MANAGEMENT OF SPASTICITY, FATIGUE, AND SLEEP DISORDERS

Jonathan L. Carter, MD
Mayo Clinic Arizona

Introduction:

Spasticity, fatigue, and sleep disorders are ubiquitous and often under-recognized symptoms in MS patients. The prevalence estimates for fatigue are as high as 70-90% in unselected MS patients. It may be the leading cause of disability in patients with mild or early relapsing-remitting MS. Fatigue is also a complex, multifaceted symptom that is poorly understood despite extensive study. Fatigue has been divided into primary fatigue, felt to be part of the MS disease process itself; and secondary fatigue, where fatigue is secondary to some other complication of MS, such as spasticity interfering with sleep. Sleep disorders have been found to be more common than expected in MS patients, including obstructive sleep apnea, central sleep apnea, and sleep disorders due to other processes such as restless leg syndrome, pain, nocturnal leg spasms, etc. Therapy for MS-related fatigue may be partially successful but many patients continue to have significant fatigue despite pharmacologic therapy. Chronic sleep deprivation can lead to worsening fatigue, depression, cognitive inefficiency, and fibromyalgia symptoms. Treatment of sleep disorders may significantly improve quality of life, but requires a high index of suspicion for the presence of coexisting sleep disorders along with MS-related fatigue. Spasticity may be helpful to maintain walking ability in patients with more advanced MS, but may cause significant morbidity if untreated. This lecture will discuss the differences between primary and secondary fatigue in MS, possible physiologic mechanisms of MS fatigue, non-pharmacologic and pharmacologic therapy of fatigue, recognition and diagnosis of coexisting sleep disorders, therapies that may help treat sleep disorders, and recognition and management of MS-related spasticity.

Fatigue in MS:

Primary versus Secondary fatigue:

Primary fatigue is fatigue felt to be related to aspects of the MS disease process itself. Possible pathophysiologic mechanisms include brain inflammation, cytokine effects, neuroendocrine abnormalities, brain structural changes, or autonomic dysfunction. Fatigue may be present primarily during MS relapses and improve upon recovery from the relapse, providing indirect evidence that brain inflammatory activity may be an important cause of fatigue. However, Mainero et al failed to show a correlation between new inflammatory brain activity on serial gadolinium-enhanced scans using triple-does gadolinium and the Fatigue Severity Scale (FSS). Inflammatory cytokines such as interferon-gamma have been shown to cause fatigue when administered therapeutically. Subtle autonomic abnormalities have been reported in MS patients and some of these, such as orthostatic intolerance, could be substrates for fatigue (Keselbrenner L, et al, Cortez M, et al). Secondary fatigue is defined as fatigue due to complications of MS including sleep abnormalities, depression, inactivity and deconditioning, and other factors. Treatment of secondary fatigue is directed towards the inciting factors.

Nonpharmacologic and CAM therapies for MS fatigue:

Nonpharmacologic approaches to MS fatigue include energy conservation techniques, exercise, attention to sleep hygiene, and napping. Energy conservation techniques are often prescribed through consultation with occupational therapy. Moderate graded aerobic exercise has shown benefit in MS fatigue in some (Mostert and Keselring) but not all studies. However, most systematic reviews of exercise in MS have shown at least a mild benefit in MS fatigue. Sleep hygiene may be helpful to maximize sleep efficiency to avoid chronic sleep deprivation. Many MS patients use CAM therapies for MS fatigue, but the efficacy of supplements and most other CAM therapies is not proven. Prokarin®, a proprietary blend of histamine and caffeine applied via skin patch, was shown in a small double-blind pilot study of 22 patients by Gillson et al to improve fatigue symptoms as measured by the MFIS compared to placebo. Data for other CAM therapies is nonexistent.

Pharmacologic treatment of MS fatigue:

A number of pharmacologic therapies have been studied for treatment of MS fatigue. Most of these studies have involved small sample sizes, short treatment duration, and significant placebo effects. As a result, there are currently no FDA-approved therapies for MS fatigue, and all therapies are used “off-label”.

