Johns Hopkins TM Regional Symposium: Neuro-Psychiatric Aspects of TM/MS

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Introduction to Transverse Myelitis (TM): TM Defined

- **Transverse:**
  - Lying or being across, or in a crosswise direction;
  - often opposed to longitudinal.

- **Myelitis:**
  - An inflammation or infection of the spinal cord.
What is Multiple Sclerosis (MS)?

MS = multiple sclerosis.
Psychosocial Impact of Multiple Sclerosis: Exploring the Patient’s Perspective

Phone interviews were used to explore psychosocial functioning, defined as intrapersonal or interpersonal processes, excluding physical symptoms.

Demographics: 100% RRMS, Northern CA; 75% women; Average: 43 years old, 63% married, 55% employed.

Psychosocial impact of MS clustered into 3 factors:
- Deterioration in Relationships: endorsed overall by 20%.
- Demoralization: endorsed overall by 30%.
- Benefit-Finding: endorsed overall by 60%.

RRMS = relapsing remitting multiple sclerosis.
Benefit-Finding: Percent Endorsing

• Relationships:
  – My friends and family have become more helpful (77%); I am closer to my family (70%); I am closer to my significant other (51%); I keep in better touch with my family (44%).

• Interpersonal Skills:
  – I have learned to be more compassionate (67%); to be more respectful of others (58%); express more feelings (55%); communicate better (48%); be a better friend (48%).

• Perspective:
  – I appreciate the importance of being independent (83%); I appreciate life more (74%); I am more introspective (72%); more conscientious and self-disciplined (60%); more motivated to succeed (59%); more spiritual (45%); more independent in many ways (38%); less inhibited (33%).
Increase in state suicide rates in the USA during economic recession

*Figure* : Time trend analysis of suicide rate in 50 US states and District of Columbia between 1999 and 2010. Vertical line shows onset of recession.
# 10 Leading Causes of Death by Age Group, United States – 2008

## Age Groups

<table>
<thead>
<tr>
<th>Rank</th>
<th>&lt;1</th>
<th>1-4</th>
<th>5-9</th>
<th>10-14</th>
<th>15-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65+</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Congenital Anomalies 5,638</td>
<td>Unintentional Injury 1,469</td>
<td>Unintentional Injury 855</td>
<td>Unintentional Injury 1,024</td>
<td>Unintentional Injury 14,089</td>
<td>Unintentional Injury 14,950</td>
<td>Unintentional Injury 16,815</td>
<td>Malignant Neoplasms 50,403</td>
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<td>Heart Disease 495,730</td>
<td>Heart Disease 616,028</td>
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<td>2</td>
<td>Short Gestation 4,754</td>
<td>Congenital Anomalies 521</td>
<td>Malignant Neoplasms 457</td>
<td>Malignant Neoplasms 433</td>
<td>Homicide 5,275</td>
<td>Suicide 5,300</td>
<td>Malignant Neoplasms 12,669</td>
<td>Heart Disease 37,922</td>
<td>Heart Disease 66,711</td>
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<td>SIDS 2,353</td>
<td>Congenital Anomalies 170</td>
<td>Suicide 4,298</td>
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<td>Homicide 5,764</td>
<td>Heart Disease 11,336</td>
<td>Chronic Low Respiratory Disease 14,042</td>
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<td>Maternal Pregnancy Comp. 1,765</td>
<td>Malignant Neoplasms 394</td>
<td>Homicide 207</td>
<td>Homicide 2,906</td>
<td>Suicide 6,703</td>
<td>Suicide 6,877</td>
<td>Unintentional Injury 12,782</td>
<td>Cerebrovascular 114,508</td>
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<td>Unintentional Injury 1,315</td>
<td>Heart Disease 186</td>
<td>Heart Disease 97</td>
<td>Congenital Anomalies 151</td>
<td>Heart Disease 1,065</td>
<td>Heart Disease 3,264</td>
<td>Homicide 2,906</td>
<td>Liver Disease 8,220</td>
<td>Diabetes Mellitus 61,673</td>
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<td>Placenta Cord Membranes 1,080</td>
<td>Influenza &amp; Pneumonia 142</td>
<td>Benign Neoplasms 59</td>
<td>Heart Disease 132</td>
<td>Congenital Anomalies 467</td>
<td>HIV 975</td>
<td>HIV 2,038</td>
<td>Cerebrovascular 6,112</td>
<td>Cerebrovascular 10,459</td>
<td>Diabetes Mellitus 50,863</td>
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<td>Bacterial Sepsis 700</td>
<td>Septicemia 93</td>
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<td>Chronic Low Respiratory Disease 64</td>
<td>Influenza &amp; Pneumonia 206</td>
<td>Diabetes Mellitus 574</td>
<td>Liver Disease 2,562</td>
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<td>Liver Disease 8,526</td>
<td>Influenza &amp; Pneumonia 48,382</td>
<td>Diabetes Mellitus 70,553</td>
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<td>Respiratory Distress 630</td>
<td>Cerebrovascular 63</td>
<td>Cerebrovascular 41</td>
<td>Cerebrovascular 56</td>
<td>Diabetes Mellitus 204</td>
<td>Cerebrovascular 2,035</td>
<td>Chronic Low Respiratory Disease 4,392</td>
<td>Suicide 5,465</td>
<td>Nephritis 39,921</td>
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<td>9</td>
<td>Circulatory System Disease 594</td>
<td>Chronic Low Respiratory Disease 54</td>
<td>Influenza &amp; Pneumonia 40</td>
<td>Influenza &amp; Pneumonia 49</td>
<td>Cerebrovascular 189</td>
<td>Liver Disease 423</td>
<td>Diabetes Mellitus 1,854</td>
<td>HIV 3,730</td>
<td>Nephritis 4,803</td>
<td>Unintentional Injury 108,563</td>
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<tr>
<td>10</td>
<td>Neonatal Hemorrhage 556</td>
<td>Septicemia 25</td>
<td>Septicemia 36</td>
<td>Complicated Pregnancy 169</td>
<td>Congenital Anomalies 379</td>
<td>Septicemia 892</td>
<td>Septicemia 2,732</td>
<td>Septicemia 4,552</td>
<td>Septicemia 27,028</td>
<td>Suicide 36,035</td>
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Major Depression Versus Sadness

