Evolving Management of Multiple Sclerosis: An Update for Primary Care Clinicians

Carrie M. Hersh, DO, MS
Multiple Sclerosis Neurologist
Cleveland Clinic Lou Ruvo Center for Brain Health
Las Vegas, Nevada

Mary Knudtson, DNSc, NP, FAAN
Executive Director, Student Health Services
University of California, Santa Cruz
Santa Cruz, California
Professor of Clinical Nursing
University of California, Irvine
Irvine, California
Faculty Disclosure

• Dr Hersh has nothing to disclose with regard to commercial interests.
Learning Objectives

• Recognize the clinical features of MS and the steps involved in diagnosis
• Counsel patients on the risks and benefits of current treatments for MS
• Implement strategies to promote long-term adherence to treatment and improve quality of life in patients with MS

MS = multiple sclerosis.
MS Overview

- CNS marked by demyelination and axonal damage
- Affects 400,000 individuals in the United States
  - 2.5 million people diagnosed with MS globally
- Leading cause of nontraumatic disability in young adults
- Typically affects persons aged between 20 and 40 years
- More common in women than in men (3:1)
- More common in Caucasians than African Americans or Latinos
  - Worse outcomes in African Americans and Latinos
- Risk factors: vitamin D deficiency, smoking, viruses

CNS = central nervous system.

Global Distribution of MS

HIGH RISK
PROBABLE HIGH RISK
LOW RISK
PROBABLE LOW RISK
NORTH-SOUTH GRADIENT RISK
OTHER RISK

Case: Marie, a 32-Year-Old Woman With Fatigue and Visual Problems

- Marie is a 32-year-old research scientist and 5K enthusiast
- She is physically active and maintains a healthy diet
- She presents complaining of fatigue
  - Began approximately 6 weeks ago
  - Disrupted her 5K training, which is central to her social life
- She has also noticed transient episodes of blurred vision
Case (cont’d)

- Physical examination
  - BP: 123/70 mm Hg
  - Body mass index: 22.9 kg/m²
- Current medications
  - Oral contraceptive
  - Ibuprofen as needed for muscle aches
- Family/social history
  - No family history of autoimmune or neurologic disorders
  - Drinks socially (2-4 drinks/wk)
  - Nonsmoker

BP = blood pressure.
Based on her initial presentation, what is an appropriate next step in evaluating Marie?

1. Depression screen
2. Neurologic examination
3. Referral to an ophthalmologist
4. Sleep study

Use your keypad to vote now!
Based on her initial presentation, what is an appropriate next step in evaluating Marie?

1. Depression screen
2. Neurologic examination
3. Referral to an ophthalmologist
4. Sleep study

Use your keypad to vote now!
Signs and Symptoms of MS

- Signs and symptoms of MS vary by person and differ over the course of the disease
- Classic signs and symptoms
  - Prominent, intractable fatigue
  - Vision disturbances
  - Sensory or motor changes
    - Weakness or numbness

## Spectrum of Signs and Symptoms Consistent With Demyelinating Disease

<table>
<thead>
<tr>
<th>Visual</th>
<th>Motor</th>
<th>Cerebellar</th>
</tr>
</thead>
</table>
| • Blurred vision  
• Unilateral vision loss  
• Oscillopsia  
• Diplopia | • Trunk/limb weakness  
• Spasticity  
• Hyperreflexia  
• Gait disturbance  
• Balance problems | • Tremor  
• Ataxia  
• Incoordination |

<table>
<thead>
<tr>
<th>Sensory</th>
<th>Genitourinary</th>
<th>Neurologic/Psychiatric</th>
</tr>
</thead>
</table>
| • Numbness  
• Paresthesias  
• Dysesthesia  
• Lhermitte’s sign  
• “MS hug”  
• Trigeminal neuralgia  
• Allodynia  
• Proprioceptive deficits | • Urgency, frequency, retention  
• Incontinence  
• Frequent UTI  
• Constipation  
• Impotence  
• Anorgasmia  
• Dyspareunia | • Impairment of memory, concentration, attention, and/or processing speed  
• Depression  
• Irritability  
• Anxiety |

UTI = urinary tract infection.

