

Implementing an Outcome Improvement Program for Multiple Sclerosis by Integrating With a Specialty Pharmacy Partner

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Summary

Multiple sclerosis (MS) is the most common disabling neurologic disease of young adults. The costs to patients and to managed care are significant. Preventing symptomatic episodes of the disease through the use of biologic agents, such as glatiramer acetate and interferon-beta, may prevent or slow the development of disability. Managed care can cost-effectively improve clinical outcomes by implementing a disease-management program for MS patients. Partnering with a specialty pharmacy to provide portions of the disease management program has many advantages for managed care.

Key Points

- Multiple sclerosis is the most common disabling neurologic disease of young adults.
- Conservatively, the national annual cost of MS is \$6.8 billion, with the direct costs of MS related to the severity of relapses.
- Biologic agents, glatiramer acetate and interferon-beta, are effective at reducing relapses, but there is no evidence that any of the biologic agents are better at reducing the severity of relapses.
- Reducing relapses and delaying disability with appropriately used biologic agents should reduce the overall cost of MS.
- Specialty pharmacies have advantages in delivering disease management related to biologic agents in the treatment of MS.
- In addition to other advantages, an MS disease-management program will allow the needed data collection to manage inappropriate use of new or unproven medications.

MULTIPLE SCLEROSIS (MS) IS AN inflammatory and neurodegenerative autoimmune disorder of the central nervous system (CNS), and the most common disabling neurologic disease of young adults, with a lifetime risk of 1 in 400.^{1,2} The peak age of onset for MS is the third decade of life, with most cases striking between ages 15 and 45.³ Like many other autoimmune diseases, women with MS outnumber men by a ratio greater than 2:1.⁴ One of the more puzzling aspects of MS is the increase in prevalence with distance from the equator, which is noted in both hemispheres and similar in Europe and the U.S.² There are between 8,500 and 10,000 new cases of MS diagnosed in the U.S. each year, and the disease affects a total of approximately 350,000 people.¹

Overview of MS

The clinical diagnosis of the disease is based on demonstrating the dissemination of lesions in the CNS in time and space (i.e., the occurrence of a second clinical episode at a different site in the CNS).⁵ Although the cause of MS is unknown, studies support a complex interaction of environmental and genetic factors.¹ There are four MS subtypes:

- Relapsing-remitting MS (RRMS)
- Secondary progressive MS (SPMS)
- Primary progressive MS (PPMS)
- Progressive-relapsing MS (PRMS).^{2,5}

The majority of MS patients (approximately 85 percent) initially present with RRMS, characterized by clearly defined episodes of neurologic disturbance

(also known as attack or relapse) with full recovery, or with sequelae and residual deficit upon recovery. RRMS is not classified as a progressive form of MS, but residual deficits can be established with each exacerbation. At least 50 percent of patients with RRMS will transition into SPMS, characterized by disease progression with or without occasional relapses, minor remissions, and plateaus. Approximately 10 percent of the MS population present with a disease progression from onset, with occasional plateaus and temporary improvements (PPMS). The least common form, PRMS, is a progressive disease from onset with acute relapses, with or without full recovery, and with periods between relapses characterized by continuous progression.⁵ Although the course of the disease is variable, the average patient experiences two exacerbations (of about two to three weeks' duration) every three years.⁶

Simplistically, MS is an imbalance between inflammatory (e.g., tumor necrosis factor [TNF], interleukin 12 [IL-12], interferon gamma [IFN γ]) and anti-inflammatory (e.g., interleukin 4 [IL-4], interleukin 10 [IL-10], transforming growth factor beta [TGF β]) cytokines in the body (Exhibit 1).⁷ When inflammation is severe, damage goes beyond demyelination. Axonal degeneration occurs, which leads to permanent loss of axonal function. The cumulative loss of axons is the probable cause of permanent and progressive neurological dysfunction and disability with MS.⁸

Normal CNS axons are surrounded by an insulating myelin sheath that speeds the conduction of action potentials that carry a signal from one neuron to another. During the relapse phase of RRMS, activation of the immune system results in migration of T-cells and macrophages, as well as increased amounts of tumor necrosis factor, nitric oxide, and antimyelin antibodies within the CNS.⁹ The macrophages and inflammatory cytokines act together to destroy myelin. As the myelin sheath is damaged, conduction velocity within the axon

