Multiple Sclerosis: Managing the Whole Patient
Jacquelyn Bainbridge, PharmD, FCCP
Professor, Department of Clinical Pharmacy and Neurology, University of Colorado
Ellen Whipple Guthrie, PharmD
Medical Advisory Board, MS Foundation
Clinical Assistant Professor, University of Georgia College of Pharmacy

Supported by independent educational grants from Elan Pharmaceuticals, Inc., EMD Serono, Inc. and Genzyme.

Disclosures
• Ellen Guthrie, Pharm D declares the following conflicts:
  • Medical Communications – Contractor
  • Teva Neuroscience - Stockholer

• Jacquelyn Bainbridge Pharm.D. declares the following conflicts:
  • NIH - Research grant funding
  • TEVA Neurosciences – Honoraria
  • UCB Pharma – Honoraria

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Learning Objectives
• Review the current clinical management of multiple sclerosis (MS) including long-term efficacy and safety of treatment options
• Differentiate new and emerging therapies for MS and discuss the role of the pharmacist in adherence
• Describe symptoms that are commonly associated with MS and pharmacologic options for managing them
• Discuss the role of biomarkers in MS
• Explain strategies for promoting patient adherence, managing adverse events, and assisting patients with medication administration

Which Drug Used to Treat Multiple Sclerosis Requires a First Dose Observation Period?
0% 1. Dalfampridine
0% 2. Glatiramer acetate
0% 3. Fingolimod
0% 4. Interferon Beta 1a

EG Reports Severe Flu-Like Symptoms with her Multiple Sclerosis Therapy. Which First Line Drug Would be your Next Choice?
0% 1. Fingolimod
0% 2. Glatiramer acetate
0% 3. Interferon Beta 1b
0% 4. Interferon Gamma 1a
MB is Experiencing Fatigue and Depression. Which Drug is a Good Option for this Patient?

0% 1. Amitriptyline
0% 2. Mirtazapine
0% 3. Imipramine
0% 4. Fluoxetine

RP is Complaining of Problems Walking. You Recommend Which of the Following Drugs at add to his Multiple Sclerosis Therapy?

0% 1. Dalfampridine
0% 2. Bupropion
0% 3. Modafinil
0% 4. Natalizumab

Which Option Below has Proven to Promote Adherence in Multiple Sclerosis Patients

0% 1. Set realistic expectations
0% 2. Nonadherence is not a problem
0% 3. Give a drug holiday
0% 4. Defer the drug copay

The Basics

- MS is a chronic inflammatory disease characterized by myelin destruction and axonal damage
- The term multiple sclerosis refers to 2 characteristics of the disease:
  - The numerous affected areas of the brain and spinal cord producing multiple neurologic symptoms that accrue over time
  - The characteristic plaques or sclerosed areas that are the hallmark of the disease

Epidemiology

- >400,000 American victims, 2.7 million worldwide
- 200 new cases of MS are diagnosed each week in the U.S.
- MS is the second most common cause of neurologic disability in the U.S.
- 80% develop MS between 16 and 45 years of age
- Female to male risk ratio 2.4:1
- Outcomes Untreated:
  - 50% of patients require a cane or more support for ambulation within 10 years of onset.
  - 30% of patients will become wheelchair or bed bound
  - Average life span decreased by <5 years
- Health-related costs: $47,215/Pt/yr*

Etiology

- The exact cause(s) of MS are not fully understood
- Evidence suggests that MS is probably caused by a combination of factors including:
  - Genetics
  - Altered immune system
  - Environmental factors (e.g., measles, mumps, rubella, Epstein-Barr virus, human herpes virus 6)
**Multiple Sclerosis**

- An immune-mediated disease in genetically susceptible individuals
- Dual nature: inflammatory and neurodegenerative
- Demyelination leads to slower nerve conduction
- Axonal injury and destruction are associated with permanent neurologic dysfunction
- Lesions occur in optic nerves, periventricular white matter, cerebral cortex, brain stem, cerebellum, and spinal cord


**Behavioral Changes**

- Vitamin D deficiency associated with risk of MS; not clear if addition to diet alters risk at this point
- Higher vitamin D levels associated with a lower relapse risk
- Smoking increases risk for:
  - Conversion to CDMS, 51% vs 75% at 3 years
  - Development of MS in general
  - Development of disability in MS
  - MRI abnormalities predictive of poor outcome
- Excess body weight associated with risk of MS;
  - What is the role of weight reduction in changing the course of the disease?