- Major depression is a syndrome.
- It is not just severe sadness.
- Sadness is to major depression what cough is to pneumonia.
  - Cough can be an indicator of pneumonia.
  - Not every cough is the result of pneumonia.
  - Sometimes pneumonia presents without a cough.
  - Consider the company the cough keeps.
    - Productive sputum, tachypnea, fever, consolidation
DSM IV Inventory: SIGEMCAPS

- Sleep (↓ / ↑)
- **Interest** (or pleasure)
- Guilt (or worthlessness)
- Energy (fatigue)
- Mood
- Concentration
- Appetite (↓ / ↑ or weight loss or gain)
- Psychomotor retardation (or agitation)
- Suicidal ideation (or thoughts of death)
- ≥5/9 Sx for ≥2 weeks

*DSM IV* = *Diagnostic and Statistical Manual of Mental Disorders* criteria; Sx = symptoms.
Medical Causes of Depression:

- **Neurologic disorders**: CVA (30-50%), subdural hematoma, epilepsy (45-55%), brain tumors (30%), **Multiple Sclerosis (37-62%)**, Parkinson's disease (40-50%), Huntington's disease (40%), syphilis, Alzheimer's disease (15-50%)

- **Autoimmune disorders**: **Multiple Sclerosis (37-62%)**, rheumatoid arthritis (30-50%), DM (30%), SLE (25-44%).

- **Drug induced**: reserpine (15%), interferon-alpha (10-57%), $\beta$-blockers, corticosteroids, estrogens, benzodiazepines, barbiturates, ranitidine, Ca$^{2+}$-channel blockers

- **Substance induced** (25%): EtOH, sedative-hypnotic, cocaine & psychostimulant withdrawal

- **Metabolic**: hyper/hypothyroidism, Cushing's syndrome, hypercalcemia, hyponatremia, diabetes mellitus

- **Nutritional**: vitamin B12 deficiency

- **Infections**: HIV, HCV (25%), mononucleosis, influenza

- **Cancer** (20-45%): especially pancreatic CA (40-50%)
Burden of Depression in MS Patients
(Patten & Metz, Psychother Psychosom, 1997, 66:286-92)

