Early Recognition and Intervention in MS: A Continuum of Care Model

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Learning Goals

- **Recognize the neurological symptoms that should raise clinical suspicion of a diagnosis of multiple sclerosis.**
- **Initiate prompt referral to a neurologist in patients presenting with symptoms that may be indicative of a diagnosis of multiple sclerosis.**
- **Establish a communication strategy with the treating neurologist to discuss treatment, side effects, and barriers to adherence in patients with multiple sclerosis.**

Aaron Boster, MD

Disclosures

- ***Research/Grants:*** **Actelion Pharmaceuticals Ltd; Biogen Idec; EMD Serono, Inc.; Jazz Pharmaceuticals, Inc.; National Institutes of Health (NIH); National Multiple Sclerosis Society; Questcor Pharmaceuticals, Inc.; Roche**
- ***Consultant:*** **Biogen Idec, Inc.; Genzyme Corporation; Medtronic, Inc.: Novartis Pharmaceuticals Corporation; Questcor Pharmaceuticals, Inc.; Teva Pharmaceuticals**

Jacqueline Nicholas, MD, MPH
Disclosures

- Research Funding: National Multiple Sclerosis Society, Biogen Idec, NIH, Actellion, Malenkroft, Roche, Novartis
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- CME: Peer View Institute University of Florida, Peer View Penn State College of Medicine, Prime-Med

What Is Multiple Sclerosis?

- A chronic, inflammatory, demyelinating disorder of the central nervous system of uncertain etiology, likely autoimmune, associated with destruction of myelin sheaths and axons

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.

Ideal Management of Multiple Sclerosis

- **As a dynamic disease, multiple sclerosis (MS) requires a multitude of healthcare providers with various expertise to help patients throughout their lives.**
- **"In an ideal [patient-centered medical home], a patient with MS would receive both primary care and specialty care at the appropriate time, moving seamlessly between providers who communicate with each other and the patient."**

Wallin MT. *J Rehabil Res Dev* 2010;47:ix-xiv.

Sources of MS Care[a]

Provider	Number (%)
Neurologist[a]	1,510 (72.2)
Primary care physician	362 (19.6)
Another physician	76 (3.7)
Nurse	15 (.07)
Unknown or nonmedical provider	71 (3.4)
No MS care	22 (1)

[a]Data from 2056 participants in the Sonya Slifka Longitudinal Multiple Sclerosis Study
[b]Includes MS specialist, neurology clinic, MS clinic

Minden SL, et al. *Neurology* 2008;70:1141-9.

Initial Presentation to the Primary Care Provider

Susan F.

- **29-year-old woman from Iowa**
- **Right eye**
  - **Blurred vision**
  - **Pain with extraocular movement**
- **Denies history of similar symptoms**
- **Recalls 1-week episode of left-arm paresthesias 10 years ago that resolved spontaneously**

Photo: CDC/ Amanda Mills

MS Presentation

Common Initial Presentation of MS

Optic neuritis	Lhermitte sign
Subacute onset of unilateral vision loss	Pathologic fatigue
Pain with extraocular movements	Heat intolerance (Uhthoff phenomenon)
Transverse myelitis	
Bilateral leg numbness, weakness, and tingling (could be asymmetric)	
Bowel and bladder dysfunction	

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.

Presentation of MS on Neurologic Examination

Upper motor neuron syndrome
Weakness
Hyperreflexia
Spasticity
Clonus
Babinski sign
Brainstem syndromes
Dysfunction of cranial nerves or cerebellar connections
Diplopia
Internuclear ophthalmoplegia
Vertigo
Dysarthria
Dysphagia
Incoordination
Poor balance

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.

Presentation of MS on Ophthalmologic Examination

Pale optic disk
Poor visual acuity
Pain with extraoccular movement
Relative afferent pupillary defect
Red color desaturation
Internuclear ophthalmoplegia

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.

Red Flags That the Diagnosis Is Likely not MS

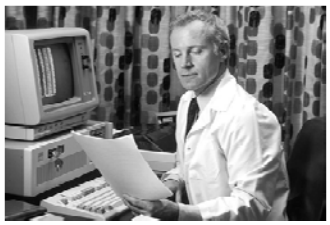
Acute onset of symptoms
Age, years
< 10
> 50
Altered level of consciousness
Aphasia
Apraxia
Fasciculations
Parkinsonism
Peripheral neuropathy
Prominent early encephalopathy/dementia

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.

What Are the Next Steps for the Primary Care Provider?

