National Multiple Sclerosis Society

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Information for Health Professionals

# Cognitive Dysfunction in Multiple Sclerosis

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Neuropsychological studies have provided evidence of disease-based cognitive loss in a substantial number of patients with MS. Among volunteer patients from the general community or patients with recently diagnosed or mild MS, the frequency of cognitive impairment is 30–40%[1–3]. Among patients attending an MS clinic the frequency is roughly 60%[4]. These cognitive deficits are often not appreciated or addressed by the treating physician, and sometimes go unrecognized even by the patients themselves[5,6]. However, they can have a significant impact on the lives of the patients and their family members[7–11]. Cognitive changes are a primary cause of early departure from the workforce. In addition, cognitive changes can impact a person's self-esteem and self-confidence, and interfere with communication and interpersonal relationships.

## COGNITIVE FUNCTIONS AFFECTED BY MS

MS is a disease that impacts the brain in many different ways, including the hallmark demyelinating lesions in the central nervous system (CNS), less visible but equally important types of injury to myelin and axonal fibers, ventricular enlargement, and atrophy of whole brain as well as specific tissue compartments such as the mesial temporal lobe, thalamus, and deep gray matter structures [12–16]. As a result, there is wide variation in degree and type of cognitive impairment among MS patients[17–19]. Some people are not affected at all while others are severely impaired. Some have primarily memory impairment, and others have marked slowness of mental processing speed. In large sample studies examining the profile of cognitive impairment in MS[2–4], slowed processing speed and memory are the most commonly affected functions, followed closely by impairment in executive function and visual/spatial processing. Below are some examples of what these deficits imply in a functional sense:

- **Memory impairment:** difficulty learning new information, remembering recent conversations or tasks to be done, following book or movie plots, keeping appointments.
- **Slowed information processing speed:** difficulty keeping up with conversations and processing incoming information, particularly when it is coming from multiple sources at the same time; difficulty with multi-tasking; thinking feels slowed.

- **Impaired executive function:** difficulty with organization, planning and prioritizing, sequencing, and abstract reasoning.
- **Visual/spatial processing:** difficulty with right-left orientation, reading maps and diagrams, navigating in familiar or unfamiliar places.

Cognitive impairment is difficult to predict on the basis of clinical indicators[17]. In general, relapse rate and neurologic disability as measured by the Expanded Disability Status Scale (EDSS) are poor predictors of the degree of cognitive dysfunction. Patients may be mildly affected physically but present with significant cognitive dysfunction. The converse is also true—some patients are severely physically disabled and yet neuropsychologically intact. Research has shown, however, that patients with a secondary-progressive course are more likely to be cognitively impaired, and there is also some evidence suggesting that male MS patients and those with less education or lower baseline intelligence are at higher risk for cognitive decline.

## COGNITIVE FUNCTION AND BRAIN MRI IN MS

Association between cognitive impairment and white matter lesion burden is well established[19,20]. Better correlation is achieved, however, when neuropsychological tests are measured against amount of volume decrease (atrophy) of the whole brain[22] or of specific brain regions such as the deep gray matter[13] , corpus callosum[23], cerebral cortex[24–25], mesial temporal lobe[26,27], and even specific sub-regions of the cortex[28]. These measures of brain atrophy are thought to be markers of the most destructive aspects of MS pathology[29]. In general, brain volume correlates better with cognitive performance than lesion volume, both in cross-sectional[20] and longitudinal[30] studies.

In addition to studies of brain volume, recent studies using double inversion recovery and phase-sensitive inversion recovery sequences have shown an increase of cortical lesions over time that correlates with impairment on neuropsychological testing[31,32]. Abnormalities in the normal-appearing white matter are known to contribute to cognitive impairment in MS patients. These kinds of subtle abnormalities can be observed with quantitative MRI techniques such as magnetization transfer imaging, diffusion tensor imaging, and proton MR spectroscopy[33]. These techniques reveal pathology that is also correlated with impairment on cognitive testing in MS[34–41]. Thus, different aspects of MS-related brain pathology as seen on brain MRI influence mental abilities in MS. Damage to white matter tracts impairs cognitive functions that rely on rapid transfer of information, while degeneration of neurons in the gray matter affects a wide range of cognitive functions ranging from mental speed to memory and executive function.

