PTNow
Multiple Sclerosis Clinical Summary

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detail/multiple-sclerosis-ms

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Multiple sclerosis (MS)

Overview

What Is MS? | Prevalence | Signs and Symptoms | Medical Diagnosis

Approximately 400,000 people in the United States and 1 million people between 16 and 65 years of age worldwide have MS. It is more prevalent in women than in men by a ratio of approximately 3.2:1. Average age of onset ranges from 30.5 to 33 years.

Signs and Symptoms

Table 1. Prevalence of Common Signs and Symptoms of Multiple Sclerosis (6, 7)

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>83.1%</td>
</tr>
<tr>
<td>Heat sensitivity</td>
<td>up to 80%</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>67.2%</td>
</tr>
<tr>
<td>Stiffness and spasms</td>
<td>63.1%</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>59.8%</td>
</tr>
<tr>
<td>Memory and other cognitive problems</td>
<td>55.8%</td>
</tr>
<tr>
<td>Pain and other unpleasant sensations</td>
<td>54.3%</td>
</tr>
<tr>
<td>Emotional or mood problems</td>
<td>37.5%</td>
</tr>
<tr>
<td>Vision problems</td>
<td>37.4%</td>
</tr>
<tr>
<td>Dizziness or vertigo</td>
<td>36.2%</td>
</tr>
<tr>
<td>Bowel problems</td>
<td>34.5%</td>
</tr>
<tr>
<td>Tremors</td>
<td>30.2%</td>
</tr>
<tr>
<td>Sexual problems</td>
<td>29.9%</td>
</tr>
<tr>
<td>Difficulty moving arms</td>
<td>23.5%</td>
</tr>
<tr>
<td>Swallowing problems</td>
<td>21.8%</td>
</tr>
<tr>
<td>Speech problems</td>
<td>20.2%</td>
</tr>
<tr>
<td>Seizures</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Medical Diagnosis

It is difficult to correctly diagnose MS as there is no “typical” set of signs and symptoms, nor is there a definitive laboratory test or examination method. Anecdotally, many people with MS have transient signs and symptoms over months or years. The most current criteria for diagnosing MS are the Revised McDonald Criteria, which results in a diagnosis of MS if the criteria are met; “possible MS” if partially met; and “not MS” if there is another diagnosis that better explains the clinical presentation.

Clinically Isolated Syndrome (CIS)

People with no previous history of MS who have a single exacerbation-like event might be diagnosed with clinically isolated syndrome (CIS), a first and single acute demyelinating and/or inflammatory lesion in the CNS with a duration of at least 24 hours. With only a single episode, a diagnosis of MS cannot be made, even in the presence of clinical and laboratory evidence of demyelination. Many episodes of CIS are mild and resolve without treatment; in others, high-dose oral or intravenous methylprednisolone is recommended.

Classification

Disease Subtypes | Severity

There are 2 important ways to classify MS: by disease subtype, which describes the behavior of the disease over time; and by disability severity, which typically measures how the disease limits the person’s activity and participation.

Disease Subtypes

Multiple sclerosis can be classified into 4 fairly distinct subtypes (Table 2).
Table 2. Four Subtypes of Multiple Sclerosis (MS)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent of All MS</th>
<th>Characteristics of Exacerbation and Recovery</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-remitting MS (RRMS)</td>
<td>55% (11)</td>
<td>Exacerbations (relapses) and remissions (Fig. 1) can be mild or severe and last days, weeks, or months. Full or partial recovery during remission; can be slow and gradual or almost instantaneous.</td>
<td>Majority of patients eventually develop secondary progressive subtype. Important to differentiate from pseudoexacerbation.</td>
</tr>
<tr>
<td>Secondary progressive MS (SPMS)</td>
<td>30% (12)</td>
<td>May or may not have relapses and minor remissions</td>
<td>Steady progression (Fig. 2), with or without superimposed relapses and minor remissions.</td>
</tr>
<tr>
<td>Primary Progressive MS (PPMS)</td>
<td>About 10%-15% (12)</td>
<td>Differs from RRMS and SPMS in that (a) the age of onset is typically later and (b) cognitive or behavioral symptoms are less likely.</td>
<td>Gradual progression with no superimposed relapses and remissions (Fig. 3).</td>
</tr>
<tr>
<td>Progressive-Relapsing MS (PRMS)</td>
<td>About 5% (12)</td>
<td>Significant recovery immediately following a relapse, but between relapses there is a gradual worsening of symptoms.</td>
<td>Steady progression of clinical neurological damage with superimposed relapses and remissions (Fig. 4).</td>
</tr>
</tbody>
</table>

Table 2. Four Subtypes of Multiple Sclerosis (MS)

Approximately 80% of people with MS have an initial acute episode, which might include multiple pathology locations and varied signs/symptoms. This episode develops into either the relapsing-remitting, relapsing-progressive, or secondary progressive subtype. In the remaining 20%, the initial onset is the primary progressive type. It is important to differentiate true exacerbation from pseudoexacerbation, which is a transient worsening of symptoms that can occur due to stress, infection, overheating, or overexertion and from which full recovery occurs. A person with a pseudoexacerbation due to exercise, for example, might have a temporary change in sensory symptoms but will recover completely within a short period of time.

Severity
The EDSS (14) is the best-known and most widely used scale for quantifying disability in people with MS. It is an ordinal scale ranging from 0 ("normal neurologic exam") through 10 ("death from MS"). Severity is categorized as follows (14):

- 0-3.5 (normal to mild disability)
- 4-5.5 (mild to moderate disability)
- 6.0-7.5 (moderate to severe disability)
- 8.0-9.5 (severe disability with restriction to bed or wheelchair)

The EDSS quantifies disability in 8 "functional systems" and allows neurologists to assign a functional system score (FSS) in each of these systems. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6:

- Pyramidal
- Cerebellar
- Brainstem
- Sensory
- Bowel and bladder
- Visual
- Cerebral
- Other

Steps 1.0 to 4.5 on the EDSS are used to refer to people with MS who have no limitation in ambulation, and they are scored based on disability in the functional system. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation. Despite being the standard method of evaluating disability, the EDSS has been criticized for placing too much emphasis on ambulation and being insensitive to clinical change.

The Disease Steps Scale (DS) is an ordinal clinical rating scale developed to provide a simple measure of disability based on ambulation ability. Scores range from 0 (normal) to 6 (essentially confined to wheelchair). There is a separate category for patients who are not classifiable, that is, for people who do not fit any of the stated classifications due to major cognitive or visual impairment, overwhelming fatigue, or major impairments related to bowel and bladder function.

Screening
See "Examination"

Examination
- MS-Specific History
- Impairment
- Activity
- Participation

History
People with MS may have a number of occult signs, symptoms, and comorbidities that should be screened. Common modifiable comorbidities and their prevalence are (17):

- Depression (50%)
- Hypertension (30%)
- Alcohol misuse (14%-18%)

The review of systems (http://guidetoptpractice.apta.org/content/1/SEC4.body) which identifies symptoms potentially associated with occult disease, medical conditions, or adverse medication events that may mimic conditions that are amenable to physical therapist intervention.
The physical therapist examination (Tab. 3) must capture patient problems that are primary (due to MS pathology), secondary (a consequence of another impairment, activity limitation, or participation restriction), or a combination. Important considerations include:

- MS disease phenotype and severity
- Health care setting in which the patient is being treated
- Premorbid and comorbid conditions
- Goals identified by the patient
- Issues raised during the history and interview
- Any occult issues not be obvious at the outset

Table 3. Areas of Focus for the Examination

MS-Specific History Questions
- When was the most recent worsening of your disease? If recent, what was your prior level of function?
- What is your current level of physical function? How far can you walk?
- Do you have a history of falls or near falls?
- Are you followed by a neurologist? Is the physician an MS specialist?
- How long were you experiencing symptoms before you received a diagnosis of MS?
- Do you take medications (name, dosage, timing, side effects, benefits)?
- Do you experience dizziness or vertigo? If so, do certain activities trigger it?
- Do you have any problems with vision?
- Do you have fatigue?
- What is your current level of work and exercise participation?
- Do you have any problems with breathing or coughing?
- Do you have pain or notice sensory changes?
- Do you have a deficit in memory or cognition?
- Do you have signs or symptoms of emotional or mood problems?
- Do you have stiffness and spasms?
- Do you have any problem with gastrointestinal or genitourinary function?
- Do you have any problems with speech or swallowing?
- How is your home environment set up? Do you have support at home?
- What is your current driving status?

