Multiple Sclerosis: More Than Your ABC’s
Janene L. Marshall, PharmD, BCPS
Clinical Associate Professor
Internal Medicine Clinical Pharmacist
Chicago State University College of Pharmacy

Disclosure and Conflict of Interest
Janene Marshall declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

Pharmacist Objectives
At the conclusion of this program, the pharmacist will be able to:
1. Describe the epidemiology and pathophysiology for Multiple Sclerosis
2. List therapeutic options for patients with Multiple Sclerosis
3. Given a patient case provide a pharmaceutical care plan for Multiple Sclerosis patients.
4. Describe the role of the pharmacist for Multiple Sclerosis patients.

Technician Objectives
At the conclusion of this program, the technician will be able to:
1. Describe the epidemiology and pathophysiology for Multiple Sclerosis
2. List therapeutic options for patients with Multiple Sclerosis
3. Describe the role of the pharmacy technician for Multiple Sclerosis patients.

Pretest Question
Which of the following is/are an etiology for MS? Select all that apply.
A. Male
B. Scandinavian descent
C. Epstein Bar Virus
D. Lives below the equator

Pretest Question
Common signs and symptoms for MS include?
Select all that apply
A. fatigue
B. spasticity
C. pseudobulbar affect
D. increased concentration
Pretest Question
JH has progressive relapsing MS. Her main symptom is fatigue. JH comes to you for a recommendation. She states the fatigue is so great she does not want to get up in the morning to go to work. Which of the following is an appropriate recommendation?
A. onabotulinumtoxin A
B. amantadine
C. dalfampridine
D. tolteridine

Pretest Question
A counseling point for patients on interferon therapy may include:
A. pre-treat with acetaminophen to prevent flu-like symptoms
B. Inject in the morning (you should inject in the evening)
C. All of the above
D. None of the above

Pretest Question
In addition to an MRI scan of brain and spine, which of the following tests can be helpful in MS diagnosis?
A. EEG
B. CT of brain
C. CSF analysis
D. ECG

LET’S MEET OUR PATIENTS

Meet VM
VM is a 20 yo Caucasian Female. She is experiencing bilateral vision blurriness.
• PMH: seasonal allergies
• FH: Mother’s sister has Relapsing-remitting MS
• Medications: loratadine 10mg po daily prn
• MRI: 1 plaque in L periventricular matter

Meet JW
JW is a 56 yo AAF. She is experiencing a worsening of her MS symptoms for the past 2 years (limb weakness, vision blurriness, spasticity, and hand tremor)
• PMH: RRMS (diagnosed 15 years ago), HTN, hyperthyroidism
• FH: NC
• Medications: enalapril 10mg po BID, interferon beta 1a 30mcg IM q week, PTU 50mg po TID
• MRI: no new enhancing lesions as compared to previous MRI
MS Epidemiology

- 400,000 affected in the United States — 2.5 million worldwide
- Usually diagnosed between the ages 15-45 years old
- Women are affected more than men by 2:1
- Higher prevalence the greater the distance from the equator
- Occurs more frequently in Caucasians of Scandinavian ancestry
- Inverse relationship between MS risk and 24-hydroxyvitamin D levels proposed

Etiology
Unknown but multifactorial

- Gender: Female sex
- Northern European Origin
- Geography: Northern climate
- Environment
  - Vit D levels
  - Excess body weight
  - Smoking
- Viral Infections
  - Epstein Bar Virus

Vitamin D

- MS occurs less often in regions of the world where exposure to sunlight is high
- Vitamin D reduced an MS-like disease in lab mice
- Three independent studies published in the journal Neurology suggest that higher levels of vitamin D may reduce disease activity in people with MS
- Two of these studies showed conflicting results on a possible interaction between vitamin D levels and treatment with interferon beta.
- These studies add to the rapidly increasing evidence that vitamin D may play a beneficial role in MS.
- An accompanying editorial suggests that, although there is not enough evidence to recommend high doses of vitamin D for people with MS, ensuring that people with MS have sufficient year-round levels of vitamin D should be part of routine care.