## ASSESSMENT OF COGNITIVE IMPAIRMENT IN MS

Given the heterogeneity of cerebral pathology in MS, it is of no surprise to learn that there is no single, brief test that is sufficiently sensitive to screen for cognitive impairment in this disease[42,43]. Fortunately, research has identified two relatively brief neuropsychological batteries that are useful in monitoring cognitive function in MS. Both are validated and have reached a threshold of wide acceptance and replicability: the Rao Brief Repeatable Neuropsychological Battery (BRNB) [44] and

**TABLE 1**
**Neuropsychological Tests Included in the BRNB and MACFIMS**

| Rao BRNB | Cognitive Domain | MACFIMS |
|---|---|---|
| PASAT | Auditory Processing Speed and Working Memory | PASAT |
| SDMT | Visual Processing Speed and Working Memory | SDMT |
| SRT | Auditory/Verbal Episodic Memory | CVLT2 |
| 10/36 | Visual/Spatial Episodic Memory | BVMTR |
| COWAT | Expressive Language | COWAT |
| | Spatial Processing | JLO |
| | Executive Function | DKEFS Sorting |

SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test; SRT = Selective Reminding Test; CVLT2 = California Verbal Learning Test, second edition; 10/36 = 10/36 Spatial Recall Test; BVMTR = Brief Visuospatial Memory Test—Revised; COWAT = Controlled Oral Word Association Test; JLO = Judgment of Line Orientation; DKEFS = Delis-Kaplan Executive Function System.

the Minimal Assessment of Cognitive Function in MS (MACFIMS)[4,45]. The tests from each battery are listed in Table 1.

As can be seen, there is considerable overlap between these batteries. Yet there are some subtle advantages to each approach. The BRNB requires less time and has been translated into multiple European languages. The MACFIMS has a stronger psychometric foundation and includes assessment of spatial processing and higher executive function abilities. The batteries were recently compared psychometrically by Strober, Rao and Benedict[46].

Both the BRNB and the MACFIMS include the Symbol Digit Modalities Test (SDMT)[47] which measures visual processing speed. This is a traditional, person-administered test that requires only five minutes and can be combined with motor tests to form a reliable version of the Multiple Sclerosis Functional Composite (MSFC)[48]. The SDMT is also among the more reliable and sensitive[42] tests in the MS literature and despite its brevity is probably the most robust correlate of abnormal brain MRI in MS studies[6,13,25,49–53].

## TREATMENT AND MANAGEMENT OF COGNITIVE LOSS IN MS

Data are limited regarding the effects of immunomodulating agents on cognitive dysfunction as studies have not employed neuropsychological tests as primary outcomes. However, clinical trials have suggested that such disease modifying therapies do improve some aspects of cognition, as would be expected[54,55].

**TABLE 2**
**Summary of Symptomatic Medication Studies**

| | Drug | No. of Treated Pts. | Findings | Comment |
|---|---|---|---|---|
| Giesler 1996[59] | Amantadine<br>Pemoline | 16 | –– | Trend observed favoring amantadine showing positive effects on SDMT |
| Wilken 2008[60] | Modafinil | 23 | ++ | No placebo control<br>Unclear analysis<br>No control for multiple comparison s |
| Harel 2009[55] | Methylphenidate | 14 | ++ | Single dose<br>Trt Grp↑ at baseline |
| Benedict 2008[57] | l-Amphetamine | 19 | ++ | Treated n = 19<br>Single dose |
| Morrow 2009[58] | l-Amphetamine | 108 | –– | Positive effects seen on tests of episodic memory, which were secondary outcomes |
| Krupp 2004[61] | Donepezil | 35 | ++ | Groups differ on disease course |
| Shaygannejad 2008[62] | Rivastigmine | 30 | –– | Poor design<br>Insensitive outcome measure<br>Differences on baseline NP testing<br>Differences in education level |
| Krupp 2011[63] | Donepezil | 61 | –– | Groups differ on disease course |

