SYMPTOM MANAGEMENT IN MULTIPLE SCLEROSIS: NEUROPSYCHOLOGICAL ISSUES

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I have received honoraria from Teva pharmaceuticals, Novartis, and Bayer pharmaceuticals.
Obtaining CME Credit

• If you would like to receive CME credit for this activity, please visit:

http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.
Objectives:

- Identify common psychiatric issues in MS
- Discuss the impact of cognitive dysfunction in MS and management of these symptoms
- Examine the impact of fatigue in MS
- Recognize the interdependence of the “cycle of symptoms” in MS
Common multiple sclerosis symptoms

- Spasticity
- Fatigue
- Cognitive dysfunction
- Depression
- Bladder dysfunction
- Bowel dysfunction
- Paroxysmal symptoms
- Pain
- Sexual dysfunction

Crayton H et al. Neurology 2004;63:S12-S18
Psychiatric Implications of MS

No man trods this earth alone! We are all together; one generation taking up where the other generation has left off!

You're right, Lucy! You're right! You've made me see things differently...

I realize now that I am part of this world... I am not alone... I have friends!

You've got the whole world to live in! There's beauty all around you! There are things to do... great things to be accomplished!

You should be ashamed of yourself, Charlie Brown!

This is ridiculous! I feel lonely... depressed...

And so I can't help it...

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Psychiatric disorders in MS

<table>
<thead>
<tr>
<th>Psychiatric Disorder</th>
<th>Prevalence in MS (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>22.8–54.0</td>
<td>Joffe et al, 1987⁹; Minden et al, 1987⁴; Patten et al, 2000¹⁰</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>13</td>
<td>Joffe et al, 1987⁹</td>
</tr>
<tr>
<td>Pseudobulbar affect</td>
<td>10</td>
<td>Feinstein et al, 1997⁴²</td>
</tr>
<tr>
<td>Anxiety</td>
<td>25</td>
<td>Feinstein et al, 1999³⁸</td>
</tr>
</tbody>
</table>

MS indicates multiple sclerosis.
Depression

- Occurs in more than 50% of MS patients
  - May occur in very mild cases
  - Mixed results on correlation with degree of disability and duration of disease

- 30% of MS patients will have thoughts of self harm or suicide.
- Rates of suicide are 7 times higher than in the general population.

Causes of depression in MS:

<table>
<thead>
<tr>
<th>TABLE 2. Suspected Causes of Depression in Patients With MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroanatomic location of brain lesions</td>
</tr>
<tr>
<td>Immune dysregulation</td>
</tr>
<tr>
<td>Neuroendocrine abnormalities</td>
</tr>
<tr>
<td>Psychological reaction to the effects of disease on work, social, and family relationships</td>
</tr>
<tr>
<td>History of depressive disorder</td>
</tr>
<tr>
<td>Fatigue or other somatic complaints (e.g., sleep disturbances)</td>
</tr>
<tr>
<td>Unrealistic expectations from disease-modifying treatment</td>
</tr>
<tr>
<td>Lack of social support</td>
</tr>
<tr>
<td>Social stress</td>
</tr>
<tr>
<td>Disease exacerbation or activity</td>
</tr>
<tr>
<td>MS-related cognitive dysfunction</td>
</tr>
</tbody>
</table>

MS indicates multiple sclerosis.
## Localization

<table>
<thead>
<tr>
<th>Study</th>
<th>Depression Measure</th>
<th>MRI Correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pujol et al, 1997(^6)</td>
<td>BDI</td>
<td>Left suprainsular white matter brain lesions</td>
</tr>
<tr>
<td>Berg et al, 2000(^9)</td>
<td>HDS, MADRS, BDI, GHQ</td>
<td>Right temporal brain lesions</td>
</tr>
<tr>
<td>Di Legge et al, 2003(^10)</td>
<td>BDI, STAI</td>
<td>Right temporal brain lesions</td>
</tr>
<tr>
<td>Bakshi et al, 2000(^11)</td>
<td>BDI, HDI</td>
<td>Frontal and parietal white matter lesions; atrophy</td>
</tr>
<tr>
<td>Rabins et al, 1986(^5)</td>
<td>GHQ</td>
<td>Atrophy</td>
</tr>
</tbody>
</table>

MS indicates multiple sclerosis; MRI, magnetic resonance imaging; BDI, Beck Depression Inventory; HDS, Hamilton Depression Scale; MADRS, Montgomery and Asberg Depression Scale; GHQ, General Health Questionnaire; STAI, State-Trait Anxiety Inventory; HDI, Hamilton Depression Inventory.
Medications associated with depression

- **Interferons**
  - Conflicting results, but overall appears to have shown no increased risk of depression with interferons.

