

# Implications for Multiple Sclerosis in the Era of the Affordable Care Act: A Clinical Overview

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## Abstract

Multiple sclerosis (MS) is a chronic, often debilitating disease of the central nervous system (CNS) that affects between 400,000 and 570,000 persons in the United States, with an incidence among females 2 to 3 times that of males. The cause of MS is currently unknown, but immediate family history, low blood levels of vitamin D, and cigarette smoking, among other factors, appear to increase the risk of developing MS. MS is considered an immune-mediated disease, whereby immune cells target and attack the CNS, predominantly the axonal membrane known as the myelin sheath. Depending on which areas of the brain or spinal cord are affected, this can result in a variety of waxing and waning neurologic symptoms. Most patients will eventually suffer from progressive disability that can greatly impact their quality of life. Symptoms such as fatigue, difficulty with ambulation, and depression are common among patients with MS and can affect their ability to work and care for themselves. Costs due to treatment and lost productivity place a significant economic burden on patients, caregivers, families, and society. Current and future treatments may help limit the personal and societal costs of MS by delaying disability and disease progression.

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For author information and disclosures, see end of text.

**M**ultiple sclerosis (MS) is an immune-mediated inflammatory disorder of the central nervous system (CNS) that is both chronic and debilitating.<sup>1</sup> The term “multiple sclerosis” refers to the numerous characteristic sclerotic plaques or areas of scar tissue that affect the brain and spinal cord.<sup>1,2</sup> The primary site of damage in MS is the myelin sheath surrounding the nerve fibers in the CNS, which causes a disruption in nerve impulses.<sup>1</sup> Symptom presentation and severity can vary widely, but the majority of patients with MS will develop neurologic disability (especially in gait) and cognitive dysfunction over time. The disability associated with MS not only impacts the patient’s quality of life, but is linked to significant economic burden to patients, their caregivers and families, and society as a whole.<sup>3</sup>

## Epidemiology

The most commonly cited estimate of prevalence of MS in the United States, based on census data from 2000, is approximately 400,000 individuals, or 0.13% of the US population,<sup>4</sup> but more recent studies have estimated the prevalence to be slightly higher, at over 570,000 persons, or approximately 0.21% of the US population,<sup>3</sup> and global estimates for the current prevalence of MS range from 2.3 million to 2.5 million.<sup>4,5</sup> High-risk populations (eg, middle-aged Caucasian women in Northern climates) have a prevalence approaching 1% or more, although this estimate was made prior to recent revisions to diagnostic criteria.<sup>6</sup> An estimated 12,000 new diagnoses of MS are made annually, mostly in persons between the ages of 20 and 50 years, with the peak incidence occurring around age 30 years.<sup>7,8</sup> The rate of diagnosis in women is approximately 2 to 3 times that of men,<sup>7,8</sup> and this ratio appears to be increasing over time,<sup>9</sup> with a recent analysis published in 2008 demonstrating an estimated increase in the female-to-male incidence ratio of 6% for each 5-year period since 1955.<sup>10</sup>

MS also appears to have a higher prevalence in areas of the world that are more distant from the equator,<sup>8</sup> although

■ **Table 1. MS Risk and Protective Factors**<sup>5,7,8,10,12-24</sup>

Risk Factors	Protective Factors
Having a first degree relative with MS <sup>8,12,13</sup>	Fatty fish intake <sup>24</sup>
HLA DRB1* 1501 haplotype <sup>5,13,15</sup>	More exposure to sunlight/ultraviolet radiation <sup>5,12,16-18</sup>
Vitamin D (25(OH)D <sub>3</sub> ) levels <75 nmol/L <sup>5,14,19,20</sup>	Vitamin D (25(OH)D <sub>3</sub> ) levels >100 nmol/L <sup>5,19-21</sup>
Cigarette smoking <sup>7,12,13,16,21,22</sup>	Alcohol consumption <sup>23</sup>
High EBV immunoglobulin G antibodies/infectious mononucleosis <sup>5,13</sup>	Early infection or having never been infected with EBV <sup>5,12</sup>
Being born in a region farther from the equator <sup>7,12,16</sup>	Being born in a region closer to the equator <sup>5,16</sup>
Caucasian, northern European ancestry <sup>9</sup>	Migrating to an area closer to the equator <sup>5,16</sup>
Female sex <sup>8,10</sup>	

