Fatigue – better understanding, better therapy?

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Summary

Penner I-K, Schläger R. Fatigue – better understanding, better therapy? Schweiz Arch Neurol Psychiatr 2006;157:46–53.

Fatigue affects 75–95% of all multiple sclerosis (MS) patients. It belongs to one of the most disabling symptoms in multiple sclerosis causing social and occupational problems and affecting quality of life in a markedly negative way. Fatigue can be present at all stages of the disease including disease onset and often persists throughout the disease course. The pathophysiology is still unknown although several reasonable suggestions have been made. In this context peripheral and central abnormalities as well as neuroendocrine alterations were discussed as causal factors for fatigue. Even though these factors might contribute in part to the pathology they are not able to explain the entire complexity of the symptom. The current understanding of fatigue as a multicausal symptom complicates a reliable assessment. At present, methods to assess fatigue in an objective way are still missing. The knowledge about the pathology itself therefore mostly depends on subjective measures such as self-reports from patients. Without quantitative measures, however, it is difficult to define fatigue and to differentiate it from non-pathological tiredness. By developing different fatigue scales one has aimed at least at standardising the fatigue symptom and quantifying its dimension. However, these scales often suffer from insufficient discriminatory power between patients and controls, they often do not differentiate between cognitive and motor fatigue, and they were not validated according to methodological standards. At present, therefore, no reliable self-report instrument is available to diagnose patients' fatigue in clinical routine. Objective measures as might be provided by electrophysiological methods are employed even considerably less frequently but might be an interesting methodological approach for the future. The definition of fatigue being difficult and the pathophysiology still unknown, the development of specific therapeutic standards consequently is problematic as well. Various drugs that are supposed to raise the level of neuronal activity have been investigated for the management of MS fatigue. Significant benefits were described for some of the drugs in some subgroups of patients while in others adverse reactions were observed before a benefit could be noticed. It is recommended to combine non-pharmacological treatments and pharmacological approaches in treating MS fatigue. However, one has to be aware that a specific fatigue treatment is still lacking and that the options available today cannot be regarded as a standard treatment for fatigue. The present article will introduce the complexity of MS fatigue by discussing the major issues, assessment and treatment options.

Keywords: fatigue; multiple sclerosis; fatigue assessment; fatigue therapy

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Introduction

Fatigue is a complex symptom with a pathophysiology of unknown origin. It affects 75 to 95% of all MS patients [1, 2]. Fifty to 60% of these patients declare that it is the most annoying and disabling symptom that interferes with daily living and reduces quality of life [3–5]. Fatigue is known as one of the main reasons for half-time employment, early retirement and even invalidity [6]. Thus, to ameliorate the understanding from employers' and insurance companies' perspectives as well as from patients' relatives' side there is a clear need to assess fatigue reliably during clinical routine and to offer behavioural and drug therapy.

The relation between fatigue and physical disability as measured by EDSS is discussed con-

troversially. The competing results may be due to methodological problems, which are especially based on the use of different fatigue scales. A paper by Bakshi et al. [7] concluded that MS fatigue and physical disability are independent measures as well as disease course and fatigue. In addition, fatigue seems to be unrelated to disease duration [8]. It is therefore not surprising that fatigue is a symptom that may occur at any stage of the disease also including the time of disease onset, and may persist throughout the disease course [3, 9, 10]. A further problem in the assessment of fatigue consists in the coincidence of several comorbidities such as depression, cognitive decline and sleep disturbances. Most studies reported no relation between fatigue and depression [10–12]. However, more recent studies report a clear association between fatigue and depression and suggest that common neuroanatomic or psychological mechanisms may underlie both symptoms [7]. As cognitive decline affects more than 50% of all MS patients [13], the probability that a patient suffers from cognitive impairment and fatigue at the same time is very high. However, it is still unclear whether the cognitive aspects of fatigue are a consequence of cognitive problems that cause recruitment of additional mental resources or whether cognitive problems are caused by fatigue. Sleep disturbances and reduced sleep efficiency are known in multiple sclerosis [14] and are often provoked by pain and bladder dysfunction. A recent study has investigated the relation between sleep disturbances and MS fatigue [15]. The main outcome measures were sleep disturbances and circadian rhythm abnormalities. The results support the hypothesis that fatigue is significantly correlated with disrupted sleep or abnormal sleep cycles. In summary, MS fatigue is one of the most common symptoms in multiple sclerosis but also one of the most complex and least understood. Therefore, reliable assessment of the fatigue symptomatology and its comorbidities is essential for an accurate diagnosis. Here, fatigue scales that account for different fatigue aspects and fulfil the methodological criteria are needed as well as reliable instruments to assess the comorbidities.

