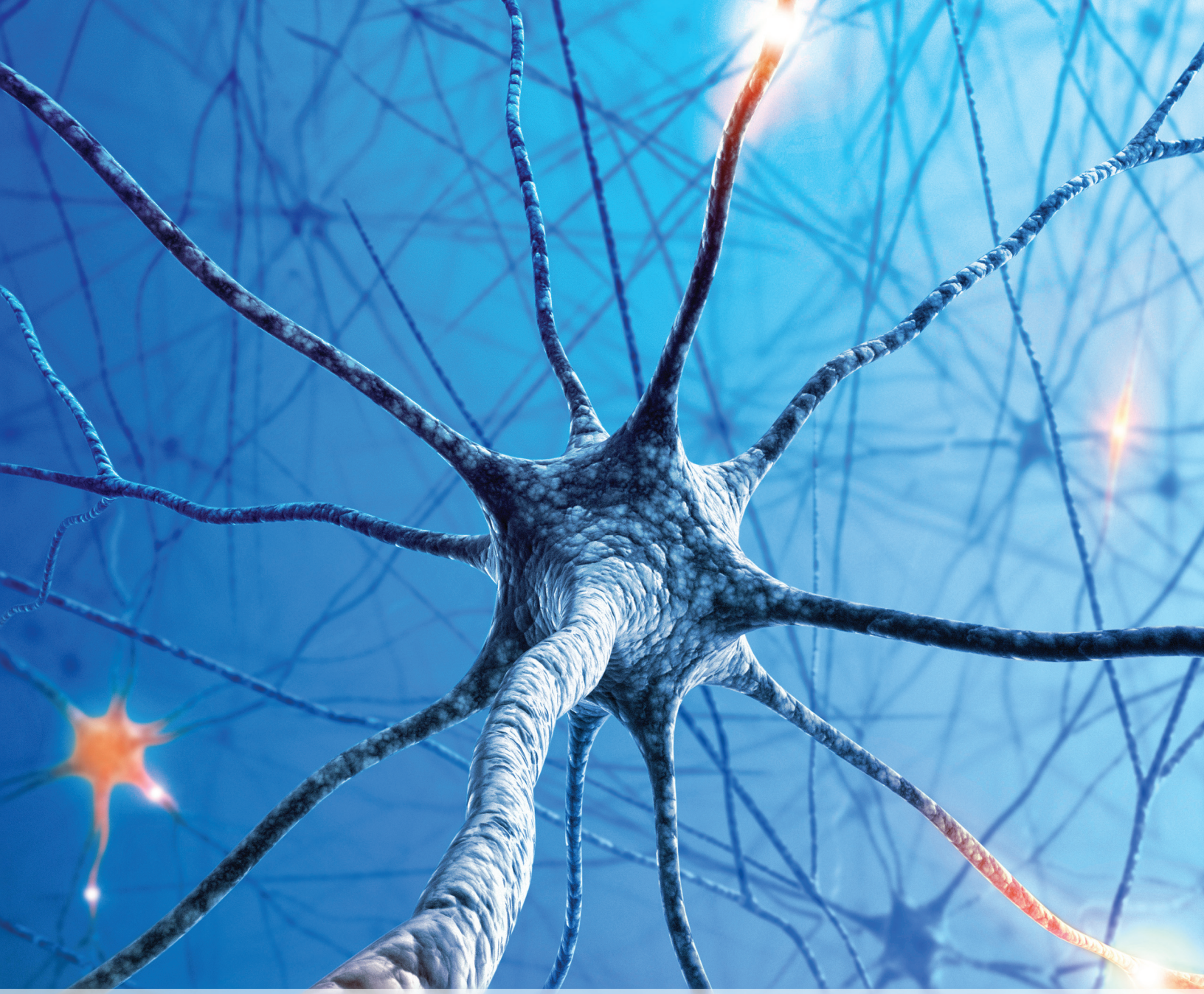


# The Multiple Sclerosis Trend Report

**Perspectives from Managed Care, Providers and Employers**

Second Edition

Sponsored by

National Multiple Sclerosis Society

TEVA Neuroscience



The 2008 publication **The Multiple Sclerosis Trend Report: Perspectives from Managed Care, Providers, and Patients** was awarded the Hermes Gold award and the APEX award for publication excellence.

**Dear Healthcare Colleague:**

The National Multiple Sclerosis Society and Teva Neuroscience are pleased to offer you *The Multiple Sclerosis Trend Report 2nd Edition*, a landmark study on multiple sclerosis (MS). Like many rare disorders treated with orphan drugs, MS combines a relatively low prevalence with disproportionate costs of care. Further complicating its treatment are its elusive etiology and the ambiguities that surround its diagnosis.

The challenges inherent in providing care for patients with MS led our two organizations to survey three groups whose efforts have direct bearing on the outcomes of care. Our aim in asking physicians, managed care organizations, and specialty pharmacies for their confidential replies to the survey questions was twofold: we hoped that these participants would share their frank perspectives on care for people with MS, and that from their replies would emerge a basis for greater efficiencies and collaboration among the major providers of treatment and care management.

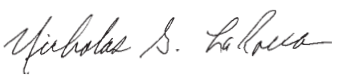
These opportunities do emerge from the survey responses. For example, participants highlighted the key role of coordinated care in the lives of people with MS, and demonstrated that specialty pharmacies are becoming more engaged in this strategy. Neurologists, on the other hand, outlined the urgency of strategic initiatives: they are feeling overwhelmed by the administrative barriers to diagnosing and treating MS, they said, and 64% said they would prefer not to take on more MS patients. The answers to this dilemma, we believe, can be inferred from the replies of neurologists and other participants to many of the survey questions.

We are grateful to all our participants for helping to shape better care for people with MS. *The Multiple Sclerosis Trend Report 2nd Edition* shows that by working together more closely, managed care organizations, neurologists, and specialty pharmacies can diagnose and treat MS earlier, increase adherence to MS therapies, improve the management of care, and lower the costs of treatment in the long run.

We invite all these participants to a new level of collaboration in improving the quality of care for persons with MS.

Should you have questions of any kind, please feel free to contact us.

Sincerely,



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# Executive Summary

The questions that characterize medical treatment for multiple sclerosis (MS) reflect the complexity of the condition. Will the benefits of new treatments outweigh their risks? Will rising copayments discourage adherence and lead to more frequent relapse? In order to grow in our understanding of the relationship between treatment adherence and disease activity in MS, how can we more clearly assess the complicating factors of patient age, gender, stage of disease, neutralizing antibodies, and the time between the discontinuation of treatment and relapse? *The Multiple Sclerosis Trend Report 2nd Edition* considers these themes and more within the framework of the managed care environment, where the mandate to balance the needs of MS patients and the disproportionate costs of their treatment is posing a significant challenge.

During the 1990s, the management of multiple sclerosis was transformed by the introduction of several effective disease-modifying therapies (DMTs). These products were proven to be safe and well tolerated, and they soon became the cornerstone of treatment for most patients with MS. Patients, prescribers, pharmacists, and other healthcare professionals, as well as MS societies themselves, have embraced disease modification using Copaxone® (glatiramer acetate injection) or beta interferon as a core component of the management of MS, and are generally satisfied with the efficacy and safety of these agents.

With the September 2010 approval of Gilenya™ (fingolimod), the first oral medication for the treatment of MS, prescribers and managed care professionals may find choosing therapeutic options will become more complex. Although the concept of an oral treatment is naturally appealing to many patients, the safety and tolerability of this new therapy is less well understood than the DMTs, which have been established over a long period of use. Managed care professionals and physicians will need to understand how to integrate this new treatment option into the management of MS in order to balance trade-offs between efficacy, safety, convenience, and cost.

## Methodology of this Report

In seeking a more complete understanding of MS management in the managed care environment, we invited key stakeholders to share their views. The participants included managed care medical and pharmacy directors, specialty pharmacy and pharmacy benefit managers (PBMs), and neurologists.

These participants were asked to complete survey questionnaires by means of confidential and secured Internet platforms or via fax. Market research techniques were employed to collect and analyze the data, and industry professionals were asked to help explore the results. In addition, 7 representatives of U.S. companies were asked to share their observations on the ways in which employees with MS, along with their coworkers, cope with MS on the job.

What follows are selected highlights from the surveys of managed care organizations (MCOs), specialty pharmacies and PBMs, and neurologists.

## Managed Care Organizations

*The Multiple Sclerosis Trend Report 2nd Edition* indicates that managed care organizations are

becoming increasingly interested in balancing the needs of patients who have MS and the costs of treating it, which are disproportionate to its incidence. The report also suggests that the emergence of new oral drugs to treat MS may have a bearing on benefit design and coverage.

An overwhelming majority of respondents cover the first-line, self-injectable MS drugs under the pharmacy benefit. In this group are Avonex® (interferon beta-1a intramuscular injection), Betaseron® (interferon beta-1b subcutaneous injection), Copaxone® (glatiramer acetate injection), Rebif® (interferon beta-1a subcutaneous injection), and Extavia® (interferon beta-1b subcutaneous injection). Tysabri® (natalizumab), an infused product, is most frequently covered under the medical benefit.

- Although the first-line drugs all target forms of MS, Copaxone (33%) and Avonex (26%) are placed on a preferred drug list more often than the other injectables. None of the respondents have designated Tysabri as a preferred drug.

- One-fifth (20%) of the respondents said they do not cover Extavia, while a large majority of plans cover the other first-line drugs.

- About three-quarters of surveyed plans (76%) use specialty pharmacy providers for MS drugs; of this number, 29% mandate the use of specialty pharmacy providers, and 45% place their use on a voluntary basis.

- When respondents were asked what restrictions they set for covering different immunomodulators, prior authorization took precedence for the 6 available MS drugs when the survey was conducted. Limiting the use of immunomodulators to FDA-approved indications is another popular restriction, followed by setting quantity limits and restricting the pharmacy network. Therapeutic interchange ranked last in the list of management tools. On average, 14% of respondents said they do not place any restrictions on the 6 drugs; Tysabri faces more limitations than the others.

- Almost two-thirds of respondents said they find that developing relationships with pharmaceutical manufacturers proves valuable in supporting patient education (59%) and individualized self-injection training (56%). Almost half (48%) said that phone advice from MS-certified nurse care managers is of value.

- The number of plans that do not use patient-outcomes data to determine appropriate switching among MS agents (58%) outweighs those that use them (42%) to validate decisions. On the other hand, 58% of plans use data to determine which MS drugs should be on a preferred list. Forty percent of plans collect and assess data to inform contracting discussions with manufacturers.

- When asked about the effect of head-to-head studies on formulary placement, 15% of respondents said they use them in the decision-making process, and 42% said they are unaware of the effect of the studies. See page 15 for more information.

- Nearly three-fifths (58%) of respondents said their organization allows concurrent treatment with more than one FDA-approved immunomodulating drug.

- Sixty-one percent of respondents said they do not place a moratorium on a new molecular entity before initiating coverage. Most plans (71%) that do establish a moratorium on new drugs wait 6 months before covering the drug.

- Respondents said that plan sponsors are expressing concern about the effects of MS in the work environment; 57% expressed concern about the rising medical expenses that accompany progression of the disease; 41%, loss of

productivity; and 38%, absenteeism. Thirty-five percent said they are concerned about preventing early disability in employees with MS.

- In assessing the use of nonpharmacologic therapies for MS, 91% of plans always, almost always, or sometimes cover physical therapy; 71% cover occupational therapy; and 70% cover speech therapy. Only a few plans cover plasma exchange therapy (29%), massage therapy (13%), or meditation (6%).

- More plans than not (59% versus 41%) cover Ampyra® (dalfampridine), which received U.S. Food and Drug Administration (FDA) approval as an orally administered drug indicated to improve walking speed in MS patients. Most respondents (73%) said that Ampyra requires prior authorization. Sixty-seven percent limit its use to FDA-approved indications, and 54% set quantity limits.

- Fifty-three percent of respondents are aware of Gilenya™ (fingolimod), an oral drug approved by the FDA to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability for patients with relapsing forms of MS. They indicate that they will welcome an oral formulation as an alternative to the injectable immunomodulators (86%). Respondents also anticipate that patients will demand the oral formulation even if another therapy is a better option (74%), and more than three-fifths (63%) expect that Gilenya will improve adherence because of its oral formulation. Respondents hold similar expectations for cladribine, another oral immunosuppressant now being evaluated by the FDA.

## Specialty Pharmacies / Pharmacy Benefit Management (PBM)

The specialty pharmacy and PBM survey on MS elicited responses from a total of 59 clinical pharmacists, directors of pharmacy, medical directors, senior and executive managers, staff pharmacists, and product managers working in independent PBMs, independent specialty pharmacies, PBMs owned by health plans or pharmacy retailers, and specialty pharmacies owned by PBMs or health plans. Questions focused on distribution channels, emerging oral therapies, strategies for optimizing use of MS medications, and support for disease management.

- Of all the prescriptions that were written for injectable MS therapies in the United States in 2009, more than half were filled through a specialty pharmacy; 24% through a retail pharmacy; and 20% by mail order. Since larger retail pharmacies have specialty and mail-order components, it can be difficult to identify exactly what drug-distribution channel is being used.

- Respondents said that 70% of their clients — managed care organizations — mandate use of specialty pharmacy providers for MS immunomodulators always or frequently. About one-fifth said the use of specialty pharmacies is sometimes required. Four percent said a specialty pharmacy is never required for dispensing these drugs.

- Copaxone® (glatiramer acetate injection) ranked as the number 1 MS therapy covered for members of specialty pharmacies and PBMs. All the interferons except Extavia® (interferon beta-1b subcutaneous injection) — Avonex® (interferon beta-1a intramuscular injection), Rebif® (interferon beta-1a subcutaneous injection) and Betaseron® (interferon beta-1b subcutaneous injection) — ranked in the second highest category for coverage of MS therapies.

- The cost of MS therapy continues to rise, increasing its visibility across drug classes. Approximately 400,000 individuals in the United States are living with a diagnosis of MS, and

respondents to the specialty pharmacy and PBM survey said that in 2009, immunomodulating drugs used in the treatment of MS represented a disproportionate 9% of their total medication costs.

- Because MS treatments are costly, health plans usually put some utilization management strategies in place. Prior authorization was the most widely used strategy across all available drugs, while quantity limits and a restricted pharmacy network were also used quite frequently.

- Respondents said that among the services specialty pharmacies and PBMs offer to help MS patients, overnight delivery of medications (66%) and post-shipment follow-up (53%) are the most used. Less than half of the respondents said they offer care-coordination programs, 24/7 patient support, or registered nurses who provide telephonic support.

- Among the value-added pharmacy-related programs that specialty pharmacies and PBMs provide to managed care organizations, patient education (90%) ranked the highest, followed by refill reminders (86%), patient assessment prior to shipment of medications (65%), and billing and collections (53%).

- Trial data for emerging oral drugs, such as cladribine and Gilenya™ (fingolimod), show that these new treatments are effective for the treatment of MS. The new oral drugs may also improve compliance among patients who dislike self-injecting. The long-term safety profile for these new treatments is as yet unknown, so patients, physicians, and the FDA will need to weigh their risks against the benefits.

## Neurologists

The neurologists' survey examines the diagnosis and treatment of patients with MS. Areas of inquiry include the recognition and management of patients with early disease, goals of therapy, clinical tools to monitor disease activity in the long term, patterns of medication prescribing, and views on emerging therapies.

Key findings of the neurologist survey include the following:

- Neurologists who participated in the survey treat significant numbers of patients who have MS. The typical practice size was between 1,000 and 2,000 active patients; on average, respondents said 23% of their patients have MS.

- Care is coordinated by a primary care physician (PCP) for an average of 45% of MS patients seen by the survey participants. Less than one-third (29%) of respondents said that coordinated care increases or greatly increases the administrative burden on their practice. About the same proportion (30%) said their burden was decreased or greatly decreased by the use of coordinated care; 41% felt the impact was neutral.

- Nearly all of those surveyed (96%) agreed or strongly agreed that inflammation is intimately involved in the pathogenesis of MS, and 93% agreed or strongly agreed that it is important to begin treatment with immunomodulators as soon as possible after diagnosing MS.

- However, the survey results suggest that many patients are not receiving early DMT after a diagnosis of RRMS or clinically isolated syndrome (CIS). For CIS, only 36% of respondents said they begin treatment for all patients once the diagnosis is made. For RRMS, 85% of those surveyed said they begin treatment within 30 days for all patients.

- Copaxone® (glatiramer acetate injection) was selected as a first-line DMT more often than any other treatment (for 32% of newly treated

patients, on average), followed by Avonex® (interferon beta-1a intramuscular injection) (24%), Rebif® (interferon beta-1a subcutaneous injection) (22%), Betaseron® (interferon beta-1b subcutaneous injection) (16%), Extavia® (interferon beta-1b subcutaneous injection) (3%), and Tysabri® (natalizumab) (3%). On average, the respondents reported that 1% of their patients use some other first-line therapy (eg, immunomodulators).

- Copaxone® (glatiramer acetate injection) is also the most commonly selected second-line DMT (29% of patients, on average), followed by Rebif (23%), Betaseron (16%), Avonex (15%), Tysabri (12%), and Extavia (2%), with 2% receiving some other second-line strategy.

- The survey results suggest that many patients are not attaining important goals of MS therapy. Only 33% of neurologists said that more than 75% of their patients attained the therapeutic goal of preventing relapses after one year, and only 22% said that 75% of patients attained a reduction in disability after one year.

- More than half the respondents (53%) said they are open to prescribing new therapies as soon as they are available if they meet the patient's clinical needs; 44% said they would wait until a new product is integrated into the recommendations or guidelines of their professional society; and another 3% said they would wait until a new therapy is accepted by health plans as medically necessary before prescribing it.

- Most participants said they are familiar with the oral MS drug Gilenya™ (fingolimod) as well as cladribine, another oral therapy currently under FDA review. Approximately 70% said an oral therapy might improve patient adherence to therapy, but more than 80% are concerned about the safety profiles of these newer agents, and more than 20% believe these new agents may add to the costs of MS treatment without improving patient outcomes.

*Note to Readers: In the early stages of development, surveys were distributed to managed care medical and pharmacy directors, neurologists, and specialty pharmacy and pharmacy benefit management personnel. Since Gilenya™ (fingolimod) was not yet approved by the FDA, questions were formulated using only the generic name. With approval of Gilenya on September 21, 2010, the report has been revised accordingly. The authors of this report do not feel use of the generic drug name in the survey impacted responses.*

# Emerging Therapeutic Strategies in the Multiple Sclerosis Marketplace: What Do They Mean for Managed Care?

## The Changing Marketplace

During the 1990s, the management of multiple sclerosis (MS) was transformed by the introduction of several effective disease-modifying therapies (DMTs) **(Table 1)**. A series of large clinical trials demonstrated that Copaxone® (glatiramer acetate injection) and 3 interferon beta products — Avonex® (interferon beta-1a intramuscular injection), Betaseron® (interferon beta-1b subcutaneous injection), and Rebif® (interferon beta-1a subcutaneous injection) — significantly reduced disease exacerbations in patients with relapsing-remitting MS (RRMS), and introduced the concept of long-term disease modification in this chronic and disabling condition. These products were proven to be safe and well tolerated, and they soon became the cornerstone of treatment for most patients with RRMS. Patients, prescribers, pharmacists, other healthcare professionals, and MS societies have become comfortable with the safety and efficacy of these agents which now form a core component in the management of MS.

Copaxone is indicated for reduction of the frequency of relapses in patients with RRMS, including patients who have experienced a first clinical episode and have MRI features consistent with MS.[1] Avonex and Betaseron are indicated for relapsing forms of MS and for patients who have experienced a first clinical episode and have MRI features consistent with MS.[2,3] Rebif[4] is indicated for relapsing forms of MS. Extavia® (interferon beta-1b subcutaneous injection)[5] was approved by the FDA in 2009. It is the bioequivalent of Betaseron and as such has the same indication for MS treatment.

The monoclonal antibody Tysabri® (natalizumab)[6] is indicated as monotherapy for RRMS to delay physical disability and reduce the occurrence of clinical exacerbations. An increased risk of developing progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, is associated with Tysabri, which is generally reserved for patients who have not responded to or are unable to tolerate other RRMS therapies.[6]

Novantrone® (mitoxantrone for injection concentrate)[7] is a synthetic antineoplastic anthracenedione for intravenous use. Novantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary-progressive, progressive-relapsing, or worsening RRMS.

As the therapy choices expand, the treatment of MS will become much more complex for prescribers and for managed care professionals. Two oral agents, cladribine[8,9,10,11,12] and Gilenya™ (fingolimod),[13,14] have completed pivotal trials in RRMS. These agents may present new challenges in the treatment of RRMS. The concept of an oral medication is naturally appealing to many patients, but while safety and tolerability have been established over time with DMTs, the long-term safety and efficacy are still unknown with the emerging therapies. Managed care pharmacists and medical directors will need time to integrate these new treatment options into the management of RRMS. This section of *The Multiple Sclerosis Trend Report 2nd Edition* considers the treatment of MS in light of its clinical and economic implications for managed care.

## Table 1

**Indications and usage of first-line disease-modifying therapies for RRMS**

| Disease-Modifying Agent | Indications | Contraindications/Warnings |
|---|---|---|
| Avonex® (interferon beta-1a intramuscular injection)[2] | Indicated for the treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations, including patients who have experienced a first clinical episode and have MRI features consistent with MS. | *Contraindications*<br>• History of hypersensitivity to interferon beta, albumin, or other components of the formulation<br>*Warnings*<br>• Depression/suicide<br>• Anaphylaxis<br>• Decreased peripheral blood counts<br>• Hepatic injury |
| Betaseron® (interferon beta-1b subcutaneous injection)[3] | Indicated for patients with relapsing forms of MS to reduce the frequency of clinical exacerbations, including patients who have experienced a first clinical episode and have MRI features consistent with MS. | *Contraindications*<br>• History of hypersensitivity to interferon beta, albumin, or other components of the formulation<br>*Warnings*<br>• Depression/suicide<br>• Injection site necrosis<br>• Anaphylaxis |
| Copaxone® (glatiramer acetate injection)[1] | Indicated for reduction of the frequency of relapses in patients with RRMS, including patients who have experienced a first clinical episode and have MRI features consistent with MS. | *Contraindications*<br>• Known hypersensitivity to glatiramer acetate or mannitol<br>*Warnings*<br>• Post-injection reaction<br>• Chest pain<br>• Lipoatrophy/skin necrosis<br>• Potential effects on immune response |
| Extavia® (interferon beta-1b subcutaneous injection)[5] | Indicated for patients with relapsing forms of MS to reduce the frequency of clinical exacerbations, including patients who have experienced a first clinical episode and have MRI features consistent with MS. | *Contraindications*<br>• History of hypersensitivity to interferon beta, albumin, or other components of the formulation<br>*Warnings*<br>• Depression/suicide<br>• Injection site necrosis/reactions<br>• Anaphylaxis<br>• Flu-like symptom complex<br>• Hepatic enzyme elevations |
| Rebif® (interferon beta-1a subcutaneous injection)[4] | Indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. | *Contraindications*<br>• History of hypersensitivity to interferon beta, albumin, or other components of the formulation<br>*Warnings*<br>• Depression/suicide<br>• Hepatic injury<br>• Anaphylaxis |
| Tysabri® (natalizumab)[6] | Indicated as monotherapy for the treatment of patients with relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The efficacy of Tysabri beyond 2 years is unknown. | *Contraindications*<br>• History of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability<br>• Hypersensitivity reaction to Tysabri<br>*Warnings*<br>• Increases the risk of PML<br>• Hypersensitivity reactions (eg, anaphylaxis)<br>• Immunosuppression, increased risk of infections<br>• Hepatotoxicity |

## MS: A Chronic, Progressively Disabling Autoimmune Disease

MS is an autoimmune disorder of the brain, spinal cord, and optic nerves that is typically characterized by inflammation of the central nervous system (CNS), loss of myelin, neurodegeneration (including axonal transection and cerebral atrophy), and eventual permanent neurologic dysfunction.[16,17] MS is the leading cause of neurologic disability among young adults.[17] The onset of MS peaks in the early 30s, with approximately 75% of cases diagnosed between the ages of 20 and 50. Onset of MS after the age of 55 is rare. Approximately two-thirds to three quarters of patients with MS are female.[18] The risk of MS is higher in individuals who smoke or who have low vitamin D levels, due either to inadequate vitamin D intake or lower exposure to sunlight.[19] Other risk factors include Epstein-Barr virus and a family history of MS. Genetic studies have indicated that genetic susceptibility plays a role in MS. This susceptibility is complex and involves a number of sites on the human genome.[19]

MS is more common among people who grow up in areas further from the equator. MS is more common among certain ethnic groups, notably northern Europeans, and less common among others, such as Asians, Inuits, and black Africans.[19,20,21]

A great deal of recent research has examined the economic impact of MS, including the cost implications of worsening relapses and disability and the effects of DMTs on clinical and economic outcomes. In addition, the emergence of new oral MS therapies may have significant implications for managed care. These include assessment of mechanisms by which some of these agents may affect the immune system, the relative lack of long-term safety data, and the need to make formulary decisions about the place of these new agents in clinical practice.[22] Continuous safety monitoring of some of these new treatments may be recommended or required,[23] and this could introduce costs for laboratory procedures or specialist care.

### MS Presentation and Diagnosis

The presentation and clinical course of MS vary considerably from one patient to another. The 4 most common types of MS are illustrated in **Table 2**. Relapsing-remitting MS accounts for approximately 85% of patients with newly diagnosed MS,[24] and is characterized by alternating periods of acute relapses and remissions. Symptoms may appear suddenly or gradually, and they may resolve completely or only partially between episodes.[24] RRMS is usually followed by a transition to secondary-progressive MS (SPMS), which is characterized by progressing neurologic dysfunction, the gradual disappearance of acute relapses, and the presence of fewer active MS lesions on MRI.[24] The proportion of patients with SPMS increases with time after a diagnosis of RRMS; 50% of patients transition to SPMS after approximately 19 years.[25] Primary-progressive MS (PPMS), which accounts for approximately 10% to 15% of cases of MS at diagnosis, is defined by the gradual, progressive development of neurologic symptoms from the first onset of disease. These patients do not exhibit episodes of relapses and remissions, and they may experience periods of stable disease without further loss of function.[24,26] Finally, progressive-relapsing MS (PRMS) is characterized by a gradual, progressive loss of neurologic function from the initial disease onset that resembles PPMS but that includes superimposed acute episodes that resemble those of RRMS. This uncommon presentation of MS affects approximately 5% of patients.[24]

MS manifests in a broad range of symptoms that often evolve over time as the disease progresses. Common symptoms include weakness, incoordination, spasticity, sensory loss, visual disturbances, fatigue, depression,[24,27] pain, bowel and bladder dysfunction, and sexual dysfunction.[24] MS is also associated with high rates of physical and psychiatric comorbidities, disability,[27,28] and unemployment.[28]

The diagnosis of MS requires evidence of disease activity that includes both dissemination in time (that is, evidence of 2 or more episodes of disease activity) and dissemination in space (evidence of at

**Table 2**

| Multiple Sclerosis: Disease Course and Frequency | | |
|---|---|---|
| **Type** | **Frequency** | **Characteristics** |
| **Relapsing-Remitting MS (RRMS)** | • Most common<br>• ~ 85% at onset | • Clearly defined flare-ups (relapses) or episodes of acute worsening of neurologic function<br>• Partial or complete recovery periods (remissions) between attacks that are free of disease progression |
| **Secondary-Progressive MS (SPMS)** | • Left untreated, 50% of people with RRMS develop SPMS within 10 years of initial diagnosis | • Initial period of relapsing-remitting disease (see above)<br>• Worsening disease course with or without occasional flare-ups, minor remissions (recoveries) or plateaus |
| **Primary-Progressive MS (PPMS)** | • Relatively rare<br>• ~10% at onset | • Nearly continuous worsening of disease from the onset<br>• No distinct relapses or remissions<br>• Variations in rate of progression over time, occasional plateaus, and temporary minor improvements |
| **Progressive-Relapsing MS (PRMS)** | • Relatively rare<br>• ~5% at onset | • Steady worsening disease from the onset<br>• Clear acute flare-ups (relapses), with or without recovery<br>• Periods between relapses characterized by continuing disease progression |

Adapted with permission from the National Multiple Sclerosis Society

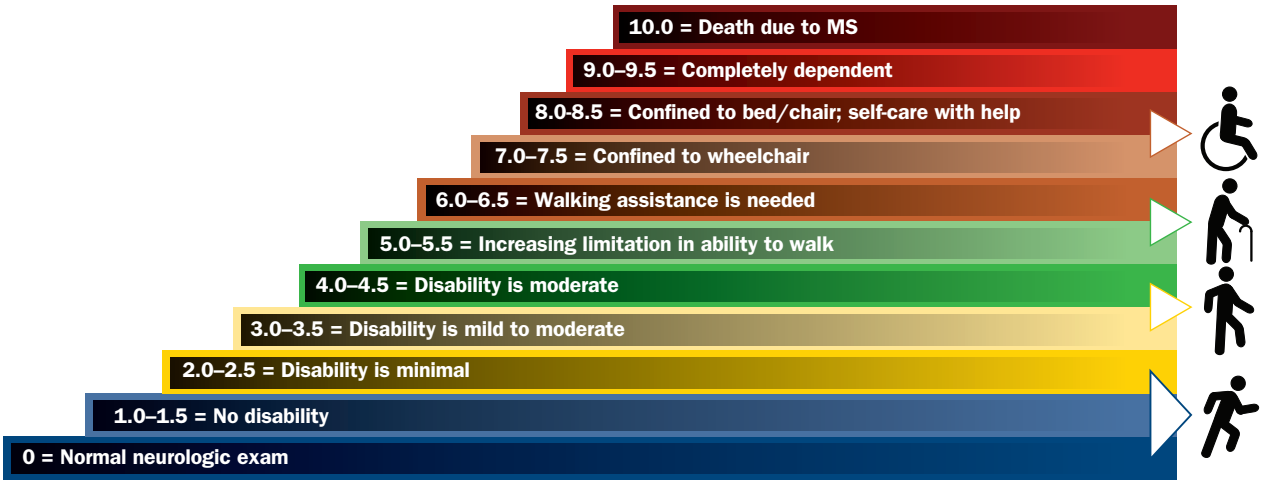
least 2 lesions within the CNS).[29] In current practice, MS is diagnosed by means of the McDonald criteria, in which evidence of MS disease activity may be provided by a combination of clinical signs and symptoms, MRI of the brain and spinal cord, testing of cerebrospinal fluid, and neurophysiological tests.[29] In older studies, MS was often diagnosed by means of criteria developed by Poser and colleagues (the Poser criteria), before validated MRI measures of MS disease activity were available. The Poser criteria for definite MS required the occurrence of at least 2 clinical attacks that could be linked to 2 separate CNS lesions. Demonstration of 2 lesions could be documented by clinical symptoms, or one of the lesions could be identified on the basis of paraclinical markers such as visual or somatosensory-evoked potentials.[29] Patients could also be classified with "laboratory definite MS" based on the presence of oligoclonal banding of CSF or elevated IgG index. Some of these patients would not meet the diagnostic criteria for definite MS that are generally required today by the McDonald criteria; instead, they would be classified as having "possible MS."[29] Changes in the diagnostic criteria for MS have led to more accurate and earlier diagnosis for many patients.[30] Progressive long-term disability is usually rated by means of the Expanded Disability Status Scale (EDSS), which varies from 0 (normal neurologic function) to 10 (death from MS). An EDSS score of 3 indicates mild-to-moderate disability; a score of 6 means that the patient requires assistance with walking; and a score of 8 indicates that the patient is confined to a bed or chair and requires assistance with self-care[17] (**Figure 1**).