EBV indicates Epstein-Barr virus; MS, multiple sclerosis.

the latitude gradient seems to be decreasing over time.<sup>9,10</sup> Alonso and Hernán reported that in studies done prior to 1980, a 10-degree increment in latitude was associated with a significant increase in MS incidence: 31% among women and 54% among men. Since that time, studies have shown only a nonsignificant increase of 15% in women and 11% in men for the same latitude increment.<sup>10</sup> Interestingly, Ascherio and Manger found that the incidence of MS in those who migrate from one area of the world to another appears to fall somewhere between the incidence seen in their place of origin and that of their final residence.<sup>11</sup> Further, while the risk of MS appears to decline in those migrating from high- to low-risk areas, risk does not always increase when migration occurs in the opposite (low- to high-risk) direction.<sup>11</sup>

### Etiology and Pathophysiology

While the exact etiology of MS remains unknown, the disease is likely caused by a combination of genetic and environmental factors (Table 1).<sup>5,7,8,10,12-24</sup> Family history of MS is the strongest known risk factor, with siblings of affected individuals carrying an approximately 30-times higher risk than the general population.<sup>8,12</sup> The average individual has an approximately 1-in-750 (0.1%) chance of developing MS, first-degree relatives of a person with MS have a risk of approximately 2.5% to 5%,<sup>8</sup> and identical twins of individuals with MS are estimated to have a 25% chance of developing MS.<sup>8,13</sup> The only specific gene that has been firmly linked to a risk of developing MS is the HLA-DRB1 locus on chromosome 6p21, but this is thought to account for 50% of the entire genetic basis of the disease.<sup>5,12,14-15</sup>

Sunlight and vitamin D are also thought to play important roles in the risk of developing MS.<sup>12,16</sup> Epidemiologic studies have demonstrated that outdoor work, residence in high-sunlight areas, and greater amounts of time spent outdoors during the summer season, particularly during childhood and adolescence, may have a protective effect against MS.<sup>12,16-18</sup> This falls in line with the apparent lower risk found in tropical areas closer to the equator, where people are exposed to greater amounts of sunlight.<sup>16</sup> Longitudinal studies have also shown that women who take vitamin D supplements and individuals with higher blood levels of vitamin D appear to have a lower risk of developing MS.<sup>12,19,20</sup> Munger et al found that women with an intake of at least 400 IU of vitamin D per day had a 41% lower risk of developing MS compared with women with no vitamin D supplementation ( $P = .006$ ).<sup>19</sup> Further research is needed to determine if proactive supplementation with vitamin D would reduce the risk of developing MS.

Smoking is a risk factor that has been consistently cited in the literature for MS.<sup>12,16,21,22</sup> According to Ascherio and Manger, prospective studies have found the relative risk of developing MS to range from 1.3 to 1.8 for women smokers compared with nonsmokers.<sup>21</sup> Among heavy smokers, the absolute risk of developing MS may be up to 70% higher than for nonsmokers.<sup>12,22</sup> Assuming that approximately 20% of adults aged 18 to 44 years in the United States are smokers, smoking could account for up to 6% of MS cases in the country<sup>12,25</sup>; therefore, it is a key preventable risk factor that should be discussed with individuals at high risk for MS.

Exposure to infectious agents such as bacteria and viruses during childhood has also been etiologically

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linked to MS,<sup>5,12,16</sup> one explanation for which is sometimes referred to as the “hygiene hypothesis.”<sup>11,12,26</sup> According to this hypothesis, exposure to infectious agents, especially in childhood, decreases the risk of MS,<sup>12</sup> which seems to complement the geographic distribution of MS incidence, as tropical and subtropical areas (which tend to have lower rates of MS) generally favor the transmission of common viruses, bacteria, and parasites in early childhood.<sup>12</sup> Somewhat contrary to this hypothesis is the finding that patients infected with mononucleosis due to Epstein-Barr virus (EBV) have an approximately 20 times higher risk of developing MS than individuals who are seronegative for EBV<sup>11,12</sup>; however, the development of infectious mononucleosis tends to occur after later-life exposure to EBV (ie, during adolescence or adulthood, as opposed to during childhood), which does fit in with the hygiene hypothesis.<sup>11</sup> Other infective agents that have been correlated with the risk of MS include the herpes simplex virus, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Chlamydia pneumoniae*,<sup>5,16</sup> but the mechanisms by which these infectious organisms modify MS risk are still unclear.