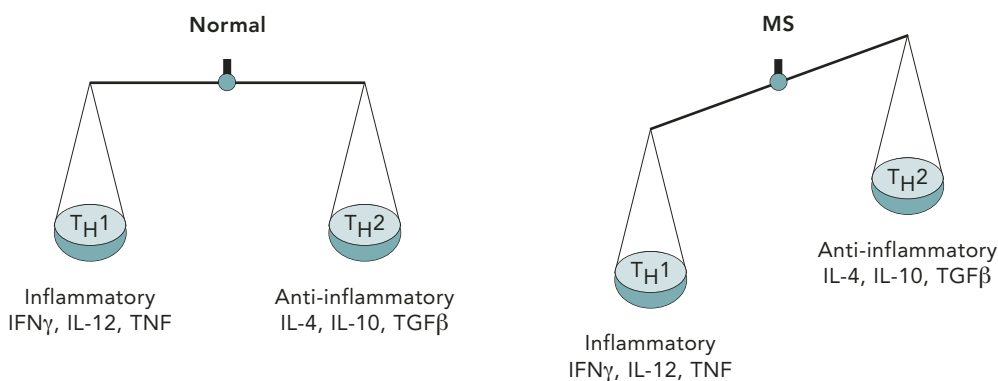
decreases, and severe damage can lead to nerve conduction block. Remodeling of the demyelinated axon membrane is hypothesized to increase the number of sodium channels in the remission phase of RRMS, resulting in improved conduction of action potentials. Remission may also result from remyelination.

In patients with MS, damage to white matter occurs throughout the CNS, often near ventricular zones, which results in a broad spectrum of signs and symptoms. During a relapse, a patient will suddenly get much worse along one or more functional dimensions for a few weeks to a few months. Fatigue is the most common symptom reported by 75 to 90 percent of persons with MS.¹⁰ Fifty to 60 percent of patients report fatigue as the worst symptom of their disease.¹¹ Up to 80 percent of MS patients suffer from pain syndromes, such as extremity dysesthesia, back pain, leg spasms, or abdominal pain.² Other common signs or symptoms associated with MS are spasticity, bladder and bowel dysfunction, sexual dysfunction, and optic neuritis.¹²⁻¹⁹

Depression is another serious issue for MS patients. Forty to 50 percent of MS patients will experience significant clinical depression at some point in time. Furthermore, MS patients are seven times more likely than the general population to commit suicide.^{12,13} Depression is a side effect of several medications used in the management of MS or its symptoms, particularly glucocorticoids, interferon (IFN) beta, and benzodiazepines.

The natural history of MS is that the majority of patients will exhibit a progressive neurologic deterioration. Approximately 90 percent of MS patients will transition to a progressive form of the disease 25 years from the time of diagnosis, and can be characterized as having substantial clinical disability.^{8,20-21} The timing of accrued disability is strongly influenced by the number of exacerbations during the early phases of

Exhibit 1: Immune Imbalance in MS¹⁸



the disease.²⁰ Irreversible deficits can be established with each exacerbation. Consequently, MS treatment should be initiated at the earliest possible time to prevent disability.⁵

Disability related to MS is most commonly assessed using the Kurtzke Expanded Disability Status Scale (EDSS) (see Exhibit 2).²² A standard neurologic exam is used to evaluate functional abnormalities involving several systems: pyramidal, cerebellar, brain stem, sensory, bladder and bowel, visual, and mental. For example, an EDSS score of 4.0 to 4.5 means disability is moderate. The patient can only walk 330 to 550 yards without assistance or rest.²²