Amantadine was the first therapy that showed efficacy, albeit modest, for treatment of MS fatigue. Cohen and Fischer showed that amantadine produced “small but statistically significant” improvement in four out of seven domains including overall energy level, problem solving, concentration, and sense of well-being, in a randomized controlled trial. This was based on subject’s daily diary ratings recorded during the trial. Amantadine and pemoline were compared to placebo in a double-blind, placebo-controlled randomized parallel group trial by Krupp et al. Amantadine produced a significant (p=0.04) reduction in fatigue based on the MS Fatigue Scale compared to placebo. Pemoline did not produce a statistically significant effect. Neither agent produced a significant reduction in the Fatigue Severity Scale (FSS), the other primary outcome measure in the study. At the end of the trial, 79% of amantadine treated patients, 52% of placebo treated patients, and 32% of pemoline treated patients favored their assigned therapy over no therapy.

Pemoline was shown effective in treatment of MS fatigue by Weinshenker et al in a randomized controlled trial. “Excellent or good” relief of fatigue was found in 46.3% of patients treated with pemoline versus 19.5% treated with placebo, using a crossover design with two 4-week treatment periods. However, patient tolerability was a concern in 25% of patients during pemoline treatment, and 7% discontinued therapy. Pemoline carries a black box warning from the FDA due to life-threatening liver failure, and written informed consent from the patient is advised before starting therapy. As there are safer agents with equal or better efficacy, pemoline has fallen out of favor for treatment of MS-related fatigue.

Modafanil and armodafinil are novel compounds approved for treatment of narcolepsy and excessive daytime sleepiness associated with shift work and obstructive sleep apnea. Moller et al studied 121 MS patients randomized 1:1 to modafinil 200 mg daily or matching placebo for 8 weeks. Eligible patients had a score on the FSS of 4.0 or more, and EDSS <7.0. No difference in the primary outcome measure, the FSS, was seen after 8 weeks with modafinil. Cognitive performance was also not improved consistently. Rammohan et al studied 72 MS patients in a Phase II 2-center single blind crossover design starting with placebo for 2 weeks, modafinil 200 mg daily for 2 weeks, modafinil 400 mg daily for 2 weeks, and then placebo for 3 weeks. He reported improvements in the FSS and Modified Fatigue Impact Scale (MFIS) in patients during the modafinil 200 mg daily phase, but not in the modafinil 400 mg daily phase of the study. A French randomized, double-blind placebo-controlled multicenter study by Stankoff et al evaluated 115 patients randomized to placebo or escalating doses of modafinil starting at 200 mg daily. No difference in the MFIS was seen between modafinil treated patients and placebo after 5 weeks.

Aspirin (ASA) has been studied in several small pilot studies for MS fatigue. Wingerchuk et al reported that 1300 mg ASA daily improved fatigue, as measured by the MFIS, compared to placebo using a crossover design in 30 patients. A larger study by Wingerchuk et al was conducted using a randomized, double-blind, placebo-controlled parallel-group design studying ASA 1300 mg/day, ASA 162 mg/day, or placebo. This study was terminated early after an interim analysis indicated no significant difference between ASA and placebo in the primary outcome measure, the MFIS.

Dalfampridine (4-aminopyridine) has been reported anecdotally to help MS-related fatigue, although approval of this medication was based on its effects on ambulation. Rossini et al found no difference in FSS scores, cognitive measures, or EDSS in 54 progressive MS patients treated with immediate-release 4-aminopyridine in a randomized, double-blind, placebo-controlled cross over study. No other randomized controlled trials focusing on fatigue outcome measures have been conducted with dalfampridine.

