Sleep and fatigue in multiple sclerosis

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Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients, OR
2. I have the following relationships with entities producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Sanofi-Genzyme, Genentech-Roche</td>
</tr>
<tr>
<td>Consultant</td>
<td>Jazz Pharmaceuticals</td>
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<td>Speakers' Bureaus</td>
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<tr>
<td>Financial support</td>
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<tr>
<td>Other</td>
<td>Patent application for sleep apnea treatment</td>
</tr>
</tbody>
</table>

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR
4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1. 
2. 
3.
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Multiple Sclerosis

- Autoimmune disease
- Affects the brain, spinal cord, optic nerves
- Clinical onset between 20-40 years old
- Close to 1,000,000 affected in U.S.
- Still no cure...
Clinical features of MS

• Symptoms may be relapsing or progressive
• Common **physical** symptoms:
  • Paraparesis/hemiparesis
  • Sensory disturbances
  • Incoordination/ataxia
  • Visual disturbances/diplopia
  • Bowel/bladder dysfunction
The Invisible Symptoms of MS

- FATIGUE
- Chronic pain
- Cognitive impairment
- Depression
- Neurogenic bladder
Fatigue in MS: Epidemiology and Impact

- Affects up to 90% of persons with MS (PwMS)
- The first manifestation of MS in approximately 1/3 of PwMS
- Does not correlate consistently with standard measures of disease severity
- Most incapacitating symptom in over 40% PwMS
- Strong predictor of:
  - Employment
  - Reduction in work hours/productivity
  - Social participation
  - Quality of life
  - Adherence to treatment (other aspects of clinical care)?

Fatigue: one of the most difficult symptoms to treat

• Main challenges/barriers
  • No unified definition of fatigue
  • Limitations of current measures used in research/clinical care
  • Multifactorial nature of fatigue
  • Available treatments have not been fully optimized → Decisional uncertainty
Sleep Disturbances in MS

• At least 60% of MS patients report sleep disturbances (neuroanatomical, behavioral and immunological influences)
• Sleep disorders under-recognized in patients with MS, yet TREATABLE
• Timely and thorough evaluations and treatment for underlying sleep disorders can have a profound impact on patients’ health and wellbeing
  • Fatigue
  • Pain
  • Cognitive dysfunction
  • Depression
  • Quality of life
  • Overall Health and Mortality
• Concomitant sleepiness can confound diagnosis and management of fatigue, and vice versa

Characteristics of MS that increase the risk of sleep disorders

- Brainstem lesions→ Sleep Apnea, REM Sleep Behavior Disorder
- Spinal cord lesions→ Restless Legs Syndrome
- Comorbid symptoms (depression, pain, spasticity, urological)→ Insomnia
- Medications→ Insomnia, RLS, Sleep Apnea, RBD

*Braley et al, Neurology 2012
Manconi et al, Mult Scler, 2008
Rizzo et al, Sleep Med 2019
Sleep disordered breathing (SDB)

• Obstructive sleep apnea (OSA)
  • Characterized by repeated upper airway obstruction during sleep, despite attempts to resume respiration
  • Obstructions can be complete (apneas) or partial (hypopneas)
  • Leads to nocturnal hypoxia and sleep fragmentation

• Central sleep apnea (CSA): complete or partial impairment of airflow in the absence of respiratory effort due to lack of respiratory drive

• MS patients are at increased risk for both OSA and CSA

*Braley et al JCSM 2014
Brass et al JCSM 2014
Kaminska et al Mult Scler 2012
Veauthier et al Mult Scler 2011
†Braley et al, SLEEP 2016
Braley et al, JCSM Feb 2014

• Clinic-based survey study (U-M MS clinic)
• Assessed the prevalence and predictors of sleep disturbances and their relationship to fatigue
• N=195 surveys completed
4 validated scales:
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- STOP-BANG questionnaire (screening tool for OSA)*
- Insomnia Severity Index (ISI, for n=109 patients dissatisfied with their sleep)