Treatment of MS

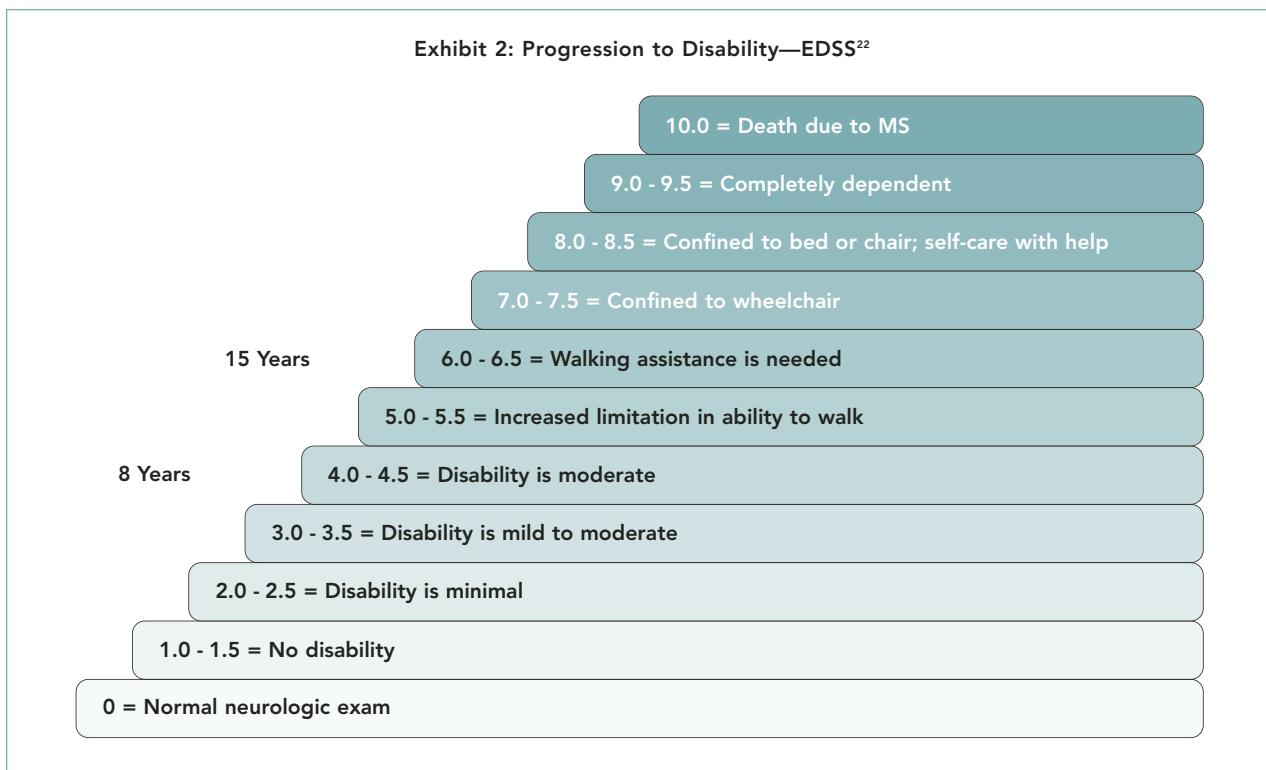
The therapeutic approaches to the various forms of MS have changed dramatically over the past decade, and various disease-modifying therapies have successfully been introduced and established.²³⁻²⁵ Five agents are FDA approved for treating RRMS: subcutaneous IFN beta-1b, Betaseron®; intramuscular IFN beta-1a, Avonex®; subcutaneous IFN beta-1a, Rebif®; glatiramer acetate, Copaxone®; and mitoxantrone, Novantrone®.²⁵⁻²⁹ Mitoxantrone is reserved for severe MS because of its cumulative cardiac toxicity.

Interferon Beta

Interferon (IFN) beta currently is recommended by the American Academy of Neurology guidelines for the management of patients with relapsing-remitting

MS, relapsing forms of secondary progressive MS, and in patients at high risk of developing clinically definite MS.²⁵ Its precise mechanism of action, however, remains unclear. Nevertheless, several biological activities have been described such as inhibitory effects on the proliferation of leukocytes and antigen presentation, the modulation of cytokine production, and the potential to inhibit T-cell migration across the blood-brain barrier by down-regulating the expression of adhesion molecules and inhibiting the activity of T-cell matrix metalloproteinases.³⁰⁻³³

Although not curative, interferon beta appears to reduce the frequency of relapses and produces a beneficial effect on several magnetic resonance imaging (MRI) measures of disease activity.³³ Immunomodulators, such as interferon beta, appear to be of little use once axonal degeneration has reached a critical threshold and clinical progression of the disorder is established.³³ Decisions to initiate interferon beta therapy in clinical practice, however, must be tempered by an understanding that the magnitude of the reported clinical benefits of interferon beta is modest. The rate of neurologic attacks and disease severity measures used as outcomes in clinical trials has an uncertain relationship with long-term disability outcome. Some patients will experience notable adverse effects to therapy, and some patients with MS (even without specific therapy) may have a relatively benign disease course.³³ Although many patients subjectively report



improvement in various manifestations following initiation of interferon beta therapy, the drug is ineffective in the treatment of some common symptoms of MS (e.g., bladder dysfunction, spasticity, fatigue), for which other pharmacologic agents (e.g., antispasmodic agents, skeletal muscle relaxants) generally are indicated.³³

There currently are two types of recombinant interferon beta commercially available in the U.S., interferon beta-1a and interferon beta-1b. Important differences in beneficial effects (clinical, MRI measures of response) between these different types of interferon beta have not been reported.³³ The optimal preparation, dosage, and route of administration of interferon beta for the management of MS has not been determined. In addition, interferon beta preparations and other disease-modifying agents (e.g., glatiramer acetate, mitoxantrone) have not been compared in well-designed, controlled studies.