**Diagnosis**

- There is no single test used to diagnose MS
- Diagnosis should be based on history and clinical findings
- Tests used to aid the diagnosis of MS:
  - MRI scans
  - Visual evoked potentials
  - Lumbar puncture (CSF evaluation)
  - Optic coherent tomography

*CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; J Neurol 2011;258:728-739; Pharmacotherapy. 2010;30:916-927; Neurology 2007;68:S46-S53.*

**Biomarkers in MS**

- May be useful in monitoring progression of MS and treatment response instead of clinical end points or current practice
- Monitoring progression
  - The complement regulator factor H
    - Allows progressive MS to be distinguished form RRMS
  - Monitoring treatment response
    - The development of neutralizing antibodies (Nabs)
    - Accelerated disease progression:
      - Persistent neutralizing antibodies to interferon beta appears to accelerate disease progression in some patients
      - One study showed 24% of patients were Nabs + after 25 months of stopping the interferon, in patients with persistent Nabs
    - Associated with:
      - Increase in annual relapse rate
      - Reduction in the time to reach a score of 6 on the Expanded Disability Status Scale (EDSS)
      - Increase in the probability of changing to a second-line drug


**Measuring Neutralizing Antibodies**

- IFNβ → IFNβ induced proteins
  - β2-Microglobulin, Neopterin, TRAIL, myxovirus resistance protein A (MxA)
- Binding antibodies (BAb) + IFNβ → IFNβ induced proteins
- Neutralizing antibodies (NAb) + IFNβ → # IFNβ induced proteins, therefore; decreased clinical effect of IFNβ*
- In Scandinavian countries discontinuation of IFNβ and change of therapy is strongly recommended with persistent, moderate, or high NAb titers**


**Biomarkers in MS**

- Cerebrospinal fluid (CSF)
  - Oligoclonal bands
  - CXCL13
  - IgG synthesis
  - MRZ reaction
- Neurodegenerative CSF
- Serum
  - Autoantibodies against myelin - Anti-MOG (IgG), anti-MBP (myelin basic protein), anti-PLP (myelin-associated oligodendrocyte glycoprotein)
- Structural MRI
  - Gd enhancing lesions, T1, T2, spinal cord, gray and white matter atrophy, etc.
- Single-photon emission computed tomography (SPECT), Positron emission tomography (PET), Optical coherent tomography (OCT), N-acetyl – aspartate (NAA) , Evoked potentials (EP), Visual evoked potentials (VEP)

Approach to Multiple Sclerosis Therapy

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

Case Study (Part I)

- July 2006
- TG is a 17 year-old, white female who lives in Boston
- CC: Currently things are blurry in her right eye
- Normal findings on MRI
- Patient’s aunt has MS
- Patient diagnosed with optic neuritis and CIS
- How should this patient be managed?

Acute Exacerbations

- Development of focal neurologic deficits along with physical findings for at least 24 hours and 30 days apart from the previous event
- Return to baseline by 3 months
- Anti-inflammatory therapies can reduce inflammation in brain and spinal cord
- There may be relief of signs and symptoms, including severity and duration
- Adrenocorticotropic hormone (ACTH)
- Intravenous immunoglobulin (IVIG)

Treating Exacerbations

- 1st line: corticosteroids.
  - Methylprednisolone 0.5-1gram IV every day for 3 to 7 days (per American Academy of Neurology).
- 2nd line: IVIG or plasmapheresis.
- When should 2nd line treatments be considered?
  - Patient unresponsive to corticosteroids.
  - Corticosteroids contraindicated (e.g., severe osteoporosis; brittle diabetes).

Clinically Isolated Syndrome (CIS)

- A single, symptomatic neurologic episode that is consistent with MS
- Typically the first clinical event to take place among patients with MS
- Symptoms may include optic neuritis, ocular motor syndromes, ataxia, sensory or motor syndromes, partial myelitis, and/or bladder or bowel dysfunction

CDMS

- McDonald Criteria:
  - Requires the presence of ≥2 lesions separated by time and space (allows for MRI scans, CSF, and evoked potential findings to identify second attacks)
  - Calls for one of 3 outcomes:
    - 1) Diagnosis of MS
    - 2) “Possible” diagnosis of MS
    - 3) No diagnosis of MS
- Can be diagnosed on one MRI (MAGNIMS)
  - Dissemination in time (DIT) – 2 Gd enhancing lesions in different areas of the brain (one causing symptoms)
  - Dissemination in space (DIS) – at least 1 T2 lesion in a least 2 out of 4 areas of the brain

CIS=clinically isolated syndrome; CC=chief compliant; MRI=magnetic resonance imaging.
Case Study (Part II)

- August 2006
- Patient and neurologist discuss the first-line DMTs
- The patient inquires if she will need treatment for the CIS.

Why Treat CIS?

- 60-80% of patients with CIS who have demyelinating lesions on MRI, eventually develop CDMS
- 20% of patients with normal MRIs develop CDMS
- The ultimate goal is to delay disease progression to CDMS, through the use of early therapeutic intervention.

Prognosis in CIS

Rate of Conversion to CDMS

<table>
<thead>
<tr>
<th>Baseline Measure</th>
<th>% Converting to CDMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>0</td>
</tr>
<tr>
<td>1-3 Lesions</td>
<td>20</td>
</tr>
<tr>
<td>4-10 Lesions</td>
<td>40</td>
</tr>
<tr>
<td>&gt;10 Lesions</td>
<td>60</td>
</tr>
</tbody>
</table>

Adapted with permission from Sivas et al. [1], Neurology. 2006;67:1242-49.

