Energy Conservation Management and Physical Behavior in fatigued people with Multiple Sclerosis

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Chapter 1

General Introduction

MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a chronic progressive neurological disease affecting many young and middle-aged adults.[1] The current World Health Organization (WHO) and Multiple Sclerosis International Federation (MSIF) database 'Atlas of MS' (2013) estimates that around 17000 people in the Netherlands have MS, representing a prevalence of 1/1000, with a female/male ratio of 2.46. Most MS cases (85%) are initially diagnosed as relapsing remitting MS (RRMS), but up to 80% of these patients will eventually develop progressive MS (secondary progressive MS).[2] MS is characterized by multiple symptoms, including fatigue, spasticity, paresis, ataxia, sensory disorders, neurogenic bladder and bowel disorders, cognitive problems and impairments of varying severity. These impairments lead to increasing limitations in activities and participation[3-5], including changes in body posture and the performance of movement and activities in daily life (i.e. a patient's physical behavior).[6]

FATIGUE

Fatigue is a frequent, frustrating, overwhelming and often disabling symptom of MS, affecting up to 80% of all people with MS.[7,8] The Multiple Sclerosis Council for Clinical Practice Guidelines defines fatigue 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".[9] MS-related fatigue severely limits daily activities and restricts participation, i.e. performance of social roles.[10] It also has a major impact on quality of life.[11] Primary fatigue is a complex and multidimensional symptom, and while the exact etiology of fatigue is still unknown, current evidence suggests a role for multiple pathophysiological mechanisms. Proposed mechanisms of fatigue include primary causes such as cortical atrophy, demyelination and axonal loss, functional cortical reorganization (e.g. activation of neural circuits), neuroendocrine dysregulation (such as the hypothalamo-pituitary-adrenal (HPA) axis), as well as immune system dysfunction (e.g. the influence of pro-inflammatory cytokines).[12] In addition, secondary causes including musculoskeletal problems (pain, posture, gait, etc.), sleep problems, medication, and depression all have suggested associations with MS-related fatigue.[13] The subjectivity and multidimensionality of fatigue hampers consensus on

the definition of fatigue, a problem that is reflected in the many questionnaires that are used to measure fatigue.[13]

PHYSICAL BEHAVIOR

MS also affects a patient's physical behavior. Physical behavior is an umbrella term, covering diverse components of physical behavior. One of the most frequently studied components – including in MS research - is the amount of physical activity. In general, people with MS are known to be less physically active than healthy persons.[14] However, as the level of physical activity is not the only relevant aspect from a clinical perspective, treatments in MS rehabilitation often focus on multiple dimensions of physical behavior. In addition, a more detailed view of physical behavior may provide additional insights into the consequences of disease and the effects of treatment.[15,16] For example, data on the daily pattern of activities and the distribution of active and sedentary activities can be helpful when providing advice on the balance between activity and rest, and information on the duration and intensity at which activities are performed can be a good indicator for endurance training.

The relationship between fatigue and physical behavior appears simple from one perspective – such as when considering the definition of fatigue – but is at the same time complex. Although several studies have attempted to disentangle this relationship, evidence is conflicting and there is no consensus on the association between fatigue and physical behavior.[17-20] One of the explanations for this might be that studies to date have inadequately accounted for the multi-dimensionality of both constructs, which may have resulted in the masking of potential effects or associations between fatigue and physical behavior. By using more detailed outcomes when studying physical behavior, we may be able to obtain greater insight into the physical behavior patterns of fatigued people with MS and how these insights can aid in treatment.

ENERGY CONSERVATION MANAGEMENT (ECM)

Relieving the effects of severe fatigue on daily life is an important treatment goal in MS. Fatigue is often treated using a combination of treatments, either by pharmacological means with Amantadine or Modafinil, or by non-pharmacological treatments such as aerobic training (AT), cognitive behavioral therapy (CBT), energy conservation management (ECM), mindfulness, or multidisciplinary treatment.[21,22] Evidence suggests that non-pharmacological (or rehabilitation) treatments are more beneficial than pharmacological treatments in terms of reducing the impact or severity of fatigue.[23] In current practice, rehabilitation treatments are often combined in a multidisciplinary approach to the treatment of fatigue[24,25], which makes distinguishing the effect of each individual treatment difficult. Rietberg et al.[25] showed that multidisciplinary treatment and MS nurse consultations had no effect on fatigue and participation. However, numerous other studies have reported encouraging results regarding the effectiveness of rehabilitation treatments such as AT[26,27], CBT[28,29] and ECM[30-32] on MS-related fatigue, but the findings are heterogeneous and fatigue is not always the primary outcome.[27,33] Moreover, with respect to ECM, evidence for effectiveness is based on group programs rather than on individual treatment. As people with MS are usually treated individually, study of an individual format would be of added value.

TREFAMS-ACE

The Treating Fatigue in MS with Aerobic training, Cognitive Behavioral Therapy and Energy Conservation Management (TREFAMS-ACE) study aimed to fill some of the gaps outlined above. The objective of the study was to determine the effectiveness of the three rehabilitation treatments in reducing fatigue and improving societal participation in fatigued people with MS. Another objective (not part of this thesis) was to study the general biological mechanisms of MS-related fatigue. The program included three single-blinded RCTs, all with the same two-parallel-arms design, including the duration and frequency of treatment, the individual format, the moment of the measurements, the outcomes, the control condition, and the planned sample size. The only differences between the RCTs were the experimental treatment, some

specific treatment-related outcomes, and the locations where the studies took place. Patients were randomized to either the trial-specific treatment consisting of 12 therapist sessions over 4 months, or an information-only control condition provided by an experienced MS nurse and consisting of three consultations within 4 months. Participants were followed for 1 year.[34]

ECM is a rehabilitation treatment that is given by trained occupational therapists. It is based on the 6-week group course 'Managing fatigue' by Packer et al.[35], the 'Ergotherapierichtlijn Chronische Vermoeidheid ten gevolge van MS, CVA of de ziekte van Parkinson'[36] and energy management strategies.[37] The aim of ECM is to promote a positive attitude aimed at active decision-making and the optimum use of available energy to suit the unique needs of each individual. It is also intended to increase patients' use of energy-conserving strategies and to improve their confidence in their ability to manage fatigue. Motivational interviewing is generally applied as an important communication technique during the treatment sessions, with the goal of assisting patients in exploring and resolving their ambivalence to change. Managing fatigue requires an individual approach, as fatigue affects different people in different ways. Learning how to manage fatigue can be a slow process and the lifestyle changes involved require patience and perseverance. ECM is not expected to eliminate fatigue completely, but it is assumed that improved awareness, changes in behavior and the use of strategies and assistive devices will make it possible to manage fatigue and reduce the impact of fatigue on daily life.

AIMS AND OUTLINE OF THE PRESENT THESIS

The general aim of the studies presented in this thesis was to gain insight into the effectiveness of ECM treatment in reducing fatigue and improving societal participation in fatigued people with MS. Another important topic in this thesis is the detailed measurement and description of physical behavior in fatigued people with MS, and how different dimensions of physical behavior relate to dimensions of fatigue.

