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6. Seek and publish content that does not duplicate content in the Journal of Managed Care Pharmacy.
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Managed Approaches to Multiple Sclerosis in Special Populations

Kara Sperandeo, PharmD; Lisa Nogrady, RPh; Kathleen Moreo, RN-BC, BSN, BHSA, CCM, Cm, CDMS; and Chris R. Prostko, PhD

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Target Audiences
Pharmacists, pharmacy directors, medical directors, and nurse case managers working in managed care who are responsible for managing patients with multiple sclerosis.

Learning Objectives
1. Discuss strategies for management of multiple sclerosis in cases of limited funding, maximum treatment costs, difficult-to-manage patients, and growing policy requirements such as risk evaluation and mitigation strategies (REMS).
2. Compare the relative risks and benefits of promising new therapy in multiple sclerosis with those of existing disease modifying therapy, as well as implications for managed care.
3. Assess strategies to achieve improved multiple sclerosis coordination of care among managed Medicaid care providers, third-party administrators, health plans, and state Medicaid programs.

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Managed Approaches to Multiple Sclerosis in Special Populations

Kara Sperandeo, PharmD; Lisa Nogrady, RPh; Kathleen Moreo, RN-BC, BSN, BHSA, CCM, Cm, CDMS; and Chris R. Prostko, PhD

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system that is classified as an immune-mediated inflammatory disease. In managed care, patients with MS can be managed through care coordination that engages an interprofessional approach to a comprehensive spectrum of preventive, medical, rehabilitative, cognitive, and long-term health care services. In addition, the management paradigm for MS is currently in a stage of rapid evolution, with a number of new agents, including more oral drugs, expected to become available in the near future. Pharmacy and therapeutic committees may soon be faced with evaluating a hierarchy of new scientific data to differentiate the safety and efficacy of these new agents. Decisions will need to be made regarding the utility of these potential new agents among existing therapies with longer-term safety and efficacy data available in the scientific literature. For those MS patients managed under Medicaid, formulary and medication management decisions may be further impacted by psychosocial, cultural, educational, attitudinal, and/or economic factors that may be unique to the Medicaid population. The need to maximize immediate and long-term resource utilization is usually an important consideration when managing a Medicaid population. There is also an increasing focus on quality measures and quality outcomes by the Centers for Medicare and Medicaid Services. Many managed care professionals can be involved in establishing quality measures and quality improvement processes to effectively appropriate and manage the resources required for Medicaid patients with MS. As a result, medication and medical management of this special population can involve a comprehensive approach by managed care professionals. For purposes of this article, the term “special populations” applies to patients with MS who are managed under Medicaid plans.

OBJECTIVES: To review (a) particular challenges managed care organizations (MCOs) encounter when managing special populations of Medicaid patients with MS, (b) recent efficacy and safety data for oral therapies for relapsing forms of MS, (c) costs of current MS therapies, and (d) potential strategies for managed care to improve care of their MS patient population and optimize clinical and economic outcomes.

METHODS: Review of recent published literature, abstracts related to MS presented at major medical conferences, and recommendations from key organizations including the U.S. Department of Health and Human Services and the National Multiple Sclerosis Society.

SUMMARY: The health economics of MS are a central issue for MCOs managing Medicaid patient populations. Additional challenges include the anticipated expansion of the marketplace to include several new oral agents and the lack of consensus guidelines for management of patients with MS. The benefit-risk profile of new agents will need to be considered in the context of established first-line parenteral drugs. Management of patients with MS should include an individualized approach for each patient as part of a shared decision-making process. In the overall management of special patient populations, case management and collaborative practice models in managed care may help to ensure that critical benchmarks are achieved.

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by intravenous infusion under the supervision of a health care professional. As a result, there has been ongoing interest in developing effective oral agents for MS, which would be easier to administer and conceivably may remove the requirement for a visit to the doctor's office or clinic. The first oral medication for relapsing forms of MS, fingolimod, was approved by the U.S. Food and Drug Administration (FDA) in September 2010, and several additional oral agents are in late stages of clinical development. Oral MS drugs for which phase 3 clinical trial outcomes between the 2 fingolimod dose groups (0.5 mg and 1.25 mg) in either FREEDOMS or TRANSFORMS, but the FDA approved only the 0.5 mg per day dose for fingolimod for “treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.”

Key adverse events reported in FREEDOMS that were more common in the fingolimod 1.25 mg and 0.5 mg dose groups compared with placebo, respectively, included abnormal liver function tests (18.6% and 15.8%, vs. 5.0%), bronchitis (9.1% and 8.0%, vs. 3.6%), hypertension (6.3% and 6.1%, vs. 3.8%), lymphopenia (5.4% and 3.5%, vs. 0.5%), bradycardia/arrhythmia (3.3% and 2.1%, vs. 0.7%), pneumonia (1.9% and 0.9%, vs. 0.7%), and first-degree atrioventricular block (1.2% and 0.5%, vs. 0.5%). Seven cases of macular edema (1.6%) were also reported in the fingolimod 1.25 mg per day dose group, whereas this event was not seen in the placebo or 0.5 mg fingolimod arms. Adverse events leading to discontinuation of medication occurred in 14.2% of patients in the 1.25 mg per

### Table 1: Summary of Fingolimod Phase 3 Efficacy Results in Patients with Relapsing MS

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>FREEDOMS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TRANSFORMS&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 418)</td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.40</td>
<td>0.18 &lt; 0.001</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>0.16 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>0.16 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>0.20 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse-free patients (%)</td>
<td>45.6</td>
<td>70.4 &lt; 0.001</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>74.7 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Absence of disability progression (%)</td>
<td>81.0</td>
<td>87.5 0.01</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>88.5 0.004</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline EDSS score at 24 months</td>
<td>0.13</td>
<td>0.00 0.002</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>-0.03 0.002</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>-0.08 0.02</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>-0.11 0.06</td>
<td></td>
</tr>
<tr>
<td>Selected MRI outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Gd-enhancing T1 lesions (n)</td>
<td>1.1</td>
<td>2.0 &lt; 0.001</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>2.0 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Mean new/enlarged T2 lesions (n)</td>
<td>9.8</td>
<td>2.5 &lt; 0.001</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>2.5 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>17 0.004</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>1.50 &lt; 0.001</td>
<td></td>
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</table>

<sup>a</sup>Fty720 Research Evaluating Effects of Daily Oral therapy in MS (FREEDOMS); Kappos L, et al.
<sup>b</sup>TRial Assessing injectable interferon vs FTY720 Oral in RRMS (TRANSFORMS); Cohen JA, et al.
<sup>c</sup>30 microgram intramuscularly once weekly.

EDSS = Expanded Disability Status Scale; Gd = gadolinium; IFN = interferon; mg = milligram; MS = multiple sclerosis; MRI = magnetic resonance imaging.

Fingolimod. Also referred to as FTY720, fingolimod (Gilenya) is classified as a sphingosine-1-phosphate (SIP) receptor modulator. By binding to G-protein-coupled SIP receptors on lymphocytes, fingolimod inhibits the migration (egress) of autoreactive T cells from peripheral lymphoid organs into the bloodstream, thereby restricting their access to the brain and spinal cord where MS lesions occur. The clinical efficacy and safety of fingolimod in patients with relapsing-remitting MS were evaluated in 2 large, randomized phase 3 trials known as FREEDOMS (Fty720 Research Evaluating Effects of Daily Oral therapy in MS) and TRANSFORMS (TRial Assessing Injectable interferoN vs FTY720 Oral in RRMS). Key efficacy data from these studies are summarized in Table 1.