Sleep disturbances in MS:

Sleep disturbances are under-reported and under-recognized in MS. Braley, Segal, and Chervin reported in 2014 that 21% of their series of 195 MS patients carried a formal diagnosis of obstructive sleep apnea (OSA), but 56% had STOP-BANG scores greater than or equal to 3, indicating high risk for OSA; which also correlated with higher scores on the FSS. A recent systematic review by Marrie et al examined the incidence of various sleep disturbances reported in MS. They found a prevalence of narcolepsy ranging from 0-1.6%, restless legs syndrome in 14.4-57.5%, 2.22-3.2% for REM behavior disorder, and 7.14-58.1% for obstructive sleep apnea. The authors noted that referral bias, incomplete ascertainment, and other biases may influence these rates and called for a population-based study in MS patients. Vitkova et al reported that factors associated with poor sleep quality varied by disease duration in MS. Patients with MS disease duration of less than or equal to 5 years had a lower prevalence of poor sleep (34.8%) than those with disease for greater than 5 years (51.2%). Anxiety, reduced motivation, and mental fatigue were associated with poor sleep quality in those with shorter disease duration; while pain, depression, and mental fatigue were associated with poor sleep quality in those with longer disease duration.

Other potential causes of sleep disturbances in MS besides OSA include restless legs syndrome (RLS), which has also been reported to be more common in MS patients than controls. Both Desaturation Index (DI) and RLS symptoms contributed independently to fatigue measured by the FSS in a report from Carnicka et al. Painful nocturnal spasms, chronic neurogenic pain, and insomnia from drugs used to combat MS fatigue or polypharmacy are other causes of secondary sleep disturbance in MS.

Chronic insomnia, defined as difficulty falling asleep or staying asleep, is reported frequently in MS patients, and is often associated with untreated or undertreated depression. Lack of activity and deconditioning is often present and may exacerbate the cycle of fatigue, deconditioning, and sleep disturbance. Braley, Segal, and Chervin reported frequent use of hypnotic medications, most frequently diphenhydramine, in MS patients. They showed a correlation between frequent hypnotic medication use and daytime fatigue in their clinic population.

Treatment of MS-related sleep disorders is no different than treatment of these disorders in the general population. Nasal CPAP is the mainstay of treatment for OSA, but in selected cases surgery may be helpful as well. Treatment of RLS symptoms includes iron supplementation if the serum ferritin level is <45 mg/dl, dopamine agonists, gabapentin, narcotic analgesics, etc. Rotation of medications between drug classes may be helpful as reduction in treatment effects seems to occur over the long term with single agents. Carbidopa/levodopa combinations may lead to problems with augmentation of RLS and are usually avoided. Clonazepam may be useful in REM behavioral disorder. Weight loss and exercise are important adjunctive treatments for sleep disorders in both MS patients and the general population.

Spasticity in MS:

Spasticity is commonly seen in more advanced MS, especially in progressive MS patients with significant spinal cord lesion burden. Some degree of lower extremity spasticity may be helpful for ambulation, and overly aggressive treatment may render an ambulatory patient non-ambulatory due to increased muscle weakness. Spasticity and spontaneous spasms of the lower extremities may occur together or one may predominate. Spontaneous spasms may be painful and disrupt sleep or interfere with transferring.

Treatment of MS-related spasticity includes non-pharmacologic measures such as aerobic exercise, stretching, physical therapy, and recognition and treatment of inciting factors such as urinary tract infections, severe constipation, or decubitus ulcers. Pharmacologic therapies include baclofen and tizanidine. Baclofen should be started at low doses (5-10 mg) initially at night, and slowly titrated upward in a QID schedule to 60-80 mg daily if needed. Higher doses may be used, but with caution due to risk of sedation, excessive muscle weakness, and elevated liver function tests. Tizanidine is also started at low doses (2-4 mg) at night, and slowly titrated upward in a TID schedule to avoid excessive sedation and orthostatic hypotension. Botulinum toxin injections have been FDA-approved for treatment of both upper and lower extremity spasticity, and may be useful in situations where localized spasticity interferes with functioning. In refractory cases implantation of an intrathecal baclofen pump may be considered, but carries significantly greater potential morbidity than oral therapy.

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