Diagnostic Workup for MS

- MS is a clinical diagnosis
  - Medical history
  - Neurologic examination
- Additional testing to support the diagnosis or rule out other conditions
  - Brain and spinal cord MRI
  - Cerebrospinal fluid
  - Evoked potentials
  - Blood work

MRI = magnetic resonance imaging.

MRI Findings Consistent With MS

FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium.

CSF Findings Consistent With MS

- CSF sample applied to gel and put through electrical charge to separate its components
- Oligoclonal banding is consistent with MS when seen in CSF and not in the corresponding serum sample

CSF = cerebrospinal fluid.

Diagnostic Assessment of Possible MS

- Rule out other causes of signs and symptoms
- Meet McDonald MS diagnostic criteria
  - Dissemination in time: evidence that neurologic damage has occurred at different points in time
  - Dissemination in space: evidence that neurologic damage has occurred in at least 2 separate areas of the CNS

McDonald Criteria 2010 Relapsing MS

- Accepted MAGNIMS Dissemination in Space MRI criteria:
  - Dissemination in space demonstrated by ≥1 T2 lesion in at least 2 of 4 areas of CNS:
    - Periventricular (PV)
    - Infratentorial
    - Juxtacortical
    - Spinal cord

Accepted MAGNIMS Dissemination in Time MRI criteria:
- Presence of both [asymptomatic] Gad+ and Gad– lesions on MRI, as long as Gad+ lesion is not due to non-MS pathology
- Patients without Gad+ lesion on initial scan still need second event or new lesion formation (new T2 and/or Gad+ lesion) on future MRI scans, irrespective of timing of baseline MRI

On this basis, MS diagnosis can be made in patients with clinically isolated syndrome meeting MRI criteria for dissemination in space and time (that is, MS at first episode)
### Differential Diagnosis

<table>
<thead>
<tr>
<th>Body System</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V</strong> Vascular</td>
<td>Multiple lacunar infarcts; CADASIL; spinal arteriovenous malformation</td>
</tr>
<tr>
<td><strong>I</strong> Infectious</td>
<td>Lyme disease; syphilis; human immunodeficiency virus myelopathy; PML; human T-lymphotropic virus</td>
</tr>
<tr>
<td><strong>T</strong> Traumatic</td>
<td>Spondylitic myelopathy</td>
</tr>
<tr>
<td><strong>A</strong> Autoimmune</td>
<td>Neuromyelitis optica spectrum disorder; acute disseminated encephalomyelitis; CNS vasculitis; Behcet disease; sarcoidosis; systemic lupus erythematous</td>
</tr>
<tr>
<td><strong>M</strong> Metabolic/toxic</td>
<td>Central pontine myelinolysis; vitamin B12 deficiency; vitamin B6 deficiency; radiation; hypoxia</td>
</tr>
<tr>
<td><strong>I</strong> Idiopathic/genetic</td>
<td>Spinocerebellar degeneration; Friedreich ataxia; Arnold-Chiari malformation; adrenoleukodystrophy; metachromatic dystrophy</td>
</tr>
<tr>
<td><strong>N</strong> Neoplastic</td>
<td>CNS lymphoma; glioma; paraneoplastic encephalomyelitis; metastatic cord compression</td>
</tr>
<tr>
<td><strong>S</strong> Psychiatric</td>
<td>Conversion disorder</td>
</tr>
</tbody>
</table>

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy; PML = progressive multifocal leukoencephalopathy.

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Vascular</td>
</tr>
<tr>
<td>I</td>
<td>Infectious</td>
</tr>
<tr>
<td>T</td>
<td>Traumatic</td>
</tr>
<tr>
<td>A</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>M</td>
<td>Metabolic/toxic</td>
</tr>
<tr>
<td>I</td>
<td>Idiopathic/genetic</td>
</tr>
</tbody>
</table>

**ACTION ITEM:**
Consider the differential diagnosis of MS in patients presenting with signs and symptoms suggesting demyelinating disease

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy; PML = progressive multifocal leukoencephalopathy.
### 2010 Revised McDonald MS Diagnostic Criteria

