Current and Future Directions in MS Management: Key Considerations for Managed Care Pharmacists

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Supplement Policy Statement

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7. Subject all supplements to expert peer review.

Faculty

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Faculty Disclosures

This supplement was sponsored by PRIME® through an independent educational grant from Teva Neuroscience.

Robert J. Lipsy, PharmD, BCPS, FASHP, discloses that he is a speaker/consultant for Teva Neuroscience.

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Chris R. Prostko, PhD, discloses that he is a full-time employee of PRIME®, the accreditor of this activity.

Off-Label Use

This educational activity discusses several medications that are in phase III clinical trials and have not been approved by the FDA for treatment or management of multiple sclerosis at the time of publication. This list of medications includes cladribine, dimethyl fumarate, fingolimod, laquinimod, teriflunomide, fampridine, alemtuzumab, daclizumab, and rituximab.

Acknowledgements

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*Robert J. Lipsy, PharmD, BCPS, FASHP; Randall T. Schapiro, MD, FAAN; Chris R. Prostko, PhD*

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**Target Audience**

This activity is intended for managed care pharmacists and managed care physicians. This is an application-based learning activity.

**Learning Objectives**

Upon completion of this program, participants will be able to:

1. Evaluate data submitted by managed care pharmacists pertaining to current pharmacy practice trends in multiple sclerosis (MS) management.
2. Assess newest evidence in MS diagnosis and treatment impacting pharmacy practice.
3. Identify paradigm shifts in MS treatment and management and the rapidly evolving role of the managed care pharmacist.

**Funding and Original Presentation of This Learning Activity**

This supplement was sponsored by PRIME® through an independent education grant from Teva Neuroscience. This supplement was developed based on a needs assessment conducted at a satellite symposium held on October 17, 2008, at the Kansas City Convention Center in Kansas City, Missouri, in conjunction with the Academy of Managed Care Pharmacy’s 2008 Educational Conference, which was supported by an independent grant from Teva Neuroscience.

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ABSTRACT

BACKGROUND: The management paradigm for multiple sclerosis (MS) continues to evolve and is shifting toward earlier diagnosis, differentiation of patients with varying clinical prognoses, and earlier initiation of treatment in selected individuals. Based on surveys conducted at the 2008 annual conference of the Academy of Managed Care Pharmacy (AMCP) and at regional meetings held in 2009, several topics were identified for which pharmacists indicated a need for new and updated information.

OBJECTIVE: To review (a) recent insights into the pathophysiology underlying MS, (b) the improvements in identification of patients with a clinically isolated syndrome (CIS) who will progress to clinically definite MS (CDMS), (c) the current role of magnetic resonance imaging (MRI) and other technologies in the diagnosis and ongoing management of MS, (d) the optimal time to initiate treatment in patients with CIS or MS, and (e) the potential utility of new and emerging therapies in MS management.

METHODS: The medical education company PRIME conducted an educational needs assessment regarding knowledge of recent developments and future directions in MS management at a symposium held at the Academy of Managed Care Pharmacy Educational Conference in Kansas City, Missouri, on October 17, 2008. This was augmented by an ongoing educational needs assessment initiative that involved a national series of regional dinner meetings for managed care pharmacists on the topic of MS in the first 3 quarters of 2009. Collectively, these needs assessments were designed to determine educational gaps that existed after participants attended the symposia on MS, in an effort to plan a follow-up enduring educational activity that addressed those gaps. Measures of learners’ post-program intent were collected, as well as specific topic areas recommended for a follow-up activity.

SUMMARY: Advances have been made in the understanding of CIS subtypes and refinement of MS diagnostic criteria. Early initiation of treatment in patients with a CIS has been shown to prolong the time to progression to CDMS, delay the development of disability, and may also decrease long-term health care costs. In addition, a number of novel therapies for patients with varying clinical prognoses, and earlier initiation of treatment with MS are in late stages of clinical development, including several oral medications that are of particular interest to managed care pharmacists. These will provide potentially attractive treatment alternatives for patients with MS, who currently must choose from a selection of injectable drugs.

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Acronyms used in this supplement

BENEFIT = Betaseron (IFNβ-1b) in Newly Emerging MS for Initial Treatment
CDMS = clinically definite multiple sclerosis
CHAMPS = Controlled High-Risk Subjects (IFNβ-1a) Avonex Multiple Sclerosis Prevention Study
CIS = clinically isolated syndrome
CLARITY = CLAdRilbine tablets Treating MS orally
CMSC = Consortium of MS Centers
CNS = central nervous system
CSF = cerebrospinal fluid
DIT = dissemination in time
DIS = dissemination in space
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
ETOMS = Early Treatment of MS Study
FLAIR = fluid attenuated reversion recovery
Gd = gadolinium
ICER = incremental cost-effectiveness ratio
IFNβ = interferon beta
MCST = Modified Card Sorting Test
MRI = magnetic resonance imaging
MS = multiple sclerosis
MTM = medication therapy management
ORACLE = ORAI Cladribine for Early MS
PML = progressive multifocal leukoencephalopathy
PreCiSe = Study to Evaluate the Effect of Early Glatiramer Acetate (Copaxone) Treatment in Delaying the Conversion to CDMS of Subjects with a CIS
REFLEX = Rebif (IFNβ-1a) FLEXible Dosing in Early MS
RIS = radiologically isolated syndrome
RRMS = relapsing-remitting multiple sclerosis
SPMS = secondary-progressive multiple sclerosis
T = Tesla
VEP = visual evoked potential
Multiple sclerosis (MS) is a degenerative neurologic disorder that produces a variety of symptoms, with some patients progressing to significant degrees of disability. Over the past 2 decades, advances in therapies for MS have transformed it from a disease of relative despair with few treatment options to one of therapeutic promise. With the introduction and utilization of immunomodulatory therapy in the 1990s, therapeutic goals in MS moved from palliation to disease control. With the advent of newer therapies, disease modification and the potential for a cure may be on the horizon. Advances in MS treatments have led to a wider variety of health care practitioners becoming involved in managing MS, including the introduction of multidisciplinary care coordination teams. The addition of these new MS care providers has brought with it the need to educate these professionals on the topic of MS, its therapeutic options, and future directions.

