

Practical Issues in Multiple Sclerosis: Optimal Patient Management Strategies

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Summary

Multiple sclerosis (MS) is a common cause of disability in young adults. Although not curable, effective immunomodulators, which alter the development of disability, are available and should be initiated early in the disease process. Optimizing care of patients with MS requires frequent assessment and a team approach.

Key Points

- MS is the most common neurological disease that causes disability in young adults.
- Therapy with an immunomodulator should be started as soon as possible following a definite diagnosis of relapsing remitting MS to slow the development of disability.
- The goals of MS management are to treat relapses, manage symptoms, modify or reduce relapses, delay progression to disability, and facilitate an acceptable quality of life.

ALTHOUGH MULTIPLE SCLEROSIS (MS) IS not the most common neurological disease in young adults, it is the most common neurological disease that causes disability in young adults. It is a chronic illness with no cure, but it does not shorten one's lifespan.

There are an estimated 350,000 to 500,000 people in North America with MS. About 10,000 new cases are diagnosed annually. The highest prevalence in the U.S. is among Caucasians, and the female-to-male ratio is at least 2-to-1 and possibly higher. The usual age of onset is between 15 and 55. The average age at MS diagnosis is 26.

Because this disease disables young people, the costs of MS to society are enormous. This was estimated at 27 billion dollars about 10 years ago.¹

MS is an immune mediated disease in genetically susceptible individuals. It has two aspects, inflammatory and degenerative, which leads to progressive neurological dysfunction with lesions in all areas of the central nervous system, brain, and spinal cord.

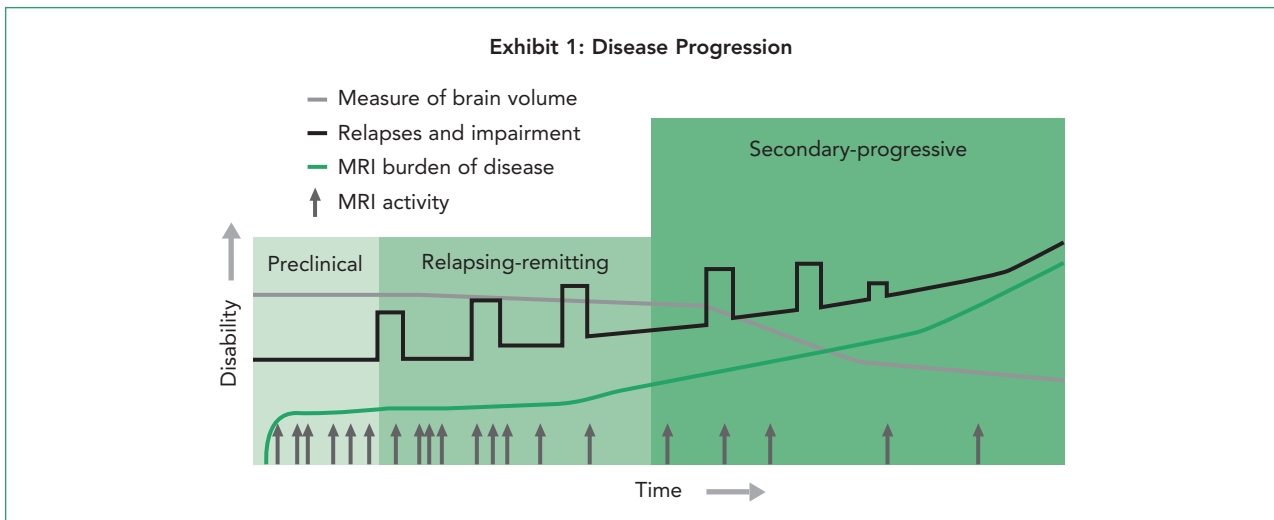
Exhibit 1 illustrates the clinical progression of MS. Initially, there is a preclinical phase where changes can be seen on magnetic resonance imaging (MRI) scans. The next stage is a relapsing remitting phase where patients will have an attack and get better. Acute attacks are relapses or episodes with acute neurological dysfunction that last at least 48 hours.

The relapsing remitting stage is where medications are most effective. In the secondary progressive phase, there is a loss of brain volume and increasing evidence of neuron loss on MRI scans. In the earlier phases, the patient will return back or nearly back to baseline after an attack or relapse. As the disease progresses, the patient accumulates damage.