Outcome Measures Across the EDSS

<table>
<thead>
<tr>
<th>(+ = Recommended by the MS EDGE Task Force) (18)</th>
<th>0-3.5</th>
<th>4-5.5</th>
<th>6-7.5</th>
<th>8.0-9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Functions and Body Structures Impairment</td>
<td>Normal to Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Disability</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disability</td>
<td>Disability</td>
<td>Disability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(restriction to bed or wheelchair)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Musculoskeletal:
- Flexibility
- Strength
- Postural alignment

Cardiopulmonary:
- Heart Rate
- Blood pressure (BP)
- Respiration rate response to exercise
- Respiratory strength
  - Maximal inspiratory and expiratory pressures

Neurological:
- Cranial nerve integrity
- Central vestibular dysfunction
- Vision
- Sensation and deep tendon reflexes
- Light touch/deep pressure
- Sharp/dull discrimination
- Proprioception/kinesesthesia

Motor impairments/movement quality
- Dual-task performance and motor planning
  - Timed Up-and-Go with Cognitive and Manual Dual Tasks
- Coordination
- Abnormalities of muscle tone

Fatigue
- Fatigue Scale for Motor and Cognitive Functions
Unfavorable Indicators

- Male sex
- Onset of symptoms after the age of 40
- Initial symptoms involving the cerebellum, mental function, or urinary control
- Initial symptoms that affect multiple regions of the body
- In the first years after onset, attacks that are frequent, or a short time between the first 2 attacks

 Favorable Indicators

- Female sex
- Onset of symptoms before the age of 40 years
- Initial symptoms that are sensory only
- Involvement of only one CNS system at time of onset
- Full recovery between attacks

Activity Limitations

<table>
<thead>
<tr>
<th>Activity Limitations</th>
<th>0-3.5</th>
<th>4-5.5</th>
<th>6-7.5</th>
<th>8.0-9.5</th>
</tr>
</thead>
</table>

Functional assessment of mobility:
- Bed mobility
- Transfers

Balance and postural stability

- Activities-specific Balance Confidence Scale
- Berg Balance Scale
- Dynamic Gait Index
- Four Square Step Test
- Functional Reach Test
- Trunk Impairment Scale
- Involvement of only one CNS system at time of onset

Mobility (including locomotion, wheelchair mobility) and gait

- Disease Steps
- 12-item MS Walking Scale
- Timed 25' Walk Test
- Timed Up-and-Go (with Cognitive and Manual Dual Tasks)
- 6-Minute Walk Test
- Stair negotiation
- Fine motor performance

- 9-hole Peg Test
- Box and Blocks Test

Composite measures of activity/mobility:

- Functional Independence Measure
- MS Functional Composite
- Rivermead Mobility Index
- Hauser Ambulation Index
- Participation Limitations

Quality of life/disease impact:

- MS Impact Scale (MSIS-29)
- International Quality of Life (MuSIQOL)
- Quality of Life-54 (MSQOL-54)
- Quality of Life Inventory

If more detail is required related to specific areas of QOL, consider using the MS Quality of Life Inventory

Diagnosis

See "Examination"

Prognosis

Predicting the progression of MS following an initial diagnosis cannot be done with certainty, but a number of epidemiologic studies have resulted in some general rules regarding MS prognosis (28, 29, 30, 31):

1. MS is not a fatal disease, except in rare cases. (10, 32, 33, 34)
2. The majority of people with MS do not become severely disabled. (35)
3. Certain disease characteristics have been associated with poorer or better prognosis (Tab. 4).

Table 4. Prognostic Indicators (28, 29, 30, 31)

<table>
<thead>
<tr>
<th>Unfavorable Indicators</th>
<th>Favorable Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>Female sex</td>
</tr>
<tr>
<td>Onset of symptoms after the age of 40</td>
<td>Onset of symptoms before the age of 40 years</td>
</tr>
<tr>
<td>Initial symptoms involving the cerebellum, mental function, or urinary control</td>
<td>Initial symptoms that are sensory only</td>
</tr>
<tr>
<td>Initial symptoms that affect multiple regions of the body</td>
<td>Involvement of only one CNS system at time of onset</td>
</tr>
<tr>
<td>In the first years after onset, attacks that are frequent, or a short time between the first 2 attacks</td>
<td>Full recovery between attacks</td>
</tr>
</tbody>
</table>
Absence or late onset of cerebellar symptoms

Interventions should be tailored to specific areas of balance loss (eg, somatosensory, vestibular, visual, motor control) as well as specific
Continued falls prevention programs and initiation of
Guidance
Implement energy conservation methods and intermittent
Limit use of walking aids (ankle-foot orthoses [AFOs], canes), as they may lead to decreased mobility as much as falls prevention
Task-specific training, emphasizing maintenance of independent performance of basic functional tasks (39)
Address pertinent and specific underlying impairments of flexibility and strength
Implement energy conservation methods

EDSS 0–3.5
Little Disability
Promote active lifestyle
Maintain mobility
Maintain continued involvement in domestic, education, work, community, social, and civic life
Task-specific training of relevant skills (eg, balance, gait, reaching)
Address pertinent and specific underlying impairments of flexibility and strength
Implement energy conservation methods

EDSS 4–5.5
Mild Disability
Continue to promote active lifestyle with adaptations as needed
Modify tasks and activities to maximize participation
Implement energy conservation methods and intermittent exercise to maintain and increase high volumes of mobility (42)

EDSS 6.0–7.5
Moderate Disability
Promote maintenance of mobility and an active lifestyle

EDSS 8–9.5
Severe Disability
Maintain focus on rehabilitative strategies for deficits that have not yet become severe

The variable nature of clinical presentations in people with MS means 2 things: (1) interventions may vary greatly among patients with similar levels of disabilities, and (2) the relative importance of rehabilitative, compensatory, and preventive strategies may change over the course of the disease.

Table 5. Summary of Physical Therapist Interventions Across Extended Disability Status Scale (EDSS) Levels

<table>
<thead>
<tr>
<th>Intervention</th>
<th>EDSS 0–3.5</th>
<th>EDSS 4–5.5</th>
<th>EDSS 6.0–7.5</th>
<th>EDSS 8–9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehabilitative</td>
<td>Little Disability</td>
<td>Mild Disability</td>
<td>Moderate Disability</td>
<td>Severe Disability</td>
</tr>
<tr>
<td>Promote active lifestyle</td>
<td>Continue to promote active lifestyle with adaptations as needed</td>
<td>Promote maintenance of mobility and an active lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintain mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintain continued involvement in domestic, education, work, community, social, and civic life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task-specific training of relevant skills (eg, balance, gait, reaching)</td>
<td>Task-specific training of relevant skills (eg, balance, gait, reaching)</td>
<td>Modify tasks and activities to maximize participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Address pertinent and specific underlying impairments of flexibility and strength</td>
<td>Address pertinent and specific underlying impairments of flexibility and strength</td>
<td>Implement energy conservation methods and intermittent exercise to maintain and increase high volumes of mobility (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensatory/Adaptive</td>
<td>EDSS 4–5.5</td>
<td>EDSS 6.0–7.5</td>
<td>EDSS 8–9.5</td>
<td></td>
</tr>
<tr>
<td>EDSS 0–3.5</td>
<td>EDSS 4–5.5</td>
<td>EDSS 6.0–7.5</td>
<td>EDSS 8–9.5</td>
<td></td>
</tr>
<tr>
<td>Promote active lifestyle</td>
<td>Continue to promote active lifestyle with adaptations as needed</td>
<td>Promote maintenance of mobility and an active lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintain mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task-specific training of relevant skills (eg, balance, gait, reaching)</td>
<td>Task-specific training of relevant skills (eg, balance, gait, reaching)</td>
<td>Modify tasks and activities to maximize participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Address pertinent and specific underlying impairments of flexibility and strength</td>
<td>Address pertinent and specific underlying impairments of flexibility and strength</td>
<td>Implement energy conservation methods and intermittent exercise to maintain and increase high volumes of mobility (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive</td>
<td>EDSS 0–3.5</td>
<td>EDSS 4–5.5</td>
<td>EDSS 6.0–7.5</td>
<td>EDSS 8–9.5</td>
</tr>
<tr>
<td>EDSS 0–3.5</td>
<td>EDSS 4–5.5</td>
<td>EDSS 6.0–7.5</td>
<td>EDSS 8–9.5</td>
<td></td>
</tr>
<tr>
<td>Falls prevention programs (47)</td>
<td>Falls prevention programs (47)</td>
<td>Falls prevention programs and initiation of appropriate caregiver training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigorous aerobic, strengthening, and flexibility exercises to minimize deconditioning, (48) relative dosage to be determined based on examination and evaluation</td>
<td>Aerobic, strengthening, and flexibility exercises to minimize risk of deconditioning</td>
<td>Aerobic, strengthening, and flexibility exercises to minimize risk of deconditioning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Management of Secondary Sequelae

