NEW DEVELOPMENTS IN THE TREATMENT OF MULTIPLE SCLEROSIS

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Disclosure

❖ Honorarium/consulting: Novartis Pharmaceuticals

❖ UVA Institutional contracts
  ❖ Adjudication committee member for Biogen, Idec
  ❖ Consulting Acorda Pharmaceuticals
  ❖ Research funding from NMSS, NIH NINDS, Biogen Idec, & Novartis.

❖ I will discuss drugs are currently not FDA approved (in development) and discuss off-label use of medications for MS-symptom management.
## Multiple Sclerosis

- Chronic inflammatory condition of the CNS induced by an environmental trigger in a genetically susceptible patient.
- CNS lesions disseminated in time and space without an alternative explanation.

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## Multiple Sclerosis: Significance

- The most common, non-traumatic cause of disability in young adults
- Estimated ~ 400,000 MS patients in the US
- More common in women: ~ 2:1
- Onset: 20-40 years old
- Treatable with 10 FDA approved agents

*With increased emphasis on early DX and TX there is greater risk of misdiagnosis*
Etiology: Nature vs. Nurture

- Genetics:
  - Identical twins (20-30%)
  - Non-Identical twins/Siblings (2-5%)
  - Racial clustering

- Environment:
  - 20% have affected family member.
  - Migration Studies

- The Search: virus, bacteria, nutrition, well water, exposure to animals, trauma, minerals, chemical agents, metals, organic solvents, geographical influences and occupational hazards.

Etiology: Nature and Nurture

- Genetics: Determine individual susceptibility to MS

- Environment: Exposure relevant in genetically susceptible individuals. Unlikely single factor.
  - Infections agent exposure
  - Lifestyle factors (smoking)
  - Geographical factors (equatorial latitude)
  - Sunlight exposure (vitamin D)

Disease Mechanism: 3 Components

- **Inflammation**
- **Demyelination**
- **Neuron Loss**

Diagnosis of MS

- **Dissemination in Space**
  - Multifocal CNS process by history, exam, MRI, EP
- **Dissemination in Time**
  - Relapses or Progression by history
  - New lesions by exam, MRI, EP
- Immune-mediated – CSF & MRI
- No other explanation by History, Exam, MRI, CSF, or Blood Studies

McDonald, Ann Neuro, 2001; Polman, Ann Neur. 2005; updated 2010
MS Disease Classification

- Radiologically Isolated Syndrome
  - static vs. dynamic
- Clinically Isolated Syndrome
  - Low Risk
  - High Risk** (2010 – RRMS)
- Relapsing- Remitting
- RR-Secondary Progression
- Primary Progressive
- PP- with Relapses

Lublin and Reingold, Neurology 1996; 46:907-911
Expression of MS Disease

- Clinical: Relapse, Residual Symptoms & Disability Accrual

- Sub-clinical: MRI changes
  - Acute $\rightarrow$ Enhancement
  - Chronic $\rightarrow$ T2 lesion burden, T1 “holes”, atrophy

RRMS: Demyelination & Repair
Acute Neuron Loss (Residual Deficits)

T1-Hypointense Lesions (Black Holes)
Demyelination & Repair

Delayed Neuron Loss (Progression)
Natural History of Relapsing MS
Clinical and MRI Measures

- Brain Volume
- Relapses and Impairment
- MRI T2 Burden of Disease (BOD)
- MRI Activity

SP-MS

Preclinical  RR-MS

0  5-10  15-20+
Disease Duration (Years)
Natural History of Relapsing MS
Clinical and MRI Measures

Relapses = Tip of the Iceberg
Treatment of MS

Requires an Interdisciplinary Approach

- Physicians: PCPs, Neurology (MS & Sleep), PMR, & Urology
- Nursing
- Physical Therapy & Occupational Therapy
- Speech Therapy
- Psychology / Psychiatry
- Social Work
Consequences of MS: Symptoms

- Spasticity
- Weakness
- **Gait dysfunction**
- Pain
- Tremor
- Vertigo
- **Bladder dysfunction**
- Bowel dysfunction
- Sexual dysfunction
- Depression
- Cognitive impairment
- Fatigue

Impact of MS disability

- Direct Health Care Costs: > **10 billion annually**
  - 47,000 per patient/year
  - 12,000 for relapse event