FDA-Approved Therapies

First-line DMTs

<table>
<thead>
<tr>
<th>DMT</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA</td>
<td>CIS, RRMS</td>
<td>20 mg SQ once daily</td>
</tr>
<tr>
<td>IFNβ-1a IM</td>
<td>CIS, RRMS</td>
<td>30 mcg IM 1x/week</td>
</tr>
<tr>
<td>IFNβ-1a SQ</td>
<td>RRMS*</td>
<td>22-44 mcg SQ 3x/week</td>
</tr>
<tr>
<td>IFNβ-1b</td>
<td>CIS, RRMS</td>
<td>250 mcg SQ every-other day</td>
</tr>
</tbody>
</table>

Efficacy in CIS

Clinical Studies

<table>
<thead>
<tr>
<th>Name</th>
<th>Agents/Dosing</th>
<th>Findings (vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreCISE</td>
<td>GA 20 mg/day vs. placebo</td>
<td>At 3 years, GA slowed the conversion to CDMS by 45%.</td>
</tr>
<tr>
<td>BENEFIT</td>
<td>IFN β-1b 250 mcg every-other day vs. placebo</td>
<td>At 2 years, IFN β-1b slowed the conversion to CDMS by 17%.</td>
</tr>
<tr>
<td>CHAMPS</td>
<td>IFN β-1a 30 mcg 1x/week vs. placebo</td>
<td>At 3 years, IFN β-1a slowed the conversion to CDMS by 15%.</td>
</tr>
<tr>
<td>REFLEX</td>
<td>IFN β-1a 44 mcg 3x/week vs. placebo</td>
<td>At 2 years, IFN β-1a slowed the conversion to CDMS by 51%.</td>
</tr>
</tbody>
</table>

Case Study (Part II-cont)

- Patient decides not to start treatment with a DMT because of “needle phobia”
Case Study (Part III)

- October 2010
- PMH: Optic neuritis resolved with corticosteroids
- CC: Patient experiencing severe vertigo
- 3 lesions in different areas of the brain are found on MRI scans
- Patient diagnosed with MS and agrees to be treated with an injectable DMT

The patient inquires further about the injectable DMTs and asks “if they are all equally effective.”

IFNβ Products

- 3 formulations (IFNβ-1b SQ, IFNβ-1a IM, and IFNβ-1a SQ)
- Pregnancy Category: C
- Drug Interactions: Possibly hepatically active drugs
- Laboratory monitoring: CBC, LFT, TSH

IFNβ (Formulations)

- IFN β-1a IM
  - Low dose IFN-β product
  - 30 mcg IM every week
- IFN β-1b SQ
  - High dose IFN-β product
  - 250 mcg SQ every other day
- IFN β-1a SQ
  - High dose IFN-β product
  - (22 mcg – low dose) to 44 mcg SQ every other day

IFNβ (MOA)

- Does not cross the BBB
- Works outside of the CNS to reduce inflammation
- Stabilizes the BBB
  - Decreases matrix metalloproteinases
- No evidence of neuroprotection

IFNβ (Safety)

- Menstrual irregularities
- Flu-like symptoms
- Injection site reactions
- Depression
IFN-β (Pivotal Trials)

| IFN β-1b SQ | Decreased frequency of relapses; more patients free of relapses over a 2-year treatment period1 |
| IFN β-1a IM | CHAMPS: Relative reduction in the volume of brain lesions, fewer new or enlarging lesions, and fewer Gd+ lesions at 18 months; fewer patients developed CDMS over a 3-year follow-up period2 |
| IFN β-1a SQ | PRISMS3EVIDENCE4: Decreased frequency of relapses; delayed the accumulation of physical disability |


Glatiramer Acetate (GA)

- Dosing: 20 mg SQ every day
- Pregnancy Category: B
- Drug Interactions: None noted in clinical trials
- Laboratory monitoring: None needed

Glatiramer Acetate (MOA)

- Not an IFN-β product
- Produces T-cells that suppress the immune attack on myelin
- Resembles myelin basic protein
- Exerts effect within the BBB
- Neuroprotective properties

Glatiramer Acetate (Safety)

- Injection site reactions
- Hives
- Post injection reaction

Case Study (Part IV-cont)

- October 2010
- Patient and MD decide on IFN β-1b SQ 250 mcg every other day
- Pharmacy consult
  - Injection training
  - Importance of adherence

ARR=annualized relapse rate; RRMS=relapsing-remitting multiple sclerosis; EDSS=Expanded Disability Status Scale; SPMS=secondary-progressive multiple sclerosis; Neurology 1985;45:1265-1270; These release, The Consortium of Multiple Sclerosis Centers, February 2010.
Injection Training

- Rotate injection sites
- Use an autojector (available at no charge from manufacturer)
- Inject medication at room or body temperature
- Ice the area before and after injecting the medication
- Massage the area before and after injecting the medication