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Evidence Summary</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic conditioning and endurance</td>
<td>Evidence Summary</td>
<td>Guidance</td>
</tr>
<tr>
<td>Aerobic conditioning in MS can be limited due to decreased activity and a more sedentary lifestyle.</td>
<td>Primary impairments may limit ability to participate in standard conditioning programs.</td>
<td>30 min of moderate intensity aerobic activity 2 times/wk (39)</td>
</tr>
<tr>
<td>Strength training</td>
<td>Strength may decrease in MS because of an increased sedentary lifestyle as well as involvement of the motor tracts</td>
<td>Strength training exercises for major muscle groups 2 times/wk (37)</td>
</tr>
<tr>
<td>Flexibility training</td>
<td>Shortening of plantar flexors, hamstrings, and hip flexors may occur due to prolonged sitting and spasticity (46)</td>
<td>Using fewer repetitions per set with longer recovery periods may allow for a greater volume of strength training to be done (41)</td>
</tr>
<tr>
<td>Balance training</td>
<td>Balance loss can be due to a decrease in activities that challenge balance or use balance skills; a detrending of balance, therefore, can occur (38)</td>
<td>Interventions should be tailored to specific areas of balance loss and activities that lead to balance loss (38)</td>
</tr>
</tbody>
</table>

Special Considerations: Thermosensitivity and Fatigue

Thermosensitivity can occur either due to external temperature (eg, warm weather) or increasing internal temperature due to infection or, more significantly, exercise. The increase in core temperature that occurs with exercise is itself a limiting factor for people with MS in attaining maximal benefit from their exercise program. Further below, details and often creative measures can limit the effects of thermosensitivity and allow people with MS to continue exercising despite a wide range of times. (37, 41, 42, 43, 44, 45, 46)
People with MS are less physically active than healthy controls (56), and the overall reduction in activity may result in diminished fitness and ability to tolerate normal physical activity without experiencing fatigue. Intermittent exercise—with bouts of exercise interspersed with periods of recovery—may allow for greater overall periods of exercise to be performed without neurogenic fatigue. (42) (43) The use of cooling modalities such as cooling garments has been shown to limit the effects of fatigue during motor tasks. (57) Energy conservation techniques have been shown to decrease self-reported measures of fatigue, (58) but their effect on mobility has not been assessed.

### Medical Management

#### Acute Exacerbations | Disease-Modifying Therapy | Symptom Management

There is no cure for MS. The goals of medical management include:

- Minimizing inflammatory response associated with an acute exacerbation of MS
- Disease modification, that is, slowing down the progression of the disease to move toward a state of remission
- Management of symptoms related to MS
- Reduction of motor complications from the disease

#### Acute Exacerbations

The first line of medical intervention for an acute exacerbation is steroids to halt the inflammatory process. (40) Short duration, high-dose methylprednisolone has been used to treat acute exacerbations.

#### Disease-Modifying Therapy (DMT)

The first-line pharmacologic interventions are disease-modifying therapies (DMT). These drugs often are used in combination in people with progressive types of MS and are being aggressively administered to individuals within 5 years of diagnosis. This method of medical intervention is associated with lower mortality rates among people with MS. (4, 60, 61)

### Table 7. Disease-Modifying Drugs (62, 63, 64)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of β-interferon (1A or 1B) or molecule</th>
<th>Route</th>
<th>Dosage</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>IA</td>
<td>Intramuscular Weekly</td>
<td>Weekly</td>
<td>Flu-like symptoms, injection site reactions, headache, fatigue, depression, fever, myalgia</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif)</td>
<td>IA</td>
<td>Subcutaneous 3 times/wk</td>
<td>3 times/wk</td>
<td>Flu-like symptoms, injection site reactions, headache, fatigue, depression, fever, myalgia</td>
</tr>
<tr>
<td>IFNβ-1b (Betaferon)</td>
<td>IB</td>
<td>SubcutaneousAlternate days</td>
<td></td>
<td>Flu-like symptoms, injection site reactions, headache, fatigue, depression, fever, myalgia</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>Synthetic polypeptide</td>
<td>SubcutaneousDaily</td>
<td>Every 4 wks</td>
<td>Flu-like symptoms, injection site reactions, depression</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>Monoclonal antibody</td>
<td>Intravenous</td>
<td>Every 4 wks</td>
<td>Increased risk of liver damage, allergic reactions, hives, itching, trouble breathing, chest pain, dizziness, rash, nausea, low BP, development of progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>Oral</td>
<td>Daily</td>
<td></td>
<td>Headache, influenza, diarrhea, back pain, abnormal liver tests</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>Oral</td>
<td>7 mg or 14 mg daily</td>
<td></td>
<td>Diarrhea, abnormal liver tests, nausea, influenza, hair thinning</td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>Oral</td>
<td>120 mg first week gastrointestinal events</td>
<td>240 mg thereafter twice per day</td>
<td>Flushing, nausea, abnormal liver tests, depression</td>
</tr>
</tbody>
</table>

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Attaining maximal benefits from their exercise program. Looping, bending, and other exercise programs can elicit the effects of thermoregulatory and allow people with MS to exercise for longer periods of time. (50, 51, 52, 53)
Fatigue Management

Table 8. Drugs Used in Fatigue Management (66a)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usually Prescribed Daily Dosage</th>
<th>Maximum Prescribed Daily Dosage</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-adamantan aminosulfate (Amantadine)</td>
<td>100 mg BID</td>
<td>600 mg</td>
<td>Restlessness, sleep disorders, visual hallucinations, visual disturbances, constipation, urinary retention, dryness of mouth, thirst, heart failure, vertigo, livedo reticularis</td>
<td>Psychoses, confusion, delirium, epilepsy, renal functional impairment, prostatic hyperplasia, glaucoma, arterial hypertension</td>
</tr>
<tr>
<td>Benzhydrylsufinyl acetamide (Modafinil)</td>
<td>100-300 mg</td>
<td>400 mg</td>
<td>Nervousness, restlessness, loss of appetite, insomnia, increased seizure potential, visual disturbances, nausea, vomiting, palpitations</td>
<td>Lactation, concomitant prazosin treatment</td>
</tr>
<tr>
<td>2-Amino-5-phenyl-2-oxazolidinone (Pemoline)</td>
<td>20 mg BID</td>
<td>60 mg</td>
<td>Insomnia, weight loss, nausea, tremor, dizziness, tachycardia, hepatic functional impairment, epileptic seizures</td>
<td>Psychoses, hepatic functional impairment, depression with suicidal tendencies</td>
</tr>
<tr>
<td>Acetyl L-carnitine</td>
<td>BID</td>
<td></td>
<td>Nausea, vomiting, stomach upset, diarrhea.</td>
<td>History of kidney stones or seizures</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td>1,300 mg</td>
<td>Black tarry stools, coughing up blood, Cefoxa, Cymbalta, severe nausea, fever, Lexapro, Prozac, lasting longer than 3 Sarafem, days, swelling or pain, Symbax, Luvox, lasting longer than 10 Paxil, Zoloft, days, hearing problems, upset stomach, heartburn, drowsiness, head ache</td>
<td>Drug interactions:</td>
</tr>
</tbody>
</table>