- Indirect Health Care Costs
  - Mean disability days/year $29.8
  - MS employees annual disability cost: $3858 vs. 414 (non-MS)
  - Total annual indirect costs: $5769 vs. 1417 (non-MS)
  - **Level of MS-related disability is related to indirect costs**

Mathis, AJMC 2013
MS Disability Accrual over Time

- DSS 5 = Disability precludes working; able to walk unaided up to 500 meters
- DSS 7 = Wheelchair bound

Mobility & Employment

- Figure 2: Employment status stratified by mobility impairment score among patients with multiple sclerosis. (A) Women. (B) Men.
Instrumental ADLs & T25FW

Treatment of MS
Definition of a Relapse

McDonald Criteria

- Neurological disturbance of kind seen in MS
  - Underlying inflammatory/demyelinating pathology
- Subjective report or objective observation
- At least 24 hours duration
- Exclude “pseudoattacks” - residual symptoms from previous relapses
- 30 days between onset of event 1 & event 2

McDonald, Ann Neuro, 2001

Treatment of MS Relapses

- Precipitating factors (*infection/fever*)
- Corticosteroids (IVSM 1000 mg x 3 days)
- Plasma Exchange (refractory patients)
- Symptomatic Management
- Neurological rehabilitation
Treatment of MS

Relapses → Symptoms

Patient → Disease

Approval Time Line


Jan 2010: Dalfampridine
## Administration & FDA Indication

<table>
<thead>
<tr>
<th>Name</th>
<th>Administration</th>
<th>FDA Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl Fumarate (Tecfidera)</td>
<td>120 mg PO twice daily</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>0.5 mg PO daily</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Glaterimer Acetate (Copaxone)</td>
<td>20 mg SQ daily</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Interferon-beta 1a (Avonex)</td>
<td>30 mcg IM weekly</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Interferon-beta 1a (Rebif)</td>
<td>22 or 44 mcg SQ three times wk</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Interferon-beta 1b (Betaseron, Extavia)</td>
<td>250 mcg SQ every other day</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>12 mg/m² IV q3M Max dose 140 mg/m²</td>
<td>Worsening RRMS, SPMS, PRMS</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>300 mg IV every 4 wks</td>
<td>Relapsing Forms</td>
</tr>
<tr>
<td>Teriflunimod (Aubagio)</td>
<td>7 or 14 mg PO daily</td>
<td>Relapsing Forms</td>
</tr>
</tbody>
</table>

### Natalizumab (Tysabri):

- Humanized monoclonal antibody to α4-integrin
- α4-integrin antagonist
- Designed to decrease immunogenicity and increase half-life

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Progressive Multifocal Leukoencephalopathy

- February 2005: Biogen Idec voluntary suspends Natalizumab use after 3 PML cases.
- March 2006: FDA votes to re-release Natalizumab. TOUCH Program initiative
- April 2013: 347 total PML cases worldwide
  - 112,181 patients treated worldwide
  - Mortality: 79/347 deceased (23%)
  - Mortality: Mild (13%); Moderate (50%), Severe (37%)*

*Biogen press release, 1/2012 & Vermersch Neurology 2011

Progressive Multifocal Leukoencephalopathy

- Reactivation of polyomavirus JC (papovaviridae family) inducing a lytic infection of oligodendrocytes, resulting in demyelination.
- Virus resides in latent form in up to 80% of healthy adults
- Factors leading to activation are not fully understood
- Presenting symptoms can include:
  - Impaired cognition (behavioral changes)
  - Cortical blindness
  - Hemiparesis
  - Seizure (17%)
PML Update: April 2, 2013

* 347 cases of 112,181 treated patients

PML Update: January 2012

Table 1: Estimated Incidence of PML Stratified by Risk Factor

<table>
<thead>
<tr>
<th>Tysabri Exposure*</th>
<th>Anti-JCV Antibody Positive*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prior Immunosuppressant Use</td>
</tr>
<tr>
<td>1-24 months</td>
<td>&lt;1/1,000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>4/1,000</td>
</tr>
</tbody>
</table>

Notes: Based on postmarketing PML data and Tysabri use data as of September 1, 2011.
*Data beyond 4 years of treatment are limited.
*Risk in anti-JCV antibody positive patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated MS patients are anti-JCV antibody positive.