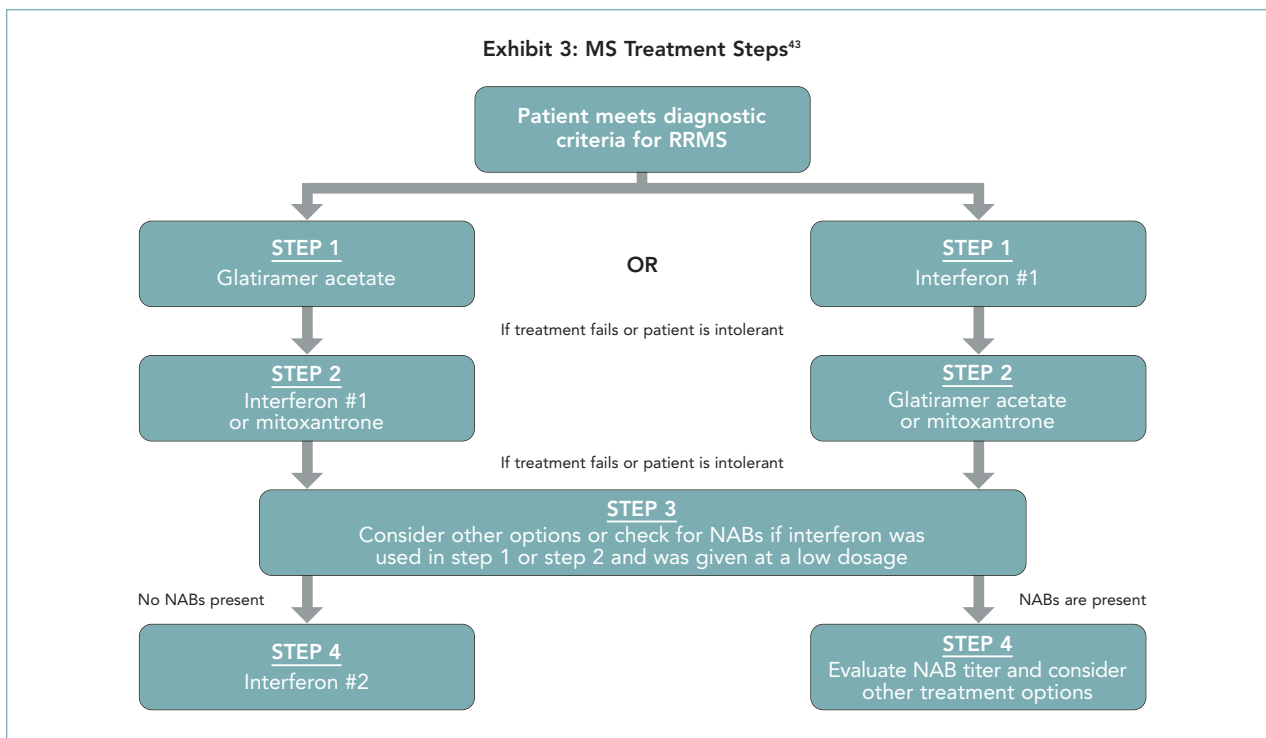
IFN beta therapy often causes side effects, such as flu-like symptoms, injection site reactions, and laboratory abnormalities, such as elevation in liver function tests or lymphopenia.²⁶⁻²⁸ However, these side effects are generally mild and tend to disappear within the first months of treatment. The adverse effects frequently can cause patients to discontinue therapy. Several switch studies have demonstrated effectiveness of glatiramer acetate if side effects or inadequate response have caused a patient to discontinue interferons.

Glatiramer Acetate

Glatiramer acetate, a mixture of synthetic polypeptides composed of random sequences of the amino acids L-alanine, L-glutamine, L-lysine and L-tyrosine, inhibits the binding of some myelin proteins to the major histocompatibility complex.³⁴ Its immunological mechanisms of action are not completely understood, and some differ from those known for IFN beta.