*Bid=twice daily

Depression Management

Depression is the most frequent psychiatric diagnosis in people with MS. A number of reasons may explain the association of MS with depression, including (67):

- Psychosocial effects of MS disability
- Direct effect of lesions on brain structure involved in regulating mood state
- Side effect of mood change from the first-line medical treatment (interferon)
- Immune dysfunction

Male sex, onset of MS before the age of 30 years, and feelings of hopelessness are recognized as important predictors of suicide in people with MS. (67)

Table 9. Drug Interventions Used in Depressive Disorder Management (67)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medication and Daily Dosage</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine reuptake inhibitor (tricyclic antidepressants)</td>
<td>Nortriptyline 50-200 mg</td>
<td>Anticholinergic symptoms, lethargy, cardiovascular effects</td>
<td>Anticholinergic properties may help with neurogenic bladder symptoms</td>
</tr>
</tbody>
</table>
Selective serotonin reuptake inhibitor
Sertraline 50-200 mg
Fluoxetine 20-80 mg
Citalopram 20-40 mg

Selective norepinephrine reuptake inhibitor
Mirtazapine 15-45 mg
Nefazodone 300-600 mg

Norepinephrine dopamine reuptake inhibitor
Bupropion 150-450 mg

Selegiline 5-15 mg

Serotonin norepinephrine reuptake inhibitor
Venlafaxine 75-225 mg

Management of Gait Limitations
Dalfampridine is a potassium channel blocker whose antagonistic action allows demyelinated neurons to carry the electrical impulse, increasing neuronal signaling and conduction, which decreases walking difficulty. (68) In general, people taking dalfampridine have the ability to walk for longer periods of time with a self-perceived improvement in gait pattern. (68)

Spasticity Management
Spasticity is a common problem in people with MS and can lead to pain, spasms, loss of function and flexibility, and difficulty with daily care.

Table 10. Drugs Used in Spasticity Management (69)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen (Lioresal)</td>
<td>20 mg</td>
<td>Somnolence, headache, dizziness, nausea</td>
<td>May inhibit transmission of reflexes at spinal level, binds to GABA-B receptors</td>
</tr>
<tr>
<td>Dantrolene (Dantrium)</td>
<td>100 mg</td>
<td>Diarrhea, weak or shallow breathing, nausea, lightheadedness, muscle weakness</td>
<td>Produces relaxation by affecting the contractile response of the skeletal muscle at a site beyond the myoneural junction</td>
</tr>
<tr>
<td>Tizanidine (Zanaflex)</td>
<td>12 mg</td>
<td>Lightheadedness, hallucinations, confusion, nausea, dizziness</td>
<td>Acts as a short-acting muscle relaxer, works by blocking nerve impulses, selective α2-adrenergic receptor agonist</td>
</tr>
<tr>
<td>Diazepam/clonazepam (Valium/Klonopin)</td>
<td>0.25-0.5 mg at night</td>
<td>Drowsiness, sedation, reduced attention and memory impairment</td>
<td>Modulates GABAergic transmission through GABA-A-receptors</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>600 mg</td>
<td>Drowsiness, somnolence, dizziness</td>
<td>GABAergic drug, mechanism of action unknown</td>
</tr>
<tr>
<td>Cannabis</td>
<td>No identified dosage</td>
<td>Irritation to the lungs, decreased concentration, short-term memory difficulties</td>
<td>Results in altered state of consciousness, increased sensitivity</td>
</tr>
</tbody>
</table>

Cases
In Development

Cases are in development.

Overview
Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States and 1 million people between 16 and 65 years of age worldwide. (1) It is a neurodegenerative pathology that can be characterized by a course of demyelination-mediated relapses and remissions, superimposed on gradual neurologic deterioration, resulting in a clinical course that is unpredictable in progression and severity. (1)

There is some evidence of a genetic component to MS susceptibility. Certain population subgroups (eg, those of Northern European ancestry) have a greater risk of developing MS than other subgroups within the same geographic region. This genetic link is further strengthened by the elevated risk of developing MS that is found in the first- and second-degree relatives of people with MS. (1)

Current thinking is that the etiology of MS is an interaction between genetic predisposition and an inciting environmental antigen, resulting in an autoimmune response in a susceptible host. The pathophysiology classically associated with MS is the slowing or stopping of saltatory conduction of action potentials along myelinated axons in the CNS because of demyelination; however, there is some evidence that the pathophysiology is related instead to axonal loss rather than to demyelination. (2)

Prevalence
Multiple sclerosis is more prevalent in women than in men by a ratio of approximately 3.2:1. (3) Average age of onset ranges from 30.5 to 33 years, (4) though recent evidence shows that approximately 5% of people with MS had their first symptoms during childhood. (5)

Signs and Symptoms
Although the clinical presentation is varied and unpredictable in age of onset, disease progression, and signs and symptoms, some signs and symptoms are more prevalent than others (Table 1).

Table 1. Prevalence of Common Signs and Symptoms of Multiple Sclerosis (6, 7)

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>83.1%</td>
</tr>
<tr>
<td>Heat sensitivity</td>
<td>up to 80%</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>67.2%</td>
</tr>
</tbody>
</table>
**Stiffness and spasms**

- 63.1%

**Bladder problems**

- 59.8%

**Memory and other cognitive problems**

- 55.8%

**Pain and other unpleasant sensations**

- 54.3%

**Emotional or mood problems**

- 37.5%

**Vision problems**

- 37.4%

**Dizziness or vertigo**

- 36.2%

**Bowel problems**

- 34.5%

**Tremors**

- 30.2%

**Sexual problems**

- 29.9%

**Difficulty moving arms**

- 23.5%

**Swallowing problems**

- 21.8%

**Speech problems**

- 20.2%

**Seizures**

- 2.1%

**Medical Diagnosis**

It is difficult to correctly diagnose MS as there is no “typical” set of signs and symptoms, nor is there a definitive laboratory test or examination method. Anecdotally, many people with MS have transient signs and symptoms over months or years. An accurate history may reveal vague complaints that have gone on for years without being diagnosed correctly, if diagnosed at all. The most current criteria for diagnosing MS are the Revised McDonald Criteria, (8) a framework that physicians use to rule in or rule out a diagnosis of MS. Diagnostic tools include the history, the clinical neurologic examination, magnetic resonance imaging (MRI), positive findings on testing of cerebrospinal fluid (http://www.nlm.nih.gov/medlineplusency/article/003631.htm) (elevated IgG index, presence of oligoclonal bands, or both), and visual evoked potentials (http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-multiple-sclerosis/diagnosing-ms/evoked-potentials/index.aspx). (8) To confirm a diagnosis of MS, there must be evidence of multiple lesions disseminated in both space (different anatomical locations) and time (onset of different signs and symptoms separated by at least 30 days). Application of the most recent version of the McDonald criteria results in a diagnosis of MS if the criteria are met; “possible MS” if partially met; and “not MS” if there is another diagnosis that better explains the clinical presentation. The National Multiple Sclerosis Society provides a full description of the McDonald diagnostic criteria (http://www.nationalmssociety.org/NationalMSSociety/media/MSSNationalFiles/Brochures/Paper-TipSheet_-_2010-Revisions-to-the-McDonald-Criteria-for-the-Diagnosis-of-MS.pdf).

**Clinically Isolated Syndrome (CIS)**

People with no previous history of MS who have a single exacerbation-like event might be diagnosed with clinically isolated syndrome (CIS), which refers to a first and single acute demyelinating and/or inflammatory lesion in the CNS with a duration of at least 24 hours. (9) With only a single episode, a diagnosis of MS cannot be made, even in the presence of clinical and laboratory evidence of demyelination. Many episodes of CIS are mild and resolve without treatment. In other cases, treatment with high-dose oral or intravenous methylprednisolone is recommended. (9) An MS disease-modifying medication often is recommended to delay a second attack for people who are considered more likely to progress to clinically diagnosed MS. (9)

**Classification**

There are 2 important ways to classify MS: by disease subtype, which describes the behavior of the disease over time; and by disease severity, which typically measures how the disease limits the person’s activity and participation. (1, 10)

**Disease Subtypes**

Multiple sclerosis can be classified into 4 fairly distinct subtypes (Tab. 2).

