

Comprehensive Care in Multiple Sclerosis: A Core Curriculum

DRAFT EDITION



THE CONSORTIUM OF
MULTIPLE SCLEROSIS CENTERS

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Note to Readers: This is a “draft edition” of **Comprehensive Care in Multiple Sclerosis: A Core Curriculum**. We welcome comments, revisions and suggested references as we continue to update and expand the information in this study guide. Please send your comments and suggestions to: info@msscure.org.

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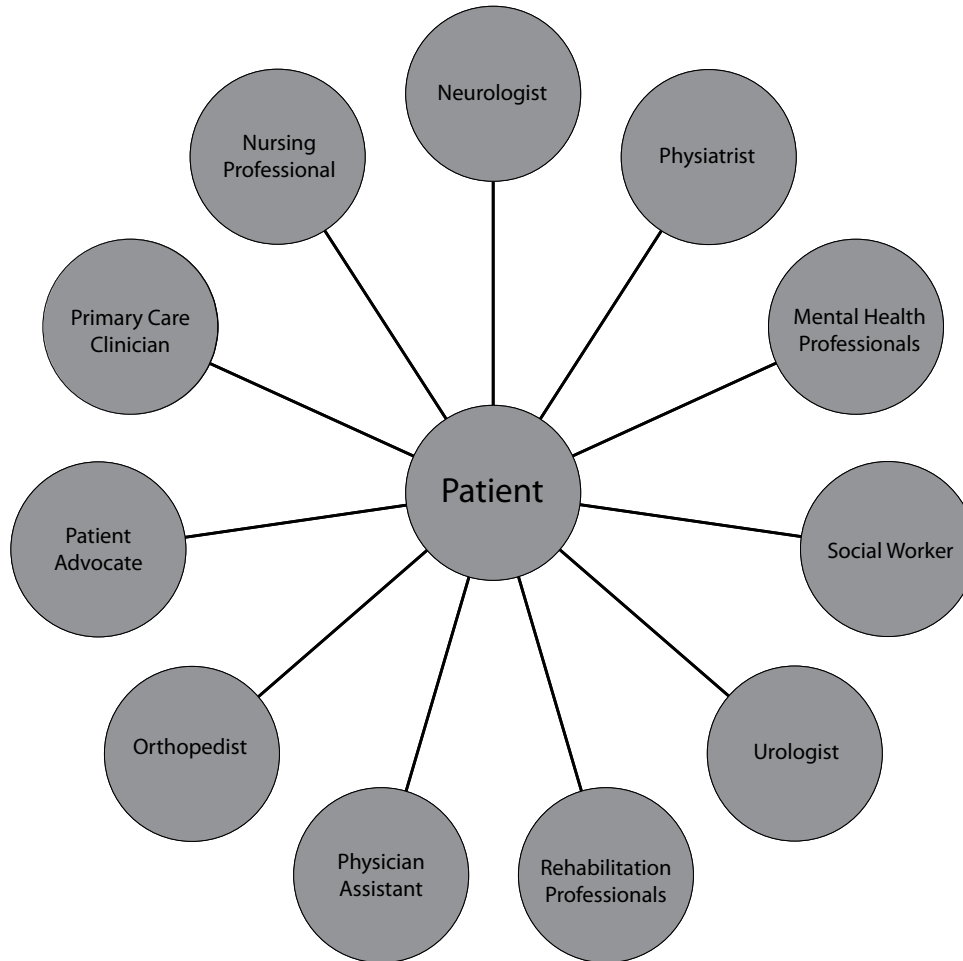
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INTRODUCTION

Multiple sclerosis (MS) is a chronic, frequently disabling neurological disease that has an unpredictable and variable impact on a person's physical and cognitive abilities, emotions, and quality of life. There is emerging evidence that the optimal way to address the complex needs of people with MS is to utilize a comprehensive, patient-centered approach (Figure 1) with a dynamic, multidisciplinary plan of coordinated care, combined with a solid team of healthcare professionals.

Figure 1: Multidisciplinary Team Approach



MS HEALTHCARE TEAM

There are many professional specialists that provide care of patients with MS, encompassing the varied specialties including neurology, nursing, mental health (psychiatrist, psychologist, neuropsychologist), social work, orthopedics, physiatry, physician assistant, primary care, rehabilitation (physical therapist, occupational therapist, speech-language pathologist, vocational counselor, recreational therapist), and urology. Each specialist brings expertise and knowledge to meet the varied needs of patients and their families.

In order to enhance knowledge and skills of healthcare professionals the Consortium of Multiple Sclerosis Centers (CMSC) has developed this study guide entitled, "Comprehensive

Care in Multiple Sclerosis: A Core Curriculum.” The information in this guide provides a baseline of knowledge that all members of the MS healthcare team need to know to help promote the highest quality care possible for patients with MS. Fundamentals of MS, its diagnostic parameters, multidisciplinary management, up-to-date treatment options, tools for patient empowerment, advocacy as well as patient and family education are included.

Every member of the MS healthcare team participates and contributes to ongoing patient care, thus promoting the most comprehensive and effective care of patients with MS. Working in a collaborative environment, any member of the team may identify a patient experiencing a relapse (i.e. if the patient’s physical therapist notices weakness that was not evident in previous weeks, he or she can contact the neurologist to express concerns about the patient). This communication between care providers will positively impact the care of the patient as the relapse will be detected and managed early. This effective care model is possible only when all healthcare providers on the team have an organized network of communication and a solid understanding of the disease process, diagnosis, and treatment options. Although MS is often managed by the neurologist, coordination of care may also be handled by the primary care clinician, physician assistant, nurse practitioner, case manager/social worker, patient advocate or MS nurse.

Although Figure 1 identifies a number of different specialties that may be part of the MS healthcare team, not every patient consults with every subspecialty. For example, some patients do not see a physiatrist or orthopedist, while others might require consultation with an urologist. However, all care providers working together as a team will provide the most benefit to the patient.

VALIDATION OF EXPERTISE AS A MULTIPLE SCLEROSIS CERTIFIED SPECIALIST (MSCS)

Armed with information about specialization in MS care, healthcare providers may elect to become a Multiple Sclerosis Certified Specialist (MSCS). Any member of the MS healthcare team with at least one year of experience in MS care and at least 20% of professional time spent with MS patients and/or families is eligible to take this certification examination. With this credential, healthcare providers can validate their knowledge and expertise in the field of MS. Patients and families, can be assured of the knowledge and MS expertise of the healthcare provider. All certified specialist providers serve the same goal: to provide comprehensive, coordinated, expert care to improve the physical function, emotional well-being, and optimal quality of life of patients with multiple sclerosis.