MS management involves (a) disease management, (b) symptomatic treatment, and (c) patient management. Disease management is of primary importance; as such, disease-modifying therapies (DMTs) are a mainstay of MS management. However, many would advocate that symptomatic treatment is equally important from the standpoint of quality of life. Often forgotten is the fact that there is a person behind the disease and that person management (e.g., psychological, vocational, and marital issues) is essential to any effective MS management program. The pharmacist has an opportunity to be involved in many aspects of MS management.

As with many diseases, advocates of multidisciplinary care for patients with MS believe that such an approach is beneficial in improving patient outcomes. While overall data are inconsistent, studies have suggested that multidisciplinary treatment programs that include a rehabilitation component may result in improved patient experiences. Multidisciplinary treatment programs must include the pharmacist as a core member of the team, especially with the recent upsurge in medication therapy management (MTM) programs following implementation of the Medicare Modernization Act of 2003. While there have been no studies investigating the benefit of MTM programs for patients with MS or their role in the provision of multidisciplinary care for patients with MS, the components of such a program—medication therapy review, personal medication record, medication-related action plan, intervention and/or referral, and documentation and follow-up—are all appropriate methods for the pharmacist to use when interfacing with the MS patient in an ongoing fashion. Based upon this, education of the pharmacist is vital to optimizing outcomes for patients with MS because pharmacists may improve therapy adherence and provide patients with valuable education on disease information and treatment modalities.

Methods
The medical education company PRIME conducted an educational needs assessment on MS at a symposium held at the Academy of Managed Care Pharmacy (AMCP) educational conference in Kansas City, Missouri, on October 17, 2008. This was augmented by an ongoing educational needs assessment initiative conducted via a national series of regional dinner meetings for managed care pharmacists on the topic of MS in the first 3 quarters of 2009. Collectively, these needs assessments were designed to determine educational gaps that existed after participants attended the symposia on MS in an effort to plan a follow-up enduring educational activity that addressed those gaps. Measures of learners’ post-program intent were collected, as well as specific topic areas recommended for a follow-up activity.

Results of Educational Needs Assessment
More than 100 pharmacists attended the AMCP symposium on MS in October 2008, and to date, more than 350 pharmacists have attended follow-up sessions held throughout the United States. Through PRIME’s continuous assessment process, all attendees were surveyed regarding competence and performance in managing MS patients. Data collected during this assessment process showed that approximately 80% of attendees stated that they had a better understanding of current therapeutic options for MS following the AMCP symposium or regional meetings, and 65% of attendees stated that they would seek educational opportunities to enhance their overall knowledge of MS. Topics on which pharmacists requested more education included recent insights into the pathophysiology of MS, the role of imaging in the diagnosis and ongoing management of MS, the optimal time to initiate treatment for MS, and new and emerging MS therapies. As a result of this needs assessment, content for this enduring article was planned with these specific topics in mind.

Immunopathology of MS
Traditionally thought to be primarily an inflammatory demyelinating disease, MS is now recognized to have a significant neurodegenerative component. While heterogeneity exists, most patients with MS exhibit a dual-phase pattern of disease activity, with the early phase dominated by central nervous system (CNS) inflammation caused by infiltration of activated T cells, B cells, and macrophages (Figure 1). Selective demyelination then begins as neurons are attacked by macrophages, T cells, and antibodies secreted from B cells that have differentiated into plasma cells. Although Figure 1 shows only Th1 cells entering the CNS, it has recently been recognized that other T-lymphocyte subtypes (particularly Th17 cells that secrete interleukin-17) are important in the pathogenesis of MS.

Some axonal loss also occurs early in the MS disease course, perhaps even in pre-clinical stages. Patients with MS gradually transition to a later stage disease that is dominated by neurodegeneration and widespread axonal loss, even though inflammation tends to subside. Because of advances in the understanding of the pathophysiology of MS, the management paradigm has evolved to include both earlier diagnosis and early treatment using...
In 2008, an international consensus on the differential diagnosis of MS was published, which provides an algorithm to help guide the clinical, laboratory, and MRI evaluations of patients with suspected MS. These recommendations also consider nearly 80 clinical and paraclinical “red flags” of various “strength” classifications that suggest alternative diagnoses. Clinically Isolated Syndrome

Current McDonald criteria emphasize the importance of early diagnosis of patients with clinically isolated syndrome (CIS). CIS is defined as a single, symptomatic neurologic episode that is consistent with MS. The most common symptoms on initial presentation are optic neuritis, ocular motor syndromes (internuclear ophthalmoparesis, nystagmus), ataxia, dysarthria, sensory or motor signs, partial myelitis, and bladder or bowel dysfunction. Many patients with a CIS will have already have lesions on an MRI scan. To improve diagnosis of CIS, the 2005 revisions to the McDonald criteria placed greater significance on the presence of spinal cord lesions on MRI. Approximately 60% to 80% of individuals with a CIS and demyelinating lesions on an MRI will eventually develop
clinically definite multiple sclerosis (CDMS), as will about 20% of CIS patients with normal MRI scans.20-22 The McDonald criteria recognize a new T2 MRI lesion occurring any time after 30 days from CIS onset as evidence of DIT. This facilitates earlier diagnosis of MS by allowing for 2 separate MRI scans (instead of 3) to evaluate disease progression, and 1 clinical attack (instead of 2) if MRI lesions demonstrate DIT or DIS.14 By eliminating the requirement for DIT and/or a second clinical event, the McDonald criteria speed the diagnosis and more quickly resolve the period for patients when uncertainty exists regarding a definitive diagnosis.

