

Economic Burden of Multiple Sclerosis and the Role of Managed Care Organizations in Multiple Sclerosis Management

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Current Health Insurance/Medicare Utilization Landscape for Patients With MS

In the United States, multiple sclerosis (MS) affects approximately 400,000 individuals, and worldwide, the disease affects 2.5 million individuals, varying greatly by geographic region.¹ Patients with MS utilize healthcare services considerably more than those without chronic illnesses.² A patient who is newly diagnosed with MS will visit their physician an average of 8 times annually, approximately 3 times as often as an individual without the disease.^{2,3} It is also important to note that the frequency with which patients with MS require medical care usually increases with disease progression, adding to substantial pharmacy costs that increase over time.²

Data suggest that most patients with MS have health insurance coverage.² The results of a survey report compiled by the National Disability Institute (NDI) and the Multiple Sclerosis Association of America (MSAA) in 2012 showed that actual access to health insurance is not a significant barrier to care for the patients with MS who responded to the survey. Data demonstrated that 53.9% of patients with MS had private health insurance and almost 39% received federally funded healthcare, namely Medicare (32.5%) and Medicaid (6.0%). A total of 7.7% of participants were uninsured at the time of the survey.⁴

While data such as that from the NDI and the National Multiple Sclerosis Society (NMSS) highlight that the majority of patients with MS are covered by some form of health insurance, the landscape for actual coverage of MS treatment and management can be highly variable and potentially inaccurate. For example, while accurate data are not available on the number of patients with MS receiving Medicaid benefits (because these programs are administered by individual states instead of through a single federal program), the NMSS currently estimates that approximately 25% to 30% of patients with MS receive Medicare.^{5,6} However, the cost of specialty

Abstract

Multiple sclerosis (MS) is disease that has an early age of onset and may intensify and subside with disease relapses or exacerbations interrupted by periods of stability. Because of this, patients, their families and caregivers, employers, and the entire healthcare system carry substantial clinical and economic burdens associated with the disease over a period of many years. Although most patients with MS are covered by health insurance, the management landscape has become increasingly complex over the past decade with the introduction and approval of several new disease-modifying therapies that, while remarkably effective and well tolerated, usually come with a very high cost. Whereas the main goal of treating patients with MS is to prevent disease progression and disability, healthcare and benefit providers are faced with an ever-tipping balance point between effectively managing the disease and maximizing the value of high-cost disease-modifying therapies in an already overburdened healthcare system. Treatment of MS should be individualized, and shared decision making between patients and healthcare providers must be preserved. Healthcare providers and payers need to collaborate to ensure that resources are used optimally and not wasted, reducing both the clinical and economic burdens related to this complex chronic disorder.

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drugs for the treatment of complex disorders such as MS can be very high, even with Medicare Part D enrollment and coverage; this is especially true when the costs that must be covered by patients are taken into consideration.⁷

Specialty-tier drugs, defined by Medicare as drugs that cost more than \$600 per month for an individual patient, represent a limited number of Part D drugs used by a small proportion of enrolled patients.^{8,9} An analysis of such specialty-tier drug use and cost was performed by researchers at Georgetown University and the Kaiser Family Foundation and was published in December 2015; it covered 12 specialty drugs used to treat 4 specific disease areas: hepatitis C, MS, rheumatoid arthritis, and cancer. Results demonstrated that approximately 2% of patients enrolled in Medicare Part D used these agents and other specialty-tier drugs, according to the Centers for Medicare & Medicaid Services (CMS).

Recent data suggest that out-of-pocket costs for patients with complex conditions, such as cancer, may reach as high as \$11,538 for a single current drug, with estimates for patient out-of-pocket costs for 3 sample MS agents ranging from \$5979 to \$6448 annually. For the 3 MS drugs studied, an average of 34.7% of out-of-pocket costs were incurred by Part D enrollees after their spending reached the catastrophic coverage phase of the Part D benefit. The data demonstrated that a substantial share of the out-of-pocket costs for these specialty-tier drugs can be incurred even after enrollees' drug spending reaches the drug benefit's catastrophic threshold, which was intended to protect against high costs, but not established as an absolute limit on actual out-of-pocket spending.⁹