PI updated 1/2012
PML Monitoring/Accessment

Clinical assessment of new neurologic symptoms if suggestive of non-MS-related disease
- Suspend dosing
- Cannot exclude PML
- MRI assessment
  - PML unlikely
    - Dosing may be resumed
  - JCV not detected and low clinical suspicion
    - Repeat assessment
- CSF assessment
  - JCV not detected and high clinical suspicion
    - Treat as PML
  - JCV detected
    - Repeat assessment

Kappos, Lancet 2007

PML Treatment & IRIS*

- Discontinue Treatment
- Plasma Exchange 3-5 exchanges
- IRIS after PLEX
  - 7-14 days post PLEX
  - IV steroids (Prophylactic?)
- MS Reactivation following Tysabri ~ 3 mos
- Treatment options post PML
**Fingolimod (Gilenya)**

Sphingosine-1-phosphate receptor agonist/modulator

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**Fingolimod: Adverse Events**

- **Common and Mild/Moderate Events:**
  - Bradycardia (Asymptomatic)**
  - Headache
  - Lymphopenia
  - URI/Nasopharyngitis
  - Elevated ALT/AST
  - Macular Edema (reversible)

- **Serious Events**
  - Fatalities: HSV encephalitis and systemic VZV
Fingolimod Treatment Plan

- **Pre-Treatment Recommendations**
  - CBC, LFT, Bilirubin levels
  - **Baseline ECG** patients on beta-blockers, calcium channel blockers Class Ia and III antiarrhythmics, HR <55 bpm, irregular HR**
  - Baseline ophthalmologic exam
  - VZV titers and vaccination (other vaccinations?)
  - Contraception use

- **First Dose: 6 hours of observation**
  - Repeat 14 day holiday

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Fingolimod: Updates

- Dec 2011: 59 y/o unexplained death in sleep reported
- Jan 20, 2012: EMA changes guidelines for monitor recommendations and highlights 11 total “possibly related to treatment”
- Jan 26, 2012: Novartis reports on total 31 deaths in Clinical Development Program (2003 – 2012)
- ~ 32000 patients treated to date

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Fingolimod safety guidelines, Novartis
**Fingolimod: Updates**

- **20: Thought not likely related to drug**
  - 6 Suicides
  - HSV & VZV trial subjects

- **11: Possibly relate to Drug (EMA)**
  - 3 Complicated Advance MS
  - 3 Myocardial Infection
  - 1 HTN Cardiovascular Death (unexplained)
  - 2 Drowning
  - 2 Sudden Unexplained Death (Sleep)

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**Fingolimod: Updated Monitoring Plan**

- EKG All patients: baseline & 6hrs post dose
- 6 Hour Monitoring & Overnight monitoring

**UVA Monitoring**

- Short Stay Unit: Last Monday of Month
  - 6 Hour Observation w/hourly BP & HR

- **SSU: 23 Hour Observation**
  - Hx of cardiac disease &/or Concurrent Medication
  - Med w/history of QT prolongation/Torsades
  - Hx of Bradycardia, Syncope, Hypotension (Title table)
  - Sleep Disordered Breathing
  - Possible Brainstem Disease/Autonomic dysfunction?
**Terflunomide: Oral Therapy**

- Active metabolite of Leflunomide -- RA
- Dihydro-orotate dehydrogenase inhibitor
- Blocks pyrimidine synthesis & appears to decrease APC activity.

- FDA Approval: 9/2012

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**Terflunomide: Oral Therapy**

- Phase II: RRMS & SPMS, 179 subjects with 2 doses (7 & 14 mg, Plcb), 36 wks
  - Significant reduction in MRI activity (>61%), both doses
  - Trend to reduced relapse rate and # relapse-free (both doses)

- AE: Nasopharyngitis, alopecia, nausea, LFT changes, diarrhea
Terflunomide

- TEMSO: 1088 RRMS
- 7 & 14 mg dose/Plcb 2 yr study
- 31% relative reduction ARR c/w Plcb
- Disability Progression 20.2% 14 mg c/w 27.3% Plcb
- SE: No deaths; Pyelonephritis; nausea, alopecia, LFTs, N/D


Terflunomide: Safety

<table>
<thead>
<tr>
<th>SE/AE</th>
<th>14 mg</th>
<th>7 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Carpel Tunnel Synd</td>
<td>3</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>ALT increase</td>
<td>14</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>18%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

** Warfarin: 25% decrease in peak INR**
**Fumaric Acid: Oral Therapy**  
(Dimethyl Fumarate, BG-0012, Tecfidera)

- Intermediate product of the citric acid cycle
- Initially used for treatment of psoriasis (1959)
- MOA: Multiple potential effects, clear MOA remains uncertain. Impact on T-cells, B-cells, and Dendritic Cells, endothelial and glial cells (CNS activity).