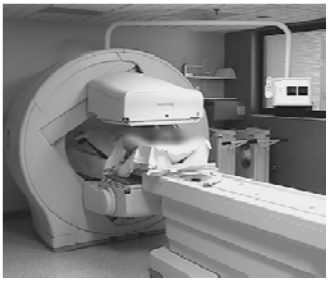
- Recognize that this is likely a demyelinating CNS disorder

Refer?



Photographer: Ernie Branson

Continue work-up?



Referral to the Neurologist

- Susan comes to the neurologist (in this case, an MS specialist) for further workup of her symptoms.

Photo: CDC/ Amanda Mills

The Diagnosis of MS Key Factors
Exclude alternative etiologies

MS Differential Diagnosis

- **Metabolic: SCD (B_{12} deficiency),**
- **Connective tissue diseases: Sjögren syndrome, SLE**
- **Infectious: HIV, HTLV1, Lyme disease, syphilis**
- **Structural: Chiari malformation, spinal cord compression**

Genetic: ataxias, paraplegias, mitochondrial disorders, adrenomyeloneuropathy

Neoplastic: CNS lymphoma, paraneoplastic disease

"MS variants": ON, TM, ADEM, NMO

Other: neurosarcoidosis, CNS vasculitis

Psychiatric

SCD = subacute combined degeneration of the spinal cord; SLE = systemic lupus erythematosus; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus; CNS = central nervous system; ON = optic neuritis; TM = transverse myelitis; ADEM = acute disseminated encephalomyelitis; NMO = neuromyelitis optica

Trojano M, et al. *Neurol Sci*. 2001;22 Suppl 2:S98-102.

Laboratory Studies to Rule Out Other Disorders in the Differential

- B_{12} levels
- Rapid plasma regain or fluorescent treponemal antibody
- Antibody confirmation
  - HIV
  - HTLV-1
- Extractable nuclear antigens panel

Maloni HW. *Nurse Pract* 2013;38:24-35..

Laboratory Studies to Rule Out Other Disorders in the Differential

- Antinuclear antibody panel
- Antiphospholipid antibodies
- Erythrocyte sedimentation rate
- C-reactive protein
- Thyroid function
- Long-chain fatty acids
- Lyme titer

Maloni HW. *Nurse Pract* 2013;38:24-35..

The Diagnosis of MS Key Factors
MRI Findings

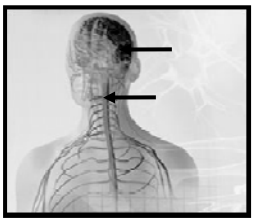
MS Diagnostic Criteria

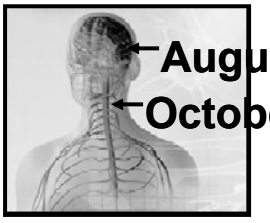
- Dawson criteria: 1916
- Schumacher criteria: 1965
- Poser criteria: 1983
- McDonald criteria: 2001
- Revised McDonald criteria: 2010
- All criteria require:
  - Dissemination in space and time
  - No better explanation

Polman CH, et al. *Ann Neurol* 2011;69:292-302.

Dissemination in Space and Time

1. **Dissemination in space: Objective evidence of neurologic deficits localized to 2 separate parts of the CNS**
2. **Dissemination in Time: Onset of neurologic deficits separated by at least 1month**
3. **Rule out other explanations!**

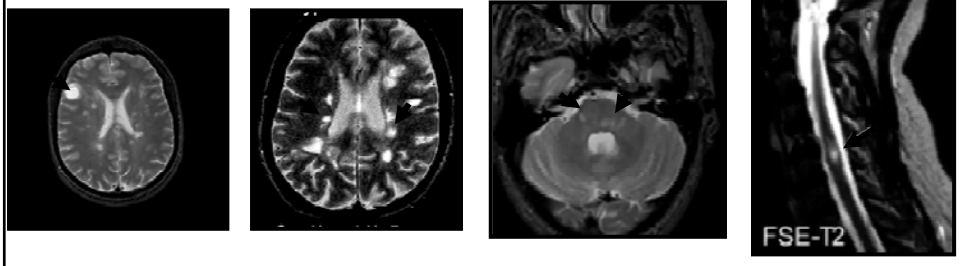




Polman CH, et al. *Ann Neurol* 2011;69:292-302.