Glatiramer acetate reduces the rate of exacerbation and improves mean disability scale scores in patients with RRMS.³⁵⁻⁴⁰ Exacerbation rate is decreased approximately 30 percent in patients with mild relapsing-remitting disease. The number of CNS lesions decreases with treatment, and there is a tendency for the disease to progress in fewer patients with relapsing-remitting disease who receive glatiramer acetate than in placebo recipients. Mean disability status scores improve with treatment and deteriorate without it.⁴¹ In patients with secondary progressive multiple sclerosis, the rate of disease progression was reduced, but not significantly, by treatment with glatiramer acetate compared with placebo; however, further trials with larger patient numbers may be warranted.⁴¹

Potential limitations to glatiramer use are 1) the number of patients with relapsing-remitting disease progression is not significantly different between active and placebo treatment groups at 30 months, six years, and eight years; 2) reactive antibodies to glatiramer acetate form in most patients receiving long-term therapy; the effect on efficacy is unclear; and 3) efficacy still has to be established in patients



with secondary progressive multiple sclerosis.⁴¹

Glatiramer acetate, which is injected, is well tolerated. Local injection site reactions are the most common adverse effect and are usually mild. A transient benign systemic reaction occurs in some patients; the influenza-like symptoms commonly associated with IFN-beta treatment have not been reported.²⁹

Comparison of Agents

There have been no direct comparisons of glatiramer, interferon-β-1a, and interferon-β-1b. Direct comparisons of these drugs in well-designed trials are obviously necessary before conclusions may be drawn about their relative advantages and disadvantages. The potential advantages of combining these agents need to be evaluated. Glatiramer acetate and interferon-β-1b, both of which cause immunomodulatory changes in T helper-1 cell lines, have been studied in combination in one study. Their action was found to be additive.⁴²

Based on available evidence, any of the three agents could be chosen for initial therapy for RRMS. If the initial choice fails, then one of the other agents can be selected. A treatment algorithm for MS is presented in Exhibit 3.⁴³

Future Agents

Thirty-six percent of agents in late-stage development are for MS.⁴⁴ A significant number of these agents are targeted toward altering the immune system response and are injectable agents that will be expensive.

Disease Management of MS

The cost of treating MS, particularly since the development of immunomodulators, is significant. In the United States, the annual per-patient cost of MS has been estimated at \$34,000, with a total lifetime per-patient cost of \$2.2 million; a conservative estimate of the national annual cost is \$6.8 billion.⁴⁵ The annual cost for immunomodulators for MS is \$2 billion.

As more biological agents become available for treating MS, managed care organizations (MCOs) are applying various strategies to control costs and improve outcomes in their MS populations. Some of these possible strategies include

- appropriateness of therapy
- cost sharing
- formulary management
- reimbursement management
- disease management/outcome improvement.

When managing any disease category, one of the first goals is to determine whether therapy is appropriate for a given patient. Cost sharing by increasing co-pays or through tiered co-pays is one way to manage the costs, but it will not change the outcome and may

worsen it. Formulary management is tied into cost sharing, but it too will not change the clinical outcome. Reimbursement management decreases the reimbursement for different products, but does not change the outcome. A disease management program involves more than just drug maximization (i.e., appropriate therapy, adherence, compliance). A true disease management program targets various issues to improve clinical outcomes with the result of reducing acute care costs (e.g., hospitalizations) significantly more than the increased cost of medications when patients comply with appropriate therapy.

One method that may both improve outcomes and manage costs of MS is the use of specialty pharmacy providers for biologic agents. Distribution of biologics through a specialty pharmacy may seem unrelated to disease management, but a specialty pharmacy may actually be the best site of care for disease management because of the way it operates.

Use of a specialty pharmacy by an MCO can assist physician providers by helping them avoid the many administrative and legal issues related to obtaining and stocking medications within a physician's office. These include ordering, up-front costs, collection of co-pay or co-insurance, insurance billing, and legal storage and handling requirements.

In addition to reducing workload issues related to biologics, specialty pharmacies have other significant advantages (see Exhibit 4). One of the most important roles specialty pharmacies perform is to communicate by phone with the patient every month. At its essence, disease management is good personal communication between two parties. Specialty pharmacy companies routinely call each patient every month to check in before sending a refrigerated, expensive medication through the mail.

