Invisible Symptoms in Multiple Sclerosis:

Fatigue, Cognitive Dysfunction and Pain

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**MS Symptom Overview**

- **Fatigue (most common)**
- Sensory symptoms
- Decreased visual acuity, diplopia
- Pain
- Sexual dysfunction
- Emotional disturbances – Depression or Anxiety
- Cognitive difficulties
- Heat sensitivity
- Spasticity
- Gait, balance, and coordination problems
- Speech/swallowing problems
- Tremor
- Weakness
- Bladder and/or bowel dysfunction

Multiple sclerosis symptoms can be interrelated

Crayton, H. et al. Neurology 2004;63:S12-S18
Symptoms may be primary, secondary or tertiary symptoms

- **Primary symptoms:** directly due to CNS damage
- **Secondary symptoms:** complications that arise due to primary symptoms
  - Example:
    - bladder dysfunction may cause UTIs
    - Sleep disturbance can contribute to fatigue
- **Tertiary symptoms:** trickle down effect of MS; social, psychological and vocational complications
  - Examples:
    - Problems with bladder control may cause individuals to avoid social situations
    - Limitations in overall functioning from MS may cause depression

- Many symptoms may have a primary, secondary or tertiary cause
Management of MS Symptoms

- Many MS symptoms can be managed by:
  - Lifestyle changes
  - Seeking support
  - Working with your MS physician as well as a multidisciplinary team

- The key is recognizing symptoms and addressing these issues with your physician.
Fatigue

“a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities”

Fatigue

- The most common and disabling symptom of MS \(^1,^3\)
  - Experienced by up to 95% of patients \(^2\)

- May refer to mental or physical fatigue

- Reported in all disease stages and subtypes \(^2\)

- Some evidence that lesions in the basal ganglia and hypothalamus may play an important role \(^2\)

Clinical Characteristics of Fatigue

- Overwhelming sense of sleepiness
- Constant sense of tiredness
- Lack of energy
- Feeling of exhaustion
- Not necessarily related to level of disability
- May affect motor function
- May affect cognitive function
- Not fully understood

Potential Causes and Effects

- **Psychologic Health**
  - Depression
  - Anxiety
  - Stress

- **Medications**
  - Anti-spasmodics, analgesics, sedative-hypnotics, anticonvulsants, interferons

- **Environment**
  - Heat sensitivity
  - Physical activity

- **Multiple sclerosis**
  - Primary MS symptom

- **Multiple sclerosis**
  - Secondary symptom: depression, sleep disturbance, pain

- **Physical Health**
  - Other health issues: anemia, thyroid disease, anemia, infections

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Fatigue management.

1. Treat sleep disturbances
2. Improve mobility
3. Cooling techniques; heat avoidance, cooling garments
4. Evaluate other medications and metabolic problems (e.g., thyroid function)
5. Treat depression
6. Energy conservation
7. Pharmacologic treatment

Crayton H et al. Neurology 2004;63:S12-S18
Fatigue Management

- Exercise
- Nutrition
- Cooling techniques
- Energy conservation techniques
  - Space out activities and pace yourself
  - Prioritize tasks
  - Rest when needed
  - PT and OT can help individuals establish energy conservation techniques
- Stress management

Non-pharmacologic treatments

- **Exercise**
- **Rehabilitation**
  - Energy conservation strategies
  - Gait dysfunction
    - AFO
    - Bioness or Walk-Aid
- **Cooling devices**
## Fatigue: Pharmacologic Treatments

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effects in improving fatigue</th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Widely used and moderately effective</td>
<td>Effect on fatigue is unclear, but known to have monoaminergic, cholinergic and glutaminergic effects</td>
<td>Neuromalignant syndrome</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dizziness</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Evaluated in several studies with varying results [Lapierre and Hum, 2007]. Although it is commonly used in clinical settings with good results</td>
<td>α-1 adrenergic properties. It is widely used as a wake-promoting agent for the treatment of narcolepsy</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dizziness</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Elevated blood pressures</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Acetyl L-carnitine</td>
<td>Recently evaluated in a small study by Tomassini and colleagues who found it to be better tolerated and more effective than amantadine [Tomassini <em>et al.</em> 2004]</td>
<td>Carnitine is a cellular component involved in energy metabolism</td>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td>Dalfampridine</td>
<td>Has been shown to be effective in reducing fatigue and may also improve weakness and heat sensitivity.</td>
<td>Potassium channel blocker intended to improve conduction in demyelinated pathways</td>
<td>May increase serum potassium level</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ECG changes were observed in clinical trials but were not felt to be significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seizures</td>
</tr>
</tbody>
</table>

# Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>100-200 mg/d</td>
<td>Hallucinations, Livido reticularis, Nausea, Lightheadedness, Insomnia, Constipation</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Up to 400 mg/d</td>
<td>Headache, Nausea, Rhinitis, Insomnia</td>
</tr>
</tbody>
</table>

# Pharmacologic Treatment

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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl L-carnitine</td>
<td>Up to 4,000 mg/d</td>
<td>Loose stools, Abdominal discomfort</td>
</tr>
<tr>
<td>Dalfampridine</td>
<td>10mg BID</td>
<td>Seizures, UTIs</td>
</tr>
</tbody>
</table>

