

# Expert Opinion Paper

Medical Advisory Board of the National Multiple Sclerosis Society

Treatment Recommendations for Physicians

## Assessment and Management of Cognitive Impairment in Multiple Sclerosis

### INTRODUCTION

This document is based on existing literature and expert opinion derived from clinical practice and experience. It is designed to help clinicians be sensitive to the possibility of cognitive deficits in their patients with MS, be more aware of the impact of such deficits, and learn about potential interventions to alleviate the negative consequences of these deficits.

### SUMMARY

- ◆ Cognitive deficits appear to be present in more than half of MS patients, *however the majority of persons with MS do not have impairments that significantly impair daily functioning.*
- ◆ Learning/memory, speed of information processing, working memory, cognitive flexibility and other executive functions appear to be most commonly impaired.
- ◆ Periodic screening for such deficits is recommended.
- ◆ Intervention for such deficits is recommended:
  - ◆ Training in strategies to compensate for deficits
  - ◆ Counseling/psychotherapy for patients and family to address accompanying behavioral changes and emotional responses, and develop realistic expectations
  - ◆ Treatment with medications (disease-modifying and/or symptomatic therapies)

### BACKGROUND

#### Prevalence of Cognitive Dysfunction and MS

Studies suggest that cognitive impairment may occur in up to 50% of all MS patients *although the prevalence has not been adequately determined by prospective, population-based studies.*<sup>1,2,3,4</sup> The most common cognitive impairments are:

- ◆ Impaired learning and memory,<sup>5,6,7,8</sup> i.e., encoding, storage, manipulation, retrieval of information, especially episodic memory (experiential knowledge of events)
- ◆ Slowed information processing,<sup>9,10,11,12</sup> i.e., reductions in speed of thinking that can affect efficiency of cognitive function
- ◆ Impaired working memory,<sup>13,14</sup> especially alternating attention (or shifting attention back and forth between two stimuli—cognitive flexibility) and complex attention (simultaneously attending to multiple stimuli)
- ◆ While less common, deficits in spatial abilities and higher executive function are recognized and are detrimental to adaptive behavior<sup>15,16</sup>

### Impact of Cognitive Function

Studies have clearly shown that individuals with cognitive decline are at greater risk for employment problems.<sup>17</sup> Those with moderate to severe cognitive dysfunction also have difficulty with activities of daily living, may require personal assistance, and may experience problems in social situations.<sup>18,19,20</sup> The impact on family relationships is also significant.<sup>21,22</sup> Furthermore, the impact on driving may be great enough that the individual is no longer safe behind the wheel.<sup>23,24</sup>

Often patients require cognitive evaluation to determine the extent to which their complaints, or the concerns of others, are related to actual MS related cognitive decline, or other confounding factors such as fatigue,<sup>25,26,27</sup> and/or mood disorder.<sup>28,29,30</sup> Adherence to medication and other therapeutic regimens may also be affected by cognitive dysfunction; for example, training in injection techniques for disease modifying agents may present greater challenges in patients with cognitive dysfunction.<sup>31</sup>

### Correlation between Cognitive Dysfunction and Other MS Characteristics

Cognitive impairment is difficult to predict on the basis of clinical presentation alone.

- ◆ Heterogeneity in cognitive deficits related to different disease courses is well established.<sup>32,33,34</sup>
- ◆ Based on several studies,<sup>35,36,37</sup> no or minimal correlation has been found between physical disability and cognitive deficits. In fact, some studies have shown defective cognitive function in patients with minimal physical disability.<sup>38,39,40</sup>
- ◆ Depression can give rise to deficiency in working-memory capacity.<sup>41</sup>
- ◆ Correlation between cognitive dysfunction and fatigue has been observed in some studies although not consistently.<sup>42,43</sup> In one study, subjective fatigue across the work-day increased more for MS patients than for a control group but cognitive test performance was equal for the two groups.<sup>44</sup>