Fatigue – definition

A definition of fatigue is difficult, because, similar to pain, it is a symptom that is experienced subjectively and therefore not easy to measure and quantify. According to patients' reports, fatigue 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" [1]. The symptoms worsen in the afternoon [3, 10] and are often triggered by stress and heat [3]. Fatigue can occur in a variety of forms, including motor and cognitive fatigue separately, global fatigue or acute fatigue that affects specific muscle groups [1, 16]. Fatigue can be distinguished from normal tiredness in that it affects the patients unexpectedly without a specific external correlate.

Fatigue – assessment

When one aims at assessing fatigue reliably one has to take into account two things:

1. Fatigue has two main components, i.e. physical or motor fatigue on the one side and cognitive or mental fatigue on the other side. Whether these components have the same pathophysiological basis or whether they are completely independent is still unknown. It is therefore important to assess both components separately to increase our understanding of the interrelation between these components.
2. Fatigue has three major comorbidities, i.e. depression, cognitive decline and sleep disturbances. These comorbidities have to be considered when diagnosing MS fatigue.

As mentioned earlier, we exclusively depend on the patients' reports and their ability of self-evaluation and introspection. A good fatigue instrument should thus support the patient in reporting as accurately as possible what he or she experiences in everyday life. Here, ad hoc reports by patients and relatives are only of low reliability as they may be influenced by situational aspects and emotional circumstances. Estimations by the treating physician are also problematic because they exclusively depend on the physician's knowledge about the fatigue pathology and therefore do not provide a standardised tool for diagnosis. Recommended measures that have the potential to assess fatigue reliably are fatigue diaries, fatigue scales and electrophysiological measures.

Fatigue diaries

Diaries provide the advantage to document the course of a symptom more precisely than any other instrument [17]. Its application is particularly recommended whenever a symptom fluctuates over time. In many MS patients fatigue is provoked by external circumstances like stress or heat. The symptoms therefore are not constant in frequency and extent. Thus, fatigue diaries represent a good

complement to fatigue scales and electrophysiological measures.

Fatigue scales

From 1989 to 1999 eleven fatigue scales were developed. Some of these scales have reached high popularity as e.g. the Fatigue Severity Scale (FSS) by Krupp et al. [18], the Fatigue Impact Scale (FIS) by Fisk et al. [4], the Fatigue Assessment Instrument (FAI) by Schwartz et al. [19] or the Modified Fatigue Impact Scale (MFIS) by the MS Council [1] while others have never been used routinely in other studies. One main problem of the existing fatigue scales is based on their weakness in scale construction and validation. In the FAI for instance the relevance of the two different fatigue aspects is obviously underestimated as 3 items for cognitive aspects are opposed to 11 items for physical fatigue. With respect to scale validation, most of the developed scales suffer from methodological deficits. These deficits consist either in a complete lack of a validation procedure or in an insufficient realisation of the validation process by ignoring the critical sample size (e.g. FSS). In addition, control groups were often not appropriate because no comparison between fatigued and non-fatigued MS patients had been made. Besides, imprecise item formulation often leads to misunderstandings. Given e.g. the item "fatigue interferes with my work, family, or social life" may lead to confusion because many patients are not able to consider the or-function and thus this item finally remains unanswered as the three conditions together are not relevant to the patient. Another problem consists in a low differentiation between fatigue and normal tiredness (e.g. "resting lessens my fatigue; sleeping lessens my fatigue; I feel drowsy when I am fatigued") which finally leads to low discriminatory power between patients and healthy controls. In conclusion, there is at present no instrument that measures fatigue reliably and thus there is a clear need to change and improve this situation for the patients.