Another avenue for treating cognitive disorders in MS patients are the emerging medications for clinical symptoms. Some of this research is summarized in Table 2. Psycho-stimulants present an opportunity for adjunctive symptomatic therapy for MS-associated inattention or slowed information processing. Two studies, examining the effects of methylphenidate [56] and l-amphetamine[57], showed positive effects on cognitive testing when the tests were administered shortly after drug administration. However, the effects of the latter on processing speed tests were not replicated in a large sample study of daily 30 mg dose (of note: there were positive effects on tests of episodic memory but as these tests were secondary outcomes, the significance of this observation is unclear)[58].

Two, well designed, placebo-controlled studies of acetyl-cholinesterase inhibitors have been conducted with MS patients. Krupp and colleagues[61] examined the effects of donepezil over 24 weeks. While there were a few methodological shortcomings (e.g., small sample, treatment groups not matched on disease course) positive effects favoring the active arm of the study were seen on an adapted version of the Selective Reminding Test and a clinician impression of change. However,

these findings were not replicated in a study examining the effects of a similar medication, rivastigmine[62], or in a follow-up study with donepezil[63].

Cognitive rehabilitation has rarely been examined in MS patients. As noted in recent reviews of this emerging literature[64,65], the findings are mixed on the efficacy of cognitive rehabilitation in MS. O'Brien et al. critically reviewed the literature and found very few studies that used methodology that would yield reliable conclusions. A large proportion of these studies have been poorly controlled. On exception may be a study by Chiaravalloti et al. examining the effects of an internal, compensatory strategy for verbal learning[66]. This work is based on the idea that impaired verbal learning in MS[67] is primarily related to impairment of efficient encoding of new information.

Overall, the best management approach at this point appears to be to recognize and diagnose cognitive loss early, and to provide appropriate support and consultation for patients and families in order to minimize the psychological, social and vocational impact. If the problem is ignored, the result can be calamitous. That being said, there is no definitive treatment for cognitive loss in MS. Therefore, while a number of interventions can be tried, the needs and specifications for each patient are likely to be unique. The family plays an important role, both in diagnosis and management. The steady support of family members is key in assisting the patient's process of acceptance and in facing any social or vocational role changes that occur. Referrals to neuropsychologists for comprehensive assessment can be helpful in many cases, particularly if the individual is experiencing challenges at work or is applying for Society Security Disability (cognitive changes being one of the four recognized criteria for disability in MS). Some occupational therapists and speech/language pathologists also provide assessment and treatment of cognitive dysfunction in people with MS, focusing on compensatory strategies to deal with any changes or losses that have occurred.

## TIPS FOR CLINICIANS

- A person's cognitive impairment can be significant enough to interfere with everyday activities without being apparent to you during a brief office visit; it is important not to base your assessment of the person's cognitive status on her or his physical status.
- Patients may or may not mention their cognitive challenges; it is helpful and appropriate to ask if they are experiencing any, as that will help guide your work with them.
- Patients with MS may have difficulty remembering their appointments or arriving on time for them; reminders are extremely helpful.
- Providing instructions in written form as well as orally can help to improve treatment adherence.
- Patients may ask to bring a tape recorder to their appointment so that they can review their conversation with you, or bring a relative or friend to help them remember the important information.

