

Mellen Center Approaches: Fatigue in Multiple Sclerosis

What is MS fatigue?

Fatigue in the context of MS has been defined as a “subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.” Similar to pain, fatigue is a subjective symptom that can have a profound impact on patients’ quality of life. Fatigue is different from normal exertion in healthy individuals.

REFERENCE: Multiple Sclerosis Council for Clinical Practice Guidelines, Fatigue management in multiple sclerosis. Consortium of Multiple Sclerosis Centers. 2003.

How common is fatigue in MS?

A: Fatigue is very frequent in MS (prevalence above 80% in some studies), at any stage of the disease. It is the most frequently reported symptom, and is often cited as the most bothersome symptom by MS patients.

Fatigue affects physical and cognitive function, and quality of life. Fatigue has been identified as a source of disability, independent of other neurologic impairments. Work, social, and leisure activities are also impacted by fatigue. Fatigue has been associated with increased health care utilization.

How is fatigue quantified?

Fatigue severity is mostly assessed through patient interview and questionnaires. The most commonly used fatigue questionnaires are the Fatigue Severity Scale and the Modified Fatigue Impact Scale.

Measures of physical and cognitive endurance often show a more rapid decline in motor and/or cognitive performance in MS patients compared to healthy controls, but correlate poorly with patient-reported fatigue severity.

REFERENCE:

Krupp, L.B., et al., The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*, 1989. 46(10): p. 1121-3.

What causes MS fatigue?

The pathophysiology of primary MS fatigue has not been elucidated. Immune system dysfunction, neuroendocrine dysregulation (particularly of the hypothalamo-pituitary-adrenal axis), conduction blocks, hypometabolism in specific areas of the central nervous system, and the need for more widespread cortical activation to perform functional tasks, have been investigated as potential causes of fatigue.

Should any tests be performed in MS patients with fatigue?

A: There is no diagnostic test for primary MS fatigue. At any time in the presence of chronic fatigue, and more particularly in the context of new onset or acute worsening of fatigue, potential treatable causes and contributing factors should be ruled out. For example:

- current medications should be reviewed, looking for drugs that can cause sedation and could be decreased or stopped, before adding a symptomatic medication for fatigue.
- depression should be ruled out (we use the Patient Health Questionnaire – 9 (PHQ-9) as a screening tool)
- labwork should be ordered to rule out acute or chronic comorbidities that can be secondary causes of fatigue (e.g. urinary tract infection, hypothyroidism, anemia, liver or kidney disease, B12 deficiency)
- new MS disease activity should be ruled out through a detailed interview, thorough examination, and if appropriate imaging studies. Fatigue can be the initial symptom of an MS exacerbation, or reflect acute CNS inflammation in the absence of clinical exacerbation
- other factors that are amenable to lifestyle changes should be explored (e.g. sleep deprivation, alcohol/recreational drug abuse, heat)

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Are there any non-pharmacological interventions for MS fatigue?

Non-pharmacologic interventions should always be considered.

Physical deconditioning has been linked to fatigue. There is published evidence showing improvement of fatigue with aerobic exercise. Therefore, exercise is recommended, however the type, frequency, and intensity of exercise should be adjusted to meet the patient's abilities and to avoid transient worsening of neurologic symptoms. A referral to physical therapy is often helpful to design an individualized home exercise program, and to optimize gait efficiency. Patients should be aware of the fact that the benefit is usually not felt until several weeks after starting the exercise program.

Energy effectiveness strategies (usually taught by an occupational therapist) can help patients optimize the use of energy throughout the day. The general goals of these strategies are to allow patients to use their limited energy on the most important and meaningful activities, to reduce as much as possible the energetic cost of their activities, and to address secondary causes of fatigue. Recommendations include the use of assistive devices, environmental modifications, planned naps or rest periods, use of an activity diary, sleep hygiene recommendations, and stress management resources.

Cooling devices have been used to address fatigue due to heat sensitivity, either in hot weather or during exercise.

