

## Improving Quality of Life in Multiple Sclerosis: An Unmet Need

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### Multiple Sclerosis and Its Cost Burden

Multiple sclerosis (MS) is a disorder in which inflammation and damage to the insulation surrounding nerve fibers (demyelination) impairs nerve signaling.<sup>1,2</sup> MS afflicts approximately 400,000 people in the United States<sup>3,4</sup>—twice as many women as men<sup>2,5</sup> and 2.1 million people worldwide.<sup>4</sup> Although most patients with MS are treated at community physician practices, more than 200 centers in the United States, Canada, and Europe are affiliated with the Consortium of Multiple Sclerosis Centers (CMSC), and serve more than 150,000 patients in a specialized setting.<sup>6</sup>

MS is the most common chronic, non-traumatic neurological disorder among young people.<sup>7</sup> Onset usually occurs during the peak productive ages of 20 to 50 years.<sup>1,2,7,8,9</sup> MS severely impacts the labor force with both direct and indirect costs (Table 1).<sup>9,10,11</sup> Direct medical costs in the United States may exceed \$10 billion per year.<sup>2</sup> Annual direct costs are estimated to average \$47,000 per patient,<sup>10</sup> with treatment for a single average MS episode estimated at \$12,879.<sup>11</sup> In a retrospective claims database analysis, compared with healthy comparison subjects, patients with MS had significantly higher annual total costs and costs for inpatient services, radiology, office visits, and therapies ( $P < .001$ ).<sup>9</sup> MS drugs were \$4436 per patient per year.<sup>3</sup>

Indirect costs include those of reduced employment or unemployment, assistive equipment, disability-related home modifications, and paid or unpaid personal care.<sup>11</sup> Depending on the locations of damaged myelin, MS affects sensation, cognition, and motor function,<sup>1</sup> all potentially essential to productivity. Fatigue, one of the most common MS symptoms, can be a critical reason for poor job performance and attendance. A 1994 estimate of total lifetime costs per patient (\$2.2 million) attributed 57% to non-healthcare costs of lost earnings, home and workplace alterations, equipment, and formal and informal care.<sup>12</sup> Although lost income has greatest impact on the patient and family, companies also bear tangible costs (eg, sick days, private insurance disability benefits), as does society as a whole (eg, social security disability benefits). Productivity loss may constitute the largest societal cost burden of MS, with absenteeism or reduced work hours plus early retirement equaling 44% of total costs (Table 1).<sup>10</sup> A claims database study found employees with MS had 29.8

### Abstract

Multiple sclerosis (MS) affects approximately 400,000 people in the United States and 2.1 million people worldwide. It is the most common chronic, non-traumatic neurological disorder afflicting young people during their peak productive ages. MS can diminish quality of life (QOL) by interfering with the ability to work, pursue leisure activities, and carry on usual life roles. Symptoms that affect QOL may include impaired mobility, fatigue, depression, pain, spasticity, cognitive impairment, sexual dysfunction, bowel and bladder dysfunction, vision and hearing problems, seizures, and swallowing and breathing difficulties. Direct medical costs of MS in the United States are estimated in excess of \$10 billion per year. Indirect costs of MS include costs of reduced employment or unemployment, assistive equipment, disability-related home modifications, and paid and unpaid personal care. Although direct medical costs predominate in the earlier stages of MS, indirect costs of productivity loss are responsible for higher costs later. Disease-modifying therapies (DMTs) lessen symptoms, reduce relapses, and delay disability progression. Unfortunately, many DMTs might produce only modest improvements in QOL. Although symptom-specific therapies do not delay disease progression, they may delay unemployment and dependency, thereby reducing indirect costs.

