Cognitive Impairment in Multiple Sclerosis

DR. SARAH A. MORROW MD, MS, FRCPC

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Impact of Cognitive Impairment (CI) in MS patients

Rao *Neurology* 1991

- 48 cognitively impaired, 52 normal MS
- Assessed with
  - 2 Hour OT home visit
  - Self-report scales
  - Friend and family reports
- Also looked at premorbid IQ, education, disease characteristics
Cognitive Impairment Significantly Impacts Daily Functioning in MS

![Graph showing differences in mean scale scores between cognitively intact and impaired groups across various daily functioning categories.]

- Work Status: Cognitively intact (n=52), Cognitively impaired (n=48)
- Social Activity
- Personal Assistance
- Community Services
- Financial Status
- Transportation
- Personal Residence

*Environmental status scale.

Impact on quality of life

Cognitively impaired MS patients report
- Loss of self-esteem
- Sexual dysfunction
- Higher rates of divorce

Impair family life and social relationships
- Participate in fewer social activities

Have significantly more car accidents than cognitively intact MS patients or healthy controls
- May be needed to maintain employment
- Loss of independence, restricted mobility

Harper J Neurosci Nur 2003
Schultheis Arch Phy Med Rehabil 2002
Effect on Employment

- Cognitive decline is the major reason for disability and withdrawal from the work force
- Cognitive factors and physical fatigue are the two biggest barriers to employment patients
- Within 10 years of diagnosis (Poser criteria)
  - 50-80% of MS patients are unemployed
  - Not related to degree of physical neurological disability (accounted for < 14% of variability)
  - Not related to other demographic variables
97 employed MS patients
Re-tested 41.3 17.6 months later
Compared those who had changes in employment to those who did not
Definition of vocational change
- Conservative: receiving formal disability benefits at 2nd assessment
- Liberal: Any reduction in work responsibilities
Controlling for EDSS, OR for a worsening of 1.0 on CVLT2-TL was 2.0, and for a worsening of 3.0 on the SDMT was 1.9.
Cognitive Dysfunction and MS

- Weak correlation with physical disability

- Amato et al *Neurology* 2008

- ‘Benign’ MS
  - Little or no physical disability after 15 with MS

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics of cognitively preserved and cognitively impaired benign multiple sclerosis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP-MS patients</td>
</tr>
<tr>
<td>No. (men/women)</td>
<td>36 (7/29)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>45.4 ± 8.5</td>
</tr>
<tr>
<td>Education, mean ± SD, y</td>
<td>11.9 ± 4.1</td>
</tr>
<tr>
<td>Disease duration, mean ± SD, y</td>
<td>22.2 ± 5.8</td>
</tr>
<tr>
<td>EDSS score, mean ± SD</td>
<td>1.3 ± 0.9</td>
</tr>
<tr>
<td>Depression (MADRS score &gt;8), no./total</td>
<td>15/36</td>
</tr>
<tr>
<td>Treatment, treated/nontreated</td>
<td>7/4</td>
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</tbody>
</table>

CP-MS = cognitively preserved; CI-MS = cognitively impaired; NS = not significant; EDSS = Expanded Disability Status Scale; MADRS = Montgomery and Asberg Depression Rating Scale.
Recognizing cognitive impairment

- Why is cognitive function in MS a “new” topic?

- Charcot (1877):

  “At a certain stage of the disease, patients with MS may show marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their entirety.”
Neurologists tend to think of cognitive impairment as the severe, global progressive dementia associated with Alzheimer’s disease

- In MS cognitive impairment, intellectual function and language skills remain intact

If a neurologist suspects an MS patient as cognitively impaired, correct 90% of the time

BUT

If a neurologist does not suspect cognitive impairment, he/she is wrong 50% of the time.

