Fatigue in Multiple Sclerosis

Anjali Shah, MD

KEYWORDS

• Multiple sclerosis • Fatigue • Neurorehabilitation • Human
• Quality of life • Treatment of fatigue

MS is a chronic, debilitating, inflammatory, and neurodegenerative disease of the CNS. There is no cure for the disease, and its management includes use of symptomatic agents and disease-modifying therapies to reduce and/or prevent relapses and disease progression. MS affects approximately 350,000 persons in the United States.[1,2] Its estimated prevalence is 1/1000 individuals in North America, and it is one of the most common causes of disability in young adults.

The symptoms of MS are numerous and include weakness, paresthesias, visual changes, spasticity, cognitive dysfunction, ataxia, and fatigue. Fatigue remains one of the most common and debilitating symptoms in MS and is quoted as one of the single most disabling symptoms.[3] Forty percent of MS patients state fatigue as their most disabling symptom.[4] It has been reported to cause profound disruption of quality of life in MS patients.[5] Approximately 20% of patients evaluated in primary care clinics experience fatigue.[6] In contrast, 96% of MS patients experience fatigue, 88% of whom report fatigue as a moderate to high problem.[5,7]

DEFINITION

There is no universally accepted definition of fatigue in MS patients. One common definition describes a ''subjective lack of physical and/or mental energy, perceived by the individual or caregiver to interfere with usual and desired activities.'' Some other definitions include ''pathologic exhaustion,'' ''reversible motor and cognitive impairment with reduced motivation and desire to rest,'' and ''difficulty with initiation of or sustaining voluntary activities that does not correlate with muscle weakness, depression, or muscle fatigue.'' Researchers in the United Kingdom interviewed MS patients first in face-to-face interviews and then using a questionnaire format to learn about patients' perceptions of fatigue. Patients described fatigue as a ''reversible motor and cognitive impairment, with reduced motivation and desire to rest.''[8]

Conflict of Interest: The author is a paid consultant for Biogen Idec, EMD Serono, and Teva Pharmaceuticals.
Department of Physical Medicine and Rehabilitation, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Mail Code 9055, Dallas, TX 75390-9055, USA
E-mail address: anjali.shah@utsouthwestern.edu

Phys Med Rehabil Clin N Am 20 (2009) 363–372
doi:10.1016/j.pmr.2008.12.003 **pmr.theclinics.com**
1047-9651/08/$ – see front matter

It is important to differentiate between peripheral and central fatigue, as each has a unique etiology and treatment recommendation. Peripheral fatigue equates to muscle fatigue due to physical exertion and is alleviated with rest and associated with fatigability. Fatigue differs from fatigability, which is a generalized sense of exhaustion, not present at rest, affecting the patient after a few minutes of physical activity, and alleviated with rest. Central fatigue is much more subjective and is associated with difficulty with arousal and attention. The subject reports a feeling of constant exhaustion, which can lead to worsening vision or function. MS patients experience both central and peripheral fatigue. Therefore, differentiation between both types is vital to proper management.

IMPACT OF FATIGUE

Fatigue in the MS patient can have profound negative effects. Patients frequently need to nap, take frequent breaks, or sleep early. This may interfere with family activities, cause avoidance of the outdoors due to fatiguing effects of heat, or lead to an inability to participate in events that require prolonged physical effort. Social activities with friends and family are difficult to plan, as some days MS patients may awaken with an overwhelming sense of fatigue that cannot be alleviated with rest.[9] Cognitive processing, memory, and concentration are impaired during periods of fatigue.[10] Fatigue can negatively affect vocational performance and maintenance, especially if workplace accommodations are not achievable. The presence of fatigue has significant negative implications on quality of life in MS patients. Interestingly, as disease progresses, the effect of fatigue in MS frequently diminishes due to overall decreased ability of persons to perform previous routine activities.