Dissemination in Space

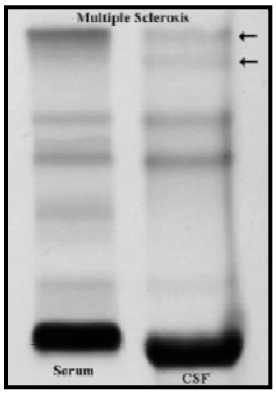
- **At least 1 asymptomatic T2 lesion in at least 2 of 4 locations**



Swanton JK, et al. *Lancet Neurol* 2007;6:677-86.

CSF Analysis

Most helpful for suggesting an alternative diagnosis

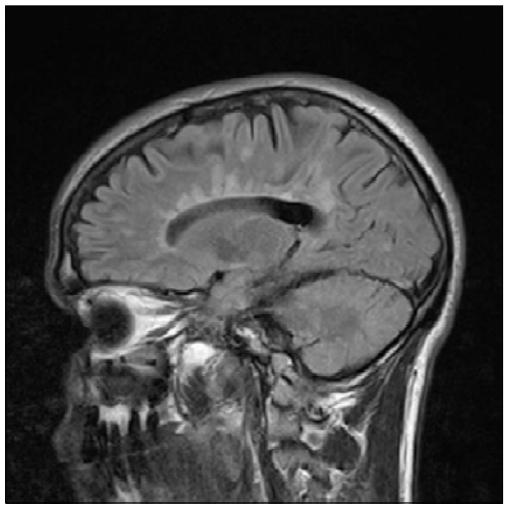


- **High protein, marked pleocytosis, PMNs**
- **Elevated IgG Index ≥ 0.7**
  - **Increased CNS IgG synthesis with normal serum IgG *is consistent with MS***
- **Oligoclonal bands**
  - **Presence of ≥ 2 distinct bands in CSF and none in serum *is consistent with MS***

CSF = cerebrospinal fluid; PMN = polymorphoneuclearcytes; IgG = immunoglobulin G

Petzold A. *J Neuroimmunol* 2013;262:1-10.

Susan's MRI Findings



MS Treatment

FDA-Approved Treatments for MS

Disease-modifying Therapy: Injectable

Generic name	Trade Name	Laboratory Assessments	Side Effects
Interferon β-1a	Avonex	Check LFTs and CBC quarterly or every 6 months	Flu-like symptoms Liver dysfunction Bone marrow suppression Other Endocrine abnormalities Depression Spasticity Headaches
	Rebif	Check LFTs and CBC quarterly or every 6 months	

LFT = liver function tests; CBC = complete blood count

FDA-Approved Treatments for MS

Disease-modifying Therapy: Injectable

Generic name	Trade Name	Laboratory Assessments	Side Effects
Interferon β-1b	Betaseron	Check LFTs and CBC quarterly or every 6 months	Flu-like symptoms Liver dysfunction Bone marrow suppression Other Endocrine abnormalities Depression Spasticity Headaches
	Extavia	Check LFTs and CBC quarterly or every 6 months	
Glatimer acetate	Copaxone		Injection site reactions Idiopathic injection reactions Lipoatrophy

LFT = liver function tests; CBC = complete blood count

FDA-Approved Treatments for MS

Disease-modifying Therapy: Infusion

Generic name	Trade Name	Laboratory Assessments	Side Effects
Mitoxantrone	Novantrone	This drug is rarely used because of adverse effects	Treatment-related acute leukemia (1/100) Cardiotoxicity
Natalizumab	Tysabri	Check JC virus antibody status every 3-4 months	Infusion reactions PML Other infections

PML = Progressive multifocal leukoencephalopathy

FDA-Approved Treatments for MS

Disease-modifying Therapy: Oral

Generic name	Trade Name	Laboratory Assessments	Side Effects
Fingolimod	Gilenya	ECG, VZV titer, LFTs, and ophthalmologic exam[a] before beginning treatment. Biannual LFTs and ophthalmologic exam.	Macular edema Transient bradycardia Liver dysfunction
Teriflunomide	Aubagio	Pregnancy test and TB skin test before beginning treatment. Monthly LFTs for 6 months and then every 3 to 6 months	Teratogenicity Transient alopecia
Dimethyl fumarate (BG-12)	Tecfidera	Annual CBC	Facial flushing Gastrointestinal side effects

[a]To check for macular edema. ECG = electrocardiogram; VZV = varicella zoster virus; LFTs = liver function tests; TBC = tuberculosis; CBC = complete blood count