The primary targets of the immune-mediated attacks in MS are the oligodendrocytes that create and maintain the myelin sheath surrounding nerve axons in the CNS.<sup>14</sup> The disease process involves cycles of inflammation, demyelination, remyelination, oligodendrocyte depletion, and neuronal and axon degeneration.<sup>2</sup> The particular antigen that triggers this immune cascade has not been firmly established, but potential candidates include the myelin-associated proteins proteolipid protein, myelin oligodendrocyte glycoprotein, and myelin basic protein.<sup>27,28</sup> The pathogenesis of MS lesions is likely a heterogeneous process that varies from patient to patient and even within the same patient from one relapse to another.<sup>29</sup>

Although the exact trigger remains unclear, autoreactive T cells and other immune cells in the peripheral lymphoid tissue are thought to somehow become activated, and then, following traffic into the circulatory system, bind to adhesion molecules on the endothelial surface of the CNS and penetrate the blood-brain barrier (BBB). In the BBB, autoreactive T cells secrete interleukin-17 and interleukin-23, allowing the entry of T cells, B cells, and macrophages into the CNS. Once within the CNS, the T cells become reactivated and produce inflammatory cytokines, and macrophages release other stressors such as proteases, free radicals, glutamate, and nitric oxide, all of which contribute to the damage of myelin through mito-

chondrial injury and oligodendrocyte apoptosis.<sup>14,27,30,31</sup> Disease-modifying treatments (DMTs) generally target 1 or more of these inflammatory steps.<sup>28</sup>

Most axons will survive the demyelinating process and, likely through the recruitment of oligodendrocyte precursor cells, repair themselves through remyelination.<sup>2,29,32,33</sup> Demyelinated axons may also attempt to repair themselves through redistribution of sodium channels.<sup>27,30,33</sup> Eventually, however, the capacity for tissue repair becomes exhausted, leading to irreversible axonal degeneration and formation of sclerotic plaques.<sup>2,28</sup> Although an element of axonal loss is likely present at the earliest stages of pathology, the accumulating damage is what is thought to contribute to the permanent neurologic disability seen in patients with MS.<sup>29,33,34</sup> Therapies that promote neuroprotection or regeneration would be highly valuable in preventing disease progression in MS.

### Clinical Course

The clinical presentation of MS can vary widely depending on what area of the CNS is initially affected.<sup>2,14,30,35</sup> Approximately 80% to 90% of patients with MS will initially present with an acute episode known as clinically isolated syndrome (CIS).<sup>2,30</sup> The nature of this first clinical event depends on the location of the lesion and the extent of tissue destruction (**Table 2**).<sup>2,36</sup> The probability of a second clinical event (ie, relapse), indicating conversion to clinically definite MS (CDMS), is approximately 16% after 1 year, 50% after 2 years, 63% after 20 years, and 80% after 25 years.<sup>2,37,38</sup> Approximately 50% to 70% of patients with CIS will have clinically silent white matter brain lesions present at the time of presentation, and the presence of these lesions is correlated with a higher risk of developing CDMS.<sup>38</sup> DMTs have shown benefit in delaying subsequent clinical or radiographic events.<sup>34</sup> Total lesion volume is also closely correlated with long-term disability.<sup>38</sup> Occasionally, lesions suggestive of MS are incidentally detected via magnetic resonance imaging (MRI) in patients presenting without signs of neurologic disability; this has been called radiologically isolated syndrome (RIS) and is also occasionally referred to as subclinical MS.<sup>35,39-41</sup> Several prognostic factors have been identified that may play a role in the conversion of RIS and CIS to CDMS (**Table 3**).<sup>13,30,37,38,41</sup> Patients with detectable brain lesions on MRI at the time of CIS presentation (present in approximately 50%-70% of patients with CIS) have an approximately 90% risk of developing CDMS within 10 years.<sup>35,38</sup>