In chapter 2, we describe the design of the TREFAMS-ACE study protocol, including a thorough description of the content of ECM treatment. In Chapter 3, we

focus on how fatigued people with MS and age and gender matched healthy controls differ in terms of physical behavior. In chapter 4, we studied the associations between the multidimensional constructs 'fatigue' and 'physical behavior' in people with MS. Chapter 5 presents a systematic review and meta-analysis of energy management treatment. In Chapter 6, we describe the results of the randomized controlled trial of the effectiveness of ECM treatment on fatigue and participation. In Chapter 7, we investigate which determinants are related to the probability of being a responder to ECM treatment. Finally, in Chapter 8 the main findings are summarized and discussed.

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Chapter 2

The effectiveness of aerobic training, cognitive behavioral therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE program

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Trials. 2013;14(1):250

ABSTRACT

Background: TREFAMS is an acronym for TReating FAtigue in Multiple Sclerosis, while ACE refers to the rehabilitation treatment methods under study, that is, Aerobic training (AT), Cognitive behavioral therapy (CBT), and Energy conservation management (ECM). The TREFAMS-ACE research program consists of four studies and has two main objectives: (1) to assess the effectiveness of three different rehabilitation treatment strategies in reducing fatigue and improving societal participation in patients with MS; and (2) to study the neurobiological mechanisms of action that underlie treatment effects and MS-related fatigue in general.
Methods/Design: Ambulatory patients (*n* = 270) suffering from MS-related fatigue will be recruited to three single-blinded randomized clinical trials (RCTs). In each RCT, 90 patients will be randomly allocated to the trial-specific intervention or to a low-intensity intervention that is the same for all RCTs. This low-intensity intervention consists of three individual consultations with a specialized MS-nurse. The trial-specific interventions are AT, CBT, and ECM. These interventions consist of 12 individual therapist-supervised sessions with additional intervention-specific home exercises. The treatment period lasts 16 weeks. All RCTs have the same design and the same primary outcome measures: fatigue - measured with the Checklist Individual Strength, and participation - measured with the Impact on Participation and Autonomy questionnaire. Outcomes will be assessed 1 week prior to, and at 0, 8, 16, 26 and 52 weeks after randomization. The assessors will be blinded to allocation. Pro- and anti-inflammatory cytokines in serum, salivary cortisol, physical fitness, physical activity, coping, self-efficacy, illness cognitions and other determinants will be longitudinally measured in order to study the neurobiological mechanisms of action.
Discussion: The TREFAMS-ACE program is unique in its aim to assess the effectiveness of three rehabilitation treatments. The program will provide important insights regarding the most effective treatment for MS-related fatigue and the mechanisms that underlie treatment response. A major strength of the program is that the design involves three almost identical RCTs, enabling a close comparison of the treatment strategies and a strong overall meta-analysis. The results will also support clinical practice guidelines for the treatment of MS-related fatigue.

BACKGROUND

Multiple sclerosis (MS) is a neurodegenerative disease characterized by demyelinisation, axonal loss and inflammation of the central nervous system (CNS). Although the first description of MS dates back to the mid-19th century, in spite of this long history the etiology is still unknown and no curative treatment is available.[1] The disease is most probably caused by an interplay between immunological, environmental and genetic factors.[2,3] MS affects young and middle-aged people, with women twice as likely to be affected as men, and is known to cause a variety of clinical symptoms such as neurological impairments, fatigue, depression and pain.[2]

Fatigue is one of the most often reported and disabling symptoms in MS and restricts societal participation and performance in daily life at home, at work and in leisure activities.[4-6] Although the importance of fatigue as a disabling symptom of MS is widely acknowledged, there is no consensus on the definition of fatigue. DeLuca[7] defines fatigue as the reduction in performance with either prolonged or unusual exertion. Furthermore, fatigue can be sensory, motor, cognitive or subjective. The Multiple Sclerosis Council for Clinical Practice Guidelines[8] defines fatigue in MS 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. Chaudhuri and Behan[9] distinguish central fatigue from peripheral fatigue, and define central fatigue as the failure to initiate and/or sustain attentional tasks (mental or cognitive fatigue) and physical activities (physical fatigue). Peripheral fatigue is described as muscle fatigability due to disorders of muscle and neuromuscular junctions. The definitions of DeLuca[7], the MS Council for Clinical Practice Guidelines[8] and the concept of central fatigue outlined by Chaudhuri and Behan[9] concur with our view that MS-related fatigue is a multifaceted symptom. Fatigue in MS can also be subdivided into primary and secondary. Primary fatigue relates to specific pathophysiological mechanisms that are the direct consequence of the MS disease process. On the other hand, a number of factors, while not considered primary causes of MS-related fatigue, may be secondary contributors. These factors are not unique to MS, but are the result of symptoms of MS such as sleep problems due to spasm or urinary problems,

depression or physical deconditioning. Fatigue might also be a side effect of disease modifying drugs. Although the exact pathophysiological mechanism behind MS-related fatigue is unknown, it is most likely multifactorial. A number of pathophysiological mechanisms have been proposed including dysregulation of the immune system, dysfunction of the CNS, impaired nerve conduction, neuro-endocrine/neurotransmitter dysregulation, the involvement of the autonomic nervous system and energy depletion.[10,11] Available information can be combined in a biological model in which environmental stressors such as infections, immunization, trauma and life events influence genetically predisposed variables such as the sensitivity of the hypothalamic-pituitary-adrenal axis (HPA-axis), glucocorticoid receptors and the noradrenaline system.[9,12,13] Consequently, fatigue is triggered in susceptible individuals. In addition to disease-related, genetic and environmental factors, psychological mechanisms may play an important role in causing and sustaining MS-related fatigue.[12-14]

In clinical practice, MS-related fatigue is often treated with a combination of therapies, which makes it difficult to distinguish the effect of each treatment component. Due to the limitations of available evidence, current pharmacological approaches to treating MS-related fatigue are mainly based on preliminary studies and expert consensus. Amantadine, Modafinil and Aminopyridine are pharmacological strategies mainly used by neurologists.[15] Current evidence supporting the effectiveness of non-pharmacological treatments such as Aerobic Training (AT)[16-22], Cognitive Behavioral Therapy (CBT)[23] and Energy Conservation Management (ECM)[24-26] on MS-related fatigue is encouraging, but findings are heterogeneous and only a few studies have evaluated MS-related fatigue as the primary outcome measure.[27] Moreover, the methodological quality of non-pharmacological trials is often hampered by issues such as the complexity of the (multidisciplinary) treatment, the lack of adequate control groups, treatment blinding of patients and assessors, and the expertise of the involved therapists. These issues have resulted in an extension of the CONSORT statement for non-pharmacological trials.[28] Systematic reviews of exercise therapy and energy conservation management trials are underway or recently published.[29,30]

TREFAMS is an acronym for the TReating FAtigue in MS program, and ACE refers to the rehabilitation treatment methods under study, that is, Aerobic training, Cognitive behavioral therapy, and Energy conservation management. The program has two main objectives: (1) to assess the effectiveness of three different rehabilitation treatment strategies in reducing fatigue and in improving societal participation in individual MS patients; and (2) to study the biological mechanisms that underlie treatment effects and MS-related fatigue in general. The TREFAMS-ACE research program includes three randomized clinical trials (RCTs), and one explanatory study on the biological mechanisms of action that underlie treatment effects and MS-related fatigue in general.