<table>
<thead>
<tr>
<th>Clinical Attacks</th>
<th>Lesions</th>
<th>Additional Evidence Needed to Confirm MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2</td>
<td>Objective clinical evidence of ≥2 lesions or 1 lesion with reasonable historical evidence of prior attack</td>
<td>None; clinical evidence alone will suffice. Additional evidence is desirable but must be consistent with MS</td>
</tr>
<tr>
<td>≥2</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS; or await further clinical attack indicating different CNS site</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of ≥2 lesions</td>
<td>DIT; or await second clinical attack</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS; or await further clinical attack indicating different CNS site and DIT; or await second clinical attack</td>
</tr>
<tr>
<td>0(^a)</td>
<td></td>
<td>1 year of disease progression and at least 2 of: DIS in brain based on ≥1 T2 lesion; DIS in spinal cord based on ≥2 lesions, or positive CSF</td>
</tr>
</tbody>
</table>

\(^a\)Progression from onset.

DIS = dissemination in space; DIT = dissemination in time.

MS Diagnostic Algorithm

Symptoms consistent with IDD

Exclude nondemyelinating syndrome

Classify IDD

Not MS

Consistent with MS

2010 Revised McDonald Criteria

MS established

MS not established

IDD = inflammatory demyelinating disease.

Case (cont’d)

• Upon further discussion of her symptoms, Marie reveals that she began experiencing numbness and weakness in her left arm 1 month ago

• Neurologic examination
  – Normal funduscopic and cranial nerve examination
  – Normal strength in the upper and lower extremities, with mild gait disturbance
  – Mild paresthesia on the left to touch and decreased pin sensation diffusely on the left arm

• MRI findings
  – Multiple brain and spinal cord lesions identified; none enhance
  – No spinal cord swelling
Based on your history, examination, and workup, what is Marie’s diagnosis?

1. Clinically isolated syndrome (CIS)
2. Primary progressive MS (PPMS)
3. Relapsing-remitting MS (RRMS)
4. Secondary progressive MS (SPMS)

Use your keypad to vote now!
Based on your history, examination, and workup, what is Marie’s diagnosis?

1. Clinically isolated syndrome (CIS)
2. Primary progressive MS (PPMS)
3. Relapsing-remitting MS (RRMS)
4. Secondary progressive MS (SPMS)

Use your keypad to vote now!
Clinically Isolated Syndrome

- CIS is the first neurologic event consistent with demyelination.
- Indicates high risk for developing confirmed MS if the neurologic event is accompanied by multiple asymptomatic lesions on MRI suggestive of MS.

Types of MS

• At the time of diagnosis
  – 85% to 90% of patients are classified as having RRMS
• If untreated, natural history suggests 80% will eventually develop SPMS
  – 15% have PPMS

Marie is concerned about taking a newer medication. Which of the following do you recommend as the most appropriate option for her?

1. Initiate fingolimod
2. Initiate GA
3. Initiate natalizumab
4. No treatment at this time

Use your keypad to vote now!
Marie is concerned about taking a newer medication. Which of the following do you recommend as the most appropriate option for her?

1. Initiate fingolimod
2. Initiate GA
3. Initiate natalizumab
4. No treatment at this time

Use your keypad to vote now!
Rationale for Early Treatment in MS

- Reduce the risk and severity of relapses and disease progression
- Prevent axonal damage
  - Axonal damage occurs early in the disease process
- Potential to improve long-term outcomes

Rationale for Early Treatment in MS

- Reduce the risk and severity of relapses and disease progression
- Prevent axonal damage
  - Axonal damage occurs early in the disease process
- Potential to improve long-term outcomes

ACTION ITEM: Consider early treatment initiation to improve long-term outcomes for patients with MS

Treatment Goals in MS

- Freedom from disease
  - Absence of new lesions detected by MRI
  - Absence of relapses
  - Absence of disability progression/worsening

# FDA-Approved DMTs: Injectable Agents

<table>
<thead>
<tr>
<th>DMT</th>
<th>Route/Frequency of Administration</th>
<th>Routine Monitoring</th>
<th>Adverse Events</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN β-1a</td>
<td>SC/intramuscular 3 times per week or weekly</td>
<td>CBC, LFTs at BL and every 6 months</td>
<td>Injection-site reactions, flu-like symptoms, LFT elevation, leukopenia, depression</td>
<td>Increases anti-inflammatory cytokine production and suppresses proinflammatory cytokine production, decreases inflammatory cell movement across the BBB</td>
</tr>
<tr>
<td>IFN β-1b</td>
<td>SC every other day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegylated IFN β-1a</td>
<td>SC every 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>SC daily or 3 times per week</td>
<td>None</td>
<td>Injection-site reactions, benign systemic reaction (dyspnea, palpitations)</td>
<td>Increases production of anti-inflammatory cytokines and reduced production of proinflammatory cytokines, production of regulatory T cells</td>
</tr>
</tbody>
</table>

BBB = blood brain barrier; BL = baseline; CBC = complete blood count; DMTs = disease-modifying therapies; FDA = Food and Drug Administration; IFN = interferon; LFT = liver function test; SC = subcutaneous.