Adequate sleep hygiene should be emphasized.

Cognitive behavioral therapy and other behavioral or relaxation techniques have been proposed in the management of fatigue.

REFERENCE:

Motl, R.W., E. McAuley, and E.M. Snook, Physical activity and multiple sclerosis: a meta-analysis. *Mult Scler*, 2005. 11(4): p. 459-63.

Are there any medications for MS fatigue?

Symptomatic medications can be considered concurrently with other interventions. There are no medications approved by the FDA for the treatment of MS fatigue. The most commonly used off-label symptomatic medications are amantadine and modafinil. Clinical trials have shown conflicting evidence regarding their efficacy.

Amantadine is indicated as an antiviral and in Parkinson's disease, and has dopaminergic effects. Usual doses are between 100 and 200 mg per day taken in am and mid day if necessary. Side effects are mostly mild and reversible. The most frequently reported side effects are: anxiety, insomnia, nightmares, and livedo reticularis.

Modafinil was initially approved for narcolepsy. The starting dose is usually 100 mg daily. The dose can be titrated up to 400 mg per day, with an average dose of 200 mg per day. The most frequent side effects are: headaches, nervousness, irritability, anxiety, and nausea. Modafinil is a controlled substance. More recently armodafinil (the R-enantiomer of modafinil) has been proposed off label to treat MS fatigue, but there is no published data on its efficacy.

Antidepressants, particularly selective serotonin reuptake inhibitors, may help with fatigue. This effect could be mainly related to the improvement of depression and associated sleep disturbance. Activating antidepressants, such as fluoxetine, venlafaxine, and bupropion, can also be helpful.

Dalfampridine, an extended release formulation of 4-aminopyridine (4AP), was recently approved by the FDA to improve walking in patients with MS. 4AP is a potassium channel blocker, which improves conduction of the action potential along demyelinated axons. 4AP was anecdotally reported to improve fatigue, but no significant effect on fatigue was observed in a clinical trial of dalfampridine. At the same time, dalfampridine sometimes improves leg strength, it is conceivable that physical fatigability associated with weakness may improve in some patients. Dalfampridine has been associated with a risk of seizure.

The use of amphetaminic CNS stimulants for MS fatigue is controversial, and their potential side effects and complications should be taken into consideration.

Results of one clinical trial suggested that two 325 mg aspirin twice a day can be effective on MS fatigue.

Caffeine is generally not recommended to treat MS fatigue, for several reasons: caffeine has a diuretic effect which may result in dehydration in MS patients with already limited fluid intake, and in increased urinary frequency/urgency. There is also evidence suggesting that the effects of caffeine persist up to 9

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hours after ingestion, and alters the sleep pattern.

Some complementary and alternative therapies are claimed to improve energy level. Objective evidence supporting these claims is lacking.

REFERENCES:

Pucci E, Brañas Tato P, D'Amico R, Giuliani G, Solari A, Taus C. Amantadine for fatigue in multiple sclerosis. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD002818. DOI: 10.1002/14651858.CD002818.pub2

Rammohan KW, Rosenberg JH, Lynn DJ Efficacy and safety of modafinil (Provigil(R)) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study J Neurol Neurosurg Psychiatry 2002 Feb;72(2):179-83

A randomized controlled crossover trial of aspirin for fatigue in multiple sclerosis Wingerchuk DM, Benarroch EE, O'Brien PC Neurology 2005;64:1267-1269

Is fatigue taken into consideration when MS patients apply for disability?

Fatigue can be a reason for applying for disability in MS. This question is discussed in the Mellen Center Approach document on disability issues.

USEFUL RESOURCES:

- The MS International Federation recently published an issues of MS In Focus on fatigue, which can be downloaded free at <http://www.msif.org/en/>
- The Clinical Practice Guidelines on Fatigue Management in MS can be downloaded free at <http://www.ms-care.org/cm-sc/CMSC-Clinical-Practice-Guidelines.html>

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