A significant body of evidence now implicates both HPA-axis abnormalities and immune markers in the pathophysiology of MS-related fatigue. MS patients with fatigue exhibited a higher activity of the HPA-axis than patients without fatigue.[13,31] Earlier studies have examined a possible relationship between cytokines and fatigue in MS.[32,33] A study of pro-inflammatory (IFN-γ, TNF-α) and anti-inflammatory (IL-10) cytokine production in MS patients showed that patients with fatigue had a significantly higher production of IFN-γ and TNF-α than patients without fatigue. IL-10 production did not significantly differ between the two groups.[32] Flachenecker and Bihler[33] found a relationship between TNF-α mRNA expression and fatigue, but not between fatigue and IFN-γ or IL-10. In view of a relationship to inflammatory markers found in two independent studies and the higher HPA-axis reactivity in MS, we hypothesize that fatigue in patients with MS is stress-related and that it is caused by an inflammatory mechanism. In addition, we assume that the extent of imbalance between pro-inflammatory and anti-inflammatory cytokines is associated with the severity of fatigue.

AT is aimed at improving physical fitness and at reducing an inactive, deconditioning lifestyle. Improved physical fitness may lead to normalization of HPA-axis functioning[34], a reduction in pro-inflammatory cytokines and/or an increase in anti-inflammatory cytokines[35], leading to a reduction in MS-related fatigue. We hypothesize that an improved physical fitness due to AT will be accompanied by reduced fatigue and, as a consequence, improved societal participation.

CBT focuses on fatigue-maintaining cognitions and behavior, examples of which are insufficient coping with MS or MS-related fatigue, fear of disease progression, dysregulation of activity or sleep, low social support and focusing on fatigue. The general aim of CBT is to improve daily functioning and to decrease fatigue by changing fatigue-maintaining cognitions and behavior, within the limits of the MS.[36] We hypothesize that CBT may reduce perceived stressors (for example, environmental, psychological and biological), and consequently may lead to normalization of HPA-axis functioning and cytokine profiles.

ECM includes energy conservation strategies, ergonomic advice and coaching aimed at more efficient use of available energy. Energy conservation strategies have been defined as the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home and leisure activities in all relevant environments.[8] Packer et al.[37] were the first to develop an ECM treatment protocol for a 6-week group course. In a clinical trial, this group course proved to be effective in patients with MS, both immediately following the course and after 1 year.[24,25] The treatment goal of ECM is to promote a positive attitude aimed at stimulating active decision-making and the optimal use of available energy in relation to the unique needs of each individual. We hypothesize that ECM may lead to a reduction in environmental and psychological stressors and consequently to the normalization of biological stressors (HPA-axis functioning, cytokines), which may in turn lead to reduced fatigue and improved participation.

Accordingly, the following research questions have been formulated in the TREFAMS-ACE program:

1. What is the effectiveness of Aerobic Training on fatigue and participation? Can this effect be attributed to an increase in fitness parameters?
2. What is the effectiveness of CBT on participation and fatigue? Can this effect be explained by altered cognitions regarding fatigue?
3. What is the effectiveness of Energy Conservation Management advice on fatigue and participation? Can this effect be attributed to the implementation of ergonomic advice or adherence to altered time-schedules?

4. Which treatment strategy reduces fatigue and improves participation most effectively?
5. Does effective treatment lead to normalization of HPA-axis function, a reduction in pro-inflammatory cytokines or an increase in anti-inflammatory cytokines?

METHODS/DESIGN

Design

TREFAMS-ACE is a multicenter program that includes three single-blinded RCTs with repeated measurements in time, in which the effectiveness of AT, CBT and ECM on MS-related fatigue and participation in patients with MS will be investigated. All RCTs will use the same two-parallel-arms design (Figure 2.1), the only difference being the specific treatment applied.[28] Patients will be randomized to receive either a high-intensity trial-specific treatment, which consists of a series of 12 therapist-led sessions in 4 months, or a low-intensity treatment by an experienced MS-nurse, which consists of three consultations in 4 months. Participants will be followed for 1 year.

In addition to the three clinical trials, a fourth study has been defined that will focus on biological outcome measurement and understanding the biological mechanisms of action underlying MS-related fatigue.[38,39] This study should also help to improve our understanding of the biological mechanisms of the four treatments under study (see Figure 2.1).

The medical ethics committee of the VU University Medical Center approved the TREFAMS-ACE program. Additionally, local feasibility statements were obtained from each participating medical center.

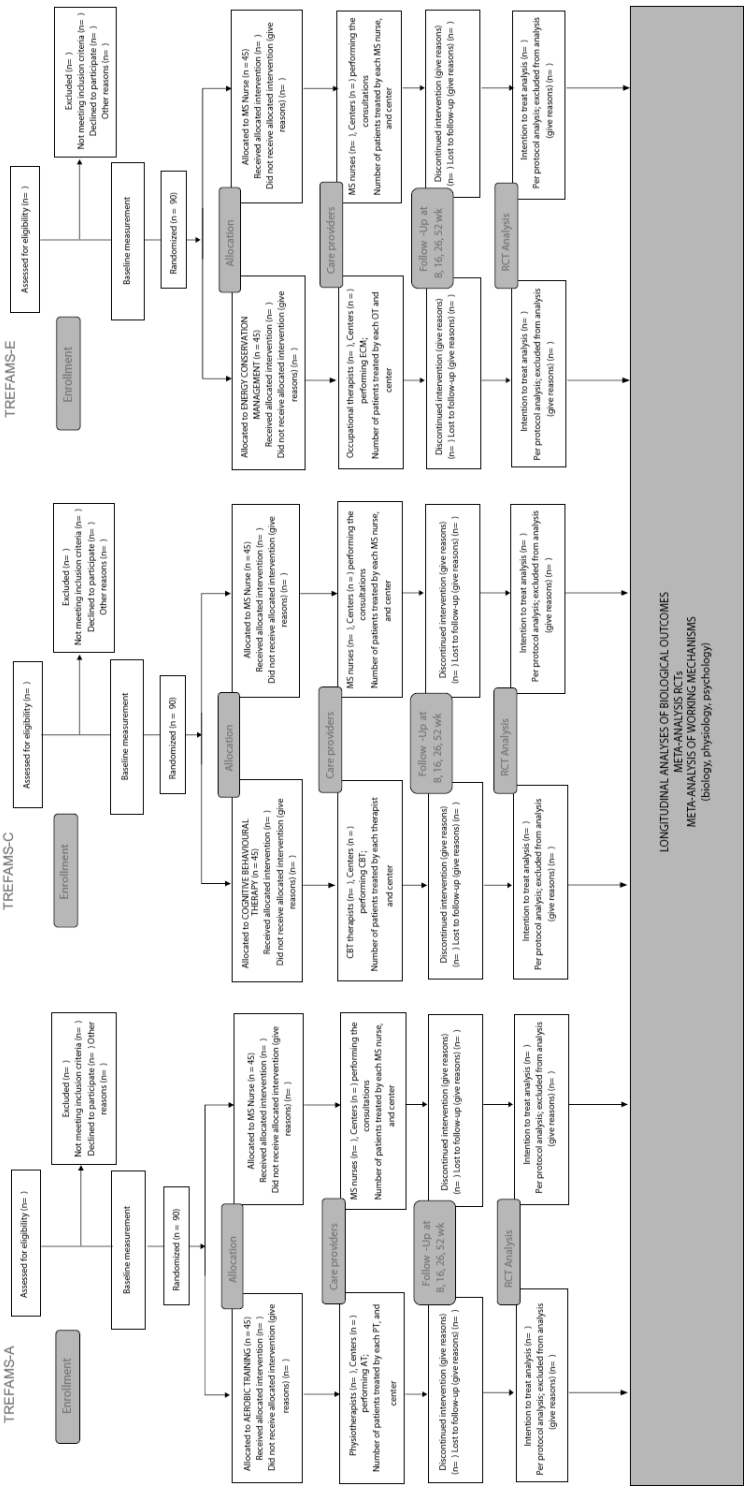

Figure 2.1. The design of the TREFAMS-ACE program.