Electrophysiological measures

Motor fatigue can be defined as an exercise-related reduction of maximal muscle force or power [20]. According to Merton [21] it can be divided into central and peripheral components. While central motor fatigue is defined as an inability to sustain central drive to spinal motoneurons, the term "peripheral motor fatigue" relates to changes occurring in the muscle itself or at the neuromuscular junction (as e.g. observed in myasthenia gravis) which leads to an exercise-dependent decrease in twitch or tetanic force. As mentioned previously, the mechanism of fatigue in MS patients is not yet fully understood. Given the nature of the underlying disease, MS-related fatigue is most likely to be predominantly central in origin with peripheral components playing only a minor role. A good explanation for the reversibility and heat sensitivity of symptoms in multiple sclerosis would be the presence of a frequency-dependent conduction block. Sheean et al. [22], however, did not find evidence for this phenomenon, using a single and paired transcranial TMS paradigm during and after a fatiguing exercise. By this method large-diameter, fast-conducting fibres are examined, which might not necessarily be the same fibres activating pathways in which the patient is experiencing fatigue. In healthy volunteers Andersen et al. [23] observed a reduction of amplitudes of motor-evoked potentials (measured by triple stimulation technique) and an increase of the silent period – a period of electromyographic silence after a TMS stimulus to a maximal voluntary contracted muscle – after a fatiguing grip exercise. Gandevia et al. [20] and Taylor and Gandevia [24] found an increase in the duration of the silent period by more than 50 ms during a sustained maximal voluntary contraction with a recovery after 30 sec of rest. In their experiments the change of the silent period was found to be dependent on the level of voluntary activation. If motor fatigue in multiple sclerosis is caused by a pathologically enhanced but similar mechanism as motor fatigue in healthy subjects, an abnormal decrease of motor-evoked potential amplitudes and an abnormal increase of the silent period as well as a correlation between subjective fatigue and measured parameter must be postulated.

Fatigue – therapy

The first step in managing fatigue in MS patients is to identify and treat any underlying secondary cause: non MS-related comorbidities – infectious, endocrinologic, rheumatologic disorders, primary sleep disorders or malignancies – should be ruled out and treatment of MS-related factors which might aggravate fatigue – as e.g. reactive depression, deconditioning and secondary sleep disorders due to bladder dysfunction, pain, dysaesthesia or spasticity – should be optimised. For a detailed differential diagnosis of fatigue in MS patients see table 1.

Table 1 differential diagnosis of fatigue in patients with multiple sclerosis

non MS-related	*infectious:* mononucleosis, CMV, EBV, chronic hepatitis, HIV, Lyme disease, toxoplasmosis
	endocrine: hypothyroidism, diabetes
	rheumatologic: rheumatoid arthritis, SLE
	electrolyte imbalances
	malignancies
	primary sleep disorders
MS-related	depression
	learned helplessness
	deconditioning
	secondary sleep disorders due to – bladder dysfunction – pain/dysaesthesia – spasticity

Table 2 drugs with potential sedative side effect

antidepressants
analgesics
antispastic agents, muscle relaxants
anticonvulsants
hypnotics
anti-inflammatories
immunomodulating agents
antihistamines

Special attention should be put on medication as many drugs used in the symptomatic treatment of multiple sclerosis have a sedating potential as e.g. antispastics, analgesics, antidepressants (see table 2). These agents have to be strictly checked according to their indication and cautiously titrated when prescribed. A possible potentiation of the sedative effect should be kept in mind when using these agents in combination. Knowledge about the pharmacological consequences of a partially disrupted blood-brain barrier in MS patients during relapses and in the interval for these and other agents is still limited.