FREEDOMS was a 2-year, placebo-controlled study, whereas TRANSFORMS was a 1-year trial with an active-comparator (IFNβ-1a) arm; both studies evaluated 2 doses of fingolimod (0.5 and 1.25 milligrams [mg] per day). In TRANSFORMS, IFNβ-1a was given by intramuscular (IM) injection once weekly—thus, this trial had a design that included placebo injections for subjects randomized to the fingolimod groups, whereas patients in the IFNβ-1a arm took daily oral placebo capsules. In both studies, fingolimod was associated with significantly lower annualized relapse rates (ARR), the primary endpoint (Table 1). Among secondary endpoints, the proportion of patients who were relapse-free was higher with fingolimod compared with the control groups. Fingolimod treatment was associated with small effects on disability progression in FREEDOMS and no difference compared with the IFN active comparator in TRANSFORMS. The Expanded Disability Status Scale (EDSS) scores at 24 months decreased or were unchanged for fingolimod in the 2 randomized controlled trials (RCT) compared with a small increase in the placebo group in FREEDOMS. Magnetic resonance imaging (MRI) outcomes were favorable for fingolimod compared with placebo and interferon. Notably, there were no differences in efficacy outcomes between the 2 fingolimod dose groups (0.5 mg and 1.25 mg) in either FREEDOMS or TRANSFORMS, but the FDA approved only the 0.5 mg per day dose for fingolimod for “treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.”

Key adverse events reported in FREEDOMS that were more common in the fingolimod 1.25 mg and 0.5 mg dose groups compared with placebo, respectively, included abnormal liver function tests (18.6% and 15.8%, vs. 5.0%), bronchitis (9.1% and 8.0%, vs. 3.6%), hypertension (6.3% and 6.1%, vs. 3.8%), lymphopenia (5.4% and 3.5%, vs. 0.5%), bradycardia/arrhythmia (3.3% and 2.1%, vs. 0.7%), pneumonia (1.9% and 0.9%, vs. 0.7%), and first-degree atrioventricular block (1.2% and 0.5%, vs. 0.5%). Seven cases of macular edema (1.6%) were also reported in the fingolimod 1.25 mg per day dose group, whereas this event was not seen in the placebo or 0.5 mg fingolimod arms. Adverse events leading to discontinuation of medication occurred in 14.2% of patients in the 1.25 mg per...
day fingolimod group versus 7.5% for the 0.5 mg per day fingolimod group and 7.7% for placebo.

The adverse events reported for fingolimod in TRANSFORMS were similar to FREEDOMS and included macular edema in 6 patients treated with fingolimod; 4 in the 1.25 mg dose group (1%) and 2 in the 0.5 mg arm (0.5%). There was also an increased number of malignancies in the fingolimod 0.5 mg (n = 8) and 1.25 mg (n = 4) arms in TRANSFORMS compared with IFNβ-1a (n = 1), including basal cell carcinoma, breast cancer, and melanoma. There were 2 fatal infections (disseminated primary varicella zoster and herpes simplex encephalitis) in the 1.25 mg fingolimod group. The product label for fingolimod currently recommends that all patients being considered for fingolimod therapy have a complete blood count, hepatic transaminase and bilirubin assays, electrocardiogram (ECG), and a baseline ophthalmologic examination prior to initiation of treatment. Patients selected for therapy should also have their pulse and blood pressure closely monitored for 6 hours after the first fingolimod dose. Ongoing clinical studies of fingolimod in MS include EPOC (ClinicalTrials.gov Identifier: NCT01216072), a phase 4 trial in which the active comparator group is enrolling patients who are currently using any of the available injectable IFNβ-1 formulations or glatiramer acetate.

**Cladribine.** The molecular structure of cladribine (cladribine) is a prodrug that requires phosphorylation to become an active purine nucleoside analog. Cladribine becomes highly activated within lymphocytes and makes them preferentially vulnerable to its cytotoxic effects. The accumulation of cladribine nucleotides leads to DNA strand breaks, interferes with DNA synthesis and repair, and ultimately results in lymphocyte apoptosis. A parenteral form of cladribine is currently FDA-approved for the treatment of hairy cell leukemia.

Oral cladribine was evaluated in patients with relapsing-remitting MS (n = 1,326) in the 96-week, placebo-controlled, phase 3 CLARITY (CLAdRibe tablets Treating multiple sclerosis orally) study. In this trial, both cladribine doses (3.5 mg per kilogram [kg] and 5.25 mg per kg) or placebo were given in 2 or 4 short courses for the first 48 weeks, then in 2 short courses at week 48 and week 52 (for a total of 8 to 20 days per year). Significantly lower ARR (0.14 vs. 0.33; P < 0.001), and higher relapse-free rates (79.7% and 78.9% vs. 60.9%; P < 0.001) were reported for the 3.5 mg and 5.25 mg cladribine groups versus placebo, respectively. There was also a reduced risk of 3-month sustained disability progression in the cladribine groups (hazard ratio [HR] = 0.67 and 0.69 vs. placebo, P ≤ 0.03) and reduced numbers of brain lesions on MRI scans (P < 0.001 for all comparisons). As expected, lymphopenia (as defined by Medical Dictionary for Regulatory Activities [MedRA]) occurred more frequently in patients receiving cladribine tablets (21.6% and 31.5% in the 3.5 mg per kg and 5.25 mg per kg dose groups, respectively) compared with placebo (1.8%). Median lymphocyte counts reached nadir values at week 9 for the 3.5 mg per kg cladribine group and week 16 for the 5.25 mg per kg group. Gradual but modest increases in lymphocyte counts were seen, and at week 48, prior to initiation of the second dosing cycle, median lymphocyte counts were -35.6% and -49.6% in the low and higher dose cladribine groups, respectively. Serious adverse events reported in the combined cladribine arms included herpes zoster infections (n = 20; 2.3%) and neoplasms (n = 10; 1.1%), whereas these events were not observed in the placebo group.

Cladribine was approved in 2010 in Russia and Australia for the treatment of patients with relapsing MS but was rejected by the European Medicines Agency (EMA) in a regulatory decision upheld in 2011. A revised new drug application for cladribine for relapsing MS based on the CLARITY data was submitted to the FDA in June 2010. In March 2011, the FDA requested additional data on the safety and the benefit-harm ratio for cladribine, stating that while there was evidence for the clinical efficacy of this agent in relapsing MS, ongoing safety concerns (e.g., malignancies, viral infections) required a more complete understanding of cladribine's overall benefit-risk profile, either through additional analyses of existing data or new clinical studies. However, in June 2011, the pharmaceutical company developing this agent (Merck/EMD Serono) announced that they would no longer pursue the global approval process for cladribine as a treatment option for MS and would also remove this agent from the 2 markets (Russia and Australia) where the drug had been approved for use.