• **Lifetime Prevalence:**
  – 37-62% MS
  – 17% General Population (NCS)

• **Current Prevalence:**
  – 14-27% MS
  – 5% General Population (NCS)

• **Cognitive Impairment in MS:**
  – Lifetime prevalence 45-65%
SIGEMCAPS → MS/TM

- Sleep (↓ / ↑) → Insomnia (sedative)
- Interest (or pleasure) → Adjustment to new normal
- Guilt (or worthlessness) → Barrier to rehab and Tx
- Energy (fatigue) → MS Fatigue (stimulant)
- Mood → Sadness
- Concentration → MS memory loss
- Appetite → Weight loss
- Psychomotor retardation → MS memory loss,
- Suicidal ideation → Hopelessness, death
- Magnification of suffering → Chronic Pain (marijuana)
Depression and MS

• Depression is common in patients with MS and is associated with considerable morbidity and mortality.

• The available evidence suggests that depression in MS is caused by the effects of inflammatory insults to the brain.
  – No correlation with physical disability.
  – No genetic loading.
  – Periods of immune activation correlate with increased depression and suicides.
Depression and Quality of Life

- Multiple studies have shown that depression is the primary determining factor in a patient’s self reported quality of life, with greater impact than other variables investigated, including physical disability, fatigue, and cognitive impairment.

- Also, depression is the number 1 correlate of the quality of life of the patient’s caregiver.
Are you getting enough oxygen?
MS Depression and Suicide: Epidemiology

- 30% lifetime incidence of suicidal intent in patients with MS.
- 6%–12% of patients with MS attempt suicide.
- Suicide in MS patients occurs at 7.5 times the rate of the general population.
- Suicide was the 3rd leading cause (15%) of death of 3000 outpatients in Canadian MS clinics from 1972–1988.
  - MS patients dying from suicide were younger and less disabled than patients dying from pneumonia (23%) and cancer (16%).

“Of course your daddy loves you. He’s on Prozac--he loves everybody.”
Treating Depression May Improve MS Disease Severity

• Patients with depression had biological evidence of worse MS disease severity.
• Treatment of depression in MS patients (with either medication or psychotherapy) correlated with improvement in their autoimmune disease status.
• Suggests that treatment of depression may be an important component in the management of patients with MS:
  – “Treatment of depression may provide a novel disease-modifying therapeutic strategy as well as a symptomatic treatment for patients with MS.”

Effects of fluoxetine on disease activity in relapsing multiple sclerosis: a double-blind, placebo-controlled, exploratory study

J P Mostert, F Admiraal-Behloul, J M Hoogduin, J Luyendijk, D J Heerema, M A van Buchem, J De Keyser

Table 3 MRI outcomes during the past 16 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine (n = 19)</th>
<th>Placebo (n = 19)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative number of new enhancing lesions</td>
<td>1.21 (2.5)</td>
<td>3.16 (6.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0 (0–11)</td>
<td>1 (0–22)</td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>90 (231)</td>
<td>227 (485)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cumulative volume of new enhancing lesions (mm³)</td>
<td>0 (0–951)</td>
<td>35 (0–2095)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12 (63%)</td>
<td>5 (28%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of patients with no new enhancing lesions</td>
<td>9 (24%)</td>
<td>13 (47%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Scans showing new enhancing lesions</td>
<td>9 (24%)</td>
<td>13 (47%)</td>
<td>0.03</td>
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<td>Scans showing enhancing lesions</td>
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Depression-MS-Inflammation Triad

- A. Lithium
- B. SSRI
- C. COX-2 Inhibitors (e.g. celecoxib)
- D. Omega 3 Fatty Acid (e.g. fish oil)

MS ↔ Inflammation
Relationship Between Depression & Autoimmune CNS Diseases

- Depression and MS: A Two-Way Street
  - MS causes depression.
  - Depression worsens MS.
  - Treating depression improves MS.
  - Treating MS improves depression.
  - Autoimmunity and depression are a two-way street.
- Depression is a lethal consequence of MS if left untreated.
- Depression is common and important, caused by the immune system in autoimmune diseases, and treatable.
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  - often opposed to longitudinal.

- **Myelitis:**
  - An inflammation or infection of the spinal cord.