## FDA-Approved DMTs: IV Agents

<table>
<thead>
<tr>
<th>DMT</th>
<th>Route/Frequency of Administration</th>
<th>Routine Monitoring</th>
<th>Adverse Events</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>IV every 4 weeks</td>
<td>CBC, LFTs at BL and every 6 months; JCV serology every 3 months in JCV-seronegative patients</td>
<td>Infusion reactions, PML, herpes virus, encephalitis/meningitis, hepatotoxicity</td>
<td>Selectively inhibits very-late antigen-4 (α4β1) integrins and hinders lymphocyte movement across the BBB</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>IV 5 days year 1; 3 days year 2</td>
<td>Thyroid function at BL and every 6 months; monthly platelet monitoring and urinalysis</td>
<td>Infusion reactions, secondary autoimmunity infections</td>
<td>Monoclonal antibody that targets CD52, decreases lymphocyte populations</td>
</tr>
</tbody>
</table>

CD52 = cluster of differentiation 52; IV = intravenous; JCV = John Cunningham virus.

**FDA-Approved DMTs: Oral Agents**

<table>
<thead>
<tr>
<th>DMT</th>
<th>Route/Frequency of Administration</th>
<th>Routine Monitoring</th>
<th>Adverse Events</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod</td>
<td>Oral daily</td>
<td>First dose monitoring with ECG, CBC, LFTs at BL and periodically; BL ECG and VZV serology; ophthalmologic exam at BL and at 3-4 months</td>
<td>Bradyarrhythmia, macular edema, herpes virus infections (especially VZV), transaminitis, PML</td>
<td>Blocks T cells from leaving lymph nodes, lowering their number in the CNS</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Oral daily</td>
<td>ALT monthly for 6 months, then every 6 months, then periodically; BL pregnancy and tuberculosis test; regular BP monitoring</td>
<td>Hepatotoxicity, teratogenic risk</td>
<td>Reduces expansion of harmful T cells and B cells disrupts proliferation of rapidly dividing cells</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Oral twice daily</td>
<td>CBC with differential at BL and every 6 months</td>
<td>Dose-related flushing, gastrointestinal symptoms, lymphopenia, PML</td>
<td>Neuroprotective and anti-inflammatory effects via the activation of the nuclear factor erythroid 2–related factor 2 pathway</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; ECG = electrocardiogram; VZV = varicella zoster virus.

## Emerging Agents for MS

<table>
<thead>
<tr>
<th>DMT</th>
<th>Route/Frequency of Administration</th>
<th>Efficacy Data</th>
<th>Adverse Events</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclizumab (high-yield process)</td>
<td>SC injection once monthly</td>
<td>Decreased relapsed rate in RRMS vs IFN β-1a</td>
<td>Infection, rash, eczema, elevated LFTs</td>
<td>Modulates IL-2 signaling by blocking the α subunit (CD25) of the IL-2 receptor</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>IV infusion every 6 months</td>
<td>Decreased relapsed rate in RRMS vs IFN β-1a; reduced disability progression in PPMS vs placebo</td>
<td>Infusion-related reactions, infection</td>
<td>Suppresses immune activity by targeting mature CD20-positive B lymphocytes</td>
</tr>
</tbody>
</table>

IL = interleukin.

Considerations for Initial MS Treatment

- Disease course and prognostic factors
- Benefits vs risks of DMTs
- Side effect profile
- Frequency and route of administration
- Patient comorbidities
- Treatment cost
- Patient preferences
- Patient readiness for treatment

Risk Factors for Poor Prognosis

- MS clinical course is unpredictable and highly variable
- Negative prognostic factors
  - Frequent multifocal attacks
  - Heavy lesion burden on initial MRI
  - Ataxia, weakness, bladder/bowel abnormalities
  - Cognitive symptoms
  - High 5-year accumulation of disability
  - Progressive disease
  - Spinal cord lesions on MRI
  - Male gender
  - African American or Latino descent
  - Older age at onset

Treatment Preferences in Patients With MS

N = 156.