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## Reports

disability days per year versus 4.5 days for control employees ( $P < .0001$ ) and significantly higher annual disability costs (\$3868 versus \$414,  $P < .0001$ ), absenteeism costs (\$1901 versus \$1003,  $P < .0001$ ), and total indirect costs (\$5769 versus \$1417,  $P < .0001$ ).<sup>13</sup> Using quality-adjusted life-years valued at \$60,000, reduced QOL has been estimated to add \$15,315 to annual costs per patient.<sup>10</sup>

Furthermore, as disease severity increases, costs also increase.<sup>14</sup> Direct medical costs predominate in earlier stages, but indirect costs of productivity loss lead the cost distribution later, suggesting that early interventions to delay disease progression may help reduce the cost burden. Disease severity and type of immunomodulatory treatment affect lost work hours.<sup>15</sup> Therefore, early treatment that impedes disease progression and delays productivity loss could potentially be cost-effective. However, none of the current disease-modifying treatments cure the disease, stop progression completely, or improve all effects of MS in individual patients, especially reduced QOL.

### Disability: Affected by Phenotype and Relapses

MS has 4 main phenotypes which affect progression and influence disability over time. Of all patients with MS, 85% have the relapsing-remitting type (RRMS),<sup>16</sup> with symptoms for at least 24 hours followed by remission for at least 1 month.<sup>16,17</sup> In many patients, RRMS evolves to secondary progressive MS (SPMS),<sup>16</sup> with steady neurologic and functional deterioration independent of relapses, which also may occur.<sup>2,5,17</sup> Progressive relapsing MS (PRMS) is continuously progressive from onset, but includes superimposed relapses.<sup>2,17,18</sup> Primary progressive MS (PPMS) progresses from onset without relapses and remissions.<sup>2,5,17,18,19</sup>

MS-related disability, commonly measured with the Kurtzke Expanded Disability Status Scale (EDSS) (Figure),<sup>20</sup> accumulates from incomplete recovery after a relapse or deterioration independent of relapse in progressive types.<sup>16</sup> In a study of patients given placebo in several clinical trials, at 64 days post relapse, 28% had residual deficit of at least 1.0 EDSS point and 42% had residual deficit of at least 0.5 point.<sup>21</sup>

In a retrospective review of patients with PRMS, time to EDSS 6.0 (assistive device required to walk ~100 meters) was associated with time to first relapse ( $r = .80$ ,  $P = .0004$ ).<sup>18</sup> In another study, early relapse in relapsing-onset patients increased immediate risk of reaching EDSS 6.0 and reaching SPMS by 48% and 29%, respectively.<sup>16</sup> Once SPMS was reached, relapses had no discernible effect on further progression, suggesting an early window of opportunity for treatments that reduce relapses.<sup>16</sup> RRMS may become SPMS

■ **Table 1. Components Contributing to the Economic Burden of Multiple Sclerosis in the United States<sup>10</sup>**

Component	Contribution
Early retirement	34%
Disease-modifying drugs	22%
Informal care	12%
Sick leave and reduced working time	10%
Prescription and OTC drugs	6%
Adaptations	5%
Ambulatory care	4%
Hospital inpatient care	3%
Services	2%
Tests	2%

OTC indicates over-the-counter.

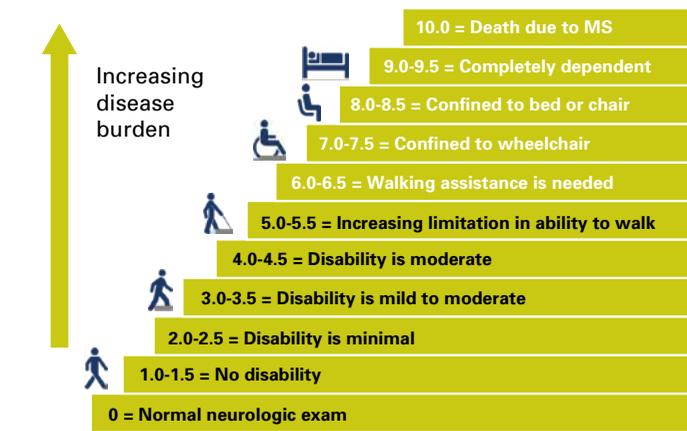
when accumulating damage reaches a threshold after which functional deterioration becomes irreversible.<sup>2</sup> This would also imply that disease-modifying treatments (DMTs) should be started early during RRMS because they would have reduced effect in SPMS.<sup>2</sup> No DMT has received Food and Drug Administration (FDA) approval for PPMS,<sup>22</sup> which is more resistant to DMT treatment.<sup>2</sup>