MS patients often avoid physical activity to avoid fatigue. Additionally, patients may be concerned about thermosensitivity secondary to elevated body temperatures. Therefore, many MS patients engage in minimal physical activity, which may progressively worsen their weakness, fatigue, and other health issues. Limited mobility can play a role in worsening spasticity, constipation, and bone loss. In exercise studies, people with MS were shown to have decreased peak oxygen levels during maximal incremental exercise compared with those of healthy subjects.[11] This finding may suggest that MS patients have reduced cardiovascular fitness related to deconditioning. Insufficient activity in MS patients is linked to muscle changes that occur independently of CNS damage (ie, lowered oxidative capacity, lowered muscle dynamic properties, increased muscle fatigue, impaired metabolic responses to muscles to load, impaired excitation–contraction coupling).[12] Therefore, there may be an imbalance between the increased metabolic need in MS patients and their lowered cardiovascular supply. Rampello and colleagues[11] found that maximum exercise tolerance improved after patients completed 8 weeks of aerobic training, with a significant change in walking capacity. Similar results occurred after a 4-week aerobic treadmill training in MS patients with no worsening of fatigue scores.[13] Several studies have demonstrated clear benefit of regular physical activity in MS patients with improved fitness levels and quality-of-life measures.[6,11,12,14,15] However, not all results are linked with corresponding decreases in fatigue; conversely, no worsening of fatigue was reported.

In addition to the effect on health, personal life, and vocation, the costs of MS should be considered. Unexpectedly, healthcare costs increase with increasing disability.[16,17] The MS patient is responsible for the majority of the financial burden. The proportion of costs directly attributable to fatigue is unknown.

ASSESSMENT TOOLS

The Fatigue Severity Score (FSS), the Fatigue Impact Scale (FIS), and the Modified Fatigue Impact Scale (MFIS) are the most commonly used scales for fatigue assessment in MS patients.[18] The FSS is composed of 9 items that assess perceived fatigue.[19] Subjects are asked to assign a number from 1 (strongly disagree) to 7 (strongly agree) stating their agreement with each statement.[4] Responses are summed and averaged, with a score of 4 or more indicating significant fatigue.[20]

The FIS has been identified by the Multiple Sclerosis Council for Clinical Practice Guidelines "as the most appropriate for assessing the impact of MS-related fatigue on quality of life."[21] The FIS is a retrospective tool designed to evaluate fatigue during the past month. The FIS has separate subscales for physical, psychosocial, and cognitive functions, which span more than 40 statements.[9] Subjects are asked to score the effect of fatigue on those 4 dimensions using a 5-point scale from 0 (no problem) to 4 (extreme problem). Since the FIS takes approximately 10 to 20 minutes to be administered, followed by 5 minutes to score, shorter versions of the scale have been created. The MFIS is a modified version of the FIS and consists of a long (21-question) and short (5-question) version.[22] The total time to administer and score is about 10 to 15 minutes.

Kos and colleagues[22] developed a Visual Analog Scale that assesses the impact of fatigue on daily life, and they reported reliability and validity comparable to the FSS and MFIS. A score of 59 or more on a 100-mm line signifies individuals with fatigue that has a high impact on daily life. This may be helpful for the clinician to quickly assess fatigue in patients in the context of an office visit.

Although several scales are available for evaluation of fatigue in MS patients, none of them is an objective scale. All currently available scales are self-report questionnaires or surveys. Due to the fluctuating nature of MS, it is possible that patient's perception of fatigue is highly dependent on the time of day the survey was performed. A study evaluating walking parameters and fatigue in MS patients reported no significant difference in walking speed, stride length, cadence, or double-limb support time from 10 AM to 3 PM on the same day, whereas the self-reported fatigue score increased significantly.[23] This study is supported by findings from Krupp and colleagues[4] who found no relation between neurologic disability level and fatigue. This finding supports the need for objective measures in evaluating fatigue. However, the challenge in measuring the biological impact of fatigue is that the mechanisms of fatigue are largely unknown.

PATHOGENESIS—PRIMARY FACTORS

When evaluating the pathogenesis of fatigue in MS, it is important to distinguish primary fatigue from secondary fatigue. Primary fatigue is a result of the disease process, and secondary fatigue results from medications or disease-related manifestations.[24] Due to the multimodal aspect of fatigue in MS, it is difficult to differentiate primary fatigue from secondary fatigue, as several factors contribute to fatigue manifestation.

