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Review Article

Fatigue in multiple sclerosis: a short clinical update

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Abstract

BACKGROUND: To study the dimensions of fatigue in multiple sclerosis, its pathophysiology, the efficacy, tolerability and safety of drug and non-drug treatments and measurement of fatigue.

METHODS: Relevant articles from PubMed and Google scholar search engines from January 1987 until September 2006 were studied to compose a short clinical update (not a systematic review) and make the required clinical information available for the clinicians.

RESULTS: There is evidence that fatigue is very common in all types and stages of multiple sclerosis, but its pathophysiology is not well explained. Consequently, few drug options have been offered for its treatment. Amantadine is the best-known drug, though its efficacy and duration of action are limited. Pemoline and modafinil are alternatives and have some effects on fatigue. DAP (diaminopyridine), ASA (acetylsalicylic acid), methylphenidate and fluoxetine are other possible options but await further confirmation. Neurorehabilitation, regular exercise and cooling are confirmed to be of value in MS treatment. Measurement of fatigue is a complicated issue. At present fatigue does not have a laboratory marker.

CONCLUSIONS: The results of this short clinical update provide guidelines for diagnosing MS-related fatigue and differentiating it from other similar physical and psychological conditions. It also examines prescription drug options and other therapies for MS patients with fatigue.

KEYWORDS: Multiple sclerosis, fatigue, pathophysiology, treatment, measurement.

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Multiple sclerosis (MS) is a chronic disease associated with a variety of symptoms and functional deficits that result in a range of progressive impairments and handicaps. It is the third most common neurological diagnosis cited as the cause of disability, presenting a significant problem both for people with the disease and for society [1]. Symptoms that contribute to loss of independence and restrictions in social activities lead to a continuing decline in quality of life [2]. In some patients, their histories indicate that fatigue, lack of energy, weight loss, and vague muscle and joint pains had been present for several weeks or months before the onset of neurologic symptoms [3]. Fatigue is a very common symptom and a major complaint in MS, yet it is the least understood [4-8]. It is cited as the most common symptom of MS and often the most disabling symptom early in the disease course [7,9-11]. In fact, it is a characteristic finding in MS [5,12]; excessive fatigue that severely limits and interferes with daily activities is experienced by at least two-thirds of the people with MS [13,14]. These data confirm that fatigue results in disability, but the cognitive and psychological dimensions of fatigue remain independent. Fatigue also causes depression

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and a lower quality of life [12]. In order to prepare a short clinical update (not a systematic review) that gives greater weight to clinical aspects of the problem and to current and newer treatments, a literature search was performed in the U.S. National Library of Medicine for relevant articles published between January 1987 and September 2006, using Google scholar and PubMed. Criteria for selection of articles were as follows: the literature search found all papers and articles that included the terms multiple sclerosis, fatigue, pathophysiology and measurement. Articles about either therapy or treatment also met the following criteria: 1) were relevant to efficacy, safety or tolerability; 2) involved human subjects only; 3) were one of the following types of studies: reviews; meta-analyses; randomized controlled trials; cohort, case-control, observational, or case series; and 4) were original articles in English or translated to English. Articles were excluded from the study if they were unrelated to multiple sclerosis applications of the described treatments, unless they addressed safety concerns or detailed basic drug mechanisms.

Clinical aspects

Fatigue is a subjective lack of physical/mental stamina that is perceived by the individual or caregiver to interfere with usual and desired activities [10,15]. However, patients often use the term "fatigue" to describe a much broader range of symptoms [4]. People with MS may describe several patterns of fatigue. One is a feeling of tiredness and weakness that occurs with increasing exercise or other physical activity. Another kind of fatigue is a general feeling of exhaustion, which can be more annoying and limiting than the activity-associated type. This can be mild or severe, intermittent or continuous. Patients may experience this type of fatigue quite suddenly during a normal day; it may come over like a wave, making it difficult to continue with whatever they were doing [16]. This physical/mental exhaustion is unrelated to the amount of activity performed but may be partially or completely relieved by rest [13]. It may be aggravated by overdoing activity or a lack of sleep, but it may also be present even when the individual has done nothing and has had a good night's sleep [13,16]. When people with MS are asked to list the symptoms that bother them the most, fatigue is usually at the top of the list. There is a poor correlation between fatigue and the overall severity of the disease, or with the amount of physical disability caused by the disease, because it is noted in more than 50% of patients with early MS [8,13]. Likewise, it is not associated with the presence of any particular symptom or sign of MS [13]. Fatigue is not related to age and gender, because it is noted with the same frequency by patients younger than 30 and older than 50 and of both genders [8]. Unlike cognitive deficits, no MRI findings can be correlated with fatigue or with depression [13] Fatigue is more likely to occur when there is fever, and it may be worse in a hot environment [3,15]. It is also seen in association with an acute attack, or as a prodromal symptom of an impending exacerbation, and may persist long after the attack has subsided [3,8,13].