- AE: headache, mild infections, GI symptoms, LFT changes & Flushing.

- FDA Approval 3/2013

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**FULL PRESCRIBING INFORMATION**

**WARNING: HEPATOTOXICITY and RISK OF TERATOGENICITY**

Hepatotoxicity  
Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Concomitant use of AUBAGIO with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO [see Warnings and Precautions (5.1)]. If drug induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or charcoal [see Warnings and Precautions (5.3)]. AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4.1)]. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.

Risk of Teratogenicity  
Based on animal data, AUBAGIO may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting AUBAGIO. AUBAGIO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during AUBAGIO treatment or prior to the completion of an accelerated elimination procedure after AUBAGIO treatment [see Contraindications (4.2), Warnings and Precautions (5.2), and Use in Specific Populations (8.1)].

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1. **INDICATIONS AND USAGE**

AUBAGIO® is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS).
Fumaric Acid: Oral Therapy
(Dimethyl Fumarate, BG-0012, Tecfidera)

– MOA
  • Cytokine shift to more anti-inflammatory, Th2 cytokine milieu
  • Upregulated of nrf2 pathway (protective)

– Phase 3 data
  • DEFINE - 2 year, placebo controlled 240mg bid (n=1,011)
    – 54% reduction in ARR
    – 38% reduction in SAD
    – 85% reduction in new T2; 90% reduction in Gd
  • CONFIRM - 2 year, BG-12 vs placebo vs Copaxone
    – 44% reduction in ARR vs placebo; Copaxone 29% reduction
    – 71% reduction in T2; 65% reduction in Gd

– Safety: Annual CBC recommended
  • Flushing, especially first month (aspirin may reduce)
  • GI side effects, including diarrhea initially

NEJM April 2013 – Letters to Editor
• 3 Cases thought to be related to Fumaderm in 180,000 patient years
• Tecfidera 2,600 patients for up to 4 yrs
• Multiple medication exposure/history
• FDA aware of cases prior/during review & approval process
Limitations of Available MS Therapies

- Expense
- Several administered by injection
- Side effects

- Partial effectiveness
  - Optimal dose is uncertain
  - Neutralizing antibodies
  - Pathological heterogeneity

- Order of Progression/Escalation
  - Comparative Efficacy Unknown
  - Relative and sequential safety uncertain

Phase III Trials: ARR Risk Reduction

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ARR &amp; Select MRI</th>
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<tbody>
<tr>
<td>Interferon</td>
<td>33</td>
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<tr>
<td>GA</td>
<td>30</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>68</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>54</td>
</tr>
<tr>
<td>Terifluromide 7 mg</td>
<td>92</td>
</tr>
<tr>
<td>Terifluromide 14 mg</td>
<td>90</td>
</tr>
<tr>
<td>Dimebly fumarate</td>
<td>80</td>
</tr>
<tr>
<td>Dimebly fumarate*</td>
<td>69</td>
</tr>
</tbody>
</table>
**Injection Comparative Trials**

![Graph showing Relative Risk Reduction for various injection trials.]

**Relapse Rate Relative Risk Reduction**

<table>
<thead>
<tr>
<th></th>
<th>Avonex</th>
<th>Betaseron</th>
<th>Copaxone</th>
<th>Rebif</th>
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<tr>
<td>Phase III</td>
<td>32</td>
<td>34</td>
<td>30</td>
<td>33</td>
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<tr>
<td>CIS trials</td>
<td>30</td>
<td>38</td>
<td>42</td>
<td>24</td>
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<tr>
<td>Avonex DD</td>
<td>47.7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>INCOMIN</td>
<td>49.3</td>
<td>67.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVIDENCE</td>
<td>50.8</td>
<td></td>
<td>58.5</td>
<td></td>
</tr>
<tr>
<td>REGARD</td>
<td></td>
<td></td>
<td>71.3</td>
<td>69.1</td>
</tr>
<tr>
<td>BEYOND</td>
<td></td>
<td>78</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Comparison Trials w/ Non-injectables

