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Management of Fatigue in Patients with Multiple Sclerosis

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Abstract

As long as no causal treatment is available for multiple sclerosis (MS), and as long as only some patients with MS respond to immunomodulators, symptomatic treatment is of paramount importance. Fatigue is the most common symptom of MS and is associated with a reduced quality of life. It is described as the worst symptom of their disease by 50–60% of patients.

The first step in managing MS-related fatigue is identifying and eliminating any secondary causes. Primary fatigue syndrome can be alleviated with drug treatment in many cases. Modafinil has been shown to be effective in some studies, and amantadine is an alternative for patients who do not respond to or cannot tolerate modafinil. The nonpharmacological management of fatigue in MS includes inpatient rehabilitation and aerobic endurance exercise.

This article describes the pathophysiology, diagnosis and treatment of MS-related fatigue – the most common symptom of MS.

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the CNS; peripheral nerves are not affected. Its initial course is often marked by multiple exacerbations and remissions. Onset in young adults and gradual progression over decades are the rule. The prevalence of MS varies

widely from 6–10 per 100 000 population in the southern US and in Southern Europe to 30–80 per 100 000 population in Central and Northern Europe, the northern sections of the US and Canada; MS affects around 2.5 million individuals throughout the world.[1]

Clinically, MS manifests itself in a variety of symptoms, mainly determined by the location of the plaques in the brain and the spinal cord. Fatigue is the most common symptom; it is reported by 70–90% of all patients.[2] For 50–60% of patients it is also considered the most annoying symptom and the main reason for inability to work and social isolation despite otherwise minor physical deficits.[3]

1. Overview of Fatigue in Multiple Sclerosis (MS)

1.1 Definition

The syndrome of fatigue is characterised by uncontrollable apathy, exhaustion, fatigability and lack of energy not experienced to the same extent before the onset of the disease. Fatigue is not related to disease duration or disability. Patients may have mental or physical fatigue, which can be dissociated in some cases. Fatigue in MS may be associated with physical stress, but it characteristically occurs even without stress. This needs to be elicited from the history before diagnosing MS-related fatigue syndrome. Patients typically report that fatigue hinders them in performing professionally or socially. Fatigue may be present for any length of time, and may be transient or persistent. Patients report that they often fall asleep during the daytime.

Exaggerated fatigue needs to be present for >6 weeks to justify the diagnosis of fatigue syndrome.

1.2 Diagnosis

A carefully taken patient history to elicit such signs as the need for repeated rests, problems in coping with normal activities of daily living and feelings of exhaustion is the basis for detecting fatigue syndrome in patients with MS.

The only objective diagnostic indicator is the ratio between the area under the time curve during isometric muscle contraction and the theoretical peak strength.[4] However, determination of this ratio is cumbersome and requires computer-assisted muscle strength tests and it is, therefore, generally reserved for research purposes.

Recording activities of daily living with the help of an actigraph is a relatively simple alternative. The actigraph is strapped to the wrist and records physical activity throughout the day. However, generally valid normal ranges are not known, and there are no data on the utility of actigraph in measuring fatigue in MS. Actigraph recordings are nevertheless helpful for evaluating the intra-individual effectiveness of therapeutic interventions.

As the fatigue syndrome in patients with MS cannot be evaluated objectively in the routine clinical setting, a number of scales have been developed for history taking and assessing the severity of the condition in a standardised format. The Krupp Fatigue Severity Scale (FSS) is a general scale, which is also used in other conditions.[5] The MS-Specific FSS (MS-FSS), which was also developed by Krupp, and the Fatigue Questionnaire are specifically designed for MS-related fatigue syndrome and have been applied in several instances.[6] Additional scales that have been tested in MS include the Fatigue Impact Scale[7] and the Fatigue Descriptive Scale.[8] The use of such scales is important both for research and objective outcome monitoring. Patients with MS reporting both daytime fatigue and daytime sleepiness are best evaluated with the Epworth Sleepiness Scale (ESS).[9]

As for all symptoms that can only be assessed on the basis of what the patients subjectively report, visual analogue scales and patient diaries are useful tools.

1.3 Differential Diagnosis

Primary fatigue syndromes without any identifiable cause should be distinguished from secondary fatigue syndromes in patients with MS. In the latter, causative factors underlying the occurrence of fatigue can be elicited. These are summarised in table I.

