Overview of New Medications for Multiple Sclerosis

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Conflict of Interest Declaration

- I or my spouse have no actual or potential conflict of interest in relation to this activity.

Assessment Question

1. Which classification of MS responds to currently available disease modifying therapies which prevent new attacks and stabilize EDSS score?
   a. RRMS – Relapsing-Remitting MS
   b. SPMS – Secondarily Progressive MS
   c. PPMS – Primary Progressive MS
   d. PRMS – Progressive Relapsing MS

Assessment Question

2. Which of the following parameters must be closely monitored during the first 6 hours after initiation of Gilenya?
   a. Blood Pressure
   b. Heart Rate
   c. Hepatic Function
   d. Vision

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3. Which of the following should be monitored for efficacy of Ampyra?
   a. Expanded Disability Status Scale
   b. Brain MRI
   c. Timed 25-foot Walk
   d. Clinical report of relapse

Objectives

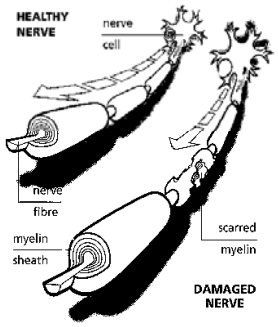
- Describe the etiology of multiple sclerosis (MS)
- Recognize new treatment options for MS

Pathophysiology of MS

- An autoimmune disorder with both environmental and genetic predispositions[1]
- Possible viral or bacterial infection link
- Dual nature[1]
  - Inflammatory
  - Neurodegenerative
    - Demyelination leads to slower nerve conduction
    - Axonal injury is associated with permanent neurologic dysfunction
- Neurologic disability is correlated with atrophy in the spinal cord, cerebellum and cerebral cortex in patients with MS[1]
  - Both gray and white matter brain atrophy are found in patients with MS[2]

1. Trapp BD, et al. *N Engl J Med.* 1998;338:278-285.
2. Zivadinov R, et al. *Mult Scler.* 2007;13:490-501.

Demyelination to Transection of Axon



MS Symptom Presentation

- **VISION CHANGES**
  - **Optic Neuritis**
- **PARESTHESIS**
- Gait changes
- Ataxia
- Pain
- Spasticity
- Weakness
- Speech difficulty
- Psych changes
- Recurrent UTI
- Bowel/bladder dysfunction
- Sexual dysfunction
- Pressure Sores
- Muscle contractures
- Respiratory infections
- Poor nutrition
- Depression
- Cognitive changes
- Fatigue

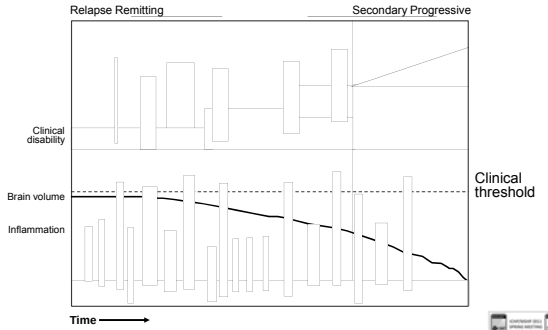
Classifications of MS

- **Relapsing-remitting MS (RRMS)**
  - clearly defined relapses with full recovery
  - or with sequelae and residual deficit upon recovery
  - There is no disease progression between
- **Secondary-progressive MS (SPMS)**
  - initial RR disease course
  - followed by progression with or without occasional relapses, minor remissions, and plateaus.