Pathophysiology

Significant, reproducible fatigue of motor function with substantial muscle weakness on repetitive activity results from neurological dysfunction in areas of the central nervous system that are known to be pathologically involved in the multiple sclerosis process [1]. However, little is known about the pathophysiological mechanisms of fatigue and researchers have yet to discover its cause [6,9,11]. Evidence from studies of chronic fatigue syndrome and sickness behavior suggests that immune and neuroendocrine factors may play a causative role in the development of fatigue [6]. Theoretically, fatigue may be related to neuromodulation by soluble products of the autoimmune process, or by disruption of the central nervous system pathways necessary for sustained activity, but little empirical evidence supports these possibilities [4].

Differential diagnosis

Factors like depression, medication side effects, physical exhaustion from gait alterations, lack of sleep (e.g. because of nocturia), hypothyroidism, chronic hepatitis C, or long-term cancers should be excluded before initiating

drug treatment. Furthermore, drugs with a sedative effect must be stopped [8,10,13,15,17]. Patients with chronic fatigue syndrome have more depressive symptoms but less cognitive impairment than MS patients [18]. Fatigue and depression are different constructs though there is a considerable overlap between them [10]. Some, but not all, individuals who complain of fatigue will also be depressed, but nearly everyone with a major depression will experience fatigue as well. Vegetative or somatic symptoms tend not to be good diagnostic discriminators for depression in MS [17].

MS patients are frequent users of non-prescription medicines [19]. Excessive intake of fat-soluble vitamins could lead to hypervitaminosis, the effects of which could exacerbate or mimic MS symptoms [19]. Vitamin D is the most likely vitamin to cause toxicity leading to hypercalcemia, with muscle weakness, apathy, headache and anorexia. However, vitamin D supplements may be beneficial in those MS patients that are largely housebound, with minimal exposure to sunlight coupled with a deficient diet. Low levels of 25-hydroxyvitamin D have been associated with accelerated bone loss in MS patients. The other two commonly over-used fat-soluble vitamins have similar effects. Large doses of vitamin E can cause gastrointestinal disturbances, fatigue and weakness, while vitamin A toxicity is characterized by fatigue, irritability and anorexia [19].

Treatment

There is no cure for MS, and alleviation of symptoms forms the cornerstone of the care [14]. Interventions identified for the treatment of fatigue in MS include 1) behavioral advice, 2) drugs, 3) training, rehabilitation and devices, and 4) alternative therapies [11,14].

Behavioral components are the main element of initial clinical management, though no rigorous research on their effectiveness exists. These components include correction of comorbid conditions, poor sleep hygiene, pain, iatrogenic causes, lifestyle changes and workplace adjustment. Psychological interventions include the acceptance of limitations, behavioral techniques, and the identification and amelioration of depression [8,11,20]. Often the fatigue associated with MS responds to brief naps [8]. Pharmacotherapeutic options for MS-related fatigue are limited and comprise amantadine, modafinil, pemoline, potassium-channel blockers (DAP), fluoxetine and other selective serotonin reuptake inhibitor (SSRI) antidepressants, amphetamines, caffeine, and aspirin (ASA) [20,21]. Table 1 shows a review of the current drug treatment used in MS-related fatigue.

