers.117

VITAMIN D
Vitamin D insufficiency is a risk factor for MS,6,118 and Runia et al have reported that low serum vitamin D levels are associated with a higher risk for relapse in patients with MS.119 A recent paper by Dr. Allen Bowling recommends considering vitamin D status as part of an overall therapeutic strategy for patients with MS.120 MS patients are at higher risk for osteopenia/osteoporosis especially if they are not ambulatory, have gait disturbance and have been treated with courses of IV steroids. Many MS patients tend to avoid being out in the sun as they are heat sensitive, further increasing their risk for Vitamin D deficiency.121 Vitamin D deficiencies are relatively common (an estimated 80% of those with MS have levels below 20 ng/mL independent of disease stage) and can be detected by blood testing measuring 25-hydroxyvitamin D.122 Monitoring serum vitamin D in patients with MS at baseline, with recheck at 3 to 6 months following initiation of a supplementation protocol or change in treatment regimen is recommended.120 While a definitive protocol for vitamin D supplementation for persons with MS has not been established, a desirable range for serum vitamin D levels of 30-55 ng/mL has been suggested; supplementation with 1,000 to 4,000 IU/day may
be needed to achieve this goal. More research is needed and prospective studies may help with a more comprehensive understanding of any cause and effect relationship of vitamin D and immune system function.

**COMORBIDITIES**

Many individuals with MS will also be diagnosed with other medical conditions in their lifetime. There is increasing evidence that the presence of comorbidity (physical or mental) in patients with MS is associated with diagnostic delays, disability progression, health-related quality of life, and progression of lesion burden on MRI. Reported prevalence of comorbidity in patients with MS in the literature is variable, due to characteristics of the study population and specific conditions studied. Marrie et al recently conducted a systematic review of the incidence and prevalence of comorbidity in MS. Their study included 249 publications, based on studies conducted primarily in Europe and North America, with fewer studies from Asia, Australia, New Zealand and South America. Based on their meta-analysis, the most common comorbidities were depression (23.7%), anxiety (21.9%), hypertension (18.6%), irritable bowel syndrome (12.2%), hyperlipidemia (10.9%), and chronic lung disease (10.0%). An earlier study of patients in the North American Research on Multiple Sclerosis (NARCOMS) registry indicated that 36.7% of this patient population self-reported at least one physical comorbidity. Among the NARCOMS population, the most frequently reported comorbidities were hyperlipidemia (37%), hypertension (30%), arthritis (16%), irritable bowel syndrome (13%), and lung disease (13%). Comorbid conditions such as diabetes, hypertension, hyperlipidemia, obesity, and smoking have been shown to affect the progression of MS. As part of individualized treatment for patients with MS, the presence of comorbid medical and/or psychiatric conditions is an important consideration with selection of DMT and symptomatic MS medications. It is essential for patients with MS to have a primary care provider to help prevent or better manage non-MS-related concerns as well as provide age appropriate recommended screenings including:

- Mammogram/clinical breast exam
- Pap test and HPV test for cervical cancer
- PSA/clinical testicular and rectal exam
- Hemoccult stool test/colonoscopy
- Influenza vaccine and other recommended age- or risk-based immunizations
- Bone density testing
- Electrocardiogram
- Screen for anemia, diabetes, thyroid disease, liver disease

**COMPLEMENTARY AND ALTERNATIVE MEDICINE**

According to a report of the Guideline Development Committee of the American Academy of Neurology, 33-80% of patients with MS use complementary and alternative medicine (CAM) therapies. CAM use is particularly prevalent in those who are female, have higher education levels, and report poorer health. The 2014 AAN report included the following recommendations:

- **Cannabinoids**
  - Oral cannabis extract
    - Effective for reducing patient reported symptoms of spasticity and pain
    - Probably ineffective for improving objective spasticity measures or tremor
  - Synthetic tetrahydrocannabinol
    - Probably effective for reducing patient reported symptoms of spasticity and pain
    - Probably ineffective for improving objective spasticity measures or tremor
  - Nabiximols oromucosal spray
    - Probably effective for reducing patient reported symptoms of spasticity, pain or urinary frequency
    - Probably ineffective for improving objective spasticity measures or urinary incontinence episodes
- Smoked cannabis
  - Data are inadequate to support or refute the use for spasticity, pain, balance/posture and cognition

- Ginkgo biloba
  - Established as ineffective for improving cognitive function in MS
  - Possibly effective for reducing fatigue

- Low-fat diet with omega-3 fatty acid supplementation
  - Probably ineffective for reducing MS-related relapse, disability or MRI lesions, or for improving fatigue or quality of life

- Lofepramine (Cari Loder regimen when combined with L-phenylalanine and vitamin B12)
  - Possibly ineffective for reducing MS-related disability, symptoms, depression, or fatigue

- Reflexology
  - Possibly effective for reducing MS-associated paresthesia

- Bee venom
  - Possibly ineffective for reducing MS-related relapses, disability, fatigue, total MRI lesion burden, new gadolinium-enhancing lesion volume, or health-related quality of life

- Magnetic therapy
  - Probably effective in reducing fatigue in RRMS
  - Probably ineffective for reducing depression

The report concluded that the data were insufficient to determine if CAM therapies worsen MS or interfere with DMTs. Inquiry by the care team about the use of CAM in patients with MS is warranted, as some strategies may actually stimulate the immune system, which would not be advantageous for this patient population. Drs. Allen and Nathaniel Bowling provide information about a range of alternative medicinal approaches and considerations for use in patients with MS (http://www.neurologycare.net/cam).128

In addition, the NIH has a website (https://nccih.nih.gov/) with extensive information about complementary and integrative health, including searchable safety information for products/practices and uses and side effects of herbs and botanicals.129
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44. Glatiram er acetate (Copaxone).


47. Glatiram er acetate (Glatopa).


49. Dimethyl fumarate (Tecfidera).


55. Fingolimod (Gilenya).


62. Teriflunom ide (Aubagio).

63. Teriflunom ide (Aubagio).

64. Fingolimod (Gilenya).