**Teriflunomide.** Teriflunomide is a selective reversible inhibitor of dihydroorotate dehydrogenase that blocks de novo pyrimidine synthesis in rapidly proliferating cells, including autoreactive T and B lymphocytes. This oral agent is the active metabolite of leflunomide, an anti-inflammatory drug that is used in patients with rheumatoid arthritis. Leflunomide is a produg with little or no immunomodulatory activity until nonenzymatic conversion to teriflunomide, primarily in the gut wall and liver. Teriflunomide is undergoing evaluation in 6 phase 3 clinical trials for MS (HMR1726: NCT01252355, NCT00134563, NCT00622700, NCT00883337, NCT00791881, NCT00803049). In the 2-year phase 3 TEMSO study (NCT00134563) of teriflunomide in patients with relapsing MS, patients were randomized to receive teriflunomide at a dose of 7 mg per day (n = 365), 14 mg per day (n = 358), or placebo (n = 363). The ARR (primary efficacy endpoint) was 0.37 for teriflunomide 7 mg and 14 mg, relative reductions of 31.2% and 31.5% compared with placebo (0.54; P < 0.001 for both comparisons; Table 2). The proportion of patients with sustained disability progression (defined as an increase in the EDSS score of at least 1.0 point [or at least 0.5 points for patients with baseline EDSS score greater than 5.5] for at least 12 weeks) was lower for teriflunomide 14 mg...
Teriflunomide significantly reduced disease activity measured by MRI outcomes, all of which were secondary endpoints in TEMSO. Teriflunomide also significantly reduced disease activity compared with placebo in both teriflunomide dose groups, where there were significantly fewer T1-gadolinium (Gd) enhancing lesions per scan (P < 0.001). There were also significantly fewer T1-hypointense lesion volume (mL; change from baseline) (P = 0.003) and 67.4% (P < 0.001) in the 7 mg and 14 mg dose groups, respectively, compared with placebo. In both teriflunomide dose groups, there were also significantly fewer T1-gadolinium (Gd) enhancing lesions per scan (P < 0.001) and higher percentages of patients who were MRI-lesion free (51.4% and 64.1% in the 7 mg and 14 mg active treatment arms, respectively) relative to controls (39.0%; P < 0.001). Teriflunomide did not have a significant effect on brain parenchymal fraction (atrophy), also a secondary outcome, over the course of this study (Table 2).

Teriflunomide was generally well tolerated, with a similar number of patients reporting serious treatment-emergent adverse events in the active treatment and placebo arms. Adverse events occurring at higher rates in the 7 mg and 14 mg teriflunomide groups compared with placebo, respectively, included diarrhea (14.7% and 17.9% vs. 8.9%), nausea (9.0% and 13.7% vs. 7.2%), elevated alanine aminotransferase (ALT) activity (12.0% and 14.2% vs. 6.7%), and mild hair thinning or hair loss (10.3% and 13.1% vs. 3.3%).

Laquinimod. Laquinimod is a derivative of linomide, a structurally related compound that had previously reached phase 3 studies in patients with MS, but whose clinical development was halted due to adverse effects as serositis and myocardial infarctions. Laquinimod, a pharmacologically and chemically distinct molecule, was selected based on structure/function testing as well as efficacy and safety in experimental autoimmune encephalomyelitis (EAE) models. Although the exact mechanism(s) of action of laquinimod is/are incompletely understood, this drug has been reported to (a) decrease secretion of proinflammatory cytokines and (b) upregulate brain-derived neurotrophic factor. In addition, laquinimod was shown in an in vitro study to suppress genes associated with antigen presentation and inflammation in peripheral blood mononuclear cells from both healthy controls and patients with relapsing MS include the placebo-controlled TOWER study (NCT00751881) and TENERE (NCT00883337), the latter comparing teriflunomide with IFNβ-1a (≤ 44 microgram [mcg] 3 times weekly).

Laquinimod has been evaluated in 2 large, randomized phase 3 studies known as ALLEGRO (Assessment of oral Laquinimod in prEventing proGRession Of MS; NCT00509145), which has a placebo control arm, and BRAVO (Benefit-Risk Assessment of Avonex and Laquinimod; NCT00605215), in which the active comparator is IFNβ-1a (≤ 44 microgram [mcg] 3 times weekly).

Data from the ALLEGRO trial were reviewed in an oral presentation by Dr. Giancarlo Comi at the April 2011 annual conference of the American Academy of Neurology (AAN). In ALLEGRO, patients were randomized to receive laquinimod at a dose of 0.6 mg per week.

### Table 2: Summary of Efficacy Results from Teriflunomide Phase 3 TEMSO Study

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Placebo (n = 363)</th>
<th>Teriflunomide 7 mg (n = 365)</th>
<th>Teriflunomide 14 mg (n = 358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate (%)</td>
<td>0.54</td>
<td>0.37 &lt; 0.001</td>
<td>0.37 &lt; 0.001</td>
</tr>
<tr>
<td>Absence of relapse during week 108 (%)</td>
<td>45.6</td>
<td>53.7 0.01</td>
<td>56.5 0.003</td>
</tr>
<tr>
<td>Patients with sustained disability progression (%)</td>
<td>27.3</td>
<td>21.7 0.08</td>
<td>20.2 0.03</td>
</tr>
<tr>
<td>Total lesion volume (mL; change from baseline)</td>
<td>2.21</td>
<td>1.31 &lt; 0.001</td>
<td>0.72 &lt; 0.001</td>
</tr>
<tr>
<td>Gd-enhancing T1-lesions per scan (n)</td>
<td>1.33</td>
<td>0.57 &lt; 0.001</td>
<td>0.26 &lt; 0.001</td>
</tr>
<tr>
<td>Patients free from Gd-enhancing T1-lesions (%; n)</td>
<td>39.0 (135)</td>
<td>51.4 (180) &lt; 0.001</td>
<td>64.1 (218) &lt; 0.001</td>
</tr>
<tr>
<td>Unique active lesions per scan (n)</td>
<td>2.46</td>
<td>1.29 &lt; 0.001</td>
<td>0.75 &lt; 0.001</td>
</tr>
<tr>
<td>T1 hypointense lesion volume (mL; change from baseline)</td>
<td>0.53</td>
<td>0.50 0.19</td>
<td>0.33 0.02</td>
</tr>
<tr>
<td>Brain atrophy (mL; change from baseline)</td>
<td>-0.004</td>
<td>-0.003 0.19</td>
<td>-0.003 0.35</td>
</tr>
</tbody>
</table>

*O’Connor P, et al., TEMSO Trial Group. Teriflunomide is an investigational drug not approved by the U.S. Food and Drug Administration. EDSS = Expanded Disability Status Scale; Gd = gadolinium; mg = milligram; mL = milliliter; TEMSO = Teriflunomide Multiple Sclerosis Oral.*
Needle phobia has been reported in up to 22% of the general population. The prospect of being able to administer a drug orally rather than by sometimes painful injections is a desirable option for these patients. Oral dosing is also more convenient for both patients and caregivers, although this may not necessarily translate into improved adherence.

As with all formulary decisions, it is important to first review the overall profile of new products and, as applicable, compare this with existing drug entities. As noted previously, patients who receive fingolimod must undergo additional screening prior to therapy initiation as well as ongoing monitoring during treatment. This includes evaluations of cardiac function as fingolimod is associated with both bradycardia and ativoventricular block. These steps are not required with the established platform (first-line) agents for MS. Added costs associated with ECG and additional billing of associated physician services should be evaluated and calculated. Avoidance of visits to physician offices or ambulatory care centers for infusion therapy, such as is necessary when natalizumab is prescribed, may ease the patient’s burden of administration and decrease costs spent by the MCO for physician or outpatient services.

Information provided by the pivotal clinical trials on new oral agents is an important evaluation tool, but the length of these studies must also be taken into consideration. Additional data are needed from long-term trials as well as direct comparison studies so that these data can be utilized when evaluating novel products. It should be noted that an extension analysis of the TRANSFORMS study of fingolimod was recently published, with no new unexpected safety concerns reported.