Comparative Study Summary

- **Injection Comparative studies are limited by:**
  - Lack of patient/researcher blinding
  - Small numbers and short duration
  - Differences in baseline treatment arms
  - Possible shift in MS natural history/population

- **Majority of studies suggest no significant difference between MS injectable therapies.**

- **Non- Injection Trials**
  - Fingolimod and Dimethyl fumarate preformed better than injectables in head to head study
  - **CAUTION:** Comparing new therapies across studies
Clinical Trials Comparison: ARR @ 2yrs

| ARR | 1.27 | 0.74 | 0.54 | 0.364 |

Defining Treatment Failure

- Consensus lacking of Definition of Failure
- Recent Meeting 2012: Free of Disease Activity

- Three domains of failure
  - Patient: intolerance
  - Clinical: relapses or disease progression
  - MRI: Recurrent Gde & Accrual of lesion burden

- Current Tx are most effective in early inflammatory stage of disease

- Vigilance for treatment response in early years is critical in patient therapy management.

Freedman, et al. 2004
Evaluating Treatment Failure

- Alternative diagnoses
- Adverse effects and Compliance
- Interferon- Neutralizing Antibodies
- MRI: Scanner Quality and Strength
- Disease progression (SPMS)
  - Incomplete recovery from relapses
  - Continuous (insidious) progression

Treatment of MS

Symptoms

Relapses

Patient

Disease
Common MS Symptoms

- Spasticity
- Weakness
- Fatigue
- Pain
- Tremor
- Vertigo
- Gait dysfunction
- Bladder dysfunction
- Bowel dysfunction
- Sexual dysfunction
- Depression
- Cognitive impairment

Treatment of MS Symptoms

Non-pharmaceutical approaches

- Look for contributing factors to eliminate
- Consider therapies & lifestyle changes
  - PT for spasticity
  - Timed voiding for bladder or bowel symptoms
- An alternative approach may be better
  - Counseling for emotional distress
  - Education/Resources for family & employment issues
Treatment of MS Symptoms

**General Principles for medications**

- Ask about troublesome symptoms
- Try to keep things simple
  - Prioritize
  - Balance symptoms and function
  - Monotherapy when able
  - Start low and go slow
- Aim to improve function & quality of life
- Symptom treatment is a fluid process
  - Review medications and assess ongoing need

**MS Symptom Management**

**Spasticity**
Spasticity Management

Non-pharmacologic
- Stretching
- Massage
- Acupuncture

Medications
- Baclofen
- Tizanidine
- Neurontin
- Benzodiazepines

Interventions
- Botulinum Toxin
- Intrathecal Baclofen

Other Medications
- Cannabis - Sativex
- Naltrexone

Gait Dysfunction

- Contributors: Weakness, Spasticity, Fatigue, sensory changes

- Impact: Loss of independence, inability to remain in workforce, reduced quality of life, secondary medical complications.
Mobility & Employment

Figure 2. Employment status stratified by mobility impairment score among patients with multiple sclerosis. (A) Women. (B) Men.


MS Symptom Management

Gait Dysfunction
Dalfampridine (Ampyra)
Dalfampridine (Ampyra)

- Potassium Channel Blocker
- Improved axonal conduction
- Oral therapy taken twice daily
- FDA Approval 1/2010
- Available 3/2010
Dalfampridine: Phase III Trial

- Placebo vs. Ampyra 10 mg twice daily
- 301 MS: 83 RR, 45 PP, 160 SP
- Responder:Non-Responder Model
- Timed 25 Foot Walk Test (8-45 sec)
- Responders: 35% of treated group
  - Improved walking time (25%)
  - Improved MSWS-12
  - Improved strength and reduced spasticity

Instrumental ADLs & T25FW

<table>
<thead>
<tr>
<th>Assistance required</th>
<th>Median T25FW</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Help</td>
<td></td>
</tr>
<tr>
<td>Some Help</td>
<td></td>
</tr>
<tr>
<td>Unable</td>
<td></td>
</tr>
</tbody>
</table>

- Housework
- Laundry
- Grocery Shopping
- Preparing meals
- Taking medication

Confidential: Prepared/Provided by Dr. Myla D. Goldman
Goldman, et.al. AAN 2013
Dalfampridine: Recommendations

- MS Patients with impaired walking
- Timed 25 Foot Walk, **5-45 seconds**
- Monitor for response over 4-12 weeks
- Caution/Contra-indications
  - Seizure Hx
  - Renal Impairment
  - Poorly managed Neurogenic bladder.