For more information about the MSCS examination and requirements, please go to the CMSC website at www.mscares.org at: http://www.mscares.org/?page=about_mscs. The CMSC supports this voluntary certification process. In addition to validating the healthcare provider’s expertise and commitment to MS, the MSCS certification will increase the provider’s marketability and opportunity for career advancement.

The CMSC is developing a database of MSCS certified specialists for the CMSC website so that patients and their families will have easy access to healthcare providers who specialize in MS.

Part 1: FUNDAMENTALS OF MULTIPLE SCLEROSIS (cont'd.)

4. Diagnosis of Relapse¹¹

a. Relapse Defined

1. Appearance of a new neurological symptom lasting 24 hours or longer
2. Accompanied by a finding – a change in functional ability
3. MRI change may occur corresponding to relapse
3. No current history of infection, illness or fever
4. No other cause e.g. migraine, natural visual change, sciatica, nerve entrapment, physical injury, inner ear problem
5. Ensure not a pseudorelapse (see b.2. below)

b. MS relapse is a clinical diagnosis (consider red flags)¹³

1. Reappearance of a previous symptom or acute worsening of existing symptoms for longer than 24 hours
2. Consider pseudorelapse defined as occurring in the absence of infection/fever or even ambient increase in body temperature

B. Clinical Course and Disease Process^{14–17}

1. Forms of MS

- a. Relapsing Remitting (RRMS) – Includes periods of acute decline or exacerbation of neurologic function followed by clinical stability periods between attacks. Total and/or partial remission of symptoms usually occurs, especially early in the disease.
- b. Secondary Progressive (SPMS) – Gradual worsening of the disease occurs independently of continued exacerbations (follows relapsing MS).
- c. Primary Progressive (PPMS) – Patients experience a gradual onset of symptoms which worsen over time (often spinal cord predominant; no female predominance; age similar to conversion to SPMS).
- d. Progressive Relapsing (PRMS) – Progression of the disease continues between relapses. (this form considered uncommon).
- e. Clinically Isolated Syndrome (CIS) – One-time neurologic event consistent with demyelination or inflammation of the central nervous system.¹⁸ CIS may include optic neuritis, transverse myelitis, isolated brainstem or cerebellar syndromes. Conversion to MS is a high risk for patients with CIS (if MRI lesions look like MS).¹⁶
- f. Evolving concept: Radiologically Isolated Syndrome (RIS) – Incidental finding of MS-looking lesions on MRI.¹⁹ Patients have lesions on MRI but no clinical signs or symptoms of MS.

Part 1: FUNDAMENTALS OF MULTIPLE SCLEROSIS (cont'd.)

2. Clinical Phenotypes of MS: The 2013 revisions¹⁵

a. Clinically Isolated Syndrome (CIS)

1. Not active
2. Active

b. Relapsing-remitting (RRMS) Disease

1. Not active
2. Active

c. Progressive Disease

1. Primary Progressive (PPMS): Progressive accumulation of disability from onset
 - a. Active and with progression
 - b. Active but without progression
 - c. Not active but with progression
 - d. Not active and without progression (stable disease)
2. Secondary Progressive (SPMS): Progressive accumulation of disability after initial relapsing course
 - a. Active but with progression
 - b. Active but without progression
 - c. Not active but with progression
 - d. Not active and without progression (stable disease)

3. Pathophysiology^{10,20}

- a. Immune Dysfunction
- b. Destruction of Myelin
- c. Axonal Damage

C. Natural History^{10,21,22}

1. Theories of Etiology

- a. Genetics
- b. Environmental
- c. Other

2. Epidemiology

- a. Geographic Distribution
- b. Gender – MS is more common in women than in men with data suggesting a male to female ratio of 1:2 to as high as 1:4.^{23–25}
- c. Age of Onset – peaks between 25-35 years of age. Only 2-5% of people with MS experience their first symptom before age 16.^{24–26}
- d. Ethnicity

NOTES

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Part 2: MULTIDISCIPLINARY MANAGEMENT OF MULTIPLE SCLEROSIS

A . Relapse

1. Recognition¹
 - a. Classic presentation of MS relapse may include blurred vision, diplopia, weakness or numbness in an extremity or the trunk, vertigo, ataxia, bladder/bowel dysfunction, or significant cognitive changes (classic presentation may vary from patient to patient)
 - b. Criteria: new or worsening neurologic symptom lasting at least 24 hours
 - c. Rule out pseudorelapse, a recrudescence of previous neurologic symptoms in the setting of fever, underlying infection or illness (thermal effects)
 - d. Typically there is some improvement, but often there is some residual disability after a relapse
2. Interventions^{1,2}
 - a. Pharmacologic Management
 1. Steroids (IV methylprednisolone, high dose oral prednisone)
 2. Intramuscular adrenocorticotrophic hormone (ACTH)
 3. Plasmapheresis
 4. Intravenous immunoglobulin (IVIG)
 - b. Rehabilitation Services and symptomatic therapy
 1. Physical therapy and/or occupational therapy for weakness, gait or arm dysfunction, endurance, assessment of assistive devices; energy conservation, cognitive strategies
 2. Bladder and bowel management (including urinary catheter for acute urinary retention)
 3. Antispasmodics for spasticity
 4. Analgesics or anti-epileptics for pain
 5. Antiemetics and phenothiazines for vertigo
 6. Antiepileptics for tonic spasms
 7. Eye patch or prisms for diplopia
 - c. Psychosocial Support
 1. Emotional support as needed to treat concerns that arise during relapse (stress management, social support)
 2. Patient education regarding MS relapses in general and management of side effects due to pharmacologic medications including steroids

B. Disease Modifying Therapies^{3,4}

1. Purpose and Expectations: The goal is no evidence of disease activity (NEDA)^{5(p90)}
 - a. Reducing relapse rate
 - b. Delaying disability progression as measured by Expanded Disability Status Scale (EDSS) and/or Multiple Sclerosis Functional Composite (MSFC)
 - c. Reducing new MRI activity (T2 hyperintensities, T1 hypointensities, enhancing lesions)
 - d. Some consider adding brain atrophy to NEDA

Part 2: MULTIDISCIPLINARY MANAGEMENT OF MULTIPLE SCLEROSIS (cont'd.)