Beyond offering a communication system, other advantages of specialty pharmacies include a ready distribution system and the ability to bill both pharmacy and medical benefit portions of a health plan. Forty to 60 percent of specialty pharmacy charges are paid through the medical claim system, not pharmacy benefits.⁴⁶

Exhibit 4: MS Disease Management—Most Efficient Site

Specialty Pharmacies

- Dispensing site for much of the medication
- Already knowledgeable
- Monthly calls to patients
- Integration of medical and pharmacy benefits
- Ability to collect/track data over time
- Differentiation opportunity

Specialty pharmacies address the reasons for noncompliance and achieve savings for the payer by helping to avoid the consequences of noncompliance. For one MCO, the mean unit cost in 2002 of a “low-intensity” MS relapse, which could result in physician office visits and symptom-related medications, was \$243 per patient.⁴⁶ The mean unit cost of a “high-intensity” episode, which could result in hospitalization and post-discharge rehabilitation, was \$12,870 per patient.⁴⁶ Adherence rates for injectable MS medications achieved by one specialty pharmacy were reported to be 98 percent for Avonex[®] and Rebif[®].⁴⁶ Adherence rates for Copaxone[®] and Betaseron[®], the other two common MS therapies, were around 95 percent.⁴⁶

Disease Management Process

The initial step in building a disease management program for MS is to identify and assess the plan’s MS population (see Exhibit 5). Interventions to alter the disease outcomes can then be developed and implemented. The components of a disease management program for MS include drug management (adherence and compliance to the medication, safety, tolerability), tracking of patient outcomes including relapses and disease progression, data analysis, and outcome improvement (see Exhibit 6).

The major reasons MS patients stop taking medications are intolerable side effects and a perceived lack of treatment efficacy. An estimated 20 percent of