- ◆ There is an ambiguous relationship between disease duration and cognition. Some researchers find correlation between length of disease and cognitive status, while others find no relationship.<sup>45,46,47</sup>
- ◆ A recent study showed a gender-related effect of clinical and genetic variables on cognitive impairment in MS. Cognitive decline was predominant in men and was associated with clinical and genetic variables while cognitive dysfunction in women was independent of these variables.<sup>48</sup>

## MRI Findings and Cognitive Dysfunction

While many factors can contribute to cognitive impairment (e.g., depression, premorbid ability), the strong relationship between neuropsychological testing and brain MRI demonstrates that much of the problem is due to cerebral disease (recent studies show large effects on the order of  $r = 0.71$ .<sup>49,50</sup>).

- ◆ Many studies have shown that lesion volume is correlated with cognitive dysfunction in MS.<sup>51,52,53,54,5</sup>
- ◆ Stronger correlations have emerged with measures of brain atrophy,<sup>56,57</sup> and cognitive deterioration depends more on the development of brain parenchymal atrophy than on the extent of lesion burden in the brain.<sup>58</sup>
- ◆ There are other promising MRI indicators that account for cognitive declines in MS, such as regional brain atrophy,<sup>59</sup> diffusion-tensor imaging,<sup>60</sup> and N-acetylaspartate (NAA—indicative of axonal integrity) levels<sup>61</sup>, to name a few.

A goal for future research is to develop reliable neuroimaging methods that may be used to identify patients at risk for cognitive impairment.<sup>62,63,64</sup>

## RECOMMENDATIONS

### Recommendations for Screening and Assessment

- ◆ *Providers should consider periodic screening and/or assessment for cognitive deficits in MS, as such deficits may not be always be apparent or reported.* Cognitive dysfunction may be difficult to detect because language skills and intellectual function are generally preserved.<sup>65</sup> Because of the high incidence of cognitive impairment in MS, its potentially devastating consequences, as well as the advent of new therapies, periodic screening (e.g., every 1–2 years) is recommended. Screening refers to the application of a simple, inexpensive test that attempts to identify patients that (a) may have a specified illness or condition and (b) would benefit from further evaluation (and in turn, treatment).

Recommended approaches:

- ◆ Query the patient as well as the family regarding cognitive function. Report by family members is closely correlated to cognitive deficits in the individual with MS.<sup>66</sup> Note that

patient reports that are not confirmed by the family may reflect elevated depressive symptoms (e.g., poor self image) rather than true or measurable cognitive deficits. On the other hand, patients may not report symptoms that the family recognizes.

- ◆ Utilize self- and informant-report questionnaires The most appropriate self-report instrument available at this time is the MS Neuropsychological Screening Questionnaire (MSNQ). This is a brief (5-minute) questionnaire that is completed by the patient and by a family member, and does not require a neuropsychologist or rehabilitation professional to administer or score.<sup>67</sup>

Several other methods for screening for cognitive impairment have been proposed. (See tables on the next page.) Financial and time constraints in an outpatient practice may limit the use of these instruments.

The evaluation approach should be tailored to the clinical needs of the patient or clinic. Brief objective testing batteries have been proposed for MS patients with known or suspected cognitive deficits.<sup>68,69</sup> There is also increasing interest in the use of single neuropsychological tests that can be administered to identify patients who are cognitively impaired.<sup>70,71</sup>

Neuropsychological data can help identify areas of cognitive or behavioral change for such at-risk patients, and provide baseline data for later comparisons. However, before neuropsychological deficits are ascribed to multiple sclerosis, the influence of other medical conditions and medications should be considered.

In certain circumstances, *comprehensive* neuropsychological evaluation is appropriate to consider, including detailed exploration of deficits commonly associated with multiple sclerosis.<sup>72</sup> Other forms of cognitive evaluation may be administered by occupational and speech/language therapists (as well as other health care providers) as part of the assessment process, and to guide clinical care.

