

Fatigue in multiple sclerosis

Leigh Charvet, Dana Serafin and Lauren B. Krupp*

Stony Brook, Department of Neurology, Stony Brook Medicine, NY, USA

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Background: Fatigue is the most commonly reported symptom in multiple sclerosis (MS). **Purpose:** This brief narrative review addresses the clinical features, pathophysiology, and management of MS fatigue, as well as the varied approaches to its definition and measurement. **Methods:** A literature search was conducted through Medline of studies published since 1984, with a focus on findings reported since 2008. **Results:** Studies of MS fatigue have primarily relied on the definition of fatigue as a subjective sense of tiredness measured through self-report. Additional studies have measured fatigability in MS, as demonstrated by a decline in cognitive or motor performance over time. The pathogenesis of fatigue remains poorly understood but disease characteristics, including structural and physiologic cerebral alterations as well as immune, endocrine, and psychological factors, may all contribute to its expression. Fatigue therapy has included pharmacologic approaches which have had either methodological limitations (e.g., small sample sizes) or inconclusive results and non-pharmacologic interventions, some of which have been effective in reducing fatigue. **Conclusions:** Fatigue remains a challenging symptom in MS. The most effective measurement approaches will likely be multidimensional and include both subjective and objective indicators, whereas therapy will likely require more than one type of intervention.

Keywords: multiple sclerosis; fatigue; fatigue measurement; non-pharmacological treatment; pharmacological treatment

Introduction

Fatigue is one of the most common and debilitating symptoms in multiple sclerosis (MS). However, it remains poorly understood and effective treatments have been elusive. This article serves to summarize the available evidence regarding its clinical and pathophysiologic features.

Multiple sclerosis

Multiple sclerosis (MS) is the most common central nervous system disorder of young adulthood, affecting approximately 400,000 people in the United States.[1] This immune-mediated disorder targets the central nervous system and is marked by demyelination and axonal injury. For 85% of patients, the initial course is relapsing–remitting,

*Corresponding author. Email: lauren.krupp@stonybrookmedicine.edu

and for the remainder the onset is followed by a progressive decline.[2] The disease is more common in women and has a typical onset between the ages of 20 and 50 years, although it can occur at almost any time across the lifespan. The symptoms can be tremendously varied, including problems with gait, cognitive function, sensation, vision, bladder and bowel control, and strength. However, the most common symptom is fatigue, which can be persistent and frequently overwhelming.

General features of MS fatigue

No universally accepted definition of fatigue has been established. MS fatigue is usually defined by the patient's report of a sense of exhaustion and increased effort to perform physical or even mental activities.[3] The MS Council for Clinical Practice Guidelines defined fatigue as a "subjective lack of physical and mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities." [4] Individuals with MS can differentiate their experience of fatigue from physical feelings of weakness or emotional feelings of depression or listlessness.

This subjective sense of fatigue is the most common symptom of MS (reported by >80% of patients [5]) which occurs across all subtypes of the disorder,[6–8] although patients with secondary progressive disease are possibly at the greatest risk. Fatigue risk increases with relapses,[9] the accumulation of disability and, particularly, the loss of ambulation.[8,9] Fatigue in MS can be exacerbated by heat [10,11] and may improve with cooling.[12,13]

In general, fatigue has been linked to disease severity and overall severity of neurological impairment, but not disease duration.[8] Lower education has consistently been demonstrated as a risk factor for fatigue in MS.[14,15] Age does not appear to be strongly linked to fatigue, although this finding has not been consistent across studies.[14,15] Gender differences in fatigue frequency appear not to be large.[14,15]

Fatigue exacts a tremendous toll in individuals with MS as it can influence all aspects of daily functioning and markedly compromise quality of life.[6,16,17] Studies have linked fatigue to both unemployment and early retirement.[14,18,19]

Multidimensionality of fatigue

The term "fatigue" can encompass multiple constructs.[20] Fatigue as reported by patients typically refers to a state of exhaustion or tiredness (distinct from depression, weakness, or sleepiness) which renders an individual unable to either initiate or complete tasks or activities that he/she would otherwise be able to accomplish. Fatigue can be influenced by MS-associated disease factors such as pain, weakness, mood, and mental and physical endurance, or an individual's degree of motivation. Fatigue can also be manifested as "fatigability," i.e., declining performance on either motor or cognitive tasks during a period of exertion. Research on fatigue ideally should incorporate patient-reported assessments, objective measures of fatigability, and instruments addressing potential moderating factors such as mood and pain.