The actions of DMTs to reduce relapses and delay disability progression (which may lessen symptoms)<sup>22</sup> are critical to employment and activities of daily living (ADLs). However, none of the DMTs have data to suggest they are effective to completely arrest disease progression. Additionally, adherence can be problematic regardless of the route of administration. In a retrospective study of pharmacy claims data (injectable medication), the mean medication possession ratio over 24 months was 68.0% and decreased with increasing drug copayments.<sup>23</sup> Within 14 months, 43% of patients were non-compliant with their DMT.<sup>23</sup> Hospital admissions were higher in patients who were non-adherent (24.7%) than adherent patients (17.7%),<sup>23</sup> suggesting that efforts to increase adherence might help control hospital costs.

### QOL Burdens on MS Patients and Families

QOL is a subjective measure of a patient's life satisfaction that is affected by mood, coping mechanisms, life experiences, and emotional support as well as disease state.<sup>24</sup> Clinicians cannot appreciate any of these factors without information from the patient. Initial and ongoing MS management should include QOL assessment with structured interviews or formal instruments (eg, MSQOL-54) and additional patient-specific, open-ended questions. Patient feelings about autonomy, empowerment, and QOL can significantly impact adherence to medications and affect physical rehabilitation. Therefore,

■ **Figure. Progression of Disability: EDSS<sup>20</sup>**



EDSS indicates Expanded Disability Status Scale; MS, multiple sclerosis.

the CMSC recommends interdisciplinary team care that provides emotional support and promotes self-efficacy as well as skill development.<sup>25</sup>

According to the National Multiple Sclerosis Society (NMSS), MS diminishes QOL by interfering with ability to work, pursue leisure activities, and carry on usual life roles.<sup>26</sup> QOL domains include physical and occupational function, psychological state, and social interaction,<sup>27</sup> all of which may be affected in MS. Physical composite QOL scores on the MSQOL-54 are inversely related to disability.<sup>28</sup> QOL scores in Physical Functioning and Role-Physical Functioning on the Short Form-36 (SF-36) predict change in EDSS.<sup>29</sup> A study found that patients with MS had poorer QOL than other disabled persons and that poor QOL was associated with fatigue, unemployment, and mobility limitations on stairs.<sup>30</sup> Thus, QOL is a practical concern related not just to satisfaction or happiness, but to function and productivity in society.

Currently, no cure for MS exists, so it is imperative that decision makers and clinicians consider QOL and the patient's ongoing experience of MS. Compared with clinicians, patients with MS show less concern about physical role limitations and more concern about mental health and emotional role limitations.<sup>31</sup> Psychosocial factors sometimes affect QOL more than physical symptoms,<sup>24</sup> and in MS, psychosocial impairments may be independent of disease severity.<sup>32</sup> One study found the strongest correlation with poor QOL was the interference of MS with social activities,<sup>30</sup> a question clinicians might not ask when assessing disability and progression. Unfortunately, by not asking about QOL, an important need is being overlooked. When clinicians do investigate QOL with patients and caregivers, they may discover issues affecting adherence and gain insight into more effective treatment individual-

ization. Formal assessment instruments include the Multiple Sclerosis Quality of Life-54 (MSQOL-54),<sup>33</sup> the Multiple Sclerosis Quality of Life Inventory,<sup>34</sup> the Beck Depression Inventory,<sup>28</sup> and the Multiple Sclerosis Modified Fatigue Impact Scale.<sup>35</sup>

In addition to optimizing symptom management and delaying disability progression, assessing and promoting QOL should be a principal goal of treatment. For many MS patients, this remains an unmet need. Ideally, patients diagnosed with MS should be evaluated in MS specialty centers with multidisciplinary teams, such as those in the CMSC, to identify individual needs and design therapy to minimize progression and maximize QOL. Although DMTs may reduce symptoms and relapses and delay progression,<sup>1,2,8</sup> many DMTs produce little improvement in QOL.<sup>32</sup> Other treatments, which do not impede the underlying disease process, improve specific symptoms and function, which may positively impact QOL.