Other measured outcomes:
- Perceived sleep latency, duration, number of nocturnal awakenings
- RLS diagnostic criteria
- Formal OSA diagnosis and treatment type
- Specific nocturnal symptoms that interfered with sleep (pain, spasticity, nocturia, inability to shut off mind)
- Type and frequency of prescription and over the counter hypnotic use

Medical charts reviewed:
- Confirm MS diagnosis
- Determine MS subtype
- Dichotomize disability score
- Presence of depression
- Presence of disease-modifying therapy

*Chung et al, Br J Anaseth 2012
<table>
<thead>
<tr>
<th>Variable</th>
<th>All MS patients (n = 195)</th>
<th>STOP-Bang ≥ 3 (n = 110)</th>
<th>STOP-Bang &lt; 3 (n = 85)</th>
<th>History of formal OSA diagnosis Yes (n = 41)</th>
<th>History of formal OSA diagnosis No (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep duration (mean ± SD)</td>
<td>6.6 ± 1.3</td>
<td>6.5 ± 1.3</td>
<td>6.7 ± 1.4</td>
<td>6.4 ± 1.5</td>
<td>6.6 ± 1.3</td>
</tr>
<tr>
<td>Number of nocturnal awakenings per night (mean ± SD)</td>
<td>2.1 ± 1.2</td>
<td>2.2 ± 1.2*</td>
<td>1.9 ± 1.2</td>
<td>2.4 ± 1.1†</td>
<td>2.0 ± 1.2</td>
</tr>
<tr>
<td>Sleep latency ≥ 1 hour, n (%)</td>
<td>86 (44.6)</td>
<td>53 (48.2)</td>
<td>33 (39.8)</td>
<td>21 (51.2)</td>
<td>65 (42.8)</td>
</tr>
<tr>
<td>Fatigue Severity Scale score (mean ± SD)</td>
<td>4.6 ± 1.8</td>
<td>5.1 ± 1.6*</td>
<td>4.0 ± 1.8</td>
<td>5.0 ± 1.6</td>
<td>4.5 ± 1.8</td>
</tr>
<tr>
<td>STOP-Bang score (mean ± SD)</td>
<td>3.2 ± 1.7</td>
<td>4.3 ± 1.3*</td>
<td>1.6 ± 0.6</td>
<td>4.8 ± 1.6†</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score (mean ± SD)</td>
<td>8.1 ± 5.1</td>
<td>9.1 ± 5.0*</td>
<td>6.9 ± 5.1</td>
<td>9.0 ± 5.6</td>
<td>7.9 ± 5.0</td>
</tr>
<tr>
<td>Insomnia Severity Index score‡ (mean ± SD)</td>
<td>14.6 ± 5.6</td>
<td>14.8 ± 5.6</td>
<td>14.4 ± 5.7</td>
<td>17.0 ± 4.5†</td>
<td>14.0 ± 5.8†</td>
</tr>
<tr>
<td>Use of hypnotics (occasionally, frequently, or always, n (%))</td>
<td>89 (46.8)</td>
<td>51 (47.2)</td>
<td>38 (46.3)</td>
<td>20 (50.0)</td>
<td>69 (46)</td>
</tr>
<tr>
<td>Use of wake-promoting agents, n (%)</td>
<td>45 (24.1)</td>
<td>35 (32.4)*</td>
<td>10 (12.7)</td>
<td>18 (43.9)†</td>
<td>27 (18.5)</td>
</tr>
<tr>
<td>Restless Legs Syndrome, n (%)</td>
<td>56 (29.8)</td>
<td>39 (36.8)*</td>
<td>17 (20.7)</td>
<td>17 (42.5)†</td>
<td>39 (26.4)</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD or n (%). Values followed by * indicate p < 0.05 for difference between STOP-Bang groups. Values followed by † indicate p < 0.05 for difference between history of formal OSA diagnosis groups. ‡Insomnia Severity Index scores for n = 109 (56.8%) subjects who endorsed difficulty sleeping.
Brass et al, JCSM Sept 2014