Participants

The 270 adult patients (90 patients per RCT, and 45 per intervention group) required will have to fulfill the following inclusion criteria:(a) definitive diagnosis of MS; (b) severely fatigued; (c) ambulatory patients; (d) no evident signs of an exacerbation, or a corticosteroid treatment in the past 3 months; (e) no current infections; (f:) no anaemia; (g) a normal thyroid function. The exclusion criteria are: (a) depression; (b) primary sleep disorders; (c) severe co-morbidity; (d) current pregnancy or having given birth in the past 3 months; (e) pharmacological treatment for fatigue that was started in the past 3 months (for example, Amantadine, Modafinil, Ritalin, Pemoline); (f) non-pharmacological therapies for fatigue that took place in the past 3 months. See Table 2.1 for the operationalization of the inclusion and exclusion criteria.

Table 2.1. Inclusion and exclusion criteria TREFAMS-ACE trials

Inclusion criteria	Exclusion criteria
Definitive diagnosis of MS	Depression (HADS depression >11)
Severely fatigued (CIS20r-fatigue ≥35)	Primary sleep disorders
Aged between 18 and 70 years	Severe co-morbidity (CIRS item scores ≥3)
Ambulatory patients (an EDSS score ≤6)	Pharmacological treatment for fatigue ≤ 3 months
No evident signs of an exacerbation or a corticosteroid treatment ≤ 3 months	Current pregnancy or having given birth ≤ 3 months
No infections (normal leukocytes and C-reactive protein in blood)	Non-pharmacological therapies for fatigue ≤ 3 months
No anaemia (normal haemoglobin and haematocrit in blood)	
No thyroid dysfunction (normal thyroid stimulating hormone (TSH) in blood)	

Recruitment strategy

To avoid contamination of interventions, each RCT will be carried out at a different (university) medical center: the AT study will be conducted in the St Antonius Hospital, Nieuwegein, in collaboration with the University Medical Center Utrecht, the CBT study will be conducted at the VU University Medical Center in Amsterdam and at the University Medical Center Nijmegen (UMCN), and the ECM study will be conducted at the Erasmus MC-University Medical Center, Rotterdam, and Rehabilitation Center Leijpark in Tilburg. Patients will initially be recruited through the participating main

study centers. The Dutch patient organization Multiple Sclerosis Vereniging Nederland (MSVN) has been involved since the design phase of the research program, and has offered to help with recruitment. If the main study centers are not able to recruit sufficient participants, recruitment will also take place in hospitals and rehabilitation centers in the neighbourhood of the main study centers. MS-nurses, neurologists and residents in neurology and rehabilitation medicine will inform potentially eligible patients about the TREFAMS-ACE study. A neurologist or a rehabilitation physician will check the inclusion and exclusion criteria listed in Table 2.1 in the case of a potentially eligible patient. Subsequently, patients eligible for participation will be asked to complete an informed consent form before participating in the study.

Interventions

Aerobic training (AT)

AT aims to improve the participant's fitness and consists of 12 physiotherapist-led exercise sessions on a bicycle ergometer (Table 2.2). Moreover, participants will be provided with an identical bicycle ergometer at home on which they will be asked to perform additional training sessions, leading to the recommended three sessions per week. Each 30-min interval-type training session consists of six cycles of 5 min. Each cycle consists of 3 min of low intensity exercise, 1 min of moderate intensity exercise and 1 min of high intensity exercise. At the start of the treatment and after 8 weeks of training, current fitness levels will be assessed with a graded maximal exercise test to volitional exhaustion. Following the 8-week maximal exercise test, exercise intensities will be adjusted to meet the newly obtained fitness level. After completion of the supervised training program, patients will be encouraged to continue exercising and to remain physically active. Generally, physiological adaptations to aerobic training occur when: (1) the training intensity is at least 60% VO2max, and (2) the training is carried out at least three times a week.[40] The current treatment protocol addresses both factors.

Table 2.2. AT program

45-min session of bicycle ergometer training	Details
Warming-up	• 5 min at 25% to 40% Wmax
Aerobic Training	• Six cycles of 5 min: 3 min 40% Wmax, 1 min 60% Wmax and 1 min 80% Wmax • Cadence: 60-80 revolutions per min (rpm). • Heart rate should not exceed 80% of the predicted maximal heart rate • Training intensity will be updated once during the training, according to the 8-week maximal exercise test • The work rate can be adjusted, based on the clinical expertise of the supervising physiotherapist
Cooling down	10 min • All training sessions and adjustments to the work rate are recorded in the training log
Home exercises	Participants will be provided with an identical bicycle ergometer at home so that they can perform additional training sessions, leading to the recommended three sessions per week

Cognitive behavioral therapy (CBT)

CBT is directed at behaviors or cognitions that perpetuate fatigue. Examples are dysfunctional cognitions with respect to MS, fatigue or pain, persistent focusing on symptoms, deregulation of physical and social activities and a lack of social support.[41,42] It is thought that fatigue will decrease if these perpetuating factors are identified by the patient him/herself and changed. CBT consists of 12 sessions over a 4-month period. Ten different modules have been developed to target specific fatigue maintaining factors[43] (Table 2.3). CBT will be customized to each individual patient using indicator criteria for each module that are based on cutoff scores on questionnaires and on a diagnostic interview (Table 2.3). In the final treatment sessions, special attention will be paid to integrating the skills obtained into daily life and how to handle behavioral relapses. The effectiveness of this theory-based CBT strategy has already been investigated in several other patient populations and healthcare settings.[44-48]

Table 2.3. CBT modules

Module	Questionnaires and instruments
1. Formulating goals This module applies to all participants. Concrete and obtainable treatment goals are formulated during treatment. Goals comprise activities that the participant wishes to do when the fatigue has decreased or disappeared.	For all participants
2. Sleep/wake rhythm The importance of a regular sleep/wake rhythm and good sleep hygiene is explained to the patient. Furthermore, the sleep/wake rhythm of will be discussed and suggestions for improvement given.	SIP sleep and rest ≥60[49]
3. Beliefs regarding MS Participants will receive realistic information about MS. Dysfunctional cognitions about MS or the future are identified and challenged, and the participant is supported in forming more functional cognitions. Problems regarding acceptance of the disease are also addressed.	Impact of Event Scale (IES) ≥20[50] Pictorial Representation of Illness Measure (PRISM): Burden of MS heavier than burden of fatigue[51] Illness Cognition Questionnaire (ICQ), concentration ≤12[52] Cognitive Behavioral Responses to Symptoms Questionnaire (CBRSQ)[53,54]: Resting behavior >14,3; All-or-nothing behavior >12.9; Symptom focusing > 15.5; Catastrophising >12.6; Embarrassment >16.4; Damage >20.5; Fear avoidance >15.3 HADS[55]: Depression >9, Anxiety >9 Fear of disease Progression Questionnaire (FoP-Q), ≥4 on at least 75% of the 34 Anxiety items[56,57]
4. Beliefs regarding fatigue Participants are supported in changing dysfunctional views about fatigue such as a lack of self-efficacy, catastrophising fatigue and somatic attributions.	SES-28 fatigue ≤19 Jacobsen Fatigue Catastrophising Scale ≥16[58,59]
5. Focusing on fatigue The concept of persistent focusing on fatigue and its consequences are discussed.	Illness Management Questionnaire (IMQ), focusing on symptoms ≥4[60]