## REFERENCES

1. Patti F, Amato M, Trojano M, Bastianello S, Tola M, Goretti B, et al. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: Baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. *Mult Scler* 2009; 15(7):779–788.
2. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41:685–691.
3. Rovaris M, Riccitelli G, Judica E, Possa F, Caputo D, Ghezzi A, et al. Cognitive impairment and structural brain damage in benign multiple sclerosis. *Neurology* 2008; 71(19):1521–1526.
4. Benedict RHB, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, et al. Validity of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006; 12:549–558.
5. Carone D, Benedict RHB, Munschauer FE, III, Fishman I, Weinstock-Guttman B. Interpreting patient/informant discrepancies of reported cognitive symptoms in MS. *J Int Neuropsychol Soc* 2005; 11:574–583.
6. Benedict RHB, Carone D, Bakshi R. Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. *J Neuroimaging* 2004; 14(3 Suppl):36S–45S.
7. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis: Impact on employment and social functioning. *Neurology* 1991; 42:692–696.
8. Kalmar JH, Gaudino EA, Moore NB, Halper J, Deluca J. The relationship between cognitive deficits and everyday functional activities in multiple sclerosis. *Neuropsychology* 2008; 22(4):442–449.
9. Goverover Y, Genova HM, Hillary FG, DeLuca J. The relationship between neuropsychological measures and the Timed Instrumental Activities of Daily Living task in multiple sclerosis. *Mult Scler* 2007; 13(5):636–644.
10. Knight RG, Devereux RC, Godfrey HPD. Psychosocial consequences of caring for a spouse with multiple sclerosis. *J Clin Exp Neuropsychol* 1997; 19:7–19.
11. Benedict RHB, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, et al. Predicting quality of life in multiple sclerosis: Accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci* 2005; 231:29–34.
12. Stankiewicz JM, Glanz BI, Healy BC, Arora A, Neema M, Benedict RH, et al. Brain MRI lesion load at 1.5T and 3T versus clinical status in multiple sclerosis. *J Neuroimaging* 2011; 21(2):e50–e56.
13. Houtchens MK, Benedict RHB, Killiany R, Sharma J, Jaisani Z, Singh B, et al. Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69:113–123.
14. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, Bakshi R. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology* 2006; 66(5):685–692.

15. Zivadinov R, Bakshi R. Role of MRI in multiple sclerosis I: Inflammation and lesions. *Frontiers Biosci* 2004; 9:665–683.

16. Bermel RA, Innus MD, Tjoa CW, Bakshi R. Selective caudate atrophy in multiple sclerosis: A 3D MRI parcellation study. *Neuroreport* 2003; 14(3):335–339.

17. Benedict RH, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nat Rev Neurol* 2011; 7:332–342.

18. Benedict R, Bobholz J. Multiple sclerosis. *Semin Neurol* 2007; 27:78–86.

19. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7(12):1139–1151.

20. Rovaris M, Comi G, Filippi M. MRI markers of destructive pathology in multiple sclerosis-related cognitive dysfunction. *J Neurol Sci* 2006; 245(1–2):111–116.

21. van Walderveen MA, Kamphorst W, Scheltens P, van Waesberghe JH, Ravid R, Valk J, et al. Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. *Neurology* 1998; 50(5):1282–1288.

22. Simon JH, Jacobs LD, Campion M, Rudick RA, Cookfair DL, Herndon RM, et al. A longitudinal study of brain atrophy in relapsing multiple sclerosis. *Neurology* 1999; 53:139–148.

23. Rao SM, Bernardin L, Leo GJ, Ellington L, Ryan SB, Burg LS. Cerebral disconnection in multiple sclerosis. Relationship to atrophy of the corpus callosum. *Archiv Neurol* 1989; 46(8):918–920.

24. Amato MP, Bartolozzi ML, Zipoli V, Portaccio E, Mortilla M, Guidi L, et al. Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. *Neurology* 2004; 63(1):89–93.

25. Benedict RHB, Bruce JM, Dwyer MG, Abdelrahman N, Hussein S, Weinstock-Guttman B, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Archiv Neurol* 2006; 63:1301–1306.

26. Benedict RH, Ramasamy D, Munschauer F, Weinstock-Guttman B, Zivadinov R. Memory impairment in multiple sclerosis: Correlation with deep grey matter and mesial temporal atrophy. *J Neurol Neurosurg Psychiatry* 2009; 80(2):201–206.

27. Sicotte NL, Kern KC, Giesser BS, Arshanapalli A, Schultz A, Montag M, et al. Regional hippocampal atrophy in multiple sclerosis. *Brain* 2008; 131:1134–1141.