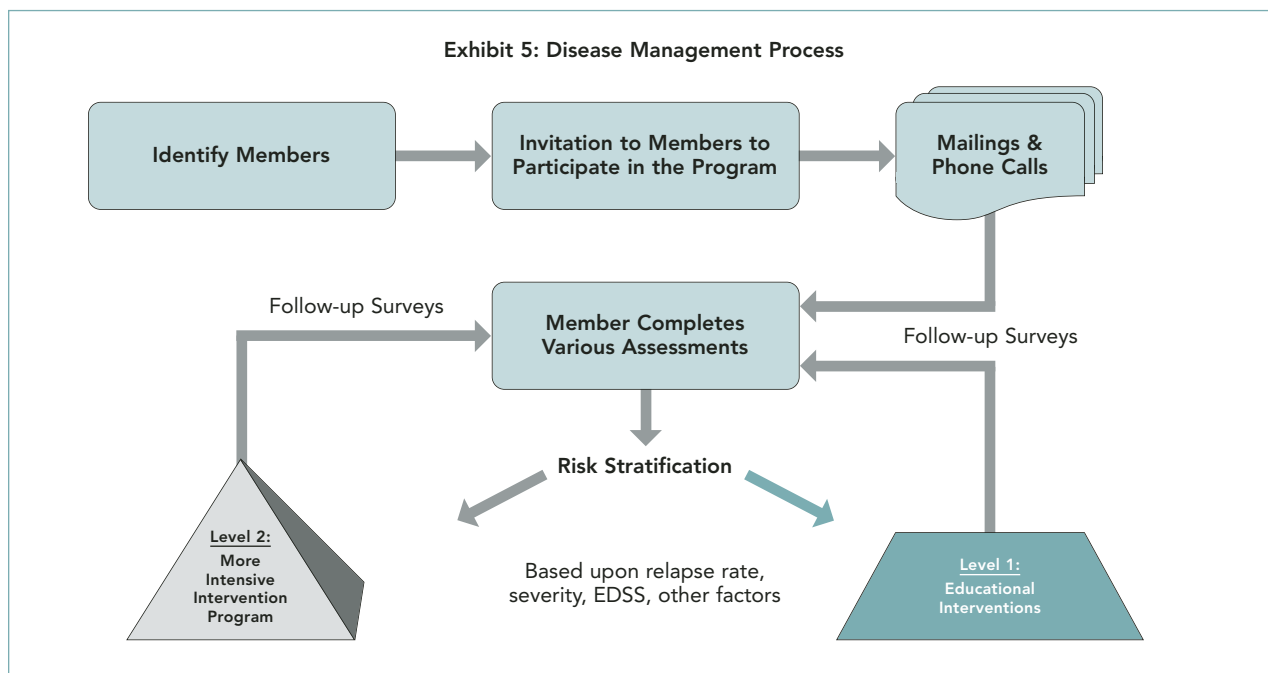


Exhibit 6: Component of MS Disease Management

- **Monitoring/Documenting:**
 - > Adherence
 - > Relapses
 - > Disease Progression
 - > Safety/Tolerability
 - > EDSS
- **Interventions:**
 - > Co-morbid condition(s)
 - > Symptom management assistance
- **Data Analysis**
- **Outcome Improvement**

Exhibit 7: Suboptimal Treatment Response Lack of Efficacy

- **Clinical Event**
 - > Increase in severity and/or number of relapses
 - > Recovery time after a relapse
 - > Progression of EDSS
- **MRI**
 - > Increased lesion load (especially if Rx > 6 months)
- **Neutralizing Antibodies**
 - > Present with clinical change (especially if Rx > 6 months)
 - > Cross reactivity with interferons (1a & 1b)

MS patients in the U.S have been on therapy but have stopped for some reason.⁴⁶ Patients often have an unrealistic expectation of their MS therapy and are likely to drop their injectable medications because they don't feel they're getting better, or they are having adverse effects such as flu-like symptoms. In many such cases, education about the common side effects of the biologic agents will help patients complete the initial treatment period when these effects are most prominent. Encouraging patients to stay on therapy through the initial tolerance building phase may help patients stay on therapy long enough to determine if efficacy has occurred. Although many of the adverse effects of biologic agents are transient, some, such as liver function and blood cell abnormalities, are only amenable to therapy discontinuation.

Once patients have remained on therapy for an adequate amount of time, efficacy must be assessed. The only way for an MCO to know if

medications are working in a particular population is to develop a tracking and intervention process. Markers of suboptimal treatment response in MS are provided in Exhibit 7.

A claims base analysis published in 2000 found that the yearly cost of MS increases with each exacerbation (see Exhibit 8).⁴⁷ Economically, reducing relapses leads to fewer acute care costs, decreases ancillary costs (i.e., occupational therapy, physical therapy), and improves patient productivity. The biologic agents, as discussed earlier, will reduce relapses.

Additionally, direct costs increase as the severity of relapses worsen.⁴⁸ There is currently no data that the biologic agents vary in ability to control severity of relapses. Because relapses are associated with increasing disability, a disease management program needs to monitor the severity of individual relapses, the recovery time, and how much therapy is required. Relapses may also indicate the need to switch to immunologic therapy.

Using data from pre-marketing studies involving biologic agents, Ollendorf and colleagues published an analysis of the clinical and economic impact of these agents (see Exhibit 9).⁴⁹ Study results indicate that use of glatiramer therapy in patients with MS results in a lower rate of relapse relative to those receiving interferon-beta therapies. In addition, therapy with glatiramer acetate appeared to be more "durable" than that of the interferon-beta—patients receiving the

Exhibit 8: Total MS Costs by Number of Exacerbations⁴⁷

- No exacerbations \$6,007
- One exacerbation \$8,180
- Two exacerbations \$14,521
- Three to eight exacerbations \$20,519

(Claim-based analysis, 1996 dollars)

Exhibit 9: Cost of MS Related Care⁴⁹

	Galtiramer acetate	IFN -1a	IFN -1b	
	N=1,674	N=5,031	N=1,752	P value
Medication				
Study Therapy	\$6,740	\$7,547	\$7,648	<0.001
Other MS-Related Medication	\$516	\$445	\$435	0.764
Total Medication				
	\$7,256	\$7,992	\$8,083	<0.001
Outpatient care				
	\$1,291	\$1,202	\$1,083	0.459
Inpatient care				
	\$975	\$763	\$1,019	0.168
Total MS-Related Costs				
	\$9,522	\$9,957	\$10,185	0.004

former did not switch or add on immunomodulatory therapy, while nearly 10 percent of those receiving interferon beta therapy did experience a therapy change. Finally, total costs of MS-related care were reduced by \$1,100 to \$700 among glatiramer acetate patients relative to the interferon-beta; findings persisted in multivariate analyses controlling for age, sex, and propensity scores for immunomodulatory therapy. Based on this analysis, six years is required to prevent one relapse with interferon beta-1a (Avonex®) and two years is required with interferon beta-1b (Betaseron®) and glatiramer (Copaxone®). One and a third years are required with interferon beta-1a (Rebif®) but because it is a high-dose therapy, few patients tolerate it well. This analysis illustrates a key point that pharmacy and total medical costs are different for different biologics. To identify the true costs and outcomes, the MCO should monitor relapses and how each medication is being used.