There are several theories on the pathogenesis of fatigue, with strong evidence for an inflammation mediated process. Giovannoni[7] and Heesen and colleagues[25] state that fatigue is inflammation driven, citing that fatigue caused by viral or bacterial infections can be reproduced by proinflammatory cytokines, such as interferon α or β or interleukin-2. Several MS patients experience fatigue as a side effect of interferon treatment. The potential effect of hypothalamo-pituitary-adrenal (HPA) axis dysfunction on fatigue has been evaluated by multiple researchers with varying results. HPA

hypoactivity occurs in chronic fatigue syndrome, and researchers have searched for a connection with MS and fatigue. Some studies report no correlation between fatigue scores and abnormal dexamethasone–corticotropin-releasing hormone scores, whereas others report hyperactivity of the HPA axis.[26] Gadolinium (Gd) enhancing lesions, the quintessential marker for inflammation in MS, failed to demonstrate correlation between fatigue and Gd-enhancing lesions.

Some aspects of fatigue suggest that it may be related to underlying demyelinating pathology, which results in slowing and desynchronization of nerve transmission or partial or complete conduction block.[6,27] The peripheral causes of fatigue have been investigated using repetitive nerve stimulation (RNS). RNS failed to demonstrate improved impulse conduction along demyelinated nerves. Finally, central motor conduction time is prolonged in MS patients, supporting the use of evoked potential testing in MS patients for diagnostic purposes.

Some researchers correlate hypometabolism detected in positron emission tomography in the bilateral prefrontal cortex, premotor and supplemental motor cortex, putamen, and white matter extending from rostral putamen to the head of the caudate nucleus, with fatigue symptoms.[6,28] Diffuse axonal damage and brain atrophy are also linked as possibly related to causing fatigue.[29,30] No correlation between brain atrophy and fatigue has been found.[31,32] Functional magnetic resonance imaging displays impaired interaction between cortical and subcortical areas, which is inversely related to results on the FSS.

Researchers have raised the question whether MS fatigue is more of a peripheral than central phenomenon.[5] The hallmark of peripheral fatigue is muscle fatigability, frequently due to neuromuscular or myopathic disorders.[6] Sustained muscle fatigue leads to disuse atrophy, thereby limiting endurance in MS patients. This can lead to cardiovascular decline, increased spasticity, contracture development, and overall deconditioning. Central fatigue is characterized by a feeling of constant exhaustion and is associated with several neurologic disorders, including MS. Central fatigue is implicated in MS due to the correlation between fatigue and cognitive dysfunction.

PATHOGENESIS—SECONDARY FACTORS

There are several additional factors that may worsen fatigue for patients with MS (**Box 1**). Thermosensitivity is common in people with MS, leading to instability and delay in signal conduction in demyelinated nerves. Increased body temperature induces conduction block, resulting in deterioration of neurologic function, which is known as the Uhthoff phenomenon. MS fatigue secondary to heat sensitivity differs from that in normal healthy adults (NHAs) in that heat intolerance causes difficulty in sustaining physical activities and interferes with physical functions and responsibilities.[4] MS patients should be encouraged to precool with ice water or sit in a cool bath for 20 minutes before engaging in exercise or other forms of physical activity.[33]

Mood disorders, such as depression and anxiety, are common in MS patients. Depression occurs in approximately 50% of MS patients.[18] It may either occur as a secondary reaction to living with a chronic, debilitating condition, or it may be embedded in a mood disorder such as bipolar disease. Treatment with the serotonin reuptake inhibitor, fluoxetine, in combination with 4-aminopyridine (4-AP), has demonstrated reduced levels of fatigue in MS patients. A link between fatigue and psychiatric illness, most commonly depression, has been suggested. The results are mixed, with some reports finding no correlation and some finding strong correlation between psychiatric illness and MS fatigue.[34–37] Many researchers strongly support the fact that timely identification and management of mood disorders are vital. Psychiatric illnesses are rarely the sole cause of fatigue.