CDMS can be categorized into 4 different disease phenotypic courses: (1) relapsing-remitting MS (RRMS); (2) primary-progressive MS (PPMS); (3) secondary-progressive MS (SPMS); and (4) progressive-relapsing MS (PRMS).<sup>14,41</sup> While these subtypes are generally accepted clinical shorthand to describe a disease course, the rigid classification of MS into these 4 phenotypes is problematic and subjective.<sup>42</sup> Approximately 85% to 90% of patients will initially be diagnosed with RRMS,<sup>30,37</sup> which is characterized by discrete new periods of clinical activity, with or without recovery, followed by periods of remission.<sup>14</sup> Exacerbations tend to occur at random frequencies, and the time between attack and recovery will generally decrease steadily over time.<sup>2,14</sup> It is estimated that 50% of patients with RRMS who are left untreated will progress to SPMS within 10 years, and 75% to 90% within 25 years.<sup>13,14</sup> Patients with SPMS will generally experience fewer well-defined attacks and have an element of worsening gait disability.<sup>14</sup>

Similar benefits have been observed in SPMS and RRMS with DMTs in terms of relapse rate, MRI activity, and quality-of-life (QOL) measures.<sup>42,43</sup> However, a definite effect of prolonged use of DMTs on reducing future disability has only been demonstrated in a few trials with MS, and SPMS in particular is not well studied.<sup>42</sup> Four studies of interferon use in SPMS show a reduction in relapse rate and a reduction of MRI lesions, and 2 of the 4 studies demonstrate the slowing of disease progression (based on Expanded Disability Status Scale [EDSS] scores in 1 study and Multiple Sclerosis Functional Composite [MSFC] scores in the other). However, due to a lack of appropriate and sensitive clinical outcomes for SPMS, the prevention of disability that is required for the purpose of regulatory labeling has not been demonstrated.<sup>44</sup>

PPMS is diagnosed in approximately 10% of patients with MS and is characterized by a gradual and mainly continuous progression of illness from disease onset, without discrete periods of relapse or remission.<sup>14,30</sup> PPMS tends to first occur in the fifth or sixth decade of life, and rapidly leads to significant disability.<sup>35</sup> PRMS is the rarest form of MS, diagnosed in approximately 5% to 10% of patients at disease onset. Although it has a presentation similar to that of RRMS, with patients experiencing

■ **Table 2.** Common Signs and Symptoms of MS<sup>2,36</sup>

Site of Brain Tissue Damage <sup>2</sup>	Signs and Symptoms
<b>Brainstem</b>	<ul style="list-style-type: none"> <li>• Diplopia (double vision)</li> <li>• Nystagmus (jumping vision)</li> <li>• Dizziness</li> <li>• Vertigo (less common)</li> </ul>
<b>Cerebellum</b>	<ul style="list-style-type: none"> <li>• Ataxia</li> </ul>
<b>Cerebrum</b>	<ul style="list-style-type: none"> <li>• Cognitive impairment (memory, attention and concentration, information processing, executive functions, visuospatial functions, verbal fluency)</li> <li>• Depression</li> <li>• Emotional changes (mood swings, irritability, uncontrollable laughing and crying)</li> </ul>
<b>Optic nerve</b>	<ul style="list-style-type: none"> <li>• Optic neuritis (blurring or graying of vision, blindness, scotoma)</li> </ul>
<b>Spinal cord</b>	<ul style="list-style-type: none"> <li>• Bladder dysfunction (frequency, urgency, hesitancy, nocturia, incontinence)</li> <li>• Bowel dysfunction (constipation, diarrhea)</li> <li>• Sexual dysfunction (erectile dysfunction, reduced sensation, vaginal dryness, pain, anorgasmia, infertility in men)</li> <li>• Spasticity (extremities, joints, lower back)</li> <li>• Muscle weakness</li> </ul>
<b>Unknown</b>	<ul style="list-style-type: none"> <li>• Tingling and numbness (facial, body, extremities)</li> <li>• Fatigue</li> <li>• Pain (trigeminal neuralgia, dysesthesia, Lhermitte's sign, back and musculoskeletal pain)</li> </ul>