Who has Multiple Sclerosis

Assessment Question 1

Which of the following is/are an etiology for MS? Select all that apply.
A. Male
B. Scandinavian descent
C. Epstein Bar Virus
D. Lives below the equator
Feedback: Correct Answer B and C. A-(female>male 2:1) D-(it is those that live above the equator)

What is MS
CNS

- Brain
  - Optic nerve
  - Cerebellum
  - Brainstem
  - Periventricular white matter
- Spinal Cord

Demyelination Mechanisms

Common Early MS Signs/Symptoms

- Visual Dysfunction
  - Optic neuritis
  - Blurry vision
  - Diplopia
- Fatigue
- Sensory dysfunction
- Weakness
- Muscle spasm
- Gait and balance impairment
- Bladder dysfunction
Vision dysfunction

- Eye pain
- Color vision distorted
- Blurry vision
- And/or temporary vision loss

MS and Fatigue

What makes MS fatigue different?
- Usually occurs everyday
- Occurs even with sufficient sleep during the previous night
- Worsens in the late afternoon
- Worsens and is aggravated by heat & humidity
- Generally more severe than normal fatigue
- Interferes with normal daily life (i.e., work, cleaning, cooking, speed of thinking and movement)

Assessment Question 2

Common signs and symptoms for MS include?
Select all that apply
A. fatigue
B. spasticity
C. pseudobulbar affect
D. increased concentration
Feedback: A, B, and C correct. Concentration is decreased with MS not increased.

Diagnosis

MS diagnosis

- No specific test/symptom
- Medical & family history
- Neurological exam: symptoms/deficits
- Imaging & laboratory tests:
  - MRI
  - and/or CSF analysis
- Blood tests
  - CBC with diff, CMP, TSH, B12 level
Clinically Isolated Syndrome (CIS)

- 1st episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation and demyelination in one or more sites in the CNS. Can be either monofocal or multifocal:
  - Monofocal episode: The patient experiences a single neurologic sign or symptom i.e. an attack of optic neuritis caused by a single lesion.
  - Multifocal episode: The patient experiences more than one sign or symptom i.e., an attack of optic neuritis accompanied by Right sided weakness caused by lesions in more than one place.

Clinically definite MS

- At least two episodes of symptoms (2 acute exacerbations) &/or supported by MRI (or combination)
  - Occur at different points in time
    - (1) Dissemination in time
  - Result from involvement of different areas of the CNS
    - (2) Dissemination in space

Assessment Question 3

In addition to an MRI scan of brain and spine, which of the following tests can be helpful in MS diagnosis?
A. EEG
B. CT of brain
C. CSF analysis
D. ECG

Feedback: C. Guidelines Recommend MRI and CSF analysis

Assessment Question 4

VM had f/u MRI 3 months later 2 plaques L and R periventricular matter

Based on the above:
A. VM has clinical isolated syndrome.
B. VM has clinically definite multiple sclerosis.

Feedback: B- has the symptoms and dissemination in space (f/u MRI with 2nd plaque)
**Definitions - National MS Society**

- **Relapse**: A relapse (also known as an *exacerbation* or *attack*) is conventionally defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least one month.

- **Pseudo-exacerbation**: A temporary aggravation of disease symptoms, resulting from an elevation in body temperature or other stressor (e.g., an infection, severe fatigue, constipation), that disappears once the stressor is removed. A pseudo-exacerbation involves symptom flare-up rather than new disease activity or progression.

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**Types of MS**

- **Relapsing-remitting MS (RRMS)**
- **Secondary Progressive MS (SPMS)**
- **Primary Progressive MS (PPMS)**
- **Progressive Relapsing MS (PRMS)**

**MS Treatment Approach**

- Treatment of acute exacerbation
- Modification of disease progression
- Managing symptomatic complications

**Exacerbation Treatment (acute relapses)**

- **Goals**: relief of acute symptoms & faster recovery
- First-line therapy glucocorticoids:
  - IV methylprednisolone 1g daily for 3-7 days
  - Or Oral prednisone 625-1250 mg/day for 3-7 days