Classifications of MS

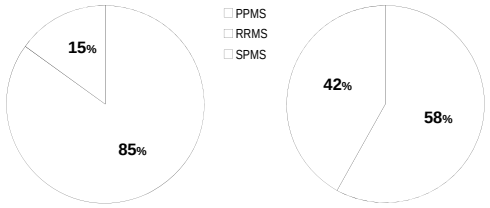
- **Primary-progressive MS (PPMS)**
  - disease progression from onset with occasional plateaus
  - temporary minor improvements allowed
- **Progressive-relapsing MS (PRMS)**
  - characterized by progressive disease from onset
  - clear acute relapses with or without full recovery
  - progression continues during the periods between disease relapses

Disease progression[5]



3. Adapted from Ziemssen T. *J Neurol* 2005;252(suppl 5):V/38-V/45.

Disease type and natural history[4]



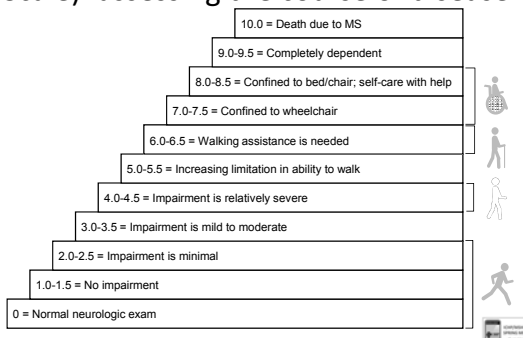
Disease type at diagnosis

Disease type 11-15 years after diagnosis among patients with RRMS at diagnosis

PPMS = primary progressive multiple sclerosis.
RRMS = relapsing-remitting multiple sclerosis.
SPMS = secondary progressive multiple sclerosis.

4. Weinshenker BG, et al. *Brain.* 1989;112:133-146.

The EDSS (Expanded Disability Status Scale): assessing the course of disease[5]

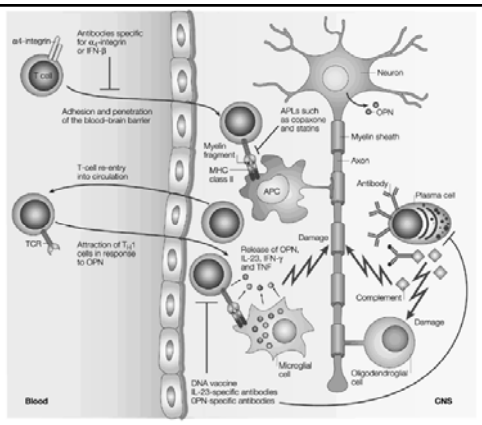


5. Kurtzke JF. *Neurology*. 1983;33:1444-1452.

FDA-approved RRMS therapies[6-12]

Agents	Administration	Cost/Mo
IFNβ-1b (Betaseron®)	SC 250 mcg/q other day[21]	$2519
Low-dose IFNβ-1a (Avonex®)	IM 30 mcg/wk[19]	$1034
High-dose IFNβ-1a (Rebif®)	SC 22 mcg or 44 mcg tiweek[20]	$1869
Glatiramer acetate injection (Copaxone®)	SC 20 mg qday[18]	$3400
Natalizumab (Tysabri®)	IV 300 mg q4wk[22]	$2200 - vial
Mitoxantrone (Novantrone®)	IV 12 mg/m^2 over 5-15 min q3mo[23]	$3000 annually
Fingolimod (Gilenya)	PO 0.5mg qday	$4000

6. Copaxone® prescribing information. Teva Neuroscience, Inc.
7. Avonex® prescribing information. Biogen Idec Inc.
8. Rebif® prescribing information. Biogen Idec Inc.
9. Betaseron® prescribing information. Bayer HealthCare Pharmaceuticals Inc.
10. Tysabri® prescribing information. Biogen Idec Inc.
11. Novantrone® prescribing information. EMD Serono, Inc.
12. Gilenya Prescribing information. Novartis AG, Inc.