Catastrophic limits vary depending on the insurance plan, and may be limited to a specific event or illness.¹⁰ Although Medicare Part D has set that limit at \$4850 for Medicare beneficiaries, the limit is not an absolute limit on out-of-pocket cost, because Medicare still requires enrollees to pay an additional 5% of the specialty drug's cost even after the catastrophic limit is reached. In addition, if Medicare enrollees take a drug that has been excluded from the formulary for their particular insurance plan, their costs for care can be extremely high, and the out-of-pocket cost of treatments, even for lower-priced drugs, can vary widely from plan to plan.⁷ However, each patient has the right to request that his/her plan provide or pay for a drug they believe should be covered, provided, or continued. Patients also have the right to request an appeal if they disagree with their plan's decision regarding whether or not to provide or pay for a drug.¹¹ Such data show that while the insurance landscape demonstrates substantial

coverage for care, individual coverage can vary significantly and may not be enough for optimal management of the overall disease and symptoms for patients with MS.

The Affordable Care Act (ACA) was designed to improve access to healthcare and health insurance coverage through the adoption of changes at the federal, state, and employer levels. The ACA was created to provide new consumer protections surrounding healthcare, increase access to affordable healthcare options, and standardize benefit offerings of healthcare insurance companies. Aspects of this law are of particular interest: the potential benefits for patients with MS include prohibiting insurance companies from denying coverage based on preexisting conditions, eliminating annual or lifetime coverage benefit limits, offering Medicare donut hole relief and prescription drug discounts, providing healthcare access to uninsured individuals with preexisting conditions, allowing states to cover more individuals with Medicaid, and increasing Medicaid eligibility and access, among other provisions.^{5,12}

However, the long-term effects of the ACA related to specialty pharmacy (which encompasses the bulk of the current disease-modifying therapies [DMTs] for MS) have yet to be fully determined.⁵ MS is an expensive and very individualized disease to manage, and patients with MS must consider a substantial number of factors related to their individual cost of care when determining appropriate healthcare coverage. Because of this, the MSAA has created an acronym for patients to consider when applying for coverage: "PLAN" stands for prepare, look, analyze, name. Specific questions for patients to consider when enrolling include¹³:

- Are their medications covered and what are the costs for them?
- Are there any "step" requirements for accessing their drugs?
- Which plans offer the most flexibility relating to access to drugs, doctors, etc?
- If a medication must be changed due to the plan chosen, what alternative drugs are available?

Even with health insurance, a substantial number of patients with MS still have plans that may challenge their ability to pay for prescription drugs, as well as limited networks of hospitals and MS providers.¹⁴ However, in addition to current insurance options, several programs are now available to help patients better afford and pay for their MS medications. Because of the often high out-of-pocket costs for patients with MS, assistance

programs are important in the management of patients with MS. For example, the co-pay relief program of the Patient Advocate Foundation has added new prescription coverage designed to benefit patients with MS. This new source of funding is available to financially eligible patients with MS, with health insurance coverage to assist in supporting the costs of needed treatment medications. Originally launched in 2004, this program now approves qualified patients with MS for up to \$8000 in assistance per award-year. It offers individualized services for patients, including technology tools for patients and their healthcare providers, in addition to financial assistance.¹⁵ Assistance programs are also available to patients with MS from the Patient Access Network Foundation.¹⁶

Economic Burden of MS

Costs of MS for the Patient: Disease State, Progression, Comorbidities, and Disability

Overall, MS is a very costly chronic disease, with direct costs of prescription drugs and indirect costs being the most significant cost drivers, according to available data.¹⁷ The disease usually has an early age of onset and symptoms that intensify and subside with disease relapses and remissions. Because of this, patients, their families, and caregivers carry an extreme disease burden.¹⁸ Along with the high costs of therapies for the disease, the common sequelae of MS also contribute substantially to the total cost of care and economic burden of this chronic disease. A study of commercially insured patients with MS by Carroll et al found that mean MS charges were significantly higher for patients with common disease sequelae, including malaise/fatigue, paresthesia, depression, and development of gait abnormalities.¹⁹ These conditions were found to be additional cost drivers in the management of MS.