• Anonymous survey study of n=2,375 patients with self-identified MS, though National MS Society database
• Validated scales: FSS, ESS, ISI, STOP-BANG, Berlin
• RLS diagnostic criteria queried
• Questions about sleep latency, duration, nocturnal awakenings
• Subjects also asked about formal sleep diagnoses (“Has your healthcare provider ever diagnosed you with...?”)
Brass et al, JCSM Sept 2014

• Screening questionnaire n (%)  
  • STOP-BANG positive = 898 (37.8%)  
  • Berlin score positive = 887 (37.3%)  
  • Insomnia Severity Index (Moderate) = 576 (24.4%)  
  • Insomnia Severity Index (Severe) = 170 (7.2%)  
  • Restless legs syndrome (4 criteria) = 866 (36.8%)  

• Has your healthcare provider ever diagnosed you with…” n (%)  
  • OSA = 101 (4.3%)  
  • Insomnia = 253 (10.6%)  
  • RLS = 287 (12.1%)
Factors that may exacerbate SDB in MS

- Medications
  - Opioids
  - Benzodiazepines
  - Antispasmodics
- Increased disability level
- Progressive MS subtypes
- Obesity
- Brainstem dysfunction (OSA and CSA)*

*Braley et al, Neurology 2012
Other consequences of OSA in MS...
Objective: To characterize associations between objective polysomnographic measures of sleep (with an emphasis on OSA) and cognitive function in patients with MS
Sleep and Cognitive Function in MS

• 38 adults with MS with concerns about sleep or cognition
  • Mean age 48 years
  • 65% RRMS (mean Expanded Disability Status Scale=3.4)
  • 55% female
  • Mean years of education: 15

• Underwent clinical PSG and neuropsychological testing

• Minimal Assessment of Cognitive Function in MS (MACFIMS)*
  • 7 cognitive tests – SDMT, PASAT, BVMT, CVLT, COWAT, JLO, DKEFS
  • 5 domains: processing speed/working memory, learning, executive function, visuospatial processing, and language function