Participants practice redirecting their attention from fatigue to activities and other sensations. Talking about fatigue is discouraged.	
6. Regulation of physical activity Depending on their level of activity, participants learn how to divide their activities, followed by a systematic increase in regular physical activity to obtain predefined goals.	Activity Interview and Activity Monitor
7. Regulation of social activity Patients are empowered to expand social activities and deal with problems that can arise during social interaction.	SIP social interaction ≥100[49] SF36 social functioning ≤65[61]
8. Regulation of mental activity Participants are supported with regards to practicing and expanding mental activities such as working on the computer or reading. Participants learn how to deal with possible cognitive deficits such as concentration or memory problems.	CIS20r concentration ≥18[62]
9. Role of the environment Unrealistic expectations of the environment are addressed and more realistic expectations are promoted. Participants learn how to express their limits and boundaries to 'significant others'.	Social Support List (SSL)[63] Discrepancies ≥50; Negative interactions ≥14
10. Handling pain Dysfunctional cognitions about pain are challenged and replaced by more functional cognitions.	SF36 bodily pain ≤60[61] Pain Catastrophising Scale (PCS) ≥16[64]

Energy conservation management (ECM)

The ECM treatment protocol is based on a group course for energy conservation developed by Packer et al.[37] The TREFAMS intervention, called Individual ECM treatment (IECM), is individualized and consists of 12 45-min sessions over 4 months, given by a trained occupational therapist. For the IECM, the original content of the Packer et al. group program will be divided up to fit the 4-month treatment period. Attention will also be paid to individual learning and approaching styles to assimilate the program contents. Motivational interviewing will be used as a communication technique to assist patients in exploring and resolving ambivalence to change. Table

2.4 shows the content of the IECM. A variety of teaching methods will be used, including providing information, discussions, long-term and short-term goal setting, practice activities and homework activities, to assist the patient's integration of energy conservation principles into the performance of everyday tasks. The aim of ECM is not so much to correct the underlying mechanisms of fatigue, nor to accept that the solution is to decrease activity levels or reduce the breadth and extent of activities. Instead, the aim is to promote a positive attitude aimed at active decision-making and the optimum use of the available energy to fit the unique needs of each individual. ECM is also intended to reduce the impact and severity of fatigue, to increase patients' use of energy-conserving strategies and to improve their confidence in their ability to manage fatigue.[37] Additional to Table 2.4, Appendix 2 of this thesis include an overview of the ECM intervention.

Table 2.4. Individual Energy Conservation Management

Sessions	Content of the sessions
Introduction session	• Getting to know the patient, identification of problems in daily life with help of the COPM, impact of fatigue on daily life • Hand out workbook IECM, activity list per day/week to give insight in load and loadability of the patient, and learning style assessment
Analysis of the problems	• Discuss activity/participation problems, outcomes of load and loadability from the activity lists • Analysis of problems, determine questions of help, and the learning and approaching style • Formulate the problems and treatment goals
Treatment sessions	*a. Information about fatigue* • types, causes and factors influencing fatigue • banking (saving) and budgeting (deciding how to spend) energy *b. Importance of rest* • how fatigue can influence your daily life • rest as a way of relieving fatigue *c. Balancing your schedule* • components of a balanced lifestyle • how to balance (light and heavy) activities • planning a weekly schedule *d. Communication* • expressing needs to others • breaking down negative attitudes about fatigue and rest *e. Priorities and standards* • breaking down activities in order to simplify them as much as possible • budgeting energy, making decisions about priorities and standards *f. How to do activities* *g. Ergonomics, body positions and assistive devices* • organization of needed environments (work, home) to promote good body mechanics • organization of needed environments to save energy • technology and equipment that can save energy • structure of body/biomechanics • how to use body properly/ergonomics
Evaluation session	

MS-nurse consultations

The low-intensity treatment by experienced MS-nurses consists of three consultations of 45 min over a 4-month period. The content of the consultations led by the MS-nurse will cover two important aspects to control for: (1) reliable information on MS-related fatigue; and (2) attention from an experienced MS professional in order to reassure the patient that his/her concerns or questions will be taken seriously.[65]

In the first consultation, the patient receives a booklet containing general information about MS-related fatigue and factors that may influence fatigue. This booklet was designed by the TREFAMS-ACE research team to provide patients with standardized information about fatigue, without adding details regarding specific treatments so as to avoid overlap with the trial-specific interventions. In the remaining two consultations, participants will have the opportunity to discuss their personal experiences in coping with fatigue, ask questions about the booklet and discuss other fatigue-related issues. The consultations with the MS-nurses should not be considered as 'usual care' because, due to the TREFAMS-ACE study design, the MS-nurses are restricted in referring patients to a psychologist, physiotherapist or other healthcare professional within the hospital. In the Netherlands, timely referral is an important aspect of normal MS-nursing practice.

Therapist training

All involved therapists were selected based on their experience with the treatment and with treating MS patients. Furthermore, all received training that was focused on one of the four treatment protocols used in the TREFAMS-ACE study.

Physiotherapists experienced in cardio-respiratory training were introduced to the exercise protocol, the use of the bicycle ergometer, study materials and measurements in TREFAMS-AT.

The psychologists involved in the TREFAMS-CBT study all received an additional 4-day CBT training course at the Expert Center Chronic Fatigue of UMCN. The training course consisted of an introduction to the protocol, training in the content of each treatment module and how to determine which modules are indicated for a specific participant. The skills needed to change patient cognition and

behaviors were practiced during role-playing, with the help of simulated patients. To ensure the quality of the CBT, weekly peer conversations between therapists, in which experiences with the TREFAMS-CBT participants will be shared, are part of the therapist training.

Occupational therapists already familiar with energy conservation strategies and the Packer group course 'Managing Fatigue' received a 1-day training course in the implementation of the individual Energy Management Course (IECM). This course was given by the researcher, together with an expert therapist in energy conservation management. Training consisted of a thorough explanation of the content of the 12 sessions and how sessions can be individually tailored. In addition, occupational therapists not yet qualified in applying Motivational Interviewing had to attend a 3-day Motivational Interviewing course.

All MS-nurses involved in one of the RCTs participated in a 1-day training course. In this course the MS-nurses shared their approach to taking a fatigue-related nursing history, they were instructed as to how to provide relevant information on MS-related fatigue without giving concrete therapeutic advice, and they were informed of the restrictions concerning the referral of patients to other healthcare professionals within the hospital (MS team members). These newly-learned skills were practiced using role-playing.