2. Injectable Agents - see Appendix 1 on page 18. Appendix 1 provides details on mechanism of action, indication, administration and adverse effects of injectable therapies.
 - a. Interferons
 1. Interferon β -1b (Betaseron[®], Extavia[®])
 2. Interferon β -1a (Avonex[®], Rebif[®])
 3. Peginterferon β -1a (Plegridy[®])
 - b. Glatiramer Acetate (Copaxone[®], Glatopa[™])*
*Glatopa[™] is FDA approved and will be available soon.
3. Infusible Agents - see Appendix 2 on page 20. Appendix 2 provides details on mechanism of action, indication, administration and adverse effects of infusible therapies.
 - a. Alemtuzumab (Lemtrada[®])
 - b. Mitoxantrone (Novantrone[®])
 - c. Natalizumab (Tysabri[®])
4. Oral Medications - see Appendix 3 on page 22. Appendix 3 provides details on mechanism of action, indication, administration and adverse effects of oral therapies.
 - a. Dimethyl Fumarate (Tecfidera[®])
 - b. Fingolimod (Gilenya[®])
 - c. Teriflunomide (Aubagio[®])
5. When to switch (breakthrough disease)^{3(p90,110)}
6. Evolving therapies (daclizumab, ocrelizumab, ofatumumab, rituxumab)

C. Symptoms

1. General Guidelines
 - a. Rule out other sources of symptoms; note: If a patient with MS has a symptom, it is not always due to MS.
 - b. Symptoms may be acute, sub-acute or chronic
 - c. All symptoms of MS may be identified as primary, secondary or tertiary (For more information, please review Ben-Zacharia, AB. Therapeutics for multiple sclerosis symptoms. Mt Sinai J Med. 2011;78(2):176-91.)⁶
 1. Primary symptoms are directly related to MS, demyelination and axonal loss. Example: weakness or vision loss.
 2. Secondary symptoms are the result of primary symptoms. Example: urinary tract infection resulting from urinary retention.
 3. Tertiary symptoms are the result of social and psychological effects of MS. Example: depression or social isolation may occur as a result of bladder or bowel dysfunction.
 - d. Goals of symptom management⁷
 1. Eliminate or reduce symptoms that impair functional abilities
 2. Improve quality of life
 3. Avoid secondary and tertiary complications
 4. Provide targeted and individualized treatment of symptoms, essential in the management of MS
 - e. Rehabilitation Specialties in MS^{8,9} – Rehabilitation strategies are often recommended for acute, sub-acute and chronic symptoms. Most want to improve mobility, albeit safely.
 1. Physical Therapy
 2. Occupational Therapy

Part 2: MULTIDISCIPLINARY MANAGEMENT OF MULTIPLE SCLEROSIS (cont'd.)

- e. Rehabilitation Specialties in MS (cont'd.)
 - 3. Cognitive Rehabilitation
 - 4. Vocational Rehabilitation
 - 5. Speech-language Therapy
 - 6. Assistive Technology
 - 7. Orthotics
- 2. Invisible Symptoms¹⁰⁻¹² - See Appendix 4, pages 24-28, for detailed information on symptoms including description, rehabilitation strategies, pharmacologic interventions and psychosocial support
 - a. Fatigue
 - b. Pain
 - c. Cognitive Impairment
 - d. Emotional Disorders
 - e. Sensory Disturbances
- 3. Visible Symptoms¹⁰⁻¹² - See Appendix 4, pages 24-28.
 - a. Motor Dysfunction
 - 1. Spasticity
 - 2. Tremor
 - 3. Coordination (ataxia)
 - 4. Weakness
 - b. Ambulatory Dysfunction
 - 1. Motor dysfunction
 - 2. Sensory disturbance
 - 3. Balance
 - c. Visual Impairment
 - d. Elimination dysfunction
 - 1. Bladder dysfunction (Failure to store, failure to empty, mixed)
 - 2. Bowel dysfunction (Failure to store, failure to empty)
 - e. Sexual Dysfunction
 - f. Dysarthria and Dysphagia
- 4. Other, Less Common Symptoms¹²
 - a. Seizures
 - b. Breathing difficulties
 - c. Pruritus
 - d. Headache
 - e. Hearing loss
 - f. Altered taste
 - g. Altered smell

D. Assessment Tools¹³

- 1. Diagnostic Measures
 - a. Magnetic Resonance Imaging (MRI)
 - b. Expanded Disability Status Scale (EDSS)¹⁴
 - c. Optical Coherence Tomography (OCT)
- 2. Symptom Specific Measures
 - a. Timed 25-Foot Walk (T25FW)
 - b. 9-Hole Peg Test (9HPT)

Part 2: MULTIDISCIPLINARY MANAGEMENT OF MULTIPLE SCLEROSIS (cont'd.)

2. Symptom Specific Measures (cont'd.)

- c. Symbol Digit Modalities Test (SDMT)
- d. Low contrast visual acuity testing
- e. Timed Up and Go (TUG)
- f. Beck Depression Inventory-Fast Screen (BDI-FS)
- g. Fatigue Severity Scale (FSS)
- h. Modified Fatigue Impact Scale (MFIS)
- i. 12-Item Short Form Survey (SF-12, a 12-items scale that includes mental health and physical health components)

E. Health Maintenance

1. Wellness Strategies¹⁵⁻¹⁷

- a. Nutrition – Good nutrition is vital for reducing risk of heart disease, cancer stroke and diabetes; weight management; managing fatigue and increasing energy, promoting bowel health and preventing constipation, prevention of osteoarthritis.
- b. Exercise and Fitness – Promotes general health and disease prevention; helps prevent osteoporosis; improves fatigue; may be effective in treating depression and other mood disorders; promotes brain health and may improve cognitive impairment; may play a role in protective, regenerative and adaptive nerve processes; alternatives include yoga, tai chi, water exercise; patients should consult health care professional before starting an exercise program.
- c. Immunization – Recommendations: seasonal flu vaccine, varicella vaccine, hepatitis B vaccine, human papillomavirus vaccine; to be discussed with healthcare practitioner: shingles vaccine; smallpox vaccine only considered for people with MS who are directly exposed to smallpox. For detailed information see: <http://www.nationalmssociety.org/For-Professionals/Clinical-Care/Managing-MS/Immunization>.
- d. Recreation – Travel and recreation leads to more enjoyment and improves quality of life and overall mood. It is important for patients to consult doctors for tips on travelling safely and comfortably despite limitations.
- e. Health Screening – Recommendations: mammogram/clinical breast exam, pap test and HPV test for cervical cancer, PSA/clinical testicular and rectal exam, hemoccult stool test/ colonoscopy, skin inspection for pressure ulcers and melanoma, influenza vaccine, bone densitometry, EKG, comprehensive metabolic profile, CBC, thyroid function tests.
- f. Stress Management – Stress and stressful life events may have an effect on MS. When possible, lower stress by eliminating the causative factor; manage stress with exercise, relaxation, meditation, prayer, psychotherapy, mind/body exercises, rest.
- g. Spirituality – As an important dimension of wellness, spirituality may contribute to a person's strength and general wellbeing.
- h. Activities of Daily Living – may be limited in people with multiple sclerosis. The healthcare team may provide recommendations for home care and/or personal care as needed.