- **Corticosteroids**
  - Increased energy, insomnia, mood lability, euphoria, depression, psychosis, delirium
    - Occurs in 5-8% of patients
  - Mania/hypomania more common with acute use but long term use more commonly associated with depression

- **Anti-cholinergics**
  - Reports of cognitive dysfunction, anxiety and hallucinations

- **Anti-spasmodics**
  - Confusion, euphoria or depression, anxiety, somnolence

Bipolar Disorder

- Prevalence in MS varies from 0.3 to 32%
- Multifactorial
  - Lesion burden
    - Temporal lesions and diffuse white matter changes
  - Genetics
    - Similarities between HLA class II genes
  - Medications such as corticosteroids, baclofen, dantrolene, tizanidine have been implicated to cause hypomanic or manic episodes.
Anxiety

- Estimated prevalence of 36%
  - Generalized anxiety disorder most common
  - Increased prevalence of panic disorder and obsessive convulsive disorder
- More suggestion that anxiety is a reactive response
- Localization is less clear

Anxiety Disorders in MS

Table 1: Prevalences of DSM-IV anxiety disorders in subjects (n = 140) with MS and the general population

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime prevalence in MS (% (n))</th>
<th>Point prevalence in MS (% (n))</th>
<th>Lifetime prevalence in general population [23] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder</td>
<td>10.0 (14)</td>
<td>2.1 (3)</td>
<td>3.5</td>
</tr>
<tr>
<td>Social phobia</td>
<td>7.8 (11)</td>
<td>2.1 (3)</td>
<td>13.3</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>10.8 (15)</td>
<td>2.9 (4)</td>
<td>11.0</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>8.6 (12)</td>
<td>5.7 (8)</td>
<td>2.5</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>18.6 (26)</td>
<td>10.0 (14)</td>
<td>5.1</td>
</tr>
</tbody>
</table>
Stressful life events and exacerbations

- A prospective study of 36 MS patients followed with monthly MRIs found that stress increased the risk of developing a new Gd+ enhancing MRI lesion.

- A prospective study of 26 females with MS found:
  - Experiencing 3 or more stressful life events was associated with a 5-fold increase in relapse rate.
  - At least one long term stressful life event was associated with a 3-fold increase in the risk of relapse.
Stressful life events and Exacerbations

- Meta-analysis evaluating the association between stressful life events and exacerbations
- Included 14 publications
- Mean effect size was 0.53

Pseudobulbar affect

- Occurs in up to 10% of MS patients
- Sudden episodes of laughing or crying that occur spontaneously or out of proportion to the stimuli
- Thought to be due to loss of cortical inhibition of brainstem centers involved in activation of laughing and crying
PBA: Management

- Dextromethorphan/Quinidine (Neudexta)
  - First FDA approved therapy for PBA
  - MOA: DM modulates glutamate by inhibiting its release and acting as a NMDA antagonist
    - Quinidine needed to prevent the metabolism
  - Randomized, double blinded trial involving 150 MS patients to investigate the use of DM/Q in PBA

Dextromethorphan/Quinidine (DM/Q)

Center for Neurologic Study-Lability Scale (CNS-LS) for pseudobulbar affect (PBA)