**Table 2. Four Subtypes of Multiple Sclerosis (MS)**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics of Exacerbation and Recovery</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-remitting MS (RRMS)</td>
<td>Exacerbations (relapses) and remissions (Fig. 1)</td>
<td>Majority of patients eventually develop secondary progressive subtype</td>
</tr>
<tr>
<td></td>
<td>Full or partial recovery during remission; can be slow and gradual or almost instantaneous</td>
<td>Important to differentiate from pseudoexacerbation</td>
</tr>
<tr>
<td>Secondary progressive MS (SPMS)</td>
<td>May or may not have relapses and minor remissions</td>
<td>Steady progression (Fig. 2) with or without superimposed relapses and minor remissions</td>
</tr>
<tr>
<td>Primary Progressive MS (PPMS)</td>
<td>Diffsers from RRMS and SPMS in that (a) the age of onset is typically is later and (b) cognitive or behavioral symptoms are less likely</td>
<td>Steady progression (Fig. 3) with or without superimposed relapses and remissions (Fig. 4)</td>
</tr>
<tr>
<td>Progressive-Relapsing MS (PRMS)</td>
<td>Significant recovery immediately following a relapse, but between relapses there is a gradual worsening of symptoms</td>
<td>Steady progression of clinical neurological damage with superimposed relapses and remissions (Fig. 4)</td>
</tr>
</tbody>
</table>

**Pseudoexacerbation**

It is important to differentiate true exacerbation from pseudoexacerbation, which is a transient worsening of symptoms that can occur due to stress, infection, overheating, or overexertion and from which full recovery occurs. A person with a pseudoexacerbation due to exercise, for example, might have a temporary change in sensory symptoms but will recover completely within a short period of time. (13) Approximately 80% of people with MS have an initial acute episode, which might include multiple pathologic locations and varied signs/symptoms. (11) This episode develops into either the relapsing-remitting, relapsing-progressive, or secondary progressive subtype. In the remaining...
Severity

Two clinical measures of disability severity commonly used in MS are the Extended Disability Status Scale (EDSS), also known as the Kurtzke Scale, and the Disease Steps Scale. Although physical therapists do not administer these tests, they interpret the scores.

The EDSS (14) is the best-known and most widely used scale for quantifying disability in people with MS. It is an ordinal scale ranging from 0 ("normal neurologic exam") through 10 ("death from MS"). Severity is categorized as follows (11):

- 0-3.5 (normal to mild disability)
- 4-5.5 (mild to moderate disability)
- 6-6.5 (moderate to severe disability)
- 6.5-7.5 (severe disability with restriction to bed or wheelchair)

The EDSS quantifies disability in 8 "functional systems" and allows neurologists to assign a functional system score (FSS) in each of these systems. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6:

- Pyramidal
- Cerebellar
- Brainstem
- Sensory
- Bowel and bladder
- Visual
- Cerebral
- Other

Steps 1.0 to 4.5 on the EDSS are used to refer to people with MS who have no limitation in ambulation, and they are scored based on disability in the functional system. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation. (14) Despite being the standard method of evaluating disability, the EDSS has been criticized for placing too much emphasis on ambulation and being insensitive to clinical change. (15)

The DS is an ordinal clinical rating scale developed to provide a simple measure of disability based on ambulation ability. (16) Scores range from 0 (normal) to 6 (essentially confined to wheelchair). There is a separate category for patients who are not classifiable, that is, for people who do not fit any of the stated classifications due to major cognitive or visual impairment, overwhelming fatigue, or major impairments related to bowel and bladder function. Although the rating itself is simple and brief, the information needed to arrive at a rating generally requires a medical history and both a general physical examination and a neurological examination.

Screening

See "Examination"

Examination

History

During the history-gathering phase, physical therapists seek information about all major body systems to determine whether there are symptoms that suggest the need for referral for additional medical evaluation. People with MS may have a number of occult signs, symptoms, and comorbidities that should be screened. Common modifiable comorbidities and their prevalence are (17):

- Depression (50%)
- Hypertension (30%)
- Alcohol misuse (14%-18%)

The review of systems—which identifies symptoms potentially associated with occult disease, medical conditions, or adverse medication events that may mimic conditions that are amenable to physical therapist intervention—would include the cardiovascular/pulmonary, integumentary, and neurologic/musculoskeletal systems. People with MS may be referred to a physical therapist for a concomitant problem, such as back pain or a shoulder injury, and the therapist prepares a plan that includes both the primary reason for referral and the impairments of body function and structure, activity limitations, and participation restrictions associated with MS.

The physical therapist examination (Tab. 3) must capture patient problems that are primary (due to MS pathology), secondary (a consequence of another impairment, activity limitation, or participation restriction), or a combination. Important considerations include:

- MS disease phenotype and severity
- Health care setting in which the patient is being treated
- Premorbid and comorbid conditions
- Goals identified by the patient
- Issues raised during the history and interview
- Any occult issues not be obvious at the outset

Table 3. Areas of Focus for the Examination

MS-Specific History Questions

- When was the most recent worsening of your disease? If recent, what was your prior level of function?
- What is your current level of physical function? How far can you walk?
- Do you have a history of falls or near falls?
- Are you followed by a neurologist? Is the physician an MS specialist?
- How long were you experiencing symptoms before you received a diagnosis of MS?
- Do you take medications (name, dosage, timing, side effects, benefits)?
- Do you experience dizziness or vertigo? If so, do certain activities trigger it?
- Do you have any problems with vision?
- Do you have fatigue?
- What is your current level of work and exercise participation?
- Do you have any problems with breathing or coughing?
- Do you have pain or notice sensory changes?
- Do you have a deficit in memory or cognition?
- Do you have signs or symptoms of emotional or mood problems?
- Do you have stiffness and spasms?
- Do you have any problem with gastrointestinal or genitourinary function?
- Do you have any problems with speech or swallowing?
- How is your home environment set up? Do you have support at home?
- What is your current driving status?

Outcome Measures Across the EDSS

(+ = Recommended by the MS EDGE Task Force) (18)

Body Functions and Body Structures Impairment

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3.5</td>
<td>Normal to Mild</td>
<td>0-3.5</td>
</tr>
<tr>
<td>4-5.5</td>
<td>Moderate to Severe</td>
<td>4-5.5</td>
</tr>
<tr>
<td>6-7.5</td>
<td>Severe</td>
<td>6-7.5</td>
</tr>
<tr>
<td>8.0-9.5</td>
<td>Death from MS</td>
<td>8.0-9.5</td>
</tr>
</tbody>
</table>

0-3.5: Normal to Mild
4-5.5: Moderate to Severe
6-7.5: Severe
8.0-9.5: Death from MS
### Musculoskeletal:
- Flexibility
- Strength
- Postural alignment
- Pain

### Cardiopulmonary:
- Heart Rate
- Blood pressure (BP)
- Respiration rate response to exercise
- Respiratory strength
  - Maximal inspiratory and expiratory pressures

### Neurological:
- Cranial nerve integrity
- Central vestibular dysfunction
- Vision
- Sensation and deep tendon reflexes
  - Light touch/deep pressure
  - Sharp/dull discrimination
  - Proprioception/kinesesthesia

### Motor impairments/movement quality
- Dual-task performance and motor planning
  - Timed Up-and-Go with Cognitive and Manual Dual Tasks

### Coordination
- Abnormalities of muscle tone
  - Modified Ashworth Scale
  - Fatigue
    - Fatigue Scale for Motor and Cognitive Functions
    - Modified Fatigue Impact Scale
    - Visual Analog Scale for fatigue