## MS: Pathogenesis, Natural History, and Disease-Modifying Therapies

Research into the pathogenesis of MS continues to reveal its complexity. The clinical manifestations of MS are thought to reflect an imbalance of normal immune function. It has long been recognized that self-reactive type 1 helper T lymphocytes (Th1 cells) migrate through the blood-brain barrier and into the CNS, where they release a variety of inflammatory cytokines that result in CNS inflammation, demyelination, and neurodegeneration.[31,32]

## Figure 1

Assessing Disability Progression: The EDSS




Adapted from Kurtzke, JF. *Neurology*. 1983;33:1444-1452.
EDSS: Expanded Disability Status Scale

These immune cells are thought to respond to a protein antigen or antigens that are structurally similar to a component of CNS myelin.[32] More recently, it has been recognized that the pathophysiology of MS also involves the abnormal activation of many other immune cell populations, including Th17 cells, peripheral B lymphocytes, dendritic cells, and killer T cells.[31]

Currently available DMTs are thought to reduce these inflammatory and neurodegenerative processes by several different mechanisms. Interferons produce a variety of immune-modulating effects, including the regulation of T cell activation and proliferation, apoptosis of autoreactive T cells, modulation of inflammatory cytokines, and suppression of immune cell migration into the CNS.[32] In contrast, Copaxone® (glatiramer acetate injection) is a polypeptide mixture that was designed to mimic the myelin protein that triggers the autoimmune response in MS.[33] Copaxone acts with the immune system to restore the normal balance of immune surveillance by inducing a shift in the T cell population from a Th1 to Th2 (anti-inflammatory) T cell cytokine profile.[33] Th2 cells are thought to accumulate within the CNS of patients with MS, and to release anti-inflammatory cytokines upon reexposure to CNS myelin antigens. In addition, T cells from patients who have been treated with glatiramer acetate have been shown to produce growth factors that are important for the survival of nerve cells, and that may help to prevent nerve damage.[33]

Tysabri® (natalizumab) is a monoclonal antibody that binds selectively to the α4 subunit of the lymphocyte cell-surface protein α4β1, a cell adhesion molecule that participates in lymphocyte infiltration into the CNS. Through this mechanism, Tysabri inhibits lymphocyte migration through the blood-brain barrier, thus reducing the inflammation that leads to lesion formation and axonal damage. Tysabri may also continue to decrease ongoing inflammation once leukocytes have entered the parenchyma of the CNS.[34]

Novantrone® (mitoxantrone for injection concentrate) is an antineoplastic agent that causes DNA crosslinking and strand breaks, as well as inhibition of B cells, T cells, macrophages, and antigen presentation. In clinical studies of patients with SPMS, PRMS, or worsening RRMS with residual neurologic deficit between relapses, Novantrone significantly reduced EDSS deterioration and relapse rate.[7]

Although approved for the treatment of MS, Novantrone® (mitoxantrone for injection concentrate) (SPMS, PRMS, worsening RRMS) and Tysabri® (natalizumab) (relapsing forms of MS) are generally recommended for patients who do not respond to another disease-modifying agent.[6,7,17]

### The Natural History of Untreated MS

Patients with untreated RRMS typically experience a second neurologic episode within 2 years of an initial demyelinating event,[25] with additional relapses following at an average rate of approximately one-half to one relapse per year.[15] The median time from disease onset until transition to SPMS is approximately 19 years, and the median time to reach an EDSS score of 6 is approximately 15 to 20 years.[25] Disability is more severe for patients with a higher rate of early relapses and for patients with attacks that involve multiple neurologic pathways or that include motor or cerebellar involvement.[15]

DMTs make it possible to significantly alter the natural history of MS. Reducing the number of relapses is an important goal of MS therapy.[36] Many prospective, randomized, placebo-controlled clinical trials have demonstrated that Avonex® (interferon beta-1a intramuscular injection), Betaseron® (interferon beta-1b subcutaneous injection), Copaxone® (glatiramer acetate injection), Extavia® (interferon beta-1b subcutaneous injection), and Rebif® (interferon beta-1a subcutaneous injection), significantly reduce the incidence of new relapses in patients with RRMS compared with placebo.[37,38,39,40] It should be noted that in these early studies, patients were diagnosed using the Poser criteria, and most patients were probably untreated for longer periods of time than is typical in contemporary practice. DMTs have also been studied for the delay of conversion to clinically definite RRMS in individuals who have a single episode of neurologic disease that is suggestive of MS but that does not meet the full diagnostic criteria, a presentation that has been referred to as clinically isolated syndrome (CIS). Individuals with CIS have a very high likelihood of converting to RRMS in the future, especially when there is evidence of CNS inflammation on brain MRI.[41] Recent clinical studies have demonstrated that interferon beta and Copaxone significantly delay the conversion to definite RRMS in these patients. These observations have led to the widespread adoption of earlier and more aggressive MS therapy utilization.[41]

### Disease-Modifying Therapies: Head-to-Head Studies and Other Comparative Trials

Several clinical trials have compared treatment response rates among interferon beta products. The results of these studies have suggested that high-dose interferon beta regimens are more effective than lower doses. The INCOMIN study[42] reported that over a 2-year period, interferon beta-1b administered every other day reduced the relapse rate by 51% (n = 49), compared with a reduction of 36% (n = 33) with interferon beta-1a once weekly ($P = 0.03$). In the EVIDENCE study,[43] more patients were relapse free after 24 weeks with interferon beta-1a 44 µg SC 3 times weekly (74.9%; 254 out of 339) than with interferon beta-1a 30 µg IM once weekly (63.3%; 214 out of 338; $P = 0.0005$). However, at least some of the between-group differences in these trials may have been attributable to extraneous factors such as different baseline levels of disease activity or rates of neutralizing antibody formation.[44]

The efficacy and safety of glatiramer acetate injection were compared with interferon therapy in the BEYOND and REGARD multicenter clinical trials. In the REGARD study,[45] patients with RRMS were randomly assigned to interferon beta-1a SC (n = 386) or glatiramer acetate (n = 378). After 96 weeks, the time to first relapse was nearly identical for the interferon and glatiramer acetate groups. The annualized relapse rates were also similar for the 2 groups (0.30 versus 0.29 with beta-1a and glatiramer acetate, respectively; $P = 0.828$). The incidence and severity of adverse events were similar for the interferon and glatiramer acetate groups. Events that were more common with interferon included flu-like syndrome, headache, myalgia, and increased alanine aminotransferase (ALT); events

that were more common with glatiramer acetate included dyspnea and injection-site reactions.

The BEYOND study[46] compared interferon beta-1b and glatiramer acetate in 2447 patients. Patients with RRMS were randomized to high-dose subcutaneous interferon beta-1b (500 µg), low-dose interferon beta-1b (250 µg), or glatiramer acetate. The annualized relapse rates were 0.33 for the 500 µg interferon beta-1b group, 0.36 for the 250 µg interferon beta-1b group, and 0.34 for the glatiramer acetate group. None of the between-group comparisons were statistically significant. The rates of flu-like reactions over the course of study are shown in **Figure 2**. The incidence of flu-like reactions was higher with both interferon beta-1b doses and remained greater throughout the study. Injection-site reactions were more common with glatiramer acetate, although the differences between groups decreased over time.

The available data from prospective, randomized clinical trials suggests glatiramer acetate and interferon beta produce similar improvements in relapse rates after the first 2 years of treatment in patients with RRMS. Both options are acceptable first choices for DMT in patients with RRMS.

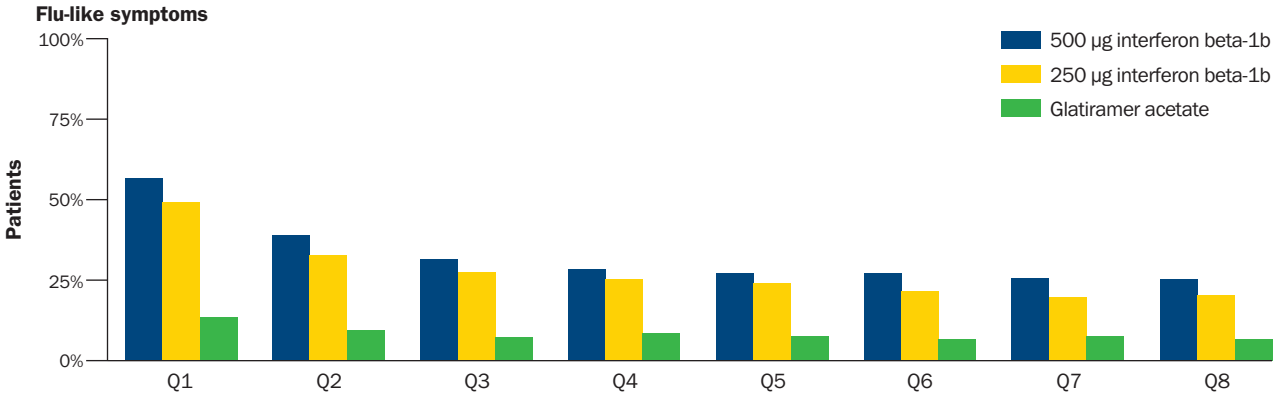
## Long-Term Outcomes

An ongoing U.S. open-label clinical trial of glatiramer acetate that first began enrolling patients in 1991 is the longest-running prospective study of continuous immunomodulatory therapy in patients with RRMS.[47] Of the 232 patients who entered the study in 1991, 100 patients remained on treatment with glatiramer acetate at a follow-up evaluation in February 2008.[47] The mean duration of glatiramer acetate exposure for these patients was 15 years, and the total mean duration of MS was approximately 22 years. The mean relapse rate decreased from 1.12 per year at baseline to 0.25 per year at long-term follow-up. EDSS scores of 4, 6, or 8 had been reached by 38%, 18%, and 3% of patients, respectively. More than 80% of patients remained ambulatory without assistance.[47]

Encouraging data are also available from longer-term studies of the interferon betas. The 15-year ASSURANCE study[48] represents the long-term follow-up of patients who participated in the original phase 3 pivotal trial supporting the approval of interferon beta-1a IM. This open-label, retrospective, observational study targeted 372 patients who had been treated with interferon beta-1a IM for 10 years or longer (median 13.8 years). Another recent

**Figure 2**

**Frequency of Flu-Like Symptoms**




O'Connor P, et al. *Lancet Neurol.* 2009;8:889-97.
Reprinted with permission.

report[49] described a lower incidence of mortality for patients in a clinical trial who were originally randomized to interferon beta-1b than for those on placebo after 16 years of follow-up. Other outcomes were not reported. A second recent report[50] described outcomes after 5 years in patients with CIS who were treated with early or delayed interferon beta-1b. Early interferon therapy significantly reduced the transition from CIS to definite RRMS but did not affect long-term disability progression after 5 years.[50,51] Open-label extension phases of interferon beta randomized controlled trials have demonstrated continued benefit, with approximately 45% to 50% of patients remaining on interferon therapy after 5 to 8 years. Less is known of the long-term profile of natalizumab, though accumulating data should provide insight in regard to its long-term safety (eg, the risk of PML) and its efficacy over time.

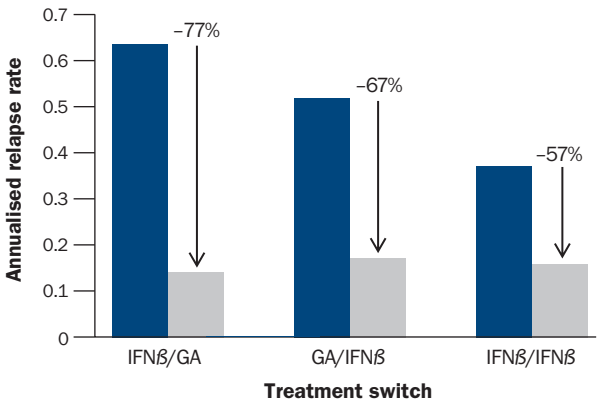
### Suboptimal Treatment Response and Medication Switching

Because MS is a chronic disease in which early inflammatory lesions or subclinical disease activity may significantly contribute to long-term axonal loss, neurodegeneration, and disease progression, it may be important to identify individuals who are not responding to therapy as early as possible in order to modify their treatment regimen and limit future neurologic impairment.[15] Consensus criteria for treatment switching include continued frequent relapses after at least 6 months on therapy (ie, either a continued rate of 1 relapse per year or an increase in relapse rate from baseline), incomplete recovery from multiple attacks, evolution of attacks involving multiple CNS regions, recurrent brain or spinal cord lesions, and cumulative loss of neurologic function that is sufficient to cause impairment of normal daily activities.[15] Treatment switching should also be considered for patients who have intolerable side effects following the attempt to optimize therapy.[35] In the pivotal trials of interferon beta for patients with RRMS, the most common adverse events leading to the premature discontinuation of treatment included depression, influenza-like symptoms, aminotransferase elevations, fatigue, and injection-site reactions.[2,4,5] Treatment with interferon beta induces neutralizing antibodies in approximately one-third of patients with MS. In some studies, but not all, the appearance of neutralizing antibodies has been associated with decreased clinical benefit.[52] Among patients who were treated with glatiramer acetate in blinded placebo-controlled trials, the most common adverse reactions were injection-site reactions, vasodilatation, rash, dyspnea, and chest pain.[1] Approximately 5% of the subjects discontinued treatment because of an adverse reaction. Injection-site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity were the adverse reactions most commonly associated with discontinuation.

When adverse events or lack of efficacy causes patients to switch from one agent to another, it may be reasonable to switch to an agent that has a different mechanism of action. A prospective, open-label observational study compared 3 medication-switching strategies involving first-line DMTs for patients with RRMS who had inadequate responses or intolerable side effects with an initial course of therapy.[53] In 2 study cohorts, patients who discontinued either interferon beta or glatiramer acetate due to adverse events or lack of efficacy were switched to the other drug (**Figure 3**). Patients who switched from interferon beta to glatiramer acetate exhibited a mean 77% reduction in annualized relapse rate, from 0.63 to 0.14 per year. Patients who switched from glatiramer acetate to interferon exhibited a mean 67% reduction in relapse rate, from 0.52 to 0.17 per year. Although EDSS scores continued to increase in patients who were switched from glatiramer acetate to interferon beta or from one interferon beta dose to the other, EDSS scores did not progress in patients who were switched from interferon to glatiramer acetate.[53] In a third cohort, patients could be switched from low-dose interferon beta to a higher dose if they discontinued their initial interferon therapy due to lack of efficacy but not as a result of adverse events. These patients exhibited a 57% reduction in relapse rate after switching from one interferon

**Figure 3**

**Annualized relapse rates before (blue columns) and after (grey columns) switching between immunomodulatory treatments. Percentages indicate the reduction in relapse rate following treatment switch.**




IFNb = interferon b; GA = glatiramer acetate

Carrá A, Onaha P, Luetic G, et al. *Eur J Neurol.* 2008;15(4):386-393. Reprinted with permission.

to another, from 0.37 to 0.16 relapses per year.[53] Thus, this study demonstrated that switching from one class of therapy to another is a reasonable strategy for patients who do not respond to or cannot tolerate their initial therapy.

Other recent studies have specifically examined the switch from interferon beta to glatiramer acetate. A study that was recently reported at the annual meeting of the American Academy of Neurology enrolled 60 patients with RRMS who had been treated with interferon beta for at least 6 months and who were switched to glatiramer acetate due to lack of efficacy (21 patients) or intolerable adverse events (39 patients).[54] For patients who discontinued because of lack of efficacy, the mean relapse rate decreased from 1.39 per year on interferon beta therapy to 0.52 after they were switched to glatiramer acetate. For patients who discontinued because of adverse effects, the relapse rate of 0.36 per year on interferon therapy was maintained after they were switched to glatiramer acetate (mean number of relapses, 0.35 per year). These observations suggest that a switch to glatiramer acetate is a reasonable strategy for patients with RRMS who do not respond to or cannot tolerate interferon beta. Similar observations were reported in a previous study from the U.S., in which patients were switched from weekly interferon beta-1a to glatiramer acetate for either lack of response or intolerable adverse events after 18 months.[55] Switching to glatiramer acetate reduced the mean annual relapse rate in patients who switched due to lack of efficacy, and it sustained the previously achieved reduction in patients who switched due to adverse events.[55]

Finally, an open-label prospective study[56] compared the response to glatiramer acetate for newly diagnosed patients with RRMS with the response among patients who had been previously treated with interferon beta-1b (n = 247). The annual relapse rate was reduced to a similar extent in both cohorts (0.42 relapses per year in the prior treatment cohort and 0.34 in the treatment-naive cohort; $P = 0.1482$). Most patients remained relapse free throughout 3.5 years of follow-up, including 68.4% in the prior treatment cohort and 69.5% in the treatment-naive cohort. Adverse event rates and discontinuations due to adverse events were also similar for the two cohorts. Thus, glatiramer acetate is an effective and safe option for patients with or without prior exposure to interferon beta therapy.

## Safety and Tolerability of Disease-Modifying Therapies

Each DMT has a unique safety and tolerability profile.

All currently available DMTs are generally well tolerated. The interferon beta products that are used to treat MS have been associated with an increased risk of depression and suicide, and these agents should be used with caution in individuals with depression.[2,3,4,5] Interferon beta has also been associated with a number of other common side effects, including flu-like symptoms, allergic reactions (including rare cases of anaphylaxis), decreased blood counts (eg, thrombocytopenia and leukopenia), hepatic enzyme elevation, and injection-site

reaction or necrosis. Each of these agents is in pregnancy category C.[2,3,4,5]

The most common adverse events associated with glatiramer acetate were subcutaneous injection-site reactions, including lipoatrophy and, rarely, skin necrosis.[1] Other events included vasodilation, rash, dyspnea, and transitory chest pain without clinical sequelae. An immediate post-injection reaction has been noted in approximately 16% of patients, and includes flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. These symptoms are transient and self-limited, and do not require specific treatment. The labeling does not include warnings for immunosuppression or serious infections, and there are no specific monitoring requirements. Glatiramer acetate is in pregnancy category B.[1]

The most common adverse effects with natalizumab were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea and rash. Natalizumab also increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability.[6] As of December 2, natalizumab had been associated with 79 reported cases of PML. Sixteen of these cases of PML resulted in death.[57] The risk of PML in association with the use of natalizumab is a significant concern because there are no established markers to identify patients who are at risk.[58]

The most common adverse events associated with mitoxantrone were nausea, alopecia, urinary tract infection, and menstrual disorders, including amenorrhea. Mitoxantrone is also associated with potentially serious adverse events, including the risk of severe local tissue damage if extravasation occurs during injection, severe bone marrow suppression, infection, and acute myelogenous leukemia. Mitoxantrone has also been associated with a risk of cardiotoxicity, which is potentially fatal and which has occurred in some cases months or years after the discontinuation of mitoxantrone.[7]

## Economic Impact of MS

Because MS is usually diagnosed in patients at a relatively young age, and because of the costs associated with DMT, the total economic impact of MS exceeds that of other debilitating diseases that usually occur later in life, such as stroke or Alzheimer's disease.[59] A number of recent studies have examined the costs of MS and its treatment, including the direct medical costs, the costs associated with relapses, the impact of disease severity or disability, and indirect costs such as diminished productivity at work.

### Economic Impact of MS, Relapses, Increasing Disability, and Treatment Switching

An analysis of administrative claims data for patients with MS who were enrolled in more than 80 U.S. health plans revealed that the annual direct treatment costs averaged $12,879 per patient per year.[59] Pharmacy costs accounted for 65% of all MS-related treatment costs, and 57.5% of patients received at least one disease-modifying drug.[59] The authors did not directly assess the impact of disease severity on MS-associated costs, but they noted that direct treatment costs were higher for patients who had several comorbid conditions that are commonly associated with more severe MS. For example, the average annual cost was $20,376 for patients with spasms, $20,871 for patients with gait abnormalities.[59]

MS relapses are associated with considerable costs in regard to direct treatment, especially for patients who suffer more frequent or more severe relapses. For example, one study reported that the treatment cost for a relapse that required only low-intensity care (eg, office visits and routine tests with the patient's usual provider) averaged $243 per episode in 2002 U.S. dollars.[60] For patients who required medium-intensity treatment (eg, an ER visit, IV methylprednisolone, follow-up office visits, or physical or occupational therapy), the per-relapse cost increased markedly, to an average of $1,847 per visit. Finally, for high-intensity services (eg, hospitalization, rehabilitation, skilled nursing), the mean cost was $12,870 per relapse, or approxi-

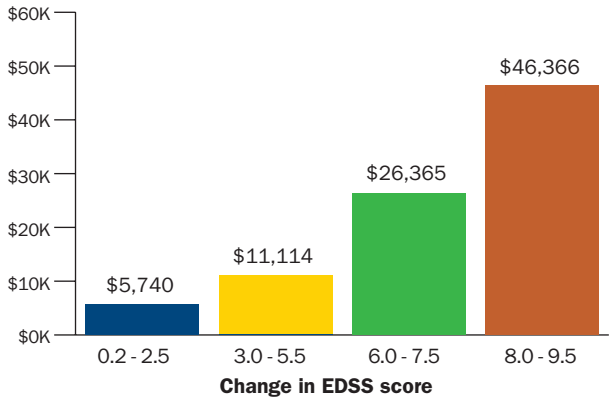
mately 6 times the cost of a medium-intensity visit. The authors concluded that management strategies that reduce the frequency or intensity of relapses would substantially lower the cost of managing them.[60]

A second study from 2000 examined how overall treatment costs for patients with MS were affected by the number of relapses.[61] Analysis of claims data from a managed care medical and pharmacy database revealed that the total cost of treating patients with MS over a 2-year period increased from $6,007 for patients with no MS exacerbations to $8,180 for those with a single exacerbation, $14,521 for those with 2 exacerbations, and $20,519 for those with 3 to 8 exacerbations.[61] A correlation has also been shown between worsening EDSS scores and rapidly rising annual treatment costs[62] **(Figure 4).**

Kobelt and colleagues[63] performed a broader assessment of the economic impact of MS that included both direct costs (inpatient and ambulatory care, prescription and over-the-counter drugs, and other services) as well as indirect costs (eg, lost workplace productivity) in a survey of patients from the NARCOMS MS patient registry. DMTs were used by 94% of those surveyed, and constituted the largest single cost item, with an average per-patient cost of $16,050 per year. The mean estimated per-patient total of all MS-related direct and indirect costs was $47,215 per year. This study may have actually underestimated total costs since it did not include adequate proportions of more severely disabled patients in residential facililties and their associated costs. Direct medical costs averaged $29,634 per patient, or approximately 63% of all costs. The average indirect costs totaled $17,581 per year, the largest portion of which was contributed by early retirement. More than 40% of those surveyed had either stopped working or taken early retirement owing to their MS. The need for informal care was also a large expense for patients with MS, with an average annual per-patient cost of $4,614. Annual costs increased from an average of $32,297 for patients with EDSS scores <4.0 to $64,492 for those with EDSS scores >6.0, despite the fact that many patients with more severe disability had already discontinued DMT. The average cost of treating a single relapse was $1,561.Finally, the authors examined the impact of MS, relapses, and disability by means of health utility scores, which assign values to various health states on a scale of 1 (perfect health) to 0 (death). Utility scores were lower for patients with MS than for matched healthy subjects, and were also lower for those with EDSS scores >6.0 (mean, 0.533) than for those with EDSS scores <4.0 (mean, 0.824).

**Figure 4**

**Annual cost increase with change in EDSS level**




Data derived using a literature-based Markov model. Inflation compounded annually at 2% through 2010.

Together, these studies show that MS is associated with a large per-patient economic burden, that much of this burden is attributable to indirect costs, and that relapses and progressive disability markedly increase the costs of MS management while decreasing patients' overall health. Treatment with DMTs may reduce the direct and indirect medical costs associated with MS. For example, one recent study[64] used a privately insured employer claims database from 17 U.S.-based companies to compare direct medical costs and indirect employer costs (payments for disability and medically related absenteeism) for patients with RRMS who were starting DMT with these same costs for those who never used DMT. Over a 12-month follow-up

period, patients who started DMT had an average overall reduction of $1,794 in direct medical costs (inpatient, outpatient, physician, laboratory, physical therapy, and other services) and a lower average indirect cost of $801.[64]

A more recent study by Goldberg and colleagues[65] added additional insight. Goldberg analyzed the cost effectiveness of 4 DMTs in the treatment of RRMS over a 2-year period using data from pivotal randomized, double-blind, placebo-controlled trials. Cost-effectiveness was defined as a reduction in relapses (compared to placebo) and a delay in disease progression. Only direct costs were examined and observations were confined to the 2-year study period not extrapolated over a longer period of time. The study revealed that Rebif® (interferon beta-1a subcutaneous injection), Betaseron® (interferon beta-1b subcutaneous injection) and Copaxone® (glatiramer acetate injection) were more cost-effective as compared to Avonex® (interferon beta-1a intramuscular injection) ($80,589; $87,061; $88,310; $141,721; respectively). The reduced number and severity of relapses resulted in short-term budgetary impact that partially offsets the cost of DMT with the drugs studied.

Tappenden and colleagues[66] responded to a request from the Centers for Medicare and Medicaid Services (CMS) to evaluate the cost-effectiveness of drug therapy in the treatment of MS. Using a mathematical model designed to simulate the natural history of MS, Tappenden compared 7 active treatment options (including various dosage levels of interferon beta-1a and interferon beta-1b, and glatiramer acetate) to best support care in patients with RRMS or SPMS. The patient sample representing the Medicare population was drawn from the Sonya Slifka data set. EDSS scores were used to track disease progression and disability. In addition, each EDSS state was assigned a utility score which described the mean level of health-related quality of life (HRQL) associated with the degree of disability. Interestingly, the study revealed that costs for treatment with interferon beta-1a 44µg and interferon beta-1b 8 MIU were below $100,000 per quality-adjusted life-year (QALY) but only if treatment was stopped at EDSS 7.0. After this point, significant increases in the cost of care produced little additional health gain. While the authors speculate that treatment discontinuation guidelines could improve the cost-effectiveness of DMTs, they conclude that further research is needed.