Outcome measures

Outcome measures consist of validated self-reported questionnaires, blood and saliva, activity monitoring and physical fitness tests. All primary and secondary outcomes will be assessed 1 week prior to, and at 0, 8, 16, 26 and 52 weeks after randomization. The self-reported questionnaires will be offered to patients via the internet or on paper, and will be completed at home. Within each self-reported questionnaire, the sequence of questions will be randomized between measurement occasions. The drawing of blood samples (according to the study protocol), physical fitness tests and assessor-based interviews will take place at the outpatient clinic of the participating centers. Saliva sampling will take place at home and includes several time-points per day.

Primary outcome measures

1. Fatigue will be measured with the Checklist Individual Strength (CIS20r), domain fatigue.[62,66] This multidimensional questionnaire consists of 20 items, divided into four dimensions of fatigue and related behavioral aspects, including: (a) the subjective experience of fatigue (8 items); (b) reduction in motivation (4 items); (c) reduction of physical activity (3 items); and (d) reduction in concentration (5 items). The CIS20r focuses on fatigue in the past 2 weeks. Each item is answered using a 7-point scale. The CIS20r fatigue score is a sum score that can vary between 8 and 56 points. Recently, the reproducibility, distribution-based responsiveness and concurrent validity of the CIS20r were investigated in patients with MS[67]. Despite good test-retest reliability, a smallest detectable change of 11.8 points was found, leading to the recommendation to monitor trial participants repeatedly over time using a set of complementary fatigue scales.[67] A systematic review of the measurement properties of 31 fatigue questionnaires confirms this recommendation.[68]

2. Societal participation will be assessed with the Impact on Participation and Autonomy questionnaire (IPA).[69] The IPA questionnaire was developed to assess the severity of restrictions in participation and individual needs related to participation and autonomy. The IPA is a generic questionnaire that addresses:(a) perceived participation, reflected in 31 items in five domains, that is, autonomy indoors, autonomy outdoors, family role, social relations, work and education; and (b) the experience of problems related to every aspect of participation, reflected in eight problem experience scores.[69] An anchor-based responsiveness study in a heterogeneous outpatient rehabilitation population showed that the IPA was moderately able to detect within-patient improvement over time.[69] No studies on the responsiveness and minimal important change of the IPA in patients with MS are yet available.[70]

Secondary outcome measures

MS-related fatigue is a multifaceted symptom with various types of expression. Therefore, several other fatigue measures are also included. The impact of fatigue will be measured with the Modified Fatigue Impact Scale (MFIS) and the Fatigue Severity

Scale (FSS).[71,72] The MFIS assesses the effects of fatigue in terms of physical, cognitive and psychosocial functioning. The FSS evaluates the severity and impact of fatigue in patients with MS. A patient-reported diurnal course of fatigue during 1 day will be assessed using short message services (SMS) technology. Moreover, the Rehabilitation Activities Profile (RAP) and the Medical Outcome Study Short Form 36 (SF36) will be used to measure daily functioning and participation.[61,73]

Determinants

These include descriptive variables, mediators (that is, intervening causal variables), confounding or effect-modifying factors that have been shown to be related to the treatments, and fatigue and participation in MS patients.[53,74] In multifactorial, complex situations such variables can act in different ways in different situations or different analyses and will therefore be further specified in forthcoming articles.

Demographic and disease characteristics

Demographic information includes age, gender, ethnicity, living situation, level of education, work and income. The disease-related variables that will be assessed include the type of MS, neurological symptoms, the Expanded Disability Status Scale (EDSS), the number of exacerbations in the year prior to inclusion, the use of disease modifying drugs and other medication, co-morbidities and healthcare use. The EDSS and the Cumulative Illness Rating Scale (CIRS) will be assessed by a physician at baseline and after 52 weeks.[75-77] Cognitive deficits will be assessed at baseline by the Mini Mental State Examination.[78]

Physical activity and physical fitness

The amount of physical activity and frequency of movement will be registered by means of a tri-axial activity monitor (ActiGraph GT3X+) that will be worn for 7 days. The Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) is a self-reported questionnaire that assesses physical activity over the preceding 7 days. The PASIPD assesses physical activity in three domains: recreation, household and occupation activities.[79,80]

In a subgroup of participants, cardio-respiratory fitness will be assessed by means of a maximum capacity test (VO2max test). Participants will perform this test on an electromagnetic bicycle ergometer. Work rate will be progressively increased by 25 + 10 W/min (women) or 25 + 15 W/min (men) until volitional exhaustion, rpm <45 or for safety reasons. In addition, patients will walk as far as possible during a 2-min walk test (2MWT).

Cognitive and behavioral factors

Coping style is measured with the Coping Inventory for Stressful Situations (CISS-21).[81,82] Three main coping styles can be distinguished: task-oriented coping, emotion-oriented coping and avoidance coping. The General Self Efficacy Scale will be used to assess optimistic self-beliefs for coping with a variety of difficult life demands.[83] Possible mood disorders will be assessed with the Hospital Anxiety and Depression Scale (HADS).[55] The HADS consists of two subscales: depression and anxiety. The tendency to fall asleep during daytime is measured with the Epsworth Sleepiness Scale.[84] Perceptions of fatigue will be measured with the Brief Illness Perception Questionnaire (B-FPQ), which assesses cognitive and emotional representations of fatigue.[53] The B-FPQ is an adaptation of the Brief Illness Perception Questionnaire (B-IPQ), which measures illness perceptions.[85] Fear of progression of MS is measured with the Fear of disease Progression Questionnaire (FoP-Q).[56,57] Five factors are distinguished: affective reactions, partnership/family, work, loss of autonomy and coping. The Illness Cognitions Questionnaire (ICQ) measures three different generic illness cognitions: helplessness, acceptance and disease benefits.[52] The Social Support List is used to measure the level of social interactions, discrepancies and negative interactions.[63]

Biological markers

An important part of the TREFAMS research program concerns the integration and longitudinal study of clinical parameters and biological parameters.[38] HPA-axis functioning will be assessed through the collection and analysis of salivary cortisol. To determine the Cortisol Awakening Response (CAR), saliva will be collected

immediately after awakening and after respectively 30 min, 45 min and 60 min post-awakening. Following the fifth sample at 22:00 the participant takes 0.5 mg dexamethasone (low dose dexamethasone suppression test) and saliva is again collected the next morning, immediately after awakening.

Blood will be drawn to determine levels and activity of pro-and anti-inflammatory cytokines.[39,86] Blood and saliva will be collected at the same fixed time-points as for the other outcome measures.

Energy saving strategies

To assess which strategies the participants in all three RCTs use to influence their fatigue, we developed the Fatigue Strategies Questionnaire (FSQ). This questionnaire is based on the Energy Conservation Strategies Survey (ECSS)[87] to which we have added a number of strategies on physical activity, cognition and behavior. Participants will be asked about the strategies they use and how effective these strategies are. To facilitate the meta-analysis of ECM treatments, the participants of the TREFAMS-ECM trial will fill in the original ECSS at 16 weeks.[87]

Sample size

Sample size was calculated based on the CIS20r subscale fatigue. In order to detect a clinically relevant difference of 8 points on the CIS20r subscale fatigue between the study groups in an MS population, with a SD of 12.7, a power of 80%, an alpha of 0.05 and an attrition rate of 20%, 45 patients per group will be needed.[47,88] This amounts to 90 patients for each trial and 270 patients for the entire TREFAMS-ACE program. Sample size calculation was not adjusted for longitudinal data analyses with repeated measures[89], or for an eventual clustering by care providers or participating centers. Balancing these two factors, we expect that the power of our study will be >80%.