Importance of Adherence

- Between 17% and 40% of patients stop taking DMTs within 1 year of initiation
- Multifactorial
  - Perceived lack of efficacy
  - AEs
  - Depression
  - Within 6 months of treatment initiation, 41% of patients had new or increased depression
  - Decreased adherence in patients with untreated depression
- 50% of patients on a DMT stopped taking their medications within 4 years of diagnosis*
  - 56% of treated and 37% of nontreated patients were employed full time

Establish Realistic Expectations

- DMTs decrease relapses, reduce MRI activity, and attenuate disease activity
- Only work if patients take them
- May not eliminate MS symptoms
- Do not completely eliminate future disease activity
- Attenuated disease activity may lead to more patients retaining employment
- Patients with MS must also realize that DMTs do not “cure” MS

Benefits of Adherence to DMTs

- Relapse free at 1 year: 51%–80%
- Relative decrease in ARR: 30%–80%
- Absolute ARR: 0.15–0.7
- Relative decrease in sustained progression: 31%–42%
- Absolute rate of disease progression: 9%–18%
- What this means?
  - Untreated MS patient: relapse about every 6 months
  - Treated MS patient: relapse about every 2 to 5 years

Case Study (Part V)

- January 2011
- TG has been receiving IFNβ-1b SQ since diagnosis of MS
- No new lesions on MRI
- No new problems
- CC: Minor flu-like symptoms from IFNβ-1b SQ
- At routine neurologist visit, TG asks about switching to an alternative DMT (GA, natalizumab, or fingolimod)

Natalizumab

- Dosing: 300 mg IV every 4 weeks
- Infusion reactions (e.g., rash, drowsiness, fever, chills, nausea, flushing, decreased blood pressure, shortness of breath, chest pain) are common
  - Usually occur within 2 hours of the start of the infusion
  - Generally subside when the drug is stopped and/or treatment with is given with diphenhydramine and/or steroids

*Neurology Reviews. 2012;20(2):5..
Natalizumab (Pivotal Trials)

**AFFIRM:**
- At 2-years, natalizumab decreased clinical relapses rates by 66% and decreased ARR, compared to placebo


**SENTINEL:**
- IFN β-1a IM treated patients who continued to experience disease activity were randomized to receive IFN β-1a IM monotherapy or IFN β-1a IM + natalizumab
- At 1-year the addition of natalizumab to IFN β-1a IM resulted in a 51% reduction in the rate of clinical relapses over IFN β-1a IM monotherapy; ARR also favored patients who received IFN β-1a IM + natalizumab


Natalizumab (Safety)

- Progressive multifocal leukoencephalopathy (PML)
  - 150 cases confirmed as of September 30, 2011, 39 fatal
  - Approximately 92,000 patients have received at least one dose of natalizumab
  - Risk increases with exposure, particularly >24 months of therapy
  - Testing for JC-virus?

- Hypersensitivity reactions – use diphenhydramine and methylprednisolone
- NAbs
- Melanomas/other cancers
- Liver injury
- Reactivation of latent viruses
- Immune reconstitution inflammatory syndrome (IRIS)

TOUCH Prescribing Program

- Natalizumab should only be used as monotherapy
- Natalizumab should only be used in patients who have not responded adequately to, or who cannot tolerate, first-line DMTs
- Natalizumab can only be administered to patients enrolled in TOUCH
- Prior to initiating therapy, patients must receive MRI scans
- Patients must be evaluated 3 and 6 months after the first infusion and every 6 months thereafter


Fingolimod

- Dosing: 0.5 mg orally once daily
- Pregnancy Category: C
- Drug Interactions:
  - Class Ia or III antiarrhythmic drugs
  - Ketoconazole
  - Live virus vaccines
  - Antineoplastic, immunosuppressive, or immunomodulating therapies
  - Drugs that lower heart rate (eg, beta blockers, diltiazem)

GlaxoSmithKline Product information.

Fingolimod (Safety)

- First-dose Effects
  - Bradycardia
  - Second degree Wenckebach atrioventricular block
- Lymphopenia
  - Reversal of lymphopenia can take weeks after the end of dosing, depending on the dose
- Opportunistic infections
- Malignancies

Fingolimod

- 11 Deaths reported as of January 20, 2012
- 1 in the US
  - Patient on at least a beta blocker and calcium channel blocker
- 10 in Europe
  - 6 unexplained deaths
  - 3 heart attacks
  - 1 EKG change
- Updated monitoring to include at least:
  - Do not use Fingolimod in any patient on a beta blocker or calcium channel blocker
  - Increase monitoring to include telemetry on all patients monitored with the first dose

Fingolimod (Pivotal Trials)

- FREEDOMS study
  - Examined the safety and efficacy of fingolimod in 1272 patients with RRMS
  - Patients received either placebo or fingolimod 0.5 mg or 1.25 mg once-daily
  - After 2 years, the patients who received fingolimod (either dose) had reduced ARR compared to the patients who received placebo

Fingolimod (Pivotal Trials)

- TRANSFORMS study
  - Examined the safety and efficacy of fingolimod in 1292 patients with RRMS
  - Patients were randomized to receive oral fingolimod (0.5 mg or 1.25 mg) once-daily or IFNβ-1a IM 30 mcg IM once per week
  - At 12 months, patients who received fingolimod (either dose) had decreased ARR and MRI lesion activity, compared to the patients who received IFNβ-1a IM 30 mcg IM once per week

Case Study (Part VI)

- March 2011
- TG currently receiving IFNβ-1b SQ
- No new lesions on MRI
- No new problems
- CC: Minor flu-like symptoms from IFNβ-1b SQ
- At routine neurologist visit, TG inquires about the treatments of MS that are under development.