MRI scanning is very important in diagnosis and in following patients. An MRI scan will demonstrate approximately 90 to 95 percent of white matter lesions in the brain and 50 to 75 percent of lesions in the spinal cord. Cost and availability are limiting factors in repeated MRI scans in the clinical setting.

The National Multiple Sclerosis Society states that initiation of therapy with an immunomodulator is advised as soon as possible after a definite diagnosis of MS with a relapsing course.² Therapy may be considered for selected patients with a first attack who are high risk for RRMS.² Early therapy is intended to slow both the inflammatory and degenerative aspects of the disease. Treating patients early has a better chance to affect and modulate the immune system. The goals of pharmacologic therapy in MS are given in Exhibit 2. Importantly, control of disability is a major goal of therapy.

Immunomodulators that are approved for relapsing remitting multiple sclerosis (RRMS) include glati-



glatiramer acetate (Copaxone[®]), interferon beta-1a (Avonex[®] and Rebif[®]), interferon beta-1b (Betaseron[™]), and natalizumab (Tysabri[®]) (Exhibit 3). Natalizumab was briefly withdrawn from the market because of several cases of progressive multi-focal leukoencephalopathy, which can be fatal. It was recently reintroduced to the market. Mitoxantrone (Novantrone[®]), a chemotherapeutic agent, and corticosteroids are used as immunosuppressants in relapsing forms of MS. Patients at times will respond to one agent and not to another. All of the FDA-approved immunomodulators reduce the number of relapses.

Among untreated patients, 50 percent will reach a level of disability, requiring assistance with walking, within 15 years (expanded disability status scale [EDSS] score of 6, Exhibit 4).³ Data shows glatiramer acetate and interferons alter the natural history of this disease.⁴ ⁶ For example, in one glatiramer study, only 8 percent of patients progressed to an EDSS of 6 at 10 years.⁷

Although these medications can decrease disability, they are not without side effects. The major adverse effects of the agents are given in Exhibit 5. Glatiramer acetate causes less significant adverse events, which is very important for patient quality of life. Additionally, glatiramer has a pregnancy category B labeling (safe in animals, no human data) versus C (adverse events in animals) or D (known fetal risk) for the other agents. Since women are diagnosed with MS more often than men, this distinction between the agents is important.

Untreated, almost half of the patients will not fully recover from an acute attack. It is very important to treat acute attacks to prevent or reduce long-term disability. High dose intravenous corticosteroids are the standard treatment. In the past, this treatment would have required a three-to-five-day hospital stay. Now, this treatment is almost exclusively given in the home.