- **Treatment frequency:** 42.2%*
- **Route of administration:** 37.5%*
- **Frequency of side effects:** 20.3%

*P < .05 vs frequency of side effects
Treatment Preferences in Patients With MS

ACTION ITEM:
Consider patient preferences for MS treatment, including the efficacy/safety balance, route and frequency of administration, and side effect profile

N = 156.
Predictors of Poor Adherence to Oral DMTs

<table>
<thead>
<tr>
<th>Oral DMT Feature/Event</th>
<th>Patients Predicting Nonadherence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher frequency of daily administration</td>
<td>17.4</td>
</tr>
<tr>
<td>Hair thinning</td>
<td>14.8</td>
</tr>
<tr>
<td>Severe side effects</td>
<td>13.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.7</td>
</tr>
<tr>
<td>Backache</td>
<td>8.8</td>
</tr>
<tr>
<td>Headache</td>
<td>4.5</td>
</tr>
<tr>
<td>Flushing</td>
<td>3.0</td>
</tr>
</tbody>
</table>

N = 319.
Trends in Switching First-line MS Therapy
Top 3 Reasons for Switch by Administration Route

N = 1234 switching events.
## Reasons for Switching First-line MS Therapy

<table>
<thead>
<tr>
<th>Reason</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe side effects</td>
<td>37.6</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>25.1</td>
</tr>
<tr>
<td>Physician’s advice</td>
<td>15.6</td>
</tr>
<tr>
<td>Ease of use of new drug</td>
<td>13.2</td>
</tr>
<tr>
<td>Worsening quality of life</td>
<td>3.2</td>
</tr>
<tr>
<td>Safety concerns</td>
<td>3.1</td>
</tr>
<tr>
<td>Insurance barriers</td>
<td>1.1</td>
</tr>
<tr>
<td>Drug cost</td>
<td>0.6</td>
</tr>
</tbody>
</table>

N = 1234 switching events.

Case (cont’d)

- Marie has been on GA 3 times/wk for 2 years
  - She experienced mild injection-site reactions during her first several months of treatment, but they were not bothersome
- At her current follow-up appointment, she reports increased fatigue and difficulty remembering things
- She has intermittent bouts of nausea and is complaining of hair thinning
- She also describes feeling depressed
- Repeat MRI findings reveal a number of new silent lesions
- Marie is diagnosed with RRMS
Case (cont’d)

- MRI findings: sagittal FLAIR view and postcontrast view
Which of the following do you recommend as the most appropriate next step for Marie?

1. Increase frequency of GA dosing
2. Switch to an alternate first-line MS agent
3. Start low-dose oral corticosteroid therapy
4. Switch to a second-line MS agent

Use your keypad to vote now!
Which of the following do you recommend as the most appropriate next step for Marie?

1. Increase frequency of GA dosing
2. Switch to an alternate first-line MS agent
3. Start low-dose oral corticosteroid therapy
4. Switch to a second-line MS agent

Use your keypad to vote now!
Defining Relapse in MS

- New symptom or sudden worsening of prior symptoms lasting $\geq 24$ hours
  - Symptom consistent with MS
  - Not related to infection, fever, or other potential causes
- Separated by $\geq 30$ days from last relapse onset
- Usually accompanied by objective changes in neurologic findings

Relapse Management

• Short-term corticosteroid therapy is appropriate when relapse significantly interferes with daily functioning
  – Example regimens
    • 3- to 5-day course of high-dose IV methylprednisolone (with or without oral taper)
    • High-dose oral prednisone (eg, 1250 mg)
• Rehabilitation can be helpful in restoring function after relapse

Adjusting Treatment in MS

- First-line therapies
  - IFNs
  - GA
  - Teriflunomide
  - DMF
- Second-line therapies
  - Fingolimod
  - Natalizumab
  - Alemtuzumab