### Activity Limitations
- Functional assessment of mobility:
  - Bed mobility
  - Transfers
    - Balance and postural stability
      - Activities-specific Balance Confidence Scale
      - Berg Balance Scale
      - Dynamic Gait Index
      - Four Square Step Test
      - Functional Reach Test
      - Trunk Impairment Scale
  - Mobility (including locomotion, wheelchair mobility) and gait
    - Disease Steps
    - 12-item MS Walking Scale
    - Timed 25’ Walk Test
    - Timed Up-and-Go (with Cognitive and Manual Dual Tasks)
    - 6-Minute Walk Test

### Fine motor performance
- 9-hole Peg Test
- Box and Blocks Test

### Composite measures of activity/mobility:
- Functional Independence Measure (http://www.ptnow.org/ClinicalTools/Tests/Detail.aspx?cid=a1d79f4ab-439e-bdd2-85d9984a2f148.VK72Z_90zL8) (Self-care, Locomotion (walking/wheelchair) and transfers) + + + +
- MS Functional Composite + + + +
- Rivermead Mobility Index (http://www.ptnow.org/ClinicalTools/Tests/Detail.aspx?cid=ee6b3db-08e4-448d-8051-ae9362ea70a1) + + + +

**Participation Limitations**

<table>
<thead>
<tr>
<th>Quality of life/disease impact:</th>
<th>0-3.5</th>
<th>4-5.5</th>
<th>6-7.5</th>
<th>8-9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS Impact Scale (MSIS-29)</td>
<td>+ + + +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS International Quality of Life (MuSIQOL)</td>
<td>+ + + +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS Quality of Life-54 (MSQOL-54)</td>
<td>+ + + +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS Quality of Life Inventory</td>
<td>+ + + +</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If more detail is required related to specific areas of QOL, consider using the MS Quality of Life Inventory.

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### Impairment of Body Functions and Body Structures

**Strength.** A deficit in muscle strength is common in people with MS and may be due to denervation or axonal loss in the neural pathways and/or disease. (19)

**Flexibility.** Movements that commonly show decreased flexibility in MS include ankle dorsiflexion, knee extension, hip extension, trunk extension and rotation, and shoulder elevation, especially in people confined to bed or chair and in those with significant spasticity. (19)

**Pain.** Pain may be a primary impairment (eg, dysesthesias, trigeminal neuralgia) or a secondary complication (eg, disease or overuse due to use of compensatory movements, pain from spastic muscles).

**Visual/vestibular dysfunction.** Many people with MS have complaints associated with vestibular dysfunction, such as dizziness or vertigo. This dysfunction may result in deficits in balance or in control of extracocular muscle movement and may be caused by the effects of the disease on the vestibular tracts; however, peripheral causes should be considered as part of the differential diagnosis. (21) Vestibular involvement can result in balance impairment and oculomotor dysfunction such as nystagmus, problems with smooth pursuit, or accuracy of saccades. In addition, pathology along the visual pathways may result in problems with visual acuity or in visual field deficits.

**Fatigue.** Fatigue is one of the most common symptoms of MS and can be a major reason for mobility limitations. Multiple sclerosis–related fatigue is multifactorial: primary fatigue is due to disease-specific mechanisms, whereas secondary fatigue is due to non–disease-specific factors. Sleep disturbance, (22) depression, (23) polypharmacy. (24) and increased energy cost of mobility due to spasticity or ataxia (25) all may contribute to fatigue. Many people with MS report that fatigue is worsened by heat (eg, increases in environmental temperature, increases in internal temperature during sustained exercise). (26) Changes in muscle strength in MS have led some researchers to postulate that there may be primary peripheral mechanisms underlying MS-related fatigue, but these changes are more likely due to deconditioning than to a primary disease process. (27)

**Activity Limitations**

As with impairments, the activity limitations that should be examined are selected during the history and systems review and should include all components of the movement system that require the use of tests and measures to rule in or rule out specific diagnoses and to determine the extent or severity of the condition and its impact on the individual's functional capacity and performance. These components may include:

- Bed mobility and transfers
- Balance control in sitting and standing
- Gait (level and uneven surfaces, stair negotiation, obstacle negotiation, turns)
- Reaching
- Dual task performance
- Fine motor performance
- Activities of daily living (ADLs)

Depending on the patient's abilities, gait examinations might range from observational analysis of short-distance walks or trials with various assistive devices to assessments of running and aerobic exercise tolerance (eg, 12-minute run). Careful analysis of functional activity performance, including ambulation, can lead to hypotheses for contributing primary impairments, which will lead to prioritized intervention. For example, inadequate ankle dorsiflexion during the swing phase of gait may be caused by a wide variety of impairments or combinations of impairments (eg, ankle plantar-flexor hypertonia or contracture, primary or secondary weakness of ankle dorsiflexor musculature, abnormal motor control of ankle dorsiflexor musculature, fatigue).

**Participation Restrictions**

Four quality of life (QOL) measures were recommended by the MS EDGE Task Force for use across all EDSS levels in MS (18):

- MS Impact Scale (http://www.ptnow.org/ClinicalTools/Tests/Detail.aspx?cid=a9af1196-5230-4f4c-b5ad-e30fe1648c4a.VE0rlv90zUJ) (MSIS-29) (18, pp.283-270)
- MS Quality of Life-54 (MSQOL-54) (18, pp.281-286)
- MS International Quality of Life (MuSIQOL) (18, pp271-280)
- MS Quality of Life Inventory (MSQOL-54) (18, pp.287-292)

The MSIS-29 is a self-report QOL measure (5-point Likert scale, 29 questions) that asks the person to rate how much their MS has affected specific activities related to their life in the past 2 weeks. The MSQOL-54 (54 questions) is a multidimensional health-related QOL measure that uses several scales to rate QOL over the past 4 weeks. The MuSIQOL (6-point Likert scale, 31 questions, 9 dimensions comprising activities of daily living, psychological well-being, symptoms, friend relationships, family relationships, satisfaction with health care, sentimental and sexual life, coping and rejection) is a self-administered multidimensional questionnaire that asks the person with MS to rate their daily activities during the past 4 weeks. The MSQOL is a self-administered battery of tests consisting of 138 items divided into 10 individual scales that can be used in combination or separately and relate to different QOL aspects. Of the 4 tests, the MSIS-29 and MSQOL-54 are more commonly used and are reasonably fast to administer.

**Diagnosis**

See "Examination".

**Prognosis**

Predicting the progression of MS following an initial diagnosis cannot be done with certainty, but a number of epidemiologic studies have resulted in some general rules regarding MS prognosis (28, 29, 30, 31):

1. MS is not a fatal disease. Except for rare cases, MS is not a fatal disease. Although deaths can be associated with MS, they are almost always due to complications associated with the disease, such as infections or falls, rather than the disease itself. The rare exception to this is Marburg MS, also known as fulminant or tumefactive MS, which frequently is lethal. (10, 32, 33, 34)

2. The majority of people with MS do not become severely disabled. (28, 35) Twenty percent of people remain ambulatory without a wheelchair. (35) Many may use a cane or crutches with a gait that is at least moderately compromised, resulting in increased fall risk and decreased walking endurance. (36, 37, 38, 39) About 20% of people remain asymptomatic or become only mildly symptomatic after an initial exacerbation. (35) Another 20% experience a rapidly progressive condition. Most people, however, will have some degree of disease progression affecting their mobility. (35)

3. Certain disease characteristics have been associated with prognosis. Certain characteristics are associated with a poorer prognosis, others with a better prognosis (Tab. 4).
The development of effective disease modifying therapy (DMT) has greatly changed MS prognosis. These medications have been shown to significantly decrease both the frequency and severity of MS exacerbations. Unfortunately, the effectiveness of these medications for progressive forms of MS has not been shown. There is some evidence that use of DMT slows the progression of RRMS to SPMS. The use of steroids to limit severity of exacerbations can speed the recovery from a relapse but does not influence disease progression. Medications to treat MS symptoms such as spasticity and fatigue can reduce activity limitations and participation restrictions by decreasing the impact of secondary complications. Similarly, physical therapist intervention can improve overall prognosis for functioning and prevent complications that lead to loss of mobility such as spasticity, weakness, fatigue, and pain.