Emerging Oral Therapies for MS

- Dimethyl fumarate (BG0012)
- Laquinimod
- Teriflunomide

Dimethyl fumarate

- Being studied as an oral agent in MS
- Proposed MOA:
  - Induces “good” T-cells to kill “bad” T-cells, leading to a reduced migration of lymphocytes into the CNS
  - Inflammatory and neuroprotective properties
Dimethyl Fumarate (Pivotal Trial)

- **Study design:** A total of 257 patients in this Phase II study received either 120 mg daily (low-dose), 120 mg three times daily (medium-dose), or 240 mg three times daily (high-dose).
- **Primary outcome:** Comparison of the total number of new, active brain lesions at 4-week intervals starting at week 12.
- **Findings:**
  - Compared with those on placebo, the high-dose treatment group had a 69% reduction in the mean total number of new enhancing MRI lesions from weeks 12 to 24.
  - The drug also reduced the number of other types of new or enlarging MRI lesions.

Dimethyl fumarate (Safety)

- Gastrointestinal problems and flushing are the most commonly reported AEs.
  - Dissipate after ~6 weeks of treatment.

Laquinimod

- An orally-administered, once-daily DMT being studied in MS.
- **Proposed MOA:**
  - Appears to decrease inflammation in the CNS by increasing “good” T-cells (Th2) and by decreasing “bad” T-cells (Th1).
  - Appears to reduce leukocyte infiltration into the CNS, which decreases demyelination and axonal damage.

Laquinimod (Pivotal Trial)

- **Study design:** A total of 306 patients in this Phase Iib study received either placebo, low-dose laquinimod (0.3mg/day), or high-dose laquinimod (0.6mg/day).
- **Primary outcome:** Cumulative number of Gd+ at weeks 24, 28, 32, and 36.
- **Findings:**
  - When compared with placebo, a statistically significant 40.4% reduction was found in the mean cumulative number of Gd+ lesions on the last four scans with the 0.6 mg dose.
  - The difference between results with the 0.3 mg dose and placebo was not statistically significant.

Laquinimod (Safety)

- No serious AEs emerged in clinical trials.
  - Structurally related to roquinimex, a product shown to be efficacious in MS in previous studies.
  - Development of roquinimex was abandoned when it was discovered that it caused Mls and systemic inflammatory syndromes.
  - While laquinimod does not appear to be associated with these AEs, continued vigilance is needed, because serious AEs are commonly not evident until Phase III studies or during post-marketing surveillance.

Case Study (Part VII)

- March 2012
- TG stopped INFβ-1b SQ in April 2011
- Five lesions on MRI
- CC: Many symptomatic problems (ie, bladder dysfunction, cognitive problems, depression, and fatigue).
- What needs to be done?
Approach to Treatment of Secondary MS Complications

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

Common Issues Facing Patients with Multiple Sclerosis

- Decreased cognition
- Depression
- Bladder dysfunction
- Neuropathic pain
- Spasticity
- Walking/mobility issues
- Fatigue
- Sexual dysfunction

> All drugs in this section are off label for MS.
> All issues may be less severe or averted if patients are adherent to DMTs!!

Cognition

- ~50% of patients develop cognitive dysfunction, affecting their ability to think, reason, concentrate, or remember
- 5%–10% of patients suffer from moderate to severe cognitive impairment
- Treatments include behavioral coping strategies, sometimes in combination with cholinesterase inhibitors (eg, donepezil) or stimulants
  - Donepezil may have modest effects on verbal learning (ability to recall a list of words), memory, and attention

Cholinesterase Inhibitors & Noncompetitive NMDA Receptor Antagonist

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne/Razadyne ER)
- Memantine (Namenda)

> REMEMBER to remove anticholinergics if cognitive dysfunction starts after their initiation!

Stimulants or Activating Drugs

- Amantadine (Symmetrel)
- Methylphenidate (Ritalin)
- Dextroamphetamine (Dexedrine)
- Modafinil (Provigil)
- Fluoxetine (Prozac)
- Dalfampridine (Ampyra)

Cognition

- Since cognitive impairment can negatively impact patient adherence, pharmacists should make all attempts to simplify drug regimens
  - Suggest medications that can be given once per day rather than multiple times per day
  - Recommend monotherapy options instead of multidrug ones
  - Attempt to use drugs for >1 use
## Depression

- ~50% of all MS patients suffer from depression
- The exact cause of MS-related depression is not known
  - Psychological reaction to a chronic illness
  - Part of the grieving process (3-6 months)
  - Related to the neuropathology of MS
  - Interferons may precipitate or worsen
- Relationship between fatigue/depression
  - Fatigue → Depression → Fatigue