One of the ongoing management challenges is to further improve the identification of patients with CIS who are at high risk for developing CDMS. To address this challenge, 2 modifications or simplifications to the McDonald MRI criteria were proposed in 2006 by Swanton et al: (a) that DIS require at least 1 T2 lesion in at least 2 of 4 CNS locations; and (b) that DIT require a new T2 lesion on a follow-up scan regardless of timing of the baseline scan.26 Recent data support the second recommendation, with Tur et al. (2008) reporting that the presence of new T2 lesions in patients with CIS increased the risk of relapse regardless of the timing of the reference MRI scan.24

In a subsequent publication, Swanton et al. (2007) conducted a comparison of McDonald MRI criteria with their proposed changes for predicting progression of CIS to CDMS.25 This was a retrospective analysis of 208 patients from 4 centers in Europe who had 2 MRI scans within 12 months of CIS onset in whom the specificity and sensitivity of MRI criteria for CDMS were assessed after 3 years. Table 2 provides a more detailed summary of the 2 MRI criteria for DIT and DIS, as well as estimates of their specificity and sensitivity. While the specificity of both criteria was roughly equivalent, the sensitivity of the Swanton criteria was higher than that of the McDonald criteria (72% vs. 60%; no P value provided). For both MRI criteria, a higher risk of conversion from CIS to CDMS was seen in patients with both DIS and DIT, compared with those with either DIS or DIT. The DIT component of both criteria was also more specific than DIS alone. While acknowledging some of the study’s limitations, the authors concluded that their revised MRI criteria simplified the McDonald criteria without compromising specificity or accuracy.25

Korteweg et al. (2009) recently attempted to identify simpler and more sensitive criteria for DIS based on CNS lesion characteristics at the onset of CIS based on single MRI scans.26 The authors were unable to improve the performance of the current diagnostic criteria for DIS alone using a single unenhanced MRI and concluded that follow-up scans with and without contrast are needed to improve the diagnostic algorithm.26

Diagnostic criteria for MS will continue to be updated and refined. This is particularly true regarding the role of MRI; technical advancements will need to be incorporated into clinical practice. Other imaging technologies are likely to play an increasing role in the future for both the diagnosis and longitudinal monitoring of patients with CIS and MS.

**Is the Current Definition of CIS Adequate?**

Several criticisms have been noted regarding current use of the term “clinically isolated syndrome.” For example, although CIS is the clinical presentation of relapsing-remitting MS (RRMS), the current definition of CIS does not consider initial presentations that may not be clinical but might be detected by paraclinical and laboratory results.27 In addition, the current CIS definition does not differentiate between 2 patient populations with different prognoses: individuals who have a single clinical presentation with or without additional symptomatic MRI lesions.20-22
Okuda et al. (2009) published an analysis of a cohort of asymptomatic patients (n = 44) with incidental white matter abnormalities in the CNS suggestive of MS detected in an initial MRI. Neurological examination at baseline was normal in nearly all cases, and every attempt was made to rule out other diseases as responsible for the radiologic abnormalities. Longitudinal clinical and MRI follow-up were conducted in 30 and 41 patients, respectively. Evidence of radiologic progression was seen on an MRI (defined as presence of new foci, gadolinium (Gd) enhancement, or enlargement of pre-existing lesions) in 59% (24/41) of the patients. However, only 33% (10/30) of the individuals converted to CIS or CDMS at a median of 5.4 years using McDonald criteria. In patients who had lumbar puncture, CSF profiles were positive (i.e., presence of unique oligoclonal bands or an elevated IgG index) in 67% (18/27) of the patients; 8 of these patients (44%) developed clinical symptoms of MS. The authors proposed additional diagnostic criteria for RIS (i.e., type 5 CIS) that attempt to eliminate other potential etiologies and improve identification of clinical situations that are actual precursors to MS. It should be noted that 7 patients in this study had already been prescribed a DMT for MS despite the lack of clinical symptoms at the time of presentation.

In an editorial in the same Neurology issue that published the Okuda et al. analysis, Bourdette and Simon acknowledged the value of the Okuda study for establishing a framework for which patients with RIS or type 5 CIS might be evaluated and monitored to provide useful insight on the risk of conversion to CDMS but emphasized restraint in using MS medications in these patients in the absence of clinical symptoms, since this is inconsistent with current McDonald guidelines. Notably, there are several different medical conditions in which similar lesions can appear on MRI scans, such as Behcets disease or CNS malignancies. In addition, some individuals may exhibit neurological changes on an MRI that are consistent with MS but remain asymptomatic.

### Imaging Modalities in MS

MRI plays a major role in the diagnosis and ongoing management of patients with MS. In addition, MRI results have been used as outcome measures in many clinical trials. In 2006, the Consortium of MS Centers (CMSC) published a consensus MRI protocol for imaging of the brain and spinal cord during baseline evaluations and follow-up in patients with MS. The CMSC has recently proposed revisions to their MRI guidelines. According to the 2009 proposed revisions, MRI sequences to be used include sagittal and axial FLAIR (fluid attenuated inversion recovery), axial T2-weighted scans, and axial T1 scans pre- and post-Gd-enhancement. For patients with a CIS (and suspected MS), a baseline brain MRI with Gd is recommended. Spinal cord MRI is recommended when (a) persisting uncertainty exists regarding the diagnosis or the brain MRI is equivocal; and (b) presenting symptoms are at the level of the spinal cord.
patients with established MS, brain MRI with Gd-enhancement should only be considered every 1 to 2 years in individuals with subclinical disease activity but is recommended in patients with unexpected clinical worsening.\textsuperscript{34}

While conventional MRI has provided the framework for diagnosis and monitoring of patients with MS and contributed significantly to our understanding of the pathophysiology underlying MS, it has some recognized limitations. Conventional MRI sequences have a relatively weak correlation to clinical status, low sensitivity to grey matter involvement and diffuse white matter damage, and limited ability to predict clinical progression.\textsuperscript{35,36} Additionally, prolonged T2 relaxation identifies areas with tissue injury, and Gd-enhancement indicates when there is breakdown of the BBB, but neither quantifies the degree of tissue damage.\textsuperscript{37}