### Pharmacologic Treatment (cont.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>10-60 mg/d</td>
<td>Nausea, Lightheadedness, Insomnia, Constipation, Hypertension, Tachycardia</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>5-40 mg/d</td>
<td>Nausea, Feeling faint, Insomnia, Constipation, Hypertension, Tachycardia</td>
</tr>
</tbody>
</table>

Patient Resources


COGNITIVE DYSFUNCTION
Cognitive dysfunction in MS

- Occurs in up to 70% of patients
  - Including early MS, CIS and pediatric MS patients

- The most important factor associated with loss of work for MS patients

- May disrupt social life, impair ability to live independently irrespective of physical disability, impedes participation in rehabilitation, and impair ability to follow more complex treatment regimens.

Characteristics of MS-related Cognitive Dysfunction

- Does not correlate with physical disability
- May be subtle
- May be under-recognized or denied by patient, family, friends, or employers
- Deficits are not diffuse or global such as seen in Alzheimer’s Disease

Risk Factors

- Does not correlate with disease duration or physical disability
- May occur even in early MS
- Does appear to correlate with brain atrophy

**Risk factors:**
- Low average or inferior intelligence
- Smoking
- Inhaled cannabis

## Areas of cognition affected

<table>
<thead>
<tr>
<th>Cognitive Domains Affected by MS</th>
<th>Domains typically impaired in MS</th>
<th>Domains typically not affected in MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td><strong>Short term - working memory</strong></td>
<td>Long-term memory</td>
</tr>
<tr>
<td>Attention</td>
<td><em>Complex attention tasks - selective, divided or alternating attention</em></td>
<td>Semantic memory (ie, general fund of knowledge)</td>
</tr>
<tr>
<td>Multitasking</td>
<td></td>
<td>Procedural memory</td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td>Language</td>
</tr>
<tr>
<td>Executive Function</td>
<td><em>Organizing, prioritizing, problem solving, decision making</em></td>
<td>IQ</td>
</tr>
<tr>
<td>Visual spatial tasks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Cognitive Impairment

▪ May be secondary to other issues:
  ▪ Fatigue
  ▪ Depression
  ▪ Sleep disruption
  ▪ Medications
Neuropsychological testing

- Mini mental status exam is not an appropriate screening tool
  - Sensitivity is only 30%

- Screening tools used in the office
  - Symbol Digits Modalities Test (SDMT)
    - Timed test that requires individuals to substitute a number for geometric figures; can be performed in a few minutes in office setting
    - Assesses attention, concentration and processing speed

- These screening tools do not replace a full battery of neuropsychological tests which is often required for better assessment
Managing Cognitive Impairment: Non-pharmacologic Treatment

- Neuropsychological testing can be used to provide individualized feedback regarding specific areas of dysfunction and practical approach for compensating for these issues.

- Discuss the problem openly; include family or significant other

- Cognitive rehabilitation for coping and “compensatory strategies”

- Physical and/or occupational therapy for safety strategies and environmental modifications

Managing Cognitive Impairment: Non-pharmacologic Treatment

- **Strategies that may be helpful:**
  - Perform more difficult cognitive tasks at your best time of day
  - Use organizers, calendar, smartphones, etc
  - Make lists
  - Take notes
  - Create an environment free of distractions
  - Concentrate on one task at a time
  - Divide complex projects into steps
  - When learning new information repeat yourself and practice new tasks
  - Assign particular locations for certain items
Managing Cognitive Impairment: Non-pharmacologic Treatment

- Keep challenging yourself: Perform puzzles, problem solving games such as crosswords, sudoku, brain age games

- Physical exercise
  - Increasing evidence that individuals that maintain an active lifestyle have better cognitive performance and less brain atrophy
Managing Cognitive Impairment: Pharmacologic Treatment

- Disease-modifying therapies to slow disease progression
  - Some studies have shown a beneficial effect of natalizumab (Tysabri) on cognitive function.

Pharmacologic

- **AchE Inhibitors**
  - **Donepezil (Aricept)**
    - 69 MS treated for 24 weeks
      - showed improvement in verbal learning and memory test.
      - Treatment group reported improvement in cognitive function
    - 120 MS patients randomized to Donepezil versus placebo but no effect found in performance on various cognitive tests after 24 weeks.
  - **Rivastigmine (Exelon)**
    - 12-week trial of 60 cognitively impaired patients showed no improvement with rivastigmine
Pharmacologic

- **Memantine (Namenda)**
  - 1 year, randomized trial suggests that high dose (30mg/day) memantine may induce reversible neurologic impairments
  
  - 16 week trial showed no improvement on the CVLT-II or PASAT
# Pharmacologic Treatments