## Copayments, Adherence, and Outcomes

Even for patients who have insurance, it has been estimated that the annual out-of-pocket expenses for MS are more than $3,000.[67] Rising copayments for DMTs increase the cost burden for patients and can lead to a significantly higher risk of medication discontinuation. A recent analysis of DMT use for patients enrolled in 8 Blue Cross/Blue Shield health plans[68] found that for those with out-of-pocket expenses above $200, the abandonment rate was 6-fold higher than for individuals with out-of-pocket expenses of $100 or less[68] **(Figure 5).**

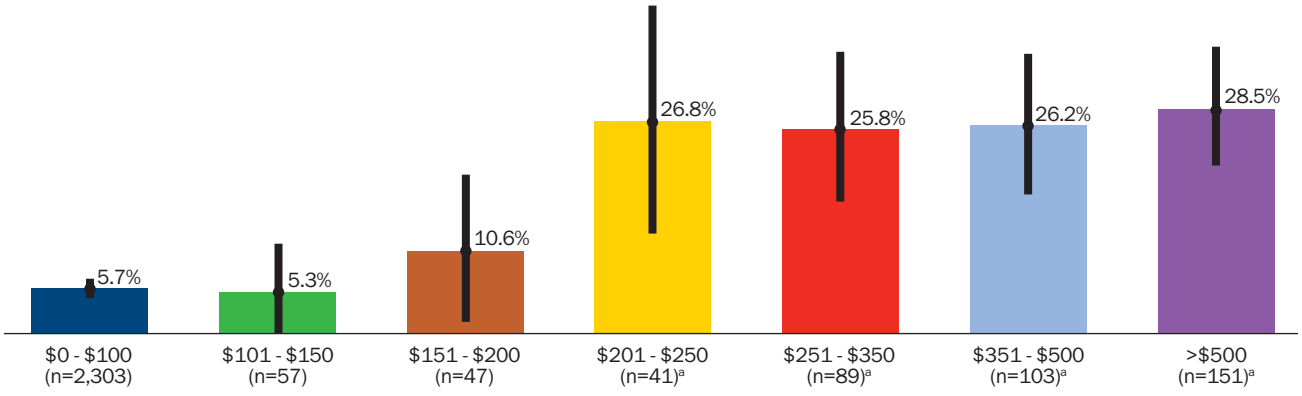
The decision of patients to stop using their medication may have adverse effects on various health outcomes. In other conditions (eg, cardiovascular disease), increasing patients' cost burden for prescription medication has been shown to boost hospitalization rates among adults who underused medications due to cost.[69] At the same time, relating adherence to disease activity in MS is complicated by patient age, sex, stage of disease, neutralizing antibodies, and the lag time between treatment discontinuation and relapse.[70] Although the effect of out-of-pocket costs on health outcomes has not been specifically examined in MS, decreasing adherence to interferon beta therapy has been associated with significantly increased risk of relapse.[70]

## Emerging Therapies

Many new MS therapies are in clinical development. Pivotal clinical trials to evaluate the safety and efficacy of cladribine and Gilenya™ (fingolimod) have been successfully completed. Applications for these 2 oral agents have been submitted to the FDA. In September 2010, Gilenya was the

## Figure 5

**Unadjusted Multiple Sclerosis Prescription Abandonment Rate by Out-of-Pocket Member Expense**




Source: Pearson chi-square test
[a]P < 0.001 compared with $0-$100 group.
Bars represent 95% confidence intervals.

*Gleason PP, et al. J Manage Care Pharm. 2009;15(8):648-58. Reprinted with permission.*

first oral agent approved by the FDA to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability for patients with relapsing forms of MS.[71] Cladribine is still under FDA review. Although the clinical trials have provided safety data concerning these 2 agents, their long-term safety is obviously not as well established as that for the currently approved DMTs, the first of which entered clinical practice in 1993.[72] These agents affect the immune system in a number of different ways, including the killing of lymphocytes (cladribine) and the suppression of lymphocyte migration (fingolimod).[31,73] As demonstrated by the experience with PML and Tysabri® (natalizumab), critical safety issues may not emerge until a significant number of patients have been treated over long periods of time. The putative link between PML and Tysabri was not detected until after the drug was approved by the FDA and launched. Thus, as is the case with any new treatment, the safety profiles of these two new drugs will require careful consideration on the part of prescribers. In particular, it will be important to consider the potential impact of the agent's mechanism of action on the immune system when determining a course of treatment.

### Cladribine

Cladribine is a purine nucleoside that confers increased resistance to the enzyme adenosine deaminase, resulting in accumulation of cellular deoxynucleotides and the selective killing of lymphocytes.[73] The phase 3 CLARITY clinical trial[9,11] examined the efficacy and safety of oral cladribine 5.25 mg/kg (n = 456), 3.5 mg/kg (n = 433), or placebo (n = 437) for 96 weeks. Compared with placebo, cladribine was associated with a significantly lower relapse rate, a smaller proportion of patients with relapses, and a more extended time to relapse (all $P < 0.001$). Cladribine was associated with a high rate of lymphopenia (26.7% versus 1.8% for cladribine-treated and placebo-treated patients, respectively), which was an anticipated effect of the drug's mechanism of action. Dermatomal herpes zoster was noted for 1.9% of patients with cladribine versus 0% with placebo, and uterine leiomyomas were noted for 1.0% versus 0.2%. Treatment was discontinued owing to adverse events by 5.8% of patients with cladribine and 2.1% with placebo. Five malignancies were noted in the cladribine groups, including one case each of ovarian, cervical, and pancreatic carcinomas; one malignant melanoma; and one case of choriocarcinoma after the end of the study.[9]

### Gilenya™ (fingolimod)

Fingolimod is an oral immunosuppressant that acts at the lymphocyte $S1P_1$ receptor to inhibit migration of lymphocytes from lymphoid tissues to CNS.[31] Two recent large clinical trials have evaluated the efficacy and safety of daily oral fingolimod at doses of 0.5 mg and 1.25 for the treatment of RRMS. In the FREEDOMS study,[13] both doses of fingolimod significantly reduced the mean annualized relapse rate ($P = 0.001$), likelihood of MS progression ($P = 0.02$), and MRI-related measures (gadolinium-enhanced lesions, new or enlarged T2 lesions, brain volume; $P<0.001$ at 24 months). The TRANSFORMS study[14] also demonstrated that both fingolimod doses significantly reduced relapse rates ($P<0.001$) in comparison with interferon beta-1a IM after 12 months.

In the placebo-controlled FREEDOMS study,[13] adverse events associated with fingolimod included bradycardia at initial dose for 9 of 425 patients (2.1%) in the low-dose fingolimod group vs 3 of 418 patients (0.7%) in the placebo group; atrioventricular block was noted for 2 patients (0.5%), vs 3 patients (0.7%) for the low-dose fingolimod groups and placebo, respectively. Elevated liver enzymes were noted for 67 of 425 (15.8%) patients in the low-dose fingolimod group vs 21 of 418 patients (5.0%) in the placebo group; mild hypertension in 26 patients (6.1%) and 16 (3.8%) for the low-dose fingolimod groups and placebo group, respectively. In TRANSFORMS,[14] bradycardia at initial dose was noted for 2 of 429 patients (0.5%) in the low-dose fingolimod group; atrioventricular block was noted for 2 patients (0.5%) for the low-dose fingolimod group, respectively. No cases of bradycardia or atrioventricular block were noted for the interferon beta-1a group (n = 431).

Investigational DMTs being evaluated in clinical trials for patients with RRMS include laquinimod, BMG0012, alemtuzumab, and teriflunomide. Manufacturers of these agents are expected to seek marketing approval in the U.S. over the next few years.

### Laquinimod

Laquinimod is an investigational oral immunomodulator that is in phase 3 trials for the treatment of MS. Its mechanism of action is believed to involve an anti-inflammatory effect caused by a Th1-Th2 shift in cytokines[74,75] and increased neurotrophic factors.[76,77] Data from the first 24-week phase 2 study in patients with RRMS found a 44% reduction in MRI active lesions with oral daily 0.3 mg laquinimod ($P = 0.0498$).[78] A subsequent 36-week, phase 2 study demonstrated improved MRI disease activity with laquinimod at a dose 0.6 mg in RRMS patients with highly active disease, along with a 40% reduction of mean ($P = 0.0048$) and 55% reduction of median cumulative Gd lesions (4.0 vs 9.0 for the placebo group).[79] A trend ($P = 0.0978$) for a 33% reduction in annualized relapse rate was also seen, although the study was not statistically powered to evaluate clinical symptoms.

The incidence of adverse events was similar in the 3 groups: 84.7% for laquinimod 0.3 mg, 77.4% for laquinimod 0.6 mg, and 82.4% for placebo. An increase in liver enzymes occurred more frequently in the laquinimod groups with 23 of 98 patients (23.4%) in the 0.3 mg laquinimod group; 35 of 106 patients (33.0%) in the 0.6 mg laquinimod group and 11 of 102 patients (10.8%) in the placebo group. Viral infections (herpes simplex, herpes zoster) were more common in the laquinimod 0.3 mg group; cough and dyspnea more common in the placebo group.[79]

### BG00012

BG00012 is an oral fumarate that produces anti-inflammatory and neuroprotective effects that have reduced clinical and MRI evidence of MS activity in some studies.[22] A recent phase 2 clinical trial[22] found that oral BG00012 taken 3 times per day significantly reduced several MRI measures of disease activity in comparison with placebo. Treatment tended to reduce the average relapse rate, although the study was not powered to detect a difference between groups for this outcome. Most common adverse events included abdominal pain and flushing.

In the BG00012 group receiving 240 mg 3 times a day, adverse events led to treatment discontinuation in 25% of patients.[22]

### Alemtuzumab

Campath® (alemtuzumab) is a monoclonal antibody against the CD52 cell-surface marker. Binding of alemtuzumab to this protein on T cells, B cells, and monocytes rapidly induces cell lysis and depletes these immune cell populations.[31] The CAMMS223 phase 2 clinical trial reported that alemtuzumab administered as a single once-yearly infusion reduced the MS relapse rate by 72% and 88% for the 12 mg and 24 mg alemtuzumab groups, respectively($P<0.0001$) compared with interferon beta-1a IM, and significantly reduced disease progression ($P<0.01$).[31] Alemtuzumab has a black-box warning for risk of serious and potentially fatal cytopenias and infusion reactions. It is also associated with severe, prolonged lymphopenias and risk of infection.[80] In patients with MS, it has been associated with immune thrombocytopenia purpura and thyroid disorders.[31]

### Teriflunomide

Teriflunomide is an inhibitor of pyrimidine synthesis with antiproliferative activity that produced anti-inflammatory effects in animal models and initial human studies of MS.[31]

In a 36-week Phase II study in patients with RRMS or SPMS receiving low (7 mg) or high (14 mg) doses of teriflunomide or placebo, participants showed a significant decrease in the number of active lesions (new T2, enlarging T2 or gadolinium-positive T1 lesions) after 12 weeks of treatment.[31]

The phase 3, placebo-controlled TEMSO clinical trial was completed in July 2010.[81]

### RRMS Therapies: Potential Impact on the Immune System

Like Tysabri® (natalizumab) and Novantrone® (mitoxantrone for injection concentrate), some investigational agents reduce the number or distribution of immune cells.[6,7] One potential limitation of approaches that interfere with immune surveillance is an increased risk of certain immune-mediated adverse effects. For example, reductions in circulating immune cells have been associated with serious opportunistic infections and with malignancies. It should be noted that some consequences of reduced immune function may not appear until after extended treatment. For example, in recent years the unexpected occurrence of PML with Tysabri demonstrated that even large phase 3 studies cannot provide the assurance of long-term safety data. The potential long-term consequences of this type of mechanism are unknown. In contrast, Copaxone® (glatiramer acetate injection) is believed to shift the body's T lymphocyte population from a pro-inflammatory to an anti-inflammatory profile, and it may also promote the production of neurotrophic factors.[33] Although not systematically studied, Copaxone has not been associated with diminished tumor surveillance or defenses against infection. In theory, Copaxone could interfere with immune function.[1] The beta interferons have no known negative impact on the immune system.

## Trends in the Management of Specialty Pharmaceuticals

The number of specialty drugs in use has increased markedly over the last decade, from approximately 30 in the mid-1990s to more than 200 today.

Growth in specialty pharmacy spending is expected to continue at an annual rate of approximately 10% over the next several years, and may exceed 40% of health-plan drug expenditures by 2030.[82] Specialty pharmaceuticals have usually been defined as high-cost injectable biologic agents, but high-cost oral agents that may require close supervision and monitoring might also be classified as specialty drugs.[83] In a recent survey of the MS pharmaceuticals market, Decision Resources, a company specializing in healthcare analysis and data, forecasts substantial growth in the use of monoclonal antibodies, oral immunomodulators, and oral immunosuppressants, with sales growth in these 3 categories expected to

exceed $2.5 billion per year in the U.S. This will be offset partially by an expected decline of approximately $1.0 billion annually for recombinant interferons; peptide and polypeptide therapies are projected to decline by an estimated $100 to $200 million.[84]

Depending on the degree of immune impact, the use of some oral agents may require oversight by managed care pharmacists and other health-care professionals. Issues may include evaluating the potential for adverse events when using agents that have novel mechanisms of action and that have been in clinical trials for a relatively short period of time, and for which the risk-benefit ratio may be less well known than those of existing DMTs.[22] It will also be important to develop management and payment plans for patients who are well controlled on current therapy but who want to switch from an injectable drug to an oral agent.[22]

### Copaxone Indication

Copaxone® (glatiramer acetate injection) is indicated for reduction of relapses in patients with relapsing-remitting multiple sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

### Important Safety Information

Most common adverse effects were injection site reactions (including lipoatrophy and, rarely, skin necrosis), vasodilatation, rash, dyspnea, and chest pain. Patients should be advised to follow proper injection technique and to rotate injection sites daily.

About 16% of patients experienced an immediate postinjection reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria). The symptoms were transient and self-limited, and did not require specific treatment.

Transient chest pain was noted in 13% of Copaxone patients (vs 6% placebo); no long-term sequelae.

## Summary and Conclusions

MS is a chronic autoimmune disease with a relatively young age at onset that is characterized clinically by frequent acute episodes of neurologic impairment and a generally progressing course over time. The pathogenesis of MS is complex, and includes acute CNS inflammation, demyelination, axonal transection, and cerebral atrophy. The economic burden of MS is significant, and costs increase with relapse frequency and intensity and with worsening disease. DMTs such as Avonex® (interferon beta-1a intramuscular injection), Betaseron® (interferon beta-1b subcutaneous injection), Copaxone® (glatiramer acetate injection) and Rebif® (interferon beta-1a subcutaneous injection) have long been used to treat MS, and have well-established safety and tolerability profiles. Tysabri® (natalizumab) and Novantrone® (mitoxantrone for injection concentrate) are generally reserved for patients who have not responded adequately to other therapies, and are associated with potentially serious adverse events. The treatment of MS is rapidly becoming more complex as a growing number of newer agents with novel immune-mediated mechanisms of action progress through late-stage clinical trials. Novel oral agents and potent immunosuppressants may provide additional alternatives for patients with MS, although the long-term safety of these agents is not yet well defined. Initial studies have demonstrated promising results for some of these agents, but understanding their unique safety and tolerability profiles is likely to be an important issue for managed care.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## WHEN THEY CAN SEE YOUR SYMPTOMS

**by Marcella Durand**
Associate editor, *Momentum* magazine
**A publication of the National Multiple Sclerosis Society**

Cindy Miller realized that her MS had become visible to others at a very bad time. Namely, in a crowded elevator, on her way to her office.

"A co-worker asked me what in the world was wrong with me," Miller recalled. "I told her I was tired."

But it didn't end there. "About two weeks later, I decided to start using a cane. I saw her again—the same person!—in the same elevator and she asked why I was using a cane."

Miller tried to laugh it off with a joke. "It was no big secret—I had already disclosed to people I worked directly with, but I wasn't ready to tell the entire story in an elevator."

Miller had just experienced what many people with visible MS symptoms go through daily—stares, intrusive questions, or unwanted advice. While she was able to fend off her interrogator at the time, her MS had entered the public arena—and she was going to have to learn how to deal with that.

### Telling visible from invisible

"Visible symptoms are just that—visible," said Randall T. Schapiro, MD, author of *Managing the Symptoms of Multiple Sclerosis*. "You can't hide."

Dr. Schapiro thinks of visible symptoms as symptoms that get in the way of function. So he includes dizziness and numbness, along with tremor, spasticity, loss of balance, or speech difficulties. But he admitted there's no easy division between invisible symptoms and visible ones.

"We may think of bladder symptoms as invisible, but when you have to run to the bathroom because you're leaking—that's visible," he said. Symptoms like fatigue, weakness or cognitive difficulties can shade from invisible to visible. In addition, fatigue can worsen many other symptoms, making them become visible. "If you walk to the grocery store instead of using a scooter or cart, you may get tired, lose your balance and fall," said Cindy Gackle, OTR/L, MSCS, an occupational therapist at the University of Minnesota Medical Center, Fairview. "Falling is certainly visible. Symptoms are all intertwined."

*"Assistive devices can be the most visible sign that a person has MS. And that is one of the big reasons why people delay using them."*

### Playing the head game

Miller calls it the "head game." She used to play with the thought that her doctors had made a mistake when she was diagnosed in 1986. When her symptoms eventually became visible, 10 years after diagnosis, "I tried to deny that I needed a cane, until I couldn't ignore it anymore," she said. "It started with left-foot drop. It dragged at first only when I was tired, but after a time it started dragging all the time," Miller remembered. "I'd hold onto walls, thinking no one would notice. People with MS do this all the time—you can convince yourself that nobody notices, but they do."

### Putting the "assist" into assistive devices

Assistive devices can be the most visible sign that a person has MS. And that is one of the big reasons why people delay using them.

For Miller, it took a rude question in an elevator to get her moving. "The doctor said an ankle foot orthosis would make me more stable, but I really resisted wearing it," she said. "Then I used it and I walked so much better I couldn't believe it."

But, she admitted, change never comes easy. Each time she has changed devices—from a cane to crutches to a scooter to a wheelchair—she felt as though she was starting all over again. "You never get over that self-consciousness. You can feel people you don't know watching you—people are looking at the device rather than looking at your face. Even now, after five years, I would be lying if I said I'm not bothered at all by people looking at me in a wheelchair. It's very hard to learn how to cope with that."

But learn to cope she has. "All you can do really is tell yourself that the assistive device is there for a reason.

It's not something to attract attention or be embarrassed about. You actually function better when you use those devices. It's what you need to live your life."

## Honesty can be the best policy

Miller chose not to talk about her MS in an elevator at the whim of a stranger. But, that said, trying to hide the unhideable can lead to embarrassment, anxiety, stress and, worse, to avoiding tools that could help.

"I'm not trying to tell you if you fall down, you're not going to be embarrassed. But if you're honest about why you fell, at least people don't think you've been drinking or taking drugs," Dr. Schapiro said. "When your symptoms are visible and you're trying to hide them, as some people with MS do, the stress level rises. And when you're trying to hide symptoms, you can't ask for accommodations," he added. "But you can make decisions about some accommodations once you come to accept the symptoms. So it becomes really important to get there."

Cindy Gackle sees people with tremor or weakness who stop going out to eat with friends because it's too difficult to use regular tableware. "There is adaptive tableware that can help. In fact, there are many tools to use at different times for different activities," she said.

## How to ask for (and get) help

"I often ask people to try an experiment," Gackle said. "I ask them to pick something that they need help with, but find it hard to ask, and practice until they feel successful about asking." She encourages people to think about the big picture and prioritize. "For instance, if vacuuming is strenuous and challenging, asking for help with it could mean they'd have energy for something more important."

Put yourself in someone else's shoes, she recommends. "If you had a friend or family member with similar difficulties, you would want to help." Then she laughed. "It's so much easier to offer help than to accept it!"

An interesting study on "Visible vs. Invisible Symptoms of MS: Which Cause More Distress?" published in the *Journal of Neuroscience Nursing* last year, found that invisible symptoms, particularly pain and depression, were more predictive of distress. The researchers noted that "people with invisible MS symptoms may anguish over whether to forgo needed assistance and accommodations or let others know about these symptoms and possibly elicit expressions of disbelief, rejection, humiliation, or disapproval."

*"Just as there are many adaptive devices, there are many coping strategies for visible symptoms."*

So, if there is an upside to visible symptoms, besides using a handicapped parking spot without risking reproaches, it might be not having to choose to let the world know.

## The right attitude

Just as there are many adaptive devices, there are many coping strategies for visible symptoms. Cindy Miller likes turning her symptoms into opportunities to advocate.

"I advocate for people with visible symptoms to be accepted, and I like to teach people why someone would need assistive devices," she said. "When people express interest, hopefully it's just curiosity. But if they're making a judgment, that's their problem, not mine." If she sees a child, she waves and smiles to let them know, "I'm a person, too."

But more than anything, Miller knows the right attitude helps her most of all. "I could either live life angry and miserable and make everyone around me that way too, or I could choose to make the best of my problems," she said. "That's the one thing you can control—you can control your reactions to MS. No matter what it throws in front of me, I can find a way to work around it. I've become an expert problem-solver. I truly believe you come up with ideas you'd never come up with if you were still able to do everything."

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## NO SMALL THING

**by Sheri Horn Hasan**
*Writer, Professional Astrologer, and Patient Advocate*

Numb from the waist down and having difficulty walking — that was my condition when I first heard the words "multiple sclerosis."

I was told I had a back tumor, or some form of general encephalitis, or maybe MS. My back MRIs showed no tumor, so ... a weekend in the hospital receiving methylprednisolone infusions and one spinal tap later, the diagnosis was conclusive.

Now what? Go home, learn all I can, and pray I don't end up in a wheelchair in ten years?

While I lived then in absolute terror of the prediction by not one, but two well-respected MS neurologists that I might relapse within three to four months of my initial diagnosis — I know now that I defied the odds. *Not* only did I not experience a relapse within the months following my diagnosis; I have been relapse-free for more than ten years — ever since I first heard the dreaded words "multiple sclerosis" in March 2000.

Since then, I attribute my "positive" experience with this incurable disease to immunomodulatory drug therapy, my decision to be proactive, and a positive mindset. This doesn't mean I escaped such symptoms as overwhelming fatigue, vertigo, tingling, numbness, and bouts of optic neuritis during the first two years or so after my diagnosis, or that it did not take nearly three full years for the burning in my right leg to subside slowly before it all but disappeared.

*"At the time of my diagnosis, the National MS Society had already released its 1998 statement that anyone diagnosed with relapsing-remitting MS should initiate drug therapy as soon as possible because medical research had proven that MS progresses regardless of the manifestation of symptoms."*

The realities of the disease were tough at first to digest. It was even tougher to believe that I would at some point fully recover the feeling in my lower body and be able to walk normally and take care of my then almost-five-year-old son without succumbing to total exhaustion. I resolved early on to become my own advocate and to act as decisively as possible.

After doing my own research on MS drugs and soliciting the opinion of another MS specialist, I chose a different MS drug than the one originally recommended by the doctor who diagnosed me. Terrified at the prospect of a relapse, I realized that I had to become an active participant in decisions concerning my treatment. Claiming the choice to determine which drug to take turned out to be instrumental in my ability to maintain control of my life and to face the threat posed by this unpredictable disease.

And I realize now that I am representative of a new generation of MS patients.

I credit my choice of drug therapy and my life decisions with allowing me to lead a normal life, nowhere near as badly affected by my MS as my original MRI suggested.

While I pray for a cure for MS, I also count my blessings — which include coverage, by my insurer, of my drug of choice at a reasonable co-pay, and the benefit, at times (depending on my insurer), of an MS wellness and education program.

Finally, ongoing MS research gives me the greatest hope that, when I picture my future, it does not contain a wheelchair.

And believe me — that is no small thing.


# Managed Care Organizations

**Thanks to the following pharmacy professionals and medical directors who contributed to this article:**

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## Overview

*The Multiple Sclerosis Trend Report 2nd Edition* reflects the views of surveyed managed care organizations (MCO) on the most relevant and most pressing aspects of managing multiple sclerosis (MS). Survey respondents were asked to reflect on pharmacy benefit design for managing MS; cost and utilization management strategies; the use of specialty pharmacy, outcomes data, and head-to-head studies of drugs to treat the condition; and other trends in managing the illness. Respondents also expressed their views on a variety of therapies that may soon be made available for patients who are living with MS.

Of the 109 respondents to this survey, 40% are HMO/PPO pharmacy directors; 27% are clinical pharmacists; and 13% are HMO/PPO medical directors. Geographically diverse, respondents mainly represented the New England area (24%), the Midwest (19%), and the Mountain States (19%). The least represented area (10%) was the south central region of the United States (**Table 1**). In regard to plan type, regional plans (42%) and single-state plans (39%) had the largest representation. Slightly more than one-fifth of the respondents (23%) represented national plans.

Respondents said that most of their members (72%) are in fully insured plans; 22% are in self-insured employer groups; 6% were covered under other options. Seven percent of the surveyed plans said they serve fewer than 10,000 members. Four percent serve from 10,001 to 25,000 members; 7%, 25,001 to 50,000 members; 8%, 50,001 to 100,000 members. Twenty percent serve between 100,001 and 250,000 members; 10%, 250,001 to 500,000 members; and 14%, 500,001 to one million members. Twenty-nine percent of the respondents said they serve one million members or more.

Of the plans represented in the survey, an average of 59% work with commercial products, 20% work with Medicare products, 17% with Medicaid products, and 4% with other types of products. Most plan members have a pharmacy benefit (**Figure 1**).

The number of plan members with MS ranged from fewer than 50 to as many as one thousand: 22% of the surveyed plans have fewer than 50 members with MS; 12%, 51 to 100 members; 8%, 101 to 250 members; and 9%, 501 to 1,000 members.

As there is no cure for MS, treatment is aimed at managing relapses and symptoms and at modify-

**Table 1**

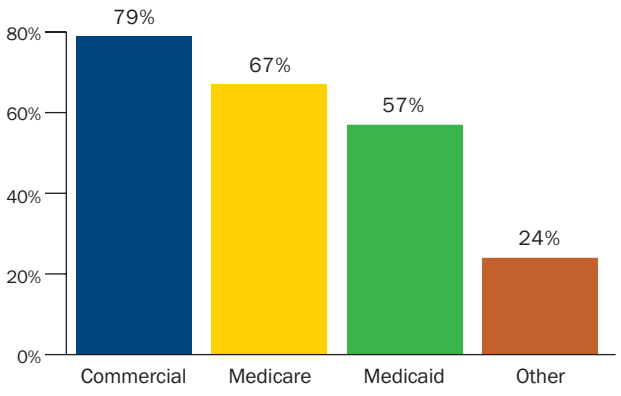
**Which region(s) do your responsibilities include either wholly or partially?**

| | Response Percent |
|---|---|
| **New England** (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) | 24% |
| **Mid-Atlantic** (New Jersey, New York, Pennsylvania) | 14% |
| **South Atlantic** (Delaware, D.C., Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia) | 14% |
| **South Central** (Alabama, Arkansas, Kentucky, Louisiana, Mississippi, Oklahoma, Tennessee, Texas) | 10% |
| **Midwest** (Illinois, Indiana, Michigan, Ohio, Wisconsin) | 19% |
| **Plains** (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota) | 12% |
| **Mountain** (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming) | 19% |
| **Pacific** (Alaska, California, Hawaii, Oregon, Washington) | 14% |

ing the disease. The most widely used therapies began to emerge less than 20 years ago. In 1993, the U.S. Food and Drug Administration (FDA) approved Betaseron® (interferon beta-1b subcutaneous injection). Since then, six other drugs that affect the course of MS have won approval. Four of them are self-administered injections: Copaxone® (glatiramer acetate injection); Avonex® (interferon beta-1a intramuscular injection), Rebif® (interferon beta-1a subcutaneous injection), and Extavia® (interferon beta-1b subcutaneous injection). Two drugs administered by infusion — Tysabri® (natalizumab), a monoclonal antibody medication, and Novantrone® (mitoxantrone for injection concentrate), a chemotherapy drug which acts as an immunosuppressant — have also received FDA approval. The FDA is currently reviewing cladribine, an oral nucleoside. Gilenya™ (fingolimod), an oral immunosuppressant was approved by the FDA in September 2010. As such, the questions and data in this document do not reflect Gilenya™.

**Figure 1**

**What percentage of members enrolled in each type of product have pharmacy benefits in 2010?**




Guidelines for the treatment of MS were developed in 2002[1] and, at present, are being updated by the American College of Neurology. The response has not been unanimously positive. For instance, one medical director from a major health plan believes the current guidelines are vague; however, he anticipates that they may become more explicit as new oral formulations come into use.

MS, rheumatoid arthritis and other autoimmune disorders, and cancer remain the 3 largest contributors to the specialty drug trend.[2] In 2009, MS was the greatest contributor despite its relatively low prevalence rate of between 250,000 and 350,000 physician-diagnosed known cases in the U.S.[2,3]

## Balancing Needs and Costs

Per-member per-year costs for MS were expected to rise by 84.6% over the next three years as of 2009.[4] James Kenney, pharmacy operations manager at Harvard Pilgrim Health Care, said that while less than 1% of his members have MS, the plan's drug spend for MS is 2%, and managing the condition is one of the plan's important concerns.

Understandably, the high cost of MS drugs has made managing the condition a priority for many

managed care organizations. "It is one of our top 10 concerns," said Richard Wagner, PharmD, director of Kaiser Permanente in Laguna Niguel, CA. "The cost of each unit of therapy is growing more quickly than the number of people with MS, which is the primary reason for a higher cost trend for MS. Small increases in utilization also drive costs," he explained.

Irene Girgis, PharmD, director of pharmacy services for Colorado Access, said the greatest challenge in managing MS is the dual reality that there is no cure for the condition and that every patient needs to be on some kind of drug to control symptoms. She is always mindful of the tension between clinical outcomes and costs. "We want to cover the most optimal product, not necessarily the least expensive," she said. "If a patient responds well to a specific drug, [its use] would ideally decrease costs in the long run by preventing adverse episodes that would require attention and money."

Controlling the high costs of MS drugs ranks high on the list of challenges in managing the category. Dr. Wagner said that Kaiser Permanente uses a two-tiered formulary, for generic and branded drugs, to avoid the burden of too much cost sharing. Utilization and costs, he said, are controlled through the use of preferred therapies, clinical guidelines, and electronic medical records, and by providing flexibility for patients in their choice of medications.

A pharmacy director for a regional office of a national health plan finds that dosing of MS drugs requires continuous evaluation, and that another set of challenges arises from the necessity of relying on the self-reporting of patients to measure their response to treatments.

Choosing a course of treatment may pose the greatest challenge. "Patients are often offered information via videos and asked to make a decision based on that information," he said, and if that isn't puzzling enough, it is difficult to draw distinctions in efficacy and cost among the five first-line drugs.