**Does VM need steroids?**

A. Yes
B. No
Disease Modifying Drugs

THE ABC’S AND R AND NOW THE ORALS

Avonex, Betaseron, Rebif

- **Mechanism of Action:** unknown
- **Pregnancy Category:** C
- **Common Adverse Effects:** flu-like symptoms
- **Serious Adverse effects:** depression, ↑AST, ALT, bilirubin, seizures
- **Evidence Trial**
  - Compared Avonex 30mcg once a week vs Rebif 44mcg three times per week
  - Patients with Rebif were more likely to remain relapse free at 24 (0.68 [95% CI: 0.54-0.86]) and 48 weeks (0.81 [95% CI: 0.68-0.96])
  - Patients on Rebif had no new or enlarging lesions (p=0.001)

Peginterferon beta-1a

- **Mechanism of Action:** unknown
- **Pregnancy Category:** C
- **Common Adverse Effects:** flu-like symptoms, candidiasis, UTI
- **Serious Adverse effects:** depression, ↑AST, ALT, bilirubin, seizures
- **Advance Trial**
  - Peginterferon beta-1a vs placebo
    - Improved decreased annualized relapse rate (p=0.0007)
    - Dec number of new lesions and enlarged lesions (p=0.0001)

Lab monitoring

- **AST, ALT, bilirubin**
- **CBC**
  - WBC’s, RBC’s, and platelets can be decreased
- **TSH**
  - If history of thyroid dysfunction, thyroid function tests are recommended at regular intervals,
  ~every 6 months
- **Neutralizing antibodies**
Flu-like symptoms

- Prevention/management
  - Slow dose titration
  - Injection in the evening
  - Use of ibuprofen or acetaminophen

Glatiramer acetate

- **Mechanism of Action**: Unknown. Appears to block myelin-damaging T-cells
- **Dose**: 20mg SQ daily, 40mg SQ TIW
- **Pregnancy Category**: B
- **Forte Clinical Trial**
  - Glatiramer acetate 40mg vs 20mg
  - MS with ≥ 1 documented relapse in 12 months prior to screening, or ≥ 2 documented relapses in 24 months prior to screening, and Expanded Disability Status Scale (EDSS) score 0 to 5.5 were enrolled.
  - Primary endpoint was rate of confirmed relapses observed during 12-month study
  - Both doses were safe and well-tolerated, with no gain in efficacy with the 40mg dose.

Immediate post-injection reaction

- ~15 min
  - flushing, chest tightness, palpitations, anxiety and SOB

Injection Site Reactions

- **SUBQ>IM**
- **Prevention**:
  - Rotate the injection sites
  - Use areas with more SubQ fat
  - Bring medication to RT before injection
  - Massage the area before injection
  - Ice the injection site pre and post-injection (not for glatiramer)
  - Use autoinjector
  - Use hydrocortisone 1% cream

Dimethyl fumarate (BG-12)

- **Mechanism of Action**: Unknown. Nicotinic acid receptor agonist and in vitro activator of nuclear factor like 2 involved in cellular response to oxidative stress
- **Pregnancy Category**: C
- **Common Adverse Effects**: Flushing (use aspirin), GI side effects, Leukopenia
- **Serious Adverse Effects**: Rare cases of PML, anaphylaxis and angioedema
- **Monitoring**: CBC-Baseline, 6 months, then every 6-12 months
Assessment Question 5

A counseling point for patients on interferon therapy may include:
A. pre-treat with acetaminophen to prevent flu-like symptoms
B. Inject in the morning
C. All of the above
D. None of the above
Feedback: A- You should inject in the evening

Fingolimod

- **Mechanism of Action:** retaining lymphocytes in the lymph nodes, thereby preventing those cells from crossing the blood-brain barrier into CNS.
- **Monitoring:**
  - **Baseline:** Varicella serology, Ophthalmic examination, AST/ALT, CBC
  - ophthalmologic exam in 4 months after initiation, ALT/AST q6months, CBC q6months, HR, BP, ECG
- **Common Adverse Effects:** HA, inc AST/ALT, cough, sinusitis, AV block, inc HR/BP

Fingolimod - Appropriate Use

- ECG prior to dosing and after the 6-hour observation period.
  - A new or recent ECG in those using CV medications, those who have cardiac risk factors, or those who on examination have slow or irregular heart beat prior to starting fingolimod
- A new or recent CBC
- An ophthalmologic evaluation
- A new or recent blood test to evaluate liver enzyme levels
- If you re-start fingolimod after stopping for two or more weeks, you will need to take the first dose in the doctor’s office.