To address these issues, alternative imaging methodologies are currently being used or are in various stages of clinical development. Table 4 provides an overview of some newer approaches and their potential utility in patients with MS. These technologies have also been the subject of several recent comprehensive review articles to which the reader is referred for more details.\textsuperscript{35-40}

It is important to note that the MRI field strength used can have a significant influence on the classification of patients with CIS and MS using current diagnostic criteria. Wattjes et al. (2006) evaluated 40 patients with CIS using both 1.5 Tesla (T) and 3.0 T MRI systems. A total of 29 patients (72.5\%) fulfilled Barkhof MRI criteria for CIS at 1.5T. However, 11 additional patients (27.5\%) fulfilled more MRI criteria with the high-field MRI (3.0 T). Wattjes et al. concluded that MRI field strength can have a significant influence on the classification of patients with CIS and a minor influence on the classification of patients with MS.\textsuperscript{41}

Advances in imaging technologies can be expected to facilitate the diagnosis and monitoring of patients with MS, to improve our understanding of the underlying pathophysiology, and to assist in new drug development. How these new approaches will be used to complement conventional MRI and how they will be incorporated into clinical practice guidelines are still to be determined.

### Treatment of Patients with CIS: Overview of Clinical Trials

Glatiramer acetate and formulations of IFNβ are immunomodulators used as first-line DMTs for the treatment of MS. The overall efficacy and safety of these agents have been described in detail by Ryan et al. (2009).\textsuperscript{12} This supplement is designed to provide a specific overview of the use of glatiramer acetate and IFNβ in patients with CIS. Natalizumab and mitoxantrone, which are currently approved only as second-line therapies for MS, are not addressed in detail in this supplement. One of the important questions in MS management is whether early treatment in patients with CIS delays the development of a second clinical event (and therefore a diagnosis of CDMS). To date, 4 randomized, placebo-controlled, phase III clinical trials have been completed using glatiramer acetate or IFNβ formulations that have specifically addressed this question, and at least 1 additional study—Rebif (IFNβ-1a) FLEXible Dosing in Early MS (REFLEX)—is ongoing. Key patient demographics and results from the completed CIS studies are summarized in Table 5. All of the clinical trials in patients with CIS showed statistically significant reductions (39\% to 50\%) in the risk of developing CDMS when early treatment was initiated.\textsuperscript{42-45}

In addition to the probability of developing CDMS, a primary efficacy endpoint in 3 of the studies was the time to conversion to CDMS. In the PreCISe (Study to Evaluate the Effect of Early Glatiramer Acetate [Copaxone] Treatment in Delaying the Conversion to CDMS of Subjects Presenting with a CIS)\textsuperscript{42} and BENEFIT (Betaseron [IFNβ-1b] in Newly Emerging MS for Initial Treatment)\textsuperscript{43} trials, the 25th percentile time to development of CDMS was prolonged in the active-treatment compared with placebo groups by 115\% (722 days vs. 336 days, \(P<0.001\)) and 142\% (618 days vs. 255 days, \(P<0.001\)), respectively. In the Early Treatment of MS Study (ETOMS), the 30th percentile time to CDMS was significantly increased by 122\% in the IFNβ-1a arm (569 days vs. 252 days, \(P=0.034\)).\textsuperscript{45} In all 4 of the CIS trials, there also were significant reductions in either the number

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**TABLE 4 Nonconventional Imaging and Sequences with Applications in Multiple Sclerosis\textsuperscript{35-40}**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton magnetic resonance spectroscopy (1H-MRS)</td>
<td>• Generates spectra from different brain metabolites (e.g., N-acetylaspartate, choline, myoinositol, glutamate) associated with various types of neuronal damage</td>
</tr>
<tr>
<td>Magnetization transfer ratio (MTR) imaging</td>
<td>• Radiofrequency saturation pulse (RFSP) used to create magnetization gradient in protons from different molecules • Allows visualization of myelin and axolemmal membrane integrity</td>
</tr>
<tr>
<td>Diffusion tensor imaging</td>
<td>• Measures diffusion of H2O through multiple gradients • May provide for better evaluation of tissue integrity and differentiation between demyelination and axonal injury</td>
</tr>
<tr>
<td>Functional MRI (fMRI)</td>
<td>• Measures alterations in blood oxygenation • Provides insight into cortical adaptability, plasticity, and functional capacity</td>
</tr>
<tr>
<td>High field strength MRI (&gt; 1.5 Tesla)</td>
<td>• Increases sensitivity for detecting brain lesions</td>
</tr>
<tr>
<td>Optical coherence tomography (OCT)</td>
<td>• Uses light in manner similar to ultrasound • Measures alterations in retinal nerve fiber layer (RNFL)</td>
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### Summary of Completed Clinically Isolated Syndrome Clinical Trials

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<thead>
<tr>
<th>Trial</th>
<th>PrecISE</th>
<th>BENEFIT</th>
<th>CHAMPS</th>
<th>ETOMS</th>
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<tr>
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<td>IFNβ-1a</td>
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<td>IM</td>
<td>SC</td>
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<td>3 (stopped early)</td>
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<td>Active treatment (N)</td>
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<td>292</td>
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<td>Placebo (N)</td>
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<td>176</td>
<td>190</td>
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<tr>
<td>Age (mean yrs. ± range)</td>
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<td>30</td>
<td>33 ± 7</td>
<td>28 ± 6</td>
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<tr>
<td>Reduction in CDMS risk</td>
<td>45%</td>
<td>50%</td>
<td>44%</td>
<td>39%</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.047</td>
</tr>
</tbody>
</table>

*Table should not be used for comparison between independently conducted trials or estimation of the relative efficacy of individual agents.