### Symptoms That Worsen QOL

In MS, QOL is diminished by physical, emotional, and cognitive symptoms, comorbidities, and their real-life consequences (Table 2).<sup>36</sup> Symptoms that affect QOL include impaired mobility, fatigue, depression, pain, spasticity, cognitive impairment, sexual dysfunction, bowel and bladder dysfunction, vision and hearing problems, seizures, and swallowing and breathing difficulties.<sup>36,37</sup> Factors that affect QOL can also increase costs. Annual direct medical costs for MS with impaired gait have averaged \$20,871, with spasms, \$20,376, and with depression, \$13,928.<sup>38</sup>

**Mobility** is impaired in up to 90% of patients with MS.<sup>11</sup> Impaired mobility affects functional activity, employment, independence, and physical and mental components of QOL.<sup>11</sup> Several studies have suggested the importance of mobility to productivity and employment. Mobility and hand function are the 2 largest predictors of leaving the workforce.<sup>11</sup> Of factors affecting QOL in a group of patients with MS, 65% gave mobility the highest priority.<sup>11</sup> In another survey, 70% of patients with MS and walking impairment reported that it was the biggest challenge associated with MS.<sup>39</sup> Patient concerns about falling can increase social isolation.<sup>40</sup> Patients afraid of falling may decrease physical activity, which can reduce strength, endurance, and range of motion.<sup>40</sup> This can increase the risk of falling, which may lead to additional increase in medical costs.

Problems with gait (walking) in MS are thought to be due to demyelination in the central nervous system and spinal cord, but may also be related to muscle weakness, spasticity,

**Table 2. Symptoms, Comorbidities, and Effects of MS That Can Diminish QOL<sup>36</sup>**

Common	Rare
Gait and mobility impairments	Speech disorders
Fatigue	Difficulty swallowing
Spasticity	Hearing loss
Muscle weakness	Headache
Pain	Itching
Impaired balance and coordination	Tremors
Cognitive dysfunction	Breathing difficulties
Bladder and bowel dysfunction	Seizures
Paresthesias	
Loss of sensation/numbness	
Sexual dysfunction	
Vertigo, dizziness	
Vision impairments (eg, optic neuritis)	
Depression	
Anxiety	
Reduced employment or unemployment	

MS indicates multiple sclerosis; QOL, quality of life.

impaired balance, numbness in the feet, fatigue, and visual or cognitive deficits.<sup>40</sup> Gait problems can appear any time in the disease course. Fifteen years after diagnosis the probability of requiring assistance for walking is estimated at 40%, and of requiring a wheelchair, 25%.<sup>11</sup> Gait measures including walking speed and length of stride have significantly predicted dependence on assistance for ADLs ( $P < .05$ ).<sup>11</sup> Moderate walking impairment (EDSS 4.0-4.5) increases total costs 3 times, and inability to walk without assistance (EDSS 6.5) increases costs 7 times.<sup>11</sup>

Gait difficulties may worsen continuously or wax and wane and often can be improved at initial stages. Clinicians should ask about mobility difficulties and also observe the patient walking, noting coordination, position of feet, posture, and momentum.<sup>40</sup> Notably, only 52% of patients with MS treated with DMTs reported mobility improvement.<sup>11</sup>

**Fatigue** appears in all ages and phenotypes of MS and strikes 75% to 95% of patients.<sup>11,28</sup> It is often a main presenting symptom for diagnosis. Up to 69% of patients consider it one of the most disabling features of MS.<sup>11</sup> Fatigue is a primary determinant of poor QOL,<sup>28</sup> affecting both physical and mental components independent of disability level.<sup>11</sup> Primary, physiologic fatigue results from MS and secondary fatigue arises from medical comorbidities, depression, sleep disturbance, medication side effects, or exhaustion from

weakened muscles.<sup>37,41</sup> Primary fatigue can impair vocational abilities and stamina for any physical activity.<sup>37</sup> It is recognized by the Social Security Administration and cited by patients as a primary cause of MS-related unemployment.<sup>41</sup> Up to 90% of patients with MS who reduce full-time work to part-time do so because of fatigue.<sup>9</sup>

**Pain** is reported in up to 86% of patients with MS,<sup>11</sup> which may be associated with optic neuritis, paroxysmal dystonic spasms, or trigeminal neuralgia, or may occur as dysesthetic extremity pain or pain in the lower back.<sup>37</sup> Pain in MS shows correlations with both anxiety and depression and can affect all aspects of function and physical and mental QOL domains.<sup>11</sup> Almost one-half of patients with MS and pain report that it interferes with social activities, work, or sleep.