Part 2: MULTIDISCIPLINARY MANAGEMENT OF MULTIPLE SCLEROSIS (cont'd.)

2. Potential Life-altering Complications^{18,19}

- a. Osteoporosis
- b. Contractures
- c. Skin Breakdown (decubitus ulcer)
- d. Aspiration Pneumonia
- e. Sepsis
- f. Trauma due to falls
- h. Chronic urinary dysfunction

F. Psychosocial Issues^{20,21}

1. Response to Chronic Illness – depression, anger, denial, adjustment disorders, grief, loss, planning, emotional response
2. Adaptation – positive coping skills, self-efficacy, resilience, life changes, life planning
3. Social isolation
4. Strengthening support network – interpersonal relationships, MS support groups, online resources
5. Cultural and ethno-cultural factors
6. Productivity issues
7. Financial concerns
8. Issues of abuse and neglect
9. Palliative care

G. Complementary and Alternative Therapies

1. Evidence-based CAM (complementary and alternative medicine) include ginkgo biloba, magnetic therapy, medical marijuana (cannabinoids), and reflexology²²
2. Other CAM therapies that patients may use include: acupuncture, bee venom therapy, cooling therapy, meditation, hypnotherapy, massage, chiropractic medicine, dietary supplements (antioxidants: immune system; caffeine: fatigue; cranberry: prevent UTIs; senna: constipation; St. John's Wort: mild depression; valerian: insomnia; Vitamin D: preventive effects on MS and symptoms)^{16,23,24}

H. Adherence to Treatment²⁵

1. Adherence to therapy, exercise and rehabilitation
2. Adherence to medications
3. Maintaining a healthy lifestyle and social life

I. Care Settings

1. Patients may seek care in variety of settings including tele-health, primary care practice, private practice, VA, neurology MS program, Comprehensive Care Center
2. The patient's neurologist, primary care clinician, physician assistant, nurse practitioner, case manager/social worker, patient advocate or MS nurse may oversee coordination of care.

References - Part 2

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25. Harris C, Halper J, Kennedy P, McEwan L, Ross AP, Namey M. Moving Forward: Adherence to therapy and the role of nursing in multiple sclerosis. 2014. http://www.iomsn.org/images/pdf/Monograph_MovingForward-SinglePage.pdf. Accessed May 15, 2015.

Part 3: PATIENT EMPOWERMENT

A. Advocacy¹

1. Patient Rights - HIPAA (Health Insurance Portability and Accountability Act)
2. Negotiating the Healthcare System

B. Community Resources

1. Referrals
 - a. Community referrals for housing
 - b. Home health aides
 - c. Respite
2. Social Workers, Care Coordinators, Case Managers
3. Support Groups

C. Patient and Family Education

1. Disease Specific²⁻⁴
 - a. Symptom management
 - b. Support
 - c. Resources in the community
2. Goal Setting⁵
 - a. For patient
 - b. For family members
3. Information Sources
 - a. Pharmaceutical company patient assistance program – provides information on reimbursement issues and offers nursing and personal support regarding specific therapies and concerns about MS.
Information at: <http://www.medicare.gov/pharmaceutical-assistance-program/>
 - b. National and local resources
 1. American Academy of Neurology (www.aan.com)
 2. Can Do Multiple Sclerosis (www.mscando.org)
 3. Consortium of Multiple Sclerosis Centers (www.ms-care.org)
 4. International Organization of MS Nurses (www.iomsn.org)
 5. Multiple Sclerosis Association of America (www.msaa.com)
 6. Multiple Sclerosis Coalition (www.ms-coalition.org)
 7. Multiple Sclerosis Foundation (www.msfocus.org)
 8. Multiple Sclerosis International Federation (www.msif.org)
 9. Multiple Sclerosis Society of Canada (www.mssociety.ca)
 10. Multiple Sclerosis Society UK (www.mssociety.org.uk)
 11. Multiple Sclerosis Trust (www.mstrust.org.uk)
 12. National Multiple Sclerosis Society (www.nationalmssociety.org)

Part 3: PATIENT EMPOWERMENT (Cont'd.)

4. Caregivers

- a. Caregiver burden, burnout (may be a spouse or other family member)⁶
- b. Respite care
- c. Caregivers' support group (www.caregiving.com)
- d. Additional caregiver issues
 1. Long-term care⁷
 2. Caregiving in multiple sclerosis, needs of caregiver, and the multidisciplinary medical team⁸
 3. The caregiving role (parent, spouse, child)⁶

5. Legal Issues

- a. Disability - based on US Social Security definitions, disability is the inability to work
- b. Reasonable accommodations in the workplace are required for qualified employees with disabilities based on the Americans with disabilities Act (ADA)⁹
- c. Expedited process for disability claims for people with advanced forms of MS is available as part of the Compassionate Allowances Initiative¹⁰
- d. HIPAA (Health Insurance Portability and Accountability Act) – Sets national standards in the US regarding patient confidentiality and security of healthcare information
- e. Durable Medical Equipment (DME) and Adaptive Devices – Working in partnership with OT/PT to determine appropriate DME. Some are covered by Medicare and/or private insurance: <http://www.medicare.gov/Pubs/pdf/11045.pdf>

6. Advance Directives¹¹

- a. Living will
- b. Healthcare proxy (or power of attorney for healthcare decision making)

7. Clinical Research

- a. Protection of human subjects
- b. Informed consent
- c. Progressive patients

Part 4: SUGGESTED READING AND RESOURCES

Study Guide

Rochelle L. Clinical Review in Multiple Sclerosis. Halper, J; Harris C (eds). Ascend Integrated Media, Kansas, 2011.
http://c.ymcdn.com/sites/www.mscares.org/resource/collection/E4D58AD0-FE6F-4098-9001-DD8EB96920ED/ms_clinical_guide.pdf

Suggested Reading

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Giesser BS (ed). *Primer on Multiple Sclerosis.* New York: Oxford University Press, Inc.; 2011.

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Kennedy P, (ed). *The Can Do Multiple Sclerosis Guide to Lifestyle Empowerment.* New York: Demos Medical Publishing; 2013.

Polman CH, Thompson AJ, Murray TJ, et al. *Multiple Sclerosis: The Guide to Treatment and Management,* 6th ed. New York, NY: Demos Medical Publishing, 2006.