BENEFIT = Betaseron (IFNβ-1b) in Newly Emerging MS for Initial Treatment; CDMS = clinically definite multiple sclerosis; CHAMPS = Controlled High-Risk Subjects (IFNβ-1a) Avonex Multiple Sclerosis Prevention Study; ETOMS = Early Treatment of MS Study (Rebif); IM = intramuscular; PrecISE = Study to Evaluate the Effect of Early Glatiramer Acetate (Copaxone) Treatment in Delaying the Conversion to CDMS of Subjects Presenting with a CIS; SC = subcutaneous.

and/or volume of brain lesions seen on MRI. Because of favorable results at interim analyses, the placebo arms of both the PrecISE and CHAMPS (Controlled High-Risk Subjects [IFNβ-1a] Avonex Multiple Sclerosis Prevention Study) trials were closed early, and all patients were then offered open-label treatment with the active drug.

Since the studies described above were only 2 to 3 years in duration, the effects of continued DMT on the long-term risk for developing CDMS remained unclear. Two of the initial CIS studies, CHAMPS and BENEFIT were extended for longer time periods to address this question. In both the CHAMPIONS (CHAMPS extension) and BENEFIT extension studies, patients originally randomized to active treatment were continue on the same protocol ("early or immediate" treatment groups), and those who received placebo after the original randomization were then switched to open-label active drug ("delayed" treatment groups). In both extension analyses, early treatment resulted in significantly fewer patients developing CDMS. In CHAMPIONS, the risk of developing CDMS at 5 years was reduced by 43% in the immediate treatment compared with delayed treatment group (P = 0.030). In the BENEFIT extension, a 41% risk reduction for developing CDMS was observed in the immediate treatment versus the delayed treatment group at 3 years (P = 0.001). Early treatment also significantly reduced the risk for progression of disability by 40% as measured by the Expanded Disability Status Scale (EDSS) (P = 0.022). The 5-year data from BENEFIT were recently published (September 2009): early treatment with IFNβ-1b delayed the onset of CDMS by 37% (P = 0.003), confirming continuous benefit at 5 years after treatment initiation in patients with CIS.

The international REFLEX study is evaluating the effect of a new IFNβ-1a formulation on the time to conversion to MS in individuals with a first clinical event suggestive of MS. More than 500 patients with a recent isolated demyelinating event (e.g., optic neuritis, myelopathy, or brainstem syndrome) and who had brain MRI scans consistent with early MS have been randomized to receive IFNβ-1a (as subcutaneous [SC] injections in one of two dosing schedules — 44 mcg 3 times a week or once weekly) or placebo. Patients will be treated for 24 months, or up to the time when they experience a second attack leading to a diagnosis of CDMS. The REFLEX trial completed enrollment in 2008; result data are not yet available. Long-term follow-up of the REFLEX study will be conducted in an extension trial known as RELEXION (www.clinicaltrials.gov).

### Key Implications of Clinical Trials for Managed Care Pharmacists

The results of all completed CIS trials and extension analyses provide strong clinical evidence that early treatment with glatiramer acetate or IFNβ significantly prolongs the time to conversion or progression to CDMS and also delays the development of physical disability. Thus, it is generally recommended that patients with CIS be treated at the time of diagnosis or first attack.

This recommendation is supported by the National Clinical Advisory Board of the National MS Society, which states: “Initiation of treatment with an interferon-beta medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS.” The U.S. Food and Drug Administration approved labels for 3 of the available IFNβ-1 formulations (Avonex, Betaseron, Extavia), and glatiramer acetate (Copaxone) also include indications for patients with CIS (i.e., a first clinical episode and MRI consistent with MS).

Disability in patients with MS is associated with increased health care costs. Turpcu and Yu (2008) conducted an analysis of...
cardiotoxicity, so cumulative dose limits are specified. In addition, all currently approved agents for MS are administered parenterally, and tolerability and adherence are important considerations in patients using injectable medications. Thus, the need exists for development of new drugs for MS with different mechanisms of action, routes of administration, improved clinical efficacy, and more favorable safety profiles.

More than 100 clinical trials of novel strategies in patients with MS are listed on the National MS Society website (www.NMSS.org). The majority of medical therapies in advanced stages of clinical development target peripheral immune mechanisms that predominate in early stage disease—these therapies are oral agents or monoclonal antibodies. In addition, neuroprotection and/or neuroregeneration, as well as improved management of comorbid symptoms, remain as desired therapeutic goals. A list of selected investigational agents for MS and their mechanism of action is provided in Table 6; these are discussed in greater detail below.

### Oral Agents

There has been considerable interest in developing oral medications for MS. All of the oral agents discussed have recently completed or are currently in phase III evaluation.

**Cladribine.** Cladribine (2-chloro-2'-deoxyadenosine) is an adenosine-deaminase resistant purine nucleoside analogue that preferentially depletes lymphocytes. This agent currently has several approved indications in oncology for lymphoid malignancies. A number of cladribine studies have been conducted in patients with MS that have been reviewed. Three major MS studies used
an injectable form of the drug, which was found to reduce (a) the number and volume of T1 Gd-enhancing lesions, (b) T2 lesion volume, (c) relapse rates, and (d) progression of disability. An oral formulation of cladribine has also been developed that has been evaluated in patients with relapsing forms of MS, both as monotherapy or in combination with IFNβ-1a.62

Data from the phase III CLARITY study (CLAdRlbin tablets Treating MS orally) were released in 2009. Patients with RRMS (n=1,326) were randomized (1:1:1) to receive 1 of 2 doses of oral cladribine or placebo for 2 years. For the cladribine-tablet groups, subjects received either 2 or 4 courses of 0.875mg per kg given over 4-5 consecutive days in the first year, then 2 treatment courses in the second year. For the primary efficacy endpoint of relapse rates at 96 weeks, 58% and 55% reductions were seen in the lower dose and higher dose cladribine groups versus placebo, respectively (P<0.001). The frequency of adverse events was similar in all 3 treatment groups, except for lymphopenia, which was expected based on cladribine’s mechanism of action. The most common adverse events in all 3 groups were headaches and nasopharyngitis.63,64