"Of course, patients have no idea how they will react to each drug," he explained. "Physicians all have different opinions about which drug to take, and there is no real standard for monitoring patients. All this has led our plan to leave it to physicians and patients to decide on the course of treatment."

Most respondents (an average of 79.4% for all five drugs) reported that coverage of the first-line self-injectables falls under the pharmacy benefit, while 63% of respondents said that Tysabri® (natalizumab), an infused product, is covered under the medical benefit. Kenney expressed surprise that as many as 31% of respondents said they place Tysabri under the pharmacy benefit. Twenty percent of the respondents said they do not cover Extavia® (interferon beta-1b subcutaneous injection), while the vast majority of plans cover the other first-line drugs (**Figure 2**).

Of the plans represented in the survey, 26% grant preferred status to Avonex® (interferon beta-1a intramuscular injection); 33% to Copaxone® (glatiramer acetate injection); 17% to Rebif ® (interferon beta-1a subcutaneous injection); 13% to Betaseron® (interferon beta-1b subcutaneous injection); and only 1% to Extavia. Tysabri never falls on the preferred product list. Fourteen percent of respondents do not cover Tysabri. Its label states that the drug is "generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy."[5]

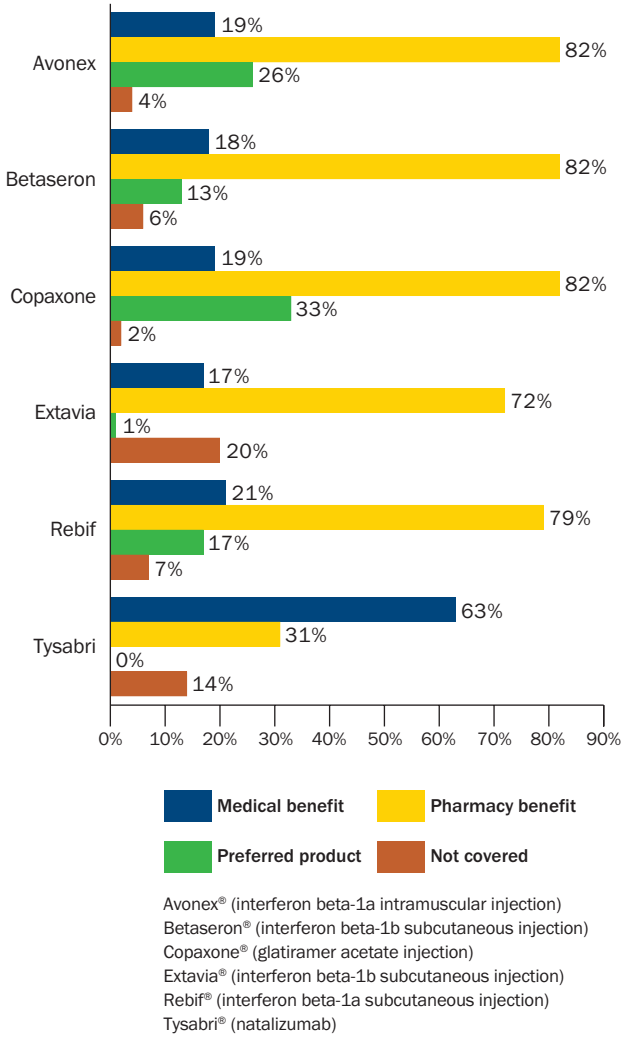
Most plans (87%) said they will cover a new oral immunomodulator under the pharmacy benefit. Only 7% said they will cover it under both the pharmacy and the medical benefits (**Figure 3**).

## Use of Specialty Pharmacy Providers

Among the 76% of respondents who said they use specialty pharmacy providers for MS drugs (**Figure 4**), 29% mandate the use and 45% make the use voluntary. Twenty-seven percent said the decision whether to use specialty pharmacies depends on benefit design (**Figure 5**).

## Figure 2

**How are the following immunomodulating drugs covered in your benefit design for most of your members?**




Avonex® (interferon beta-1a intramuscular injection)
Betaseron® (interferon beta-1b subcutaneous injection)
Copaxone® (glatiramer acetate injection)
Extavia® (interferon beta-1b subcutaneous injection)
Rebif® (interferon beta-1a subcutaneous injection)
Tysabri® (natalizumab)

Mandating the use of specialty pharmacies may be at odds with the "any willing provider law." In states that have enacted it, this law requires managed care organizations to contract with any provider who agrees to meet the terms and conditions of the organization,[6] whether or not that provider meets both the quality standards and the geographic access needs of the health plan.

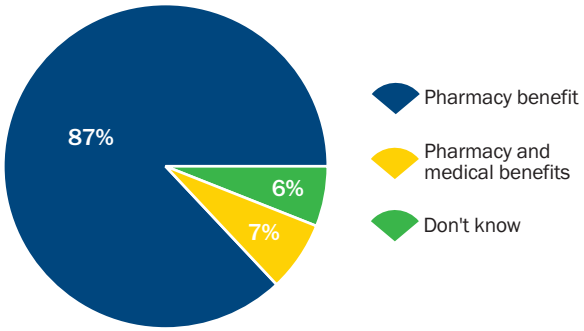
A regional medical director at a large national health plan said that his organization allows any pharmacy to carry MS drugs, and reimburses as it would a specialty pharmacy. "We don't force the issue," he said. In fact, the plan allows physicians to buy and bill Tysabri.

Since Colorado Access includes a Medicare plan, the Centers for Medicare and Medicaid Services (CMS) allows beneficiaries to buy specialty products from any pharmacy, said Dr. Girgis, adding that Colorado Access encourages members to take advantage of specialty pharmacies, which also provide support services.

One representative of a national plan said he favors mandatory use of specialty pharmacy because the requirement saves money while providing services such as patient education and special handling of medications. He said that specialty pharmacies also do a better job of reporting and are more responsive to patient concerns. His plan allows members to use a local pharmacy, though most of these phar-

## Figure 3

**If the FDA were to approve an oral immunomodulating drug for MS, how would it be covered by your organization?**




## Figure 4

**Does your organization use specialty pharmacy providers for MS drugs?**

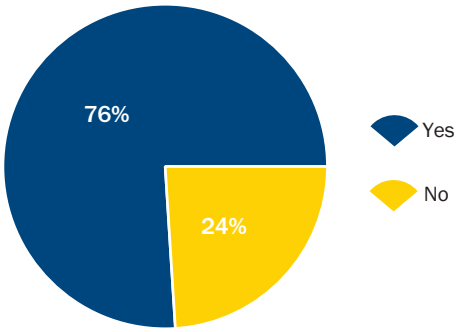
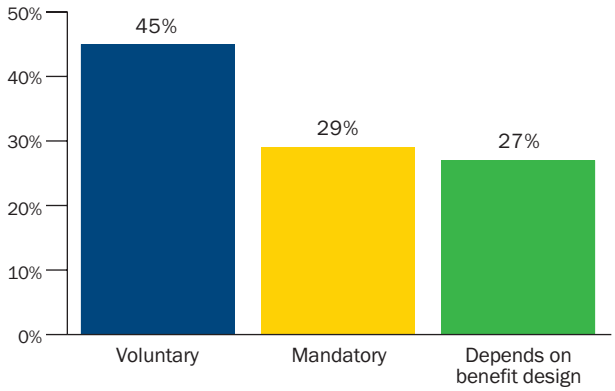


**Figure 5**

**Is the use of specialty pharmacies by prescribers voluntary or mandatory?**




macies do not carry MS drugs, since the demand is small. He noted that many members of the plan he represents are familiar with their local pharmacies and prefer to use a retail store.

Harvard Pilgrim Health Care does not have a specialty pharmacy tier on its formulary, and it uses specialty pharmacy providers without making their use mandatory. "Specialty pharmacies offer deeper discounts than retail and provide care management and quality distribution services, such as ensuring there is sufficient product on hand," said Kenney.

## Placing Restrictions

Prior authorization ranked highest among constraints that plans put in place for covering the six available MS drugs, averaging 58%. Limiting use to FDA-approved indications averaged 47% for all drugs; setting quantity limits, 38%; and restricting the pharmacy network, 29%. Most plans cover the six drugs, but few conduct therapeutic interchange (ie, substituting a therapeutically equivalent drug for the one prescribed). On average, 14% have no restrictions for the six drugs; Tysabri faces the most limitations (**Table 2**).

Dr. Wagner noted that because Extavia has been grandfathered in, it follows the pathway for biologics that was put in place before the new biosimilar regulation was established by the Patient Protection and Affordable Care Act (PPACA). The new law may require biosimilars to provide data from analytical, animal, and clinical studies to demonstrate their similarity.

Acknowledging the problem of cost, Sarah Kachur, PharmD, clinical pharmacy manager at Johns Hopkins HealthCare in Baltimore, applauded the alacrity with which patients are receiving care, soon after diagnosis. In regard to the use of restrictions,

**Table 2**

**For the following immunomodulators, which restrictions are currently in place for the majority of your members?**

| | Avonex | Betaseron | Copaxone | Extavia | Rebif | Tysabri |
|---|---|---|---|---|---|---|
| Prior authorization | 61% | 58% | 56% | 53% | 56% | 66% |
| Limit use to FDA-approved indications | 51% | 47% | 48% | 40% | 47% | 48% |
| Quantity limits | 42% | 40% | 42% | 37% | 39% | 29% |
| Dosage limits | 47% | 46% | 46% | 35% | 42% | 30% |
| Restricted pharmacy network | 31% | 29% | 30% | 27% | 30% | 25% |
| Prescribing restricted to specialist | 23% | 24% | 25% | 23% | 24% | 31% |
| No restrictions | 16% | 16% | 20% | 11% | 15% | 6% |
| Step therapy | 12% | 19% | 9% | 19% | 11% | 19% |
| Not covered | 5% | 6% | 2% | 17% | 6% | 11% |
| Therapeutic interchange | 2% | 6% | 2% | 6% | 2% | 2% |
| Not applicable | 2% | 1% | 2% | 4% | 4% | 8% |

Avonex® (interferon beta-1a intramuscular injection); Betaseron® (interferon beta-1b subcutaneous injection); Copaxone® (glatiramer acetate injection); Extavia® (interferon beta-1b subcutaneous injection); Rebif® (interferon beta-1a subcutaneous injection); Tysabri® (natalizumab)

she said that "Prior authorization is not too effective as a utilization management tool because there are very few denials for these drugs, although we do encourage use of agents that are on [our] formulary."

Colorado Access uses step therapy, which Dr. Girgis said allows the plan to funnel utilization to more effective products or to those that cause the fewest side effects. For example, the insurer uses the edits to allow members to use Betaseron® (interferon beta-1b subcutaneous injection) after documented prior use of the 2 preferred agents. The same functionality may potentially be used with Ampyra® (dalfampridine), to increase mobility if they are already taking an interferon or Copaxone® (glatiramer acetate injection), however that is still under debate. She said that Colorado Access also applies quantity limits to MS drugs.

"We are concerned that without quantity edits in place, claims may not be properly adjudicated if a provider should accidentally charge for more drugs than are actually distributed," said Dr. Girgis. "We think of ourselves as gatekeepers, the source of ultimate approval for what drugs are distributed, in order to avoid errors and drive appropriate adjudication."

## Partnering with Drug Manufacturers

Plans described the ways in which developing relationships with pharmaceutical manufacturers proves valuable to their organization: patient education (59%), individualized self-injection training (56%), and MS-certified nurse care manager phone advice (48%) headed the list (**Figure 6**).

Dr. Wagner said Kaiser Permanente does not participate in MS support programs with pharmaceutical companies because it [Kaiser Permanente] is "more focused on the disease than a particular brand." He does, however, find value in self-injection training and education.

Harvard Pilgrim also does not participate in manufacturer support programs, although Kenney said they can be helpful in managing a complex condition like MS.

Some members of the employer panel said they endorse phone support by nurse care managers, who are available 24/7, while others noted that physicians, specialty pharmacies, and other organizations provide the same patient training and education that pharmaceutical companies offer.

## Patient Outcomes Data / Head-to-Head Studies

Fifty-eight percent of respondents said they do not use patient outcomes data to determine appropriate switching among MS agents. Fifty-eight percent of

**Figure 6**

**Which features of the patient-support programs provided by pharmaceutical manufacturers are of the greatest value to your organization?**

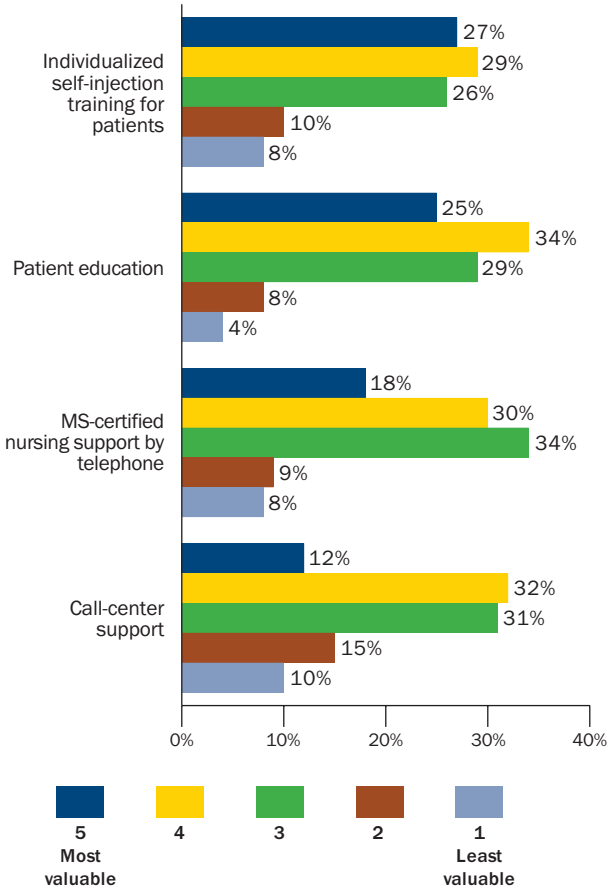
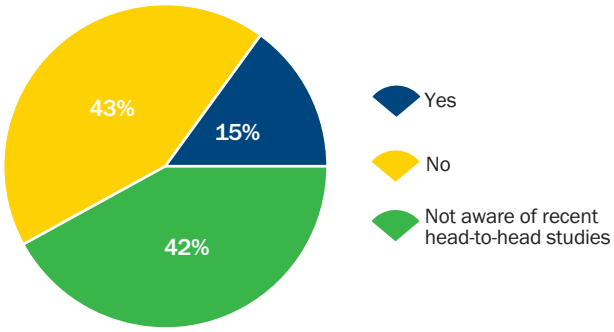


**Figure 7**

Have recent head-to-head studies involving various immunomodulating agents affected your formulary placement of MS products?




respondents also said they use data to determine which MS drugs should be on a preferred list. Forty percent of plans said they collect and assess data to inform contracting discussions with manufacturers.

Dr. Wagner said he finds it difficult to rely on outcomes data as a basis for decision making with MS, because they are much less quantitative for this disease than for conditions such as high cholesterol or blood pressure.

Most thought leaders on the panel agreed with Dr. Wagner that patient outcomes data are not yet sufficiently robust to drive decisions on MS drug use or contracting. Most panel members said they believe that if more data were available, the information would be more likely to influence formulary decisions than contracting negotiations. Kenney called the prospects for using patient outcomes data a mixed bag that will vary in accordance with the sophistication of each health plan.

David Fox, PharmD, clinical pharmacy manager at Florida HealthCare Plans in Daytona Beach, said it is difficult to manage outcomes data with so few MS patients. He questioned the reliability of the information, adding "With price parity for MS drugs, it really doesn't matter anyway."

While Dr. Kachur said that insurers request head-to-head studies, survey respondents reported only a fraction (15%) use them in making decisions on formulary placement. Of those 15%, one-half modified prior authorization criteria and one-half selected preferred MS products. Forty-two percent said they are not cognizant of recent head-to-head studies involving immunomodulating agents. (**Figure 7**). (See page 15 for more information.)

"Comparative information is the holy grail," Dr. Wagner said. He believes that head-to-head studies have the potential to affect certain decisions if they are significant and prove long-term effectiveness.

Dr. Girgis said it is difficult to rely on studies to determine effectiveness because reactions to MS drugs vary so much from one patient to another. On the other hand, Dr. Fox said that were a head-to-head study to prove one drug superior to another, it would affect formulary placement.

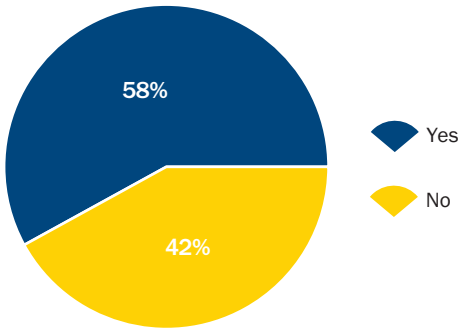
## Approving Concurrent Drug Treatment

Although various combination therapies are used in clinical practice, the available data are insufficient for guiding clinical decision making in regard to whether an agent added to a primary drug will have any effect or even an adverse effect.[7]

Fifty-eight percent of respondents said their organizations allow concurrent treatment with more than 1 FDA-approved immunomodulating drug (**Figure 8**). In extended comments, 55% of respondents said they impose no restrictions on choices, while 12% agreed that clinical guidelines, FDA approval, and mainstream literature may influence restrictions. Twenty-one percent of respondents said they designate certain combinations that may be used, while others said they consider requests case by case or rely on prior authorization or the judgment of a neurologist.

**Figure 8**

**Does your organization allow concurrent treatment with more than 1 of the FDA-approved immunomodulating agents for MS?**




One pharmacy director questioned whether the 58% of respondents who said they allow concurrent treatments have sufficient evidence to make these decisions. To him, combination drugs suggest a duplication of therapy that does not necessarily produce a better outcome. Dr. Fox agreed that there is insufficient evidence to determine the value of concurrent therapies. Members of the panel suggested that the use of two drugs in the same class does not make sense.

Dr. Wagner said there is not much discussion about the use of combination therapies, but that as new products enter the marketplace – especially oral drugs that affect the mobility of MS patients – they would be approved as supplementary medications at Kaiser Permanente. "We would not cover two drugs in the same class," he said, "because it would not only double costs but could lead to concerns over safety. Combinations may make sense therapeutically, but it is necessary to balance effectiveness and cost at the same time." He said that Kaiser Permanente relies on its physicians, who have established relationships with patients in the plan's integrated health-care system, to make the best decisions based on retrospective peer reviews.

An interview with a large national health plan revealed that it covers dual therapy if there are no resulting adverse reactions and if patients' symptoms are severe enough to warrant the use. The plan does not yet have a protocol in place for covering the use of Tysabri® (natalizumab) in conjunction with other primary MS drugs, owing to the increased risk of progressive multifocal leukoencephalopathy that is associated with its use.

## A Moratorium on New Drugs?

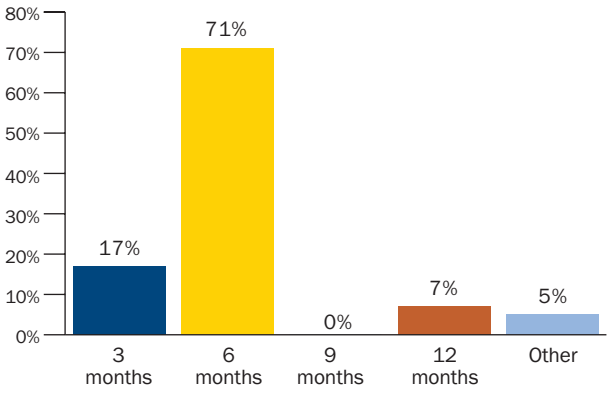
Sixty-one percent of respondents said they do not place a moratorium on a new molecular entity before they initiate coverage; 39% do require a moratorium for this purpose. "[Kaiser Permanente] will cover a drug immediately if it is seen as valuable," Dr. Wagner said. "We are looking at some desperate patients, so even if there isn't enough information, we are willing to take a chance," he added.

Seventy-one percent of the plans that establish a moratorium on new drugs said they wait six months before providing coverage (**Figure 9**).

A medical director at one national plan said it imposes moratoriums on new molecular entities for MS only if there is an indication that a drug may pose safety problems. In that case, the new drug will require prior authorization but will

**Figure 9**

**How long is the moratorium your organization requires for a new molecular entity?**



be covered. Companies can always change the formulary tier for a new drug once they have made an initial decision.

## Plan Sponsors

Respondents said that plan sponsors (ie, employers) expressed various concerns in regard to MS in the work environment: increased medical expense as the disease progresses (57%), loss of productivity (40%), absenteeism (38%), and prevention of early disability (36%). Dr. Wagner said it isn't easy to measure productivity and absenteeism, but that more communication between employers' human resource departments and health plans could facilitate a better understanding of the measures.

Employers are less concerned than the plans believe they are, said the panelists. "I don't really see much concern," Kenney said, adding that "only a small number of members have the condition." Dr. Kachur expressed surprise that there appears to be little focus on the impact of MS on productivity, absenteeism, increased medical costs, and other factors. "There seems to be a lack of connection between the condition and disability," she said.

## Nonpharmacologic Therapies

In assessing the use of nonpharmacologic therapies for MS, 91% of plans said they always, almost always, or sometimes cover physical therapy; 71% cover occupational therapy; and 70% cover speech therapy. (**Table 3**).

Many of the panel members said the same rules apply in their plans for covering nonpharmacologic therapies for MS as for other conditions. Some noted that medical procedures for MS are more likely to be covered than other therapies. Forty-two percent of respondents said they always, almost always, or sometimes cover immune therapy followed by bone marrow transplantation. "If there is evidence of a benefit, we'll cover it," said the pharmacy director of one national plan.

## Targeting Mobility

In January 2010, the FDA approved Ampyra® (dalfampridine) to improve walking speed in patients with MS. Ampyra is an oral drug that blocks potassium channels in nerves and is not a disease-modifying drug but rather a symptomatic treatment. It will be used in all forms of MS, not just

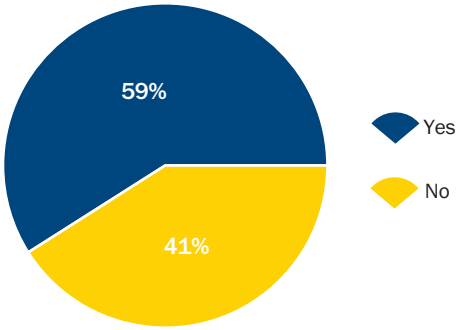
### Table 3

**Does your organization cover any of the following nonpharmacologic therapies for members with MS?**

| | 5–Always | 4–Frequently | 3–Sometimes | 2–Infrequently | 1–Never |
|---|---|---|---|---|---|
| Physical therapy | 41% | 25% | 25% | 8% | 3% |
| Diet/Nutrition | 24% | 9% | 22% | 18% | 25% |
| Chiropractic | 23% | 8% | 29% | 16% | 25% |
| Occupational therapy | 21% | 22% | 28% | 13% | 14% |
| Speech therapy | 17% | 17% | 36% | 14% | 13% |
| High-intensity immune therapy followed by bone marrow transplantation | 10% | 8% | 24% | 17% | 37% |
| Plasma exchange therapy | 6% | 6% | 17% | 27% | 40% |
| Massage therapy | 4% | 4% | 5% | 9% | 75% |
| Acupuncture | 3% | 6% | 19% | 10% | 60% |
| Meditation | 2% | 2% | 2% | 7% | 84% |

**Figure 10**

Does your organization cover Ampyra, recently approved to improve walking in MS patients?




in the relapsing-remitting form of the disease.[8] The studies upon which the FDA based its decision to approve the drug showed improvement in walking speed with Ampyra as compared to placebo.

Fifty-nine percent of respondents said they cover Ampyra® (dalfampridine); 41% do not (**Figure 10**). Unconvinced of its value, and wary of the additional cost that is imposed when Ampyra is used simultaneously with a disease-modifying MS drug, the medical director of one MCO said initially his health plan did not cover it. Now the drug is covered after prior authorization (PA) and submission of baseline results from a timed 25-foot walk (T25FW), creatinine clearance value, and documentation of ambulatory status. After 12 weeks of therapy, improvement in the patient's ambulatory status must be documented in a follow-up T25FW for treatment to continue.

Seventy-three percent of respondents said that use of Ampyra requires PA; 67% limit its use to FDA-approved indications; and 54% set quantity limits in association with the drug (**Figure 11**).

## New Oral Drugs

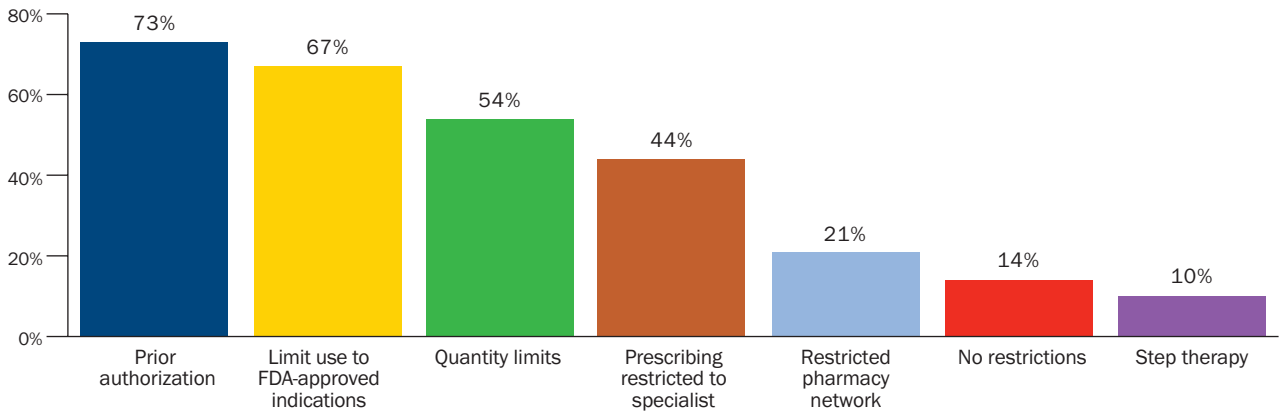
Leustatin® (cladribine injection) is currently used off-label by some physicians for treating MS. When asked about the oral formulation of cladribine, 56% of plans said they were aware that it is under FDA review for the treatment of MS (**Figure 12**).

Seventy-five percent of respondents said they will welcome an oral formulation as an alternative to the injectable immunomodulators; 65% anticipate that patients will demand the drug even if another therapy is a better option; and 54% expect that cladribine will improve adherence because of its oral formulation (**Figure 13**).

Gilenya™ (fingolimod), first in a class of new drugs

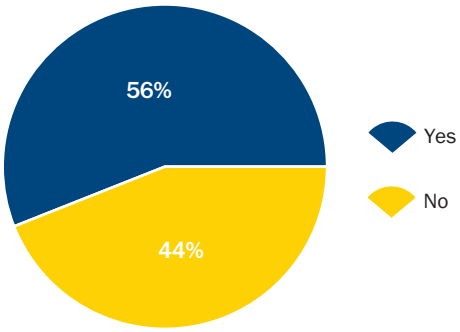
**Figure 11**

Does your organization place any restrictions on the use of Ampyra?



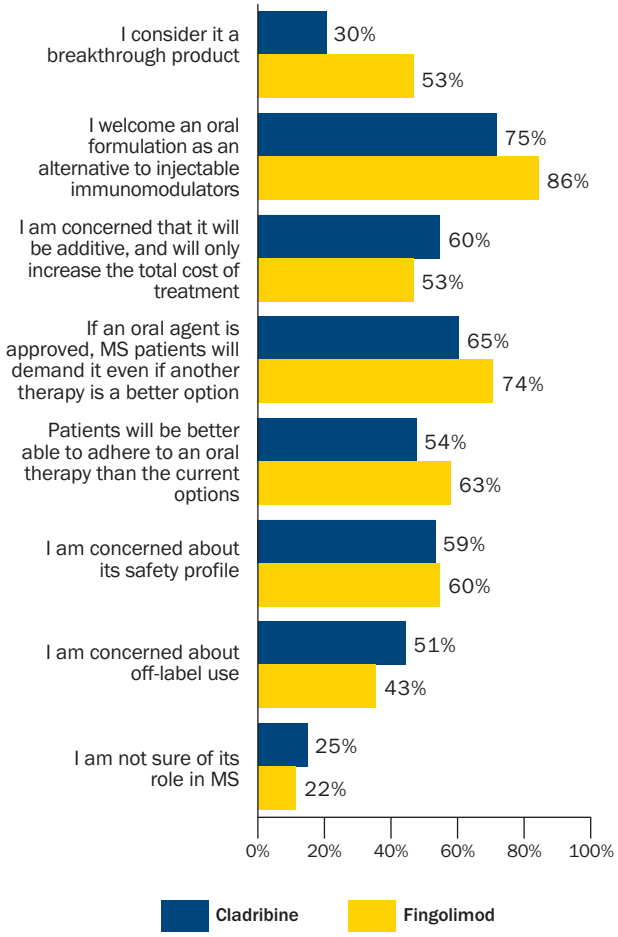
### Figure 12

**Cladribine, an oral product in the pipeline for the treatment of MS, is expected to be approved within the next two years. Are you aware of cladribine?**




### Figure 13

**What are your views regarding cladribine and fingolimod?**




called sphingosine-1-phosphate (S1P) receptor modulators, elicited responses that were similar to respondents' views of cladribine. Again, 86% of respondents indicated they will welcome the new oral formulation; 74% expect that MS patients will demand the drug even if another therapy is a better option; and 63% expect better adherence because fingolimod is an oral medication.