FATIGUE AND MS
“IT’S COMPLICATED”
MS-related Fatigue

- **Primary MS Fatigue**
  - Fatigue that worsens over the course of the day, peaking in the mid-afternoon

- **Secondary Fatigue**
  - Typically chronic unremitting fatigue
  - Temporal pattern depends on the underlying cause and can vary from patient to patient and within a patient from day to day
### Sleep Disorders

**Primary**
- Primary Insomnia
- Primary Hypersomnia
- Narcolepsy
- Circadian Rhythm d/o
- Parasomnias

**Secondary**
- Mood disturbance
- Medications
- External factors
- Sleep Hygiene
- Other medical conditions

### Insomnia in MS

- 60 MS subjects with sleep diary for 1 wk
  - 32% with ESS >10 (19/59)
  - 64% with Fatigue, FSS >4 (38/59)
  - Median 8 hours in bed
  - 73% took ≥ 2 naps/week

**Insomnia**
- **Initial**: 42% (>30 min SO ≥ 2days/wk)
- **Middle**: 53.3% (≥ 2 arousals/week)
- **Terminal**: 58.3% (≥ days/week)

*Only Middle Insomnia correlates w/ FSS*

Stanton, MS 2006
Causes of Sleep Disturbance in MS

Table 1. Reasons for insomnia

<table>
<thead>
<tr>
<th>Reason</th>
<th>Initial (n = 236)</th>
<th>Middle (n = 295)</th>
<th>Terminal (n = 146)</th>
<th>Total (n = 677)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain/discomfort</td>
<td>53 (22.6%)</td>
<td>64 (21.7%)</td>
<td>22 (15.1%)</td>
<td>139 (20.5%)</td>
</tr>
<tr>
<td>Spasms/tightness</td>
<td>34 (14.4%)</td>
<td>116 (39.4%)</td>
<td>15 (10.4%)</td>
<td>165 (24.5%)</td>
</tr>
<tr>
<td>To pass urine</td>
<td>54 (22.9%)</td>
<td>121 (41.1%)</td>
<td>14 (9.7%)</td>
<td>189 (28.0%)</td>
</tr>
<tr>
<td>Anxiety/distressing</td>
<td>63 (27.5%)</td>
<td>90 (30.5%)</td>
<td>15 (10.4%)</td>
<td>168 (25.0%)</td>
</tr>
<tr>
<td>Low mood/thoughts</td>
<td>46 (19.9%)</td>
<td>10 (0.4%)</td>
<td>16 (11.0%)</td>
<td>72 (10.7%)</td>
</tr>
<tr>
<td>External factors</td>
<td>43 (18.2%)</td>
<td>47 (15.9%)</td>
<td>53 (36.3%)</td>
<td>143 (21.1%)</td>
</tr>
</tbody>
</table>

*Percentages expressed as number of occasions reason cited/number of sleep episodes in which each type of insomnia occurred×100. Subjects were allowed to give more than one reason, therefore percentages total > 100%.

Stanton, MS 2006

MS and Polysomnography

• 37 MS (27 F-MS& 10NF-MS) & 13 Controls
• Mean ESS in MS subjects (p>0.05)
  • F-MS: 4.4 ± 2.8
  • NF-MS: 3.3 ± 3
• Restless Leg Syndrome 37% of MS subjects
  • F-MS: 40.7% (11/27)
  • NF-MS: 30% (3/10)
• Pittsburg Sleep Quality Index (PSQI) (p<0.05)
  • F-MS 7.2 (range 2-15)
  • NF-MS 4.9 (1-10)
  • Controls 2.8 (1-4)

Kaynak, EJN 2006
### MS and Polysomnography

MS subjects vs. Controls

**No significant difference**

- Sleep Architecture
  - Stage I, II, III, IV sleep
  - Stage REM sleep
  - REM sleep latency
- Apnea-hypopnea Index

---

### Treatable Sleep-Related Causes of MS-Fatigue

<table>
<thead>
<tr>
<th>Poor Sleep Hygiene</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary lifestyle</td>
<td>Nocturia</td>
</tr>
<tr>
<td>Medications</td>
<td>Pain/discomfort</td>
</tr>
</tbody>
</table>

- IFN Therapy
- Baclofen
- Tizanidine
- Tri-cyclics
- Neurontin

- Spasticity/Leg Spasms
Treatale Sleep Disorders in MS

- Restless Leg Disorders
- Periodic Limb Movement Disorder
- Obstructive Sleep Apnea
- Narcolepsy-Cataplexy Syndrome
- REM sleep behavioral disorder

Who Should Get a Sleep Study?