Immunomodulators

The effect of immunomodulatory treatment on MS-related fatigue is not yet completely clarified. Several randomised placebo-controlled multicentre studies reported increased incidence of "malaise", "asthenia" and "fatigueability" in MS patients who were treated with interferon beta 1a and 1b. However, how these adverse events may be related to MS fatigue was not addressed [25–28]. Only in one of these pivotal trials fatigue severity was measured showing no difference in FSS scores between treated and placebo group after 2 years of treatment [29]. Metz et al. [30] reported a slight improvement on the Fatigue Impact Scales in MS patients after six months of treatment with glatiramer acetate and, less pronounced, with interferon beta 1b compared to baseline using an uncontrolled and non-randomised study design. Thus, these results have to be interpreted with caution.

Supportive non-pharmacological treatment

Behavioural advice is a main element of initial clinical management and includes recommendation of general body-oriented supportive measures as regular physical exercise, sleep hygiene and avoidance of extreme temperatures as well as psychological support regarding the development of coping strategies. Moreover, some patients might profit from additional advice by occupational therapists to facilitate fatiguing activities of daily living. Several non-pharmacological treatment options are available for MS-related fatigue and should be offered to patients already early in the course of the disease.

Exercise treatment and yoga

Empirical observations suppose some beneficial effect of regular exercise on fatigue and overall activity level in MS patients in the relapse-free interval. However, evidence of efficacy is still limited. Mostert and Kesselring [31] assessed MS patients undergoing an inpatient rehabilitation programme and found an improvement of health perception, an increased activity level and a tendency to less fatigue after 4 weeks of regular exercise compared to baseline and compared to a non-training group. Surakka et al. [32] found a slight reduction of motor fatigue in women with multiple sclerosis after a 6-month exercise training compared to a non-treated control group. In a study conducted by Petajan et al. [33] regular aerobic exercise improved both mood and quality of life in patients with multiple sclerosis, with only minor improvement of fatigue at some time point. Oken et al. [34] compared the effects of a 6-month yoga class to a regular aerobic exercise programme and no intervention and found significant improvements in both intervention groups in secondary measures of fatigue compared to the control group

with no relative improvement of cognitive function. The major limitations of these studies are due to the difficulties in defining appropriate controls for behavioural interventions. In addition, training should be adapted to the individual requirements of the patients, adequately dosed with sufficient time of regeneration.

Cooling therapy

The rationale for cooling therapy is based on a frequently observed phenomenon in MS patients – a temperature-dependent worsening of deficits or so-called Uhthoff's phenomenon [35]. As shown by Humm et al. [36] temperature modification causes varying degrees of central motor conduction block in MS patients. The observed changes of central motor conduction were found to be related to the subjective temperature vulnerability of the patients as well as to their walking performance. Whether the effect of peripheral cooling is due to a consecutive change of core temperature or mediated via an indirect lowering of NO [37], which is increased in MS patients [38] and might impair conduction along demyelinated axons [39], is still not completely clarified. If the latter turns out to be true, a chemical imitation of this effect might be a passable treatment option. The feasibility of the use of cooling garments awaits further testing.

Pharmacological treatment

Stimulating antidepressants

By inhibiting predominantly and reversibly monoaminooxidase-A, moclobemid reduces the metabolic degradation of norepinephrine, dopamine and serotonin and therefore augments the extracellular concentration of these neuronal transmitters, whereas fluoxetine, citalopram and derivates selectively inhibit the neuronal reuptake of serotonin [40]. The direct effect of these drugs on mood is accompanied by an increase of psychomotor activity and motivation – which gives the rationale for their use in MS-related fatigue. Although trial-based evidence is lacking so far, clinical observations suggest an anti-fatigue effect also in non-depressed MS patients. The comparatively low side-effect profile makes them worth a trial before prescribing other agents.

Amantadine

The antiviral and antidyskinetic agent amantadine is an NMDA receptor antagonist, with not yet completely clarified additional dopaminergic and marginal anticholinergic properties. The precise mechanism of its vigilance-promoting, anti-fatigue effect in multiple sclerosis is unknown. Evidence of efficacy in MS-related fatigue is based on 4 double-blind placebo-controlled studies, all with some limitations [2, 41–43]. The usual dosage for the management of fatigue in multiple sclerosis is 100 to 200 mg daily, taken in the earlier part of the day in order to avoid sleep disturbances. Amantadine is in general well tolerated, with fewer than 10% of patients experiencing adverse effects related to the drug, the most common of which include nausea, insomnia, irritability and livedo reticularis.