MS indicates multiple sclerosis.

acute exacerbations, the disease continues to progress between these acute relapses.<sup>14</sup> The progressive forms of MS behave similarly, and rapid early progression with 3 or more symptoms is considered unfavorable in terms of long-term prognosis.<sup>14</sup> Disease severity can vary greatly even within each subtype. In an effort to deal with the nebulous definitions of RRMS and SPMS, a trend has recently developed to simply refer to patients as those with “relapsing MS” if they have a relapsing course, as both phenotypes have inevitable progression in disability and the clinical course can really only be determined in retrospect. Some patients with RRMS (as many as 17% of patients with MS) can have a very mild disease course with minimal disability, even 10 years after disease onset, and publications have referred to these patients as having “benign MS.”<sup>3,13,30</sup> Some authors suggest that these patients have about a 90% chance of remaining clinically stable over time.<sup>13</sup> However, this may be a minimization of the risk of disability, as disability progression in “benign” patients still exceeds 50% in many cohorts.<sup>45</sup> Patients with this milder form of MS will often suffer from impairments, such as cognitive impairment, which

■ **Table 3.** Prognostic Factors in MS<sup>13,30,37,38,41</sup>

Poor Prognostic Factors	Positive Prognostic Factors
Male sex <sup>13,30,37,41</sup>	Female sex <sup>13,30</sup>
Older age at onset (>40 y) <sup>13,30,37,41</sup>	Younger age at onset <sup>30</sup>
Motor, <sup>13,37</sup> cerebellar, <sup>13,30,41</sup> or sphincter <sup>13,41</sup> symptoms at initial presentation	Optic neuritis or sensory symptoms at onset <sup>13</sup>
Multifocal presentation <sup>13,37,41</sup>	RRMS <sup>13</sup>
Frequent attacks within the first 5 years <sup>13,30,37,41</sup>	
Incomplete recovery between episodes <sup>30,37,41</sup>	
Greater increase in brain lesion volume within the first 5 years <sup>38</sup>	
Short interval between the first 2 attacks <sup>13,30,37,41</sup>	
Short time to reach an EDSS level 4 <sup>13,41</sup>	
PPMS <sup>13,30,37,41</sup>	
Higher number of brain lesions at baseline <sup>38</sup>	

EDSS indicates Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary-progressive MS; RRMS, relapsing-remitting MS.

is detected in up to 45% of patients with “benign MS.”<sup>30</sup> Female sex, younger age, and the absence of motor symptoms have all been associated with “benign MS.”<sup>37</sup> Other authors have argued that use of the term “benign MS” should be restricted to a small minority of patients, and that cognitive impairment is incompatible with “benign MS.”<sup>46</sup> It should be noted that use of the term “benign MS” continues to be controversial and remains up for debate. A more appropriate classification would be “MS, currently mild.”

Symptoms of MS are sometimes divided into primary symptoms (ie, directly related to axonal damage and demyelination, which are generally reflective of the area of the CNS that is damaged; Table 2),<sup>2,36</sup> secondary symptoms (ie, complications resulting from primary symptoms), and tertiary symptoms (ie, related to the effects of the disease on everyday life).<sup>36,47</sup> Primary symptoms of acute relapses in MS tend to evolve over the course of days, and may last for weeks or months before resolving.<sup>35</sup> The most common symptoms occurring during an acute exacerbation of MS are optic neuritis (in 20%-25% of patients with CIS), acute partial myelitis (30%-50% of cases), and cerebellar dysfunction (25%-30%).<sup>35</sup> More than 20% of patients will initially present with signs and symptoms due to lesions in more than 1 location, also known as a multifocal presentation.<sup>37</sup> Optic neuritis, or inflammation of the optic nerve, typically presents with visual changes ranging from blurred vision, scotoma, and pain with eye movement to blindness in 1 or both eyes.<sup>35,36</sup> Chances of recovery from optic neuritis are generally favorable, particularly with treatment.<sup>36</sup> Myelitis,