### Favorable Indicators
- Onset of symptoms before the age of 40
- Initial symptoms that are sensory only
- Involvement of only one CNS system at time of onset
- Full recovery between attacks
- Absence or late onset of cerebellar symptoms

### Unfavorable Indicators
- Male sex
- Onset of symptoms after the age of 40
- Initial symptoms involving the cerebellum, mental function, or urinary control
- Initial symptoms that affect multiple regions of the body
- In the first years after onset, attacks that are frequent, or a short time between the first 2 attacks
- Incomplete remissions
- Rapid progression to disability

### Intervention
The potentially progressive nature of MS suggests that a different approach to physical therapist interventions is required compared with nonprogressive conditions such as stroke, acquired brain injury, or spinal cord injury. A successful approach can lead to stabilization and, possibly, remediation of activity limitations and underlying impairments.

The variable nature of clinical presentations in people with MS means 2 things: (1) interventions may vary greatly among patients with similar levels of disabilities, and (2) the relative importance of rehabilitative, compensatory, and preventive strategies may change over the course of the disease.

In general, physical therapist intervention should include:

- Promoting physical activities and exercise programs directed toward the activity limitations, participation restrictions, and underlying impairments that are specific to MS
- Managing the secondary effects of the disease brought on by fatigue and related inactivity
- Maintaining mobility while minimizing risk of falls
- Incorporating leisure and recreation activities that are enjoyed by the patient and that involve physical tasks

### Table 5. Summary of Physical Therapist Interventions Across Extended Disability Status Scale (EDSS) Levels

<table>
<thead>
<tr>
<th>Rehabilitation</th>
<th>EDSS 0.5-3.5</th>
<th>EDSS 4.0-5.5</th>
<th>EDSS 6.0-7.5</th>
<th>EDSS 8.0-9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little Disability</td>
<td>Mild Disability</td>
<td>Moderate Disability</td>
<td>Severe Disability</td>
<td></td>
</tr>
<tr>
<td>Promote active lifestyle</td>
<td>Continue to promote active lifestyle with adaptations as needed</td>
<td>Promote maintenance of mobility and an active lifestyle</td>
<td>Maintain focus on rehabilitative strategies for deficits that have not yet become severe</td>
<td></td>
</tr>
<tr>
<td>Maintain mobility</td>
<td>Task-specific training of relevant skills (eg, balance, gait, reaching)</td>
<td>Address pertinent and specific underlying impairments of flexibility and strength</td>
<td>Implement energy conservation methods</td>
<td></td>
</tr>
<tr>
<td>Maintain continued involvement in domestic, education, work, community, social, and civic life</td>
<td>Address pertinent and specific underlying impairments of flexibility and strength</td>
<td>Implement energy conservation methods</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 6. Management of Secondary Sequelae

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Aerobic conditioning and endurance</th>
<th>Evidence Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous aerobic, strengthening, and flexibility exercises to minimize deconditioning</td>
<td>Aerobic conditioning in MS can be limited due to decreased activity and a more sedentary lifestyle. Primary impairments may limit ability to participate in standard conditioning programs.</td>
<td>30 min of moderate intensity aerobic activity 2 times/wk</td>
</tr>
</tbody>
</table>

**Guidance**

- Walking with interspersed rest breaks may allow for greater walking volume than walking continuously. (42), (43)
Strength may decrease in MS because of an increased sedentary lifestyle as well as involvement of the motor tracts. Strength training exercises for major muscle groups 2 times/week (37) may be beneficial in improving strength. Using fewer repetitions per set with longer recovery periods may allow for a greater volume of strength training to be done (41).

Flexibility training: Shortening of plantar flexors, hamstrings, and hip flexors may occur due to prolonged sitting and spasticity (46). Repeated, shorter bouts of stretching may be superior to one daily bout. (46)

Balance training: Balance loss can be due to a decrease in activities that challenge balance or use balance skills; a detraining of balance tasks and activities that lead to balance loss. (38) Endurance training may improve balance, as balance decreases when individual is fatigued. (49)

Special Considerations: Thermosensitivity and Fatigue

Two important symptoms that tend to be pervasive in people with MS are thermosensitivity and fatigue. Thermosensitivity refers to decrements in performance with increasing temperature. This can occur either due to external temperature (eg, warm weather) or internal temperature due to infection or, more significantly, exercise. The increase in core temperature that occurs with exercise is itself a limiting factor for people with MS in attaining maximal benefit from their exercise program. Cooling, before, during, and after exercise programs can limit the effects of thermosensitivity and allow people with MS to exercise for longer periods of time. (50, 51, 52, 53) Cooling can be accomplished in a variety of ways, including the wearing of cooling garments or ice packs, the use of air conditioners, fans, and dehumidifiers, and the sipping of cool drinks. There is no definitive research for specific water temperature recommendations for aquatic therapy for persons with MS. The National Multiple Sclerosis Society recommends a water temperature of 80° to 84°F (26.7–28.9° C) to help keep the core body temperature low during exercise and reduce the risk of overheating. (54) However, clinicians must take into account that not all people with MS experience thermosensitivity; some are unaffected by higher water temperatures. (55)

Due to the ubiquitous nature and potential effects of fatigue on treatment outcomes, effective management strategies are essential for clinicians working with patients who have MS. Therapists should always be aware of secondary causes of fatigue, as their management may be more easily accomplished than primary causes of fatigue. Of special interest is fatigue due to deconditioning. People with MS are less physically active than healthy controls (56), and the overall reduction in activity may result in diminished fitness and ability to tolerate normal physical activity without experiencing fatigue. Regardless of whether fatigue is primary or secondary, it is a major factor in limiting mobility. Intermittent exercise—with bouts of exercise interspersed of periods of recovery—may allow for greater overall periods of exercise to be performed without neurogenic fatigue. (42, 43) The use of cooling modalities such as cooling garments has been shown to limit the effects of fatigue during motor tasks. (57) Presumably by reducing the effects of thermosensitivity on demyelinated CNS structures. Energy conservation techniques have been shown to decrease self-reported measures of fatigue, (58) but their effect on mobility has not been assessed. The physical therapist also might consider activities that target multiple muscles simultaneously to help maintain fitness while minimizing exercise-induced fatigue.

Preventive Strategies

Mobility loss is a common feature of MS that can occur due to secondary causes (eg, disease, deconditioning) as much as to primary causes. For this reason, preventive strategies must be an essential part of MS clinical management, regardless of disease subtype or severity. Maintaining fitness levels not only limits the potential consequences of inactivity; evidence exists that that regular vigorous exercise may have a neuroprotective effect. (44, 59) However, maintaining a lifelong regimen of regular vigorous exercise may be difficult given the chronic nature of MS. Clinicians must help people with MS develop lifelong exercise habits, and the physical therapist is responsible for designing a home exercise plan that is related to the impairments, activity limitations, and participation restrictions that were identified in the examination. The program should be one that can be done by the patient independently, and the therapist should make sure that the patient is clear on the specific reason for each part of the program. Because the success of a preventive program requires long-term participation, the therapist may use the following strategies to enhance that participation:

1. Identify and resolve barriers to participation in the prevention program. If there are factors that are the therapist and the patient have discovered that are associated with successful participation in the program, those factors should be used. 2. Design the exercise program with specific goals that are measurable and attainable. For example, a goal of “walking better” is too vague; however, a goal of “being able to walk to the store to do shopping” has specific measurable parameters that will allow both the patient and the therapist to track progress. 3. Schedule regular follow-up visits to assess progress, participation, or change in status and adjust the home exercise program appropriately. As MS is a chronic condition and patients often have mobility limitations, the therapist is responsible for monitoring the status of the patient’s mobility over the long term.