As patients with MS age and their disabilities progress, so do the costs of managing the disease.²⁰ Compared with healthy individuals, patients with MS are substantially more likely to utilize healthcare services. Newly diagnosed patients are 3.5 times more likely to be hospitalized, 2 times more likely to have 1 or more emergency department visits, and 2.4 times more likely to have 1 or more visits for physical, speech, or occupational therapy.^{6,20} The economic burden of MS includes the cost of diagnostics, interventions, and monitoring, and the loss of patient productivity and employment.

Meta-analyses have shown that MS ranked second behind congestive heart failure in direct all-cause medical costs for chronic conditions.¹⁷ The total lifetime cost per patient with MS is estimated to be \$4.1 million (in 2010

dollars).¹⁸ For patients using DMTs to manage their MS, approximately 75% of total MS-related healthcare costs in 2011 was for DMT monotherapy, and this percentage was similar to that previously reported in 2004. It must also be noted that cost of managing the sequelae of MS contributed extensively to the total cost of care.¹⁹ This utilization of healthcare services increases with increasing disability, with an average yearly healthcare cost of \$30,000 for those with mild to moderate disability; \$50,000 for those with moderate disability; and \$100,000 or more for those with more severe disability, such as those confined to a wheelchair or bed/chair.

As a patient's disability level progresses with increasing disease burden, as measured using the Expanded Disability Status Scale (EDSS), total MS costs rise significantly. The average cost for a patient with an EDSS score of 3.0 to 3.5 (mild to moderate disability) is \$30,000 per year. For patients with a score between 3.5 (moderate disability) and 6.5 (walking assistance is required), the average cost increases markedly to \$50,000 annually. For patients with an EDSS score of 6.5, who are confined to wheelchair or bed/chair, need help to perform self-care, are completely dependent on a caregiver, or die from complications associated with MS, the average cost is at least \$100,000 per year.^{20,21}

Actual MS spending and cost growth are driven by several factors, including that MS presents in different forms and multiple phases of disease, and each patient's experience with MS varies in complexity. While the greatest proportion of spending for MS is attributed to DMTs, other medical costs include the requirement for multiple clinical interventions (eg, diagnostics and monitoring).²² Data reported by the IMS Institute for Healthcare Informatics in 2012 documented that the average costs for all privately insured patients with MS were \$30,000 annually. However, because MS varies in severity, health spending is likely disproportionately concentrated on a smaller number of patients with more severe disease, with 25% of spending used for just 1% of the total number of patients covered in a health plan. Taking just that 1% into consideration, the per-patient cost can exceed \$66,000 per year, with the average cost of the disease elevated markedly by that small number of seriously ill patients, although many other patients with MS will have lower expenses.^{22,23}

Costs and Cost-Effectiveness of Pharmacotherapy

Pharmacotherapy contributes substantially to the overall healthcare costs for patients with MS.²⁰ DMTs

are agents designed to alter the natural course of disease in MS. They reduce the frequency and severity of attacks and the development of new brain lesions, and slow down the development of disability. Initial biologic agents for this purpose were produced and marketed in the early 1990s. At that time, prices ranged from approximately \$9000 to \$12,000 per patient annually. Multiple new and potentially more effective agents have been developed since then; however, these agents come with higher prices, and the pipeline of therapies continues to grow, adding not only to the potential for greater efficacy, but also for significantly higher costs added to the overall management of MS.²⁴

The landscape for the management of MS with DMTs has changed dramatically since these drugs were introduced, most notably within the last decade with the approval of several new therapies.²⁵ Currently, there are 12 DMTs approved for use by the FDA in patients with relapsing forms of MS, including secondary-progressive MS for patients who are still experiencing relapses. One is also approved specifically for secondary-progressive MS; however, none of these agents or any others has been approved to treat primary-progressive MS, the type that shows steady progression from disease onset.²⁶