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Domain(s)</th>
<th>Test Description</th>
<th>Score Name</th>
<th>Score Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol Digit Modalities Test (SDMT)</td>
<td>Psychomotor speed, attention, working memory</td>
<td>A written task that requires subject to use a reference key to pair numbers to geometric figures as quickly as possible in 90 sec.</td>
<td>SDMT Total</td>
<td>Total number of correct matches in 90 sec</td>
</tr>
<tr>
<td>Paced Auditory Serial Addition Test (PASAT)</td>
<td>Working memory, attention, processing speed, calculation ability</td>
<td>Single digits are presented either every 3 sec or every 2 sec on a standardized audio recording. Subject must add each new digit to the one immediately prior to it.</td>
<td>PASAT-3</td>
<td>Total correct calculations out of 60 in the 3-sec trial.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PASAT-2</td>
<td>Total correct calculations out of 60 in the 2-sec trial.</td>
</tr>
<tr>
<td>California Verbal Learning Test–II (CVLT-II)</td>
<td>Verbal Memory, Verbal Learning, Executive Functioning (Semantic Organization, Inhibition)</td>
<td>Verbal recall of 16 words is tested over five learning trials. Then, a second distractor word list is presented once, after which short-delay free recall of the first word list is tested. Long-delay free recall (after 20 min) and recognition (in a list of 48) of the initial word list is also assessed.</td>
<td>CVLT-II Total</td>
<td>An age-based standard scale score that indicates total verbal recall over the five learning trials.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CVLT-II First</td>
<td>An age-based standard scale score that indicates verbal recall after first trial.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CVLT-II Discriminability Index</td>
<td>An index score indicating ability to identify target versus distractor words.</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test – Revised (BVMT-R)</td>
<td>Visual Memory</td>
<td>A drawing task that requires subject to accurately reproduce six geometric figures from memory (after viewing stimuli for 10 sec) over three learning trials. Delayed free recall of the figures is tested after 25 min.</td>
<td>BVMT Total</td>
<td>An age-based standard T score that indicates total recall over three trials.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BVMT Delayed</td>
<td>An age-based standard T score that indicates free recall after delay.</td>
</tr>
<tr>
<td>Test Name</td>
<td>Domain(s)</td>
<td>Test Description</td>
<td>Score Name</td>
<td>Score Description</td>
</tr>
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<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test (SDMT)</td>
<td>Attention, working memory, visual processing &amp; psychomotor speed</td>
<td>A written task that requires subject to use a reference key to pair numbers to geometric figures as quickly as possible in 90 seconds.</td>
<td>SDMT Total</td>
<td>Total number of correct matches in 90 seconds.</td>
</tr>
<tr>
<td>Paced Auditory Serial Addition Test (PASAT)</td>
<td>Working memory, attention, processing speed, calculation ability</td>
<td>Single digits are presented either every 3 seconds or every 2 seconds on a standardized audio recording. Subject must add each new digit to the one immediately prior to it.</td>
<td>PASAT – 3</td>
<td>Total correct # /60 in the 3-second trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PASAT – 2</td>
<td>Total correct # /60 in the 2-second trial</td>
</tr>
<tr>
<td>California Verbal Learning Test–II (CVLT-II)</td>
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<td>Verbal recall of 16 words tested over 5 learning trials. A second “distractor word list” is then presented, followed by a test short-delay free recall of the first word list. Long-delay free recall (after 20 minutes) and recognition (in a list of 48) of the initial word list is also assessed.</td>
<td>CVLT-II Total</td>
<td>An age-based standard scale score that indicates total verbal recall over the five learning trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CVLT-II First</td>
<td>An age-based standard scale score that indicates verbal recall after 1st trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CVLT-II Discriminability</td>
<td>An index score indicating ability to identify target versus distractor words</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test – Revised (BVMT-R)</td>
<td>Visual Memory</td>
<td>Drawing task that requires subject to accurately reproduce 6 geometric figures over 3 trials. Delayed free recall is then tested after 25 minutes.</td>
<td>BVMT Total</td>
<td>Age-based standard T score that indicates total recall over three trials.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BVMT Delayed</td>
<td>Age-based standard T score that indicates free recall after delay</td>
</tr>
</tbody>
</table>