As is the case with Tysabri® (natalizumab) and PML,[5] important safety issues may not emerge for newer agents such as cladribine and fingolimod until a significant number of patients have been treated over long periods of time. Although the concept of an oral disease modifying therapy (DMT) is naturally appealing to many patients, the long-term safety and tolerability of new products are generally less well understood than current options, which have been well established over a long period of use.

Twenty-five percent of respondents questioned the role of cladribine in treating MS, and 22% questioned the role of fingolimod. Dr. Wagner expressed concern that many plans are still unfamiliar with cladribine and fingolimod because manufacturers withhold information until drugs emerge on the marketplace. Kenney said the variability in responses points to the difficulties inherent in managing MS drugs and the need for further information on the efficacy of oral drugs and their potential side effects.

## Summary and Conclusions

The concern over managing MS drugs has become a priority for many managed care organizations, mostly owing to the high cost of medications for the illness. Pharmacy benefits for MS patients are also attracting more attention with the recent approval of Ampyra® (dalfampridine) to improve the function of walking in MS patients, and the anticipated arrival of two new oral medications – cladribine, currently under FDA review, and Gilenya™ (fingolimod), which received FDA approval in September 2010.

Managed care organizations are employing a variety of utilization management tools to control the costs of MS drugs – including prior authorization, restriction of use to FDA-approved indications, quantity limits, and a restricted pharmacy network – while remaining aware that these treatments are important in ameliorating symptoms for patients with MS and in preventing the progression of the disease.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# Specialty Pharmacies and Pharmacy Benefit Management

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## Overview

With pharmaceutical costs — particularly those for specialty medications — continuing to rise, health plans are trying to ensure that multiple sclerosis (MS) therapies are dispensed and used appropriately. Over the next few years, numerous oral therapies are likely to join the current group of injected and infused drugs for the treatment of MS. As a result, just as costs are expected to rise, so will the use of management strategies associated with filling prescriptions for these treatments.

Of the 59 respondents to this survey, 25% represented independent pharmacy benefit management (PBM) service providers; 14% represented PBMs owned by a health plan; 24% represented PBMs owned by a pharmacy retailer; 20% represented independent specialty pharmacies; 12% represented specialty pharmacies owned by a PBM; and 5%, specialty pharmacies owned by a health plan. Almost 40% of the respondents were clinical pharmacists; directors of pharmacy (27%) comprised the second largest group of professionals. The balance of respondents were medical directors (2%), senior and executive managers (17%), and staff pharmacists and product managers (16%).

The organizations represented by respondents covered an average of 10.2 million lives in 2010 and processed an average of 62.3 million prescriptions in 2009. More than two-thirds of respondents said their firms conduct business on a national rather than a regional level.

The FDA has approved drugs that can help slow the progression and reduce the symptoms of MS, for which there is still no cure. Respondents said an average of 34% of their total medication costs in 2009 went to specialty pharmacy products, and about 9% of their total medication costs in 2009 went to immunomodulating MS therapies. "Now that we have better diagnostic methods, the MS patient population is increasing," said Debra Thompson, RPh, branch manager at Caremark Specialty Pharmacy in Richardson, TX. She thinks the 9% medication expenditure "seems low," because the pharmacy is "getting more MS patients." The trend toward earlier diagnosis and earlier initiation of treatment of MS patients accounts for the higher patient numbers, she believes.

Rebates in this class of drugs "are just starting to emerge over the past year," said Gary Rice, RPh,

director of specialty clinical management at MedImpact Healthcare Systems in Humble, TX. As opposed to traditional rebates, which reduce drug costs by 30%, 40%, or 50%, RRMS drug rebates generally fall in the range of single digits to low double digits, he said. However, MS therapies are averaging about $2,500 to $3,000 per month, so even single-digit rebates can add up quickly, said Kevin Leung, RPh, clinical manager at MedImpact Healthcare Systems in Walnut Creek, CA.

Health plans can choose to pay for specialty drugs through the pharmacy benefit or the medical benefit. Many payers adjudicate claims for self-injected specialty therapies — including MS therapies Avonex® (interferon beta-1a intramuscular injection), Betaseron® (interferon beta-1b subcutaneous injection), Copaxone® (glatiramer acetate injection), Extavia® (interferon beta-1b subcutaneous injection), and Rebif® (interferon beta-1a subcutaneous injection) — through the pharmacy side, where the claims can be managed with strategies that are traditionally applied to non-specialty therapies.

Since Tysabri® (natalizumab) is unlike the other MS medications in that it is infused, said Rice, it is more likely to be covered under the medical benefit. He noted that the reason so few respondents cover Tysabri (23%) may be that most of them are PBMs, which adjudicate drugs under the pharmacy benefit. "Because it is infused, you need someone infusing it," which entails a higher expenditure than a self-injectable, added Amy Davis Rorer, PharmD, clinical pharmacist at Ascend SpecialtyRx in South Portland, ME.

Moreover, Tysabri has been linked to progressive multifocal leukoencephalopathy (PML), a potentially fatal brain infection. The drug entered the U.S. marketplace in late 2004, but Biogen Idec and Elan Corporation voluntarily withdrew it in February 2005 after three patients were diagnosed with PML. Since July 2006, when Tysabri reentered the market under a strict risk-management program, more cases of PML have been reported. "Concerns about PML for a certain part of the MS population may mean more utilization management for Tysabri," said Leung.

## Distribution Channels

Almost all respondents said their firms dispense a proportion of their prescriptions through a specialty pharmacy. PBM employees, who represented more than 60% of respondents, reported that in 2009 nearly two-thirds of their prescriptions were filled through a retail pharmacy; more than one-fifth were filled through a mail-order channel; and about one-sixth were filled through a specialty pharmacy (**Figure 1**).

Respondents said that more than half of their prescriptions for injectable MS immunomodulating medications in 2009 were filled through a specialty pharmacy, a quarter through a retail pharmacy, and a fifth through mail order (**Figure 2**).

"I'm surprised it's not more [than 56% filled at specialty pharmacies], but I think the MS therapies are becoming more mainstream," said Thompson.

"Some health plans are pushing for the first fill of immunomodulators to be dispensed at retail. The

**Figure 1**

**If your organization is a PBM, what percentage of prescriptions was dispensed through the following channels in 2009?**

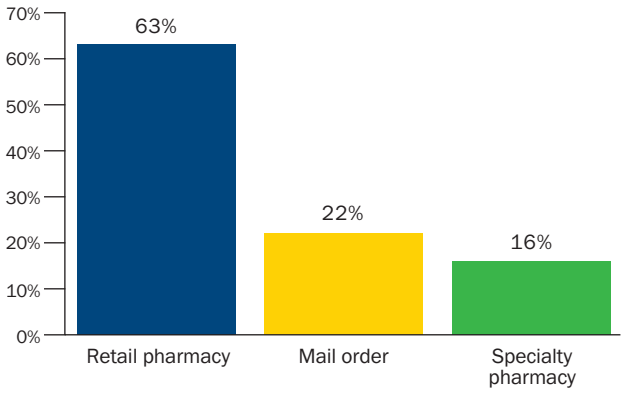
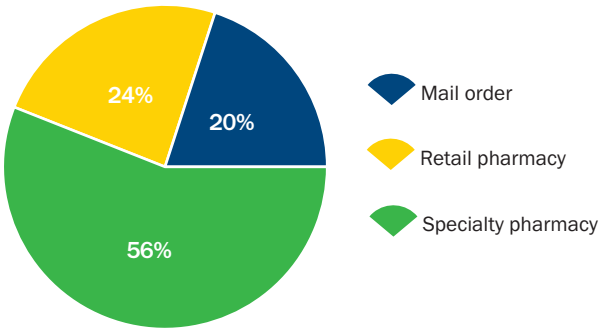


**Figure 2**

What percentage of prescriptions for injectable MS immunomodulating drugs was filled through each of these channels in 2009?




argument is that patients can get the medication quicker this way," said Leung.

Rice pointed to the trend in which larger retail pharmacies are integrating specialty and mail-order channels. This development complicates survey responses in regard to the drug-distribution channel. For example, if a drug comes from the specialty side of a company but is distributed through the retail side, how is it possible to define which drug-distribution channel is being used to fill the prescription?

## Management Strategies

Health plans customarily put utilization management strategies in place to ensure that the right drugs get to patients at the right time. In the case of high-cost therapies like the MS drugs, the need for such policies can be seen as even more critical.

One common strategy is to restrict the number of medication options a health plan will cover. This practice forces physicians to choose among a smaller number of therapies. Leung suggested that the motivation for the use of such strategies might be to take advantage of rebates within a class of therapies that are perceived as somewhat similar.

Respondents said that Copaxone® (glatiramer acetate injection) is covered for most members of specialty pharmacies and PBMs (**Table 1**). With the exception of Extavia® (interferon beta-1b subcutaneous injection), the interferons — Avonex® (interferon beta-1a intramuscular injection), Rebif® (interferon beta-1a subcutaneous injection), and Betaseron® (interferon beta-1b subcutaneous injection) — ranked second in coverage for relapsing-remitting MS (RRMS) therapies. Specialty pharmacy and PBM members were more likely not to have

**Table 1**

For the following immunomodulators, which restrictions are currently in place for the majority of your members?

| | Avonex | Betaseron | Copaxone | Extavia | Rebif | Tysabri |
|---|---|---|---|---|---|---|
| Prior authorization | 68% | 72% | 72% | 58% | 70% | 63% |
| Limit use to FDA-approved indications | 60% | 60% | 63% | 44% | 54% | 51% |
| Quantity limits | 49% | 49% | 51% | 40% | 49% | 39% |
| Dosage limits | 47% | 46% | 46% | 35% | 42% | 30% |
| Restricted pharmacy network | 40% | 39% | 37% | 32% | 35% | 33% |
| Medical therapy management | 37% | 30% | 39% | 30% | 30% | 33% |
| Step therapy | 19% | 25% | 21% | 19% | 18% | 18% |
| Prescribing restricted to specialist | 14% | 16% | 18% | 12% | 16% | 25% |
| Not covered | 2% | 5% | 0% | 18% | 5% | 23% |
| Therapeutic interchange | 5% | 11% | 7% | 5% | 5% | 4% |
| No restrictions | 9% | 5% | 4% | 4% | 4% | 4% |
| Not applicable | 4% | 4% | 2% | 7% | 4% | 7% |

coverage for Extavia (18%) and Tysabri® (natalizumab) (23%). Extavia, which received marketing approval in 2009, was a late entry to the market and was considered not to possess unique therapeutic qualities compared to Betaseron. Tysabri is administered by infusion and therefore is most often considered a medical benefit.

Another widely employed utilization management technique is to require prior authorization (PA) for MS therapies. Respondents reported that, depending on the drug in question, PA is required between 58% and 72% of the time. According to Leung, PAs for these drugs are most often structured in one of two ways: solely at the initiation of therapy or every 12 months. Thompson noted that PAs imposed only once, at the start of therapy, may require "the documentation of lesions and signs and symptoms of the disease." Annual PAs may require "follow-up paperwork on patients' brain lesions from an MRI," Leung explained.

"A lot of clients want every specialty drug to receive prior authorization because of the high prices," said Rice. "Sometimes it's kind of foolish," he added, "but they want to show" that they're trying to manage costs. But with the side effects associated with MS therapies, Dr. Rorer asked, "Who would want to take these drugs unless they were absolutely necessary?" Rice concurred; requiring PA with these drugs "creates a level of satisfaction, but it may be meaningless in this category," he said.

In contrast, survey participants less frequently cited the strategy of restricting prescribing to a specialist (12% to 25%, depending on the drug). "I thought this would be higher," said Rice, noting that the percentages were much higher for PA requirements. "Most PAs have the requirement that a specialist needs to be writing the prescription," he explained. He added that there may be some markets where, for reasons having to do with access, a primary care provider would follow up with the patient in close collaboration with a neurologist.

Thirty-nine percent to 51% of respondents cited the strategy of imposing quantity limits. Physicians can switch patients to another medication if they do not respond to a therapy within 2 or 3 months. Also, therapy regimens may change after patients have been on one particular drug for some time. "Mail order generally ships out 3 months of a therapy at one time," said Dr. Rorer. "If you've shipped out $8,000 worth of medication and the drug isn't working, what then?" Sending out 30-day supplies of a therapy can help reduce waste when patients switch to a different treatment.

## Treatment Guidelines

Rice pointed out that the national multiple sclerosis associations do not have treatment guidelines for these therapies, and therefore defer to neurologists. "Some neurologists have specific opinions about therapies and will drive patients toward these," he said. "Some want the patient to be involved in the decision" in the hopes that this engagement will increase therapy adherence. Many neurologists send newly diagnosed patients home with an array of DVDs that describe the therapies so patients can have a say in their regimen.

For example, Extavia® (interferon beta-1b subcutaneous injection) entered the U.S. market late in 2009 but is essentially the same therapy as Betaseron® (interferon beta-1b subcutaneous injection), which has been on the market since 1993. "Until Extavia proves itself as having any advantage over Betaseron, or unless there is a cost incentive for health plans, they see no need to cover it," Thompson said. Because of its relatively recent emergence, physicians are not as familiar with the Extavia brand name, and this may also be impeding its use, said Dr. Rorer.

## The Benefits of Specialty Pharmacy

Plans may also impose a restricted pharmacy network in which the use of specialty pharmacies

is mandated. "By locking out retail pharmacies," said Leung, "discounts would be higher." This approach, he said, "is fairly appropriate for this category of medications."

Moreover, specialty pharmacies have a greater focus on patient management. Many respondents said their companies' clients, including health plans, employers, and other payers, mandate the use of specialty pharmacies for providing MS therapies. Specialty pharmacies focus on treating patients with chronic conditions who need high-cost therapies that often require special handling. These firms are set apart, said Leung, by their larger array of patient services, and by the integration of clinical components in patient management that help patient adherence. This high-touch approach means that specialty pharmacies "are constantly reaching out to patients," Dr. Rorer said.

Concerns about cost reinforce the importance of adherence to therapy regimens. Health-plan costs can increase significantly if patients aren't following these regimens, said Rice. "Plans can optimize their investment in the drug by having people be compliant. There is a continued struggle in regard to managing costs and providing suitable access to drugs for MS patients," he added, and because patient outcomes are likely to improve with the clinical management that is provided by specialty pharmacies, "many plans don't feel that if they use a specialty pharmacy, they are limiting patient choice."

Rice noted that one way of looking at it is that specialty pharmacies offer a higher "level of hands-on interaction with patients. It's more than just dispensing a drug. We assess care and empower the patient to be more involved with care." In contrast, he said, "the biggest challenge with a retail pharmacy is volume — getting the right drug to the right person from a distribution standpoint." Mail-order pharmacies are "more automatic," compared to the highly personalized approach of specialty pharmacies, added Dr. Rorer.

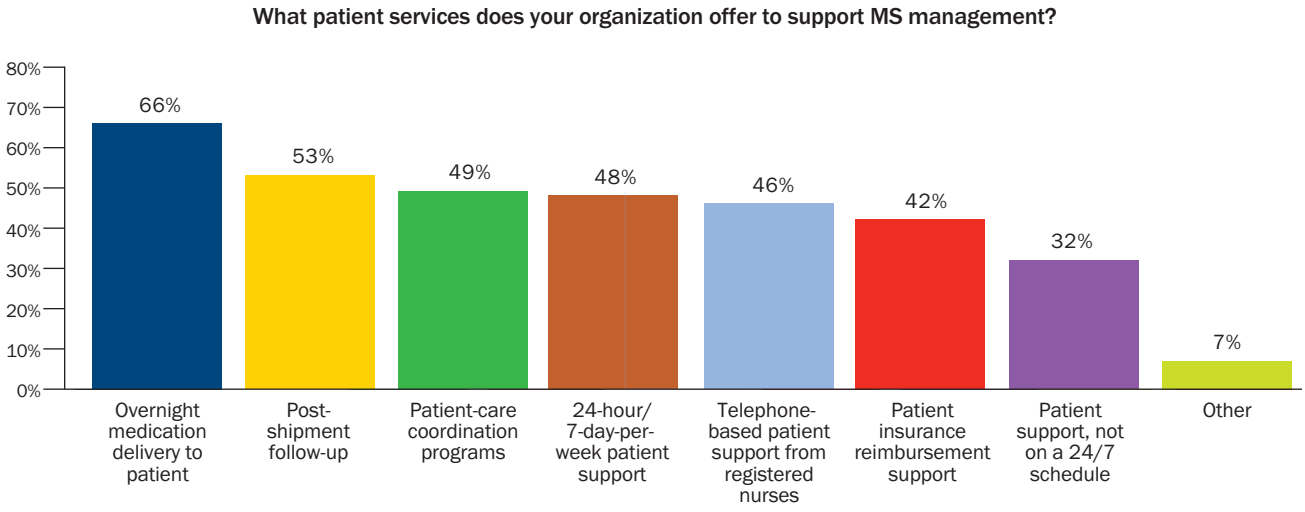
Respondents noted an array of value-added programs they offer to managed care organizations. Most said their companies offer patient education, which can include training in the route of administration for self-injectables and guidance in the proper handling and mixing of medications. Two-thirds of respondents (66%) said they offer overnight delivery of medications, and more than half (53%) said they provide post-shipment follow-up. About half the respondents (49%) said they offer patient-care coordination programs. Forty-eight percent offer 24/7 patient support; 46% provide telephone-based patient support with registered nurses; and 42% offer help with insurance reimbursement (**Figure 3**).

"Injectable administration is one of the biggest challenges with these drugs," said Leung. A core competency of specialty pharmacies, he explained, is educating patients on how to self-inject, including which areas of the body are best for this purpose, why it's important to rotate injection sites, and even what times might be best for taking the drugs. "Retail pharmacies may not be able to sufficiently educate patients, and mail-order pharmacies probably don't offer these services," he said.

Explaining the side effects that patients can expect is also crucial to compliance. "These medications require a lot of monitoring," said Thompson. "We talk to patients each month. We see if they're experiencing side effects. If they say no," she said, "Caremark follows up with more detailed questions about their adherence to the treatment regimen" because "the majority of patients experience side effects." These can include reactions at injection sites as well as depression and flu-like symptoms.

Comorbid conditions such as depression may also require treatment in patients with MS. "We look at all their medications and get a handle on the whole picture," Dr. Rorer said. "And if the patient is a new start, we call on the day they are supposed to receive their first shipment." Some organizations

**Figure 3**




perform a patient assessment before they ship medication, and most respondents said their facilities offer refill reminders.

"We like to make sure the drug is working," said Rice. "Some patients have relapses even when they're on therapy." Each month, he said, MedImpact asks patients how many doses of their medication they have left. If a patient has missed a dose, the company asks them why, and whether they have spoken with their physician. "We know which questions to ask," he said. Specialty pharmacies routinely coordinate care with patients' physicians, he added. Leung noted that the practice of tracking patients' progress provides another service. "There are additional back-end analytics that specialty pharmacies can gather…and share with the health plan," he said.

Noting that various types of companies were represented in the responses, Rice said he doesn't know "any specialty pharmacy that doesn't do insurance reimbursement support and over-night delivery." He added that "a lot of regional specialty pharmacies, especially if they're independent, may be focusing on certain disease states, and MS may be one of them." These companies, which may be one of only a few pharmacies in their area, "may provide all or most of these services," he said.

Support for patients who are seeking insurance reimbursement has become a particularly valuable service. Thompson said she has seen an increase over the last couple of years in efforts by patients to stretch out their therapy because they can't afford their copayments. "Depending on the plan, copays can be high; we ask whether people know about assistance programs offered by manufacturers," she said.

## On the Horizon

While drugs currently used in the treatment of MS are injected or infused, oral therapies that will soon emerge from the pipeline may offer other options. "Any oral medication is always preferred over an injectable product as long as it's effective," said Thompson. "If a patient is so afraid of self-injecting that they won't even start a therapy, then compliance will go way up" with the introduction of an oral alternative. Because MS can affect motor skills, "an oral therapy may be ideal" for this population, Leung added.

Generally speaking, oral alternatives "will be incredibly appealing for these patients," said Dr. Rorer. Patients may believe that if a drug is in tablet form, it won't make them feel as bad as an injected or

infused therapy. "That's not necessarily true, but perception is reality," she said.

Rice feels that "the inherent risks of cladribine and fingolimod are greater than the risks for the injectables." Ultimately, the oral treatments will offer "another alternative, another stand-alone therapy," said Thompson. Patients and physicians, as well as the FDA, will need to weigh the risks and rewards of these new drugs.

"If the cost estimates are correct, these [oral drugs] may potentially be priced quite a bit higher than the injectables," said Rice. "If a patient has coinsurance and is doing well on an injectable, the physician will probably not switch them to an oral." Experience with other new therapies with novel routes suggest that the new oral drugs will be priced at least 5% to 10% higher than existing treatments, said Leung.

It will be interesting, Rice said, to see how the oral drugs will be used in relation to Tysabri® (natalizumab). The risk of PML increases in patients who have been taking Tysabri® (natalizumab) for 24 to 36 months, and neurologists may be looking to transition these patients to another therapy at that time. "The oral products could come at the right time" to fill the treatment gap, Rice said.

"Health plans place different priorities on different disease states," said Leung. MS may fly under the radar of some plans since it is "not a highly visible disease state," relatively speaking, he added. Yet "the market for MS drugs will become crowded in the next two or three years," said Rice. As therapeutic options continue to expand, he is wondering how utilization strategies like PA, restricted networks, step therapy, and therapeutic interchange are likely to evolve.

"The future is very bright for MS medications, and very exciting," said Thompson.

## FROM DENIAL TO DREAM HOUSE

**An interview with Dave Anderson**

The year was 1990, when optic neuritis first convinced Dave Anderson to see a doctor. "I went blind in my left eye for 2 months — very scary. After a course of steroid treatments, I regained vision." When his ophthalmologist first suggested the symptoms he was experiencing are sometimes symptoms of RRMS, "I didn't pursue it further," Dave says, "as I had never heard of RRMS before. So I chose to live in denial that I might have a chronic illness." Although vision in his left eye was restored, "I've had some vision problems related to that since then," he says.

Dave's first symptoms had appeared 9 years earlier, in 1981. "My entire left side — face, arm, and leg — went numb for about a day," he says. Then the symptoms vanished, and he "chalked it up to a pinched nerve."

Life went on and "denial worked pretty well," says Dave, until the left-side numbness returned in 1996, along with "overshooting" of his left eye. "When I'd look to the left, then back to the right, my left eye wouldn't catch up right away. It was now very evident that something was seriously wrong," he says, and he realized that the problem was quickly worsening. Dave's ophthalmologist referred him to a neurologist, who, after an MRI and other tests, diagnosed him with relapsing-remitting MS in 1997.

"I felt like my future was gone," says Dave. "Everything that my wife and I had hoped and planned for our entire lives was ripped out from underneath us in a matter of seconds. It took me 2 to 3 years to overcome the devastation and get back on track." Talk therapy with a trained professional was especially helpful in dealing with the anger, anxiety, fear, and feelings of "why me?"

Dave initially tried Avonex® (interferon beta-1a intramuscular injection) for his MS relapses.

"It appeared to work well for me, but the side effects were intolerable. I had flu-like symptoms that lasted anywhere from 2 to 5 days of each week." Eventually, Dave stopped taking Avonex® (interferon beta-1a intramuscular injection) in favor of another DMT. The new therapy controls RRMS as well as Avonex, "if not better" but the side effects are now limited to an occasional short-term injection-site burning sensation, he adds.

Whether it's drug therapy, the course of aging, the vagaries of RRMS, or a combination of these, Dave began to feel relief both physically and emotionally. In fact, some of his worst symptoms, such as extreme heat sensitivity, which in turn leads to fatigue and numbness, have improved.

Despite some symptomatic improvement, however, Dave's work and home life continued to undergo turmoil. In 2003, Dave resigned from his position as website development manager with a dot-com startup, after an insurance company representative said he was eligible for the firm's long-term disability package. "I later found out she was wrong," he says. The insurance company denied his claim. "It was a huge financial blow," says Dave — one that could have been avoided if he'd stayed on the job 5 months longer.

"I made every mistake there is. The day I announced my resignation was the day I told my fellow employees that I had RRMS. They would have been very supportive, but I never gave them a chance," says Dave.

Some counselors, Dave observes, say that when a person's health is failing, "The last thing they give up is their work. They give up their family life first, which is very unfortunate, but it's the society we live in, I guess. You need that precious paycheck. So I struggled and struggled and put the focus on being able to work over maintaining a good family life," he says, until his neurologist suggested he stop working because the schedule and stress were exacerbating his RRMS-related fatigue and left-side numbness. "When I stopped working, I saw a fairly dramatic improvement in my health," he says.

Before starting medications 13 years ago, Dave was experiencing 2 to 3 relapses per year. Since beginning treatment, he has been relapse free, and he says his MRIs, done every 2 years, are "looking good, if not better than they have in the past."

Dave served in the armed forces, and thanks to his VA medical care, his medication copay is less than $10 monthly. "I maintain a separate medical/dental insurance policy that allows me to see my neurologist and family practitioner. It costs me $112 per month for this coverage, but the policy excludes prescriptions. So the VA is a critical part of my health-care resources," he says.

These days, Dave works about 10 hours per week designing and maintaining websites for small businesses. He also devotes many hours to volunteering for organizations such as MSWorld — where he served as vice president until leaving the organization in early 2010 — and the National Multiple Sclerosis Society, which in 2009 enshrined him in its Volunteer Hall of Fame. "I also volunteer at the local VA Medical Center as a lay facilitator, teaching patients how to manage chronic illness," says Dave. He and his wife founded, and for 5 years led, a chapter of Fishing Has No Boundaries, "a nonprofit organization whose goal is to open up the great outdoors for people with disabilities through the world of fishing."

Thanks to education and perseverance, says Dave, he and his wife have "come to terms with the fact that this is a manageable disease, and that life is okay. It's slightly modified from what we had planned, but certainly not the disaster we feared in the early days."

Going on disability, says Dave, forced him and his wife to change many of their long-term goals. But recent low interest rates and affordable construction costs have allowed the Andersons to finance their retirement home in Minnesota, a project they had all but given up on. This endeavor, he says, and preparing their current home for sale, keep him "very active outdoors. I rarely have time to lie around and wonder what's next."

**For more information:**
www.nationalmssociety.org
www.msworld.org
www.brainerdlakesfhnb.org

# Neurologists

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## Overview

A total of 136 practicing neurologists or multiple sclerosis (MS) specialists responded to the survey. Although most of the participants are general neurologists rather than MS specialists, the management of MS is clearly a central concern for neurologists across a broad range of subspecialties and practice settings. On average, respondents said that 23% of their patients have been diagnosed with MS or with a clinically isolated syndrome (CIS), and that MS and CIS together account for 25% of all their patient visits. The respondents identified significant challenges in the treatment of MS, including tolerability of medication, the achievement of treatment goals, and payment and reimbursement issues. Nearly two-thirds of the respondents said payers at least sometimes implement procedures to restrict the use of disease-modifying therapies (DMTs), and 15% said they always or nearly always have difficulty obtaining reimbursement for infused DMTs such as Tysabri® (natalizumab). The findings of the survey underscore the complexity of the diagnosis and management of MS and the variety of treatment approaches. In addition to the standard DMTs (ie, glatiramer acetate, interferon beta-1a, interferon beta-1b), participants reported using a broad range of other immunomodulatory and immunosuppressive drugs to treat MS. The range of options that respondents selected suggests that it is essential to provide physician education to ensure that providers are using the most effective evidence-based options for their patients with MS. The findings also emphasize that for most patients, no single agent or treatment strategy has emerged as clearly preferable to other choices. In addition, nearly one-third of those surveyed said they also typically handle non-MS medical issues for their patients with MS. The respondents noted that both physicians and patients benefit from education and patient-support programs provided by pharmaceutical companies and professional societies. Neurologists are clearly listening to the preferences of their patients, as patient feedback was routinely cited as one of the most important factors they consider in evaluating the effectiveness of these programs.

Although most respondents were not MS specialists, they expressed a high level of interest in and awareness of emerging treatment options for MS. Most of those surveyed said they are following clinical studies of new treatment options closely, although they also expressed concerns about the safety profiles of these new agents. Neurologists noted the effective-

ness of several nonpharmacologic treatments, including occupational therapy, speech therapy, and physical therapy. Though many patients express an interest in alternative therapies, few of the neurologists surveyed expressed confidence in the effectiveness of these techniques.

Respondents to the survey work in a variety of settings, including group practices (53%), solo practices (26%), hospital or integrated health systems (8%), and academia or other research settings (13%). More than 40% of the participants have been in practice for at least 20 years; only 6% have been in practice for less than 5 years. Approximately one-third of the respondents (33%) reported that they participate in clinical trials, and 30% specialize in the treatment of MS. Most of the respondents personally treat between 1,000 and 2,000 active patients of all types in their practice. Sources of payment include commercial health plans (48% of patients), Medicare (35%), Medicaid (10%), self-pay (5%), and other sources (2%). Approximately 40% of the respondents reported that their practice employs at least 1 nurse practitioner (NP) or physician assistant (PA); on average, these practices employ 2 NPs and 1 PA.

## The Future of Treatment

According to David S. Brandes, MD, director of the Northridge MS Center and assistant clinical professor at the University of California, Los Angeles, many MS experts are "very concerned that there may not be enough younger neurologists to eventually take over managing MS patients." Dr. Brandes noted that although most of those surveyed said they do not specialize in the treatment of MS, the participants do, on average, treat more patients with MS than the average community neurologist (roughly 50 patients with MS per physician). He pointed out that only about 24% of those surveyed had been in practice for 10 years or less, and that a large proportion of the physicians surveyed were older doctors who are approaching retirement. "One of the big concerns we have is that it's getting harder and harder to treat MS, and fewer young doctors seem to be going into the field," he said.