## Table 1: Symptomatic agents of cognitive impairment in MS: literature studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geisler et al. [17]</td>
<td>Amantadine/ pemoline</td>
<td>45, MS-severe fatigue</td>
<td>Placebo-controlled trial for 6 weeks</td>
<td>No effects</td>
</tr>
<tr>
<td>Lovera et al. [18]</td>
<td>Ginkgo biloba</td>
<td>43, a score between 0.5 and 2.5 SD below PASAT/ CVLT-II</td>
<td>RCT, 120 mg twice a day or placebo for 12 weeks</td>
<td>No effects</td>
</tr>
<tr>
<td>Villoslada et al. [16]</td>
<td>Memantine</td>
<td>19, MS-cognitive impaired (1.5 SD below in at least two tests BRBN)</td>
<td>1-year crossover RCT, 30 mg daily</td>
<td>Trial halted after nine patients reported neurological worsening</td>
</tr>
<tr>
<td>Krupp et al. [13]</td>
<td>Donezepil</td>
<td>120-memory- and cognitive impaired (≤0.5 SD below in RAVLT)</td>
<td>Multicenter RCT, 10 mg daily</td>
<td>No effects</td>
</tr>
</tbody>
</table>

L-Amphetamine sulfate

- Effects of L-amphetamine sulfate (Adderall) on cognition
  - 151 MS patients
  - Primary outcome – SDMT
    - No significant improvement
  - Secondary outcomes:
    - PASAT – not significant
    - CVLT II – showed significant improvements
  - Patients’ self report showed no improvement

Patient Resources


Pain and Multiple Sclerosis

- Pain occurs in approximately 29-86% at different stages of MS
- May be acute or chronic
- May be a primary or secondary symptom

Types of pain in MS:
- Neuropathic pain
- Musculoskeletal pain
  - Spasticity
Neuropathic pain

- Gain of function
- Disruption/hyperexcitability of sensory pathways within the central nervous system

- Typically described as “burning”, “electric”, “pins and needles”

- Most common neuropathic pain conditions:
  - Trigeminal neuralgia
  - Lhermitte’s sign
  - “MS Hug”
  - Painful tonic spasms
## Treatment of Neuropathic Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>100-3600 mg/d</td>
<td>Fatigue, Somnolence, Dizziness, Ataxia</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400-1000 mg/d</td>
<td>Dizziness, Drowsiness, Nausea, Unsteadiness</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150-600 mg/d</td>
<td>Dry mouth, Constipation, Unsteadiness, Somnolence</td>
</tr>
</tbody>
</table>

# Pharmacologic Treatment (cont.)

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<tr>
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<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>25-400 mg/d</td>
<td>Fatigue, Somnolence, Cognitive dysfunction, Weight loss</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10-150 mg/d</td>
<td>Drowsiness, Dry mouth, Fatigue, Constipation</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60-120 mg/d</td>
<td>Upset stomach, Vomiting, Constipation, Dizziness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20-60mg/day</td>
<td>Gi symptoms, Dizziness, Dry mouth, Somnolence</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>100-200 mg/d</td>
<td>Gi symptoms, Headache, Dizziness, Palpitations</td>
</tr>
</tbody>
</table>
Musculoskeletal Pain

- Secondary to muscular weakness, spasms, gait abnormality

Examples:
- Low back pain as a result of irregular movement or postures
- Spasticity
- May be secondary to medications
  - Interferons may be associated with muscular pain
  - Steroids may cause osteoporosis leading to compression fractures or osteonecrosis
Spasticity Management

- Functional approach
- Medications
- Interventional approach
- Surgical
- Avoid Triggers
Medications

- **Anti-spasmodics**
  - Baclofen
  - Tizanadine
  - Dantrolene - *no sedation*

- **Anxiolytics**
  - Clonazapam
  - Diazepam

- **Anti-epileptics - *helps with pain***
  - Gabapentin
  - Levetiracetam - *good for phasic spasms*
  - Carbamazepine
## Treatment of Spasticity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balcofen</td>
<td>10-80mg/day</td>
<td>Fatigue, Constipation, Nausea</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>2-36mg/day</td>
<td>Drowsiness, Orthostatic hypotension, Dry mouth, Dizziness</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25-3mg/day</td>
<td>Drowsiness, Sedation, Gait imbalance, May build tolerance</td>
</tr>
</tbody>
</table>

Botox

- Blocks release of acetylcholine (chemical responsible for muscle contraction)
- Allows for treatment of individual muscle groups
- Affect lasts approx 3 months
- Side effects may include weakness, fatigue, flu-like side effects
Intrathecal Baclofen pump

- Computer driven pump infuses baclofen directly into the spinal column
- Works well for spasticity in the legs
- Allows for less sedation and fine titration
- Complications: tube dysfunction, pump failure, withdrawal
Non-pharmacologic Treatment Measures

- Stretching for spasticity
- Massage
- Distraction
- Acupressure and Acupuncture
- Cooling
- Guided imagery
- Chronic Pain Management Program
- Physical and occupational therapy

Bashir K, Whitaker JN. *Handbook of Multiple Sclerosis*. 2002
Patient Resources

CONCLUSION
• MS is quite variable

• Some individuals may have a number of symptomatic issues and many of these symptoms may perpetuate one another leading to a “cycle of symptoms”

• It is important to consider both preventative therapies (disease modifying therapies) and symptomatic therapies in the treatment of MS

• There are many approaches to managing symptoms and often requires a team of healthcare providers.
QUESTIONS?