Box 1
Fatigue—secondary factors

- Thermosensitivity
- Depression
- Anxiety
- Sleep disturbance
- Infection
  - Viral
  - Bacterial
- Thyroid dysfunction
- Anemia
- Medications
  - Antidepressants
  - Antispasmodics
  - Narcotics
  - Sedatives

Many MS patients with fatigue also complain of sleep disturbance. This may be secondary to neuropathic pain, spasticity, or periodic limb movements. Obstructive sleep apnea should be ruled out as a contributing factor to fatigue. A significant correlation has been reported between fatigue and disrupted sleep or abnormal sleep cycles in MS patients.[38] Additionally, a study compared the incidence among French Canadians of restless leg movement (RLM) in 200 MS patients, 100 patients with rheumatoid arthritis, and 100 NHAs. They reported that 37.5% of MS patients, 31% of RA patients, 16% of NHAs fulfilled criteria for RLM.[39] A smaller study of 25 MS patients compared to 25 normal healthy controls reported RLM in 36% of MS patients. In addition, MS patients had reduced sleep efficiency and increased awakenings on 8-hour polysomnography testing.[40] Studies in this area remain limited, and further research is needed to gain a better understanding of the underlying mechanisms associated with MS sleep disturbance and fatigue. Surveillance of sleep quality is recommended in MS patients with fatigue.

Other medical conditions can contribute to fatigue, and that should be evaluated. Infections, either viral or bacterial, and, most commonly, urinary tract infections or upper respiratory infections can adversely affect energy levels in MS patients and worsen other symptoms such as spasticity and pain. Evaluation and exclusion of thyroid, liver, and hematologic profile abnormalities are encouraged.

Several of the medications prescribed for symptomatic treatment in MS patients can worsen fatigue. The clinician is encouraged to regularly review patients' medication lists for potential offenders. This includes antispasticity agents, antiepileptics, narcotics, or sedatives. Patients may report increased fatigue secondary to interferon treatment. The use of nonsteroidal anti-inflammatory drugs, such as naproxen or ibuprofen, has demonstrated efficacy over acetaminophen and is encouraged before and after interferon injection for effective management of flu-like effects.[41]

TREATMENT OF FATIGUE

Prevention

After ruling out primary and/or secondary causes of fatigue and deciding on treatment, it is important that the clinician's approach to the treatment of fatigue be global, including pharmacologic and nonpharmacologic approaches. Nonpharmacologic approaches include local cooling devices, energy management strategies (spacing out activities, performing strenuous activities during periods of increased energy stores), behavioral/lifestyle modifications (good sleep hygiene, limiting alcohol intake, tobacco cessation), nutrition management, and rehabilitative interventions.

Rehabilitative Interventions

The effect of various neurorehabilitative interventions on fatigue has been investigated. Yoga and bicycling demonstrated reduced fatigue and improved quality of life in MS patients.[42] An aerobic treadmill training program designed for MS patients of varying degrees of disability, exercising at 55% to 85% of age-predicted maximum heart rate, did not worsen fatigue.[13] Mathiowetz and colleagues[43] developed an energy conservation protocol for MS patients based on a model designed by Packer that was created for patients living with chronic illness. The 6-week, 2 h/wk energy conservation course was taught to 79 MS patients with varying types and degrees of severity of MS and was found to reduce fatigue impact and increase self-efficacy and quality of life. The use of physical and occupational therapists is encouraged to help patients with assistive devices for activities of daily living (ADL), using correct body mechanics, and assist with planning and time management to optimize energy levels.

Medications

Several medications have been found to be beneficial for reducing the severity of fatigue. Acetyl-L-carnitine (ALC) is a cellular component with a vital role in energy metabolism. ALC has demonstrated effectiveness in fatigue reductions in many chronic fatigue syndrome patients and in cancer patients undergoing chemotherapy. It has also demonstrated decrease in fatigue in MS patients.[44] ALC is believed to have direct neurotransmitter action in the brain and may play a role in the excitatory and inhibitory pathways.[45]

Amantadine, a tricyclic amine, is more widely known for its antiviral effect. Its mechanism of action is not clear, though it has monoaminergic, cholinergic, and glutaminergic effects.[18] Typical dosage is about 200 mg/d and is well tolerated. It significantly reduced fatigue in a placebo-controlled trial in MS patients.[46] When amantadine was compared with supplemental ALC in a crossover trial, ALC demonstrated superior efficacy and tolerance to amantadine.[44] Side effects of amantadine include insomnia, ankle edema associated with livedo reticularis, and nervousness.[47]