Rae- Grant AD, Fox RJ, Bethoux F, eds. *Multiple Sclerosis and Related Disorders: Clinical Guide to Diagnosis, Medical Management, and Rehabilitation.* 1st ed. New York: Demos Medical Publishing; 2013.

Schapiro RT. *Managing the Symptoms of Multiple Sclerosis.* Vol 5th edition. New York: Demos Medical Publishing; 2007.

Yadav V, Bever C, Bowen J, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. See comment in *PubMed Commons below Neurology.* 2014;82(12):1083-92.

Additional Resources

American Academy of Neurology <https://www.aan.com/practice/>

Consortium of Multiple Sclerosis Centers (CMSC). <http://www.mscares.org/>

2015 Annual Meeting of the CMSC. Annual Meeting Presentations. www.mscares.org/2015presentations

CMSC 2014 CMSC ACTRIMS Annual Meeting Presentations. <http://www.mscares.org/?page=2014amslides>

International Organization of Multiple Sclerosis Nurses. www.iomsn.org

National MS Society. Professional Resource Center. <http://www.nationalmssociety.org/For-Professionals/Clinical-Care>

US Department of Justice. Civil Rights Division. Information and Technical Assistance on the Americans with Disabilities Act. <http://www.ada.gov/>

Appendix 1: Key Features of the Disease-Modifying Agents, Injectable Therapies¹⁻⁷

Agent (Brand Name)	Interferon β -1b (Betaseron®, Extavia®)	Interferon β -1a (Avonex®)	Interferon β -1a (Rebif®)	Glatiramer acetate (Copaxone®, Glatopa™)	Peginterferon β -1a (Plegridy®)
Description	<ul style="list-style-type: none"> Recombinant agent, produced in E. coli Unglycosylated Amino acid sequence differs from naturally occurring interferon with a serine substituted for the cysteine residue at position 17 	<ul style="list-style-type: none"> Recombinant agent produced from Chinese hamster ovary cells Glycosylated Identical in amino acid content and sequence to human β-interferon 	<ul style="list-style-type: none"> Recombinant agent produced from Chinese hamster ovary cells Glycosylated Identical in amino acid sequence to human β-interferon 	<ul style="list-style-type: none"> Synthetic polypeptide Approximates the antigenic structure of myelin basic protein 	<ul style="list-style-type: none"> The “pegylated” form of interferon; polyethylene glycol is attached to molecules of interferon, which lengthens the effect of interferon and allows for less frequent dosing.
Indication^a (United States)	Relapsing forms of MS to reduce decrease frequency of relapses, CIS	Relapsing forms of MS to slow accumulation of physical disability and decrease frequency of relapses, CIS	Relapsing forms of MS to delay accumulation of physical disability and decrease frequency of relapses	RRMS to reduce frequency of relapses, CIS	Relapsing forms of MS to delay accumulation of physical disability and reduce frequency of relapses
Dosage/ Route/ Administration	0.25 mg/l subcutaneous injection every other day	30 μ g/l intramuscular injection weekly	22 μ g or 44 μ g/l subcutaneous injection 3 times weekly, preferably on same 3 days and at the same time (e.g. late afternoon or evening)	20 mg/l subcutaneous injection daily (Copaxone® and Glatopa™) Or 40 mg/l subcutaneous injection three times weekly (Copaxone® only)	125 mcg every two weeks subcutaneous
Considerations	<ul style="list-style-type: none"> Injection-site rotation and skin management Depression and/or suicidal ideation, warranting treatment cessation Laboratory monitoring^b <ul style="list-style-type: none"> Neutralizing antibodies Hematologic/hepatologic abnormalities Pregnancy Category: C 	<ul style="list-style-type: none"> Injection-site rotation and skin management Depression, suicidal ideation, and/or psychosis may occur, warranting treatment cessation Laboratory monitoring^b <ul style="list-style-type: none"> Neutralizing antibodies Hematologic/hepatologic abnormalities Pregnancy Category: C 	<ul style="list-style-type: none"> Injection-site rotation and skin management Depression, suicidal ideation, and/or suicide attempts may occur, warranting treatment cessation Laboratory monitoring^b <ul style="list-style-type: none"> Neutralizing antibodies Hematologic/hepatologic abnormalities Pregnancy Category: C 	<ul style="list-style-type: none"> Injection-site rotation and skin management Pregnancy Category: B 	<ul style="list-style-type: none"> Injection-site rotation and skin management Depression and/or suicidal ideation, warranting treatment cessation Laboratory monitoring^b <ul style="list-style-type: none"> Neutralizing antibodies Hematologic/hepatologic abnormalities Pregnancy Category: C
Common Side Effects	<ul style="list-style-type: none"> Flu-like symptoms Injection site reactions Menstrual disorders Mild neutropenia, anemia, and thrombocytopenia Abnormal liver function 	<ul style="list-style-type: none"> Headaches Mild flu-like symptoms Muscle aches Anemia 	<ul style="list-style-type: none"> Mild flu-like symptoms Muscle aches Anemia Injection site reactions 	<ul style="list-style-type: none"> Skin and injection site reactions Postinjection reaction Lipoatrophy 	<ul style="list-style-type: none"> Flu-like symptoms Injection site reactions headache Muscle and joint pain

Adapted with permission from Costello K, Halper J, eds. Multiple Sclerosis: Key Issues in Nursing Management: Adherence, Cognitive Function, Quality of Life. 3rd ed. Washington, DC: Expert Medical Education; 2010.

NOTES - Appendix 1

CIS, clinically isolated syndrome; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

^a Interferon β -1b, Interferon β -1a, and Glatiramer acetate are approved for use in the US and Canada.

^b Laboratory monitoring for hematologic/hepatologic changes is done usually at months 3, 6, 9, 12, 18 and 24 and annually thereafter. Neutralizing antibodies can be detected at 12 to 24 months.

REFERENCES - Appendix 1

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4. Rebif® (interferon beta-1a) [prescribing information]. Rockland, MA: EMD Serono, Inc; New York, NY: Pfizer, Inc. 2015. http://emdserono.com/cmgi.emdserono_us/en/images/Rebif%20PI_Jun2014_tcm115_19765.pdf?Version=-. Accessed May 18, 2015.
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6. Glatopa™ (glatiramer acetate injection) [prescribing information]. Princeton, NJ; Sandoz Inc. March 2014. <http://www.glatopa.com/pdf/Glatopa-Package-Insert-03-2014.pdf>. Accessed May 16, 2015.
7. Plegridy® (pegylated interferon beta-1a) [prescribing information]. Cambridge, MA: Biogen Idec, Inc. 2014. <https://www.plegridy.com/pdfs/plegridy-prescribing-information.pdf>. Accessed May 18, 2015.