Dr. Brandes noted two significant barriers to entry for younger doctors. "One is that it's difficult to treat MS, because there are so many different things that need to be treated, and it's very difficult and time-consuming. Second, reimbursement is very poor, especially for the time spent. It's an issue that we need to address," he said.

## Presentations of MS and Coordinated Care

Respondents said that relapsing-remitting MS (RRMS) is the most common presentation of the disease that they treat, accounting for an average of 57% of their patients with MS. Secondary-progressive MS (SPMS) accounts for 19% of their patients; CIS, for 11%; primary-progressive MS (PPMS), for 7%; and progressive-relapsing MS (PRMS), for 6%.

The respondents indicated that some kind of coordinated specialist care is involved in the treatment of a large proportion of their patients with MS. A primary care physician (PCP) is involved in coordinated care for an average of 45% of patients. The most common types of coordinated care between neurologists and their patients' PCPs include traditional referral (always or nearly always used by 81% of respondents), sharing test results (73%), and sharing medication histories (63%). Less common patterns of coordinated care include sharing full electronic medical records (always or nearly always used by 20% of respondents) and sharing histories of nonpharmacologic treatments (32%). Respondents identified several areas in which coordinated care has yielded significant improvement, including the understanding of comorbidities, patient outcomes and satisfaction, and compliance/adherence (**Figure 1**).

Less than one-third (29%) of respondents said that coordinated care has increased or greatly increased the administrative burden on their practice. About

**Figure 1**

To what extent has coordinated care improved patient care in the following areas?

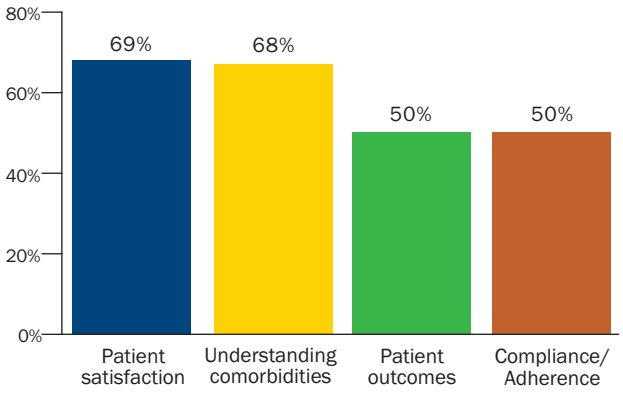
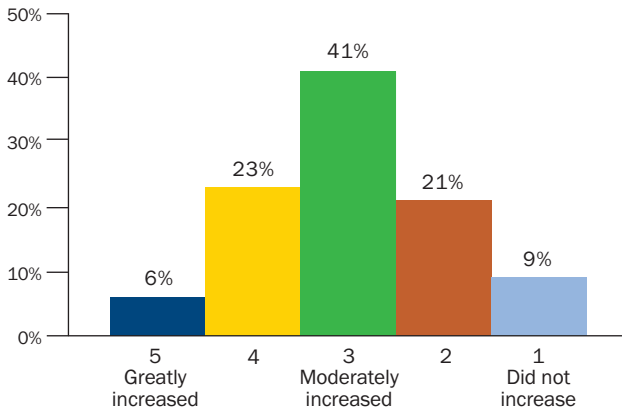



**Figure 2**

To what extent has coordinated care increased the administrative burden on your practice?




the same proportion (30%) said their burden was decreased or greatly decreased by the use of coordinated care; 41% felt the impact was neutral (**Figure 2**).

Coordinated care may take on new importance as several emergent MS therapies are poised to enter clinical practice and physicians must be prepared to anticipate and manage a range of systemic side effects, said Ronald S. Murray, MD, FAAN, director of the Multiple Sclerosis Clinic of Colorado in Lone Tree. "A high proportion of people felt that it was very important to have coordination of the patient's care to increase the knowledge of comorbidities," he pointed out. "I think that's going to become even more important when we start utilizing agents that have a little bit more risk in other organ systems – for example, a patient who has asthma and experiences an increase in airway resistance while on treatment for MS. I think all of us need to be working with primary care physicians, taking it upon ourselves to obtain very detailed medical histories from our patients, to understand how new treatments may affect underlying comorbidities." Dr. Murray also noted that there is a growing trend for neurologists to employ nurse practitioners (NPs) and physician assistants (PAs) in their practices. "They usually come in with a strong primary care background, and then they adapt to the neurological setting," he explained. "This survey indicates that neurologists are becoming more comfortable utilizing ancillary health-care providers, and I think that actually improves the care of the patient. Neurologists are seeing that integrating NPs and PAs into the practice is not only cost-effective, but is also helpful in taking care of our patients." Many respondents, he said, indicated that they often address their patients' primary care issues when they arise, and he suggested that this may be an important contributor to the growing use of NPs and PAs in neurology practices.

Dr. Murray commented that the payer mix in this survey seemed to be skewed toward government plans, with an average of 35% of patients covered by Medicare and 10% by Medicaid. He emphasized that the high rate of government-payer patients may create problems in the future, as legislative changes may significantly reduce physician reimbursement for these patients. For example, he noted that the U.S. Congress currently must vote every 6 months to defer substantial payment decreases for patients who are being treated through these government programs. "If the average neurologist is carrying 35% to 45% of patients on government plans, it's going to be a significant impact on their revenue and ability to practice" should these pay cuts eventually be implemented, Dr. Murray explained. "With the percentage of patients on these plans in most neurology practices, it's going to have a serious economic impact. There may come a day when neurologists no longer participate

in these plans because they can no longer afford to take care of a patient on Medicare or Medicaid," he said. These changes have the potential to undermine the quality of care by forcing patients to find new physicians who will work with their insurance, and by disrupting the continuity of care. Dr. Murray emphasized that it can be especially challenging to take over the care of a patient who has a long history of treatment with another physician. "Without good, objective markers of patient outcome, the best way to manage a patient is to know that patient," he explained. Changes to the payment system "have the potential to significantly affect patient care, especially with some of the newer agents that are in development or for patients who have underlying comorbidities."

Dr. Brandes noted that 89% of the patients of those surveyed have primary care physicians, but that in only about 45% of cases does the primary care physician coordinate patient care. "What doctors call coordination of care generally consists of obtaining test results, medications, and having a traditional referral. That's not real care coordination, and the primary care physicians are really not doing a lot with the MS patient." Dr. Brandes said that coordination of care may itself be an obstacle for many physicians. "At least 70% of the neurologists found that there was an increase in the administrative burden because of coordination of care. Also, about 30% of the neurologists said they handle non-MS illnesses. So even though nearly 90% of their MS patients have primary care physicians, neurologists are still providing care for many of the non-MS conditions for these patients. This may be one of the reasons that it's getting harder and harder to get neurologists to specialize in MS." Patients are often effective at communicating among one another about doctors who are most effective at managing MS, said Dr. Brandes, and this results in a higher concentration of the most challenging patients for a relatively small pool of neurologists. He also pointed out that insurance and reimbursement issues are significant barriers for some patients. For example, most of the survey respondents described some degree of difficulty with reimbursement when starting patients on infusion therapy or first-line DMT. Dr. Brandes concluded his remarks with the observation that insurance-related barriers often hinder early treatment for MS patients, despite its importance.

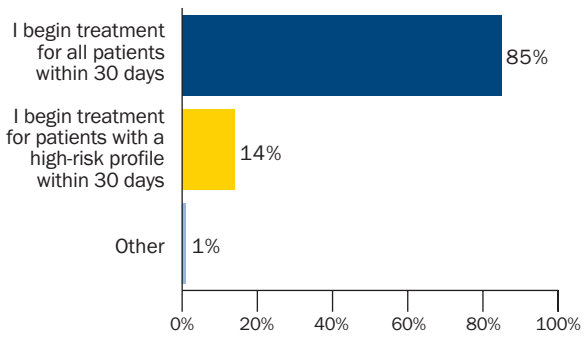
## Ambiguity of Diagnosis and Goals of Treatment

Nearly all of the participants (96%) said they agree or strongly agree that inflammation is intimately involved in the pathogenesis of MS. Most participants (62%) agreed or strongly agreed that a key goal of MS therapy is to slow the inflammatory process as early as possible, even if a definitive diagnosis of MS has not yet been established (**Figure 3**), and 93% agreed or strongly agreed that once the diagnosis is certain, it is important to begin treatment with immunomodulators as soon as possible. Most participants also agreed or strongly agreed with the importance of targeting other pathophysiologic mechanisms of MS, including B cells/T cells (78%), and of improving axonal regeneration (85%).

The tools neurologists use most often to diagnose MS (**Figure 4**) include patient history (used always or nearly always by 98% of respondents), cranial MRI (98%), spinal MRI (76%), the revised McDonald diagnostic criteria (68%), and blood tests (65%). Opinions were divided on the use of other diagnostic tools. Twenty-eight percent of respondents said

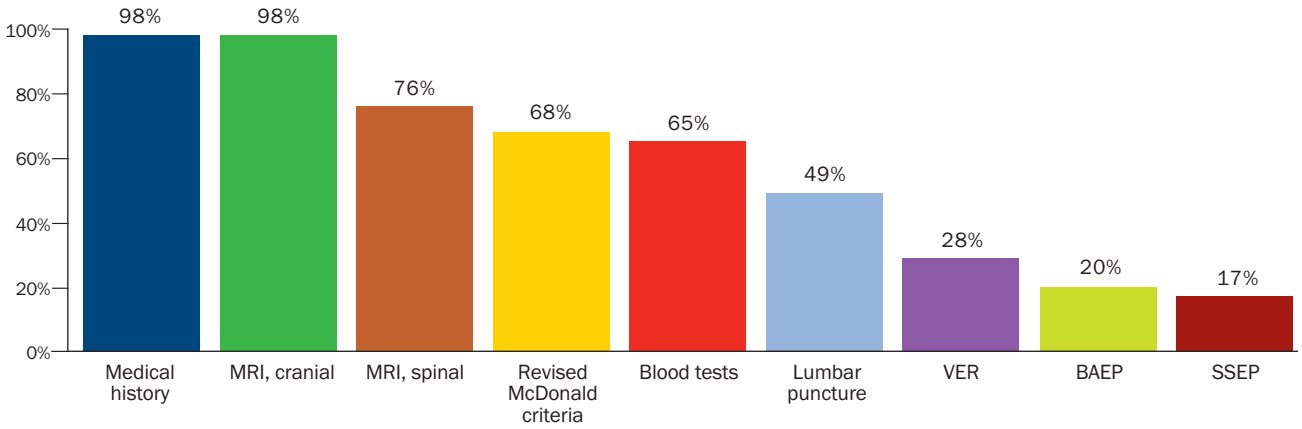
**Figure 3**

**When a patient is diagnosed with RRMS, when do you usually begin treatment with immunomodulators?**



## Figure 4

Proportion of respondents who "always" or "nearly always" use the following tools to diagnose MS.

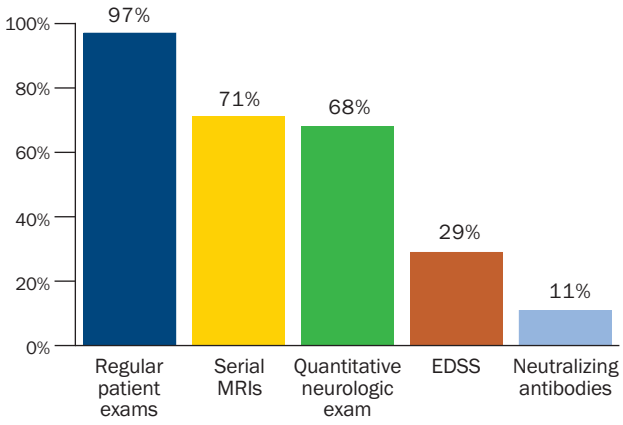



VER: Visually evoked response | BAEP: Brain-stem auditory evoked potentials | SSEP: Somatosensory evoked potentials

they always or nearly always use visually evoked response (VER), while 38% said they never or infrequently use VER. Twenty percent said they always or nearly always use brain-stem auditory evoked potentials (BAEP) as a diagnostic accessory, and 17% said they always or nearly always use somatosensory evoked potentials (SSEP), whereas 53% and 59%, respectively, said they never or rarely use these tools. Neurologists also commented on their use of strategies for monitoring patients' responses to treatment (**Figure 5**), including serial MRIs and quantitative neurologic evaluation.

## Figure 5

Proportion of respondents who "always" or "nearly always" use the following tools to assess efficacy of therapy.




EDSS: Expanded Disability Status Scale

Dr. Brandes commented on the importance of neutralizing antibodies in MS care. "I believe that neutralizing antibodies really do make a difference; this is recognized in most countries around the world. In the United States, though, very few people use neutralizing antibodies on a routine basis, which is shown in the data from this survey." Although more physicians are beginning to consider the role of neutralizing antibodies in MS care, Dr. Brandes noted that many experts in the MS community have argued that antibody testing is rarely useful in clinical decision-making. Yet in some cases, said Dr. Brandes, antibody testing can help explain why a patient is failing to respond to therapy. In Europe, he said, such testing is considered a valuable part of MS care and is performed routinely.

The survey results, said Dr. Murray, suggest that many patients are not receiving early DMT after a diagnosis of RRMS or CIS. When respondents were asked about their use of immunomodulators for patients with CIS, only 36% said they begin treatment for all patients once the diagnosis is made. Forty-seven percent said they begin treatment only for patients with high-risk profiles; 15% said they wait until there is a definitive diagnosis of MS; and 2% said they do not use immunomodulators to treat patients who have CIS. Eighty-five percent of those surveyed said they begin treatment within 30 days for all

patients with RRMS. However, a substantial number of neurologists (14%) said that even for patients who have been diagnosed with RRMS, early treatment is offered only to those who are considered to have high-risk profiles. "For years we have been promoting early intervention in treating patients with MS," said Dr. Murray. "It was good to see that 85% of respondents say they treat within 30 days. People have really taken to heart the message that early intervention is in the patient's best interest over the long term," he added. Still, he said, problems with insurance and reimbursement continue to present obstacles for many physicians and patients. "The majority of people felt that third-party payers are creating barriers to implementing therapies and payment for therapies. The prior authorization system in my own practice has gone up and is very frustrating to work through, not only for new starts on therapy but also for continuity of therapy," he said.

Dr. Brandes noted that although 85% of respondents said they treat all patients with MS within 30 days of diagnosis, this leaves a substantial number of patients at risk of undertreatment. "Some say they treat only those who have a high-risk profile. I think the data show that in general, we should be treating everybody. We don't really know who is high risk and who isn't," he said. In regard to patients with CIS, he observed that 47% of those surveyed said they treat only those with high-risk profiles. "Although we're learning more and more about early treatment, we probably should be putting all patients on it, because we don't know what an individual's prognosis is going to be," he said.

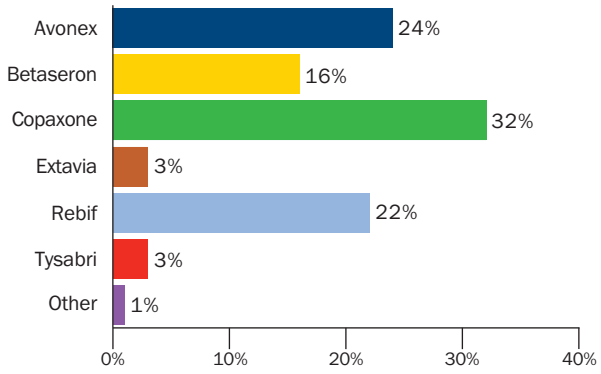
Participants largely agreed on several goals of MS therapy, calling them "very important" or "important." Ninety-seven percent of respondents said that slowing disease progression and reducing disability constitute one of these goals; 95%, reducing the rate of lesion formation; 91%, reducing inflammation; 91%, providing treatment that is safe and well tolerated; 88%, reducing the number of symptoms and alleviating their intensity; and 68%, reducing pain.

Several survey questions explored the use of disease-modifying treatments for first- or second-line therapy. On average, respondents said 85% of their patients with MS are using DMTs. The most frequently selected first-line treatments are shown in **Figure 6**. Copaxone® (glatiramer acetate injection) was selected as a first-line DMT more often than any other treatment, accounting for an average of 32% of newly treated patients. Other commonly used first-line DMTs include Avonex® (interferon beta-1a intramuscular injection) (24%), Rebif® (interferon beta-1a subcutaneous injection) (22%), and Betaseron® (interferon beta-1b subcutaneous injection) (16%). Extavia® (interferon beta-1b subcutaneous injection), a recently introduced interferon beta-1b product, was selected for first-line therapy for an average of 3% of patients, as was Tysabri® (natalizumab). Respondents said that on average, 1% of their patients use other first-line therapies, including steroids, naltrexone, immunosuppressants, (eg, azathioprine, mitoxantrone), and investigational drugs.

The most commonly selected second-line DMTs are shown in **Figure 7**. In general, the DMTs that were selected as first-line agents were also chosen as second-line agents. Copaxone was again the most commonly selected DMT, accounting for an average of 29% of patients, followed by Rebif (23%),

**Figure 6**

**What percentage of your patients begin disease-modifying therapy with each of the following products as their first-line option?**



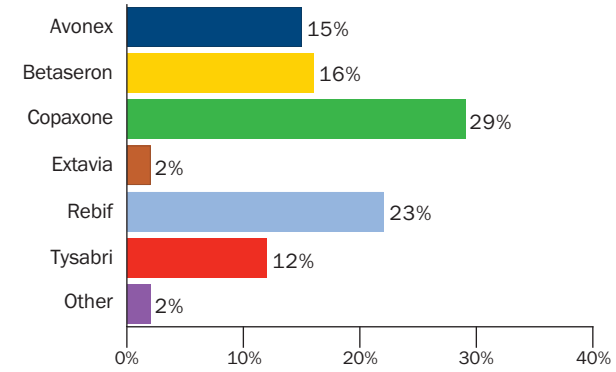
Betaseron® (interferon beta-1b subcutaneous injection) (16%), and Avonex® (interferon beta-1a intramuscular injection) (15%). Tysabri® (natalizumab) was described as the second-line agent of choice for an average of 12% of patients, despite the reported risk of progressive multifocal leukoencephalopathy (PML) for this agent. Extavia® (interferon beta-1b subcutaneous injection) was selected as a second-line option for 2% of patients, and 2% received some other second-line strategy. Additional second-line treatments include steroids, intravenous immune globulin (IVIG), immunomodulatory or immunosuppressant agents (eg, methotrexate, mitoxantrone mycophenolate), and investigational agents.

Barbara S. Giesser, MD, clinical director of MS Services and associate clinical professor at the University of California, Los Angeles, commented on the use of first- and second-line treatment options by the respondents. "I was surprised that Copaxone® (glatiramer acetate injection) was the most frequently used disease-modifying agent, with about one-third of patients receiving it as first-line therapy. In the past, Avonex has been the most common first-line therapy. This was an interesting change. I found it a bit alarming that a relatively high number of the respondents use immunosuppressants as first-line therapy. I would generally use immunosuppressants as first-line therapy only for very rare cases in which the patient presents with very malignant disease, and I hope that is the setting in which the survey respondents are using these therapies. I was also surprised that as many as 25% of those surveyed said they thought dietary modification is effective as a treatment for MS. Three percent of respondents said they use Tysabri as first-line therapy for MS. In my opinion, that number should be zero. About 12% of those surveyed said they use Tysabri as a second-line agent. It is not clear whether they switched to Tysabri directly following a single first-line agent, or only after all other first-line options had been tried. I would be more likely to recommend its use only after all other first-line therapies have been exhausted," she said.

Treatment goals for patients with MS include preventing new relapses or exacerbations, reducing the number and intensity of MS symptoms, slowing disease progression, and maintaining adequate safety and tolerability. **Figure** 8 shows the proportion of respondents who felt that their patients met these goals over a 6-month or 12-month period after beginning DMT. These results suggest that many patients are not attaining important goals of MS therapy. For example, only 33% of neurologists said that more than 75% of their patients attained the therapeutic goal of preventing relapses after one year, and only

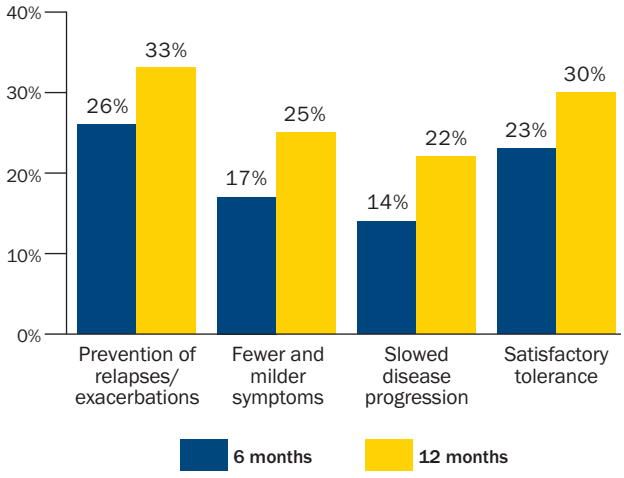
## Figure 7

**What percentage of your patients receives each of the following as their second-line option if they fail on their first disease-modifying agent?**




## Figure 8

**Proportion of respondents who said that more than 75% of their patients met each of the following goals after 6 months and 12 months.**



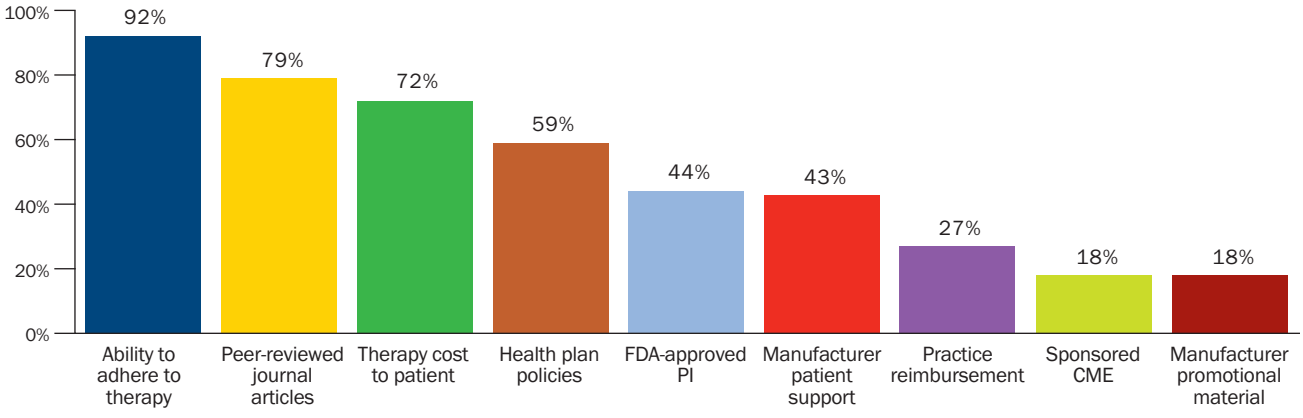
22% said that disease progression was slowed in 75% of patients. Dr. Brandes noted that the survey results raise significant questions about whether enough patients are achieving their therapeutic goals. "It looks like there is a relatively high proportion of patients who are not responding that well during the first 6 to 12 months, probably in the range of 20% to 40% of patients," he said. "They may be patients who would benefit from early conversion to a more effective drug. I think the idea of treating patients early has pretty much caught on. But I'm not sure that early conversion has caught on. CIS is now treated much earlier than it used to be, but we also need to think about converting patients sooner if they're not responding." He further noted that a relapse rate of approximately 1 relapse per year is similar to the placebo rate from clinical trials, and should be regarded as a sign of treatment failure. "I think we need to start looking at not accepting 1 relapse per year as an acceptable response," he said. "I think what we're seeing here is a little reluctance to start therapy for milder cases, and reluctance to switch in regard to patients who do not seem to be doing well in the first 6 to 12 months."

Neurologists were asked to identify considerations that influence their prescribing decisions when they select treatment options for their patients with MS. Some factors exert a strong influence on most of those surveyed. For example, more than 90% of neurologists said they are influenced or strongly influenced by the patient's ability to adhere to therapy, while more than 70% are influenced by treatment cost to the patient and by evidence from peer-reviewed journals. Opinions were more divided on information in the package insert, CME or promotional materials from pharmaceutical manufacturers, and the availability of patient support programs from pharmaceutical manufacturers (**Figure 9**).

On average, neurologists said 37% of their patients obtain their injectable MS drugs from mail-order pharmacies; 37% from specialty pharmacies; and 27% from retail pharmacies. Thirty-eight percent of the respondents thought the use of mail-order pharmacy services was higher this year than last, and 9% thought it had decreased. Thirty-five percent of respondents thought the use of specialty pharmacy increased this year, and 9% thought it decreased. Other respondents were unsure about fluctuations in the use of these services or felt that utilization had remained more or less the same. In contrast, the use of retail pharmacy services was thought to have decreased by 42% of respondents; only 3% thought these services had increased. Although it is unclear to what extent neurologists are familiar with the sources by which patients obtain their medications, the results suggest that more patients are turning to mail-order and specialty pharmacy services to obtain their DMTs.

## Figure 9

**To what extent do the following factors "influence" or "strongly influence" your prescribing decisions?**




PI: package insert

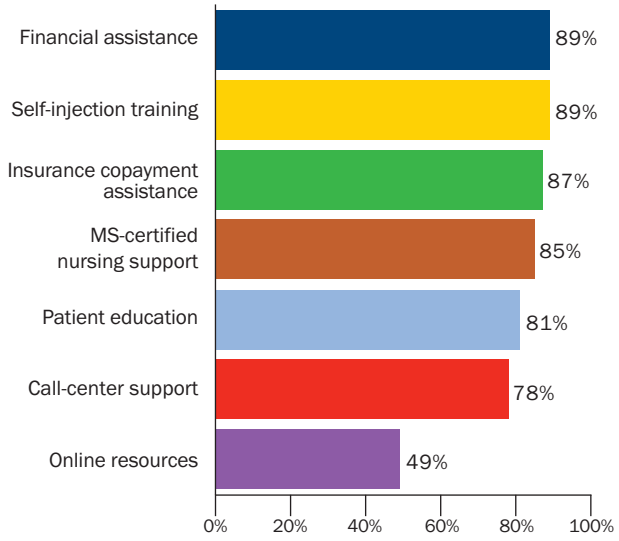
## Patient and Professional Support Services

A number of patient support programs are provided by pharmaceutical manufacturers. These programs offer a variety of services, including patient education and support, training in self-injection, and financial assistance. Respondents described these support services as very valuable to their patients with MS (**Figure 10**). In general, respondents felt that support programs offered by different pharmaceutical manufacturers are very similar (31% of respondents) or similar (52%) to one another. Support programs for Betaseron® (interferon beta-1b subcutaneous injection) and Copaxone® (glatiramer acetate injection) were chosen as superior by 15% of neurologists; support programs for Rebif® (interferon beta-1a subcutaneous injection), by 10%; for Tysabri® (natalizumab), by 8%; and for Avonex® (interferon beta-1a intramuscular injection), by 6%; 46% said no single program is superior. Respondents were also asked about the value of programs provided by the National Multiple Sclerosis Society. Patient programs are considered valuable by a high proportion of neurologists surveyed. The financial assistance program, the Next Step® online tool for newly diagnosed patients, and the MS online library are considered especially important by providers (**Figure 11**).

Respondents were also asked to rate the value of support programs that pharmaceutical manufacturers provide to clinicians. Most of those surveyed felt that many of these programs provide significant value for their practice, including self-injection training, patient education, nursing support, and insurance assistance (**Figure 12**). The respondents also identified several programs from the National Multiple Sclerosis Society that they consider valuable to themselves as practitioners. The National MS Society Resource Guide for Clinicians was regarded as an especially important resource (**Figure 13**).