or inflammation of the spinal cord, usually manifests as sensory or motor symptoms below the level of the affected spinal region. One such manifestation, Lhermitte’s sign, is characterized by shock-like sensations that radiate down the limbs or spine upon movement of the neck.<sup>35</sup> Other symptoms relating to myelitis include bladder dysfunction and focal muscle weakness.<sup>35</sup> Cerebellar dysfunction usually causes balance and gait problems such as ataxia and vertigo.<sup>35</sup> Uhthoff’s phenomenon events (involving a transient worsening of neurologic symptoms in the setting of increased body temperature), infection, metabolic abnormalities, and stress may cause “pseudo-relapses.” “Pseudo-relapses” may present as a worsening of MS symptoms that do not reflect new inflammation or require direct treatment.<sup>35</sup>

Probably the most common and disabling symptom, occurring in approximately 80% of people with MS, is fatigue.<sup>47,36</sup> A common subtype of fatigue known as MS-related fatigue or lassitude tends to occur on a daily basis, is aggravated by heat and humidity, and tends to worsen as the disease progresses.<sup>47,36</sup> Fatigue and cognitive dysfunction tend to be more chronic in nature and are likely due to more widespread cortical demyelination, axonal loss, and global brain atrophy.<sup>35</sup> Depression is also significantly more common in patients with MS than in the general population, occurring in up to 50% of patients with MS during their lifetime. This higher rate of depression also implicates an increased risk of suicide among patients with MS, which has been reported to be up to 7.5 times that seen in the general population.<sup>2,36</sup> Bladder dysfunction, such as urinary frequency, urgency,

or retention, is also very common in MS, occurring in at least 80% of patients.<sup>35,36</sup> Other common primary symptoms include spasticity, bowel problems, and pain. Less common primary symptoms include speech and swallowing problems, tremor, seizures, headache, and hearing loss.<sup>36</sup> Secondary symptoms may include recurrent urinary tract infections due to bladder dysfunction, respiratory infections due to difficulty swallowing, and osteoporosis and decubitus ulcers due to immobility.<sup>36</sup> Tertiary symptoms include social and psychological symptoms, and vocational and financial problems,<sup>36</sup> which will be discussed further in the next article in this supplement. Depression, in addition to being a primary symptom due to structural and chemical changes in the brain,<sup>47</sup> can also be considered a tertiary symptom, as it can be triggered by the disease burdens.<sup>36</sup>

### Disease Burden

MS is one of the most common causes of neurologic disability in young and middle-aged adults.<sup>3,48</sup> Although it is estimated to account for only approximately 0.04% of the total global disability-adjusted life-years according to the World Health Organization, the burden of disability on the individual patient can be devastating due to the time of onset (usually at the peak years of productivity) and chronic nature of the disease.<sup>3,49</sup> Increased healthcare utilization and direct treatment costs, and indirect costs that include reduced productivity and caregiver burden, all contribute to the cost of managing MS.<sup>3</sup> Healthcare costs have recently been estimated at \$18,000 to \$39,000 per person per year, with an estimated societal cost of approximately \$28 billion per year in the United States.<sup>50</sup> In a recent survey, among a sample of patients filing for medical bankruptcy in the United States, out-of-pocket expenses for patients with MS were the highest of any diagnosis, averaging \$34,167 per person and exceeding those of diabetes, stroke, mental illness, and heart disease.<sup>50,51</sup> Loss of income may have the greatest impact on the patient and their family members, in terms of economic status and QOL.<sup>52</sup> Other determinants of poor QOL, as related to MS, include fatigue, mobility limitations, and interference with social activities.<sup>52</sup>

Disease severity and the level of disability can be measured in a number of ways. The most commonly used instrument for evaluating impairment in MS is Kurtzke's EDSS (Table 4).<sup>13,52,53</sup> However, the EDSS does not account for upper extremity dysfunction or cognitive deficits as much as it focuses on ambulation<sup>13</sup>; other measures such as the MSFC and the Paced Auditory

■ **Table 4.** Disability According to the Expanded Disability Status Scale<sup>52,53</sup>

Score	Level of Disability
0	Normal neurologic exam
1.0-1.5	None
2.0-2.5	Minimal
3.0-3.5	Mild to moderate
4.0-4.5	Relatively severe
5.0-5.5	Increasing limitation in ability to walk
6.0-6.5	Walking assistance needed
7.0-7.5	Confined to wheelchair
8.0-8.5	Confined to bed or chair
9.0-9.5	Completely dependent
10.0	Death due to MS

MS indicates multiple sclerosis.  
Adapted from Zwibel HL, Smrtka J. *Am J Manag Care.* 2011;17:S139-S145; and Kurtzke JF. *Neurology.* 1983;33(11):1444-1452.