Mahler & Benson Neurobehavioural aspects of MS in Cognitive Dysfunction in MS (Rao, Oxford press) Benedict CNS Spectrums 2005
<table>
<thead>
<tr>
<th>Function</th>
<th>Signs of Impairment</th>
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<tbody>
<tr>
<td>Verbal/visual memory</td>
<td>Forgetfulness</td>
</tr>
<tr>
<td>Attention</td>
<td>Tendency to be easily distracted</td>
</tr>
<tr>
<td>Information-processing speed</td>
<td>Problems performing tasks quickly; problems performing multiple tasks; shifting attention</td>
</tr>
<tr>
<td>Executive function (problem solving)</td>
<td>Difficulties in solving thought problems; rigidity in solving problems</td>
</tr>
<tr>
<td>Visuospatial dysfunction</td>
<td>Impaired visual perception, recognition, and construction; difficulty completing tasks requiring hand-eye coordination</td>
</tr>
</tbody>
</table>

Affected cognitive domains in MS

COWAT=Controlled Oral Word Association Test; JLO=Judgment of Line Orientation Test; CVLT-II=California Verbal Learning Test; BVMT-R=Brief Visuospatial Memory Test; PASAT=Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modalities Test; DKEFS=Delis-Kaplan Executive Function System; TL=Total Learning; DR=Delayed Recovery; CS=Correct Score; DS=Description Score.

Long term follow up of CI in MS

Amato et al Arch Neurol 2001

- 45 MS patients followed over 10 years
- Initially 74% cognitively ‘normal’
  - Decrease to 51% at 4 years and 44% at 10 years
- No one showed improvement over time

Table 3. Evolution of Cognitive Dysfunction in Patients With MS*

<table>
<thead>
<tr>
<th>No. of Failed Subtests</th>
<th>First Testing</th>
<th>Second Testing</th>
<th>Third Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2, no impairment</td>
<td>37/50 (74)</td>
<td>25/49 (51)</td>
<td>20/45 (44)</td>
</tr>
<tr>
<td>3-5, mild impairment</td>
<td>4/50 (8)</td>
<td>16/49 (33)</td>
<td>15/45 (34)</td>
</tr>
<tr>
<td>&gt;5, moderate impairment</td>
<td>9/50 (18)</td>
<td>8/49 (16)</td>
<td>10/45 (22)</td>
</tr>
</tbody>
</table>
OTHER FACTORS IN MS THAT CAN AFFECT COGNITION FUNCTION
Relapses can affect cognitive function
Monthly SDMT administration STRATA (natalizumab re-dosing study)
Morrow SA et al J Neurol 2011

Between group main effect: \( P=0.67 \).
Within group main effect: \( P \leq 0.01 \).
Interaction: \( P=0.03 \).

Control=MS patients without relapses in STRATA; cases=MS patients with relapses in STRATA; D1=dimension 1.
Morrow SA et al. J Neurol. 2011
Identified 24 MS patients with either subjective complaints of cognitive change OR new gad positive lesions on MRI

- Cognitive testing before treatment with steroids
- Assessed 3 months later
- Compared to matched control group without a relapse
Cognitive Fatigue Contributes to Processing Speed

- Cognitive fatigue is commonly reported by MS patients
  - Harder to focus after working on a task for a while than when first started

- Cognitive fatigue and generalized fatigue do not always occur together

- Cognitive fatigue is an important component of impairment of processing speed in MS
23 MS patients with self perceived heat sensitivity vs. 19 matched “normal controls”

Tested before, during and after exposure to a dry sauna

Cognitive function worsened after exposure to heat and improved after body temperature returned to normal
Treating cognitive impairment in MS
Treatments known not to work

- **Donepezil**
  - Krupp et al, RCT Neurology 2011
- **Memantine**
  - Lovera et al RCT MSJ 2010
- **Ginko Biloba**
  - Lovera et al RCT MSJ 2012
Treatments of unknown benefit

**Modafinil**
- Two studies
  - Brioschi et al Eur Neurol 2009 (17 subjects) and Moller et al MSJ 2012 (11 subjects)
- Both studies primarily looked was fatigue
  - Most subjects were not in the impaired range on cognitive measures
- Both studies showed no improvement on cognitive outcomes

**Exercise**
- Most studies demonstrate a correlation between aerobic fitness and cognition (Prakash; Oken; Motl)
  - Cause and effect?