### Figure 10

**Which aspects of the patient support programs provided by pharmaceutical manufacturers are valuable or very valuable to your patients?**

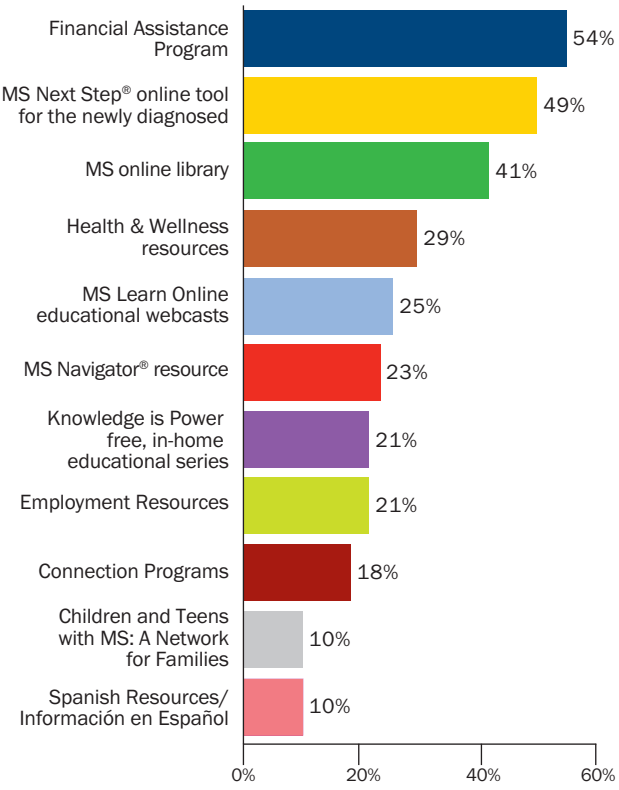



## Emerging Options and Nonpharmacologic Therapies

Several questions invited participants to share their views on new MS therapies. Most respondents (53%)

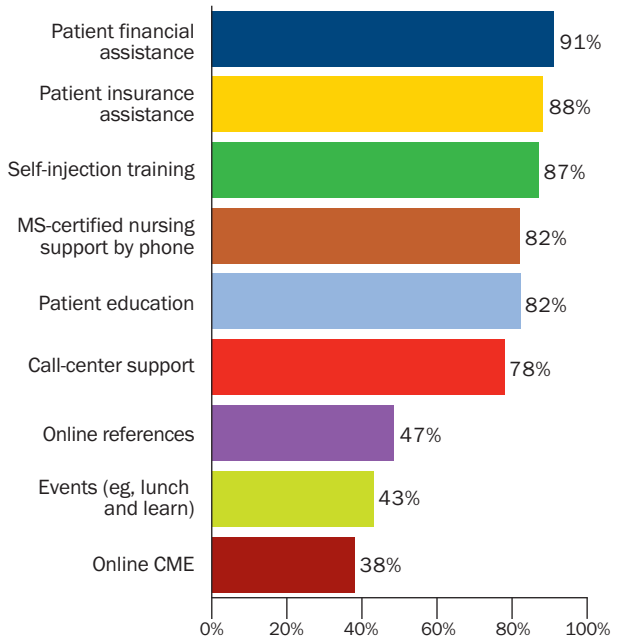
### Figure 11

**Which programs provided by the National Multiple Sclerosis Society are valuable to your patients?**



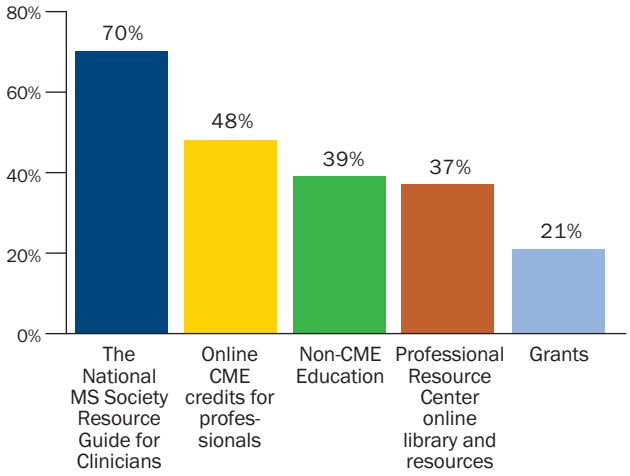
## Figure 12

**Which aspects of patient support programs provided by pharmaceutical manufacturers are of greatest value to you as a practitioner?**




## Figure 13

**Which programs provided by the National Multiple Sclerosis Society are valuable to you as a practitioner?**



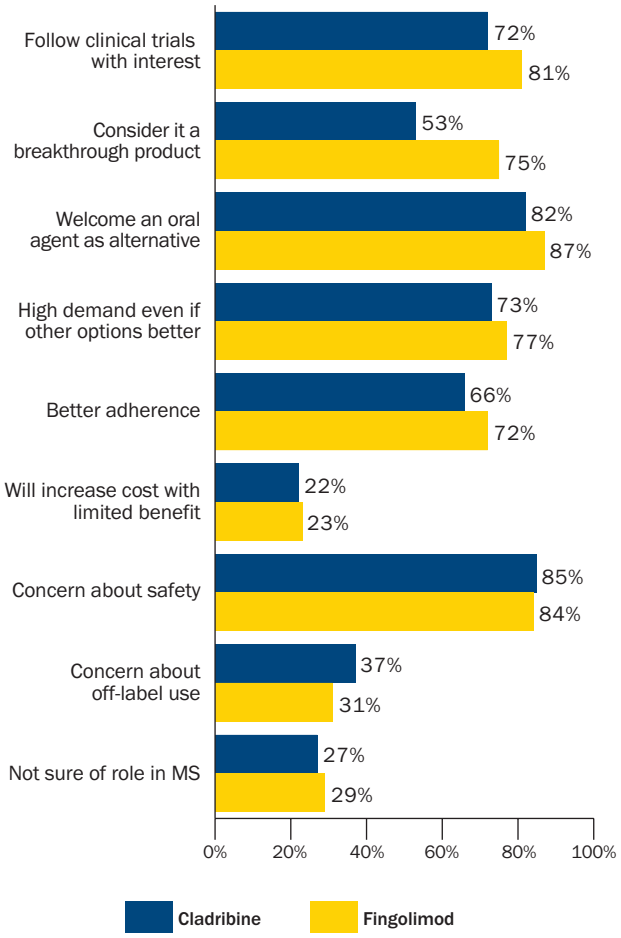

said they are open to prescribing new therapies as soon as they are available if they meet the patient's clinical needs; 44% said they would wait until a new product is integrated into the recommendations of their professional society. Three percent said they would wait until a new therapy is accepted by health plans as medically necessary before prescribing it.

Cladribine, currently under FDA review, and Gilenya™ (fingolimod), approved by the FDA in September 2010, are oral therapies (cladribine is expected to become available for the treatment of RRMS within the next year). Neurologists were asked to describe their familiarity with these agents, the roles they expect oral treatments to play in MS therapy, and the potential limitations of these novel therapies (**Figure 14**). Most participants said that they are familiar with these new agents and that they have been following the clinical trials of these drugs with interest. Most said they believe that an oral alternative to current therapies might improve patient adherence to therapy. More than 80% also expressed concerns about the safety profiles of these newer agents, and 22% strongly agreed or agreed that these new agents may add to the costs of MS treatment with limited clinical benefit. However, more than 70% said that MS patients will demand oral therapies even when another treatment is a better option. Fewer clinicians rated themselves as familiar with several other investigational compounds that are in earlier stages of development, including BG-12 (28% of respondents), alemtuzumab (39%), laquinimod (35%), and teriflunomide (25%).

A broad range of nonpharmacologic strategies are used in treating MS, including complementary and alternative therapies such as diet, nutrition therapy, and acupuncture; rehabilitation treatments such as occupational and physical therapy; and other treatments such as plasma exchange. In general, the neurologists said they have little confidence in the effectiveness of most of these methods, and they reported that few nonpharmacologic approaches are routinely used to treat MS. Respondents' assessments of the effectiveness of these nonpharmacologic approaches are presented in **Figure 15**, and the frequency with which respondents use these strategies in clinical practice is summarized in **Figure 16**. Although neurologists generally do not view

## Figure 14

**Proportion of respondents who agreed or strongly agreed with each statement about oral immunomodulators currently under review by the FDA.**



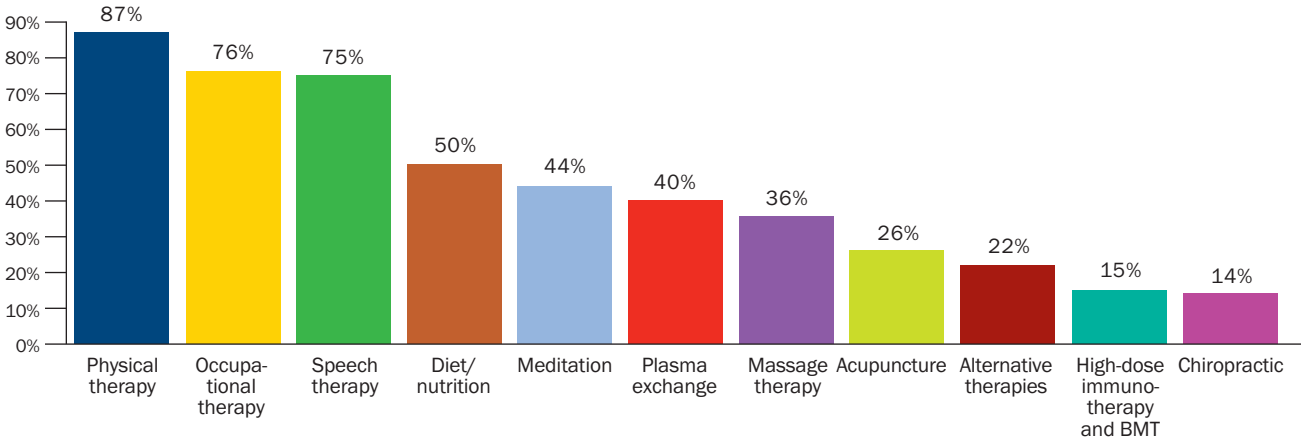

alternative or complementary therapies as highly effective, they estimated that approximately 30% of their patients want to discuss these treatments, and that 25% of patients may be using these therapies without discussing them with their physicians. Besides the limited efficacy that is associated with some alternative and complementary therapies, their use may create safety concerns if they have the potential to interfere or interact with the patient's conventional immunomodulatory treatments. Neurologists' view of the effectiveness of rehabilitative treatments, such as PT and OT, was much more positive than complementary or alternative therapies.

## Summary and Conclusions

The survey findings indicate a number of favorable trends in the treatment of MS, but they also identify causes for concern. Neurologists have largely accepted the importance of treating patients with MS as soon as possible after a definitive diagnosis, and of initiating early treatment for patients with CIS. However, a substantial number of patients with MS or CIS remain untreated. As in previous surveys, many of the neurologists noted that insurance and reimbursement issues are important obstacles to care for some patients with MS. Some of the findings in regard to treatment selection raise important questions about the management

## Figure 15

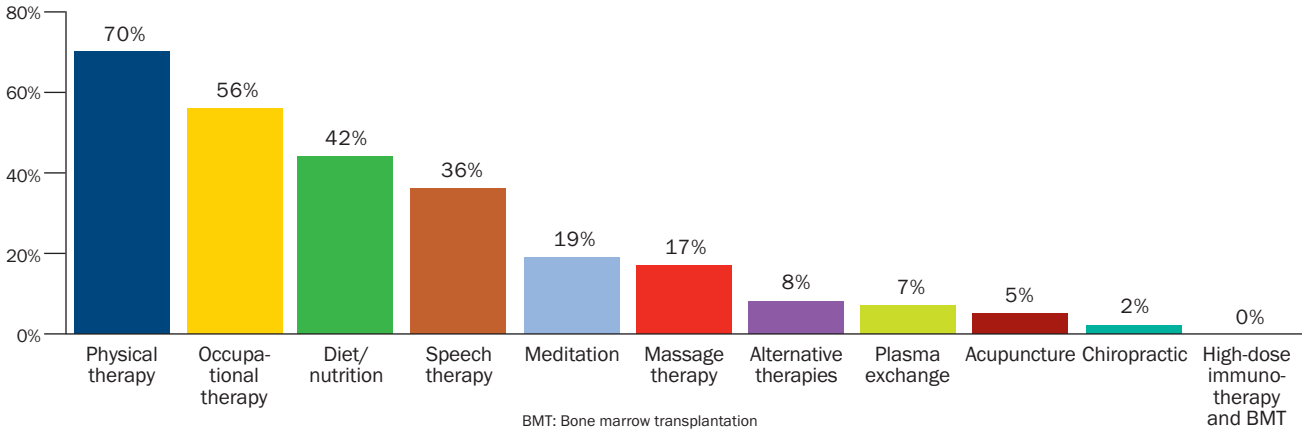
**Proportion of respondents who rated each nonpharmaceutical treatment modality for MS as "very effective" or "effective."**




BMT: Bone marrow transplantation

**Figure 16**

**Frequency with which respondents recommended nonpharmacologic treatments for MS.**




BMT: Bone marrow transplantation

of MS. For example, a relatively large proportion of respondents said they choose options such as immunosuppressants or Tysabri® (natalizumab) as first-line therapy for patients with MS. Many patients are not responding adequately to treatment within a 6- to 12-month period, which may suggest that neurologists need to improve the recognition and management of these patients.

As with any severe chronic illness, the success of treatment for patients with MS is critically linked to patient adherence to treatment and the ability to maintain continuous high-quality medical care. An encouraging finding of this survey is that approximately 90% of the respondents feel that adherence is rarely a problem for their patients. On the other hand, helping providers overcome insurance barriers may assist in ensuring long-term continuity of care for patients with MS, and may help minimize the likelihood of significant interruptions in treatment.

Most of the neurologists surveyed have been in practice for a period of many years, and younger doctors make up a relatively small proportion of those surveyed. Reimbursement and compensation issues may be important drivers of the number of neurologists who will be available in the future to care for patients with MS and other neurologic disorders.

Respondents noted that both patients and physicians benefit from a range of support services provided by pharmaceutical manufacturers and professional societies.

Finally, an important emerging trend in MS care is the identification of new pharmacologic agents that operate through novel mechanisms of action. Neurologists indicated that they are very interested in these new therapies, and most respondents said they expect to incorporate them into clinical practice. Concerns were noted about the safety and tolerability profiles of new therapies.

## NO SUBSTITUTE FOR PROPER TREATMENT AND COMPASSION

**An interview with Phyllis Johnson**

Individual results may vary.

Phyllis Johnson experienced her first MS-related symptoms in 1983, when she was 23 years old, and since then, she has encountered more than her share of bad medical advice and insensitive clinicians.

Phyllis still recalls vividly that moment in 1983 when MS began to change her life dramatically. “I was at work, and within 24 hours I went completely blind in my right eye,” she says. Her ophthalmologist diagnosed

optic neuritis. "He didn't say anything about MS or steroids. He just said, 'You'll get better in 3 months.'" Phyllis did recover her sight, but lingering optic damage required her to start wearing glasses.

"Five years later, in 1989, I woke up with double vision," says Phyllis. "My balance was off — I kept falling over." After an MRI revealed several pea-size lesions in her brain tissue, a specialist said she might have MS, but was unable to draw a conclusion.

For the next 12 years, says Phyllis, "Everything was fine. I got married and had 2 children. Then in 2001 — I used to teach aerobics — I thought I had hurt myself. My legs were numb and tingling. Every time I'd walk they were like a wet noodle."

Phyllis's physician referred her to a neurologist, who asked her if she had ever experienced problems with her vision. An MRI confirmed the doctor's suspicion that Phyllis had relapsing-remitting MS. "But he said that because this was only my third episode in my whole life, he didn't think I'd need any drug therapy," says Phyllis. "I trusted him because he was a doctor. But then in 2003, my vision went completely white. It was like looking through sheer curtains — I couldn't even see my hand in front of my face."

Phyllis sought the opinion of a second neurologist, but it was a referral to Thomas J. Whittaker, JD, MD, a neuro-ophthalmologist at the University of Kansas Medical Center that finally yielded a definitive answer. Phyllis recalls that after a 45-minute exam, Dr. Whittaker said, "This is optic neuritis. You're having a huge MS attack." He prescribed hospitalization, potent steroids, and MS drug therapy.

When the diagnosis of MS was confirmed, says Phyllis, she and her family were "overwhelmed, scared, and nervous — especially me. I thought, what do I do now? I had lots of questions." While her doctor gave her information, she also sought support from the MS Society's local chapter. "I received a huge manila envelope" packed with information in the mail. Members of the local chapter patiently answered all the questions she needed to ask.

Phyllis, who works 4 days per week as an elementary school substitute teacher and whose 2 sons are now teenagers, needed to begin therapy for RRMS right away. While she knew that everyone's experiences vary, she chose Copaxone® (glatiramer acetate injection) and has had no additional relapses. "That's the idea behind Copaxone. It's proven to reduce relapses," she says. A 2009 MRI revealed no new lesions since her last MRI 3 years earlier, she says.

These days, Phyllis says, she feels fortunate that her MS hardly affects her family's routine. The problems she experiences are manageable. "If I want to go somewhere in the evening, I have to ask someone for a ride," she says; usually her husband is able to do the driving. She has to stand near the screen when using an overhead projector, and she cannot read movie or computer text that's not black or very dark.

"I wouldn't go to a KC Royals game in the middle of the afternoon in 100° degree heat!," says Phyllis. Heat sensitivity is one of her symptoms. Spending more than 30 minutes in high temperatures causes her to feel fatigue and flu-like symptoms. "My head spins, and I feel like I'm going to melt," she says. She has declined boating trips due to an irritable bladder. "Every place I go, there's got to be a bathroom. You never know when it's going to hit you," she says.

Substitute teaching suits her, says Phyllis, because it requires a combination of standing and sitting. "You can't tell when I'm walking, but if I stand for more than an hour or two, my legs get shaky," she says.

"People are often shocked when I tell them I have RRMS, because I don't match a stereotype," says Phyllis. "I'm not in a wheelchair, I don't use a cane, and I'm not on disability. I am living as normal a life as possible."

So far, financial challenges have been manageable for Phyllis. "We've always lived within our means," she says, adding that her husband, a CPA, is a diligent saver and a financial planner. Phyllis has also received assistance from Shared Solutions,® a resource network sponsored by Teva Neuroscience. Although her husband's new job means a change in insurance coverage, copays and deductibles, Phyllis hopes to identify resources to assist with increased costs.

Phyllis sometimes feels frustrated by the ocular problems her MS has created, but she's satisfied that she's doing well. "Most of the time I'm very thankful. I still drive; I still work. I can walk my dog, and sometimes I jog. I can put on my makeup and even wear heels. Life is good. I have a few limitations, and I've learned to deal with them," she says.

**For more information:**
www.nationalmssociety.org
Shared Solutions: 1-800-887-8100

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# Multiple Sclerosis at Work

## INSIGHTS FROM AN EMPLOYER ROUNDTABLE

**Multiple sclerosis (MS) in the workplace is no longer regarded with near silence – the growth of the biologic drug market alone has spotlighted its presence – but do employers have the interest and resources to meet the challenges MS poses to workers and corporations? On June 24, 2010, Stanton Mehr, president of SM Health Communications, LLC, led executives from companies in 7 U.S. states in a discussion of trends in the treatment of MS in the managed care environment. What follows is a description of MS at work, informed by comments from the roundtable participants.**

J. Phil Belcher
Manager, Health and Welfare
*Eastman Chemical Company*
Kingsport, TN

Larry Boress
President and CEO
*Midwest Business Group on Health*
Chicago, IL

William Bunn, MD, JD, MPH
Vice President of Health, Safety, Security, and Productivity
*Navistar International Corporation*
Chicago, IL

Shirley R. Dvorin, JD
Associate Vice President, Human Resources
*Jewish United Fund/ Jewish Federation of Metropolitan Chicago*
Chicago, IL

John Neuberger, MS
Vice President, Operations
*QuadMed, LLC*
Milwaukee, WI

Bruce Sherman, MD
Consulting Corporate Medical Director
*The Goodyear Tire and Rubber Company*
Akron, OH

William Yang, MD, MPH
Health Management Physician
*The Coca-Cola Company*
Atlanta, GA

## Overview

Multiple sclerosis (MS) is a chronic disabling disorder that is diagnosed between the ages of 20 and 50 in approximately 75% of patients (peak onset is in the early 30s), at the height of their productivity.[1] Among patients with MS who have worked prior to their diagnosis, only 60% are still employed when diagnosed. Thirty percent or less are working 10 to 15 years after receiving a diagnosis of MS.[2]

At the time of diagnosis, 85% of patients have relapsing-remitting disease (RRMS), which is associated with acute flares that may involve decreased mobility; impaired bowel and bladder function; impaired vision; pain; muscle weakness; altered dexterity; spasticity; fatigue; heat sensitivity;[3,4] and/or cognitive dysfunction.[4] During remissions, symptoms can resolve completely or partially. Fifty percent of MS patients who have RRMS transition to secondary-progressive MS (SPMS) approximately 10 years after being diagnosed. SPMS is associated with increasing neurologic dysfunction and disability.[5]

Seventy-five percent of MS patients who are no longer working still wish to be employed.[2] Executives generally believe that companies are best served by doing what they can to keep employees with MS on the job.

## MS and Productivity

To remain at their most productive, employees with MS require access to effective therapies and to accommodations that help them do their jobs. While the task of fully meeting these needs can be a challenge for many employers, the consensus of roundtable participants was that in theory, at least, retaining a trained worker who incurs costs on account of an illness is still a worthwhile investment for the company. "It may be more cost-effective to provide medications and treatment to keep a skilled employee on the job and off disability than to have to recruit, hire, and train a replacement," said Bruce Sherman, MD, consulting medical director of The Goodyear Tire and Rubber Company in Akron, OH. But as the use of biologic medications steadily grows, and health-care costs continue to rise, employers are finding it increasingly difficult to provide a generous benefit package. Moreover, the provision of worksite accommodations relies in part on companies' perception that employees with MS are far better able to work to their fullest level of productivity when they have the assistance they need.

## Design of the Health Benefit

"Our cost for specialty drugs is rising at 25% per year. We're constantly trying to balance the patient's cost share, to make it reasonable and affordable," said John Neuberger, MS, vice president of Operations at QuadMed, LLC, in Milwaukee, WI. A recent Biotechnology Monitor & Survey report notes that "continuing to offer affordable benefits to all enrollees as more [of them] use high-cost biologics" is among the most difficult hurdles that confront employers today.[6] MS treatments are facing especially close scrutiny: "At Eastman, 4 of the top 7 specialty drugs, in terms of expenditures, are MS agents. When considering all pharmaceuticals, 2 of the top 20 are MS drugs," says Health and Welfare manager J. Phil Belcher of Eastman Chemical Company in Kingsport, TN. Only 38 of the company's 9,000-plus non-Medicare population of employees, early retirees, and their dependents are being treated for a disease using a drug from the specialty category. "This means we need to figure out the pinch point," says Belcher, "around balancing the cost for the individual and the cost of this care for the organization."

Prescott and colleagues[7] reported on the analysis of administrative claims data from 80 health plans collected between January 1 and December 31, 2004. This study revealed that the pharmacy costs associated with MS accounted for approximately 65% of all the health plans' direct disease-related medical costs (average total of direct treatment costs are $12,879 per patient per year). These researchers also found that 57% of patients received at least one disease-modifying drug for MS.[7]

At the same time that plans try to assess and predict the impact of costly biologics, MS patients may find that the use of disease-modifying drugs may help tamp down costs. In tracking workers with MS over a 2-year follow-up, one study[8] suggested that those with the fewest relapses incur the lowest costs. Conversely, workers who experience frequent exacerbations in their symptoms cost their companies significantly more than those who do not suffer frequent increases in the disease or symptom severity. A more recent study[9] evaluated the cost-effectiveness of DMTs over a similar time period (eg, 2 years). An analysis of direct costs suggested that a reduction in the frequency and severity of MS relapses may have substantial short-term budgetary impact that partially offsets the cost of DMTs. Additional studies that factor in the baseline differences between DMTs, indirect costs, and quality-adjusted life years may provide further insight in this area.

**The Benefit Outlook.** Managed care organizations seem to favor covering most MS medications under the pharmacy benefit. In 2009, 74% of surveyed health plan executives indicated that the use of MS biologics was covered through the pharmacy benefit; 26% of those surveyed said they cover these therapies under the medical benefit although this varies depending on the specific medication.[6]

Plans' view of the pharmacy benefit may be influenced by the tools used to manage these benefits,

such as quantity limits, step therapy, prior authorization, and specialty tier placement. In one survey, 47% of responding employers indicated that they use specialty pharmacy providers, and roughly 25% contract with them directly.[6] A report by Biotechnology Monitor & Survey indicates that employers are drawn to specialty pharmacy not only for its featured price negotiations with manufacturers, but also for its distribution networks and its promotion of disease management, particularly patient education and coordinated care.[6] "There seems to be less waste [in the use] of expensive medicines through specialty pharmacy, and more patient education," said William Yang, MD, MPH, health management physician at The Coca-Cola Company in Atlanta, GA.

Most of the panelists said their plans cover MS drugs like Copaxone® (glatiramer acetate injection) or the interferons under the pharmacy benefit, specifically through specialty pharmacy. They also indicated that this coverage may underscore for patients the high cost of these drugs due to cost-sharing provisions such as coinsurance or higher copays. High out-of-pocket maximums and other cost-sharing devices can challenge a worker's ability to afford treatment, especially biologic drugs. "The specialty drugs are driving our conversations about raising annual out-of-pocket maximums, but we want to make sure that our workers and dependents can afford them [so they can stay] healthy and productive," said QuadMed's John Neuberger, who noted the therapies' apparent value in contributing to productivity and presenteeism.

**Executive Orders.** Specific decisions on drug formulary and coverage, said the panelists, are generally the domain of health-plan or third-party administrators. "We do get involved in wanting to understand whether a new therapy is coming to market," said Belcher, "and if we don't think [the therapy is] critical because existing therapies are adequate, then we want to tightly manage access." When medications' safety is called into question, or a new, potentially high-use and high-cost agent is approved by the Food and Drug Administration, some employers confer with their benefit plan administrators to settle on a company response.

**Proving Productivity.** Panelists agreed that if the use of combination therapy for MS becomes more prevalent, health plans will be compelled to evaluate the efficacy of these therapies with more precision. Learning how these medications can influence productivity at the workplace will become more critical as their use increases, according to Dr. Sherman and William Bunn, MD, JD, MPH, vice president of Health, Safety, Security, and Productivity at Navistar International Corporation in Chicago, IL.

Ironically, the success of disease-modifying agents may make their usefulness harder for some to understand. Coca-Cola's Dr. Yang explained that because today's treatments for MS help reduce the symptoms that cause disability and absenteeism, especially in the early stages of the illness, human resources staff may not realize that patients may be doing well because they have access to MS therapies, thereby avoiding relapses that can boost corporate expenditures.

## Give and Take

Accommodations that may be perfectly tailored to employees with MS in one work setting may be less of a priority in another type of organization. Dr. Yang pointed to different priorities in manufacturing and office settings for workers with MS. "Multiple sclerosis is a much harder condition to accommodate in the manufacturing setting, because of [the disease's] physical effects," he said. "It's easier to address in the office setting, with more cognitive, mental work." In contrast to a cubicle, a private office with its own thermostat allows workers to manage heat sensitivity, a physical symptom of MS.

In a manufacturing company or other large facility, mobility may be an issue. Employees with MS may have difficulty moving around the building when they need to, and with appropriate speed. "This is often the biggest disability associated with their condition," said Dr. Yang. "We can offer scooters or

other assistance vehicles to help them move from one part of a building to another." Accommodations that are useful to employees with MS or other chronic disabling illnesses include altered work schedules; telecommuting; flexible leave time; ergonomic workstations (eg, adjustable positioning of keyboards and monitors, adjustable chairs, and foot rests); the positioning of equipment such as printers and copiers close to workstations; adaptive equipment, including communication assistance devices like voice amplification, speech recognition software, and on-screen keyboards; mobility aids such as canes, scooters, and elevators; and individualized office temperature control through such devices as portable air conditioners.[10]

Panelists were in agreement that the option of working at home, or telecommuting, is highly valued by patients with chronic physical disability. "The commute to work can be very challenging and very stressful," said Shirley Dvorin, JD, associate vice president of Human Resources for the Jewish United Fund/Jewish Federation of Metropolitan Chicago. Ms. Dvorin, who has MS, indicated that working from home during relapses, even 2 days a week, "can make a tremendous difference in the productivity of the person with MS."

In any work setting, the cycles of relapse and remission that affect the majority of MS patients at the time of diagnosis may create unpredictable needs for use of vacation time or for unpaid leave. In these situations, said Dr. Sherman, it is important for individuals to understand how the Family and Medical Leave Act (FMLA) can help ensure their job security. "Employers with knowledge of an employee with MS are encouraged to be proactive with respect to accommodation issues," he said. He recommended that employers be familiar with provisions of the FMLA and the Americans with Disabilities Act, as they apply to MS.

## MS: Impact on Coworkers

Panelists reported that coworkers may feel that they are being required to bear heavier workloads when employees who have MS experience flare-ups that lower their productivity. Coworkers may even become uncomfortable around a fellow employee who has MS, in part because they are unable to judge symptoms like muscle spasticity in relation to job performance. "The manager or supervisor may not understand the condition and may raise the issue of whether the patient with MS is capable of working at the job," said Dr. Yang.

Ms. Dvorin observed that the discomfort some coworkers feel may be worsened when employees who have MS are reluctant to share information about their condition. Dr. Bunn concurred, adding that to reduce the effects of MS at work, managers, supervisors, and coworkers need to know what to do—and what not to do—when confronted with its symptoms in a fellow employee.

## Education and Advocacy

The panelists generally agreed that on-site corporate medical teams are a likely starting point for reviewing and stepping up MS education and advocacy in the workplace. It begins with providing information on MS and on the needs of fellow employees who have the disease, noted Eastman Chemical Company's Belcher. "The medical group can help educate the worksite [as to how] employees [with MS] can be accommodated," he said. "We might also turn to health coaches from the health plan for help in coordinating this care."

Corporate medical teams can serve as effective advocates for employees with MS, said Dr. Yang. "This could be the worksite nurse, case manager, or physician. I've been that advocate myself, on occasion. Specialists are involved in various parts of it, but there is rarely one person available to coordinate care," he remarked. Health plans tend to recommend individual case management for smaller numbers of patients with high-cost disorders, like MS. But Ms. Dvorin pointed out that "though it is not unusual for patients with progressive MS to have a case manager, this is generally not so for patients with earlier-stage MS.

Their level of disability and expense may not have triggered case management to become involved" inside or beyond the corporate setting. "It's a matter of the health plan using the right tools to keep costs down," she said.