Serial Addition Test can be used to assess those symptoms.<sup>13</sup> Loss of ambulation is a major source of disability in patients with MS, with as many as 50% of patients becoming dependent on at least a walking aid within 15 years, and becoming restricted to a bed after an average of 33 years.<sup>13</sup> The EDSS score has been shown to be the strongest predictor of costs in cost utility studies.<sup>54</sup> According to a recent study by Kobelt et al, mean annual costs per patient were approximately double for those with severe disability (\$64,492 for patients with an EDSS score >6.0) compared with patients with mild disease (\$32,297 for patients with an EDSS score <4.0).<sup>54</sup>

Loss of productivity due to MS may be the disease's largest contributor to the cost burden on society.<sup>52</sup> Employment rates are reported to decline an average of 3% per year following an MS diagnosis.<sup>50</sup> Absenteeism, reduced work hours, and early retirement also play a large role in the economic burden, accounting for approximately 44% of total costs related to MS.<sup>52,54</sup> Ivanova et al found that annual disability costs for employees with MS were nearly 10 times higher than those for healthy controls (\$3868 vs \$414;  $P < .0001$ ), absenteeism costs were almost twice as high (\$1901 vs \$1003;  $P < .0001$ ), and total indirect costs were more than 4 times higher (\$5769 vs \$1417;  $P < .001$ ).<sup>55</sup> These types of costs, and overall costs in general, increase particularly in the later stages of the disease as disability further increases.<sup>52</sup> These results suggest that treatments that could delay disease progres-

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sion would be particularly beneficial in reducing costs to employers and society as a whole. Not only are relapses in MS associated with acute neurologic dysfunction, but higher rates of relapse have been linked to a greater risk of accumulated neurological damage and disability.<sup>34</sup> Therefore, DMTs, which have been shown to prevent relapses and delay the progression of disability, should ideally be started early in the course of RRMS to prevent disease progression.<sup>34</sup> This practice has been endorsed by a number of MS treatment guidelines, such as those of the American Academy of Neurology and the National Multiple Sclerosis Society.<sup>34,56,57</sup>

Unfortunately, adherence to DMTs in patients with MS is often less than ideal.<sup>34,52</sup> The use of newer oral DMTs may help with this challenge, as some nonadherence may be attributed to the mode of administration of many DMTs, which are mostly administered via subcutaneous or intramuscular injection or via infusion.<sup>34</sup> One study of adherence to injectable medications in MS showed that over the course of 14 months, only 57% of patients remained adherent to their DMT regimen.<sup>52,58</sup> In addition to the mode of medication administration, high patient out-of-pocket costs also contribute to nonadherence to DMTs in MS,<sup>34,58</sup> with medication adherence seeming to decrease with increasing co-pays.<sup>58</sup> Patient education regarding the importance of adherence to DMTs and efforts to reduce the impact of medication adverse effects (such as infusion reactions, fatigue, and nausea) are essential to the successful and effective management of MS.<sup>34</sup>

### Conclusion

MS causes significant disability in the patients it affects, and unfortunately, the incidence of MS is increasing, particularly in women. Although environmental and genetic factors are thought to play a role in the development of MS, the cause of MS remains unclear. However, there are potentially modifiable risk factors that hold promise for reducing the risk of MS, such as smoking cessation and perhaps vitamin D supplementation in persons with low levels of vitamin D. Identifying further risk and prognostic factors may help to prevent the development of MS and also improve the course of illness in diagnosed patients. Preventing relapses and delaying disease progression continue to be key priorities in the effective management of patients with MS, as progressive disability contributes to poorer QOL, lost productivity, and increasing burdens on patients, their caregivers, and society.

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