Amantadine (symmetrel) appears to have some ability to alleviate fatigue in MS, as demonstrated by statistically significant differences in some outcomes in several trials, [1,8,22-25] but ,the clinical significance of these effects is likely to have been small [1]. Nevertheless, amantadine is the most thoroughly studied agent with known effects on cholinergic, dopaminergic, adrenergic, and glutamatergic neurotransmission, but its mechanism of action on MS fatigue is still unknown [11]. Amantadine is considered a first-line treatment for mild MS-related fatigue. Amantadine [100 mg morning and noon] is usually well tolerated and may moderately improve fatigue, but often is effective for only a few months [15]. In addition, only a fraction of users benefit from this drug [14] [with an efficacy rate of 40% [13]]. The most commonly reported side effects include nausea, dizziness and insomnia. Livedo reticularis may occur in 1-5% of patients following extended use. Amantadine may precipitate or exacerbate psychotic symptoms, and caution must be taken in patients with renal insufficiency or seizure disorders [13]. The drug cost is modest [14].

Modafinil (provigil) has α1-adrenergic properties, but is not a classic sympathomimetic [11]. It is a wakefulness-promoting agent that is chemically and pharmacologically distinct from CNS stimulants, although the precise mechanism of its action is unknown. Modafinil was recently approved for use in narcolepsy [8,13]. There are open-label studies showing that modafinil is effective for fatigue in MS patients [3]. It is also prescribed as first-line therapy for cases of moderate-to-severe fatigue in MS. Oral dosage starts at 200 mg in the morning

Table 1 Current drug treatment used in MS related fatigue.

Drug	Credit	Mechanism of action	Indication	Dosage	Efficacy	Side effects
Amantadine	Well studied	Cholinergic, dopaminergic, adrenergic, glutamatergic	First line in mild MS-fatigue	100 mg BD; morning and noon	40% for a few months	nausea, dizziness, insomnia, Livedo reticularis, psychosis
Modafinil	Well studied	α1-adrenergic (wakefulness-promoting agent)	First line in moderate to severe MS-fatigue	200 mg QD (preferred dosage) to 400 mg QD	-	Transient headache and nausea
Pemoline	Less often studied	CNS stimulant with dopaminergic effect	Alternative medication when no response to amantadine	18.75 mg DB (start) to 75 mg QD	-	Anorexia, irritability, insomnia, weight loss, hepatic failure
DAP	Studied (awaits more confirmation)	Potassium channel blocker	Heat-dependent fatigue and fatigue with endurance	100 mg BD; morning and noon	-	Increased seizure risk at high doses
Aspirin	Some reports	Anti-inflammatory agent	-	650 mg BD	-	Gastrointestinal upset, peptic ulcer disease
Methylphenidate	Some studies	CNS stimulant	Fatigue in resistant cases	10-60 (even 100) mg QD (in two or three doses)	-	Generalized stimulation, tolerance
Fluxetine	Studied in depression	Selective serotonin reuptake inhibitor	Fatigue especially with depressive symptoms	10-20 mg once or twice daily	-	Nausea, headache, extrapyramidal signs, hypotension, mania

and can be increased to 400 mg, though evidence shows that a single daily 200 mg schedule is preferred [3,13,26,27]. Cytokine-induced fatigue following interferon injection may be alleviated by modafinil. The most commonly reported side effects include transient headache and nausea.

Pemoline (cylert) is a CNS stimulant with dopaminergic rather than sympathomimetic effects [11]. It has been studied less often than amantadine but shows results suggesting some effect on MS-related fatigue [1,24,25,28]. Pemoline is an alternative when no response to amantadine is seen. The starting dose is 18.75 mg twice daily that can be increased to a maximum of six tablets per day [or 20 to 75 mg each morning] [3,13]. The risk of life-threatening hepatic failure is an obstacle to using this drug as the first-line therapy [11,13]. The most commonly reported side effects include anorexia, irritability, insomnia and weight loss. Patient discontinuation due to side effects is common.

While fatigue and weakness are both reportedly ameliorated with potassium channel blockers (DAP), the use of these compounds is limited – despite controlled studies showing benefits – because of increased seizure risk at high doses [3,8,15]. DAP are also reported to be useful in alleviating heat-dependent fatigue and for fatigue associated with endurance, especially at plasma levels >30 ng/ml [15]. Nonetheless, confirmation of the benefits of DAP are required before they can come into general use [1,3].