NOTES

Appendix 2: Key Features of the Disease-Modifying Agents, Infusible Therapies¹⁻³

Agent (Brand Name)	Alemtuzumab (Lemtrada®)	Mitoxantrone (Novantrone®)	Natalizumab (Tysabri®)
Description	<ul style="list-style-type: none"> • Monoclonal antibody that targets CD52, a protein on T and B cells 	<ul style="list-style-type: none"> • Synthetic antineoplastic anthracendione 	<ul style="list-style-type: none"> • Recombinant humanized monoclonal antibody produced in murine myeloma cells
Indication^a (United States)	Relapsing forms of MS	SPMS, PRMS or abnormally worsening RRMS, for reducing neurological disability and/or frequency of relapses	Relapsing forms of MS to delay accumulation of physical disability and reduce frequency of relapses
Dosage/ Route/ Administration	Two annual treatment courses: 12mg/day IV on 5 consecutive days followed by 12 mg/day on 3 consecutive days. 12 months later.	12 mg/m ² (cumulative lifetime dose not to exceed 140 mg/m ²) IV infusion administered for 5 to 15 minutes every 3 months	300 mg IV infusion over 1 hour every 28 days
Considerations	<ul style="list-style-type: none"> • Serious side effects include autoimmune thyroid disease, autoimmune cytopenias, infections and pneumonitis • Boxed warning indicates risk of serious autoimmune conditions, life-threatening infusion reactions and notes an increased risk of thyroid cancer, melanoma and lymphoproliferative disorders. • Only available under the LEMTRADA REMS program^b • Pregnancy Category C 	<ul style="list-style-type: none"> • Cardiotoxicity increases with cumulative dose • Patients should be monitored for evidence of cardiotoxicity prior to each dose, and total cumulative lifetime dose is not to exceed 140 mg/m² • Pregnancy Category: D 	<ul style="list-style-type: none"> • Only available under TOUCH™ Prescribing Program • Patients are monitored for signs and symptoms of PML prior to each infusion and for infusion-related reactions during drug administration; follow-up visits 3 months after first infusion and 6 months thereafter with TOUCH prescriber^c • Laboratory monitoring • JCV antibody prior to initiating treatment and every 6 months if negative • Pregnancy Category: C
Common Side Effects	<ul style="list-style-type: none"> • Rash • Headache • Pyrexia • Nasopharyngitis • Nausea • Urinary tract infection • Fatigue • Insomnia • Upper respiratory infection • Herpes viral infection • Urticarial • Pruritus • Thyroid gland disorders • Fungal infection • Arthralgia • Pain in back or extremity • Diarrhea • Sinusitis • Oropharyngeal pain • Paresthesia • Dizziness • Abdominal pain • Flushing • Vomiting 	<ul style="list-style-type: none"> • Cardiotoxicity • AML • Alopecia • Upper respiratory tract infection • Increased fatigue • Nausea • Menstrual irregularities • Urinary tract infection 	<ul style="list-style-type: none"> • Hypersensitivity reactions and anaphylaxis; increased lymphocyte, monocyte, and eosinophil counts • Urinary tract infection • Liver injury • PML (rare)

Appendix 3: Key Features of the Disease-Modifying Agents, Oral Therapies¹⁻¹⁰

Agent (Brand Name)	Dimethyl Fumarate (Tecfidera®)	Fingolimod (Gilenya®)	Teriflunomide (Aubagio®)
Description	<ul style="list-style-type: none"> Mechanism of action is unknown. It has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway. The Nrf2 pathway is involved in the cellular response to oxidative stress.¹⁰ 	<ul style="list-style-type: none"> Binds to the sphingosine-1-phosphate receptor, or S1P receptor, on immune cells, including T-cells and B-cells. Induces immune cells to remain in lymph nodes, inhibiting them from migrating into the brain and spinal cord. 	<ul style="list-style-type: none"> Inhibits proliferation of stimulated T- and B-lymphocytes. Selectively and reversibly inhibits dihydroorotate dehydrogenase (DHODH), which diminishes the number of activated T- and B-cells available to migrate into the CNS. Basic functions of resting lymphocytes preserved. Normal immune surveillance maintained.
Indication^a (United States)	Relapsing forms of MS, including RRMS to reduce measures of disease activity including relapses and brain lesions, and to slow disability progression.	To reduce the frequency of clinical relapses and delay the accumulation of physical disability in relapsing forms of MS.	For the treatment of relapsing forms of MS.
Dosage/ Route/ Administration	Starting dose: 120 mg twice a day, orally, for 7 days; after 7 days, 240 mg twice a day, orally	0.5 mg once daily, orally	7 mg or 14 mg once daily, orally
Considerations	<ul style="list-style-type: none"> Obtain CBC within six months of starting therapy; CBC recommended annually. May decrease lymphocyte counts; may cause flushing and diarrhea Pregnancy Category: C 	<ul style="list-style-type: none"> Requires at least six hours of monitoring after the first-dose. Caution should be used in patients who may be at risk of developing bradycardia or heart blocks, macular edema, active infections, hypertension, hepatic dysfunction and respiratory disorders. Pregnancy Category: C 	<ul style="list-style-type: none"> Six months before starting therapy, obtain serum transaminase and bilirubin levels. Recommendations include monitoring ALT levels at least once a month for six months after initiating therapy. Obtain CBC within six months before start of therapy. Before starting therapy, screen patients with tuberculin skin test. Monitor blood pressure before start of therapy and continue monitoring periodically. Boxed warning indicates that severe liver injury may occur and there is a risk of teratogenicity. Pregnancy Category: X
Common Side Effects	<ul style="list-style-type: none"> Flushing Headaches GI symptoms (abdominal pain, nausea, vomiting, diarrhea) Dose-related elevations in liver enzymes 	<ul style="list-style-type: none"> Risk of infection (herpes virus infections; lower respiratory tract infections) Hypertension Macular edema Changes in pulmonary function Elevation in liver enzymes Alterations in blood pressure Lymphopenia Possible malignancies (e.g. skin cancer) 	<ul style="list-style-type: none"> Diarrhea Nausea Dyspepsia Increased liver enzymes Alopecia Skin rashes Infections Neutropenia Paresthesia Hypertension

NOTES - Appendix 3

ALT, serum alanine aminotransferase; CBC, Complete blood count; CNS, Central Nervous System.

Notes:

^a Dimethyl fumarate, fingolimod, and teriflunomide are approved for use in the US and Canada.