“...limited evidence to support the use of aerobic exercise to improve cognition...less than half (of studies) included cognition as an outcome and few studies continued the aerobic exercise program long enough to be considered effective”
Behavioural Techniques

- Commonly recommended
- No evidence to support benefit

**Memory tricks and aids**
- Word association
- Keeping a notebook and writing things down
- Mobile phone alerts

**Improve concentration/attention**
- Reducing the number of distractions
  - switching off the radio before talking to someone
- Avoid interruptions
- Allow extra time to take in new information
  - Ask for things to be repeated or for written information to read later
- Avoid multi-sense input
  - Don’t take notes during a lecture/meeting; listen and use a note-taker or a dictaphone
Evidence shows amphetamines improve cognitive function
- Better learning, memory in animal studies
- Improve visual memory and learning in ADHD
- Improvement on tests of executive function and working memory in schizophrenics
- Improvement in attention and working memory in TBI

Two drugs showed positive results in MS
- Methylphenidate (Ritalin)
- Lisdexamfetamine (Vyvanse)

Methylphenidate
Harel *J Neurol Sci* 2009

- 26 MS pts
- RCT, single dose 10mg MP vs. placebo
- Tested just before and one hour post dose
- No difference at baseline

- PASAT 3.0, 2.0
  - Alternative forms

![Graph showing attention process performance by PASAT3 and PASAT2 in methylphenidate treated and untreated MS patients. Gray = PASAT3; White = PASAT2.](image)
Inactive prodrug
Converted to lysine and d-amphetamine
Approve for ADHD in children and adults
Extended steady clinical effect
  - Reduced abuse potential
  - Minimizes adverse effects
Lisdexamfetamine and CI in MS Pilot Study (n=49)

- Significant improvement on processing speed compared to placebo
- Significant improvement on Verbal memory compared to placebo

Morrow et al J Neurol 2012
95% of RRMS patients endorsed psychiatric symptoms
- Dysphoria 79%
- Agitation 40%
- Anxiety 40%
- Irritability 35%

Yet --

“Despite advances in clinicians’ recognition that emotional disorders are common among individuals with MS, these disorders are often undetected and inadequately treated” (Minden et al Neurology 2013)
# Mood disorders in MS

<table>
<thead>
<tr>
<th>Depression</th>
<th>Anxiety</th>
</tr>
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<tbody>
<tr>
<td>• Lifetime prevalence in MS is close to 50%</td>
<td>• General Anxiety Disorder: 18.6% versus 5.1% in the general population</td>
</tr>
<tr>
<td>• Risk of suicide 7X higher in MS patients</td>
<td>• Panic Disorder: 10.0% versus 3.5% in the general population</td>
</tr>
<tr>
<td>○ Highest in young males within 5 years of diagnosis</td>
<td>• Obsessive Compulsive Disorder: 8.6% versus 2.5% in the general population</td>
</tr>
</tbody>
</table>
Comorbid Depression and Anxiety in MS

- In MS patients with severe anxiety
  - 57.7% also experienced moderate or severe depression
- In MS patients with severe depression
  - 77.7% suffered moderate or severe anxiety
- Associated with greater
  - Suicidal ideation
  - Alcohol abuse
  - Increased somatic complaints
  - Greater social dysfunction

Cognitive behavior therapy

Not enough evidence to recommend any antidepressant medication

“There is evidence to support pharmacologic and nonpharmacologic therapies for depressed mood and anxiety in individuals without MS”
Cognitive impairment and depression

- Depression is thought to interfere with cognitive function.
- Depression has the most negative impact on:
  - Working memory
  - Processing speed
  - Attention
  - Executive tasks such as planning
- Capacity reduction theory: depression reduces the overall capacity to process information:
  - Depressed patients allocate more resources to processing negative information.
  - Less resources available for other tasks.
Anxiety and CI in MS

Akbar et al Cog Behav Neurol 2011

- Studied 108 MS patients
- 30/39 accurately identified themselves as cognitively impaired
- 51/69 rated themselves as cognitively impaired when they were not
  - Anxiety was found to be a significant predictor of self-rated cognitive impairment, more than depression
Coping Strategies

- Two main categories of coping strategies
  - Problem focused coping (PFC): doing something active to alleviate stressful circumstances
    - Better, more effective coping mechanism
  - Emotional focused coping (EFC) strategies: doing something to try and regulate the emotional consequences of stressful events