Measuring fatigue in MS

For the clinician, a history and interview are the most helpful tools to uncover fatigue and possible contributing factors. In addition, it can be useful to ask patients to complete brief self-report measures of fatigue, mood, and pain which can be examined

during the interview. These measures can help to identify the patient's most pressing symptom(s).

In the absence of an agreed upon definition of fatigue, a variety of approaches to its measurement in research have been taken. Although subjective, the most often used measures are self-report questionnaires that identify and quantify fatigue. Experimental approaches have sought to quantify fatigability during walking tasks, sustained muscle contraction, or cognitive slowing during tests of vigilance. While of great interest, these studies have not yet provided any reliable objective measure that consistently corresponds to self-reported fatigue. Ultimately, a multidimensional measurement approach may be the most useful.

Fatigue scales

Fatigue in MS has been evaluated through a variety of self-report generic fatigue scales as well as scales specific to the disease. Fatigue can also be measured in fatigue subscales that are part of quality of life instruments. As reviewed in depth elsewhere, [21] choosing the appropriate fatigue scale for a specific investigation includes consideration of whether the scales are internally consistent, valid, and responsive to treatment. The most successful scales have been developed from items generated from patient interviews, factor analysis, and Rasch analysis. Scales that have been widely used in MS include the Modified Fatigue Impact Scale (MFIS) [22] (a 20-item measure that includes three subscales of fatigue: mental, physical, and social), the nine item unidimensional Fatigue Severity Scale (FSS), [23] the Multidimensional Fatigue Inventory, [24] the Multidimensional Fatigue Symptom Inventory, [25] and the Fatigue Scale for Motor and Cognitive Functions. [26] The MFIS is frequently used in pharmacologic clinical trials of fatigue (e.g., [27–30]), although interpreting the results of these trials is complicated by large placebo effects. [28]

Fatigue subscales contained within quality of life measures include the vitality subscale of the SF-36 (this subscale is inversely correlated with fatigue), [31,32] a fatigue–inertia subscale [33] of the Profile of Mood States, and a sleep–rest subscale [26] in the Sickness Impact Profile. [34]

Two newer fatigue measures which incorporate current scaling techniques recommended by the FDA are the Neurological Fatigue Index (NFI-MS) [35,36] and an NIH-supported fatigue measure [37,38] developed within the Patient Reported Outcomes Measurement Information System (PROMIS). Proposed values for clinically meaningful change on the NFI-MS are available. [36] To develop assessments tailored for specific research purposes, the PROMIS website provides access to a databank of 95 items (available at <http://www.nihpromis.org/default.aspx>) that can be selected in different combinations as needed. Nonetheless, neither the NFI-MS nor the PROMIS measure has been widely used in MS. Further study of these fatigue related outcome measures are needed for clinical trials focused on fatigue.

Fatigability

A relatively objective indication of fatigue may be provided through demonstration of fatigability, i.e., a decline in performance following exertion. The studies cited below have found greater fatigability in individuals with MS in both motor and cognitive performances.

MS is associated with many motor abnormalities but their relation to motor fatigability is unclear.[39,40] One study used transcranial magnetic stimulation before and after a task requiring sustained hand grip to compare MS patients with and without fatigue to healthy controls.[41] The MS patients with fatigue demonstrated reductions in motor cortical inhibition.[41] More recently, a study of 20 MS patients found a significant relation between ratings of fatigue and muscle fatigue as measured by maximal voluntary contraction.[42] Using the measure of decline in walking speed across a six-minute walking task, studies have reported a greater decline in MS patients compared to controls as well as those with moderate versus mild disability.[43,44] The decline in walking speed also correlated with self-reported physical fatigue.[43,44]

One interesting new approach to fatigability is a fatigue monitoring system (FAMOS) that continuously measures physiological and functional parameters, including body–skin temperature and motions of the feet. In a small group of MS patients compared to controls, FAMOS was associated with fatigue suggesting a link between the symptom and autonomic dysfunction.[45,46]

MS is also associated with cognitive impairment but the relation to cognitive fatigability is not clear. While self-reported fatigue has not predicted cognitive performance on a variety of measures,[47,48] it has been linked to cognitive processing speed.[49,50] A recent study demonstrated declines in cognitive processing speed (the Symbol Digit Modalities Test) and increased variability in processing speed across repeated administration of a task to assess cognitive fatigability.[51] Similarly, an earlier study demonstrated that performance on standard neuropsychological measures declined following a period of exertion in MS patients as compared to controls.[47] Other neurocognitive studies of fatigability-inducing tasks in MS have shown decreases in vigilance and working memory performances over time.[52,53] Another recent study linked self-reported fatigue to a challenging task, although findings were highly variable depending on specific tasks and scoring methods.[54]

Despite advances in understanding the types of cognitive or motor fatigability experienced by individuals with MS, this line of research has not demonstrated a consistent relation between fatigability and self-reported MS fatigue ratings. Therefore, while intriguing, at this point objective measures of fatigability cannot fully account for the overall experience of fatigue.