Fingolimod - Precautions

- Not advisable for people who have had a history or presence of specific heart and vascular conditions, including MI, stroke, arrhythmias, and patients taking beta and alpha blockers.
- If anyone with a pre-existing heart condition is started on fingolimod, after the first dose the patient should be monitored overnight with continuous electrocardiogram in a medical facility.

Fingolimod - patient selection

- Active disease
- Escalation of therapy
- De-escalation of therapy
Teriflunomide

- **Mechanism of Action:** Inhibits dihydroorotate dehydrogenase
- **Pregnancy Category:** X
- **Monitoring:**
  - Pregnancy test and TB screening prior to initiation
  - CBC, ALT, AST, t. bili, BP
- **Common Adverse Effects:** alopecia, diarrhea, inc AST/ALT, headache


Daclizumab

- **Mechanism of Action:** unknown but is presumed to involve modulation of IL-2 mediated activation of lymphocytes through binding to CD25, a subunit of the high-affinity IL-2 receptor
- **Pregnancy Category:** C
- **Monitoring:** AST/ALT, bilirubin at baseline, monthly prior to each dose, and 6 months after last dose
- **Common Adverse Effects:** liver injury, rash, influenza, colitis, depression


Natalizumab

- **Mechanism of Action:** Antibody, prevents transmigration of leukocytes across endothelium into inflamed parenchymal tissue
- **JCV Antibody Test:**
  - Only people who have been exposed to JCV appear to be at risk of PML.
  - The risks and benefits of starting or continuing treatment with natalizumab should be considered carefully in any person who is anti-JCV antibody (+) and has 1 or more of the other known risk factors for PML:
    - Longer time on treatment with natalizumab – especially over 2 years
    - Prior treatment with an immunosuppressant medication
    - A person who tests positive for anti-JCV antibodies but has no other risk factors has a less than 1 in 1000 risk of developing PML.
    - A person with all three risk factors has an 11 in 1000 risk of developing PML.


Mitoxantrone

- **Patients with secondary progressive MS, Progressive-relapsing MS, or Worsening relapsing-remitting MS**
- **Should be used only in those with normal cardiac function, once every three months**
- **Periodic cardiac monitoring is required throughout the treatment period.**
- **CBC and liver function should be evaluated prior to each dose.**

Meet VM

VM is a 20 yo Caucasian Female. She is experiencing bilateral vision blurriness.
- **PMH:** seasonal allergies
- **FH:** Mother’s sister has Relapsing-remitting MS
- **Medications:** loratadine 10mg po daily prn
- **MRI:** 1 plaque in L periventricular matter
- **Patient is needle phobic, not interested in starting a family for the next 5-7 years**

**MS RELATED ILLNESSES**

(LIST OF DRUGS IS NOT EXHAUSTIVE)
Meet JW

JW is a 56 yo AAF. She is experiencing a worsening of her MS symptoms for the past 2 years (limb weakness, spasticity, hand tremor)

- PMH: RRMS (diagnosed 15 years ago), HTN, Type 2 diabetes, hyperthyroidism
- FH: NC
- Medications: glargine 42 units SQ QHS, metformin 500mg po TID, enalapril 10mg po BID, interferon beta 1a IM q week
- Dx: SPMS

Follow-up

- Regular reassessment of:
  - patient condition/improvement – adherence
- **Recommended schedule:**
  - q3 months during the 1st year of treatment
  - q6 months or yearly thereafter
  - Or earlier if acute exacerbation
Pharmacist and Technician's Roles

- Insurance – Technician/PharmD
- Baseline labs – PharmD
- Patient education – PharmD
- Monitoring/Follow up – PharmD

Take Home Points

- Currently there is no cure for MS
- Medications slow the progression of the disease.
- Pharmacists can play a role in almost every step of the medication management of MS.
- Technicians can play a big role with the insurance.

RESOURCES

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Janene L. Marshall, PharmD, BCPS
Clinical Associate Professor
Internal Medicine Clinical Pharmacist
Chicago State University College of Pharmacy
J-marshall@csu.edu