Because the peak age of onset of MS is between 20 to 40 years, there is a high likelihood of women being within their child-bearing years, making a medication’s pregnancy safety status an important factor when reviewing for formulary inclusion. It should be noted that symptoms associated with MS tend to be reduced or masked during pregnancy, which has led to the hypothesis that estrogen may play a role in prevention of MS progression. Fingolimod and the other MS agents, with the exception of glatiramer acetate (Category B) are classified as Category C with respect to fetal risks. However, none of the DMTs are approved for use during pregnancy. It should be noted that risk/benefit decisions are still made between physician and patient when pregnancy factors into the treatment plan, and women who are taking any medications for MS should discuss their plan to become pregnant with their prescribing physician.

Based on the properties associated with each individual drug entity, MCOs must make informed choices for the populations they serve. The opinions and practice patterns of national, regional, and local specialists must become a key piece of the evaluation process for newly approved drugs. As practice guidelines and practice patterns are developed and updated, MCOs must continue to evolve with their approved drug offerings to most appropriately serve the lives that they
cover. This will require ongoing evaluation as new oral drugs for MS enter the marketplace. In addition, careful assessment of the risk/benefit profile of the various agents for relapsing MS should include an individualized approach for each patient as part of a shared decision-making process.38,39

MS Policies and the Underserved

MS is a chronic disease that currently is not curable and must be managed with a comprehensive spectrum of preventive, medical, rehabilitative, mental health, and long-term care services to assist affected individuals and their families. Thus, in 2008 the National Multiple Sclerosis Society adopted the 7 National Health Care Reform Principles to shape policies and facilitate change.40

Published reports have indicated that a significant proportion of patients with MS discontinue or interrupt treatment with DMTs. For example, up to 27% of individuals discontinued within the first 6 months of MS therapy initiation.41 In another sample of newly diagnosed relapsing MS patients starting DMT, 43% became nonpersistent within 14 months.42 One of the primary reasons cited in studies of therapy interruption is the perceived lack of clinical efficacy, often associated with unrealistic treatment expectations.43

Policies such as requirements for prior treatment authorization, “tiered” benefits, and restrictive refill policies may limit access to drugs.44 Generic equivalents, which might reduce costs, are not yet available for the relatively expensive DMTs approved for patients with MS. For those requiring additional medications for other MS-related symptoms, including ataxia, spasticity, pain, and bladder or sexual dysfunction, significant additional drug expenditures may be incurred. Neurologists and their treatment teams are usually required to fill out extensive paperwork to gain patient access to these programs and to provide prior authorization to health care insurers.44

In a survey conducted by Iezzoni and Ngo (2007) and lezzeni et al. (2008) in May through November 2005, 36.8% of uninsured individuals with relapsing-remitting MS reported having never taken their MS medications, compared with 21.2% of those with health insurance (P < 0.001).44,45 Slightly more than 16% of persons with public health plans stated that their insurer initially denied coverage for an MS medication. When queried, 22.3% reported not filling prescriptions for MS medications or skipping doses because of high drug costs, and 22.4% had significant concerns about getting their MS medications when needed.45

Additional challenges in receiving optimal health care are faced by individuals from lower-income minorities who have physical disabilities. These patients may face architectural, transportation, and attitudinal barriers with the additional potential impact of cultural and socioeconomic factors on health care quality.46 Many minority patients who live below the poverty level, particularly women, receive care in hospital outpatient clinics or other high volume facilities. In addition, the level of MS expertise varies, and the clinical focus may not include prevention of secondary complications. The opportunities for effective patient education in these settings may be limited, and some ethnic groups may encounter barriers when communicating with physicians or finding written information in their native language. When DMTs for MS are considered appropriate, patient education is an important factor not only in the choice of agent, but also with subsequent adherence/compliance with the prescribed medication. Therefore, specialist contact and effective patient education are important components of a successful ongoing management strategy for patients with MS.46

When individuals with complex chronic diseases from low-income minority groups experience challenges in accessing appropriate health care, suboptimal care and outcomes may result. As part of a performance improvement study, Shabas and Heffner (2005) described the conduct of a survey to evaluate the impact of cultural and socioeconomic factors on the quality of care for low-income minorities with MS enrolled in Independence Care System (ICS), a Medicaid long-term managed care plan for people with physical disabilities in New York City, where 89% of members were from minority groups (primarily African Americans and Hispanics).46 The lack of private insurance and minimal financial resources was cited as a factor in limiting ICS-member options for receiving specialty care. Care management teams, which included a social worker and a nurse dedicated to each ICS member, coordinated health care services. This study concentrated on 3 aspects of MS care: (1) contact with an MS specialist, (2) treatment and compliance with immunomodulatory medications, and (3) osteoporosis screening, prevention, and treatment. Several deficiencies were identified in the care of the low-income minority population with MS in each focus area. Of those surveyed, 32% were never examined by an MS specialist, and approximately one-third were not taking immunomodulatory medications, primarily due to noncompliance caused by a lack of understanding about these drugs (presumably due to inadequate education).

The prevention of osteoporosis and potential fractures in this high-risk patient population, of whom 32% were 50 years of age or older, was generally neglected by providers, even though most survey participants also reported balance difficulties and a prior history of falls. The authors concluded that education regarding the importance of prevention of osteoporosis, fall mitigation, and rehabilitation evaluations were important strategies to decrease fracture risks in this population.46

As an outcome of this ICS performance improvement project, a set of MS care guidelines and interventions was established to address the identified deficiencies.46 These focus primarily on education, are consistent with published recommendations, and can be replicated at other MCOs for members diagnosed with MS. For example, information...
Managed Approaches to Multiple Sclerosis in Special Populations

regarding immunomodulating agents and osteoporosis prevention in both English and Spanish is provided to all members, and referrals to an MS specialist are arranged for those who have never been evaluated by one. All members at increased risk for falling are referred to a rehabilitation professional for an evaluation as part of a falls prevention program. Wheelchair users who transfer independently are now evaluated for the safety of their technique. This strategy to improve MS care for this patient population is consistent with a disease management/case management approach that involves coordination of care through close collaboration among the patient, treating practitioners, and the interprofessional managed care team. These programs incorporate evidence-based practice guidelines and a set of interventions to optimize patient care and focus on patient education, as well as support systems to assist providers in monitoring patients and helping them adhere to their prescribed medications.

Elrod and DeJong (2008) reported that patients with lower household incomes and poorer health status were less likely to receive physical rehabilitation services. These findings highlight the disparities between health plans in their ability to meet plan participants’ needs. Additionally, the medical-necessity criteria of payers often require that services be inherently restorative in order to be considered a reimbursable service. Since therapy that minimizes progressive loss of function may not necessarily improve function, policymakers and health plan administrators should re-evaluate their criteria for coverage of physical rehabilitation services. Optimal design should enhance quality of life and reduce the burden of lost independence. Future policy discussions should focus on how to address potential gaps in health plan coverage that may compromise clinical outcomes, productivity, and quality of life for patients with chronic conditions such as MS. Longitudinal analyses may also be useful in identifying persistent service gaps and how these may affect health outcomes.

In an additional analysis focusing on minorities, African-American (AA) MS patients exhibited a more rapid decline in cognitive function than a non-AA comparator group. Medicaid is the primary insurance provider for AA patients in the New York State MS Consortium registry, and the proportion of this subpopulation in the consortium is relatively low (6%). Notably, there were no differences seen in this study in the types of MS or the use of DMTs in the 2 patient populations. However, AA patients were more likely to develop greater physical disability with increased disease duration. These findings from Weinstock-Guttman et al. (2003) in this minority subpopulation suggest that MS is more aggressive in AA patients and that they may be at higher risk for progression of disability than non-AA patients.