REFERENCES - Appendix 3

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4. Gilenya®. National MS Society website. <http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya>. Accessed: May 18, 2015.
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6. Gold R, Wolinsky JS. Pathophysiology of multiple sclerosis and the place of teriflunomide. *Acta Neurol Scand*. 2011;124(2):75–84.
7. Saidha S, Eckstein C, Calabresi PA. New and emerging disease modifying therapies for multiple sclerosis. *Ann N Y Acad Sci*. 2012;1247:117–137.
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9. Tecfidera®. National MS Society website. <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/medications/tecfidera/index.aspx>. Accessed: May, 18, 2015.
10. TECFIDERA® (dimethyl fumarate) [Prescribing information]. Cambridge, MA: Biogen Inc.; 4/2015. <http://www.tecfidera.com/pdfs/full-prescribing-information.pdf>. Accessed: May, 18, 2015.

Note to Readers: The information in Appendices 1, 2, 3 is current as of May, 2015. Please check the CMSC website at www.ms-care.org for the most up-to-date information on disease-modifying therapies for multiple sclerosis.

Appendix 4: Symptoms of Multiple Sclerosis ¹⁻⁵

Symptom ^a	Description	Pharmacologic Intervention	Rehabilitation Strategy	Psychosocial Support ^b
Fatigue	<ul style="list-style-type: none"> • “A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities”⁶ • The most common MS symptom • Includes physical lassitude, deconditioning, sleep difficulties, pain, depression, other 	<ul style="list-style-type: none"> • Medications including methylphenidate, aminopyridine, amantadine, modafinil, SSRI and other antidepressants 	<ul style="list-style-type: none"> • Exercise • Energy conservation • Use of assistive devices • Cooling techniques • Address secondary causes • Task analysis and modification 	<ul style="list-style-type: none"> • Stress management, social support, education
Pain	<ul style="list-style-type: none"> • A common symptom of MS • Complex, multifactorial, sensory phenomenon • Includes extremity pain, Lhermitte’s sign, trigeminal neuralgia, tonic spasms, low back pain, muscle spasms, headache⁷ 	<p>For trigeminal neuralgia, treatment may include IV or oral steroids in acute phase; anticonvulsants in chronic phase</p> <p>For painful tonic spasms, treatment consists of antispasticity medications and anti-convulsants.</p> <p>Lightning-like pain may be treated with carbamazepine, gabapentin and phenytoin.</p> <p>Lhermitte’s sign responds to carbamazepine, gabapentin and phenytoin antidepressant agents</p> <p>Headache when associated with relapse may respond to treatment with steroids</p> <p>Common medications include phenytoin, gabapentin, carbamazepine, clonazepam, baclofen, misoprostol, tramadol, topiramate, tizanidine</p>	<ul style="list-style-type: none"> • PT and OT • Stretching for spasticity • Massage • CAM • Cooling • Guided imagery • Chronic pain management program 	<ul style="list-style-type: none"> • Stress management, social support, education
Cognitive Impairment	<ul style="list-style-type: none"> • Includes processing speed, attention, memory, executive functioning, visual-spatial reasoning, verbal fluency ^{5,8} 	<ul style="list-style-type: none"> • Possible benefit from DMTs • Attention enhancing medications (modafinil, armodafinil, amphetamine type medication) • Adjust medications, treat other illnesses, treat depression, pain, fatigue⁹ 	<ul style="list-style-type: none"> • Cognitive rehabilitation, coping and compensatory strategies • PT, OT, exercise⁵ • Safety, Medication management, Financial management, etc 	<ul style="list-style-type: none"> • Referral to neuropsychologist for counseling, OT for cognitive rehabilitation, psychotherapy or CBT
Emotional Disorders	<ul style="list-style-type: none"> • Disorders include depression, anxiety, suicidality, pseudobulbar affect (PBA) 	<ul style="list-style-type: none"> • Medications including tricyclic antidepressants, mood stabilizing agents (divalproex sodium, lithium carbonate), SSRIs • Treatment for PBA: dextromethorphan hydrobromide and quinidine sulfate 	<ul style="list-style-type: none"> • Developing support systems, improving socialization skills, decreasing loneliness and social isolation 	<ul style="list-style-type: none"> • Supportive, therapeutic environment • Counseling and emotional support • Psychotherapy • Support groups • Be alert for suicidal ideation/ plan

Appendix 4: Symptoms of Multiple Sclerosis (cont'd.) ¹⁻⁵

Symptom ^a	Description	Pharmacologic Intervention	Rehabilitation Strategy	Psychosocial Support ^b
Sensory	<ul style="list-style-type: none"> Less common symptom May include pins-and-needles sensations, tingling, numbness or an itch, tightness, crawling skin sensation 	<ul style="list-style-type: none"> These sensations may cause neuropathic pain which may be treated with gabapentin, pregabalin, carbamazepine, tiopirimate, oxcarbazepine 	<ul style="list-style-type: none"> Safety Task modification Assistive devices 	<ul style="list-style-type: none"> Stress management, social support, education
Spasticity	<ul style="list-style-type: none"> Common symptom Stiffness and spasms are common in quadriceps, hamstrings, gastrocnemius muscles May worsen during an exacerbation, underlying infection and with noxious stimuli 	Medications may include baclofen, tizanidine, clonazepam, diazepam, gabapentin, intrathecal baclofen	<ul style="list-style-type: none"> Referral to physiatrist, PT, and/or OT avoid secondary complications, prevent or treat contractures, reduce muscle hypertonia, improve posture, maximize function stretching, exercise and mechanical aids orthotics relaxation techniques 	<ul style="list-style-type: none"> Stress management, social support, education
Tremor	<ul style="list-style-type: none"> Less common symptom Primary symptom caused by MS lesions in cerebellum and its pathways Can affect head, limbs, trunk, eye movements, and speech Titubation 	<ul style="list-style-type: none"> Clonazepam, gabapentin, primidone, propranolol, levetiracetam, topiramate Medication may be sedating and may have limited effect 	<ul style="list-style-type: none"> PT and OT may help but do not correct the underlying problem Proximal stability, self-care strategies, weight-bearing activities, weighting, coordination exercises 	<ul style="list-style-type: none"> Stress management, social support, education
Coordination (ataxia)	<ul style="list-style-type: none"> Less common symptom Disorganized, unsteady, or inaccurate movements² 	<ul style="list-style-type: none"> Medication may be sedating and may have limited effect 	<ul style="list-style-type: none"> Referral to physiatrist, PT, and/or OT 	<ul style="list-style-type: none"> Stress management, social support, education
Weakness	<ul style="list-style-type: none"> Less common symptom Loss of strength in a muscle or group of muscles³ 	<ul style="list-style-type: none"> Medication may be sedating and may have limited effect 	<ul style="list-style-type: none"> Referral to physiatrist, PT, and/or OT i.e. strengthening programs, compensatory skills. Task modification 	<ul style="list-style-type: none"> Stress management, social support, education
Ambulatory Dysfunction	<ul style="list-style-type: none"> Common symptom Movement impairment or difficulty walking³ 	<ul style="list-style-type: none"> Dalfampridine Surgical intervention may be considered 	<ul style="list-style-type: none"> Referral to physiatrist, PT, and/or OT Assistive devices, orthoses, adaptive equipment Exercise 	<ul style="list-style-type: none"> Stress management, social support, education