Many causes of fatigue in MS

The MS Council for Clinical Practice Guidelines assigned illness factors as either primary, relating directly to the MS disease process, or secondary, relating to issues of comorbidity.[4] For any given patient, the experience of fatigue is due to both primary and secondary factors. For instance, one large year-long study of MS outpatients indicated that fatigue was linked with overall neurological impairment, pain, and depressed mood.[7]

Primary factors

Neuroimaging studies have provided many intriguing leads towards linking the MS disease process to the experience of fatigue. Most early studies using conventional MRI measures of lesion burden or lesion location showed little association with fatigue ratings.[55] However, studies using more advanced imaging measures have demonstrated associations between fatigue and regional atrophy [56] and pathways

connecting frontal white matter to the thalamus and basal ganglia.[57,58] Other associations between MRI findings and self-reported fatigue include cortical thickness, disruption of fronto-parietal white matter lesion burden, and measures of axonal injury using MR spectroscopy.[59–61] While promising first steps, some studies have not adequately controlled for other potential confounds including depression or pain, and therefore the specificity of these associations is tentative.

Functional MRI studies have demonstrated increased cerebral activity in frontal and motor areas among individuals with MS performing a repetitive motor task [62] and more limited activation during a task requiring sustained hand grip.[63] Cognitive fatigability has also been demonstrated using fMRI wherein performance declines in MS have been linked to increased activation in the basal ganglia, frontal areas (superior, medial, middle, and inferior regions), parietal regions (precuneus and cuneus), the thalamus, and the occipital lobes.[64]

Neuroimmune and neuroendocrine mechanisms are also likely to play a role in MS fatigue but have not yet provided consistent markers. Fatigue is a feature of most autoimmune disorders, and fatigue can be induced through medications that target the immune system. However, studies to identify immune markers of fatigue have yielded mixed results.[65,66] There have also been interesting findings indicating a possible role for HPA axis function and its interaction with pro-inflammatory cytokines. One study differentiated MS patients with and without fatigue according to elevated ACTH levels,[67] whereas another investigation of fatigue in MS [68] found low circulating levels of dehydroepiandrosterone (DHEA).

Some MS patients with fatigue may also have features of autonomic dysregulation, including hypo-adrenergic orthostatic response, as suggested by the common finding of exercise intolerance.[69] As noted in the measurement section, initial studies of the FAMOS monitoring system have provided a novel link between autonomic dysregulation and fatigue.[45,46]

Secondary factors

Many secondary factors are also associated with MS that may exacerbate or cause fatigue. These include depression, anxiety, pain, and sleep disturbance, as well as side effects of some medications such as those used to treat spasticity. MS patients are at increased risk for clinical depression which may feature fatigue. Depressed and/or anxious mood has a high comorbidity with fatigue in MS.[70–75]

Furthermore, there appears to be a link between fatigue and sleep disorders in MS.[76] Sleep disruptions and disorders are common in MS patients.[77] A range of sleep disorders that occur more frequently in individuals with MS relative to healthy controls include insomnia, sleep apnea, nocturia, rapid eye movement sleep behavior disorder, periodic leg movements of sleep, and restless legs syndrome.[77] MS patients with severe fatigue were found to have more than twice as many sleep disorders than those patients with lesser or no fatigue.[78] Obstructive sleep apnea–hypopnea may have the strongest link to fatigue.[77,79] Diagnoses of sleep disorders can be made objectively through sleep studies, and treatment of comorbid sleep disorders has been shown to improve fatigue in MS patients.[77]

Fatigue is also related to pain in MS.[7] Pain is a frequent occurrence in MS resulting from muscle spasms and neuralgias. Pain can worsen fatigue and contribute to deconditioning which in combination can exacerbate functional impairments.

Treatment of fatigue in MS

Comprehensive assessment of fatigue is important to the initial management approach. Contributing factors such as depression, anxiety, pain, and sleep issues should be addressed and a medication review should be done. Unfortunately, there is no clear and consistent evidence supporting any one therapeutic approach. In general, clinical trials have yielded positive if modest effect sizes for some medications, whereas behavioral interventions have shown more substantial benefits. It is likely that individual responses vary greatly across the available treatments. For many patients, a combination of approaches tailored to individual needs is likely to be the most successful.