## Adding it Up

Panelists agreed that the use of cost-management tools such as specialty pharmacy carve-outs or higher patient cost sharing does not guarantee that MS patients will see progress in the quality of their day-to-day work lives. Better coordination of care, along with improvements in treatments, offer the most likely prospects for change in the short term. Larry Boress, president and CEO of Chicago's Midwest Business Group on Health, spoke on behalf of all the panelists when he said, "We need to emphasize the health plan, the physician, and the employer working together, with appropriate education, to help the patient with MS maintain productivity and prevent relapses. And we need to optimally use the tools that are available to do it cost-effectively."


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## THE FORGOTTEN MAN: MEN AS CAREGIVERS

**By Stephanie Watson**

Daniel Rude begins every morning with an assessment of his wife, Jean. He finds out how she slept and how well she's moving before he heads into his home office where he works as an independent IT consultant. Rude tries to schedule his client meetings around Jean's doctor's appointments, physical therapy sessions and errands, but he can only plan his days from hour to hour.

"I can't make any serious plans because I don't know what the rest of the day is going to be like," he said. "Each day has the potential for wonderful things happening, and it also has the potential for catastrophic things if she has a fall or an illness." Jean was diagnosed with MS in 2002. Rude has been caring for her since 2005.

Brian Rickman has been taking care of his wife, Terry, since they got together nearly two decades ago at Beaver College in Pennsylvania. Over 20 years, Terry has become progressively weaker. Today, she must use a wheelchair, and Rickman has to help her with even the most basic tasks—including getting out of bed and going to the bathroom. "There's been a lot of times I've felt more like a nurse than a husband," he said.

### Men who care

There is a tendency to think of caregivers as women, and, overall, that generalization holds true. Between 59% and 75% of all family caregivers are female, according to the Family Caregiver Alliance. However, MS is unique in that three-quarters of people with MS are women, and more than half of their caregivers are male (most of them spouses).

Despite the role reversal, the societal stereotype of the female as nurturing caregiver is hard to shake. "I think the community at large really doesn't expect that of men," said David Rintell, EdD, a psychologist at the Partners MS Center of Brigham and Women's Hospital in Boston. "I think there's a myth that men aren't caregivers

and men aren't good at the job." Yet, research shows male caregivers can and do tackle everything from grocery shopping and housework, to helping their loved one dress, bathe and use the toilet. "I have seen many men who are wonderful caregivers," Dr. Rintell said. "They are very dedicated, very patient, and they will pretty much do anything to help their partner remain as independent as possible."

## Overwhelming responsibilities

Caring for another person can be overwhelming, especially for anyone who is new to the role. "The first few years when Jean had MS, every time a pot would rattle in a cupboard or something would fall off a shelf, I would pop out of my chair to find out if she had taken a fall," Rude recalled. The first time Rickman had to give his wife an injection, he said, he nearly passed out. The time commitment can also be overwhelming. "I always have to be on call," Rickman said. "I have to plan my activities so that I won't be away from the house for an extended period of time." The time demands can also affect the caregiver's ability to earn a living. Rickman, who does software quality control, has a flexible work schedule that allows him to come home during the day to help Terry while Rude works in his home office.

But often caregivers can't work at all, which can have repercussions beyond finances. "There are all of these other implications having to do with social life, self-esteem and self-worth," said Nicholas G. LaRocca, PhD, vice president of Health Care Delivery and Policy Research for the National Multiple Sclerosis Society.

## The emotional toll

Caring for a spouse or family member can be emotionally draining. This can be especially hard on men, who tend to present a stoic face to the world no matter how much stress they feel inside. "Men are brought up to take care of things on their own," said Dr. Rintell. "You're supposed to handle any challenge that is thrown at you without any help." Some men fear that asking for assistance will be perceived as a sign of weakness or a concession that they can't handle their caregiving role.

*"Between 59% and 75% of all family caregivers are female... However, MS is unique in that three-quarters of people with MS are women, and more than half of their caregivers are male (most of them spouses)."*

When men's emotions become overwhelming, they may be less likely than women to open up. "Typically, men suffer in silence when they reach a boiling point, until they have an emotional or physical explosion," Rude said.

## Caring for the caregiver

One way for men to release bottled-up emotions and share specific issues they're facing is to attend an MS caregiver group. For men who don't feel comfortable discussing their feelings in mixed company, a men's-only group can sometimes be more freeing.

Another way to ease the strain is to just get out of the house. "Nobody can function well without having a break or some respite," Rintell said. Yet it can be hard for caregivers to get away, either because they don't have help or they feel guilty about leaving their loved one. "Guilt is a big part of being a caregiver," said Rude. "I had to learn to let go of that."

Rude sets aside three nights a week for himself. "I look forward to those evenings, even if there's nothing planned," he says.

## Caregiving rewards

Caring for a spouse or other family member with MS can be stressful for men, but knowing they are helping someone they love also has its rewards. Many wouldn't dream of stepping down from their position and turning over their loved one's care to anyone else. "The goal is to keep Jean in the house for as long as possible," Rude said. "For the foreseeable future, that's the way it's going to stay."

**For more information:**
www.nationalMSsociety.org
Well Spouse Association at www.wellspouse.org

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use COPAXONE® safely and effectively.**
**See full prescribing information for COPAXONE.**

**COPAXONE (glatiramer acetate injection) solution for subcutaneous injection**
**Initial U.S. Approval: 1996**

## RECENT MAJOR CHANGES

Indications and Usage (1) 2/2009

## INDICATIONS AND USAGE

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

## DOSAGE AND ADMINISTRATION

- For subcutaneous injection only (2.1)
- Recommended dose: 20 mg/day (2.1)
- Before use, allow the solution to warm to room temperature (2.2)

## DOSAGE FORMS AND STRENGTHS

- Prefilled syringe containing 1 mL solution with 20 mg of glatiramer acetate (3)

## CONTRAINDICATIONS

Known hypersensitivity to glatiramer acetate or mannitol (4)

## WARNINGS AND PRECAUTIONS

- Immediate Post-Injection Reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting (5.1)
- Chest pain, usually transient (5.2)
- Lipoatrophy and skin necrosis may occur. Instruct patient in proper injection technique and to rotate injection sites daily (5.3)
- COPAXONE can modify immune response (5.4)

## ADVERSE REACTIONS

- In controlled studies, most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact TEVA at 1-800-221-4026 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

## USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known if COPAXONE is excreted in human milk (8.3)
- Pediatric Use: The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: [2/2009]**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**
**COPAXONE (glatiramer acetate injection)**

## 1 INDICATIONS AND USAGE

COPAXONE is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dose

COPAXONE is for subcutaneous use only. Do not administer intravenously. The recommended dose of COPAXONE is 20 mg/day.

### 2.2 Instructions for Use

Remove one blister that contains the syringe from the COPAXONE prefilled syringes package. Since this product should be refrigerated, let the prefilled syringe stand at room temperature for 20 minutes to allow the solution to warm to room temperature. Inspect the COPAXONE syringe visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution in the syringe should appear clear, colorless to slightly yellow. If particulate matter or discoloration is observed, discard the COPAXONE syringe.

Areas for self-injection include arms, abdomen, hips, and thighs. The prefilled syringe is for single use only. Discard unused portions.

## 3 DOSAGE FORMS AND STRENGTHS

Single-use prefilled syringe containing 1 mL solution with 20 mg of glatiramer acetate and 40 mg of mannitol.

## 4 CONTRAINDICATIONS

COPAXONE is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Immediate Post-Injection Reaction

Approximately 16% of patients exposed to COPAXONE in the 5 placebo-controlled trials compared to 4% of those on placebo experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. The symptoms were generally transient and self-limited and did not require treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.

Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

### 5.2 Chest Pain

Approximately 13% of COPAXONE patients in the 5 placebo-controlled studies compared to 6% of placebo patients experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection of COPAXONE was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

### 5.3 Lipoatrophy and Skin Necrosis

At injection sites, localized lipoatrophy and, rarely, injection site skin necrosis have been reported during the postmarketing experience. Lipoatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites daily.

### 5.4 Potential Effects on Immune Response

Because COPAXONE can modify immune response, it may interfere with immune functions. For example, treatment with COPAXONE may interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that COPAXONE does this, but there has not been a systematic evaluation of this risk. Because COPAXONE is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

Although COPAXONE is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with COPAXONE may result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in most patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RRMS patients given COPAXONE, 20 mg, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

*Incidence in Controlled Clinical Trials*

Among 563 patients treated with COPAXONE in blinded placebo controlled trials, approximately 5% of the subjects discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity. The most common adverse reactions were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with COPAXONE than in patients treated with placebo. Adverse reactions were usually mild in intensity.

**Table 1: Adverse reactions in controlled clinical trials with an incidence ≥2% of patients and more frequent with COPAXONE than with placebo**

| | | GA 20 mg (N=563) | Placebo (N=564) |
|---|---|---|---|
| Blood And Lymphatic System Disorders | Lymphadenopathy | 7% | 3% |
| Cardiac Disorders | Palpitations | 9% | 4% |
| | Tachycardia | 5% | 2% |
| Eye Disorders | Eye Disorder | 3% | 1% |
| | Diplopia | 3% | 2% |
| Gastrointestinal Disorders | Nausea | 15% | 11% |
| | Vomiting | 7% | 4% |
| | Dysphagia | 2% | 1% |
| General Disorders And Administration Site Conditions | Injection Site Erythema | 43% | 10% |
| | Injection Site Pain | 40% | 20% |
| | Injection Site Pruritus | 27% | 4% |
| | Injection Site Mass | 26% | 6% |
| | Asthenia | 22% | 21% |
| | Pain | 20% | 17% |
| | Injection Site Edema | 19% | 4% |
| | Chest Pain | 13% | 6% |
| | Injection Site Inflammation | 9% | 1% |
| | Edema | 8% | 2% |
| | Injection Site Reaction | 8% | 1% |
| | Pyrexia | 6% | 5% |
| | Injection Site Hypersensitivity | 4% | 0% |
| | Local Reaction | 3% | 1% |
| | Chills | 3% | 1% |
| | Face Edema | 3% | 1% |
| | Edema Peripheral | 3% | 2% |
| | Injection Site Fibrosis | 2% | 1% |
| | Injection Site Atrophy* | 2% | 0% |
| Immune System Disorders | Hypersensitivity | 3% | 2% |
| Infections And Infestations | Infection | 30% | 28% |
| | Influenza | 14% | 13% |
| | Rhinitis | 7% | 5% |
| | Bronchitis | 6% | 5% |
| | Gastroenteritis | 6% | 4% |
| | Vaginal Candidiasis | 4% | 2% |
| Metabolism And Nutrition Disorders | Weight Increased | 3% | 1% |
| Musculoskeletal And Connective Tissue Disorders | Back Pain | 12% | 10% |
| Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) | Benign Neoplasm of Skin | 2% | 1% |

| *Continued* | | GA 20 mg (N=563) | Placebo (N=564) |
|---|---|---|---|
| Nervous System Disorders | Tremor | 4% | 2% |
| | Migraine | 4% | 2% |
| | Syncope | 3% | 2% |
| | Speech Disorder | 2% | 1% |
| Psychiatric Disorders | Anxiety | 13% | 10% |
| | Nervousness | 2% | 1% |
| Renal And Urinary Disorders | Micturition Urgency | 5% | 4% |
| Respiratory, Thoracic And Mediastinal Disorders | Dyspnea | 14% | 4% |
| | Cough | 6% | 5% |
| | Laryngospasm | 2% | 1% |
| Skin And Subcutaneous Tissue Disorders | Rash | 19% | 11% |
| | Hyperhidrosis | 7% | 5% |
| | Pruritus | 5% | 4% |
| | Urticaria | 3% | 1% |
| | Skin Disorder | 3% | 1% |
| Vascular Disorders | Vasodilatation | 20% | 5% |

*Injection site atrophy comprises terms relating to localized lipoatrophy at injection site

Adverse reactions which occurred only in 4-5 more subjects in the COPAXONE group than in the placebo group (less than 1% difference), but for which a relationship to COPAXONE could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia (16 x$10^9$/L), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with COPAXONE were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically relevant age subgroups.

*Other Adverse Reactions*

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled premarketing studies (n= 979), the role of COPAXONE in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used COPAXONE and reported a reaction divided by the total number of patients exposed to COPAXONE. All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse reactions are defined as those occurring in at least 1/100 patients and *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients.

*Body as a Whole:*

*Frequent:* Abscess

*Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

*Cardiovascular:*

*Frequent:* Hypertension.

*Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

*Digestive:*

*Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

*Endocrine:*

*Infrequent:* Goiter, hyperthyroidism, and hypothyroidism.

*Gastrointestinal:*

*Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

*Hemic and Lymphatic:*

*Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

*Metabolic and Nutritional:*

*Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

*Musculoskeletal:*

*Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

*Nervous:*

*Frequent:* Abnormal dreams, emotional lability, and stupor.

*Infrequent*: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

*Respiratory:*

*Frequent:* Hyperventilation and hay fever.

*Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

*Skin and Appendages:*

*Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

*Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

*Special Senses:*

*Frequent:* Visual field defect.

*Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

*Urogenital:*

*Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency, and vaginal hemorrhage.

*Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

### 6.2 Postmarketing Experience

Reports of adverse events occurring under treatment with COPAXONE not mentioned above that have been received since market introduction and may or may not have causal relationship to COPAXONE are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Body as a Whole:* sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction

*Cardiovascular System:* thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

*Digestive System:* tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

*Hemic and Lymphatic System:* thrombocytopenia; lymphoma-like reaction; acute leukemia

*Metabolic and Nutritional Disorders:* hypercholesterolemia

*Musculoskeletal System:* rheumatoid arthritis; generalized spasm

*Nervous System:* myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

*Respiratory System:* pulmonary embolus; pleural effusion; carcinoma of lung; hay fever

*Special Senses:* glaucoma; blindness; visual field defect

*Urogenital System:* urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

## 7 DRUG INTERACTIONS

Interactions between COPAXONE and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE has not been formally evaluated in combination with interferon beta.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category B.

Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, COPAXONE should be used during pregnancy only if clearly needed.

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/$m^2$ basis). In rats receiving subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

### 8.2 Labor and Delivery

The effects of COPAXONE on labor and delivery in pregnant women are unknown.

**8.3 Nursing Mothers**

It is not known if glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE is administered to a nursing woman.

**8.4 Pediatric Use**

The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age.

**8.5 Geriatric Use**

COPAXONE has not been studied in elderly patients.

**8.6 Use in Patients with Impaired Renal Function**

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

## 11 DESCRIPTION

COPAXONE is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

$$(Glu, Ala, Lys, Tyr)_x \bullet x CH_3COOH$$

$$(C_5H_9NO_4 \bullet C_3H_7NO_2 \bullet C_6H_{14}N_2O_2 \bullet C_9H_{11}NO_3)_x \bullet x C_2H_4O_2$$

CAS - 147245-92-9

COPAXONE is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of COPAXONE is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

## 12 CLINICAL PHARMACOLOGY

**12.1 Mechanism of Action**

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS are not fully understood. However, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. There is no evidence that glatiramer acetate does this, but this has not been systematically evaluated *[see Warnings and Precautions (5.4)]*.

**12.2 Pharmacokinetics**

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

## 13 NONCLINICAL TOXICOLOGY

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m$^2$ basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m$^2$ basis). No increase in neoplasms was observed.

Glatiramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m$^2$ basis) no adverse effects were observed on reproductive or developmental parameters.

## 14 CLINICAL STUDIES

**14.1 Relapsing-Remitting Multiple Sclerosis (RRMS)**

Evidence supporting the effectiveness of COPAXONE in decreasing the frequency of relapses derives from 3 placebo-controlled trials, all of which used a COPAXONE dose of 20 mg/day.

Study 1 was performed at a single center. Fifty patients were enrolled and randomized to receive daily doses of either COPAXONE, 20 mg subcutaneously, or placebo (COPAXONE: n=25; placebo: n=25). Patients were diagnosed with RRMS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurological signs for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: the frequency of attacks during the trial, and the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 2 presents the values of the three outcomes described above, as well as several protocol specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

**Table 2: Study 1 Efficacy Results**

| | COPAXONE (N=25) | Placebo (N=25) | P-Value |
|---|---|---|---|
| % Relapse-Free Patients | 14/25 (56%) | 7/25 (28%) | 0.085 |
| Mean Relapse Frequency | 0.6/2 years | 2.4/2 years | 0.005 |
| Reduction in Relapse Rate Compared to Prestudy | 3.2 | 1.6 | 0.025 |
| Median Time to First Relapse (days) | >700 | 150 | 0.03 |
| % of Progression-Free* Patients | 20/25 (80%) | 13/25 (52%) | 0.07 |

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

Study 2 was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (COPAXONE: n=125; placebo: n=126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. Table 3 presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

**Table 3: Study 2 Efficacy Results**

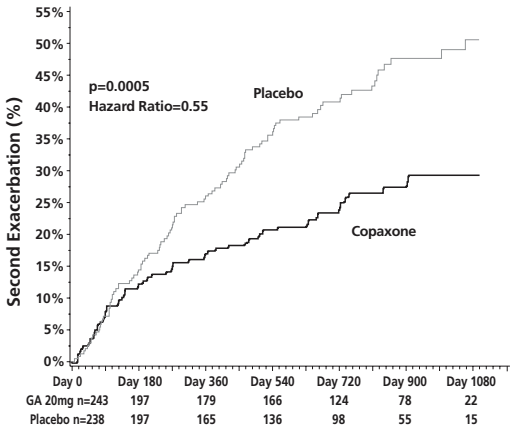
| | COPAXONE (N=125) | Placebo (N=126) | P-Value |
|---|---|---|---|
| Mean No. of Relapses | 1.19/2 years | 1.68/2 years | 0.055 |
| % Relapse-Free Patients | 42/125 (34%) | 34/126 (27%) | 0.25 |
| Median Time to First Relapse (days) | 287 | 198 | 0.23 |
| % of Progression-Free Patients | 98/125 (78%) | 95/126 (75%) | 0.48 |
| Mean Change in DSS | -0.05 | +0.21 | 0.023 |

In both studies, COPAXONE exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that COPAXONE is considered effective.

In Study 3, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either COPAXONE 20 mg/day (n=243) or placebo (n=238). The primary outcome measure was time to development of a second exacerbation. Patients were followed for up to three years or until they reached the primary endpoint. Secondary outcomes were brain MRI measures, including number of new T2 lesions and T2 lesion volume.

Time to development of a second exacerbation was significantly delayed in patients treated with COPAXONE compared to placebo (Hazard Ratio = 0.55; 95% confidence interval 0.40 to 0.77; Figure 1). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the COPAXONE group.

**Figure 1: Time to Second Exacerbation**



Patients treated with COPAXONE demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; $p < 0.0001$). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (ratio of 0.89; confidence interval 0.84 to 0.94; $p = 0.0001$).

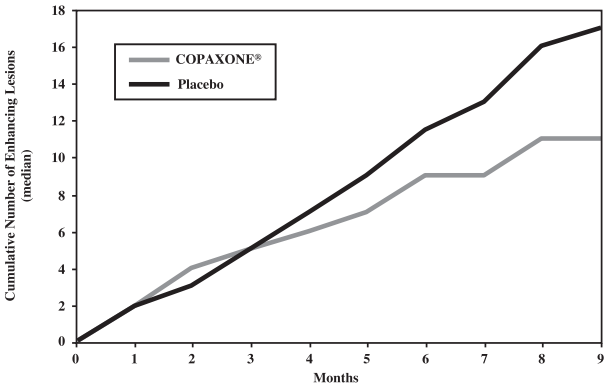
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 4 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

**Table 4: Study 4 MRI Results**

| | COPAXONE (N=119) | Placebo (N=120) | P-Value |
|---|---|---|---|
| Medians of the Cumulative Number of T1 Gd-Enhancing Lesions | 11 | 17 | 0.0030 |

Figure 2 displays the results of the primary outcome on a monthly basis.

**Figure 2: Median Cumulative Number of Gd-Enhancing Lesions**




## 16 HOW SUPPLIED/STORAGE AND HANDLING

COPAXONE is supplied as a single-use prefilled syringe containing 1 mL of a clear, colorless to slightly yellow, sterile, nonpyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol in cartons of 30 single-use prefilled syringes with 33 alcohol preps (NDC 68546-317-30).

The recommended storage condition for the COPAXONE is refrigeration (2ºC to 8ºC / 36ºF to 46ºF). However, excursions from recommended storage conditions (15ºC to 30ºC / 59ºF to 86ºF) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided. COPAXONE should not be frozen. If a COPAXONE syringe freezes, it should be discarded.

COPAXONE contains no preservative. Do not use if the solution contains any particulate matter.

## 17 PATIENT COUNSELING INFORMATION

*[See FDA-Approved Patient Labeling (17.7)]*

**17.1 Pregnancy**

Instruct patients that if they are pregnant or plan to become pregnant while taking COPAXONE they should inform their physician.

**17.2 Immediate Post-Injection Reaction**

Advise patients that COPAXONE may cause various symptoms after injection, include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms are generally transient and self-limited and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

**17.3 Chest Pain**

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation. Inform patients that the pain should be transient (usually only lasting a few minutes). Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patient should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

**17.4 Lipoatrophy and Skin Necrosis at Injection Site**

Advise patients that localized lipoatrophy, and rarely, injection site necrosis may occur at injections sites. Instruct patients to follow proper injection technique and to rotate injection areas and sites on a daily basis.

**17.5 Instructions for Use**

Instruct patients to read the COPAXONE Patient Information leaflet carefully. Caution patients to use aseptic technique. The first injection should be performed under the supervision of a health care professional. Instruct patients to rotate injection areas and sites on a daily basis. Caution patients against the reuse of needles or syringes. Instruct patients in safe disposal procedures.

**17.6 Storage Conditions**

Advise patients that the recommended storage condition for COPAXONE is refrigeration (36-46ºF /2-8ºC), although COPAXONE can be stored at room temperature (59-86ºF /15-30ºC) for up to one month. COPAXONE should not be exposed to higher temperatures or intense light.

**17.7 FDA-Approved Patient Labeling**

Read this information carefully before you use COPAXONE. Read the information you get when you refill your COPAXONE prescriptions because there may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

**What is COPAXONE?**

COPAXONE (co-PAX-own) is a medicine you inject to treat Relapsing-Remitting Multiple Sclerosis. Although COPAXONE is not a cure; patients treated with COPAXONE have fewer relapses.

**Who should not use COPAXONE?**

- Do not use COPAXONE if you are allergic to glatiramer acetate or mannitol.

**What are the possible side effects of COPAXONE?**

- **Call your doctor right away if you develop any of the following symptoms: hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site.** Do not give yourself any more injections until your doctor tells you to begin again.
- The most common side effects of COPAXONE are redness, pain, swelling, itching, or a lump at the injection site. These reactions are usually mild and seldom require medical care.
- Some patients report a short-term reaction right after injecting COPAXONE. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes after an injection, last a few minutes, and then go away by themselves without further problems.
- A permanent depression under the skin at the injection site may occur, due to a local destruction of fat tissue.
- **If symptoms become severe, call the emergency phone number in your area.** Do not give yourself any more injections until your doctor tells you to begin again.

These are not all the possible side effects of COPAXONE. For a complete list, ask your doctor or pharmacist. Tell your doctor about any side effects you have while taking COPAXONE.

**Information for pregnant and nursing women**

- COPAXONE has not been studied in pregnant women. Talk to your doctor about the risks and benefits of COPAXONE if you are pregnant or planning a pregnancy.
- It is not known if COPAXONE passes into breastmilk. Talk to your baby's doctor about the risks and benefits of breastfeeding while using COPAXONE.

**How should I use COPAXONE?**

- The recommended dose of COPAXONE for the treatment of Relapsing-Remitting Multiple Sclerosis is 20 mg once a day injected subcutaneously (in the fatty layer under the skin).
- Look at the medicine in the prefilled syringe. If the medicine is cloudy or has particles in it, do not use it. Instead, call Shared Solutions® at 1-800-887-8100 for assistance.
- Have a friend or relative with you if you need help, especially when you first start giving yourself injections.
- Each prefilled syringe should be used for only one injection. Do not reuse the prefilled syringe. After use, throw it away properly.
- Do not change the dose or dosing schedule or stop taking the medicine without talking with your doctor.

**How do I inject COPAXONE?**

There are 3 basic steps for injecting COPAXONE prefilled syringes:

1. Gather the materials.
2. Choose the injection site.
3. Give yourself the injection.

**<u>Step 1</u>: Gather the materials**

1. First, place each of the items you will need on a clean, flat surface in a well-lit area:
   - 1 blister pack with COPAXONE Prefilled Syringe
     Remove only 1 blister pack from the COPAXONE Prefilled Syringe carton. Keep all unused syringes in the Prefilled Syringe carton and store them in the refrigerator.
   - Alcohol prep (wipe)
   - Dry cotton ball (not supplied)
2. Let the blister pack with the syringe inside warm up to room temperature for 20 minutes.
3. To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.

4. There may be small air bubbles in the syringe. To avoid loss of medicine when using COPAXONE prefilled syringes, do not expel (or do not attempt to expel) the air bubble from the syringe before injecting the medicine.

**Step 2: Choose the injection site**

- There are 7 possible injection areas on your body: arms, thighs, hips and lower stomach area (abdomen) (See Figure 1).

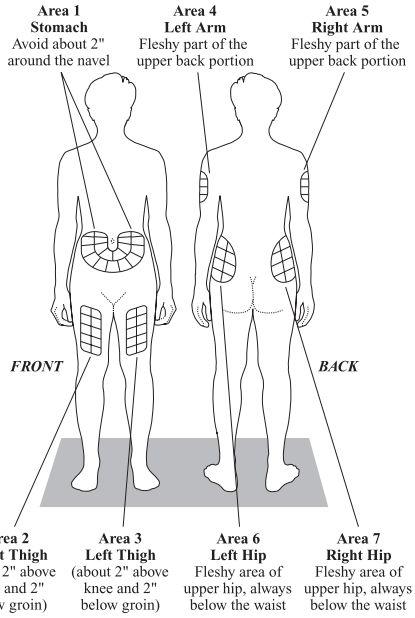



Figure 1

- Each day, pick a different injection area from one of the 7 areas. **Do not inject in the same area more than once a week**.
- Within each injection area there are multiple injection sites. Have a plan for rotating your injection sites. Keep a record of your injection sites, so you know where you have injected.
- There are some sites in your body that may be hard to reach for self-injection (like the back of your arm), and you may need help.
- Do not inject in sites where skin depression has occurred, because further injections in these sites may make the depression deeper.

**Step 3: Give yourself the injection**

1. Remove the syringe from its protective blister pack by peeling back the paper label. Before use, look at the liquid in the syringe. If it is cloudy or contains any particles, do not use it and call Shared Solutions® at 1-800-887-8100 for assistance. If the liquid is clear, place the syringe on the clean, flat surface.
2. Choose an injection site on your body. Clean the injection site with a new alcohol prep and let the site air dry to reduce stinging.
3. Pick up the syringe as you would a pencil. Remove the needle shield from the needle.
4. With your other hand, pinch about a 2-inch fold of skin between your thumb and index finger (See Figure 2).
5. Insert the needle at a 90-degree angle (straight in), resting the heel of your hand against your body. When the needle is all the way in release the fold of skin (See Figure 3).

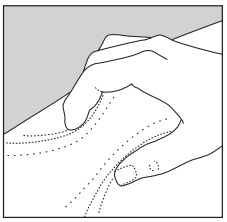


Figure 2

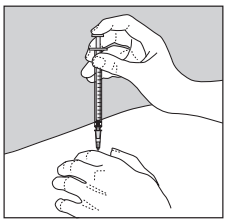


Figure 3

6. To inject the medicine, hold the syringe steady and push down the plunger.
7. When you have injected all of the medicine, pull the needle straight out.
8. Press a dry cotton ball on the injection site for a few seconds. **Do not rub the injection site**.
9. Throw away the syringe in a safe hard-walled plastic container.

**What is the proper use and disposal of prefilled syringes?**

Each prefilled syringe should be used for only 1 injection. Throw away all used prefilled syringes in a hard-walled plastic container, such as an empty liquid laundry detergent bottle. Keep the container closed tightly and out of the reach of children. When the container is full, check with your doctor, pharmacist, or nurse about proper disposal, as laws vary from state to state.

**How should I store COPAXONE prefilled syringes?**

Keep the COPAXONE prefilled syringe carton in the refrigerator, out of the reach of children.

The COPAXONE package should be refrigerated at 36-46ºF (2-8ºC). You can store it at room temperature, 59-86ºF (15-30ºC), for up to one month. Do not store COPAXONE at room temperature for longer than one month. **Do not freeze COPAXONE**. If a COPAXONE prefilled syringe freezes, throw it away in a proper container.

COPAXONE is light sensitive. Protect it from light when not injecting. Do not use the prefilled syringe if the solution contains particles or is cloudy.

**General advice about prescription medicines**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use COPAXONE for a condition for which it was not prescribed. Do not give COPAXONE to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about COPAXONE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE that is written for health professionals. Also, you can call Shared Solutions® for any questions about COPAXONE and its use. The phone number for Shared Solutions® is 1-800-887-8100.

U.S. Patent Nos. 5981589, 6054430, 6342476, 6362161, 6620847, 6939539, 7199098.

TEVA® NEUROSCIENCE

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- PRESENTATIONS
- COMPARISONS
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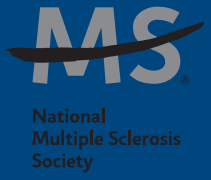
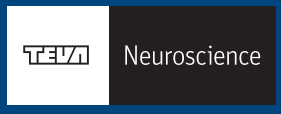
- FORMULATION OF POLICIES
- BUSINESS PLANS
- BUDGETING
- STRATEGIC FORECASTING
- ANALYSIS AND TRENDS

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