### Treating Depression

#### Pharmacologic Treatments

- Treatment similar to major depressive disorder
- Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), mirtazapine
- Consider comorbidities when selecting agent

#### Treating Depression

##### Comorbid Conditions

- Insomnia → Mirtazapine, TCAs
- Neuropathy → Duloxetine, TCAs
- Sexual dysfunction → Bupropion
- Fatigue → SNRIs (venlafaxine, duloxetine, desvenlafaxine), fluoxetine, stimulants
- Cognition/balance → Avoid TCAs
- Incontinence → SNRIs, TCAs

##### Patient Counseling Tips

- Benefits take 6–8 weeks
- Treatment duration varies
- Treatment failure anticipated
- Suicide is 7 times more common than in the general population
- Start low, go slow
  - Limiting side effects
  - Escalate to maximum tolerated dose
- Tricyclic antidepressants more lethal in overdose

### Treating Depression

#### Patient Counseling Tips

- Bupropion, fluoxetine, and SNRIs considered activating
  - May initially provide benefit for fatigue
- Sertraline, citalopram, escitalopram
  - Neutral
- Paroxetine considered sedating
  - Initially may benefit sleep
- TCAs typically cause drowsiness
  - May worsen symptoms of neurogenic bladder due to excessive urinary retention
  - Be aware of anticholinergic side effects at higher doses (salivation, lacrimation, urination, defecation)

### Treating Depression

#### Patient Counseling Tips

- Bladder dysfunction problems include failure to empty, failure to store, nocturia or a combination
- Nocturia
- Failure to empty (hyporeflexive bladder)
- Failure to store (hypermotile bladder)
  - The most common bladder problem seen in MS patients
  - Manifests as urinary urgency and frequency and voiding only small amounts of urine
  - Over time, urgency can become more difficult to control and can lead to incontinence
  - Failure to store/incomplete bladder emptying (sphincter detrusor dyssynergia)
    - May occur more frequently in men
    - Causes hesitancy, retention, and overflow incontinence

---

1. O’Connor P. In: Multiple Sclerosis and Demyelinating Diseases. Lippincott, Williams, and Wilkins; 2006:227-255.
**Bladder Dysfunction**

**Nonpharmacologic and Prophylactic Treatments**

- Hyporeflexive bladder (failure to empty)
  - Crede maneuver, timed voids, catheterization
- Long-term complications
  - Urinary tract infections (UTIs)
  - Urosepsis
- UTI prophylaxis
  - Sulfamethoxazole/trimethoprim sulfate
  - Cephalexin
  - Nitrofurantoin
  - Cinoxacin


**Bladder Dysfunction**

**Pharmacologic Treatments**

- Failure to empty (hyporeflexive bladder)
  - Cholinergic agents (bethanechol chloride)
- Nocturia
  - Desmopressin acetate (DDAVP)


**Bladder Dysfunction**

**Pharmacologic Treatments**

- Failure to store (hyperreflexive bladder)
  - Anticholinergic medications (eg, oxybutynin, tolterodine) 1,2
  - With or without low-dose imipramine (synergistic effect)
  - Remove cholinergic agent if incontinence started soon after its initiation
- Failure to store (sphincter dyssynergia)
  - Alpha blocking drugs (eg, terazosin and tamsulosin, alfuzosin, silodosin) are the drugs of choice for failure to store problems 1,2
  - Relaxes the internal sphincter


**Comparison of OAB Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dry Mouth (%)</th>
<th>Constipation (%)</th>
<th>Dizziness (%)</th>
<th>Vision Changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>85</td>
<td>40</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Oxy ER/XL</td>
<td>35</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Dry TDS</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dry gel</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>61, 23</td>
<td>13, 6</td>
<td>6, 2</td>
<td>8, 1</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>35</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Trospium</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>20</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Differentiation of Muscarinic Receptors in the CNS**

- M1: antagonists impair memory and cognition
- M2: antagonists enhance cognition
- M3: antagonists cause no deficit in memory or cognition
- M4: antagonists may enhance acetylcholine in the brain; no effect on cognition
- M5: antagonists cause no deficit in memory or cognition

**Bladder Dysfunction**

**Patient Counseling Tips**

- **Anticholinergic medications**
  - Most common adverse effects (AEs)—dry mouth and constipation
  - AEs more common with immediate-release formulations
  - Remind patients to increase fluid intake
  - Adherence very important with sustained-release formulations

- **Alpha-blocking agents**
  - These products decrease blood pressure and can cause severe dizziness, especially after the 1st dose

**Sensory and Pain Symptoms**

- **Sensory symptoms**
  - Trigeminal neuralgia (one of the more common symptoms)
  - Burning, itching, L’Hermitte’s sign, face twitching
  - Carbamazepine 200 mg PO BID or TID
  - Gabapentin, topiramate, tiagabine, tricyclic antidepressants (TCAs)