Potassium channel blockers, such as 3,4-AP and 4-AP, improve synaptic transmission and increase muscle twitch tension.[32] Titration of the drug is recommended, with doses ranging from 5 mg daily to 20 mg three times a day. Both 3,4 and 4-AP have demonstrated improvement in fatigue, weakness, and ambulation.[48–50] Side effects include vertigo, anxiety, nausea, seizures, confusion, and loss of consciousness.[34]

The effect of aspirin (acetylsalicylic acid [ASA]) on fatigue has been studied in a small double-blind, placebo-controlled study revealing modest benefit when dosed at 650 mg twice a day.[51] ASA irreversibly inhibits cyclooxygenase and blocks prostaglandin E2 production. Its effect on fatigue is believed to involve the HPA axis. Larger, long-term studies are recommended to further evaluate the benefit–risk profile.

Modafinil is Food and Drug Administration approved for use in persons with narcolepsy, obstructive sleep apnea, and shift workers. It is a central a-adrenergic agonist, acting in brain areas to increase wakefulness and increasing frontal lobe cortical activity.[52] The dosage ranges from 100 to 400 mg/d, and it is recommended that it should not be given later than lunchtime to avoid symptoms of insomnia. It has demonstrated improvement in 1 study over placebo at 200 mg/day, but not at the 400 mg/d dosage.[53] Another rigorous study reported no benefit of modafinil over placebo.[54] Additional trials are warranted, as several patients report significant relief of fatigue with modafinil. Side effects of modafinil include nervousness, headache, and nausea.[50]

Prokarin is a histamine-caffeine combination in a transdermal cream. Histamine as a therapeutic agent has been used in the treatment of Bell palsy, vasculitis, and Meniere disease for several years.[55] A 12-week, double-blind, placebo-controlled study of Prokarin demonstrated reduction in the MFIS by 37%. Serum caffeine levels were similar in both groups; therefore, the authors conclude that the primary cause of fatigue decrease was not caffeine intake alone. The cream was well tolerated, and side effects included skin rash and diarrhea.[50] Calcium supplementation is recommended to avoid increased stiffness.

SUMMARY

In summary, MS-related fatigue can be a severe problem causing interference with home and vocational activities. There are multiple factors that can contribute to fatigue in MS, and it is important for the patient, family, and clinician to be aware of potential confounders that may worsen fatigue. Clearer understanding about the etiology of fatigue is necessary. Additional larger, randomized, clinical trials are needed to evaluate etiology, pathophysiology, and both pharmacologic and nonpharmacologic interventions. Given the varying nature of fatigue and the limited evidence that fatigue in MS patients is highly dependent on self-perceived scores, additional research into the effect of psychosocial and psychological interventions is recommended. A multidisciplinary approach to fatigue is encouraged when treatments are considered for maximum benefit.

ACKNOWLEDGMENT

The author thanks Dr. Ian B. Maitin for his editorial comments on the manuscript.

REFERENCES

1. Anderson DW, Ellenberg JH, Leventhal CM, et al. Revised estimate of the prevalence of multiple sclerosis in the United States. Ann Neurol 1992;31(3):333–6.
2. Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the “common” neurologic disorders? Neurology 2007;68(5):326–37.
3. Kraft GH, Freal JE, Coryell JK. Disability, disease duration, and rehabilitation service needs in multiple sclerosis: patient perspectives. Arch Phys Med Rehabil 1986;67(3):164–8.
4. Krupp LB, Alvarez LA, LaRocca NG, et al. Fatigue in multiple sclerosis. Arch Neurol 1988;45(4):435–7.
5. Hemmett L, Holmes J, Barnes M, et al. What drives quality of life in multiple sclerosis? QJM 2004;97(10):671–6.
6. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004; 363(9413):978–88.