Non-pharmacologic management approaches

Group and individual psychotherapeutic techniques currently seem to hold the most promise for alleviating fatigue in MS patients. A controlled trial of 72 MS patients with fatigue compared cognitive behavioral therapy (CBT) to relaxation training and found clinically significant improvements with both conditions, lasting to a six-month follow-up point.[80] There was a stronger effect size for CBT, yet both groups returned to levels of fatigue reported by healthy comparison controls.[80] A recent randomized pilot trial that compared an internet-based CBT self-management intervention to usual care in 40 patients with MS found large positive effects for fatigue, as well as for mood and quality of life.[81] A large ($n = 150$) controlled trial comparing mindfulness-based training, a meditation practice that targets stress reduction, led to significant improvements in fatigue as well as in quality of life and depression when compared to usual care.[82]

Fatigue in MS does not appear to be linked to overall levels of physical activity.[83] However, selected studies have shown exercise to be of some benefit for alleviating fatigue with trials demonstrating enduring effects for six months.[84–86] Treatment trials completed with both aerobic activity and strength training suggest that aerobic training for at least 90 minutes per week is most beneficial.[87]

In addition, direct fatigue management techniques may also be helpful. For instance, one study found that MS patients experienced improvement in their fatigue after being taught energy conservation techniques.[88] Furthermore, fatigue in MS is associated with poor locus of health control and helplessness.[89,90] With an intervention tailored to educate MS patients on fatigue management and designed to improve their self-efficacy and sense of control, significant improvements were found.[91] However, another trial of an education-based management program did not find it to be effective, possibly due to a less interactive approach.[92] A recent study found a teleconference-based multi-disciplinary fatigue management program to be effective,[93] and a large controlled trial of the program is currently underway.[94] Finally, a randomized trial comparing exposure to low frequency magnetic fields to a sham treatment in 40 MS patients with fatigue found no significant benefit.[95]

Medications

Several trials of medications have been undertaken to treat fatigue in MS patients. None of the medications studied are specific to MS, but instead have been used to treat fatigue in general. Overall, no one medication has emerged consistently across studies to be an effective therapy for severe fatigue.

Large clinical trials have shown that fatigue does not typically worsen with the use of immunosuppressive or immunomodulating medications or differ between these treatments.[96] The immunomodulatory drug, glatiramer acetate, may hold the most potential to improve fatigue. One MS trial has shown significant improvements in fatigue after 12 months treatment with glatiramer acetate,[97] while a different clinical study showed improvement in fatigue in MS patients after switching from interferon beta to glatiramer acetate.[14] In another medication study, natalizumab relative to placebo increased vitality, the inverse of fatigue.[98]

Modafinil (Provigil) and armodafinil (Nuvigil) are related medications indicated to treat excessive sleepiness in narcolepsy, obstructive sleep apnea, and shift work disorder. These drugs are currently the most commonly prescribed medications for treatment of fatigue in MS, although there is no clear evidence to support their use. A small initial trial of modafinil was positive, but larger controlled trials have been inconsistent. Phase II placebo-controlled cross-over trials of modafinil showed improvement in the treated patients, but only for those treated with a lower (200 mg vs. 400 mg) dose.[99] However, two subsequent randomized and placebo-controlled trials were negative.[28] A separate open-label survey indicated that even in those patients who do experience benefit, the positive effect may not persist.[100]

Amantadine (Symmetrel) is an anti-viral medication that was used to treat the flu and is still occasionally used in individuals with Parkinson's disease. Despite the promise of initial positive trials for amantadine in MS,[101–103] its efficacy was ultimately determined to be unclear.[104] A recent cross-over trial demonstrated that both amantadine and aspirin led to significant improvements in fatigue in MS.[30] There are no controlled trials of stimulants for use in MS fatigue, although pemoline (Cylert) was used as one comparison arm in an amantadine trial, but did not show any benefit.[101] Smaller trials have examined a variety of other medications. Aspirin alone has shown some benefit.[29] Both carnitine and Prokarin, considered alternative therapies, have yielded only weak support for their use in small trials.[105,106]

Summary

While research on fatigue in MS has made notable advances, major questions remain concerning its pathogenesis and treatment. Fatigue remains a frustrating problem for many individuals living with MS. It has the potential to be debilitating, yet there are no clear treatment options. Instead, clinicians must work closely with the individual to treat contributing causes and to tailor interventions to patients that are most helpful. Progress is likely to come from the wider recognition and study of fatigue across disorders.

Notes on contributors

Dr Charvet is a Clinical Assistant Professor in the Department of Neurology at Stony Brook University School of Medicine.

Dana Serafin completed this work as a Research Associate in the Department of Neurology at Stony Brook University School of Medicine.

Dr Krupp is a Professor of Neurology and Psychology at Stony Brook University School of Medicine.

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