- **Neuropathic pain (50%)**
  - Difficult to treat
  - Carbamazepine, TCAs, gabapentin, pregabalin, duloxetine, topiramate, tiagabine, capsaicin cream, etc

**Spasticity**

- **Affects up to 70% of patients with MS**
- **Leading cause of disability in MS**
- **A velocity-dependent increase in muscle tone, derived from hyperexcitability of the stretch reflex**
  - Primarily affects the lower limbs and can lead to pain, stiffness, tremor, clonus, impaired balance, and spasms

- **Clinical manifestations include**
  - Phasic spasticity (spasms, cramps, and clonus)
  - Tonic spasticity (stiffness)
  - Can be induced by a variety of noxious stimuli (eg, urinary tract infections, constipation, pressure ulcers, poorly fitting assistive living devices)
  - IFN-β products enhance nerve conduction in the spinal cord and can exacerbate spasticity

- **The goal of therapy is to reduce symptoms in order to improve patient comfort and function, rather than to completely eliminate the spasticity**
- **Some degree of spasticity actually helps patients with lower-extremity weakness walk because it offers some limb stabilization**

**Nonpharmacologic Treatments**

- **Nonpharmacologic treatments should be used prior to pharmacologic treatments**
- **Physical therapy**
  - Exercises (stretching and range of motion)
  - Aquatic exercises are popular; critical that water temperature be approximately 85°F (warmer temperatures cause fatigue; colder temperatures exacerbate spasticity)
- **Mechanical aids**
  - Orthotics
  - Braces
Spasticity
Pharmacologic Treatments

- Always start out with the lowest possible dose and slowly escalate doses upward as needed
- Oral baclofen is the drug of choice
  - Adverse events (AEs) include somnolence and confusion
  - AEs decrease over time
  - Avoid suddenly stopping the drug
- Second-line agents; frequently used in combination with oral baclofen
  - Tizanidine
  - Diazepam
  - Clonazepam
  - Dantrolene
  - Clonidine
- Refractory spasticity
  - Botulinum toxin
  - Intrathecal baclofen

O'Connor P. In: Multiple Sclerosis and Demyelinating Diseases. Lippincott, Williams, and Wilkins; 2006:227-255.

Spasticity
Patient Counseling Tips

- It is common for patients to be on >1 antispasticity medication at the same time
- All of the oral agents cause drowsiness
  - Can worsen fatigue/cognition
- When initiating therapy with oral antispasticity agents, start in the evening (at bedtime)
- Very dangerous for patients to go "cold turkey" with baclofen (oral or intrathecal)
  - Seizures, hallucinations, and death can result
  - Refill reminders from pharmacist!

O'Connor P. In: Multiple Sclerosis and Demyelinating Diseases. Lippincott, Williams, and Wilkins; 2006:227-255.

Walking/Mobility Issues

- Gait disturbances are a common symptomatic problem
- Extended Disability Status Scale (EDSS) scoring used to assess walking mobility issues

Walking/Mobility Issues

- Traditionally have been managed using nonpharmacologic treatments (ie, exercise, physical therapy, gait training, assistive devices)

EDSS Scoring

Available at: www.msdecisions.org.uk
Dalfampridine was recently approved by the FDA: 1st approved treatment for improved walking in patients with MS.

Exactly how dalfampridine improves walking is not known. It has been proposed that dalfampridine improves conduction in nerve fibers in which myelin has been damaged, thus improving mobility.

Dalfampridine Pivotal Trials

Evaluated in 2 controlled trials involving 540 patients:
- Study 1: randomized, placebo-controlled, parallel group, 21-week study in 301 patients
- Study 2: randomized, placebo-controlled, parallel group, 14-week study in 239 patients

Primary efficacy measure in both studies was walking speed as measured by the Timed 25-foot Walk.

Dalfampridine Pivotal Trials

In both studies, dalfampridine-treated patients had significantly improved walking speeds:
- Trial 1: 34.8% vs 8.3% (P < .0001)
- Trial 2: 42.9% vs 9.3% (P < .001)

A significantly greater proportion of patients taking dalfampridine had increased walking speed of at least 10%, 20%, or 30% from baseline, vs placebo.

Dalfampridine Patient Counseling Tips

- The first dose should be taken first thing in the morning, and the second dose should be taken approximately 12 hours later.
- Tell patients to take missed doses as soon as possible unless it is almost time for the next dose (keeping 12 hours between doses to prevent adverse events).

Dalfampridine Patient Counseling Tips

- Can be taken with or without food.
- Tablets should be swallowed whole; they should never be broken, crushed, or chewed.
- Patients who have a history of seizures or moderate to severe renal impairment, or who are already taking compounded 4-aminopyridine, should not take dalfampridine.

Dalfampridine vs 4-Aminopyridine

- Not bioequivalent
- Cannot be substituted
- Dalfampridine only indicated for walking/mobility issues
**Fatigue**

- 60%–97% of patients report fatigue\(^1,2,3\)
- 15%–40% report that it is the worst symptom of their disease\(^1\)
- Traditionally, fatigue has been evaluated through patient self-reporting questionnaires
  - Subjective
  - Can be confounded by other symptoms

\(^1\) O’Conner P. In: Multiple Sclerosis and Demyelinating Diseases. Lippincott, Williams, and Wilkins; 2006:227-255.
\(^3\) Henze T. Int MS J. 2007;14:22-27.