In addition to acute attacks, patients have many

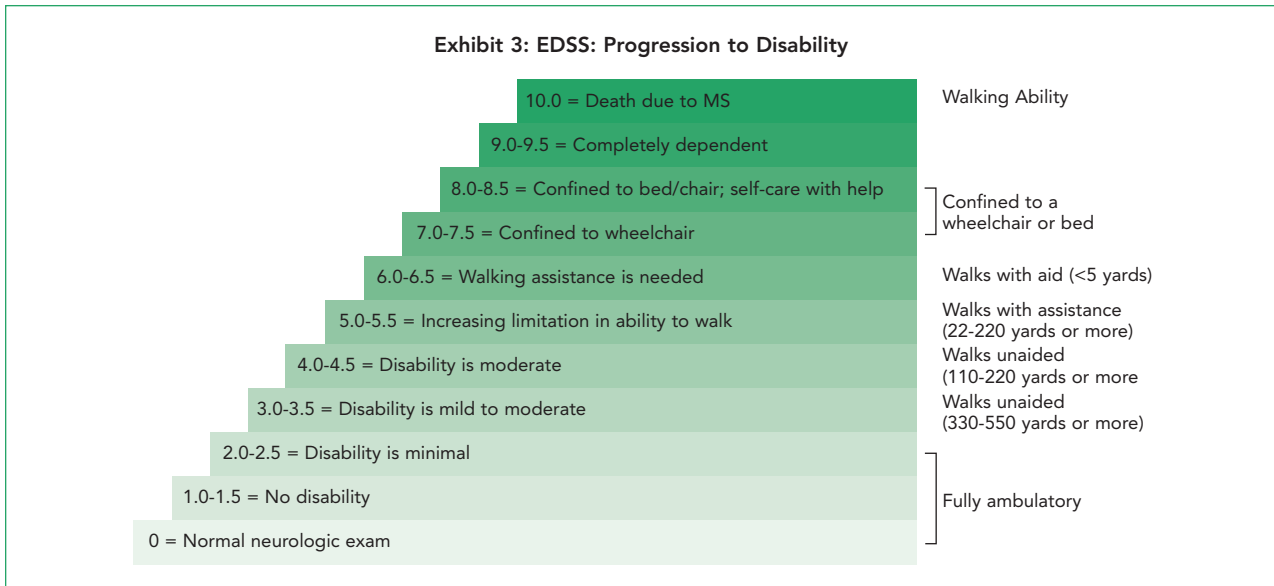
different symptoms that also require treatment. Symptoms of MS occur depending on the locations of the demyelinating plaques in the brain (Exhibit 7). For example, plaques in the cerebellum can cause ataxia or tremors. The typical symptoms of MS include fatigue, spasticity, pain, bowel & bladder problems, memory loss, swallowing difficulties, tremors, visual changes, sexual dysfunction, speech disorders, balance and mobility dysfunction, and depression. Treating these symptoms improves the patient's quality of life. Symptom management includes nonpharmacologic therapies, pharmacologic therapies, and psychological support.

Fatigue is a common symptom that may require lifestyle changes. For example, patients are taught to integrate rest times during their daily activities. Fatigue can be treated with amantadine (Symmetrel[®]), modafinil (Provigil[®]), and antidepressants. None of these agents are FDA approved for treating fatigue of multiple sclerosis.

Spasticity affects 60 to 80 percent of patients. Nonpharmacologic interventions to manage spasticity include stretching, bed and chair positioning, and physical therapy. Pharmacologic interventions, in addition to nonpharmacologic measures, are most

Exhibit 2: Goals of MS Therapy

- Affect the neurodegenerative & inflammatory components of MS
- Early intervention: initiate therapy as soon as possible for the best chance of controlling damage
- Reduction of disease activity as measured by relapses, MRI findings, & disability
- Provision of therapy that is well tolerated & safe over time



commonly used. The typical agents include baclofen, tizanidine (Zanaflex[®]), diazepam, dantrolene (Dantrium[®]), nerve blocks with various agents, and botulinum toxin (Botox[®]). Surgical interventions include baclofen pumps and rhizotomy.

Various types of pain occur with multiple sclerosis. Nonpharmacologic management of pain includes appropriate seating support to improve posture, physical therapy, gait training, assistive devices, muscle strengthening, and stretching. When treating pain, many pharmacologic agents are used off label. The most commonly used agents include amitriptyline (Elavil[®]), nortriptyline (Pamelor[®]), carbamazepine (Tegretol[®]), gabapentin (Neurontin[®]), phenytoin (Dilantin[®]), baclofen, tizanidine, and clonazepam (Klonopin[®]).

More than half of the patients with MS have issues with their bladder or bowels, which are very disabling. Aggressive management of bladder dysfunction is necessary because untreated bladder dysfunction can lead to chronic infections. Bladder dysfunction

can be managed with intermittent self-catheterization; medications such as antispasmodics, tricyclic antidepressants, DDAVP (an antidiuretic hormone), and alpha blockers; and, if necessary, indwelling catheters. With bowel dysfunction, constipation and fecal incontinence are the most common problems. Constipation is treated with fiber, fluids, activity, bowel training, laxatives, and dietary modification. Involuntary loss of bowel control can be treated with fiber, anticholinergics, and dietary modification.