**Spasticity**, which occurs in up to 75% of patients with MS,<sup>37</sup> negatively affects daily activities in up to 44%.<sup>11</sup> Spasticity can worsen gait problems, physical components of QOL, and bowel or bladder dysfunction.<sup>11,37</sup> Spasticity includes active muscle spasms, muscular tightness, stiffness, inelasticity, and weakness. Dizziness, vertigo, and numbness can also occur in MS<sup>8,36</sup> and interfere with mobility.

Prevalence estimates of cognitive impairment in MS range from 43% to 60%.<sup>42,43,44</sup> Whole brain and central atrophy predict cognitive decline,<sup>45</sup> which can include problems with working memory, language, abstract reasoning, attention, organizational skills, and information processing.<sup>46,47</sup> Patients with MS including cognitive impairment participate in fewer social activities and have more sexual dysfunction, household task difficulty, and mood disturbances than patients without this impairment.<sup>11</sup> Cognitive dysfunction can reduce vocational abilities, leading to unemployment,<sup>11,48</sup> while impairing empathy and social skills,<sup>49</sup> all leading to reduced social support.<sup>48</sup> Limitations in work and social activities correlate with cognitive decline independent of physical disability.<sup>46</sup> Eventually, cognitive impairment can interfere with ADLs<sup>48</sup> and lead to dependence on caregivers. Up to 22% of patients with MS meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria for dementia due to a medical condition.<sup>49</sup> To differentiate MS-related cognitive decline from cognitive effects of treatable comorbidities (eg, depression), clinicians should conduct evaluations<sup>47</sup> with formal assessment instruments (eg, MS Neuropsychological Screening Questionnaire, Minimal Assessment of Cognitive Function in Multiple Sclerosis). The NMSS recommends cognitive screening every 1 to 2 years. Because patients may not be aware of their own cognitive decline, the assessments are also recommended for family members to provide their observations.

## Depression and Other Psychological Impairments

Patients with RRMS have reported significantly more psychological distress on subscales of interpersonal sensitivity, depression, and anxiety, compared with healthy controls ( $P \leq .003$ ).<sup>50</sup> The lifetime risk of depression in MS is approximately 50%<sup>28,46</sup>; prevalence reports have ranged as high as 79%.<sup>46</sup> In MS, depression can reflect uncertainty about the future with a chronic disease<sup>28</sup> or may relate to the release of pro-inflammatory cytokines and other biologic factors<sup>28,46</sup> including MS lesion burden and brain atrophy.<sup>46</sup> Rarely, depression may be an adverse effect of DMTs or corticosteroids.<sup>37</sup> A primary determinant of reduced QOL in MS,<sup>28</sup> depression increases the disease burden in several ways. First, treatment success can suffer from poor adherence to medications, doctor visits, and physical therapy. Secondly, work can suffer through absenteeism or low on-site productivity. Also, physical inactivity and social withdrawal can increase, leading to anhedonia and depression. One-fourth of patients with MS have suicidal thoughts or intent.<sup>28,46</sup> In a mortality study, of patients with MS whose known cause of death was not MS complications, 28.6% were suicides.<sup>51</sup> Depression is under-recognized and undertreated;<sup>50</sup> up to one-third of patients with MS whose depression reaches suicidal ideation do not receive psychological help and two-thirds are not offered antidepressant medication.<sup>28</sup> Depressed patients with MS may respond to antidepressants, but adverse effects can be a concern.<sup>52</sup>

Furthermore, other mood-related symptoms prevalent in MS include anxiety in 40% of patients, irritability (35%), apathy (20%), and hallucinations (10%).<sup>46</sup> Euphoria, sclerotic, disinhibition, and pathological crying and laughter are associated with lesion burden and brain atrophy.<sup>45</sup> These neuropsychological impairments predict low QOL and unemployment in MS,<sup>45,48</sup> suggesting the need for ongoing attention to these disorders.