28. Tekok-Kilic A, Benedict RHB, Weinstock-Guttman B, Dwyer M, Carone D, Srinivasaraghavan B, et al. Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. *NeuroImage* 2007; 36:1294–1300.

29. Filippi M, Rocca MA, Benedict RH, DeLuca J, Geurts JJ, Rombouts SA, et al. The contribution of MRI in assessing cognitive impairment in multiple sclerosis. *Neurology* 2010; 75(23):2121–2128.

30. Zivadinov R, Sepcic J, Nasuelli D, De Masi R, Bragadin LM, Tommasi MA, et al. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2001; 70(6):773–780.

31. Roosendaal SD, Moraal B, Pouwels PJ, Vrenken H, Castelijns JA, Barkhof F, et al. Accumulation of cortical lesions in MS: Relation with cognitive impairment. *Mult Scler* 2009; 15(6):708–714.

32. Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, Favaretto A, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. *Arch Neurol* 2009; 66(9):1144–1150.

33. Bakshi R, Thompson AJ, Rocca MA, Pelletier D, Dousset V, Barkhof F, et al. MRI in multiple sclerosis: Current status and future prospects. *Lancet Neurol* 2008; 7(7):615–625.

34. Filippi M, Tortorella C, Rovaris M, Bozzali M, Possa F, Sormani MP, et al. Changes in the normal appearing brain tissue and cognitive impairment in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000; 68(2):157–161.

35. Deloire MS, Salort E, Bonnet M, Arimone Y, Boudineau M, Amieva H, et al. Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005; 76(4):519–526.

36. Amato MP, Portaccio E, Stromillo ML, Goretti B, Zipoli V, Siracusa G, et al. Cognitive assessment and quantitative magnetic resonance metrics can help to identify benign multiple sclerosis. *Neurology* 2008; 71(9):632–638.

37. Khaleeli Z, Cercignani M, Audoin B, Ciccarelli O, Miller DH, Thompson AJ. Localized grey matter damage in early primary progressive multiple sclerosis contributes to disability. *Neuroimage* 2007; 37(1):253–261.

38. Summers M, Fisniku L, Anderson V, Miller D, Cipolotti L, Ron M. Cognitive impairment in relapsing-remitting multiple sclerosis can be predicted by imaging performed several years earlier. *Mult Scler* 2008; 14(2):197–204.

39. Benedict RH, Bruce J, Dwyer MG, Weinstock-Guttman B, Tjoa C, Tavazzi E, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. *Mult Scler* 2007; 13(6):722–730.

40. Roca M, Torralva T, Meli F, Fiol M, Calcagno M, Carpintiero S, et al. Cognitive deficits in multiple sclerosis correlate with changes in fronto-subcortical tracts. *Mult Scler* 2008; 14(3):364–369.

41. Okuda DT, Srinivasan R, Oksenberg JR, Goodin DS, Baranzini SE, Beheshtian A, et al. Genotype-phenotype correlations in multiple sclerosis: HLA genes influence disease severity inferred by 1HMR spectroscopy and MRI measures. *Brain* 2009; 132(Pt 1):250–259.

42. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RHB. Screening for cognitive impairment in MS using the Symbol Digit Modalities Test. *Mult Scler* 2007; 13:52–57.

43. Benedict RHB, Cox D, Thompson LL, Foley FW, Weinstock-Guttman B, Munschauer F. Reliable screening for neuropsychological impairment in MS. *Mult Scler* 2004; 10:675–678.

44. Rao SM. *A Manual for the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis.* National Multiple Sclerosis Society, 1991.

45. Benedict RHB, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: A consensus approach. *Clin Neuropsychol* 2002; 16:381–397.

46. Strober L, Englert J, Munschauer F, Weinstock-Guttman B, Rao S, Benedict RH. Sensitivity of conventional memory tests in multiple sclerosis: Comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. *Mult Scler* 2009; 15(9):1077–1084.