The most common indicators for comprehensive neuropsychological evaluation are:

1. *Maintenance of employment*

Patients struggling to maintain competitive employment. These patients need a detailed review of residual strengths as well as weaknesses, so effective treatment can be designed and delivered, and appropriate accommodations made in the workplace. Some patients may be denied disability benefits on the basis of normal IQ testing, which lacks sensitivity to MS-associated cognitive impairment. It is important to evaluate higher executive functions in such patients.

2. *Independence in home and community*

Patients struggling with family or household management, and/or activities of daily living benefit from a clear delineation of neurocognitive and neurobehavioral strengths and weaknesses.

**Examples of MS Screening Methods (in order of time requirements)**

Name	First Author	Description	Recommended Administrator
Screening Examination for Cognitive Impairment in MS	W. Beatty (1995)	Brief selection of NP tests emphasizing tests of attention, memory and problem-solving requiring 25–30 min	Neuropsychologist, or other qualified rehabilitation specialist (e.g., occupational therapist, speech/language pathologist, nurse practitioner, etc.)
Neuropsychological Screening Battery for MS	S. Rao (1991)	Brief selection of NP tests emphasizing processing speed and memory requiring 30–35 min	Neuropsychologist, or other qualified rehabilitation specialist (e.g., occupational therapist, speech/language pathologist, nurse practitioner, etc.)
Automated Neuropsychological Assessment Metrics—ANAM	J. Wilken (2003)	A computerized selection of NP tasks emphasizing tests of reaction time, processing speed, working memory, recognition memory, visual reasoning, and fine motor coordination requiring approximately 30 min	Neuropsychologist, or other qualified rehabilitation specialist (e.g., occupational therapist, speech/language pathologist, nurse practitioner, etc.)

**Examples of MS Brief NP Test Batteries (in order of time requirements)**

Name	First Author	Description
Brief Repeatable Battery of Neuropsychological Tests in MS (BRB)	S. Rao (1991)	Tests were empirically derived from a larger battery of NP tests. Included are the Paced Auditory Serial Addition Test, Symbol Digit Modalities Test, Selective Reminding Test, 10/36 Spatial Recall Test, and the Controlled Oral Word Association Test. Approximate administration time 60 min
Minimal Assessment of Cognitive Function in MS (MACFIMS)	R. Benedict (2002)	Tests were rationally derived based on a consensus conference sponsored by the Consortium of MS Centers. Included are the Paced Auditory Serial Addition Test, Symbol Digit Modalities Test, California Verbal Learning Test—II, Brief Visuospatial Memory Test—Revised, Judgment of Line Orientation Test, Controlled Oral Word Association Test, and the Sorting Test from the Delis-Kaplan Executive Function System. Approximate administration time 90 min

### 3. Educational attainment

Students of all ages whose educational activities require cognitive acumen, and who would benefit from knowing how their residual abilities and difficulties are likely to impact success in school, are also well served by more comprehensive neuropsychological evaluation. Test results also help guide recommendations for accommodation in the classroom.

### 4. Differential diagnosis, and/or co-morbid conditions

Consider additional testing where it is necessary to rule out other neurological conditions such as Alzheimer's disease or depression. In addition, for some patients, the level of psychiatric distress or symptoms they develop may interfere with effective cognitive function, even though major cognitive deficits are not present.

Cognitive *re*-evaluation is often recommended to ascertain whether there is evidence of cognitive decline. Other clinical problems related to longitudinal analysis include:

- 1) Significant cognitive worsening has occurred, accompanied by a major depressive episode; testing is needed to differentiate probable neurocognitive changes from mood disorder, to help guide pharmacologic and other treatments.
- 2) Cognitive function has continued to worsen in an older patient with MS, despite disease modifying therapies that have helped maintain physical function; there are concerns about a new, underlying cortical dementia such as Alzheimer's disease.
- 3) A patient, placed on medical leave from work secondary to cognitive problems at the time of a major exacerbation, has improved, and the employer requests documentation of current abilities to assist with successful return to work efforts.