**Score Names**

- **SDMT Total**: Total number of correct matches in 90 seconds.
- **PASAT – 3**: Total correct # /60 in the 3-second trial.
- **PASAT – 2**: Total correct # /60 in the 2-second trial.
- **CVLT-II Total**: An age-based standard scale score that indicates total verbal recall over the five learning trials.
- **CVLT-II First**: An age-based standard scale score that indicates verbal recall after 1st trial.
- **CVLT-II Discriminability**: An index score indicating ability to identify target versus distractor words.
- **BVMT Total**: Age-based standard T score that indicates total recall over three trials.
- **BVMT Delayed**: Age-based standard T score that indicates free recall after delay.
<table>
<thead>
<tr>
<th>Polysomnographic Measure</th>
<th>Cognitive Test</th>
<th>Adjusted $R^2$</th>
<th>$R^2$ Change</th>
<th>$\beta$</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Respiratory disturbance index</td>
<td>CVLT-II Discriminability</td>
<td>0.18</td>
<td>0.11</td>
<td>-0.36</td>
<td>0.03</td>
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<tr>
<td></td>
<td>PASAT-3</td>
<td>0.35</td>
<td><strong>0.14</strong></td>
<td>-0.40</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>BVMT – Delayed</td>
<td>0.18</td>
<td>0.10</td>
<td>-0.35</td>
<td>0.05</td>
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<td>Oxygen desaturation index</td>
<td>PASAT-3</td>
<td>0.33</td>
<td><strong>0.12</strong></td>
<td>-0.38</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td>PASAT-2</td>
<td>0.29</td>
<td>0.07</td>
<td>-0.29</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>BVMT – Delayed</td>
<td>0.26</td>
<td><strong>0.18</strong></td>
<td>-0.47</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>Minimum oxygen saturation</td>
<td>PASAT-3</td>
<td>0.43</td>
<td><strong>0.21</strong></td>
<td>0.50</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td></td>
<td>PASAT-2</td>
<td>0.25</td>
<td><strong>0.14</strong></td>
<td>0.41</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td>BVMT – Delayed</td>
<td>0.31</td>
<td><strong>0.23</strong></td>
<td>0.53</td>
<td>&lt; 0.01*</td>
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<tr>
<td></td>
<td>SDMT</td>
<td>0.29</td>
<td>0.08</td>
<td>0.31</td>
<td>0.05</td>
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<tr>
<td>Total arousal index</td>
<td>CVLT-II Discriminability</td>
<td>0.43</td>
<td><strong>0.27</strong></td>
<td>-0.53</td>
<td>&lt; 0.001*</td>
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<td>PASAT-3</td>
<td>0.28</td>
<td>0.08</td>
<td>-0.29</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>SDMT</td>
<td>0.30</td>
<td>0.08</td>
<td>-0.29</td>
<td>0.05</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>CVLT-II Trial 1</td>
<td>0.19</td>
<td>0.09</td>
<td>0.30</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>CVLT-II Discriminability</td>
<td>0.26</td>
<td><strong>0.18</strong></td>
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<td>&lt; 0.01*</td>
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<td>0.01*</td>
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<td><strong>0.12</strong></td>
<td>0.36</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td>BVMT – Total</td>
<td>0.19</td>
<td>0.09</td>
<td>0.30</td>
<td>0.07</td>
</tr>
</tbody>
</table>
CPAP for the Treatment of Cognitive Dysfunction in MS

• Randomized, rater-blinded trial NCT02544373
• Funded by the National Multiple Sclerosis Society
• Determine the relationship between sleep apnea severity and cognitive dysfunction in MS patients with obstructive sleep apnea (Aim 1)
• Measure the effects of obstructive sleep apnea treatment with positive airway pressure on cognitive function in MS patients with sleep apnea (Aim 2)
Inclusion/Exclusion Criteria

• PwMS age 18-70 who either have elevated OSA risk (STOP-Bang) or pre-existing OSA diagnosis but who have not yet started PAP

• Willingness to undergo requisite testing (PSG, MACFIMS) and PAP titration if necessary

• Physical, psychiatric or cognitive impairment that would interfere with study procedures

• Epworth Sleepiness Scale (ESS) score of >=16 at baseline

• Active cardiopulmonary conditions

• Current treatment, such as PAP, for obstructive or central sleep apnea

• History of surgical treatment for OSA

• Concomitant neurological condition other than MS

• Concomitant systemic autoimmune disease with secondary central nervous system involvement

• Pregnancy

• Evidence of clinical MS relapse within the last 30 days prior to enrollment

• Steroid use within the last 30 days prior to enrollment

• Are found to have depression at screening per the Patient Health Questionnaire-8

• Anticipated medication changes that could influence cognitive test scores
Study Design

Baseline PSG

Neuropsychological testing

PAP titration and
Initiation of PAP therapy

Randomize
N=140

Baseline
N=175

Group 1 (n=93)

Month 0

Group 2 (n=47)

Month 0

Month 3

Month 3

Now Enrolling

Contact:
Marie Ringbloom
734-763-9909
Restless Legs Syndrome (Willis-Ekbom disease)

- Clinical syndrome that occurs during wakefulness
- Essential features (all 4 must be present)*
  - An urge to move the legs that is accompanied or caused by uncomfortable or unpleasant sensations
  - Symptoms begin or worsen during times of rest or inactivity
  - Symptoms are partially or totally relieved by movement
  - Symptoms are predominantly or solely present in the evening
- Symptoms must not be solely accounted for by another medical or behavioral condition
- 3-5 times more common in MS