Although DMTs have been proven to be very effective in managing MS per their indications, the costs of these agents remain a subject of much discussion, debate, and even controversy. Despite the development and emergence of newer DMTs for patients with relapsing forms of MS, costs for all DMTs approved by the FDA have increased markedly. The average annual DMT cost per patient with MS in the United States in 2004 was \$16,050, comprising approximately half of all direct medical costs for patients with the disease. In comparison, the current average annual cost for the agent interferon (IFN) beta-1b was greater than \$60,000, as noted by Hartung et al in 2015. The costs of first-generation DMTs, including IFN beta-1b, IFN beta-1a intramuscular, and glatiramer acetate have risen an average of 21% to 36% annually. Costs of the most recently FDA-approved drugs (eg, fingolimod, teriflunomide, and dimethyl fumarate) have increased 8% to 17% per year since these agents were initially approved for use in patients with MS. Compared with these agents, general and prescription drug inflation increased only 3% to 5% per year during the same time period. Overall, the costs of DMTs in the United States have increased annually at rates 5 to 7 times higher than prescription drug inflation, and substantially above rates for other drugs in similar biologic classes.²⁵

These costs substantially impact patients with MS in several ways. As noted earlier, health insurance carriers have developed tiered formularies. Additionally, another management activity by payers is to require step-therapy trials of DMTs for patients. Because many of the current agents are considered therapeutically equivalent by payer pharmacy and therapeutics committees, the formulary status of an individual agent may be determined by pricing contracts.²⁵⁻²⁷ Improving clinical outcomes and quality of life for patients with MS may be the overriding priority for health insurance carriers and plans, but decision makers within these plans are now faced with the growing complexity in the MS space with the emergence of new DMTs.

In addition to tiered formularies and step-therapy management, common current health plan strategies for managing the optimal utilization of agents for MS include: (1) approving initial therapy with 1 or more preferred first-line treatment agents, and (2) prior authorizations that delineate drug appropriateness, the care setting, and the expected duration of therapy. Case-based supervision of each patient is critical, and patient compliance with therapy is a crucial aspect of individualized management.²⁸

The improved efficacy and safety profiles of these newer agents may provide an invaluable benefit to patients with MS; however, their access to these treatments may become limited by costs. On the other hand, ensuring early and appropriate treatment initiation may alleviate some of the costs down the road due to disease exacerbations and progression. Whereas the costs of therapy are high and seem ever-escalating, use of these agents must be assessed in terms of cost-effectiveness. Several analyses have been performed and suggest that the percentage of total (direct and indirect) costs surrounding MS that are attributable to DMTs has risen from 34%, as initially reported by Kobelt et al in 2006, to between 69% and 75% (as noted earlier) of total costs in the current decade.^{18,19,29,30}

Outside of the United States, governmental medical oversight institutions often use quality-adjusted life-years (QALYs) to compare different medications and measure their clinical effectiveness, and determine cost per QALY as a measure of the cost-effectiveness of therapy.^{18,31,32} In the United States, a cost per QALY value of \$50,000 is often put forth as a financial threshold for cost-effectiveness.^{18,33,34} In 2011, Noyes et al used data from a longitudinal MS survey to 10-year generate disease-progression paths for a group of patients with MS. Medical costs were estimated using the reimbursement rates from CMS and other sources. Outcomes were measured as gains in

QALYs and relapse-free years. Results demonstrated that using DMTs for 10 years provided moderate health gains compared with treatment without a DMT. However, the cost-effectiveness of all DMTs in this analysis was greater than \$800,000 per QALY.

Reducing the cost of DMTs had the most significant impact on the cost-effectiveness of these drugs. For example, a cost reduction of 67% could improve the probability of 1 agent being cost-effective at \$164,000 per QALY to 50%. However, when compared with treating patients at all levels of MS disease severity, the study also found that starting patients on DMT earlier was associated with a lower and more favorable incremental cost-effectiveness ratio. This analysis emphasized the need for early initiation of DMT, preferably when patients with MS are at an EDSS score of 2 or less, as this may be a more cost-effective approach versus starting DMT at later disease stages.³¹

In comparison, Owens et al performed a retrospective analysis in 2013 of managed care administrative data from a health plan claims database, using claims submitted over a period of 1 year for patients with confirmed MS. This study demonstrated that the mean annual cost of managing MS in the United States in 2009 was \$23,434, with some variance depending upon the presence of comorbidities or complications in the individual patients analyzed. DMTs accounted for 69% of the total costs of disease management and were associated with high incremental cost-effectiveness, ranging widely from \$20,000 to more than \$1 million per QALY. However, as seen in the Noyes et al analysis, cost-effectiveness improved by initiating treatment during earlier stages of disease.^{18,31}