FDA-Approved Treatments for MS

Symptomatic Therapy

Generic name	Trade name	Indication
Dalfampridine	Ampyra	To improve walking in patients with MS
OnabotulinumtoxinA	Botox	Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication

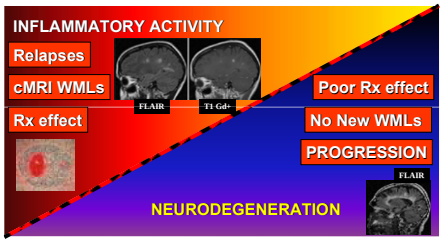
Disease Modifying Therapies: *1993-2002*

	Glatiramer acetate 1997	IFN β-1b 1993	IFN β-1a 2002	IFN β-1a 1996
Type	Polypeptide mixture	Recombinant protein	Recombinant protein	Recombinant protein
Indication	Reduce freq. of relapses in RRMS	Reduce freq. of relapses. Slow disability in relapsing forms	Reduce freq. of relapses. Delay disability in relapsing forms	Slow progression in relapsing forms. Prevent 2nd attack in CIS
Injection	SC	SC	SC	IM
Administration	Daily	Every other day	3x/week	Weekly
Dosage	20 mg	250 μg (8 MIU)	44 μg	30 μg

Freq = frequency; RRMS = relapsing remitting multiple sclerosis; SC, subcutaneous; IM = intramuscular; CIS = clinically isolated syndrome

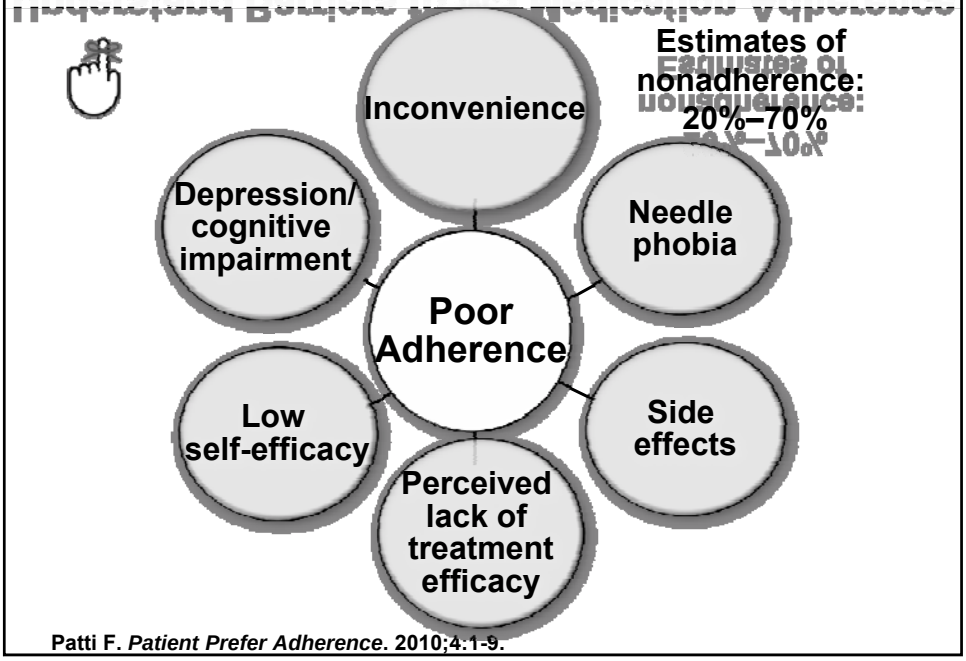
Rationale for Early MS Treatment

- **Permanent tissue damage occurs from recurrent bouts of inflammation, even during the silent periods of so-called remission.**
- **Accumulated disability is at least in part secondary to early active inflammatory disease.**
- **We can treat inflammation!**
- **During later disease stages our treatments are less effective**