<table>
<thead>
<tr>
<th>Assessment questions</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>There are times when I feel fine 1 minute, and then I’ll become tearful the next over something small or for no reason at all.</td>
</tr>
<tr>
<td>2</td>
<td>Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren’t funny.</td>
</tr>
<tr>
<td>3</td>
<td>I find myself crying very easily.</td>
</tr>
<tr>
<td>4</td>
<td>I find that even when I try to control my laughter, I am often unable to do so.</td>
</tr>
<tr>
<td>5</td>
<td>There are times when I won’t be thinking of anything happy or funny at all, but then I’ll suddenly be overcome by funny or happy thoughts.</td>
</tr>
<tr>
<td>6</td>
<td>I find that even when I try to control my crying, I am often unable to do so.</td>
</tr>
<tr>
<td>7</td>
<td>I find that I am easily overcome by laughter.</td>
</tr>
</tbody>
</table>

Total Score:

Psychotic features in MS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country of study</th>
<th>Number of patients with MS</th>
<th>% MS patients with psychotic features</th>
<th>Psychotic features/diagnosis</th>
<th>Neuroimaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinar &amp; Zadro (2007)</td>
<td>Croatia</td>
<td>250</td>
<td>2.4%</td>
<td>Hallucinations, paranoid symptoms</td>
<td>Lesion in left temporal lobe</td>
</tr>
<tr>
<td>Harel et al. (2007)</td>
<td>Israel</td>
<td>651</td>
<td>2.61%</td>
<td>Dysregulation of affect with no insight</td>
<td></td>
</tr>
<tr>
<td>Patten et al. (2005)</td>
<td>Canada</td>
<td>10367</td>
<td>2.0–4.0%</td>
<td>Non-organic psychotic disorders (schizophrenia spectrum and delusional disorders), organic psychosis</td>
<td></td>
</tr>
<tr>
<td>Diaz-Olarrieta et al. (1999)</td>
<td>Mexico</td>
<td>44</td>
<td>17.0%</td>
<td>Hallucinations, delusions</td>
<td>Moderately severe frontotemporal abnormalities</td>
</tr>
<tr>
<td>Ron &amp; Lodsad (1989)</td>
<td>UK</td>
<td>110</td>
<td>6.3%</td>
<td>Delusional disorders, atypical psychosis</td>
<td></td>
</tr>
<tr>
<td>Joffe et al. (1987)</td>
<td>Canada</td>
<td>100</td>
<td>0.0%</td>
<td>Psychosis</td>
<td></td>
</tr>
<tr>
<td>Schiffer &amp; Babigian (1984)</td>
<td>USA</td>
<td>368</td>
<td>4.6%</td>
<td>Schizophreniform psychosis and manic-depressive mood swings</td>
<td></td>
</tr>
<tr>
<td>Surridge (1969)</td>
<td>UK</td>
<td>108</td>
<td>0.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Psychotic Features in MS

- Hallucinations and Delusions, 50%
- Irritability/Agitation, 20%
- Sleep disturbance and Grandiosity, 15%
- Disorientation, Blunted Affect, Flight of Ideas, Pressured speech, 10%
- Other (catatonia, catalepsy, etc), 1%

Cognitive Dysfunction in MS
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.

## Areas of cognition affected

<table>
<thead>
<tr>
<th>Cognitive Domains Affected by MS</th>
<th>Impaired</th>
<th>Not Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term memory</td>
<td>Long-term memory</td>
<td></td>
</tr>
<tr>
<td>Explicit memory</td>
<td>Semantic memory</td>
<td></td>
</tr>
<tr>
<td>Episodic memory</td>
<td>Implicit memory</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>IQ</td>
<td></td>
</tr>
<tr>
<td>Complex attention tasks - selective, divided or alternating attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstract reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem solving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual spatial tasks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MRI and Cognitive Dysfunction

- **Diffusion tensor imaging**
  - Quantitative MR techniques allowing for the study of normal appearing brain tissue allows for more specific localization

- **Double inversion recovery**
  - Allows for superior detection of cortical lesions
  - Studies have shown strong correlation between cortical lesion volume and cognitive impairment

- **fMRI**
  - Allows for mapping of brain activity
  - Studies show increased activation in MS patients compared with controls but for patients that had poorer performance on cognitive tests there was less extensive brain activation.
Assessment of Cognitive Function

- MMSE is not an appropriate screening tool for cognitive dysfunction in MS
  - Sensitivity is only 30%