7. Giovannoni G. Multiple sclerosis related fatigue. J Neurol Neurosurg Psychiatry 2006;77(1):2–3.
8. Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. QJM 2008;101(1):49–60.
9. Fisk JD, Pontefract A, Ritvo PG, et al. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994;21(1):9–14.
10. Hubsky EP, Sears JH. Fatigue in multiple sclerosis: guidelines for nursing care. Rehabil Nurs 1992;17(4):176–80.
11. Rampello A, Franceschini M, Piepoli M, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. Phys Ther 2007;87(5):545–55 [discussion: 555–549].
12. Rasova K, Brandejsky P, Havrdova E, et al. Spiroergometric and spirometric parameters in patients with multiple sclerosis: are there any links between these parameters and fatigue, depression, neurological impairment, disability, handicap and quality of life in multiple sclerosis? Mult Scler 2005;11(2):213–21.
13. van den Berg M, Dawes H, Wade DT, et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. J Neurol Neurosurg Psychiatry 2006; 77(4):531–3.
14. Newman MA, Dawes H, van den Berg M, et al. Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis: a pilot study. Mult Scler 2007;13(1):113–9.
15. Rasova K, Havrdova E, Brandejsky P, et al. Comparison of the influence of different rehabilitation programmes on clinical, spirometric and spiroergometric parameters in patients with multiple sclerosis. Mult Scler 2006;12(2):227–34.
16. Bourdette DN, Prochazka AV, Mitchell W, et al. Health care costs of veterans with multiple sclerosis: implications for the rehabilitation of MS. VA Multiple Sclerosis Rehabilitation Study Group. Arch Phys Med Rehabil 1993;74(1):26–31.
17. Whetten-Goldstein K, Sloan FA, Goldstein LB, et al. A comprehensive assessment of the cost of multiple sclerosis in the United States. Mult Scler 1998;4(5):419–25.
18. Lapierre Y, Hum S. Treating fatigue. Int MS J 2007;14(2):64–71.
19. Packer TL, Sauriol A, Brouwer B. Fatigue secondary to chronic illness: postpolio syndrome, chronic fatigue syndrome, and multiple sclerosis. Arch Phys Med Rehabil 1994;75(10):1122–6.
20. Egner A, Phillips VL, Vora R, et al. Depression, fatigue, and health-related quality of life among people with advanced multiple sclerosis: results from an exploratory telerehabilitation study. NeuroRehabilitation 2003;18(2):125–33.
21. Mathiowetz V. Test-retest reliability and convergent validity of the Fatigue Impact Scale for persons with multiple sclerosis. Am J Occup Ther 2003;57(4):389–95.
22. Kos D, Nagels G, D'Hooghe MB, et al. A rapid screening tool for fatigue impact in multiple sclerosis. BMC Neurol 2006;6:1–8.
23. Morris ME, Cantwell C, Vowels L, et al. Changes in gait and fatigue from morning to afternoon in people with multiple sclerosis. J Neurol Neurosurg Psychiatry 2002;72(3):361–5.
24. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult Scler 2003;9(3):219–27.
25. Heesen C, Nawrath L, Reich C, et al. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J Neurol Neurosurg Psychiatry 2006; 77(1):34–9.
26. Gottschalk M, Kumpfel T, Flachenecker P, et al. Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. Arch Neurol 2005;62(2):277–80.