Randomization

Patients eligible for participation in the study will be randomized to either the trial-specific treatment or the consultations with the MS-nurse after the baseline

measurements have been completed. The randomization scheme is computer-generated with random variable block sizes. An independent investigator within each main study center will need to login to the web-based randomization facility to carry out the randomization, and will inform the patient and the therapist as to the treatment allocation.

Blinding

The assessors responsible for physical fitness tests and interviewer-based measures will be told in which week patients need to be measured but will not know which treatment patients receive. Patients will be instructed not to disclose which treatment they are receiving. Furthermore, the analyses of blood and salivary in the clinical chemistry laboratory, and the statistical analyses of the between-group differences, will be performed by research staff blinded to the treatment allocation of the participants.

Serious adverse events

Based on previous research, AT, CBT, ECM and consulting the MS-nurse are expected to be safe treatment methods in patients with MS.[16-21,23-26,90,91] However, all therapists and assessors involved in the studies will be instructed to report all serious adverse events (SAE) to the principal investigators, after which they will be reported to the Medical Ethical Committee. An SAE is any untoward medical occurrence in a participant that is not necessarily associated with the treatment, but that is lethal, and/or threatens the life of the participant, and/or requires hospitalization or prolongation of existing hospitalization, and/or causes persistent or significant disability or incapacity.

Treatment fidelity and compliance

Data regarding treatment compliance will be subtracted from the administrative hospital databases and therapist notes. Participants will receive an overview of all appointments prior to the first session. If participants cancel or do not attend a session, this session will be rescheduled within the 16-week time frame. Because

treatment consists of 12 therapist-led sessions in 16 weeks, some rescheduling is possible. Sessions will not be rescheduled if that means that the 16-week time window will be extended by >1 week.

Statistical analyses of the RCTs and meta-analyses

The primary analyses of each separate RCT will be based on the intention-to-treat principle using longitudinal data-analysis techniques, such as Generalized Estimating Equations or Hierarchical Linear Mixed Models. To detect the direct effects of the treatments, longitudinal models will be constructed to analyze the differences between the intervention groups regarding the course of within-group changes during the 1-year follow-up period. Furthermore, a meta-analysis of all TREFAMS-ACE data will be conducted to investigate the relative effects of each treatment strategy. In addition, statistical mediation analyses will be used to examine the working mechanisms of the interventions related to, among others, changes in HPA-axis functioning and changes in pro- and anti-inflammatory cytokine levels.

DISCUSSION

The TREFAMS-ACE study will investigate the effectiveness of three different non-invasive, non-pharmacological rehabilitation treatment strategies aimed at reducing fatigue and improving societal participation in patients with MS. Furthermore, the mechanisms that underlie treatment effects will be studied. This research program is expected to produce four related PhD-theses. By publication of the design, we wish to be fully transparent as to the quality of the TREFAMS-ACE program and thus aim to avoid most of the methodological weaknesses reported in current Cochrane reviews in the field of rehabilitation.[92-95]

The TREFAMS-ACE study has a number of important strengths, the first of which is a design including three almost identical RCTs on the effectiveness of AT, CBT and ECM, respectively. Our study may provide greater insight into the exact pathophysiological mechanism(s) behind MS-related fatigue and the pathways

through which AT, CBT and ECM exert their effect. Because the same design and the same outcome measures are used, at the end of the TREFAMS study an overall analysis can be performed that allows factors to be controlled for that might otherwise cause heterogeneity in a regular meta-analysis of independent RCTs. This will enable a close comparison of the treatment strategies within each trial as well as a strong overall meta-analysis. Second, the large cohort of fatigued MS patients that will be formed will enable us to study the biological mechanisms that explain fatigue and the mechanisms underlying the possible effectiveness of the treatment strategies. Recently, Fischer et al.[38] formulated four criteria for biomarker selection in clinical trials: the biomarker has to be linked to the clinical outcome, that is, MS-related fatigue in our study, and the biomarker should be modifiable in the desired direction. Furthermore, the biomarker should be validly and reliably measured, and finally, the duration of the clinical trial should be sufficiently long, with an appropriate number of assessments, to allow the biological and clinical outcome parameters to change. All four criteria will be fulfilled by the TREFAMS-ACE program.[86,96] Third, due to the follow-up period of 1 year, we will be able to investigate whether patients implement the newly-learned skills in daily life and whether the effect of treatment will be maintained over a longer period of time. Fourth, the baseline data of the three RCTs can be pooled, allowing several interesting cross-sectional analyses. Fifth, there is valuable support from the Dutch patient organization Multiple Sclerosis Vereniging Nederland (MSVN). The participation of patient organizations in health research is important when setting research agendas, during the design phase and during the study period, but it will also enhance practical relevance during later dissemination and implementation of study results.[97] Finally, a strong network of academic rehabilitation departments and MS centers will be formed, as the four study teams work together closely. This will generate high quality knowledge on the treatment of MS-related fatigue and will also promote dissemination and sharing of expertise.

Some specific issues that apply to non-pharmacological trials included in the TREFAMS-ACE program need to be discussed.[28] Regarding the blinding procedure, everyone involved in an RCT should ideally be blinded but this is not always feasible, as is often the case in RCTs evaluating rehabilitation interventions.[28,98,99] Although

patients are not blinded and the two primary outcome measures are both patient-reported, the assessment of the physical fitness parameters, the analyses of blood and salivary in the clinical chemistry laboratory and the statistical analyses of the between-group differences will all be performed by research staff blinded to the treatment allocation of the participants.

With respect to the complexity of the treatments, we decided to offer patients individual and mono-disciplinary interventions, and no multidisciplinary group intervention[100-102]. Two of the four active treatment intervention programs, that is, CBT and ECM, have long been available and further improved in recent years.[30] The AT program is largely based on the general principles of exercise physiology.[40] The scientific underpinnings of the valuable work of specialized MS-nurses is probably the weakest aspect.

Contamination of treatment interventions is another specific issue that might complicate the interpretation of the study results. To avoid contamination via caregivers in the same study centers, we designed three independent RCTs. Moreover, to avoid overlap between the CBT and the ECM interventions, in the developmental phase of the individual ECM protocol cognitive behavioral aspects were further specified and should now totally focus on managing energy. To prevent contamination caused by participants, all participants are requested not to start with co-interventions for fatigue during the treatment period of the study. Because of the intensity of the treatment, we expect that simultaneous interventions aimed at reducing fatigue will probably only occur in a small number of patients. Other co-interventions, for example, disease modifying drugs, are monitored throughout the study at every measurement.

Finally, the inclusion of participants may be slower than anticipated. In theory, a large number of MS patients are fatigued but it may be difficult to awaken the interest of every fatigued MS patient. To enhance participation, we arranged a number of patient-friendly measures, such as the setting-up of several study centers, travel allowance and the scheduling of appointments. In order to recruit a large group of MS patients, we enlarged our network by involving regional patient associations. In

this respect, the support of and close cooperation with the Dutch patient organization MSVN since the design phase of the research program has been very important.