In a study by Palsbo and Diao (2010) evaluating a disability care coordination organization (DCCO), while hospital admission rates were unchanged for enrollees, average lengths of stay (ALOS) in year 1 were significantly shorter (6.23 days) compared with ALOS 1 year prior to program enrollment (11.13 days; \( P = 0.017 \)), suggesting that these services facilitated earlier discharge to home health nursing care. As initially proposed by the Institute of Medicine, DCCOs contract with state Medicaid programs and MCOs to arrange or provide disability-competent health and social services. DCCOs typically assign a nurse or social worker to each enrollee, who collaborate to develop an individualized management plan and then interface with patients to ensure that services are appropriately provided as needed. These services include physical, dental, and mental health care; prescription and acquisition of assistive technologies and durable medical equipment; deinstitutionalization; accessible transportation; access to community services; and subsidies for utility bills.

What strategies might be employed to improve access to care for individuals with MS as well as the equity of payment to their health care providers? One possible solution to the lack of adequate payments for the care of enrollees with MS is to further adjust premiums and capitation payments for the diagnoses of plan members—so-called diagnostic risk adjustment. One of the most promising approaches to fair compensation for the medical care of MS may be supplementing this strategy with functional status measures, if possible. Pope et al. (2002) found that costs were 2-3 times higher for insured enrollees with MS compared with average insured members. For example, calculated annual all-cause medical expenditures were estimated as $7,677 per privately insured enrollee with MS versus $2,394 for all privately insured enrollees, $13,048 per Medicare beneficiary with MS compared with $6,006 for all Medicare beneficiaries, and $7,352 per Medicaid disabled recipient with MS versus $4,088 per disabled recipient without MS. The results of this analysis identified 2 important implications: (a) despite the tendency to under-identify persons with MS in claims data, MS prevalence rates are actually higher than anticipated; and (b) MS patient access to care and appropriate capitated payment levels to care providers must be adequate. Importantly, if the premiums that employers or governments pay insurers and the capitation amounts that insurers pay health care providers do not account for these higher costs, a disincentive may be created for the enrollment and care of persons with MS. Further supplementing diagnostic-based risk adjustment with functional status measurement identifies and directs greater resources to the most disabled and highest-cost patients with MS. A complete carve-out of MS-related services represents another possible approach to provider reimbursement for care.

As MS is a chronic, disabling, and potentially progressive disease, programs that promote symptom management, medication adherence, and a health-promoting lifestyle are important in the overall management of MS. One example of a disease therapy management (DTM) program that incorporated
both self-management and medication therapy management components within a structured 7-month program was evaluated by Stockl et al. (2010). This DTM program was reported to (a) significantly increase adherence to injectable medications for enrolled patients compared with community pharmacy patients (0.92 vs. 0.86; P < 0.001); (b) significantly improve persistence on therapy for both community (220 days vs. 177 days; P < 0.01) and specialty pharmacy patients (200 days vs. 188 days; P = 0.002); and (c) decrease the incidence of MS relapses from months 0 to 6 (14.0% vs. 9.1%; P = 0.03). The MS DTM program did not result in improvement in health-related quality of life or work productivity, but patients reported that the program enabled them to improve management of their health. Studies on adherence to injectable MS therapies have reported that approximately 80% of MS patients adhere 80% of the time for the first 6 months, but that only 60% to 76% adhere to therapy for 2 to 5 years. Problems with injections, perceived lack of efficacy, and side effects have been identified as major barriers to long-term adherence in patients with MS.

MCOs have an interest in clinical programs that can reduce the higher medical expenditures incurred by MS patients. A condition management program for MS described by Tan et al. (2010) was associated with improved medication adherence and persistence, reduced MS-related hospitalizations, and decreased MS-related medical costs. However, the authors concluded that the cost savings in the medical component (-$264) during the 12-month follow-up period did not offset the increased pharmacy expenditures for MS drugs (+$2,184). Interventions included direct mailing of medication and disease-specific patient education materials to patients, including refill reminder calls. Previous studies have demonstrated the feasibility of MS management programs for patient education, exercise, depression, and energy conservation in patients with MS.

Approximately 20% to 25% of MS patients will require long-term care during their disease course, and approximately 5% may eventually need care in an assisted living or nursing facility. Nursing home residents with MS represent a unique population subset, differing in a number of ways from most other residents. Many state Medicaid programs use flat-rate payment schedules that do not adjust for the care needs of individual residents, thus providing incentives to nursing facilities to limit the number of residents receiving rehabilitation therapies and minimizing financial incentives to provide these services to admitted patients. Other state Medicaid programs utilize case mix payments to reimburse nursing facilities, which theoretically links the payment level to the facility’s cost of providing care to residents. Nursing home residents who have Medicare coverage are eligible for skilled rehabilitation services if these are required to improve or maintain their condition and prevent deterioration. In a publication by Buchanan et al. (2006) evaluating nursing home residents with MS, the use of physical therapy (PT) and occupational therapy (OT) was significantly associated with the payment source, suggesting that when reimbursement was available, the specific service was more likely to be prescribed or requested. Rehabilitation efforts can potentially be confounded by comorbidities such as weakness, spasticity, cognitive dysfunction, and sensory symptoms.

As provision of rehabilitative services can be expected to lessen the impact of disability, expanded Medicaid coverage may reduce overall long-term health care costs and improve patient quality of life. Consistent with other published literature, MS residents with Medicare or private health insurance were more likely to receive PT or OT, while self-payers or those with Medicaid or VHA coverage were less likely to receive these therapies. Additional outcomes research is needed to evaluate the effects of rehabilitation therapies on the physical dependency and cognitive ability of nursing home residents with MS.

MS Medication Safety and REMS

The consequences for failing to meet medication safety expectations can lead to possible regulatory sanctions and exposure to liability. Recognizing that certain drugs may be unsafe when used without precautions or restrictions, the FDA Amendments Act (FDAAA) became law in September 2007 (PL 110–85). One of the most important components of the FDAAA was the establishment of formalized risk evaluation and mitigation strategies (REMS) to guide the safe prescribing, dispensing, administration, and monitoring of potentially problematic drugs. Components of individual REMS may vary but generally include medication guides, informed consent forms, laboratory monitoring for effective and safe initial and ongoing use (e.g., normal test results), restricted distribution/dispensing/settings, specialized training/certification/experience, specific ordering/inventory procedures, patient registries, and prescription stickers.

With several new MS therapies anticipated over the next several months and years, it is unclear whether and to what extent REMS requirements will be associated with these new approvals. The safety of newer therapies will likely be questioned and compared with the relatively well-established safety data for traditional parenteral DMTs. Under the current REMS program, however, MCOs may not find substantial assistance in evaluating new MS drugs. Therapies are initially evaluated for safety by an MCO based upon data from the initial clinical trials. Once the drug is used commercially, additional safety information may emerge, but REMS assessment reports are only required after 18 months, 36 months, and 7 years.