The costs of DMTs may be partially offset by their effectiveness in preventing relapses.^{18,35} In addition, the ultimate goal of therapy for MS is the prevention of disability, which would benefit both the patient and society. The overall costs of MS have been shown to rise significantly with increasing disease progression and severity as measured by EDSS scores. Such cost increases were driven by relapses and productivity costs more than the actual direct costs of DMTs.^{18,21} With the emergence of new DMTs and therapy strategies, cost-effectiveness studies remain an evolving process. In addition, most health benefit plans are now being designed to require cost sharing by the patient.²⁸

Higher cost sharing on the part of the patient is also a complex issue. Patients are facing ever-increasing financial burdens for treatments because of higher co-payments, multitier drug formularies, and the adoption of prescription coinsurance plans. Data suggest that

patients may forgo treatment or end treatment prematurely when their cost-sharing burden is higher. In addition, benefit plan designs that negatively impact treatment initiation and adherence may increase health resource use, the risk of relapse, and disease progression and risk of disability. More data are needed to evaluate both the cost-effectiveness of newer and emerging treatments and the impact of cost sharing in the management of MS with DMTs.³⁶

The current treatment landscape may also be altered in the future with the approval of generic versions of DMTs for MS. In April 2015, the FDA approved the first generic version of glatiramer acetate, an early-generation DMT for MS. This generic became available to the market in June 2015. Although there have been no human studies on this particular version of this DMT, another unapproved generic of this drug was compared with the proprietary version of the agent and demonstrated noninferiority.³⁷

Costs of MS to Employers, Caregivers, and Society

Indirect costs associated with MS can also be substantial, and include lost productivity, health impact on the family, and the economic effects that the disease can place on families and caregivers. Patients with MS frequently have difficulty continuing to work. Data suggest that lost productivity related to loss of employment or the need to retire early may be the largest single factor that contributes to the nonmedical financial cost of MS. The Kobelt et al study from the United States found that among patients with MS taking DMTs, just 41% were working, with 63% of these patients working full time. Approximately one-fifth of these patients changed their work or reduced their working hours, however. In addition, 31.5% took early retirement because of their MS, and an additional 10.9% reported that they ceased working without indicating receipt of any form of early retirement benefits or pension.^{29,38} Loss of income for patients with MS is also usually linked to a corresponding increase in disability claims to governmental benefit programs and insurance providers.³⁷

Patients with MS also have substantially increased use of long- and short-term sick leave, with this leave often associated with disease relapses.^{21,38} A US analysis showed that employees with MS had a higher rate of medically-related absenteeism and associated absenteeism days than those without the disease. Employees with MS had more than 6 times the number of sick-leave days compared with employees without MS. Also, the annual costs for disability were 9 times higher for employees with MS, while indirect costs, including the loss of earnings due to the use

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of unpaid leave, were more than 4 times higher for the MS cohort versus employees without MS.^{38,39}

Overall absenteeism can be high for patients with MS who continue working. Data demonstrated that absenteeism rates for employees with MS ranged from 2.98 to 8.13 days annually. Moreover, their total sick time ranged from 7.33 to 20.67 days, with associated sick-leave costs ranging from \$523 to \$1431 over a 1-year period.^{38,40} Realistically, the proportion of patients with MS in any given workplace is likely to be low; however, companies that have employees with MS may be impacted by the financial loss from reduced output while an employee is at work and from absenteeism or extra staffing costs incurred to cover sick leave for absent employees.^{38,39,41}

DMTs may allow employees with MS to continue working and could potentially reduce absenteeism and its associated costs. Studies have assessed this relationship; however, they have been limited by their size, designs, and sometimes conflicting results.¹⁸ One study of US employees with MS who had at least 1 DMT claim compared with untreated employees demonstrated that the risk-adjusted total annual medical costs for those taking DMTs was \$4393 versus \$6187 for those who were not treated. Indirect costs were also significantly lower for employees with at least 1 DMT claim compared with untreated workers: \$2252 versus \$3053 annually, respectively.^{18,42} DMTs may have a positive impact on employment and work productivity; however, benefits specific to particular DMTs are not conclusive at this time.¹⁸