DMF = dimethyl fumarate.
## Additional Considerations for Adjusting Therapy

<table>
<thead>
<tr>
<th>Treatment Adjustments</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| From one first-line DMT to another first-line DMT         | • Tolerability/safety issues  
• Inadequate response but with disease activity not suitable for escalation to a second-line DMT  
• Persistent high-titer neutralizing antibodies during treatment with IFN-β |
| From a first-line DMT to a second-line DMT                | • Patients with RRMS experiencing at least 1 relapse and with an active MRI during the previous year on treatment  
• Patients with RRMS transitioning to the secondary progressive phase with evidence of relapses or MRI activity |
| From one second-line DMT to another second- or third-line DMT | • Patients with RRMS continuing to experience relapses  
• Progressive forms of MS with relapses and/or active MRI despite treatment  
• Safety issues (eg, risk of PML on natalizumab) |
| From a second-line DMT to a first-line DMT                | • Tolerability/safety issues  
• Risk perception of patient |

Case (cont’d)

• Marie switched treatment to fingolimod (once daily oral agent, no teratogenic risk) and remained relapse-free for 8 months

• Today she presents complaining of new urinary symptoms
  – She has had 2 confirmed UTIs in the last 3 months; she saw her gynecologist for antibiotics
  – She is experiencing increasing urinary urgency; a home UTI screening kit was positive
Which of the following do you recommend as the most appropriate next step for Marie?

1. Treat with appropriate antibiotic, maintain bladder hygiene, and limit caffeine intake
2. Increase frequency of fingolimod dosing
3. Switch to an alternate first-line MS agent
4. Switch to an alternate second-line MS agent

Use your keypad to vote now!
Which of the following do you recommend as the most appropriate next step for Marie?

1. Treat with appropriate antibiotic, maintain bladder hygiene, and limit caffeine intake
2. Increase frequency of fingolimod dosing
3. Switch to an alternate first-line MS agent
4. Switch to an alternate second-line MS agent

Use your keypad to vote now!
Bladder Dysfunction

- Patients with MS are highly likely to develop bladder, bowel, and sexual problems
  - Among the most distressing problems of MS
  - Often neglected in the past, partly because of their perceived private nature
- Up to 75% of patients with MS will experience bladder dysfunction
- Due to bladder overactivity and incomplete emptying, bladder dysfunction in patients with MS produces symptoms of:
  - Urgency
  - Frequency
  - Urge incontinence
    - Urinary retention

Managing Bladder Dysfunction

- Maintain bladder hygiene and limit caffeine intake
- Anticholinergic/antimuscarinic medications
- Botulinum toxin

Long-term MS Management Principles: Monitor Patients for New Signs and Symptoms

<table>
<thead>
<tr>
<th>Visual</th>
<th>Motor</th>
<th>Cerebellar</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blurred vision</td>
<td>• Trunk/limb weakness</td>
<td>• Tremor</td>
</tr>
<tr>
<td>• Unilateral vision loss</td>
<td>• Spasticity</td>
<td>• Ataxia</td>
</tr>
<tr>
<td>• Oscillopsia</td>
<td>• Hyperreflexia</td>
<td>• Incoordination</td>
</tr>
<tr>
<td>• Diplopia</td>
<td>• Gait disturbance</td>
<td></td>
</tr>
<tr>
<td>• Trunk/limb weakness</td>
<td>• Balance problems</td>
<td></td>
</tr>
<tr>
<td>• Spasticity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hyperreflexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gait disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Balance problems</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensory</th>
<th>Genitourinary</th>
<th>Neurologic/Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Numbness</td>
<td>• Urgency, frequency, retention</td>
<td>• Impairment of memory,</td>
</tr>
<tr>
<td>• Paresthesias</td>
<td>• Incontinence</td>
<td>concentration, attention,</td>
</tr>
<tr>
<td>• Dysesthesia</td>
<td>• Frequent UTI</td>
<td>and/or processing speed</td>
</tr>
<tr>
<td>• Lhermitte’s sign</td>
<td>• Constipation</td>
<td>• Depression</td>
</tr>
<tr>
<td>• “MS hug”</td>
<td>• Impotence</td>
<td>• Irritability</td>
</tr>
<tr>
<td>• Trigeminal neuralgia</td>
<td>• Anorgasmia</td>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Allodynia</td>
<td>• Dyspareunia</td>
<td></td>
</tr>
<tr>
<td>• Proprioception deficits</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Examples of Management Strategies for Additional MS Symptoms