Secondary fatigue syndrome is often caused by the many drugs needed to treat other symptoms of MS, particularly antispasticity agents. Associated infections or sleeping disorders due to pain or spas-

Table I. Potential causes of secondary fatigue syndrome in multiple sclerosis

Cause	Examples
Adverse effects of drugs	Antispasticity agents, analgesics, anticonvulsants, antidepressants, antihistamines, anti-inflammatories, antipsychotics, gastrointestinal drugs, immunomodulators, muscle relaxants, sedatives, hypnotics, etc.
Infections	Urinary tract infections, aspiration pneumonia, etc.
Depressive states	
Sleep disorders	Due to pain, cramps, etc.
Electrolyte imbalances	
Metabolic diseases	Hypothyroidism, etc.
Dehydration	

ticity are other causes. Further factors that can be controlled well include conditions unrelated to MS, such as thyroid dysfunction or electrolyte derangements.

The differentiation of secondary fatigue syndrome from depressive states is of particular importance, and is best made with the help of depression scales and by exploration of the patient's emotional state. Symptoms such as self doubt, hopelessness, anxiety or restlessness are suggestive of depression. Ruling out depression is, however, fraught with problems because the syndrome of fatigue is often associated with other symptoms, among them depressive states.[10] In addition, there is considerable overlap between fatigue and sexual dysfunction, which in itself may be associated with MS.[11]

Consequently, all of these causes need to be ruled out before diagnosing primary fatigue syndrome and initiating treatment (figure 1).

1.4 Pathophysiology

Although extensively investigated, the mechanisms underlying fatigue in MS are still poorly understood and have so far defied any correlation with imaging data in large serial studies.

However, local demyelination and axonal damage in the reticular formation leading to exaggerated daytime fatigue and disturbances of the sleep-wake rhythm in patients with MS have been reported.[12,13] There is some evidence that involvement of the basal ganglia plays a major role in MS-associated fatigue.[3,14,15] In a female MS patient with plaques bilaterally in the hypothalamus, acute hypersomnia was found to be the only symptom during exacerbation.

Aside from these local causes, diffuse demyelination and axonal lesions associated with reduced nerve conduction velocity, prolonged refractory period and resultant increased effort needed for processing incoming signals in various CNS structures have been discussed as having a role in fatigue in MS.[4,16] Similarly, neuroendocrine abnormalities caused by inflammatory mediators and inflammatory cytokines have been incriminated in the development of fatigue in MS.[12] Another potential mechanism is increased energy demand because of the increased muscular effort needed to compensate for spasticity and because of damage to the pyramidal tract resulting in inadequate α-motoneuron activation.[17] Poor central respiratory control with consequent diaphragmatic muscle weakness is yet another potential cause of MS-associated fatigue.[18] An association with autonomous dysfunction[19] and a neuromuscular component[20] have also been reported.

While unlikely, an association between fatigue in MS and persistent chronic viral infections cannot be ruled out altogether.[21]

2. Treatment Options

2.1 Drug Treatment

Various drugs have been investigated for the management of primary MS-associated fatigue syndrome. The most important data gathered in pertinent studies are described below and summarised in table II.

2.1.1 Modafinil

Modafinil is a non-amphetamine-like drug for the management of narcolepsy.[22] It has been used in this indication since its approval in 1994 in France, 1997 in the UK and 1999 in the US. Modafinil has also been prescribed for daytime fatigue associated with other conditions such as obstructive sleep apnoea, myotonic dystrophy, fibromyalgia and Parkinson's disease.[23-25] Beneficial effects have been reported in children with poor attentiveness, in depressive states as an adjuvant to antidepressants and in night-shift workers.[11,26,27]