The economic burden of MS also extends beyond affected patients and the workplace. Because of limitations related to their disease and associated functional and cognitive impairments, patients with MS often require substantial help from caregivers, including spouses and relatives, to perform daily tasks. Data have shown that the stress and physical burden of caring for a patient with MS can substantially impact the health of caregivers, even increasing their own requirements for, and use of, healthcare resources.³⁸ Data from a US study showed that 53% of informal caregivers missed an average 7.3 days of work over a period of 1 year due to their responsibilities as a caregiver for a patient with MS. Of these caregivers, 7% reported changing their own employment to accommodate their role in caring for the patient. Also, 28% reported hypertension, 26% reported high cholesterol, 13% reported chronic headaches, 13% reported persistent sleep abnormalities, and 17% reported depression or anxiety.³⁸ Even from the earliest stages of disease, MS not only has a profound impact on affected

patients, but employers, families, and society in general, limiting productivity and creating substantial financial burden for all involved.³⁸

The Role of Managed Care Organizations in MS Management

To provide optimal patient management, managed care professionals must take into account that MS and its symptoms are associated with numerous and significant personal, professional, and economic burdens. Because of its early age of onset, the disease requires lifelong, complex, dynamic treatments, creating a substantial economic burden on patients with MS, their families and caregivers, healthcare systems, and society. Costs associated with providing benefits for MS therapy and management are rising continuously, and the increasing complexity of the MS therapy market is making a remarkable impact on disease management and those providing this care.

The cost of providing health plan benefits and insurance coverage for MS therapy is one of the most rapidly growing segments of current healthcare expenditures. Evolving drug complexity portends increasing complexity for payers and health plans. Therefore, improved action plans must be developed that balance appropriate access to optimal therapies with the need to manage the high costs of DMTs and evolving treatments. Overall, there is a need for better individualized management of patients with MS using evidence-based guideline recommendations as the basis for therapy, including initial treatments, drug switches, and the use of combination therapy.²⁸

Shared decision making is now a vital component within all areas of medical practice. Decisions about MS management are highly complex, and shared decision making between healthcare providers and patients must be improved to increase collaboration and optimize the overall management of MS. Payers need to take into account the impact of their access and coverage policies for MS drugs on individual patients. Healthcare providers and payers must work better together to assess new and emerging treatments because “one-size-fits-all” therapy cannot be rigidly applied to all patients with the disease. Variations in disease type and severity, and patient preferences for treatment should be taken into consideration to truly build collaborative and optimal strategies for disease management that address all aspects of therapy and balance efficacy and cost.⁴³

Future research and the application of prognostic indicators and treatment biomarkers may further refine future clinical algorithms for therapy and patient management.

In addition, additional comparative studies to differentiate newer and emerging treatments can help determine which drugs might work best for particular patients with MS, and under which circumstances they will function most effectively, leading to better overall treatment efficacy, safety, patient use, and cost savings. Managed care organizations need to continuously evolve with these treatments and strategies to promote optimal use of therapeutics and improve patient outcomes. This evolution will maximize cost savings and decrease the clinical and economic burdens of MS for patients, caregivers, employers, the entire healthcare system, and society.²⁸

Conclusion

The management of MS has become increasingly complex and more costly over the past several years, which is primarily related to the development and approval of new DMTs that, although well tolerated and effective, come with considerably higher costs. Managed care clinicians and providers should enable patients with MS to receive the most effective therapies while maximizing the value of these agents and achieving a reasonable balance between therapy efficacy and expense. More than ever, the management of MS must be individualized, and patients and their healthcare providers must work together to make decisions surrounding what treatments to use, and how to best manage each patient's disease. Only through consistent collaboration and shared decision making will patients, providers, and payers ensure that therapies are chosen appropriately and used optimally to help relieve the clinical and economic burdens of MS and improve patient outcomes as much as possible.

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