## Unemployment and Loss of Income

As MS often strikes working people at the height of their careers, patients may be devastated by the prospect and eventual reality of unemployment, with subsequent loss of income. Family or friend caregivers may also face employment reduction as demands of caregiving increase. In both patients and caregivers, productivity is lost due to absenteeism or sick days.<sup>13</sup> Patients may choose (or their employers may require) workload cutbacks. Deterioration over 3 years in scores on cognitive function tests was associated with reduced hours or responsibilities in 45.4% of workers with MS and with paid disability benefits in 28.9%.<sup>53</sup> Of those diagnosed with MS for less than 5 years, 67% change job status and 45% switch to a different field.<sup>9</sup> As disability increases, finding a new job

becomes more difficult. Approximately 21% of patients with MS for less than 5 years are unemployed, versus 92% of those with MS for at least 30 years.<sup>9,54</sup>

## The Changing Landscape of MS Care

Many busy healthcare practices cannot adequately address the complex needs of patients with MS. Patients should see a neurologist that specializes in MS and undergo evaluation at least annually at a specialty center such as those in the CMSC, which offer the full range of assessment instruments, technology, and equipment. At specialty centers, multidisciplinary teams manage evaluation, medical treatment, and rehabilitation, providing professional expertise and patient-centered care for all patient needs including QOL improvement.

As US healthcare costs rise rapidly and represent ever greater percentages of national expenditures, the search for cost savings takes on greater urgency. Costs of MS include expensive medications, rehabilitation, and disability costs. Indirect costs dominate the cost distribution in later MS stages, emphasizing the need to delay progression.<sup>14</sup> If a treatment could reverse disease and restore function completely, its cost would be offset by disappearing disability costs. Conversely, if treatments are incompletely effective, the disability costs remain.

Currently, DMTs dominate MS treatment, leaving 3 notable treatment gaps. First, despite their efficacy, DMTs are rarely associated with sustained remission; eventual progression is inevitable. As such, stopping disease progression entirely remains an unmet priority goal of treatment.

A second treatment gap is the need for medications that treat all forms of MS. The DMTs interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, and fingolimod have FDA indications for relapsing forms of MS only.<sup>22</sup> The association of natalizumab with progressive multifocal leukoencephalopathy has limited its use to restricted distribution at registered facilities.<sup>55</sup> Mitoxantrone is approved for SPMS and PRMS as well as RRMS, is administered by infusion at a medical facility,<sup>22</sup> and does not entirely stop progression. Currently, there is no DMT that is indicated for PPMS.<sup>22</sup> A primary research need is to develop new therapies for the progressive forms of MS.

The third treatment gap, for many patients, is failure to address QOL. Many DMTs produce only modest improvements in QOL.<sup>32</sup> Clinicians need to consider important patient needs that can be met by treatments that reduce symptoms and improve function. One example of such a treatment is high-dose corticosteroids, which may be prescribed for short-term treatment of acute relapse.<sup>56</sup> Another is the off-label use of amantadine, methylphenidate, or modafinil for fatigue.<sup>41</sup> Dalfampridine is the first medication specifically

approved by the FDA for an MS symptom; it is indicated to improve walking in patients with MS.<sup>57</sup> Although symptom-specific therapies do not delay disease progression, they may have potential to delay unemployment and dependency, thereby reducing indirect costs.

### Conclusions

MS profoundly diminishes QOL by impairing ability to work and engage in social activities. Current MS treatments cannot cure the disease or reverse its progression, so more research into potentially curative treatments is needed. Furthermore, patients need treatments that can preserve abilities as long as possible, optimize function, and promote QOL at all stages of disability. For some patients, even those receiving DMTs, improving QOL remains an unmet need. Incorporating into healthcare decisions the assessment of QOL and the consideration of symptomatic treatments can address important needs of patients with MS while potentially reducing direct and indirect costs.

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