Importantly, the goal of REMS is to ensure that the benefits of a prescribed drug outweigh the associated risks and that these risks are appropriately communicated and mitigated. Elements of the REMS applied to emerging MS therapies might...
include a combination of medication guides; patient package inserts; communication plans for health care providers; and specific requirements for prescribers, dispensers, and users of novel therapies.68,69

Opportunities to Apply Case Management to MS

While patient safety is managed at the system level through REMS, individualized patient safety, as well as adherence, can be managed through collaborative practice strategies engaged at the MCO level among pharmacists, case managers, and physicians. A study conducted among Iowa Medicaid patients taking multiple medications to treat chronic conditions demonstrated that improvements in drug therapy can be achieved from collaborative practice between physicians and pharmacists.70 Although this study defined a case management model of pharmacists and physicians in medication therapy management in the community setting, case management programs in MCOs typically involve nurse case managers. Among these models, collaboration between nurse case managers and pharmacists is increasing as the pharmacy management needs become more complex.71

Case management is defined as a collaborative practice model of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual’s and family’s health needs through communication and available resources to promote quality, cost-effective outcomes.72 In Medicaid managed care, nurse case managers could be utilized to coordinate options and services for MS patients with an intended goal to maximize both clinical outcomes and resource utilization. This may involve collaboration with managed care pharmacists to educate patients about compliance. As noted previously, one frequent reason patients with MS cease taking their medications is a perceived lack of clinical efficacy, requiring reinforcement education.73,74

At every level of intervention, MS patients appear to fit the criteria for case management services. Although the estimated prevalence of MS is relatively low—affecting approximately 400,000 persons in the United States, with 200 people newly diagnosed weekly, according to the National Multiple Sclerosis Society75—annual treatment costs for this patient population are in the billions of dollars.76 MS is a long-term, slowly progressive condition with clear, measurable outcomes affecting a relatively small number of individuals while generating high expenditures, but with a reasonable clinical return on investment. Because MS is not highly prevalent in the general population, less than 10% of MCOs surveyed in 1 study stated that they offered fully developed case management programs that incorporated reporting and clinical outcome tracking capabilities for this disorder, and an additional 27% did not track the number of members who were diagnosed with MS.76,77 This may represent an unmet need that is prime for development based on the fact that more than two-thirds of MCOs agreed that a case management program for MS could improve outcomes, increase compliance, and reduce long-term disability.77 Further, patient education provided through case management/disease management services received the highest ranking (90%) as a value-added pharmacy benefit.78

Case management is a tool often used by MCOs to manage the triad of access, quality, and affordability surrounding patient care. Among the standards of practice for case management is the responsibility to track and measure interventional outcomes that include treatment-related cost-savings.72 Not only are the numbers of new product options, including oral agents, growing in the MS arena, but the price of specialty drugs is increasing at approximately twice the rate of other outpatient pharmaceuticals. While protein-based (“biologic”) medications are evaluated in fewer numbers of subjects in clinical trials than small-molecule drugs, and rates of FDA approval are generally higher for biologic agents, these factors do not result in lower prices for the biologic agents.79

The cost of DMTs for relapsing forms of MS is an issue of ongoing concern. One study by Kobelt et al. (2006) attributed 22% of the total costs and about 48% of the direct costs of MS care in the United States to DMTs.79 Remaining total costs were divided among informal care (12%), absenteeism from work (10%), other drugs (6%), technology adaptations (5%), ambulatory care (4%), hospitalization (3%), services, and diagnostics (2% each). The largest total cost driver was identified as forced early retirement (34%). In all, 64% of costs were attributed to direct costs and 37% to indirect costs. The overall cost of MS care was estimated at $47,215 per person, per year, in 2004 U.S. dollars.79 In a similar analysis of MS costs, Prescott et al. (2007) found that 64.8% of total costs were attributable to the cost of prescription drugs and 61.4% to the cost of DMTs.80 Notably, the annual average wholesale price (AWP) of fingolimod ($56,909), the first oral agent approved for relapsing forms of MS, is significantly greater than the cost of the first-line injectable drugs.81 Current evidence pertaining to the total economic impact of DMTs for MS is variable and is influenced by factors such as contracting arrangements and benefit design that includes variables such as pre-authorization criteria and tiered copayments. As a result, all direct and indirect costs associated with MS management should be considered when considering strategies to improve outcomes for patients with MS.

In the wake of MS costs, Medicaid managed care and virtually all MCOs impacted by MS seek methods to lower costs and reduce administrative overhead, while measurably improving quality of care and patient outcomes. Among tools in the toolbox for pharmacists and case managers are process metrics and outcomes metrics to evaluate and manage patients with MS. Assessment of outcomes provides the framework for future planning, and careful and accurate assessment of outcomes of interventions will improve the ability to assist MS patients.
in establishing short-term and long-term goals. Managed care pharmacists and nurse case managers have the responsibility to identify and utilize meaningful outcome measures. Thus, it is important that each intervention has a planned outcome as well as the methodology to evaluate that outcome.82

The National Multiple Sclerosis Society suggests that the factors that must be considered when making the decision to treat are complex and perhaps best analyzed by the individual patient’s neurologist. Therapy is usually continued indefinitely, except for the following conditions: (a) there is clear lack of benefit, (b) there are intolerable side effects, and/or (c) better therapy becomes available. The society urges that payers make these therapies available as early as possible in the disease process.83

In order to measure the outcomes of MS interventions in managed care, and particularly among special populations, there are a number of strategies that may be utilized. Baseline claims data can be gathered, including clinical information, population demographics, and costs of care. Costs of MS care will typically include diagnostics, medical and pharmacy costs, and utilization, including under- and over-utilization of services. Outcomes obtained through case management interventions can also be provided, including intangible effects to augment clinical outcomes data and demographic analyses.

Descriptive and demographic statistics of value in MS outcomes can include age, sex, socioeconomic status, disease severity, and disease burden. Operational statistics may be useful to determine the impact of MS in a plan and could involve such measures as the cost of MS patient support and medical care coordination provided through the nurse case manager or time spent by the pharmacist providing reinforcement education in medication adherence. Statistics may also include the number of prescriptions filled by drug and class or costs per patient and per drug. Clinical statistics used to measure the outcomes of MS management may include adherence statistics; risk assessments, such as depression screenings; or comparative data of the percentage of drugs that met utilization criteria versus exception to benefit reports.

Outcomes measurement is a core function of case management, and case management has been established as having a positive impact on outcomes management in special populations. Bender and Nancee (2003) have previously identified the effectiveness of case management in monitoring patient outcomes within a Medicare population.84 Another study substantiated the effectiveness of nurse case managers in improving the health outcomes among patients with common chronic diseases impacting managed care: diabetes, COPD, and coronary artery disease.85 The significant role of nurse case managers in transitions of care, and their affect on outcomes of transitions of care, has been substantiated by Cotter et al. (2002).86

Outcomes measurement in transitions of care require case managers to coordinate services and health care providers under the guidance of algorithms, standards of care, clinical guidelines, and institutional or organizational protocols pertinent to the patient’s clinical condition. In the absence of clinical guidelines for treatment and management, such as in MS, case managers rely on health assessment screening tools and functional outcomes, such as the Kurtzke EDSS.7 Variances from protocols are tracked as “outliers” and identified as being caused by the patient, provider, or system. Outliers can be common among MS patients in Medicaid populations, and causes are often patient-related.87

Strategies to Optimize Costs of Drugs Used for Relapsing MS

The economic burden of MS exceeds debilitating diseases occurring later in life, such as Alzheimer’s disease or stroke because of the young age of diagnosis, with approximately 75% of cases diagnosed between the ages of 20 and 50.36 Advances in validated MRI measures of MS disease activities have led to changes in the diagnostic criteria of MS, resulting in more accurate and earlier diagnosis for many patients.88 The majority of individuals with MS will live a normal life span.89 Several DMTs were developed in the 1990s and were found to significantly reduce the number of relapses and progression of the disease.35 Goodin et al. (2011) in a poster abstract reported data from 21 years follow-up of patients previously treated with an IFNβ-1b for MS.90 Those patients originally randomized to IFNβ-1b 250 mcg had a significant reduction in all-cause mortality of 46.8% (proportion of patients deceased at 21 years was 32.3% for placebo vs. 20.5% for IFNβ-1b; HR = 0.532, P = 0.017).90 This is one of the first long-term studies to support a significant reduction in all-cause mortality. With the release of this long-term data and the potential for these results to be extrapolated to other medications in the interferon class (e.g., Rebif and Avonex), economic analysis of DMTs is necessary.