Cladribine is also being evaluated in a 4-year phase III study in patients with CIS known as ORACLE (ORAl CLadribine for Early MS).65 For enrollment eligibility, patients must have 2 or more clinically silent lesions on MRI. Subjects will be random-
ized (1:1:1) to receive 3.5 mg per kg or 5.25 mg per kg cladribine tablets (or matching placebo) administered as 2 or 4 short courses (0.875 mg per kg per course) in 2 or 4 consecutive months dur-
ing the first year. In year 2, subjects receive 2 additional short treatment courses. In participants who develop CDMS according to McDonald criteria, blinded medication will be discontinued, and maintenance therapy initiated with SC IFNβ-1a. Following the initial 2-year treatment period, CDMS-free patients can enroll in a 2-year maintenance follow-up period where they can receive open-label cladribine if they present with MRI activity. This clinical trial will provide insight into the sustained effects of early cladribine treatment of patients with CIS.65

Fumarate. BG000012 is an oral formulation of dimethyl fumarate that appears to have multiple novel effects on the immune system in patients with MS. This agent may have both anti-inflammatory and neuroprotective effects.66-68 In a phase IIb study, 257 patients with RRMS were randomized (1:1:1) to receive 1 of 3 oral doses of BG00012 (120mg once daily, 120mg 3 times daily, or 240mg 3 times daily) or placebo for 24 weeks.69 The primary efficacy outcome was the number of new Gd-enhancing MRI lesions from weeks 12 to 24. Additional endpoints included new or enlarg-
ing T2-hyperintense lesions, new T1-hypointense lesions, and relapse rates. In the 240 mg 3 times daily BG00012 dose group, significant reductions compared with placebo were reported for (a) the mean number of Gd-enhancing lesions \( (P < 0.001) \), (b) new or enlarging T2-hyperintense lesions \( (P < 0.001) \), and (c) new T1-hypointense lesions \( (P = 0.014) \). A 32% relative reduction in the annualized relapse rate was seen in the high dose BG00012 group, although the study was insufficiently powered to detect a significant difference for this outcome. Adverse events more frequently observed in BG00012 treatment groups included abdominal pain and flushing. Notably, 25% of patients in the 240 mg 3 times daily BG00012 dose group withdrew from the study or discontinued treatment primarily because of adverse events or lack of tolerance.\(^69\)

**Fingolimod.** Fingolimod (FTY720) has a unique mechanism of action. By binding to sphingosine-1 phosphate type 1 receptors on lymphocytes, this agent stops the cells from sensing signals to egress from lymphoid tissue.\(^70\) In a proof-of-concept trial for 281 patients with relapsing MS were randomized (1:1:1) to receive oral fingolimod at 1.25 or 5.0 mg per day or placebo for 6 months.\(^71\) For the 255 patients who completed the study, the total number of Gd-enhancing lesions on MRI and the annualized relapse rate were significantly lower in both fingolimod dose groups compared with placebo \( (P < 0.010) \). Dyspnea, diarrhea, nausea, and asymptomatic elevations of alanine aminotransferase were more frequent in the fingolimod treatment groups.\(^71\) In a 24-month phase II extension analysis, reductions in the relapse rate and lesion counts were seen in the patient group that switched from placebo to fingolimod (compared with the placebo phase of the trial), while these parameters remained low in patients who had received continuous fingolimod.\(^72\)

**Laquinimod.** The mechanism of action of laquinimod is incompletely understood, but it is thought that this agent exerts its anti-inflammatory activity in MS by shifting the balance of Th1 and Th2 lymphocytes and cytokine production toward a Th2-pattern and inhibiting migration of lymphocytes into the CNS.\(^73\) Laquinimod is pharmacologically distinct from and has a more favorable benefit/risk profile than linomide, a structurally related compound that had previously reached phase III studies in patients with MS. In a 24-week phase II study of patients with relapsing MS \( (n = 209) \), the group treated with oral laquinimod at 0.3 mg per day had 44% fewer active lesions on MRI compared with placebo \( (P = 0.050) \). Subgroup analysis showed that this reduction was more pronounced in patients with at least 1 active lesion at baseline \( (52\% \text{ fewer active lesions}; P = 0.005) \).\(^74\)

However, in a subsequent 36-week phase Ib trial comparing laquinimod at 0.3 and 0.6 mg per day with placebo in patients with RRMS \( (n = 306) \), only the 0.6 mg dose group had a significant reduction \( (40\% \text{ in the number of Gd-enhancing lesions on MRI scans}; P = 0.005) \). One of the key safety considerations with this agent was transient and dose-dependent increases in hepatic enzymes.\(^75\)

**Teriflunomide.** Teriflunomide is the active metabolite of leflunomide, an oral anti-inflammatory drug that is widely used in rheumatoid arthritis. This agent binds to dihydro-orotase dehydrogenase and inhibits de novo pyrimidine synthesis in T lymphocytes and other rapidly dividing cells.\(^76\) In a 36-week study of 179 patients with RRMS or secondary progressive MS (SPMS), subjects received oral teriflunomide at either of 2 doses \( (7 \text{ mg or } 14 \text{ mg per day}) \) or placebo.\(^77\) For the primary efficacy endpoint of the number of combined active unique lesions per MRI scan, significantly reduced mean numbers of lesions compared with placebo were seen in both the 7 mg \( (1.04 \text{ vs. } 2.68, P < 0.030) \) and 14 mg teriflunomide groups \( (1.06 \text{ vs. } 2.68, P < 0.010) \). Teriflunomide-treated patients also had significantly fewer T1-enhancing lesions per MRI scan \( (0.87 \text{ [7 mg] and 0.86 [14 mg]} \text{ vs. } 2.25 \text{ for placebo}, P < 0.040) \), as well as fewer new T2 lesions \( (0.17 \text{ [7 mg] and 0.17 [14 mg]} \text{ vs. } 0.3 \text{ for placebo}, P < 0.010) \).
Fampridine. Fampridine (4-aminopyridine) is a voltage-dependent potassium channel blocker. This agent is not a DMT but instead targets specific symptoms in MS. Fampridine may restore action potential conduction in poorly myelinated nerve fibers and influence synaptic transmission and neuronal excitability. Fampridine use has been associated with improvements in strength, ambulation, fatigue, and endurance in patients with MS.