Acetylsalicylic acid (ASA) may improve some self-reported measures of fatigue impact and severity. ASA mediates the febrile response at the hypothalamus by irreversibly inhibiting cyclooxygenase and blocking prostaglandin-E2 production. In MS, these effects

could modulate hypothalamic output, thereby affecting neuroendocrine and autonomic responses important in fatigue perception. It is also possible that MS fatigue shares pathogenetic mechanisms with cytokine-induced fatigue (e.g. β-interferon therapy), for which ASA and other nonsteroidal agents are effective [21]. There are some reports that high doses of enteric-coated aspirin may be helpful [16]. Some patients may respond to methylphenidate (Ritalin), 10-60 mg per day divided between two to three doses [13]. This drug has been used to control fatigue in resistant cases [8]. Generalized stimulation and tolerance are anticipated. SSRIs in addition to treating the depressive symptoms associated with MS have been used to treat fatigue. Fluoxetine (Prozac), 10-20 mg once or twice daily, has a side effect profile including nausea, headache, extrapyramidal effects, hypotension, and mania [13]. It is believed that autonomic responses correlated with fatigue resemble a hypoadrenergic orthostatic response, possibly due to a sympathetic vasomotor lesion with intact vagal heart control. Treatments to control sympathetic dysfunction for MS-associated fatigue deserve further study [29]. There is little data linking treatment of depression to improvements in other symptoms (such as fatigue or cognitive impairments) or other outcomes (such as functional status or quality of life) [1]. Depression may play a role in recalcitrant cases, although the response to pharmacological agents suggests that fatigue and depression are dissociable. Thus, antidepressants often do not improve fatigue, while drugs that alleviate fatigue, such as modafinil and amantadine, do not function as antidepressants [3].

Study confirms the effectiveness of a short comprehensive outpatient model of rehabilitative treatment in patients with MS, particularly where their quality of life is concerned [30]. Neurorehabilitation has been shown to ease the burden of symptoms by improving self-performance and independence [2]. Rehabilitation strategies include regular aerobic/endurance exercise (40 minutes 3 times weekly), energy conservation techniques, use of assistive devices, and vocational retraining. Regular aerobic muscle training may enhance well-being and improve physical capacity [15]. The symptoms of fatigue may diminish significantly with a specific training program [31]. Cooling of the body or the limbs using ice water, cold packs or cooling garments applied for 30–45 min has also been shown to be effective in reducing fatigue for several hours [15].

Non-conventional treatments of MS have also been reported. Treatment with bee venom in patients with relapsing multiple sclerosis did not reduce disease activity, disability, or fatigue and did not improve quality of life [32]. On the other hand, evidence suggests that cannabis (marijuana) can alleviate symptoms like muscle spasticity and pain in patients with multiple sclerosis [33]. Ginkgo biloba exerted modest beneficial effects on select functional measures (e.g. fatigue) among some individuals with MS [34].

Measurement

Measurement of fatigue is limited by a definition that spans several domains leading to difficulty with validation [1,7,11]. The difficulty in measuring fatigue has impeded studies of its characteristics, mechanisms, and therapeutics [4]. Early fatigue test scores consistently correlated with depression and cognitive test scores, but not with the fatigability test [35]. However, fatigue and depression are now known to be separate issues. Most approaches to fatigue assessment can be classified as either self-report scales or performance-based measures of motor or cognitive outputs [5]. The extent of fatigue can be measured using several scales such as Fatigue Severity Scale (FSS), MS-specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS), and Visual Analogue Scale (VAS) [15]. The weak correlation within various fatigue scales is best explained by the facts that fatigue is a multidimensional symptom with cognitive, physical and mental/psychological aspects, and that the available tests measure and weigh different aspects of fatigue [7,10]. By using these scales, it is possible to differentiate fatigue from clinical depression, even though they

share some of the same symptoms [36]. The most discriminating scales are believed to be FSS and MFIS.

No correlations could be found between fatigue, basal cortisol levels or other laboratory parameters [10].

In summary, the frequency, severity and impact of fatigue, and the scarcity research on the topic in this area, warrant new studies. Further research on new pharmacological therapies and additional information on the validity of instruments for fatigue measurement, including their sensitivity to change, would be helpful directions for future research [1].

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