Asche et al. (2010) analyzed the health care utilization and costs associated with newly diagnosed MS patients (over the initial 12 months after diagnosis) compared with otherwise healthy patients with similar demographic and other variables (e.g., region, insurance type, gender, age, and enrollment period).91 Total all-cause health care costs for MS patients, over a 12-month post-index period, were 4.7 times the cost for health comparison patients ($18,829 vs. $4,038, P<0.001), with 7.5-fold higher pharmacy costs.91

The economic evaluation described previously by Kobelt took into account both direct costs (inpatient and ambulatory care, prescription medications, and other services) and indirect costs (e.g., lost workplace productivity).92 Annual costs increased from an average of $32,297 for patients with EDSS scores less than 4.0 (normal neurologic exam to mild or moderate disability)93 to $64,492 for those with EDSS scores greater than 6.0 (walking assistance needed to complete dependence).7,79 O’Brien et al. (2003) utilized direct data analysis and cost modeling to derive typical costs, in 2002 dollars, for
different relapse severities. Treatment for a relapse requiring low-intensity care averaged $243 per relapse; medium intensity treatment averaged $1,847 per relapse; and high-intensity care averaged $12,870 per relapse. The large differential in the cost of relapse severity suggests the need to evaluate the cost-effectiveness in preventing relapses with DMTs.

Clinical effectiveness of DMTs in RCTs typically focuses on the number of relapses avoided. These data, along with the estimated cost of a relapse, can be utilized to determine the cost of relapse avoided. In June 2011, Becker and Dembek provided a revised economic model for cost-effectiveness based on the original 2009 Goldberg et al. study. Becker and Dembek focused on the 2-year cost-effectiveness of the 4 parenteral DMTs used as first-line options for relapsing-remitting MS. Utilizing data from randomized studies, they reported the number of relapses that could be avoided for 2 years using IFNβ-1a IM, IFNβ-1a SC, IFNβ-1b SC, and glatiramer acetate SC were 0.74, 0.75, 0.71, and 0.67, respectively. Total MS-related costs and persistency. When products are new to a drug class, they are compared with the commercially available products and current formulary offerings. If there are no specialists on the P&T committee to provide expert opinion, the MCOs will typically invite a specialist to the meeting or elicit input from the specialists prior to the meeting so that committee members can make an informed decision for formulary inclusion.

Once a formulary decision is made, MCOs may decide if a medication should be obtained through a specialty pharmacy provider (SPP). Specialty drugs may be defined as high-cost injectable, infused, oral, or inhaled drugs that generally require close supervision and monitoring of the patient’s drug therapy. Specialty drugs fall into 2 categories based on the site and method of administration: (1) those that require a health care professional to administer them in a physician’s office, infusion center, outpatient hospital department, or home. The majority of MCOs include self-administered injectables in the pharmacy benefit. Those injectables requiring office administration may be obtained by physicians who submit claims for reimbursement; this process is commonly referred to as buy and bill. Many MCOs find it challenging to control the management and costs of these medications when there are different options for dispensing and reimbursement.

SPPs oversee the distribution, management, and reimbursement of specialty pharmacy products, typically at a discounted rate. Industry trends have shown increasing utilization of SPPs, with 70% of surveyed MCOs mandating the use of SPPs for MS products “always or frequently.” Efficient distribution systems, ancillary care, and case or disease management services are some of the benefits of utilizing an SPP. SPPs may disseminate disease- and patient-specific education materials, provide telephonic intervention and care coordination between providers and the patient, provide counseling and assistance in coordination of benefits and reimbursement, monitor
compliance, coordinate nursing and social work support networks, coordinate patient assistance programs, and provide assistance with clinical management of disease state programs. An MCO with resources to provide MS case management services to their members may also utilize the SPP’s contact with the patient for monthly delivery to allow for care coordination between the health plan and the patient. Many questions asked at the time of refill by SPPs may trigger an outreach call from a member of the MCO’s case management team, who may follow the member until his/her condition is stable.

While SPPs provide many benefits to help manage patients with chronic diseases requiring specialty medications, SPPs also provide a cost savings component. Baldini and Culley (2011) described the experience of a large MCO in western Pennsylvania that initiated a Medical Injectable Drug (MID) program in 2002 that transferred a specific subset of specialty drugs from physician reimbursement under traditional buy-and-bill model in the medical benefit to MCO purchase from a SPP that supplied physician office with MIDs. It was not mandatory for physicians to change their processes; however, if they decided to continue with the traditional buy-and-bill processes, they would be reimbursed at the same discounted rate the SPPs receive. The implementation of the MID program resulted in significant drug cost savings of approximately $0.25 per member per month over 2 years in 2007 and 2008. This equated to an estimated drug cost saving of approximately $15.5 million (18.2%) or $290 per claim and about $13 million (12.7%) or $201 per claim in 2008. This savings was despite 28% of MID claims continued through the buy-and-bill system in 2007 and 22% in 2008. The Medco Health Solutions 2011 Drug Trend Report stated that drugs used to treat MS are second only to rheumatologic drugs as the primary drivers of

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**FIGURE 1** AWP Costa for MS Medications (2009-2011)b,c

![AWP Cost for MS Medications Graph](image-url)

Source: First DataBank, Inc. Drug price policy. Available at: www.firstdatabank.com/Support/drug-pricing-policy.aspx. AWP is the average wholesale price or wholesaler’s published price to buying entities (pharmacies, hospitals, etc.) and may vary by reporting source. AWP represents published catalog or list prices and may not represent actual transactional prices.

Gilenya was added to the First Data Bank drug file on September 23, 2010, with an AWP of $4,426.24. Leading up to and after the Gilenya market introduction, all medications used to treat relapse-remitting MS had price increases.

Trade names are included in this graph to help distinguish between drug formulations.

AWP = average wholesale price; MS = multiple sclerosis.
specialty drug spending. Thus, SPPs may provide a solution to the clinical, financial, and operational challenges of managing office-administered specialty pharmaceuticals.

Another factor that may be considered when selecting a formulary product is an MCO’s ability to drive utilization to those products. When all factors are otherwise equal, some manufacturers may offer rebates based on formulary placement. Placing step-therapy protocols on nonpreferred products would require patients to try preferred products first. Programming this look-back at the point of sale allows for the electronic, real-time review of the member’s claim history for evidence of use of first-line agents. In addition, with the increasing utilization of electronic prescribing, this represents another resource to drive formulary product prescribing by providers. Electronic prescribing has the ability to notify the provider when a medication is nonformulary, requires step therapy or prior authorization, allowing the provider to intervene prior to the patient leaving the office.

Many formulary management tactics are utilized by MCOs to manage costs of DMTs. However, one component that MCOs cannot control is manufacturer price increases. In the 4 months prior to fingolimod’s (Gilenya) release, all MS products had an increase in the average wholesale price (AWP). When released to the First Data Bank file on September 23, 2010, fingolimod had an AWP per month (30 days) of $4,426.24. Since then, all products have had price increases with some agents issuing 2 price increases: Rebif (44 mg) and Extavia (in January 2011 and June 2011), Avonex (in December 2010 and May 2011), and Tysabri (in December 2010 and June 2011). Annual price increases for 2009-2011 are shown in Figure 1.