In a randomized phase III study in patients with any type of MS, subjects who received sustained-release fampridine (10 mg twice daily; n = 229) had improved motor function measures compared with the placebo group (n = 72). For example, the number of responders based on a timed-walk measurement was significantly higher after 14 weeks of treatment with fampridine (35% vs. 8% for placebo, P < 0.001). In addition, timed-walk responders showed greater improvement in 12-item MS walking scale scores compared with timed-walk nonresponders (P < 0.001).

Monoclonal Antibodies

Alemtuzumab. Alemtuzumab is a humanized monoclonal that targets CD52 on T cells, B cells, and monocytes and leads to rapid immune depletion. This agent was recently compared with IFNβ-1a in a 36-month phase II study of 334 patients with RRMS. Alemtuzumab was given at doses of either 12 mg or 24 mg per day by intravenous (IV) infusion on 5 consecutive days during month 1 and on 3 consecutive days at months 12 and 24. IFNβ-1a was administered at 44 mcg 3 times weekly SC after dose escalation. For the combined group analysis, alemtuzumab was significantly more effective than IFNβ-1a for (a) reducing the rate of sustained accumulation of disability (9.0% vs. 26.2%, P = 0.001), (b) reducing the annualized relapse rate (0.10 vs. 0.36, P < 0.001), (c) decreasing lesion burden based on T2 imaging (P = 0.005), and (d) increasing brain volume (P = 0.020). In addition, the mean EDSS score improved by 0.39 points in alemtuzumab-treated patients and worsened by 0.38 in the IFNβ-1a group (P < 0.001). Adverse events that were more common in the alemtuzumab group included infections (66% vs. 47%), thyroid disorders (23% vs. 3%), and thrombocytopenic purpura (3% vs. 1%).

Daclizumab. Daclizumab is a humanized monoclonal that targets the α-subunit (CD25) of the high affinity interleukin 2 receptor (IL-2R), which is expressed on activated lymphocytes. This agent inhibits CD4+ and CD8+ T-cell activation and is currently approved for the prevention of renal transplant rejection. It is being evaluated in patients with RRMS who have had an inadequate response to IFNβ. In 2 phase II studies, daclizumab (1 mg per kg intravenously every 2 weeks for the first 2 doses, then every 4 weeks) was given in combination with IFNβ for the first 5.5 months, then as monotherapy. In a small study of 9 patients who were evaluated at 3-month intervals, daclizumab was reported to be significantly effective in reducing total and new contrast-enhancing MRI lesions (P < 0.001) when comparing pre-treatment scans (baseline) with scans taken at all treatment intervals over 27.5 months. For secondary outcomes, daclizumab also significantly reduced relapse rates (P < 0.001) and improved both timed ambulation (P < 0.050) and EDSS scores (P < 0.050) over the course of the trial. Adverse events in the daclizumab group included respiratory tract infections, rash, and transient thrombocytopenia.

Results from the larger phase II CHOICE trial have only been presented in abstract form. In this study, patients with active MS despite IFNβ therapy (n = 230) were randomized to receive daclizumab 2 mg per kg every 2 weeks (n = 75) or 1 mg every 4 weeks (n = 78) or placebo (n = 77) in addition to IFNβ. At 24 weeks, the number of new or enlarging Gd-enhancing lesions significantly decreased by a mean of 72% in the high-dose daclizumab group (P = 0.004), but only by 25% in the low-dose group (nonsignificant; P = 0.501), compared with placebo plus IFNβ. Adverse events more commonly observed in daclizumab-treated groups included serious infections.

Rituximab. Approved for more than a decade for the treatment of B-cell lymphoma, rituximab is also being evaluated in patients with RRMS. In a 48-week phase II trial, subjects were randomized to receive rituximab (1,000 mg on days 1 and 15) or placebo. Patients in the rituximab group had significantly fewer total and new Gd-enhancing lesions on MRI (primary endpoint) from weeks 12 to 24 compared with placebo, and these differences were sustained at 48 weeks (P < 0.001 for all time points). The relapse rate was also significantly lower with rituximab treatment at week 24 (14.5% vs. 34.3%, P = 0.020) and week 48 (23.0% vs. 40.0%, P = 0.040). Adverse events that were more common in the rituximab group included infusion-associated events within the 24 hours after the first infusion (78.3% vs. 40.0%), but these were predominantly mild to moderate in severity and decreased on the second infusion. Urinary tract infections (14.5% vs. 8.6%) and sinusitis (13.0% vs. 8.6%) were more frequent in the rituximab group compared with placebo.

Key Implications of Emerging Therapies for Managed Care Pharmacists

All medications currently approved for the treatment of MS are administered by SC or IM injection or IV infusion. Many patients have needle phobia or injection anxiety, particularly at the initiation of therapy. Injection-site reactions are also relatively common with SC formulations, although the introduction of auto-injector technologies has made injections easier and improved patient satisfaction. However, the requirement for being on long-term injections places a burden on patients with MS and may lead to reduced adherence that can compromise treatment efficacy. Oral medications for MS offer the potential of increasing...
convenience, comfort, and adherence to therapy. The oral treatments have different mechanisms of action, potentially significant adverse effects, and a relative lack of long-term safety data. Thus, the risk-benefit ratio may be not as favorable as that for the existing treatments. An ongoing question is how will formulary decisions be made regarding the new oral medications for MS if they are approved. In addition, consider the theoretical patient with MS who is currently using an injectable medication whose disease is well controlled with no new symptoms or relapses. What if this patient becomes aware of new oral treatment options and wants to switch therapies? Physicians and other health care prescribers will have to perform due diligence in discussing these issues with such patients. How will the decision be made regarding whether a switch is therapeutically appropriate, and should the new medication be covered by insurance? Managed care organizations can also benefit by addressing these critical issues in advance of anticipated new drug approvals.