*International Classification of Sleep Disorders, 3rd Edition (ICSD-3)
RLS in MS Study Group (REMS)*

• Largest RLS in MS case-control study to date (n=861 MS, n=649 controls)

• MS patients and matched controls given structured interviews that included a detailed description of RLS symptoms

• **19.0% of MS patients** experienced RLS symptoms at least twice per week during the 6 months (vs. 4.2% of controls)

• RLS was significantly associated with a higher intake of hypnotics, antidepressants

• **Age, increased disability, and PPMS** also predicted RLS

*Multicenter case-control study on restless legs syndrome in multiple sclerosis, Manconi et al, SLEEP 2008
RLS correlates with cervical cord damage in MS*

- Compared extent of brain and cervical cord damage between n=82 MS patients with and without RLS
- 36% MS patients had RLS
- Strong correlation between RLS and decreased myelin integrity in the cervical cord

*Manconi et al, Mult Scler, 2008
Insomnia in MS

- **As a symptom**: difficulty initiating or maintaining sleep, or awakening too early
- **As a diagnosis**: “A persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite the opportunity and circumstances for sleep, AND results in some form of daytime impairment”
- Chronic insomnia: $\geq 3$ months, $\geq 3$ times/week (o/w considered short term insomnia)

*International Classification of Sleep Disorders, 3rd Edition (ICSD-3)*
Daytime impairment

**Insomnia (ICSD-3)**
- Fatigue
- Impaired concentration or memory
- Mood disturbances
- Excessive daytime sleepiness
- Behavioral problems
- Reduced motivation/energy
- Proneness to errors
- Impaired vocational or academic performance
- Concerns or dissatisfaction with sleep

**Chronic symptoms of MS**
- Fatigue
- Cognitive impairment
- Depression
- Reduced motivation
- Impaired occupational performance
Insomnia in MS

- ICSD-3 criteria also allow for different subtypes of insomnia, based on etiology
  - Insomnia related to a medical condition
  - Insomnia related to another mental disorder
  - Insomnia related to another sleep disorder
- Under this framework, at least 30-40% of MS patients are at increased risk for insomnia*
- Large discrepancy between suspected prevalence and diagnosis*

*Stanton et al, Mult Scler 2006
Braley et al, J Clin Sleep Med 2014
Brass et al, J Clin Sleep Med 2014
Factors that may exacerbate insomnia in MS

• Medications
  • Corticosteroids
  • Stimulants/Wake promoting agents
  • Beta-interferons†
  • SSRIs/SNRIs*

• Depression/Anxiety (up to 78% insomnia prevalence)‡

• Pain**

• Spasticity**

• Nocturia**

†Jankovic, J Inflamm Res 2010

‡Baron et al, J Behav Med 2011

*Byerley et al, J Clin Psychopharmacol 1988
Dorsey et al, Neuropsychopharm 1996
Zhang et al, Sleep Med 2013
Yang et al, Biol Psychiatry 2005

**Braley et al, J Clin Sleep Med 2014
Stanton et al, Mult Scler 2006
# Sleep and fatigue in multiple sclerosis

*BR Stanton¹, F Barnes² and E Silber³*

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## 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 (22.5%)</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>35 (11.9%)</td>
<td>13 (8.9%)</td>
<td>82 (12.1%)</td>
</tr>
<tr>
<td>To pass urine</td>
<td>34 (14.4%)</td>
<td>214 (72.5%)</td>
<td>59 (40.4%)</td>
<td>307 (45.3%)</td>
</tr>
<tr>
<td>Anxiety/racing mind</td>
<td>65 (27.5%)</td>
<td>29 (9.8%)</td>
<td>17 (11.6%)</td>
<td>111 (16.4%)</td>
</tr>
<tr>
<td>Low mood/thoughts</td>
<td>46 (19.5%)</td>
<td>10 (3.4%)</td>
<td>10 (6.8%)</td>
<td>66 (9.7%)</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 x 100. Subjects were allowed to give more than one reason, therefore percentages total > 100%.*
Overlapping Symptoms