WMLs = white matter lesions; RX = treatment

Understand Barriers to MS Medication Adherence



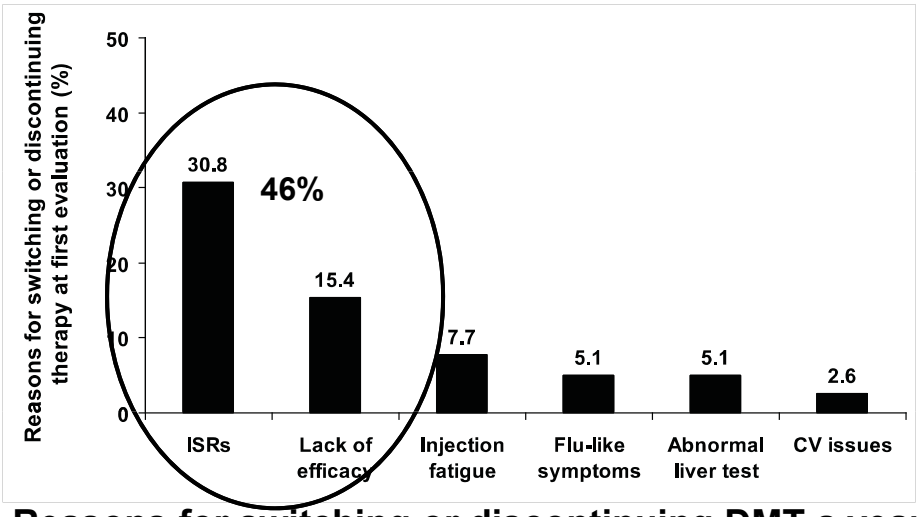
Patti F. *Patient Prefer Adherence*. 2010;4:1-9.

Understand the Challenges to Adherence

- Up to 50% patients discontinue because of side effects or lack of efficacy
- Adherence tends to decrease over time (eg, "treatment fatigue")
- Cognitive and physical limitations negatively impact adherence
- Comorbid depression carries a 3-fold risk of nonadherence
- Reimbursement challenges (eg, formulary changes; copay)

Rio J, et al. *Mult Scler.* 2005;11:306-9; Twork et al. *Curr Med Res Opin.* 2007;23(6):1209-15; O'Rourke KE, et al. *Mult Scler.* 2005;11(1):46-50; Ross AP. *Neurology.* 2008;71(Suppl 3):S1-2; DiMatteo MR, et al. *Arch Intern Med.* 2000;160:2101-7.

Understand Why Patients Discontinue DMT

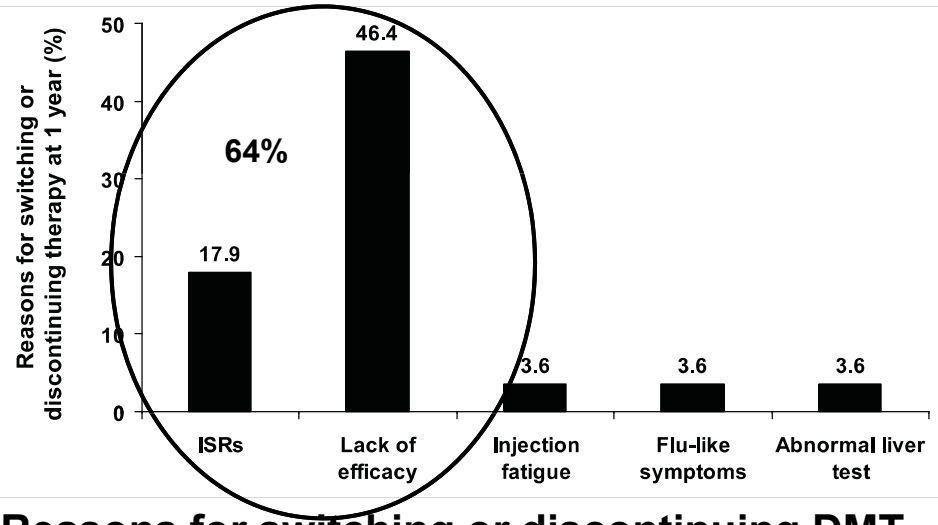


Reasons for switching or discontinuing DMT a year after the above assessment

Beer K, et al. *BMC Neurology* 2011;11:144

DMT = disease-modifying therapy; ISRs = injection site reactions

Understand Why Patients Discontinue DMT



Reasons for switching or discontinuing DMT after patient on therapy for ≥ 2 years

Beer K, et al. *BMC Neurology* 2011;11:144

DMT = disease-modifying therapy; ISRs = injection site reactions

Ongoing Communication

Referrals and Communication

- Referrals
- Team members
- Communication with PCP
  - Summarize my findings
  - Provide feedback
  - Identify laboratory tests that the PCP could monitor

Photographer: Ernie Branson

Key Points Regarding Treatment

- Biggest point is adherence
  - "Are you taking your drug?"
- Safety monitoring
  - "Are you being safe about taking your drug?"
  - "Are you having your labs checked?"
  - "Are you having your eye exams?"