27. Zwarts MJ, Bleijenberg G, van Engelen BG. Clinical neurophysiology of fatigue. Clin Neurophysiol 2008;119(1):2–10.
28. Roelcke U, Kappos L, Lechner-Scott J, et al. Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study. Neurology 1997;48(6):1566–71.
29. Marrie RA, Fisher E, Miller DM, et al. Association of fatigue and brain atrophy in multiple sclerosis. J Neurol Sci 2005;228(2):161–6.
30. Tartaglia MC, Narayanan S, Francis SJ, et al. The relationship between diffuse axonal damage and fatigue in multiple sclerosis. Arch Neurol 2004;61(2):201–7.
31. Bakshi R, Miletich RS, Henschel K, et al. Fatigue in multiple sclerosis: cross-sectional correlation with brain MRI findings in 71 patients. Neurology 1999; 53(5):1151–3.
32. Mainero C, Faroni J, Gasperini C, et al. Fatigue and magnetic resonance imaging activity in multiple sclerosis. J Neurol 1999;246(6):454–8.
33. White AT, Wilson TE, Davis SL, et al. Effect of precooling on physical performance in multiple sclerosis. Mult Scler 2000;6(3):176–80.
34. Romani A, Bergamaschi R, Candeloro E, et al. Fatigue in multiple sclerosis: multidimensional assessment and response to symptomatic treatment. Mult Scler 2004;10(4):462–8.
35. Schwartz CE, Coulthard-Morris L, Zeng Q. Psychosocial correlates of fatigue in multiple sclerosis. Arch Phys Med Rehabil 1996;77(2):165–70.
36. Johansson S, Ytterberg C, Gottberg K, et al. Use of health services in people with multiple sclerosis with and without fatigue. Mult Scler 2009;15:88–95.
37. Ytterberg C, Johansson S, Andersson M, et al. Variations in functioning and disability in multiple sclerosis. A two-year prospective study. J Neurol 2008; 255(7):967–73.
38. Attarian HP, Brown KM, Duntley SP, et al. The relationship of sleep disturbances and fatigue in multiple sclerosis. Arch Neurol 2004;61(4):525–8.
39. Auger C, Montplaisir J, Duquette P. Increased frequency of restless legs syndrome in a French-Canadian population with multiple sclerosis. Neurology 2005;65(10):1652–3.
40. Ferini-Strambi L, Filippi M, Martinelli V, et al. Nocturnal sleep study in multiple sclerosis: correlations with clinical and brain magnetic resonance imaging findings. J Neurol Sci 1994;125(2):194–7.
41. Leuschen MP, Filipi M, Healey K. A randomized open label study of pain medications (naproxen, acetaminophen and ibuprofen) for controlling side effects during initiation of IFN beta-1a therapy and during its ongoing use for relapsing-remitting multiple sclerosis. Mult Scler 2004;10(6):636–42.
42. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology 2004;62(11):2058–64.
43. Mathiowetz V, Matuska KM, Murphy ME. Efficacy of an energy conservation course for persons with multiple sclerosis. Arch Phys Med Rehabil 2001;82(4):449–56.
44. Tomassini V, Pozzilli C, Onesti E, et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J Neurol Sci 2004;218(1–2): 103–8.
45. Shug AL, Schmidt MJ, Golden GT, et al. The distribution and role of carnitine in the mammalian brain. Life Sci 1982;31(25):2869–74.
46. The Canadian MS Research Group. A randomized controlled trial of amantadine in fatigue associated with multiple sclerosis. Can J Neurol Sci 1987;14(3):273–8.

47. van Oosten BW, Truyen L, Barkhof F, et al. Choosing drug therapy for multiple sclerosis. An update. Drugs 1998;56(4):555–69.
48. Rossini PM, Pasqualetti P, Pozzilli C, et al. Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. Mult Scler 2001;7(6):354–8.
49. Sheean GL, Murray NM, Rothwell JC, et al. An open-labelled clinical and electrophysiological study of 3,4 diaminopyridine in the treatment of fatigue in multiple sclerosis. Brain 1998;121(Pt 5):967–75.
50. Lee D, Newell R, Ziegler L, et al. Treatment of fatigue in multiple sclerosis: a systematic review of the literature. Int J Nurs Pract 2008;14(2):81–93.
51. Wingerchuk DM, Benarroch EE, O'Brien PC, et al. A randomized controlled crossover trial of aspirin for fatigue in multiple sclerosis. Neurology 2005;64(7):1267–9.
52. Pozzilli C, Prosperini L, Sbardella E, et al. Interferon after 10 years in patients with multiple sclerosis. Neurol Sci 2006;27(Suppl 5):S369–72.
53. Rammohan KW, Lynn DJ. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005;65(12): 1139–43; author reply 1995–1997.
54. Stankoff B, Waubant E, Confavreux C, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005;64(7):1139–43.
55. Gillson G, Richard TL, Smith RB, et al. A double-blind pilot study of the effect of Prokarin on fatigue in multiple sclerosis. Mult Scler 2002;8(1):30–5.