- MS patients are more likely to adopt EFC and demonstrate poorer levels of adjustment
- MS patients with depression are more likely to adopt poor coping strategies (avoidant)

Cognitive impairment and depression

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- Depression has the most negative impact on
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**Dialectical Behaviour Therapy (DBT)**

- Based on cognitive-behavioral treatment
- Stresses an essential dialect (i.e. synthesis of opposing views) in finding a balance between
  - ‘accepting’ reality as it is, and
  - maintaining a strong commitment to ‘change’
- Strong skills training focus on acceptance and change strategies

- Over 29 RCTs across in- & out- patient settings has shown efficacy in various populations, including those with:
  - Chronic parasuicical behaviours
  - Borderline personality disorder
  - Substance abuse/dependence
  - ADHD
  - Eating disorders (being eating, anorexia, bulimia)
  - Depression
DBT: skills training based on acceptance and change strategies

**Acceptance-oriented strategies**
- Mindfulness Skills: Increasing awareness in the here and now
- Distress Tolerance Skills: Getting through a difficult situation without making it worse; teaches use of distraction, radical acceptance and evaluating pros & cons of strategy use

**Change-oriented strategies**
- Interpersonal Effectiveness Skills: Communicating and expressing oneself effectively
- Emotion Regulation Skills: Regulating one’s emotions by understanding the relationship between thoughts, feelings, body sensations and behaviours

**Strong focus in DBT on mindfulness training**
- Mindfulness-based training is based on Eastern Zen philosophies of focusing on the present moment in a non-judgemental manner
Proposed Pilot Project: DBT in MS for depression and anxiety

- Emphasis in DBT on acceptance and change strategies are likely important in MS
  - Help patients adjust to a lifelong diagnosis
  - Address emotional dysfunction that may be related to disease-specific & circumstantial factors

- Aim of project
  - Step 1: Examine the effectiveness of DBT for emotional dysfunction in MS
  - Conduct two pilot projects to evaluate the effectiveness of DBT as a treatment
    1) anxiety symptoms
    2) depressive symptoms

- Step 2: Examine whether any change in emotion functioning impact on the level of cognitive impairment in MS
Psychiatric side effects well known with corticosteroids: mood disorders

Reported incidence varies between 1.3% to 58%, differs by:
- dose of corticosteroids
- population analyzed, including asthma, autoimmune disease, AIDS and uveitis
- Doses ranged from 30 mg/day to a maximum of 300 mg/day,
- May be a dose response

In MS population: only one case series
- Mania in 9 of 50 consecutive MS patients treated with high dose corticosteroids for an acute relapse
- Previous diagnosis of depression increased the likelihood of mania
105 consecutive demyelinating events treated with HDC; 88 completed the study

Bipolar Disorder and Schizophrenia were excluded

Standardized questionnaire developed regarding

- Personal history of psychiatric symptoms, use of antidepressants, drug/alcohol abuse, and social support
- Family history of psychiatric diseases suicide attempts, drug/alcohol abuse
Change with HDC

- **Depressive symptoms:** 20 (22.7%) subjects increased BDIFS score between visit 1 and visit 2 (after HDC treatment)
  - No personal or family history variable significantly predicted a worsening while on HDC

- **Mania symptoms:** 34 (38.6%) increased the number of mania symptoms between visit 1 and visit 2 (after HDC treatment)

- Predictors of increased mania symptoms

<table>
<thead>
<tr>
<th>MDQ increase from visit 1 to visit 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self – any psychiatric history</td>
<td>p=0.010</td>
</tr>
<tr>
<td>Family – depression</td>
<td>NS</td>
</tr>
<tr>
<td>Family – BPD or schizophrenia</td>
<td>NS</td>
</tr>
</tbody>
</table>
Conclusion

• Quality of life in MS is more than simply relapses and physical ability
• Cognitive Function, mood and emotional disturbances play a significant role
• Other factors affect the perceived role of an MS patient in society interplay with mood disorders and quality of life
  ○ Ability to work
  ○ Choices regarding family planning
  ○ Stress on loved ones and caregivers
MS in the 21st Century Consensus Statement

- Publication in *Journal of Neurology*
The MS in the 21st Century initiative began in 2011 with the aim of:

- Defining how MS treatment and standards of care should look in the 21st century
- Developing a minimum standard of care across the world
- Motivating the broad MS community to align standards of care and challenge the current treatment paradigm
Methodology

- An expert **steering group** comprising neurologists, patient advocates, a pharmacoepidemiologist, and representatives from national MS centres in Europe and Canada was established.