The Medco 2011 Drug Trend Report for 2010 data reported 9.4% inflation for all brand drugs. The average percent change in AWP for MS products from 2009 to 2010 was 16.4%, with a maximum of 28.2% and a minimum change of 8.0%. This is a clear illustration that price increases for DMTs and specialty drugs outpaced price increases for brand medications. The price increases for specific medications for 3 years through September 2011 are shown in Table 3.

In addition to managing MS patients through case or disease management programs within an SPP or MCO, another point of contact for these patients is through the Medicare medication therapy management programs (MTMP). This allows coordination of medication management with providers, members, and disease management programs. Medicare

### Table 3: Cost (AWP) for MS Medications (2009 to 2011)

<table>
<thead>
<tr>
<th>Agentb</th>
<th>September 2009c</th>
<th>September 2010</th>
<th>September 2011</th>
<th>% Change 2009 to 2010</th>
<th>% Change 2010 to 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>N/A</td>
<td>$4,426.24</td>
<td>$4,426.24</td>
<td>N/A</td>
<td>0%</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>$3,005.51</td>
<td>$3,630.05</td>
<td>$4,170.92</td>
<td>20.8%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>$2,879.40</td>
<td>$3,691.20</td>
<td>$4,147.10</td>
<td>28.2%</td>
<td>12.4%</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif 44 mg)</td>
<td>$2,805.12</td>
<td>$3,122.04</td>
<td>$3,709.20</td>
<td>11.3%</td>
<td>18.8%</td>
</tr>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>$2,951.48</td>
<td>$3,442.46</td>
<td>$3,700.76</td>
<td>16.6%</td>
<td>7.5%</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>$2,762.40</td>
<td>$3,268.80</td>
<td>$3,674.40</td>
<td>18.3%</td>
<td>12.4%</td>
</tr>
<tr>
<td>IFNβ-1b (Extavia)</td>
<td>$2,951.40</td>
<td>$3,187.65</td>
<td>$3,615.30</td>
<td>8.0%</td>
<td>13.4%</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif 22 mg)</td>
<td>$2,805.12</td>
<td>$3,122.04</td>
<td>$3,418.80</td>
<td>11.3%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Part D sponsors utilize the CMS criteria in identifying beneficiaries for the MTMP. Targeted beneficiaries include those with multiple chronic diseases (sponsors cannot require more than 3 chronic diseases as the minimum) who are taking multiple Part D drugs (sponsors cannot require more than 8 Part D drugs as the minimum number) and are likely to incur annual costs of at least $3,100.20 in 2012. A Comprehensive Medication Review (CMR) performed by a clinical pharmacist will be completed for all members who qualify for the program who do not opt out. A letter summarizing the CMR is provided to the member’s physician and, if it was a live review, provided to the member. The CMR encourages the physician to review the clinical pharmacist’s recommendations, which typically includes interpreting, monitoring, and assessing the member’s laboratory and test results; assessing, identifying, and prioritizing medication-related problems concerning the dose and dosing regimen of each medication; and considering other therapy-related issues, such as adherence to therapy, medication cost considerations, and drug interactions or side effects. As a result of the above analysis of the member’s medications, the physician may intervene on recommendations made in the CMR resulting in improved safety and efficacy for the member and decreased costs for the MCO.

Because there are no DMTs available in the generic form at this time and the potential addition of 3 new oral medications in the near future, MCOs will continue to have challenges managing the direct costs associated with the treatment of MS. Formulary management tools, SPPs, case management and disease management programs, and MTMP will continue to provide resources to manage utilization and costs associated with this class of medications.

## Summary

The health economics of MS are a central issue for MCOs managing Medicaid beneficiaries. Management of MS can be tangibly impacted by the myriad of symptoms found in MS patients, long-term treatment-associated costs, and the complexity of the treatment and management needs of this patient population. A number of new agents, including more oral drugs expected to become available in the near future, bring promise but are anticipated to increase the cost of MS care. The benefit-risk profile of these new agents will need to be considered in the context of established first-line parenteral drugs and communicated to patients and providers. Current lack of treatment guidelines in MS can make it difficult to mitigate economic risk in special populations without algorithms to guide decision making. Case management and collaborative practice models that engage SPPs, MTMPs, and other tools in managed care can provide outcomes-based interventions aimed at controlling costs while maximizing treatment efficacy.

## REFERENCES

 Managed Approaches to Multiple Sclerosis in Special Populations


Managed Approaches to Multiple Sclerosis in Special Populations

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Posttest and Evaluation Questions: Managed Approaches to Multiple Sclerosis in Special Populations

1. Which of the following statements regarding differences in the fingolimod dose groups in phase 3 trials is correct?
   a. The severity of all adverse events was significantly increased among patients in the 1.25 mg per day group
   b. There were no differences in efficacy outcomes between patients receiving either dose of fingolimod
   c. Significant improvement in MS-related symptoms was noted in the 0.5 mg per day group, but not in the 1.25 mg per day group
   d. Both a and c are correct

2. The primary mechanism of action of teriflunomide is:
   a. Preferentially accumulates in proliferating lymphocytes
   b. Blocks lymphocyte migration into the CNS
   c. Inhibits pyrimidine synthesis and DNA replication in T and B cells
   d. Suppresses expression of genes associated with inflammation

3. All of the following statements regarding the phase 3 ALLEGRO trial of laquinimod in patients with relapsing-remitting MS are correct EXCEPT:
   a. The ARR was reduced by 23% in the laquinimod arm compared with placebo
   b. Significantly improved MRI endpoints in the laquinimod group included reductions the number of new T2 and gadolinium-enhancing lesions
   c. Progression of brain atrophy was reduced by approximately 33% with laquinimod treatment
   d. The most common adverse event in the active treatment group was bradycardia
4. According to a study by Stockl et al., which of the following outcomes were found to be associated with incorporating an MS-specific disease therapy management (DTM) program into patient care?
   a. Increased health-related quality of life
   b. Increased medication adherence
   c. Improvements in work productivity
   d. Reduced occurrence of side effects

5. How would you describe your level of understanding of current strategies available to managed care organizations in therapeutic management of Medicaid patients with MS?
   a. Limited
   b. Adequate
   c. Good
   d. Excellent

6. How would you describe your current understanding of the efficacy and safety of new and emerging oral therapies for relapsing forms of MS and their impact in managed care?
   a. Limited
   b. Adequate
   c. Good
   d. Excellent

7. What is your current level of confidence in managing patients with MS in special populations?
   a. Minimal
   b. Average
   c. Good
   d. Excellent

8. What is your current level of confidence in appreciating the role of the interprofessional team in managed care (pharmacists, nurse case managers) to manage MS patients?
   a. Minimal
   b. Average
   c. Good
   d. Excellent

9. How much can you benefit from additional CE/CME programs describing various collaborative practice models that involve pharmacists, physicians, and nurse case managers in managed care? (1 = Not at all; 5 = Extremely beneficial)
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

10. Over the next 6 months, how much do you anticipate that the knowledge you have gained from this educational activity will improve your ability to recognize areas for improvement in your organization’s management of patients with MS?
    a. No improvement expected
    b. Limited improvement expected
    c. Moderate improvement expected
    d. Significant improvement expected