47. Smith A. *Symbol Digit Modalities Test: Manual.* Los Angeles: Western Psychological Services, 1982.

48. Drake A, Weinstock-Guttman B, Morrow S, Hojnacki D, Munschauer F, Benedict R. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: Replacing the PASAT with the Symbol Digit Modalities Test. *Mult Scler* 2009; 16:228–237.

49. Christodoulou C, Krupp LB, Liang Z, Huang W, Melville P, Roque C, et al. Cognitive performance and MR markers of cerebral injury in cognitively impaired MS patients. *Neurology* 2003; 60:1793–1798.

50. Benedict RHB, Bruce J, Dwyer MG, Weinstock-Guttman B, Tjoa C, Tavazzi E, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. *Mult Scler* 2007; 13(6):722–730.

51. Benedict RHB, Zivadinov R. Predicting neuropsychological abnormalities in multiple sclerosis. *J Neurol Sci* 2006; 245:67–72.

52. Benedict RHB, Zivadinov R, Carone D, Weinstock-Guttman B, Gaines J, Maggiore C, et al. Regional lobar atrophy predicts memory impairment in multiple sclerosis. *Am J Neuroradiol* 2005; 26:1824–1831.

53. Benedict RHB, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Archiv Neurol* 2004; 61:226–230.

54. Fischer JS, Priore RL, Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Ann Neurol* 2000; 48:885–892.

55. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; 67(7):1242–1249.

56. Harel Y, Appleboim N, Lavie M, Achiron A. Single dose of methylphenidate improves cognitive performance in multiple sclerosis patients with impaired attention process. *J Neurol Sci* 2009; 276(1–2):38–40.

57. Benedict RHB, Munschauer F, Zarevics P, Erlanger D, Rowe V, Feaster T, et al. Effects of l-amphetamine sulfate on cognitive function in multiple sclerosis patients. *J Neurol* 2008; 255:848–852.

58. Morrow SA, Kaushik T, Zarevics P, Erlanger D, Bear MF, Munschauer FE, et al. The effects of l-amphetamine sulfate on cognition in MS patients: Results of a randomized controlled trial. *J Neurol* 2009; 256(7):1095–1102.

59. Geisler MW, Sliwinski M, Coyle PK, Masur DM, Doscher C, Krupp LB. The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis. *Archiv Neurol* 1996; 53:185–188.

60. Wilken JA, Sullivan C, Wallin M, Rogers C, Kane RL, Rossman H, et al. Treatment of multiple sclerosis related cognitive problems with adjunctive modafinil: Rationale and preliminary supportive data. *Int J MS Care* 2008; 10:1–10.

61. Krupp LB, Christodoulou C, Melville P, Scherl WF, MacAllister WS, Elkins LE. Donepezil improves memory in multiple sclerosis in a randomized clinical trial. *Neurology* 2004; 63:1579–1585.

62. Shaygannejad V, Janghorbani M, Ashtari F, Zanjani HA, Zakizade N. Effects of rivastigmine on memory and cognition in multiple sclerosis. *Can J Neurol Sci* 2008; 35(4):476–481.

63. Krupp LB, Christodoulou C, Melville P, Scherl WF, Pai LY, Muenz LR, et al. Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis. *Neurology* 2011; 76(17):1500–1507.

64. O'Brien AR, Chiaravalloti N, Goverover Y, Deluca J. Evidence-based cognitive rehabilitation for persons with multiple sclerosis: A review of the literature. *Archiv Phys Med Rehabil* 2008; 89(4):761–769.

65. Chiaravalloti N, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7:1139–1151.

66. Chiaravalloti ND, DeLuca J, Moore NB, Ricker JH. Treating learning impairments improves memory performance in multiple sclerosis: A randomized clinical trial. *Mult Scler* 2005; 11(1):58–68.

67. DeLuca J, Barbieri-Berger S, Johnson SK. The nature of memory impairments in multiple sclerosis: Acquisition versus retrieval. *J Clin Exp Neuropsychol* 1994; 16:183–189.

## RECOMMENDED READING

LaRocca N, Kalb R. *Multiple Sclerosis: Understanding the Cognitive Challenges.* New York: Demos Medical Publishing, 2007.