<table>
<thead>
<tr>
<th>MS Symptoms</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>• Cooling (for heat-sensitive patients)</td>
</tr>
<tr>
<td></td>
<td>• Energy-conservation techniques</td>
</tr>
<tr>
<td></td>
<td>• Exercise</td>
</tr>
<tr>
<td></td>
<td>• Getting adequate sleep</td>
</tr>
<tr>
<td></td>
<td>• Use of appropriate assistive device</td>
</tr>
<tr>
<td></td>
<td>• Pharmacotherapy</td>
</tr>
<tr>
<td>Depression</td>
<td>• Psychotherapy</td>
</tr>
<tr>
<td></td>
<td>• Pharmacotherapy</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>• May be improved by treatment for depression in some patients</td>
</tr>
<tr>
<td></td>
<td>• Cognitive rehabilitation</td>
</tr>
</tbody>
</table>

Long-term MS Management Principles: Promote Treatment Adherence

• Encourage patient engagement in managing his/her own healthcare
• Motivational interviewing
  – Cooperation
  – Activation of intrinsic motivation
  – Autonomy
• Principles are reflected in:
  – Empathetic counseling style
  – Active listening
  – Addressing the patient’s ambivalence regarding treatment continuation

Long-term MS Management Principles: Promote Healthy Lifestyle Choices

- Factors that can impact the severity of MS
  - Current smoking
  - Alcohol consumption
  - Vitamin D deficiency
  - Overweight or obesity
  - Hypertension, hyperlipidemia, type 2 diabetes, coronary artery disease, chronic lung disease
  - Low level of physical activity
  - Lower score on the dietary habits questionnaire
  - Low level of fish consumption (less than once/wk)
  - Having fewer than 6 close relationships

Long-term MS Management Principles: Encourage Shared Decision Making

- Clinician and patient go through all phases of the decision-making process together
  - Share treatment preferences
  - Bring information and values into their discussion
  - Reach an agreement on treatment choice
- Involvement of family members may also be important
- Patients who have a role in the treatment-selection process demonstrate improved adherence

Long-term MS Management Principles: Encourage Shared Decision Making

- Clinician and patient go through all phases of the decision-making process together
  - Share treatment preferences
  - Bring information and values into their discussion
  - Reach an agreement on treatment choice
- Involvement of family members may also be important
- Patients who have a role in the treatment-selection process demonstrate improved adherence

ACTION ITEM: Encourage patients with MS to participate in their healthcare decisions to enhance adherence

Case: Conclusion

- After switching to fingolimod, Marie has been relapse free for 12 months.
- She has stopped participating in 5K races due to balance and gait issues, but she continues to focus on diet and exercise to maintain motor function, cognition, and mood and to prevent fatigue.
PCE Action Plan

- Consider the differential diagnosis of MS in patients presenting with signs and symptoms suggesting demyelinating disease
- Consider early treatment initiation to improve long-term outcomes for patients with MS
- Consider patient preferences for MS treatment, including the efficacy/safety balance, route and frequency of administration, and side effect profile
- Encourage patients with MS to participate in their healthcare decisions to enhance adherence

PCE Promotes Practice Change
Q & A
Is it safe for patients to become pregnant while taking medications for MS?
If a female patient in the right age range for MS presents with intractable fatigue and has a normal neurologic exam, should an MRI be ordered?
Are there specific tests that should be done in primary care prior to referring patients with suspected MS to a neurologist?
Do MS lesions ever clear up or improve with treatment?
If we identify a patient with vitamin D deficiency and we correct it, does that lower the risk of developing MS? How strong is the vitamin D deficiency and MS link?
In a patient who has MS and is on therapy, why would we wait two years to repeat the MRI?
Why aren’t we putting patients on a second-line therapy right away?
If a patient undergoes an MRI without contrast, does he/she need to have an MRI with contrast?
Why do men, African Americans, and Hispanics with MS have a poorer prognosis?
Do patients with MS experience pain?
What are the etiologic factors for MS? Do we know what causes it?
Can you explain the Marcus Gunn pupil seen in patients with MS?
Do patients with MS have the same life expectancy as the general population?
Is there any stem cell research being conducted in MS?
Is medical marijuana effective for patients with MS?