- Candidates for the steering group were identified by an independent agency, iS Health, to meet the following criteria:

  - The Steering Group should comprise key patient groups and leading clinicians active in the treatment and management of MS.
  - Steering Group members should represent different groups in different countries in Europe.

- The project was run by an independent agency, iS Health, with the support of an **unrestricted educational grant from Merck Serono**.
Methodology

The expert steering group worked over the course of three meetings to:

- Identify the overall vision for future care of MS
- Construct the key overall principles that support this vision and guide the development of MS patient management

A stipulated objective of the MS in the 21st Century steering group was to develop a consensus statement to reach and gain endorsement from the broader MS community.
The structure of the Consensus Statement was informed by the St Vincent Declaration in diabetes.

The document establishes guiding principles to drive research, clinical management, guidelines, care pathways and the overall emphasis of care strategies.

The endorsed statement aims to have a political, social, clinical and patient resonance in the Netherlands, Spain, Czech Rep., Switzerland, Germania.
Second Steering Group meeting – Frankfurt (Sept 2011)

The main principles to guide development of MS care were narrowed down to six:

- Personalized care
- Commitment to research
- MS centres of excellence
- Regulatory body education and reimbursement issues
- New endpoints in clinical trials
- More therapy options

We agreed that iS Health should compile the draft Consensus Statement.
## Principles related to structure of MS care and research

### MS centers of excellence
- Network of dedicated MS centers of excellence
- Committed to research and willing to share resources
- Goal: to improve diagnosis and treatment of all types of MS

### Regulatory Body Education
- Treatment of MS is complex
  - Not all medications are equivalent
  - Need access to “rescue” therapy
- Reimbursement is a significant barrier to adequate treatment
- Patient groups, clinicians and industry need to work together
## Principles related to advancing knowledge and treatment of MS

### Commitment to research
- “We need to embed a culture of research in all aspects of MS care”
- Key to better understanding of the disease
  - Lead to more effective (pharmacological and non-pharmacological) treatments for all forms of MS

### New endpoints for clinical trials
- More than just relapses or disability progression
- Some ideas
  - Subclinical disease activity
  - Neuroprotection
  - Cognition
  - Fatigue
- Need better patient or physician reporting tools (PROs)
More Therapy Options

- Current medications
  - High cost is prohibitive
  - Focus on RRMS only
  - Focus on relapses/progression only

- MS patients should have greater access to comprehensive care regimens that include symptomatic car, rehabilitation and psychological support in addition to DMTs
Personalized Care -- “Patient engagement”

- Inclusive – for all types of MS
- Incorporate pharmacological and non-pharmacological strategies that focus on MS patients as individuals
- Goals:
  - Reduce disease activity
  - Slow disability progression
  - Improve management of symptoms such as depression, immobility and fatigue
The expert steering group worked over the course of two meetings and multiple teleconferences to:

- Identify themes related to patient engagement that are of particular important to MS
- Construct the key overall principles that support this vision and guide the development of MS patient engagement

Again, the objective of the MS in the 21st Century steering group was to develop a consensus statement to reach and gain endorsement from the broader MS community on patient engagement.
Patient Engagement

- Identified as a “patient centric element” as an important principle that needed further exploration
- US Center for advancing health: Actions individuals must take to obtain the greatest benefit from the healthcare services available to them
- Patients should be engaged as advocates
- Patient organizations should work more closely with clinicians, industry, and regulatory bodies for petition and secure research funds
Patient Engagement

- Move away from the idea of patient as passive recipient
- Idea is to change role of patients from healthcare “receivers” to “engagers”
- Requires health care professionals to move away from being merely “providers” and incorporate the role of “motivators” and “supporters” to help patients gain interest in their own health and to continue to take responsibility for it
- Particularly important in a lifelong chronic illness like MS