- MS patients with Chronic Unremitting Fatigue
- Who have persistent fatigue after treatment of probable secondary causes
- MS subjects with fatigue and reports of snoring or apneas.
- MS subjects with refractory fatigue who have risk factors for Sleep Apnea
- MS subjects with symptoms suggestive of other primary sleep disorders (e.g. narcolepsy)
MS Fatigue Related Medications

• Provigil (Modafinil) 100 – 400 mg daily
• Nuvigil (Armodafinil) 150 -250 mg daily
• Amantidine 100 – 400 mg daily
• Ritalin 2-10 mg three times a day

Non-Medication approaches to Primary MS related fatigue

Bladder Management
Categories of Bladder Dysfunction

- **Hypertonic – 60 - 80%**
  - Urgency
  - Frequency
  - Incontinence

- **Hypotonic – 20%**
  - Hesitancy
  - Retention
  - Overflow incontinence

- **Mixed Syndrome – 25%**
  (DSD, Detrusor-Sphincter Dyssinergia)

**Consequences**
- Recurrent Infections
- Possible Sepsis
- Vesicourtheral reflux
- Hydrenephrosis
- Renal Impairment

Bladder Management

**Non – Pharmacologic**
- Timed Voids
- NES Biofeedback
- PFMT- Pelvic Floor Muscle Training
- Self - Catheterization

**Medications**
- Anticholinergic Agents
  - SE: Dry mouth/eyes, CONSTIPATION, COGNITIVE IMPAIRMENT, FATIGUE
- Desmopressin: Nocturia
- Cannabinoids – Sativex?

**Surgical Interventions**
- Posterior Tibial Nerve Stimulation
- Sacral Neuromodulation**
- Botulinum Toxin
- Supra-pubic Catheter
- Augmentation Cystoplasty

Treatment of MS

MS Patient: Mitigating Risk Factors

- Vitamin D
  - Check & Supplement

- Smoking
  - Support Smoking Cessation Programs

- Other co-morbidities
  - Modify CV Risk Factors
  - Obesity
  - Exercise
Treatment of MS Patient

- Pregnancy & Fertility
- Osteoporosis
- Vaccinations

Pregnancy & Fertility

- MS has no effect of fertility or pregnancy course
- MS may affect delivery duration and BW (Neurology 2005)
- MS treatments can effect fertility and pregnancy
  - Immunosuppressant
  - Immune modulators (IFN)
  - Symptom directed therapies

- Pregnancy should be planned and coordinated in conjunction with Ob/Gyn or family practitioner
## MS Medications and Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer Acetate</td>
<td>B</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>C</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
</tr>
<tr>
<td>Dimethyl Fumerate</td>
<td>C</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>C</td>
</tr>
<tr>
<td>Teriflunimode</td>
<td>X</td>
</tr>
</tbody>
</table>

## Osteoporosis

- **Population**
- MS increased risk c/w sex matched peers
  - Immune disorder
  - Reduced mobility
  - Steroids
    - Pulse IV courses w/increased bone mineral density
    - Monitor with DEXA scans
- **Vitamin D & Calcium supplementation**
### Vaccinations

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Recommendations</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age or clinically appropriate vaccines (e.g. tetanus)</td>
<td>Per CDC Criteria</td>
<td>- Do not administer during serious relapse. Defer for 4-6 weeks. &lt;br&gt;- Do not administer in patients who have received IVlg in the previous 3 months</td>
</tr>
<tr>
<td>Live attenuated vaccinations</td>
<td>Per CDC Criteria</td>
<td>- Do not administer to patients receiving immunosuppressive Tx  &lt;br&gt;- Interferons and Copaxone are not immunosuppressant &amp; are safe for these vaccinations.</td>
</tr>
<tr>
<td>Flu Vaccination</td>
<td>Per CDC Criteria</td>
<td>No special considerations</td>
</tr>
</tbody>
</table>

### QUESTIONS & COMMENTS