Appendix 4: Symptoms of Multiple Sclerosis (cont'd.) ¹⁻⁵

Symptom ^a	Description	Pharmacologic Intervention	Rehabilitation Strategy	Psychosocial Support ^b
Balance	<ul style="list-style-type: none"> • Less common symptom • Balance is need to accomplish coordinated movement when standing, sitting or lying down • Balance involves the cerebellum, eyes, ears, nerves of the arms and legs³ 		<ul style="list-style-type: none"> • Referral to physiatrist, PT, and/or OT • Gait and balance training • Orthotics if needed • Safety 	<ul style="list-style-type: none"> • Stress management, social support, education
Visual Impairment	<ul style="list-style-type: none"> • Common symptom • Acuity – central vs. peripheral • Eye mobility (diplopia, nystagmus, optic neuritis)² 		<ul style="list-style-type: none"> • OT, vision rehab, specialty places such as Lighthouse for the blind (location specific) 	<ul style="list-style-type: none"> • Stress management, social support, education
Bladder Dysfunction	<ul style="list-style-type: none"> • Common symptom • Symptoms of neurogenic bladder include urgency, frequency, incontinence, hesitancy, incomplete emptying, nocturia, UTI, dysuria • Prevention of secondary symptoms: avoid UTI and reflux by effective bladder emptying¹⁰ 	<ul style="list-style-type: none"> • For inability to store: anticholinergic/antimuscarinic agents (oxybutynin, tolterodine, solifenacin succinate, darifenacin, fesoterodine fumarate, mirabegron) • For inability to empty: alpha blockers (tamsulosin, doxazosin), anti-spasticity agents/nerve blocks¹⁰ 	<ul style="list-style-type: none"> • Treatment for inability to store: limit fluid intake; frequent bathroom breaks; easy access to bathroom; protective pads; avoid bladder irritants (caffeine, aspartame, alcohol, smoking); • Treatment for inability to empty: adequate fluid intake (48-64 oz/day), timed voiding, intermittent catheterization or indwelling catheter • Scheduling bathroom breaks¹⁰ 	<ul style="list-style-type: none"> • Stress management, social support, education
Bowel Dysfunction	<ul style="list-style-type: none"> • Common symptom • Common symptoms include constipation, diarrhea, incontinence • Symptoms may be intermittent or constant • Symptoms can occur at any time in the disease¹⁰ 	<ul style="list-style-type: none"> • For constipation: bulk forming agents, stool softeners/ • Stimulants, laxatives/enemas, suppositories • For bowel incontinence: medications, suppositories 	<ul style="list-style-type: none"> • Bowel training/ dietary modification recommended for all bowel dysfunction • For constipation: fluids 1.5-2 quarts/day, 20-30g daily fiber, exercise • For bowel incontinence: bowel training, timed evacuations 	<ul style="list-style-type: none"> • Stress management, social support, education

Appendix 4: Symptoms of Multiple Sclerosis (cont'd.) ¹⁻⁵

Symptom ^a	Description	Pharmacologic Intervention	Rehabilitation Strategy	Psychosocial Support ^b
Dysarthria and Dysphagia	<ul style="list-style-type: none"> • Less common symptom • Three types of dysarthria include spastic, ataxic, mixed • Dysphagia may involve a delay in triggering swallow, difficulty with thin liquids, reduced tongue coordination, possible esophageal involvement, aversion to foods because of altered taste sensations 	<ul style="list-style-type: none"> • Treatment of dysarthria may involve management of spasticity and tremor 	<ul style="list-style-type: none"> • Refer to SLT for dysarthria when speech and voice interfere with daily communication, patients quality of life and are viewed as troublesome by patient and family • Refer to SLT for dysphagia to change posture, control volume and speed of eating, education on swallowing and eating small meals more frequently 	<ul style="list-style-type: none"> • Stress management, social support, education
Sexual Dysfunction	<ul style="list-style-type: none"> • Common symptom • Primary^a sexual dysfunction may occur as a result of MS-related physiologic changes in the CNS; primary symptoms may include genital numbness, paresthasias, erectile dysfunction, vaginal dryness, retrograde ejaculation, pain, anorgasmia or reduced libido • Secondary^a dysfunction occurs as a result of MS-related physical changes or therapies that indirectly affect sexual functioning; secondary symptoms include lesions and interference with or without pain or spasticity in non-genital areas • Tertiary^a dysfunction is related to psychological, social, cultural issues that interfere with sexual response; this may include depression, grief, self-image, role changes in family or society, anger, guilt, spousal burden. 	<ul style="list-style-type: none"> • Bupropion for decreased libido and decreased orgasm • Sildenafil, vardenafil, tadalafil for erectile dysfunction • Estrogens for vaginal dryness and clitoral sensitivity • Treat underlying symptoms/ secondary dysfunction (spasticity, fatigue, paresthasias, bladder/ bowel) 	<ul style="list-style-type: none"> • Lifestyle changes • Positioning • Lubrication • Assistive devices 	<ul style="list-style-type: none"> • Counseling of patient and family • Include culturally sensitive interventions • May involve grief counseling

NOTES - Appendix 4

Complementary and alternative medicine (CAM); Cognitive behavioral therapy (CBT); Central Nervous System (CNS); Disease Modifying therapy (DMT), Multiple Sclerosis (MS), Occupational therapy (OT), Physical therapy (PT), Speech and language therapy (SLT), Selective Serotonin Reuptake Inhibitor (SSRI), Urinary tract infections (UTI).

^aEach symptom may be a primary, secondary, or tertiary symptom. Primary symptoms are directly related to MS, demyelination and axonal loss (weakness or vision loss). Secondary symptoms are the result of primary symptoms (urinary tract infection resulting from urinary retention). Tertiary symptoms are the result of social and psychological effects of MS (depression or social isolation may occur as a result of bladder or bowel dysfunction).^{1,3}

^bPsychosocial management of each symptom is vital to comprehensive care. Proper support systems and education help to mitigate the effects of these symptoms.¹¹

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