Because of brain shrinkage, cognitive issues occur in 45 to 60 percent of patients, but result in significant changes in only 15 percent of patients.^{8,9} Early treatment to minimize the number of acute attacks will prevent this shrinkage. The most common cognitive issues are short-term memory loss or impaired judgment, learning, word finding, or executive functioning. Neuropsychological testing is used to identify and monitor cognitive issues related to MS. A brain defect secondary to the disease needs to be dis-

Exhibit 4: Disease-Modifying Therapy Indications & Administration

Agents	Indications	Administration
Immunomodulators		
Glatiramer acetate	RRMS	20 mg/d SC
IFN β-1a	Relapsing forms of MS	30 µg/week IM
		22 or 44 µg SC 3x/week
IFN β-1b	Relapsing forms of MS	250 ug SC q other day
Natalizumab	Relapsing forms of MS	300 mg IV q 4 weeks*
Immunosuppressives		
Mitoxantrone	SPMS, PRMS, & worsening RRMS	12 mg/m ² q 3 months
Corticoste	RRMS	Varies by product

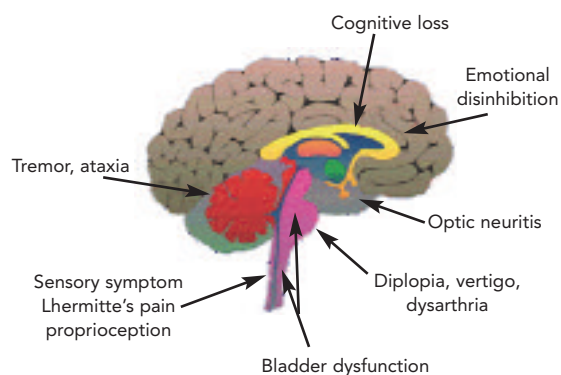
*May be administered only by specialty trained healthcare professionals trained in the TOUCH program.

Exhibit 5: Major Adverse Affects

- **Glatiramer acetate**
 - Injection-site reaction
- **IFN-s**
 - Flu-like syndrome
 - Injection-site reaction and necrosis
 - Liver function and bone marrow abnormalities
 - Neutralizing antibodies
- **Natalizumab**
 - Serious infections
 - Risk for life-threatening PML necessitates prescription only through special risk management program
- **Mitoxantrone**
 - Risk of cardiotoxicity
 - Nausea and alopecia

Exhibit 6: MS Symptoms Correspond to Brain Regions

Symptoms vary widely in incidence and severity



tinguished from depression. Treatment may include occupational therapy and cognitive retraining. Medications, approved for use in Alzheimer's disease, occasionally are used but have minimal efficacy.

Depression is common in patients with MS. Like many of the other symptoms of MS, depression contributes to a reduced quality of life. The same antidepressants are used in these patients as in someone without MS.

Sexual dysfunction is an issue that physicians often avoid discussing with the patient. Sexual dysfunction must be addressed because it can disrupt family life and quality of life. Management strategies include medications for impotence (sildenafil [Levitra®], tadalafil [Cialis®], sildenafil [Viagra®]), management of other symptoms or medical conditions that may be contributing, adjustment of medications that may be contributing, mechanical assistive devices, and emotional support.

Tremor and unsteadiness are two MS symptoms difficult to treat. Various medications can be tried including carbamazepine, ondansetron (Zofran®), clonazepam, primidone, gabapentin, propranolol, tricyclic antidepressants, and levetiracetam (Keppra®).

Optimizing therapy requires regular clinical assessment of patients. Therapies need to be evaluated for effectiveness and adverse effects. Therapy may need to be changed periodically for several reasons. The medications currently available are not all effective in every patient, and are only partially effective in many cases. Disease progression may not be well controlled in some patients. Additionally, the development of neutralizing antibodies may compromise efficacy of the interferons. Switching or combining therapies is routinely practiced although well-designed study data are limited.

Optimizing therapy also has to include the patient. Patients need to be educated about their disease and its therapies. Adherence with the prescribed therapies needs to be monitored and maintained.

Appropriate care of the patient with MS involves a team approach using many different medical professionals. Vocational counselors can be most helpful in assisting the patient with adjusting their workplace to manage many of the symptoms such as pain and fatigue. Physical therapists work with the patient to manage many of the symptoms. Nutritionists assist patients with maintaining an appropriate diet. Keeping these patients active, productive members of society is an important goal.

Conclusion

MS is a disease of an overactive immune system resulting in inflammation and neurodegeneration. Early treatment of this disease may delay progression. Optimizing nonpharmacologic and pharmacologic therapy requires frequent assessment and a team approach. **JMCM**

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