Modafinil

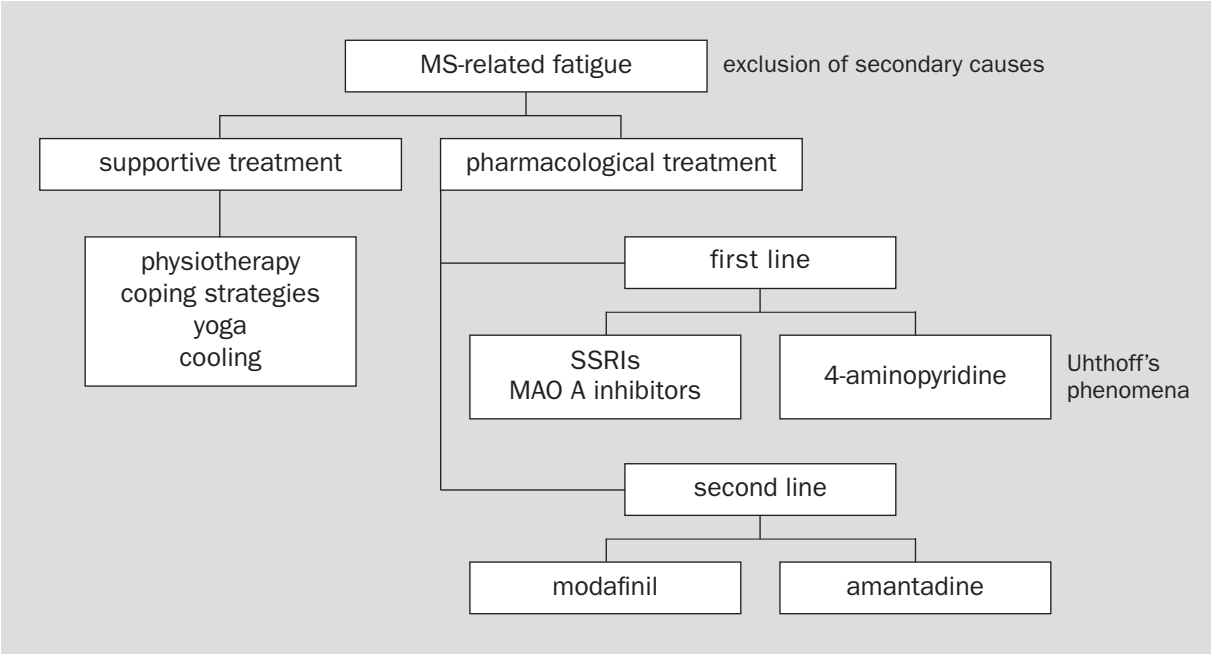
Modafinil is a non-amphetamine-like CNS stimulant with vigilance-promoting properties. Its precise mode of action is still under investigation, it may increase wakefulness through activation of noradrenergic and dopaminergic systems, possibly through interaction with the hypocretin/orexin system, a hypothalamic system involved in wakefulness and sleep regulation [44, 45].

Modafinil is approved in Switzerland for treatment of narcolepsy and obstructive sleep apnoea. Two phase-II studies suggest a slight but significant improvement of fatigue in patients with multiple sclerosis [46, 47], but short duration of treatment and follow-up periods and insufficient control and blinding limit the power of these studies. It is recommended to start treatment with 100 mg in the morning. If patients do not respond adequately but tolerate the drug well, the dosage can be doubled after one week [8]. Common side effects of treatment with modafinil include headache, nervousness, anxiety, nausea, dry mouth, insomnia, cataplexy and diarrhoea [47, 48]. A rebound effect after stop of medication was not observed. Compared to other CNS stimulants, modafinil has a low risk of addiction [48]. Taking the side-effect profile into account, modafinil seems to be a promising treatment alternative for patients who do not respond to first-line drugs. However, due to the shortcomings of the studies mentioned above further evidence of efficacy is needed.