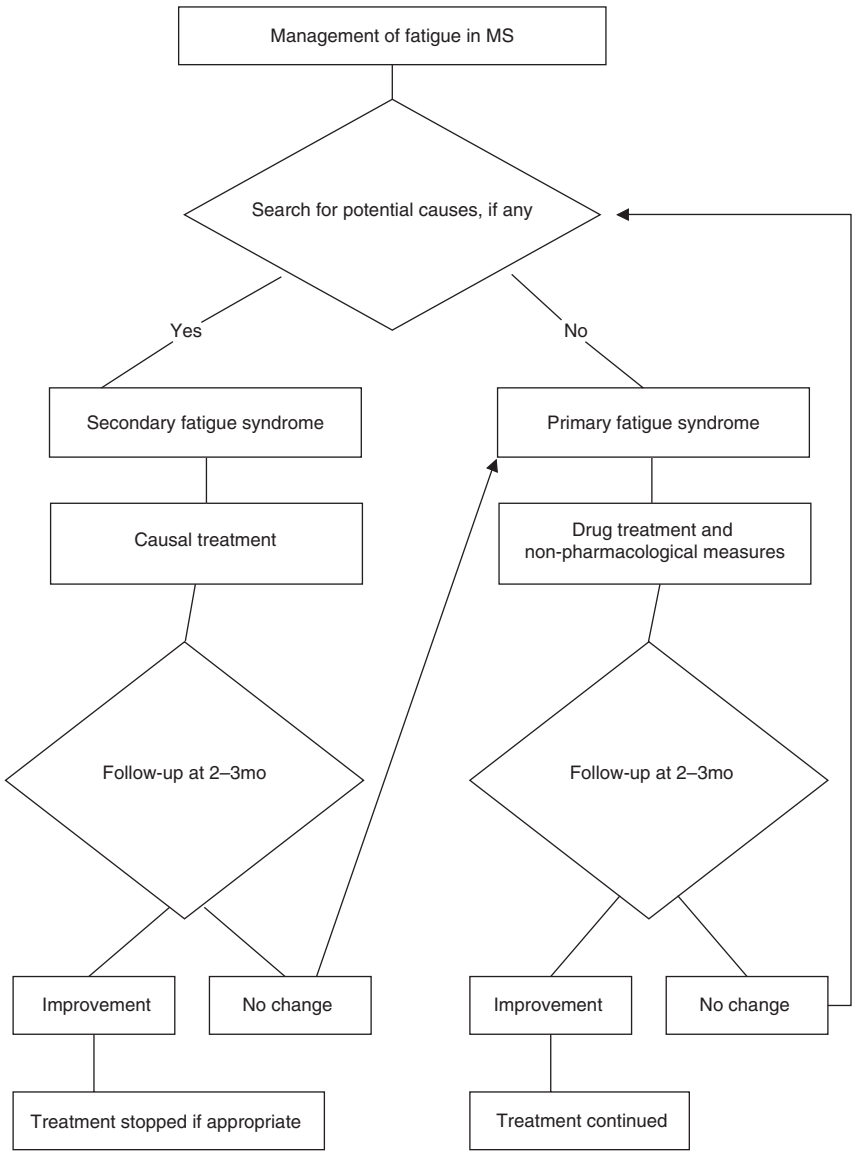

Fig. 1. Overview of fatigue management in multiple sclerosis (MS): first differentiate primary from secondary fatigue syndrome, then initiate treatment and assess treatment outcome before deciding on further management (reproduced from Zifko,[2] with permission).

Data on the efficacy of modafinil for MS-related fatigue in the three trials available are presented in table III.

In a single-blind, two-centre, crossover phase II trial of 72 patients with MS, who received modafinil at a dose of 200 mg/day (weeks 3 and 4) and 400 mg/day (weeks 5 and 6) or placebo (weeks 1, 2, 7, 8 and 9), the modafinil 200mg dose significantly improved FSS ($p < 0.001$) and ESS scores ($p < 0.001$) versus placebo.[28] At a modafinil dose of 400mg, significant improvements of ESS scores were seen versus placebo ($p < 0.001$), while FSS scores were unaffected at this dose.[28] Adverse effects were rare and included headache (15% of patients on placebo

Table II. Important drugs for symptomatic treatment of fatigue

Drug name	Chemical name	Usual daily dose	Maximum daily dose	Adverse effects	Contraindications
Amantadine	L-adamantan aminosulfate	100mg bid	600mg	Restlessness, sleep disorders, visual hallucinations, visual disturbances, constipation, nausea, urinary retention, dryness of the mouth, thirst, heart failure, vertigo, reticular livedo	Psychoses, confusion, predelirium, delirium, epilepsy, renal functional impairment, prostatic hyperplasia, glaucoma, arterial hypertension
Modafinil	Benzhydrylsufinyl acetamide	100–300mg	400mg	Nervousness, restlessness, loss of appetite, insomnia, increased seizure potential, visual disturbances, nausea, vomiting, palpitations	Lactation, concomitant prazosin treatment
Pemoline	2-Amino-5-phenyl-2-oxazolidinone	20mg bid	60mg	Insomnia, weight loss, nausea, tremor, dizziness, tachycardia, hepatic functional impairment, epileptic seizures	Psychoses, hepatic functional impairment, depression with suicidal tendencies
Fampridine (4-AP)	4-Aminopyridine	5mg od to 10–20mg tid	60mg	Nausea, vertigo, confusion, anxiety, epileptic seizures, loss of consciousness	Epilepsy, confusion, unclear disturbance of consciousness, large paracortical lesions on MRI
3,4-Di-aminopyridine (3,4-DAP)	3,4-Di-aminopyridine	10mg od to 20mg qid	80mg or 1 mg/kg	Paraesthesia mainly acral, abdominal pain, nausea, confusion, anxiety, hepatic functional impairment, hepatitis, epileptic seizures, loss of consciousness	Epilepsy, confusion, unclear disturbances of consciousness, large paracortical lesions on MRI