Implementation of an MS disease management program requires a database for tracking patients and

outcomes, telephone-based assessments and interactions, patient-based symptom and medication tracking (e.g., patient diary), procedures manual, and adequate personnel resources to implement the program and provide programmed interventions. A patient diary is a way to get the patient involved in his or her care. For example, the diary can be used to track symptoms, medication and other therapy compliance, side effects, laboratory tests, relapses, and preventive health measures such as an annual influenza vaccination. This author has published the *MS Clinician's Guidebook* as a resource for MCOs in developing a MS disease management program (see Exhibit 10).

The average total annual costs for MS patients in remission are directly related to the level of disability present (see Exhibit 11).⁵⁰ By preventing disability progression through various interventions, the patient can be maintained at a lower direct cost level. If disability is delayed, there are fewer lost productive years and lower indirect costs. Programmed interventions that can help delay disability progression in an MS population include

- compliance monitoring
- fall prevention
- urosepsis prevention
- side-effect management
- depression screening/referral.

Falls related to neurologic deficits in MS patients can have devastating consequences. Preventing urosepsis secondary to bladder dysfunction can avoid hospitalizations and a potentially life-threatening event. Since depression is frequent in MS patients, screening, referral, and treatment will help avoid the costly consequences of untreated depression.

Benefits of Disease Management

A disease management program for MS offers numerous benefits for patients and MCOs (see Exhibit 12). One benefit is the ability of the MCO to market their MS management program with proven outcomes

Exhibit 10: Multiple Sclerosis Clinician's Guidebook

- **Clinical Overview**
 - > Medical and Pharmacy Directors
 - > Case Managers
- **Patient Education**
 - > Depression
 - > Fall Prevention
 - > Bowel Dysfunction
 - > Fatigue
 - > Stress Reduction
 - > Exercise
 - > Communicating With Your Physician

Exhibit 11: Average Annual Costs per Patients While in Remission⁵⁰

	EDSS 1	EDSS 3	EDSS 6
Medical Costs	\$1,255	\$2,825	\$8,691
Patient Time Losses-work	\$6,341	\$15,995	\$24,513
Patient Time Losses-leisure	\$1,301	\$4,705	\$14,789
Unpaid caregiver time	\$1,701	\$4,554	\$3,704
TOTAL	\$10,064	\$28,079	\$51,697

Exhibit 12: What Are the Benefits?

MCO

- Scientific evidence-based formulary:
 - > “preferred therapies” prior to approval of “new/novel” and off-label therapies
- Improved Outcome:
 - > Reduced hospitalization
 - > Improved productivity (if proven, can be used to market to employers)
- Standard of Care:
 - > Allows MCOs to evaluate therapies for safety and tolerability

Patient

- Active involvement in therapy decisions
- Active involvement in management of overall disease
- Support of “appropriate” therapy
- Opportunity to discuss “side effects” regularly
- Teaching opportunity to prevent falls, improve management of depression, sign/symptom management, etc.

such as improved productivity for employers. Another significant benefit for an MCO is the ability to identify significant adverse events with new therapies.

For example, in 2004 a new biologic, natalizumab (Tysabri), was approved for treating RRMS. Use of this agent skyrocketed from November 2004 to February 2005 until the agent was removed from the market because of significant adverse effects (including several deaths).⁵¹ Intense tracking of adverse effects through a disease management program will identify significant and potentially life-threatening events early. A disease management program will allow the needed data collection to manage inappropriate use of a new or unproven medication.

Conclusion

The aim of an effective therapy in MS is to reduce the frequency and severity of relapses, shorten their duration, limit side effects, relieve symptoms, prevent disability arising from disease progression, and promote tissue repair. Progress has been made during the last decade in treating MS, especially for RRMS. Benefit and risk need to be weighed carefully in each individual patient. It is hoped that even more powerful therapies will be available in the near future to fight this disabling disease. Disease management programs, whether incorporating a specialty pharmacy or not, can help improve clinical and financial outcomes. **JMCM**

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