- Brief Repeatable Battery is the most widely used
  - Selective Reminding Test – verbal memory and delayed recall
  - 10/36 Spatial Recall Test – visual memory and delayed recall
  - PASAT - attention, concentration and processing speed
  - SDMT attention, concentration and processing speed
  - Word List Generation – verbal fluency
Figure 1  Proposed algorithm for screening of cognitive impairment in MS. PASAT-3: Paced Auditory Serial Addition Test-3 seconds; SDMT: Symbol Digit Modalities Test; SRT-LTS: Selective Reminding Test-Long Term Storage; SRT-CLTR: Selective Reminding Test-Consistent Long Term Retrieval.
Management of Cognitive Dysfunction

- Prevention
- Non-Pharmacologic
- Pharmacologic
Non-Pharmacologic

- **Lifestyle changes**
  - Smoking cessation
  - Restful sleep
  - Management of fatigue

- **Computer based programs**
  - BrainStim
    - 3 modules
      - City Map – spatial orientation
      - Find Pairs – working memory and visual memory
      - Memorize Numbers – working memory
  - AIXTENT
    - Training of attention across 4 domains (alertness, divided attention, selective attention and vigilance)

Pharmacologic

- **AchE Inhibitors**
  - **Donepezil**
    - 69 MS treated for 24 weeks
      - showed improvement in verbal learning and memory test.
      - Treatment group reported improvement in cognitive function
  - **Rivastigmine**
    - 12-week trial of 60 cognitively impaired patients showed no improvement with rivastigmine
Pharmacologic

- Memantine
  - 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>
<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>Krupp et al. [11]</td>
<td>Donezepil</td>
<td>69-Memory-impaired (RAVLT) (67 completed the trial)</td>
<td>Parallel groups, RCT, intention-to-treat analysis, 24 weeks of treatment</td>
<td>Improvement SRT, patient- and physician-reported cognition</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
    - Not significant improvement
  - Secondary outcomes:
    - PASAT – not significant
    - CVLT II – DR and BVMTR showed significant improvements
  - Patients’ self report showed no improvement

Fatigue

- The most common symptoms in MS
  - Reported in up to 87% of patients
- May exacerbate other symptoms of MS such as mood disturbance, cognitive dysfunction, and sexual dysfunction.
- May refer to mental or physical energy
Fatigue: Assessment

- Assess for other MS related issues that may contribute:
  - Depression
  - Sleep disturbance
    - Sleep apnea, PLMD, pain, nocturia

- Assess for other exacerbating factors:
  - Metabolic
    - Thyroid disease, vitamin B12 deficiency, anemia
  - Infections
  - Medication side effect
    - Anti-spasmodics, analgesics, sedative-hypnotics, anti-convulsants, IFN
Fatigue management.

- Treat sleep disturbances
- Improve mobility
- Cooling techniques; heat avoidance, cooling garments
- Evaluate other medications and metabolic problems (e.g., thyroid function)
- Treat depression
- Energy conservation
- Pharmacologic treatment

Crayton H et al. Neurology 2004;63:S12-S18
Non-pharmacologic treatments

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

**Table 1.** Medications used to treat multiple sclerosis-related fatigue.

<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>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Evaluated in several studies with varying results</td>
<td>$\alpha$-1 adrenergic properties</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>[Lapierre and Hum, 2007]. Although it is commonly used in clinical settings with good results</td>
<td>It is widely used as a wake-promoting agent for the treatment of narcolepsy</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dizziness</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 et al. 2004]</td>
<td>Carnitine is a cellular component involved in energy metabolism</td>
<td>Elevated blood pressures</td>
</tr>
<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></td>
<td></td>
<td></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>
<td></td>
<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>
Social impact of MS

- **Financial burden**
  - One of the most costly neurological disease due to early onset, chronicity and loss of employment
  - The annual cost of living with MS is greater than $57,000 per year.

- **Family burden**
  - Psychiatric symptoms as well as physical disability place a burden on the family/caregiver
  - Varying reports on divorce rate
    - 6-fold increase in divorce when patient is female
  - Children may feel fear and anxiety surrounding the diagnosis, a sense of burden, or anger
    - Children who are better informed about their parents disease have fewer problems

Multiple sclerosis symptoms can be related and interdependent.
Questions?