PCP Role in the Treatment of MS

- Keep the patient safe
  - Monitor results of recommended laboratory studies
- Identify local resources
  - Social support
  - Community resources
  - Neurologic-specific physical therapy
- Facilitate ADHERENCE

Improving Adherence

General Counseling

- **Stress adherence**
  - **Patients must immediately report significant changes**
  - **Foster realistic expectations**
    - **Expected attack rate: 1 every 3-5 years**
    - **Treatments are not curative**
      - **Cannot stop disability**
      - **Cannot repair existing damage**

International Working Group for Treatment Optimization in MS. *Eur J Neurol*. 2004;11:43-7.

PCP Role in the Treatment of MS

- **Encourage smoking cessation[a]**
- **Discuss increased risk for osteopenia[a]**
  - **Monitor bone density**
  - **Provide osteopenia prophylaxis**
- **Screen for depression, cognitive status, and fatigue on a routine basis**
  - **Beck Depression Inventory**
  - **Multiple Sclerosis Neuropsychological Questionnaire**
  - **Modified Fatigue Impact Scale**

[a]Smoking and vitamin D levels are the only currently identified modifiable risk factors to decrease the risk of developing MS and to decrease the severity of MS symptoms.

Ascherio A, Munger KL. *Ann Neurol* 2007;61:504-13.

Follow-up Primary Care Visit

- Nine months after initial diagnosis
- Prescribed DMT, which she administers via subcutaneous injection
- Being seen for annual exam
- Reports tingling sensation in her left hand
- You determine that "*something ain't right*" (SAR)
- Is this a relapse of her MS?

PCP Role in Identification of MS Relapse

- *CRITICAL*, compare with previous examinations (history and examination), whenever possible
- Be aware that relapse may be precipitated by heat, infection, and stress
  - Check urinalysis for occult urinary tract infection
- Evaluate adherence with MS treatment
  - Reinforce importance of adherence

CDC/ Doug Jordan, M.A.

CC By 2.0 aloha_pineapple – Flickr

Follow-up Visit: When SAR

Susan reports

- Adherence with injections
- No recent
  - Infection
  - Obvious physiologic or psychological stress
  - Heat exposure
- You refer her back to Dr. Boster

Photo: CDC/ Amanda Mills

Key Points

1. MS is the most common cause of neurologic disability among young adults in the US.
2. MS today is a completely different animal than it was 10 years ago.
3. Early diagnosis leads to early treatment, which has shown better outcome.

Key Points

4. **Help keep your patients with MS on their prescribed medicine and keep them safe.**
5. **Smoking is particularly bad for people with MS.**
6. **It takes a team to treat MS – the neurologist and PCP working together can provide the best care possible.**

Appendix

FDA-Approved Treatments for MS

Disease-modifying Therapy: Injectable

Generic name	Trade Name	Link to PDR.net
Interferon β-1a	Avonex	http://www.pdr.net/drug-summary/avonex?druglabelid=1623&id=255
	Rebif	http://www.pdr.net/drug-summary/rebif?druglabelid=146
Interferon β-1b	Betaseron	http://www.pdr.net/drug-summary/betaseron?druglabelid=1316
	Extavia	http://www.pdr.net/full-prescribing-information/extavia?druglabelid=428
Glatimer acetate	Copaxone	http://www.pdr.net/full-prescribing-information/copaxone?druglabelid=568

FDA-Approved Treatments for MS

Disease-modifying Therapy: Infusion

Generic name	Trade Name	Link to PDR.net
Mitoxantrone	Novantrone	http://www.pdr.net/drug-summary/mitoxantrone?druglabelid=2630
Natalizumab	Tysabri	http://www.pdr.net/drug-summary/tysabri?druglabelid=2802

FDA-Approved Treatments for MS
Disease-modifying Therapy: Oral

Generic name	Trade Name	Link to PDR.net
Fingolimod	Gilenya	http://www.pdr.net/full-prescribing-information/gilenya?druglabelid=432
Teriflunomide	Aubagio	http://www.pdr.net/drug-summary/aubagio?druglabelid=2614
Dimethyl fumarate (BG-12)	Tecfidera	http://www.pdr.net/drug-summary/tecfidera?druglabelid=3095

FDA-Approved Treatments for MS
Symptomatic Therapy

Generic name	Trade name	Link to PDR.net
Dalfampridine	Ampyra	http://www.pdr.net/drug-summary/ampyra?druglabelid=1227
OnabotulinumtoxinA	Botox	http://www.pdr.net/drug-summary/botox?druglabelid=52