• Exhaustion
• Tiredness
• Lack of energy
• Sleepiness
  • Separate construct, propensity to doze (sedentary situations exacerbate)
  • Term used interchangeably with fatigue (rho=0.3-0.5)
  • MS patients at increased risk for sleep disturbances
  • MS patients with sleep disorders may share a propensity for terms other than sleepiness to describe their symptoms

Braley et al, Mult Scler Int’l 2012
Braley et al, JCSM 2013
Brass et al, JCSM 2013
Kaminska et al, Mult Scler 2012
Popp et al, Sleep Med Rev 2017
Approach to fatigue assessment/treatment

• Requires a thorough understanding of the symptom, which may vary from person to person
• Ask patient to provide a thorough description, aggravating/alleviating factors
• Rule out/address secondary causes first, employ symptomatic treatment of residual symptoms if present
Fatigue, tiredness, low energy, or exhaustion?: Characterize the symptom
(Consider quantification with validated scales if fatigue suspected)

Sleepiness, propensity to doze, or nonrestorative sleep?
OR
Insomnia symptoms, poor sleep quality, snoring, or restless legs?

- Yes
  - Assess for sleep disorders or secondary causes of sleep disturbance, consider sleep clinic referral
  - Treat underlying sleep disorder

- No
  - No
    - Mood fluctuations, anhedonia, or lassitude suggesting depression?
      - No
        - No
          - Other chronic symptoms such as pain/spasticity?
            - Yes
              - Screen for depression, pain, etc
            - -
              - Persistent fatigue despite treatment of other conditions?
                - No
                  - No
                    - Yes
                      - +

    - Yes
      - Treat chronic symptoms

Braley and Chervin, SLEEP 2010
Multidisciplinary MS/Fatigue and Sleep Clinic

- Launched in 2015
- Mission: to provide a comprehensive, multidisciplinary approach to MS fatigue that incorporates dedicated sleep assessment
- Thorough evaluation of potential underlying causes, with an emphasis on sleep (sleep disorders and nocturnal symptoms)
- Management tailored to the patient’s clinical picture
- Sleep Fellow/Neurology Resident → MS specialist + Sleep specialist
Available Treatments for MS Fatigue

• Behavioral Approaches
  • Lifestyle changes/Activity pacing
  • Exercise (aerobic + strength training)
  • Cognitive Behavioral Therapy

• Medications
  • Amantadine
  • Modafinil/Armodafinil
  • Stimulants (Methylphenidate, Amphetamine/Dextroamphetamines)
A randomized controlled trial of telephone-delivered COgnitive behavioral-therapy, Modafinil, and combination therapy of BOth interventions for fatigue in MS (“COMBO-MS”)

- Pragmatic 2-center RCT (U Michigan and U Washington)
- Sponsor: Patient-Centered Outcomes Research Institute (PCORI)
- Measures
  - Modified Fatigue Impact Scale
  - EMA measures of fatigue impact and severity
  - Accelerometry
  - Fatigue severity/activity level = fatigability
- Inventions:
  - Modafinil (50 mg daily – 200 mg BID) X 12 weeks
  - Telephone-based CBT (8 weekly sessions + 2 biweekly booster sessions)
  - Combination therapy

Now Enrolling
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combostudy@med.umich.edu
Conclusions

• Sleep disorders are highly prevalent and yet widely under-recognized in patients with MS – contribute to fatigue in their own right
• Patients with evidence of brainstem and spinal cord involvement may be at particularly high risk for SDB, RLS, or RBD
• Diagnostic and treatment plans should take into account MS-specific medications, physical findings, and symptoms whenever possible
• Approach to fatigue treatment should begin with addressing reversible causes before pharmacological interventions
• Incorporating sleep specialists into the multidisciplinary care team can impact MS symptoms and QOL