bid = twice daily; **MRI** = magnetic resonance imaging; **od** = once daily; **qid** = four times daily; **tid** = three times daily.

Table III. Efficacy of modafinil for multiple-sclerosis-related fatigue: summary of trials

Study	Design	No. of patients	Regimen	Comparator	Efficacy parameter[a]	control	modafinil	p-value
Rammohan et al.[28]	db, pc, co, 9 wks	72	200 mg/day	Placebo	FSS – mean score	5.5	4.7	<0.001
					VAS-F	4.5	5.4	0.003
					MFIS	44.7	37.7	<0.001
					ESS	9.5	7.2	<0.001
			400 mg/day		FSS – mean score		5.3	NS
					VAS-F		4.7	NS
					MFIS		42.1	NS
					ESS		7.0	<0.001
Zifko et al.[30]	Open, 3mo	50	100–300 mg/day (mean 148 ± 61; median 100)	Baseline	ESS	9.7	4.9	<0.0001
					FSS – total score	30.3	25.4	<0.0001
					>85% of patients reported 'clear improvement'			
Terzoudi et al.[31]	Open, 12 wks	40	100mg bid	Baseline	Improved fatigue in 85% of patients, some improvement in sleepiness, no significant effects on measures of pain, depression or cognition			

a Improvement is indicated by a *decrease* in score on the following scales: FSS, MFIS, ESS. An improvement is indicated by an *increase* in score on the VAS-F scale.
bid = twice daily; **co** = crossover; **db** = double-blind; **ESS** = Epworth Sleepiness Scale; **FSS** = Fatigue Seventy Scale; **MFIS** = Modified Fatigue Impact Scale; **NS** = not significant; **open** = open-label; **pc** = placebo-controlled; **VAS-F** = Visual Analog Global Scale of Fatigue.

versus 17% on modafinil 200mg and 10% on modafinil 400mg), nervousness (3% on placebo versus 7% on modafinil 200mg and 6% on modafinil 400mg).

The anecdotal observations of Zifko et al.,[29,30] as well as the results of an open-label trial in 50 patients with MS, showed significant improvements of daytime sleepiness and daytime fatigue (figure 2) at daily doses of 100, 200 and 300mg.[29,30] These data support the results reported by Rammohan et al.,[28] that is that modafinil is effective at low dosages.

In another open-label study by Terzoudi et al.[31] (abstract only) in 40 patients with MS followed up for 3 months, daytime fatigue was also found to respond well to modafinil. Beyond this, the study showed the drug to be more effective during the early course of the condition (Expanded Disability Status Scale [EDSS]: 0–5) than in its advanced stages (EDSS: 6–8).

Although insomnia is considered a potential adverse effect of modafinil (table II), insomnia was not reported in these studies.

As documented by these three trials, modafinil appears to be an effective treatment option in the management of MS-associated daytime fatigue. In view of the social and economic implications of fatigue syndrome in patients with MS, an expansion of currently approved indications appears to be worth considering. However, as only one trial was controlled and patient numbers were relatively small, further studies are needed. Information on the post-trial efficacy of modafinil would also be useful, as the longest follow-up was 3 months.

2.1.2 Amantadine

Amantadine releases endogenous dopamine from the basal ganglia and thus acts as a nonspecific central stimulator. At a daily dose of 400mg it was found to elevate the plasma β-endorphin-lipoprotein concentration.[32]

The efficacy of amantadine in the management of MS-associated fatigue has been investigated in four randomised trials.[32-35] The most important data accumulated in these trials are summarised in table IV. Despite some shortcomings in terms of randomisation, standardisation of questions and observer blinding, amantadine was found to be superior to placebo in some, albeit not in all, endpoints. Braňas