**Proper evaluation and treatment should take into account physical conditioning; management of pain, sleep, or mood disorders; laboratory studies to rule out other potential causes of fatigue**

**Rule out other factors that may cause fatigue**
- Adverse events
- Depression
- Sleep disorders
- Other metabolic conditions or diseases
- Interferon \(\beta\) products

**Treating Fatigue**

**Nonpharmacologic Treatments**

- Management requires a multidisciplinary approach
  - physical therapy, psychology, neurology, and psychiatry
  - Fatigue resulting from extreme spasticity may be lessened by stretching exercises and/or antispasm medications
  - Fatigue resulting from an infection requires treatment of the underlying condition
  - Fatigue arising from a mood disorder may respond best to combination therapy with medications and counseling
  - Fatigue arising from lifestyle factors (ie, overexertion) may respond to teaching patients to not overexert themselves

**Pharmacologic Treatments**

- **Modafinil**\(^1-3\)
  - 100–400 mg once daily in the AM
  - First-line agent for improving daytime fatigue
- **4-aminopyridine**\(^1-3\)
  - 5–20 mg twice daily (AM and in the early afternoon)
  - Especially effective in treating heat-related fatigue
- **Selective serotonin reuptake inhibitors** (ie, fluoxetine)\(^1,2\)
  - 10–40 mg once daily in the AM
  - Improves daytime fatigue associated with depression
- **Amantadine**\(^1-3\)
  - 100 mg twice daily (AM and in the early afternoon)

**Sexual Dysfunction**

- Common in both males and females\(^1,3\)
- Affects ~75% of patients\(^1,3\)
- Can be caused by a variety of factors\(^2,3\)
  - Depression
  - Fatigue
  - Neurologic impairment
  - Pain
  - Concurrent medications

\(^1\) Henze T. Int MS J. 2007;14:22-27.
\(^2\) O’Conner P. In: Multiple Sclerosis and Demyelinating Diseases. Lippincott, Williams, and Wilkins; 2006:227-255.
Pharmacologic and Other Agents That Cause Sexual Dysfunction

- Alcohol
- Beta blockers
- Certain antidepressants, including fluoxetine, paroxetine, and sertraline
- Monoamine oxidase inhibitors
- Tricyclic antidepressants

Treating Sexual Dysfunction in Males

- First line
  - Phosphodiesterase inhibitors (eg, sildenafil)¹⁻⁴
- Second line
  - Alprostadil injections
  - Amantadine
  - Penile prosthetic devices¹⁻²

Treating Sexual Dysfunction in Females

- Not easily treated with pharmacologic agents
- Sildenafil studies not effective in women
- Lack of lubrication can also cause female-related sexual problems

Emerging MS Therapies

- GA (IFN) / Natalizumab
- Fingolimod
- Oral agents
  - Laquinimod
  - Teriflunomide
  - Fumaric acid (BG-12)
- Monoclonal antibodies
  - Daclizumab
  - Alemtuzumab
  - Rituximab
  - Ocrelizumab
- Combination therapy
  - IFN-based
  - GA-based
- Novel agents

Summary

- MS symptomatic problems significantly impact patients functioning and quality of life
- Although total elimination of symptoms may not be possible, most can be treated with a variety of nonpharmacologic and pharmacologic strategies
- Effective management of MS-related symptoms requires a coordinated, multidisciplinary approach that includes pharmacists, physical therapists, psychologists, and neurologists
- Health care practitioners should stress to patients the importance of adhering to all treatment regimens in order to reduce MS-related symptoms and improve their quality of life

Which Drug Used to Treat Multiple Sclerosis Requires a First Dose Observation Period?

1. Dalfampridine
2. Glatiramer acetate
3. Fingolimod
4. Interferon Beta 1a

© 2012 by the American Pharmacists Association. All rights reserved.
EG Reports Severe Flu-Like Symptoms with her Multiple Sclerosis Therapy. Which First Line Drug Would be your Next Choice?

0% 1. Fingolimod
0% ✓2. Glatiramer acetate
0% 3. Interferon Beta 1b
0% 4. Interferon Gamma 1a

MB is Experiencing Fatigue and Depression. Which Drug is a Good Option for this Patient?

0% 1. Amitriptyline
0% 2. Mirtazapine
0% 3. Imipramine
0% ✓4. Fluoxetine

RP is Complaining of Problems Walking. You Recommend Which of the Following Drugs at add to his Multiple Sclerosis Therapy?

0% ✓1. Dalfampridine
0% 2. Bupropion
0% 3. Modafinil
0% 4. Natalizumab

Which Option Below has Proven to Promote Adherence in Multiple Sclerosis Patients

✓1. Set realistic expectations
0% 2. Nonadherence is not a problem
0% 3. Give a drug holiday
0% 4. Defer the drug copay