## Summary

One of the ongoing goals in MS management is to improve identification of patients with CIS who will progress to CDMS and are the best candidates for early treatment with a DMT. Several recent advances have been made in the understanding of CIS subtypes and the refinement of MS diagnostic criteria. Imaging technologies other than traditional MRI are also likely to play an increasing role in MS management. Randomized clinical trials have shown that early treatment with glatiramer acetate and IFNβ formulations in patients with a CIS can prolong the time to conversion or progression to CDMS and delay the development of disability. Early treatment of CIS or MS may also decrease long-term health care costs. In addition, a number of new therapies for patients with MS are in late stages of clinical development, including several oral medications, offering promise for the near future but also potential challenges to managed care.

## References


4. A 29-year-old female presented with blurred vision when she looked to her left and numbness in her arm. She was referred to an ophthalmologist who diagnosed with optic neuritis. Her primary care provider also sent her for a battery of tests including blood analysis, MRI, and lumbar puncture. Based on the 2005 revisions to the McDonald criteria for the diagnosis of MS, which of the following findings would have greater significance?

a. The severity of the symptoms associated with the initial attack
b. An elevated IgG index in the cerebrospinal fluid (CSF)
c. The presence of autoantibodies in the serum
d. The presence of spinal cord lesions on MRI

5. Which of the following represents a key modification to MRI criteria proposed by Swanton et al.?

a. Requiring the use of gadolinium to enhance MRI sensitivity
b. Increasing the number of required T2 lesions
c. Removing the time requirement for appearance of a new T2 lesion
d. Reducing size requirements for infratentorial lesions

6. A breakdown of the current definition of clinically isolated syndrome (CIS) into additional subcategories was recently proposed. In addition to assisting in development of a rational monitoring and treatment plan, these subcategories may also predict:
a. The rate of disease progression  
b. The risk that a patient will develop MS  
c. The level of disability a patient will ultimately reach  
d. The efficacy of potential treatments

7. Which of the following statement regarding conventional MRI technology is most accurate?  
a. MRI allows for accurate quantification of the amount of brain tissue damage in patients with MS.  
b. MRI has relatively high sensitivity to identify grey matter lesions.  
c. MRI results strongly correlate with the clinical status of patients with MS and assist with determining treatment protocols.  
d. MRI field strength can influence classification of patients with a CIS.

8. A 37-year-old female was diagnosed with a CIS based on clinical symptoms and MRI scanning and is considered a good candidate for initiation of a disease-modifying therapy (DMT). In discussing with her the rationale for beginning therapy now, all of the following statements regarding clinical studies of early treatment initiation in patients with CIS would be correct EXCEPT:  
a. Early treatment with a DMT has a good chance of delaying the patient’s progression to clinically definite multiple sclerosis (CDMS).  
b. Early treatment with a DMT will probably increase the overall cost of care.  
c. The occurrence of relapses may be reduced using a DMT early in the disease course.  
d. Early treatment with a DMT may delay the development of physical disability.

9. The patient described in the previous question and her provider make the decision to initiate a DMT. Which of the following agents is NOT currently approved for treatment of patients with a CIS and MRI suggestive of MS?  
a. Glatiramer acetate  
b. Interferon (IFN) β-1a  
c. Mitoxantrone  
d. IFNβ-1b

10. Which of the following statements regarding approved MS agents is INCORRECT?  
a. Currently available agents for MS only reduce relapses by about 30%.  
b. Natalizumab is associated with progressive multifocal leukoencephalopathy.  
c. All drugs approved for MS in 2009 are administered by injection or infusion.  
d. Extension phases of clinical trials have generally failed to show long-term efficacy.

11. Which of the following correctly matches an experimental oral agent for MS with its proposed mechanism of action?  
a. Teriflunomide: inhibits purine synthesis  
b. Cladribine: pyrimidine nucleoside analogue  
c. Laquinimod: may inhibit lymphocyte entry into the CNS  
d. Fampridine: central-acting calcium-channel blocker

12. Based on clinical trial data, which of the following therapies may improve ambulation in patients with MS by increasing axonal transmission of action potentials?  
a. Fampridine  
b. Fingolimod  
c. Laquinimod  
d. Fumarate

13. Which of the following adverse events has been seen more often in active treatment groups compared with placebo across all clinical trials of experimental antibodies in patients with MS?  
a. Cardiotoxicity  
b. Infections  
c. Anaphylaxis  
d. Hepatic enzyme elevation

14. Your organization has asked you to prepare a presentation on emerging therapies for MS. All the following statements would be correct EXCEPT:  
a. Some oral agents in clinical development will most likely require multiple doses every day.  
b. Cladribine will likely be administered in several short intensive treatment courses every year, similar to chemotherapy.  
c. The majority of therapies in late-stage clinical development specifically target lymphocytes that have entered the CNS.  
d. Protection or regeneration of nerve cells remain as therapeutic goals.

15. Which of the following statements regarding clinical trials of alemtuzumab and daclizumab in combination with IFNβ for the treatment of MS is correct?  
a. Both alemtuzumab and daclizumab reduced brain lesion volume but not the number of lesions.  
b. Alemtuzumab plus IFNβ had roughly equivalent efficacy in reducing the rate of sustained disability compared with IFNβ alone.  
c. Daclizumab dose groups had similar efficacy for reducing the number of Gd-enhancing lesions.  
d. Addition of alemtuzumab and daclizumab to IFNβ significantly reduced relapse rates compared with IFNβ alone.