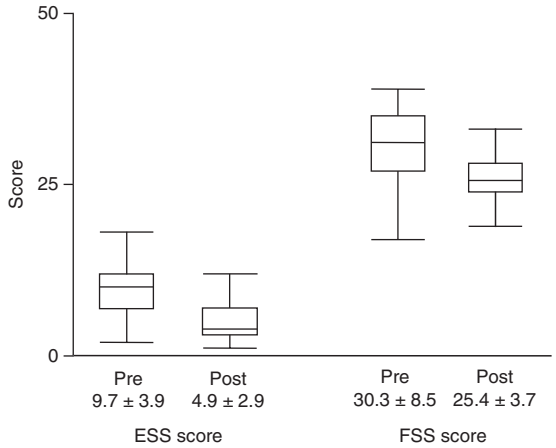

Fig. 2. Fifty patients with multiple sclerosis (age 40.4 ± 10.3 years; Kurtzke Expanded Disability Status Scale 3.8 ± 1.5) before and after 3 months' open-label observational study of daily modafinil (mean dose 148 ± 61mg; median dose 100mg).[30] Significant improvement was seen in Fatigue Severity Scale (FSS) [$p < 0.0001$; Wilcoxon's test] and Epworth Sleepiness Scale (ESS) [$p < 0.0001$; Wilcoxon's test].

et al.[36] calculated relative risks to explore the pattern of results under 'optimistic' and 'pessimistic' assumptions, which are summarised in table IV. Because all studies provided information on the patients' preferred treatment, this measurement was used for the relative risk calculation of treatment success for amantadine versus placebo.

Follow-up data documenting the post-trial efficacy of the drug are not available. However, these would be important because the longest follow-up time was 8 weeks. In their review on the effectiveness and safety of amantadine in reducing fatigue in people with MS, Taus et al.[37] concluded that amantadine treatment is overall well tolerated, but the efficacy is poorly documented and there is insufficient evidence to make recommendations to guide prescribing.

This author's experience in routine clinical practice showed amantadine to have some effects in the management of MS-associated daytime fatigue. However, definite benefits and significant improvements were rare.

2.1.3 Pemoline

Pemoline is a psychoactive central stimulant. The first ever trial of pemoline in the management of MS-related primary fatigue syndrome by Krupp et al.[32] was suggestive of some therapeutic benefit. However, this was not confirmed in subsequent studies based on patient self-assessment.[38]

The extremely high rate of adverse reactions,[38] (see table II) argues against the use of the drug in the management of fatigue.

2.1.4 Aminopyridines

Fampridine (4-aminopyridine) and 3,4-diaminopyridine (3,4-DAP) block internodal potassium channels and, thus, improve conduction by demyelinated axons. 3,4-DAP is used in the symptomatic treatment of Lambert-Eaton syndrome.

Both drugs were examined for their usefulness in the management of various MS-related symptoms in open-label trials.[39-41] Both were found to have a narrow therapeutic range and to be associated with many adverse effects (see table II). Solari et al.[42] reviewed randomised controlled trials on aminopyridines for symptomatic treatment in MS. They concluded that currently available information allows no unbiased statement about safety or efficacy of aminopyridines for treating MS symptoms.

As a result, fampridine and 3,4-DAP at best have a place in exceptional cases, but cannot be regarded as treatment of first choice for MS-related fatigue.

2.1.5 Antidepressants

No trial-based evidence is available for the efficacy of antidepressants in the management of MS-related daytime fatigue. Energising antidepressants such as selective serotonin reuptake inhibitors have a place in the treatment of daytime fatigue associated with depression, that is, in secondary fatigue syndromes. Their benefits in the management of secondary fatigue syndrome in MS have so far not been established.

2.2 Non-Drug Treatment

Various treatment options other than drug treatment are available for MS-related fatigue and should be offered to patients. Unlike some drugs, non-drug treatment modalities also have a place in the management of MS-related secondary fatigue syndrome.

2.2.1 Neurorehabilitation

The effectiveness of inpatient treatment in the management of a number of MS symptoms in general was established in several trials.[43-46] In one

Table IV. Amantadine for multiple sclerosis (MS)-related fatigue: summary of randomised trials with the relative risk (RR) of treatment success with amantadine versus placebo