4-aminopyridine

The potassium channel blocker 4-aminopyridine improves conductivity of demyelinated axons in vitro. In vivo, however, the clinical dosages are about 250–1000-fold lower than under experimental conditions – bioavailability not taken into account. Therefore, an extrapolation of experimental data to clinical effects might be questionable. Experimental data suggest that potentiation of central synaptic transmission and elevation of muscle tension force are further mechanisms of action of the drug, which might be responsible for

Figure 1 Algorithm for the management of MS-related fatigue.



the positive effect on some patients with multiple sclerosis and fatigue [49]. Rossini et al. [50] studied 54 patients with progressive multiple sclerosis and fatigue in a randomised placebo-controlled, double-blind crossover design where patients received either 4-aminopyridine 32 mg/d or placebo for 6 months and vice versa. Fatigue was assessed by the Fatigue Severity Scale. 4-aminopyridine was found to improve fatigue with regard to placebo only in patients with a high plasma level of the drug (>30 ng/ml). Cognitive functions were not improved by intake of 4-aminopyridine [51]. Empirical observations suggest that patients with heat-sensitive fatigue seem to profit most. The use of 4-aminopyridine is not approved in Switzerland, as an experimental treatment it can be ordered in selected pharmacies. As its therapeutic window is small, 4-aminopyridine should be titrated carefully – beginning with a dosage of 3 × 5 mg, which can be augmented every week up to 30–60 mg/d, when tolerated. In dosages over 60 mg/d 4-aminopyridine lowers the epileptic threshold, therefore high dosages and the use in patients with a history of seizures should be avoided. Side effects such as paraesthesias, dizziness, light-headedness or headaches appear rather seldom and are usually mild [52].

Discussion

This review clearly points out that fatigue is a symptom of high relevance in multiple sclerosis although the pathological process is not yet clarified. As the importance to patients, relatives and also insurance companies is obvious, reliable diagnosis and treatment options are required despite the pleading lack of knowledge concerning underlying mechanisms. The complete dependence on subjective measures to assess MS fatigue therefore requires better instruments than those available at present. Thus, the degree of evidence of clinical trials assessing the effect of pharmacological and non-pharmacological treatments of MS-related fatigue is not only limited by the lack of a clear definition of the phenomenon, but in addition by insufficiently validated instruments to assess fatigue. We therefore developed in our MS centre a new fatigue scale – the Fatigue Scale for Motor and Cognitive functions (FSMC) – that allows to assess the two main dimensions of fatigue separately [53]. A huge multi-centre validation study is currently ongoing to test for criterion-related validity, discriminant validity and test-retest reliability. This instrument will then be able to give a clear and reliable diagnosis on cognitive and motor fatigue and may be used as primary outcome measure for future fatigue treatment studies. Given the currently still limited understanding of the complex phenomenon of fatigue in multiple sclerosis, the rationale for the use of pharmacological and non-pharmacological treatments remains mainly empirical.

In our MS centre the following treatment algorithm has proven to be efficacious (cf. fig. 1): Before initiating any treatment, other concomitant factors potentially worsening fatigue should be identified and treated. The patient should receive behaviour-

al advice about general supportive measures as e.g. regular exercise, sleep hygiene and avoidance of extreme temperatures, as well as about non-pharmacological treatment options such as e.g. yoga or cooling therapy.

If none of these measures shows a sufficient effect, pharmacological treatment should be started. Due to the comparatively low side-effect profile we consider moclobemid and SSRIs first-line agents. Clinical observations suggest an anti-fatigue effect of these analeptic agents, also in non-depressed MS patients. Patients who describe a heat- or cold-sensitivity of fatigue (Uhthoff's phenomena) often respond well to treatment with 4-aminopyridine, which is currently not approved for use in the treatment of MS fatigue but can be ordered in selected pharmacies as an experimental treatment. If the patient does not show a response to these agents, amantadine or modafinil should be tried as second-line drugs.

The development of an efficacious treatment of MS-related fatigue requires a more profound understanding of the underlying mechanisms of fatigue as well as the development of validated instruments to measure therapeutic effects.

Acknowledgments: We are grateful to Prof. Dr. L. Kappos and Prof. Dr. P. Fuhr for their helpful comments on this manuscript.

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