## Recommendations for Intervention and Management

- ◆ *Intervention and management of cognitive dysfunction in MS is ideally performed by certified and/or licensed health professionals experienced in cognitive rehabilitation*, with medication management provided by physicians or other appropriate health care providers, e.g., nurse practitioners. Cognitive rehabilitation professionals include neuropsychologists, psychologists, speech-language pathologists, and occupational therapists. The physicians involved in medication management for cognitive problems are typically neurologists, psychiatrists, or physiatrists (rehabilitation medicine physicians). Ideally, these professionals should have an understanding of MS, including the disease process, common symptoms and findings, and medical treatments (and their side effects). In addition, an understanding of factors that may aggravate or complicate assessment, treatment and function of people with MS—especially temperature-sensitivity, fatigue, and affective disturbance—is desirable.
- ◆ *Interventions should be designed to improve the person's ability to function in all meaningful aspects of family and community life. Intervention should involve systematic, functionally-oriented, therapeutic activities that are based on understanding of specific deficits.* Most commonly, compensatory strategies (i.e., utilizing intact skills and/or external aids) are

used to improve daily functioning. Examples include: cognitive structuring (a learned, practiced approach used to routinize cognitive tasks); substitution strategies (the learned use of intact cognitive abilities to circumvent or bolster impaired abilities, such as using intact visual memory in place of impaired verbal memory function); scheduling and timelines; use of recording devices; memory strategies (e.g., lists, mnemonics, clustering, visualization techniques); templates for repeated tasks; organizational strategies; assistive technology (e.g., hand held computers, electronic calendars and memory logs), creating a structured environment; conducting conversations and activities in quiet places to minimize distraction; etc. Solution-focused, practical training in how to maximize function in spite of deficits, which can be generalized to the individual's everyday environment, is most desirable.

Therapeutic activities designed to restore function (e.g., direct retraining) have also been attempted. However, evidence of effectiveness is ambiguous and controversial. Although the main body of literature suggests some benefit of intervention for people with MS,<sup>73,74,75,76,77,78,79,80,81</sup> other studies have not demonstrated a benefit.<sup>82,83,84</sup> *Furthermore, improvement of scores on standardized tests may not necessarily be correlated with improved function in everyday work or avocational situations.*

- ◆ *In some circumstances, interventions should be accompanied by counseling/psychotherapy to address grief, decreased self-esteem, anxiety, and other emotional responses that may accompany cognitive deficits.* Concurrent emphasis on helping the individual redefine him/her-self, develop effective coping strategies, increase communication skills, and learn to take fullest advantage of his/her strengths to compensate for new areas of difficulties is paramount. Involvement of family members in counseling is critical; in order to facilitate the individual's accommodation to deficits, families need to adjust their expectations to reflect those deficits.
- ◆ *Like other clinical manifestations of MS, cognitive impairment—and especially worsening cognitive impairment as indicated by cognitive testing—is a sign of active disease, and should be viewed as justification for using disease modifying therapy or changing to a different immunomodulator, as well as other medications that may address cognitive symptoms.* (For further clarification on the use of disease modifying agents, see the Society's Disease Management Consensus Statement.<sup>85</sup>) In patients who have dementia (some 10%–20% of MS patients<sup>86</sup>), medications shown to be effective for Alzheimer's disease and other types of dementia are appropriate.<sup>87,88,89</sup> These same medications show promise for mild cognitive impairment more often seen in patients with MS. A recent trial with Donepezil HCl suggested improvement in many aspects of cognitive function<sup>90,91</sup> though a smaller, earlier trial did not.<sup>92</sup> No benefit was found with the use of Amantadine® or 4-Aminopyridine in some studies<sup>93,94</sup> while improved attention was found in another.<sup>95</sup> Symptomatic treatment of fatigue and depression may also yield improvement in functional cognitive abilities.

## Recommendations for Future Research

More research is needed to further evaluate cognitive rehabilitation and intervention in people with MS across the spectrum of the illness.

Issues to be addressed include:

- ◆ Better outcome measures
- ◆ The role that individualized assessment might play before treatment
- ◆ Specific evaluation and treatment techniques
- ◆ Duration of treatment
- ◆ Duration of benefits.

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