	The Canadian MS Research Group[35]	Rosenberg and Appenzeller[34]	Cohen and Fisher[33]	Krupp et al.[32]
Design	r, pc, co	r, pc, co	r, pc, co	r, pc, pg
Sample size				
enrolled	94	10	29	80
completed	86	10	22	66
Regimen	100mg bid for 3 wks	100mg bid for 1wk	100mg bid for 4 wks	100mg bid for 6 wks
'Optimistic' RR[a] (95% CI)	1.94 (1.20, 3.15)	6.00 (0.87, 41.22)	2.00 (0.70, 5.68)	1.52 (0.98, 2.36)
'Pessimistic' RR[b] (95% CI)	0.69 (0.50, 0.94)	1.50 (0.60, 3.74)	0.57 (0.30, 1.08)	1.27 (0.70, 2.33)

a Optimistic RR was calculated using treatment preference results as reported.

b Pessimistic RR was calculated using treatment preference results data from the intention-to-treat analysis for the parallel trial, and for the crossover trials 'no preference' and 'preference' data for washout together with the preferences for placebo were counted.

bid = twice daily; **CI** = confidence interval; **co** = crossover; **pc** = placebo-controlled; **pg** = parallel group; **r** = randomised.

trial involving 196 patients with MS, the length of the rehabilitation time was shown to be proportional to the functional gain.[47]

2.2.2 Aerobic Exercise

Petajan et al.[48] found that regular exercise reduced fatigue in MS patients to some extent, and improved both mood and the quality of life. Aerobic endurance exercises are also suitable for patients with major physical handicaps due to spasticity or muscle weakness and can be performed at home or in nursing homes on 'active/passive' exercisers.

2.2.3 Electromagnetic Fields

The benefits of electromagnetic fields for MS and, particularly, for daytime fatigue has been investigated in several studies.[49-51] In a randomised study, in which daytime fatigue was defined as one of several outcome variables, Richards et al.[49] showed electromagnetic fields to be beneficial in 30 patients. Because of a number of methodological limitations, the results still need to be confirmed before a definite statement can be made on the role of electromagnetic field therapy in the treatment of MS-related fatigue.

3. Recommendations for Management of MS-Related Fatigue

The high incidence of fatigue in MS underscores the need for adequate symptomatic treatment. Before any treatment is instituted, all other causes underlying fatigue and daytime sleepiness should be ruled out. Nonpharmacological measures, in particular aerobic exercise, should be the first treatment option. Dictated by the severity of the symptoms, this should be followed by drug treatment.

Modafinil has successfully been used for narcolepsy. It is well tolerated by MS patients and its benefits have been suggested by several studies. Although further confirmatory data would be useful, the current data along with our personal experience with the drug indicate that the use of modafinil in the management of MS-related fatigue appears to be justified. Practical experience shows that treatment should be started with 100mg in the morning (table II). Before starting treatment, the severity of fatigue should be assessed by at least one of the scales described earlier. Patients who do not adequately respond to the 100mg dose after 1 week, but tolerate the drug well, may be treated with 200mg daily. Subsequent dosages should be guided by the patient's response. Patients complaining of post-noon fatigue should be given 100mg in the morning and another 100mg at noon, while those with pre-noon fatigue benefit more from taking the full dose in the morning. Dosage increments dictated by the patient's response should not be made at intervals less than 1 week. Dosages in excess of 400mg daily should be avoided; intolerance of the drug may occur, but is rare.

Patients who do not tolerate modafinil or completely fail to respond to it should be switched to amantadine. The initial dosage of amantadine should be 100mg twice daily and may be increased to 200mg twice daily, if needed (table II).

Lack of response to both drug treatment and nonpharmacological measures should prompt suspi-

cion of a secondary fatigue syndrome, unless this was ruled out before treatment. Associated depression should also be considered and adequately treated.

The management of MS-related daytime fatigue is complex but is successful in many patients, provided a conscientious effort is made. Inpatient treatment for titrating drug dosages and evaluating associated factors combined with supervised sports and physiotherapy has proved to be helpful in severe MS-related fatigue at our institution.

4. Conclusion

Fatigue is the most common symptom of MS and, for more than half of patients with MS, is the worst symptom. Hence, treatment with the best available therapies for the fatigue syndrome is crucial for optimal management of patients with MS. Importantly, causative factors underlying the occurrence of fatigue – secondary fatigue syndrome – have to be elicited and eliminated.

Therapy of primary fatigue syndrome consists of drug treatment and non-pharmacological management. Although there are only one placebo-controlled, double-blind study and two open-label studies so far, modafinil seems to be the most effective drug in the management of MS-associated fatigue. Patients who fail to respond to or are intolerant of this drug should be switched to amantadine. The effectiveness of inpatient rehabilitation on disability and aerobic exercises on fitness and quality of life is well documented and should be part of therapy in all MS patients experiencing fatigue syndrome.

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