Fingolimod (Gilenya)[12]

- FDA approved September 2010
- Indication:
  - RRMS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
- Mechanism of Action:
  - Unknown
  - Sphignosine 1-phosphate receptor modulator
    - Blocks capacity of lymphocytes to move from lymph nodes, reducing the number of lymphocytes in peripheral blood
    - Reduce lymphocyte migration into CNS

12. Gilenya Prescribing information. Novartis AG, Inc.

Gilenya – Clinical Evidence

- Phase III Trials
  - FREEDOMS[13]
  - TRANSFORMS[14]
- Reduce attack rate in RRMS
- Produces benefit on MRI, slows sustained disability progression based on EDSS
- Possible benefit over INFß-1a IM (Avenox)

Before starting Gilenya

- Pregnancy
- Heart Rate – possible EKG
  - Bradycardia
  - AV conduction delay
  - Generally resolves within 24 hrs
- Eye exam
- CBC
- Hepatic function

Gilenya – Dosing

- 0.5mg qday
- Take with or without food
- 6 hour monitoring with 1st dose

Gilenya – Drug interactions

- 1a or Class III Antiarrhythmic drugs
- Ketoconazole (inhibitor)
- Antineoplastic, immunosuppressives, immunomodulating therapy
- HR lowering drugs
- Avoid live attenuated vaccines during & 2mo after

Gilenya - Monitoring

- Observed for 6 hrs after first dose
  - Bradycardia
- Eye exam – 3-4mo after initiation
- CBC – q 3-6 months
- BP/HR – q 3-6 months
- PFT as indicated
- LFT as indicated (3-4mo after initiation)

Dalfampridine (Ampyra)[15, 16]

- FDA approved January 2010
- Indication:
  - Improve walking in patients with MS, based on increased walking speed.
- Mechanism of Action:
  - Broad spectrum potassium channel blocker.
  - Increase conduction of action potentials in demyelinated axons through inhibition of potassium.
  - Demonstrated by an increase in walking speed.

15. Ampyra® prescribing information. Acorda Therapeutics, Inc.
16. Acorda Therapeutics, Inc. Ampryra®. Available at: http://ampyra-hcp.com/hcp/. Accessed March 14, 2011.

Ampyra – Clinical Evidence

- Phase III trials
  - MS-F203[17]
  - MS-F204[18]
- 50% of MS patients responded to therapy
- 2-4 week trial
- Risk evaluation & mitigation strategy (REMS) program

17. Goodman AD, et al. *Lancet.* 2009;373:732–738.
18. Goodman AD, et al. *Ann Neurol* 2010;68:494–502.

Before starting Ampyra

- Seizure history
- Renal function
- Pregnancy (C)/Nursing
- > 18 years old

Ampyra – Dosing

- 10mg BID
- Slow release formulation
- With or without food

Ampyra – Drug Interactions

- None identified

Ampyra - Monitoring

- Renal function
- Walking speed
  - Timed 25-foot Walk (T25W)

Future Therapies

- Mylinax (cladribine): August 2011
  - EMD Serono, an affiliate of Merck
  - 3/11: FDA has requested improved understanding of safety risks & overall benefit-risk profile via additional analyses or studies
  - CLARITY (CLAdRIbine Tablets Treating MS OrallY)[19]
- Laquinimod – Teva Pharmaceutical
- BG-12 – Biogen Idec
- Teriflunomide – Sanofi-Aventis

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4. Weinshenker BG, et al. The natural history of multiple sclerosis: A geographically based study. *Brain.* 1989;112:133-146.
5. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology.* 1983;33:1444-1452.
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9. Betaseron® prescribing information. Bayer HealthCare Pharmaceuticals Inc.
10. Tysabri® prescribing information. Biogen Idec Inc.
11. Novantrone® prescribing information. EMD Serono, Inc.
12. Gilenya® prescribing information. Novartis AG, Inc.
13. Kappos L, et al. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis*New Engl J Med.* 2010; 362: 387- 401.
14. Cohen J, et al. Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. *New Engl J Med.* 2010; 362: 402-415.
15. Ampyra® prescribing information. Acorda Therapeutics, Inc.
16. Acorda Therapeutics, Inc. Ampryra®. Available at: http://ampyra-hcp.com/hcp/. Accessed March 14, 2011.
17. Goodman AD, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet.* 2009;373:732–738.
18. Goodman AD, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010;68:494–502.
19. Giovannoni G, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;362:416-26.