Acute Exacerbations

The first line of medical intervention for an acute exacerbation is steroids to halt the inflammatory process. (40) Most recently, short duration, high-dose methylprednisolone has been used to treat acute exacerbations. The mechanism for administration is intravenous, intramuscular, or oral, with duration ranging between 3 days to 5 weeks. The use of methylprednisolone or adrenocorticotropic hormone has been effective at halting the exacerbation, but there is limited to no evidence to support the prevention of further exacerbations using these drugs. (46)

Disease-Modifying Therapy (DMT)

The first-line pharmacologic interventions are disease-modifying therapies (DMT). Interferon has been in use since 1993 for RRMS, and other DMTs have since been developed. Older DMTs used in people with RRMS—such as IFNβ-1b (Betaferon), IFNβ-1a (Avonex), IFNβ-1a (RebiFi), glatiramer acetate (Copaxone), natalizumab (Tysabri), and mitoxantrone (Novantrone)—are administered by injection or intravenously. Newer DMTs, such as dimethyl fumarate (Tecefinda), fingolimod (Gilenya), and teriflunomide (Aubagio) are administered orally and are being used both for people with RRMS and people with progressive types of MS. These drugs often are used in combination in people with progressive types of MS and are being aggressively administered to individuals within the first 5 years of diagnosis. This method of medical intervention is associated with lower mortality rates among people with MS. (4, 60, 61) All of these first-line DMTs require regular long-term administration. (62) Currently approved DMTs and their side effects are listed in Table 7.

Table 7. Disease-Modifying Drugs (62, 63, 64)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of β-Interferon (1A or 1B) or molecule</th>
<th>Route</th>
<th>Dosage</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>IA Intramuscular Weekly</td>
<td>Flu-like symptoms, injection site reactions, headache, fatigue, depression, fever, myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNβ-1a (RebiFi)</td>
<td>IA Subcutaneous 3 times/wk</td>
<td>Flu-like symptoms, injection site reactions, headache, fatigue, depression, fever, myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNβ-1b (Betaferon)</td>
<td>IB SubcutaneousAlternate days</td>
<td>Flu-like symptoms, injection site reactions, headache, fatigue, depression, fever, myalgia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fatigue Management

Fatigue is reportedly the most frequent symptom associated with MS and often is debilitating. Drug interventions to improve fatigue are listed in Table 8.

Table 8. Drugs Used in Fatigue Management (66)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usually Prescribed Daily Dosage</th>
<th>Maximum Prescribed Daily Dosage</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-adamantan aminosulfate (Amanantadine)</td>
<td>100 mg BID</td>
<td>600 mg</td>
<td>Restlessness, sleep disorders, visual hallucinations, visual disturbances, constipation, urinary retention, dryness of mouth, thirst, heart failure, vertigo, livedo reticularis</td>
<td>Psychoses, confusion, delirium, delirium, epilepsy, renal functional impairment, prostatic hypertrophy, glaucoma, arterial hypertension</td>
</tr>
<tr>
<td>Whitehead sulfinyl acetamide (Modafinil)</td>
<td>100-300 mg</td>
<td>400 mg</td>
<td>Nervousness, restlessness, loss of appetite, insomnia, increased seizure potential, visual disturbances, nausea, vomiting, palpitations</td>
<td>Lactation, concomitant prazosin treatment</td>
</tr>
<tr>
<td>2-Amino-5-phenyl-2-oxazolidinone (Pemoline)</td>
<td>20 mg BID</td>
<td>60 mg</td>
<td>Insomnia, weight loss, nausea, tremor, dizziness, tachycardia, hepatic functional impairment, epileptic seizures</td>
<td>Psychoses, hepatic functional impairment, depression with suicidal tendencies</td>
</tr>
<tr>
<td>Acetyl L-carnitine</td>
<td></td>
<td></td>
<td>Nausea, vomiting, stomach upset, diarrhea</td>
<td>History of kidney stones or seizures</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td>Black tarry stools, coughing up blood, severe nausea, fever lasting longer than 3 days, swelling or pain lasting longer than 10 days, hearing problems, upset stomach, heartburn, drowsiness, headache</td>
<td>Drug interactions: Celexa, Cymbalta, Lexapro, Prozac, Sarafem, Symbax, Luvax, Paxil, Zoloft, Effexor</td>
</tr>
</tbody>
</table>

*BID=twice daily

Depression Management

Depression is the most frequent psychiatric diagnosis in people with MS. A number of reasons may explain the association of MS with depression, including (67):
Medication and GABAergic drug, mechanism of action unknown

Venlafaxine
600 mg
Sustained hypertension, withdrawal symptoms
Produces relaxation by affecting the contractile response of the skeletal muscle at a site beyond the myoneural junction
Drowsiness, sedation, reduced attention and memory impairment
Modulates GABAergic transmission through GABA-A receptors

Bupropion
100 mg
Seizures, psychosis
Dose titration needed
Acts as a short-acting muscle relaxer, works by blocking nerve impulses, selective α2-adrenergic receptor agonist
May inhibit transmission of reflexes at spinal level, binds to gamma-aminobutyric acid (GABA-B) receptors
Minimal effect on sexual function
Anticholinergic properties may help with neurogenic bladder symptoms

Management of Gait Limitations
Another type of pharmaceutical intervention is the drug dalfampridine (Ampyra®). Dalfampridine is a potassium channel blocker that decreases the outflow of potassium ions from the potassium channels of demyelinated neurons. The antagonistic action of dalfampridine allows demyelinated neurons to carry the electrical impulse, increasing neuronal signaling and conduction, which decreases walking difficulty. (68) In general, people taking dalfampridine have the ability to walk for longer periods of time with a self-perceived improvement in gait pattern. (68) Physical therapists should suggest that patients with MS speak with their neurologist or other treating physician regarding the appropriateness of using dalfampridine.

Spasticity Management
Spasticity is a common problem in people with MS and can lead to pain, spasms, loss of function and flexibility, and difficulty with daily care. Oral medications commonly used for the treatment of spasticity are listed in Table 10. In severe cases, more aggressive management may be achieved through the placement of an intrathecal baclofen (Lioresal) pump or through the use of injectable botulinum toxin A (Botox) as appropriate.

Table 10. Drugs Used in Spasticity Management (69)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medication and Daily Dosage</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine reuptake inhibitor</td>
<td>Nortriptyline 50-200 mg</td>
<td>Anticholinergic symptoms, lethargy, cardiovascular effects</td>
<td>Anticholinergic properties may help with neurogenic bladder symptoms</td>
</tr>
<tr>
<td>Sertraline 50-200 mg</td>
<td></td>
<td>Insomnia, sexual dysfunction</td>
<td>Well-tolerated first-line agents</td>
</tr>
<tr>
<td>Citalopram 20-40 mg</td>
<td></td>
<td>Sustained hypertension, withdrawal symptoms</td>
<td>Dose titration needed</td>
</tr>
<tr>
<td>Baclofen (Lioresal)</td>
<td>20 mg 4 times/day</td>
<td>Somnolence, weight gain</td>
<td>Dose titration needed</td>
</tr>
<tr>
<td>Dantrolene (Dantromat)</td>
<td>100 mg 4 times/day</td>
<td>Diarrhea, weak or shallow breathing, nausea, lightheadedness, muscle weakness</td>
<td>Produces relaxation by affecting the contractile response of the skeletal muscle at a site beyond the myoneural junction</td>
</tr>
<tr>
<td>Tizanidine (Zanaflex)</td>
<td>12 mg 3 times/day</td>
<td>Lightheadedness, hallucinations, confusion, nausea, dizziness</td>
<td>Acts as a short-acting muscle relaxer, works by blocking nerve impulses, selective α2-adrenergic receptor agonist</td>
</tr>
<tr>
<td>Diazepam/Clonazepam (Valium/Klonopin) 0.25-0.5 mg at night</td>
<td>Drowsiness, sedation, reduced attention and memory impairment</td>
<td>Modulates GABAergic transmission through GABA-A receptors</td>
<td></td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>600 mg 4 times/day</td>
<td>Drowsiness, somnolence, dizziness</td>
<td>GABAergic drug, mechanism of action unknown</td>
</tr>
<tr>
<td>Cannabis</td>
<td>No identified dosage</td>
<td>Irritation to the lungs, decreased concentration, short-term memory difficulties</td>
<td>Results in altered state of consciousness, increased sensitivity</td>
</tr>
</tbody>
</table>

Cases
Cases are in development.

Author Disclosures
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References
Conference Abstract


Abstract.

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