The TREFAMS-ACE study will provide insight into the effectiveness of four mono-disciplinary rehabilitation treatment methods for MS-related fatigue in individual patients. The primary aim of these treatment methods is to reduce fatigue and to improve societal participation. Furthermore, to enhance our understanding of how these rehabilitation treatments work, a study on biological outcome measures has been added. To improve current practice, tailored and more focused rehabilitation programs based on the most effective treatment may represent - with a clearer picture of mechanisms of action - a first step in understanding which types of patients may better respond to certain therapies. Therefore, the TREFAMS-ACE results will also be added to systematic reviews[29,30] and used to develop and update clinical practice guidelines for the treatment of MS-related fatigue.[8,103]

Trial registrations: Current Controlled Trials ISRCTN69520623 (AT), ISRCTN58583714 (CBT), and ISRCTN82353628 (ECM)

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Chapter 3

Is physical behavior affected in fatigued persons with multiple sclerosis?

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ABSTRACT

Objective: To study physical behavior in detail in fatigued persons with multiple sclerosis (MS).
Design: case-control explorative study.
Setting: Outpatient rehabilitation department and participants' daily environment.
Participants: Fatigued persons with MS (n=23) were selected from a randomized controlled trial. Cases were matched by age and sex to healthy, nonfatigued controls (n=23). Eligible persons with MS were severely fatigued (Checklist Individual Strength fatigue domain mean score 43.2±6.6) and ambulatory (Expanded Disability Status Scale mean score, 2.5±1.5).
Interventions: Not applicable.
Main Outcome Measures: Measurements were performed using an accelerometer over 7 days. Outcomes included the following: amount of physical activity expressed in counts per day, counts per minute (CPM), and counts per day period (morning, afternoon, evening); duration of activity intensity categories (sedentary, light physical activity, moderate-to-vigorous physical activity [MVPA]); and distribution of MVPA and sedentary periods over the day.
Results: Persons with MS had fewer counts per day (mean difference, -156×10^3, 95% confidence interval [CI], -273 ×10^3 to -39 ×10^3; *P*=*.010)*, had fewer CPM (mean difference, -135, 95% CI, -256 to -14; *P*=*.030*), and were less physically active in the morning (mean difference, -200; 95% CI, -389 to -11; *P*=*.039*) and evening (mean difference, -175; 95% CI, -336 to -14; *P*=*.034*) than controls. Persons with MS spent a higher percentage of their time sedentary (mean difference, 5.6; 95% CI, 0.1 to 11.1; *P*=*.045*) and spent less time at the higher MVPA intensity (mean difference, -2.4; 95% CI, -4.7 to -0.09; *P*=*.042*). They had fewer MVPA periods (mean difference, -29; 95% CI, -56.2 to -2.6; *P*=*.032*) and a different distribution of sedentary (mean difference, .033; 95% CI, .002 to .064; *P*=*.039*) and MVPA periods (mean difference, -0.08; 95% CI, -0.15 to -0.01; *P*=*.023*).
Conclusions: Detailed analyses of physical behavior showed that ambulatory fatigued persons with MS do differ from healthy controls not only in physical activity level, but also in other physical behavior dimensions (e.g., day patterns, intensity and distribution).

INTRODUCTION

Multiple Sclerosis (MS) is a chronic progressive neurological disease leading to limitations in activities and participation.[1-3] Limitations may result from two prevalent consequences of MS: fatigue and changes to patient's posture, patient's movement, patient's activities of daily life (physical behavior).[4] Fatigue affects 80% of persons with MS,[5] and studies show that MS-related fatigue severely limits daily activities and restricts participation.[6,7]

Thus far, the effects of MS and MS-related fatigue on physical behavior (PB) have been studied primarily from the perspective of physical activity levels (e.g., total number of activity counts, number of steps). Literature in this area shows that persons with MS are generally less physically active than healthy persons.[8-12] However, it is important to recognize that physical activity level is just one dimension of PB. For example, MS rehabilitation treatments (e.g., energy conservation management)[13] do not usually focus on total amount of activity, but on issues such as balancing day patterns, frequency and intensity of activities, and distribution of activity and rest. Therefore, it is questionable whether physical activity level, as determined by total activity counts, is the most clinically relevant indicator of PB in MS.

The relevance of other PB dimensions is increasingly recognized,[4] and technological developments increasingly allow objective measurement of these dimensions. Studies of other patient populations show that more detailed information about PB provides additional insight into the consequences of disease and treatment effects. For example, Evering et al[14] showed that patients with chronic fatigue syndrome differed in afternoon and evening day patterns compared with healthy people, but they did not differ over the course of the whole day. Other studies show that similar total activity counts may result from prolonged periods of low-intensity activity or short periods of high-intensity activity.[14-16] Similarly, studies show that patients (e.g., those with Parkinson disease or chronic fatigue syndrome) differ from healthy people in the distribution of sedentary periods[17,18]; however, they do not differ in the total amount of time spent sedentary.

For persons with MS, research providing detailed analyses of PB is scarce.

Rietberg et al,[19] who studied the physical activity day patterns for specific postures and movements over a 24-hour period, found that persons with MS had lower physical activity levels in the morning which persisted throughout the day. Klaren et al[20] found that persons with MS spent less time in moderate and vigorous physical activity compared with healthy controls. Neither study included fatigued persons with MS, described >1 dimension of PB, or based their results on long measurement periods. Therefore, the research question of the present explorative study is as follows: Do fatigued persons with MS show different physical behavior compared with matched controls on detailed outcomes (e.g., day patterns, intensity of activities, distribution of activities)?

METHODS

Participants

This case-control study is part of the multicenter research program 'Treating Fatigue in MS with Aerobic Training, Cognitive Behavioral Therapy and Energy Conservation Management' (TREFAMS-ACE).[21] The research program evaluates the effectiveness of rehabilitation treatments on fatigue and participation in persons with MS. The TREFAMS-ACE inclusion criteria are as follows: definite diagnosis of MS; severe fatigue as indicated by a score of ≥35 on the fatigue domain of the Checklist Individual Strength (CIS20r); ambulatory status (i.e., Expanded Disability Status Scale (EDSS) score ≤6; no diagnosis of depression (i.e., Hospital Anxiety and Depression Scale (HADS) score <11; no initiation or change to pharmacologic treatment for fatigue during the previous 3 months; and aged 18 to 70 years.

The present study was based on available accelerometer baseline data (n=67) from the TREFAMS Energy Conservation Management RCT Study. For the present study, an additional inclusion criterion was that baseline measurements were performed during the same time period (April – September) in which the control subjects were planned to be measured. This criterion resulted in a subpopulation of 29 persons with MS who were eligible for inclusion. Each person with MS in this

subpopulation was asked to recruit a maximum of 5 control subjects of similar age (±5y) and sex from their social environment who were potentially willing to participate. The recruited control subjects were contacted and informed of their selection for inclusion by a research student. The control subjects completed a form with demographic and personal characteristics and the CIS20R and HADS questionnaires. Control subjects were eligible if they scored CIS20R fatigue <35, HADS <11, and had no mobility limitations that affected their physical activity. Included control subjects were matched for age and sex with the persons with MS. Demographic and personal characteristics were recorded for both groups.

The protocol for this study was approved by the medical ethics committee of the VU University Medical Center, Amsterdam, The Netherlands. All participants provided written informed consent.

Measurements

PB assessment was performed using 3-dimensional accelerometry (ActiGraph GT3X+ model[a]; 4.6×3.3×1.5cm; 19g). This device has demonstrated validity and reliability in measuring PB in persons with MS and healthy adults.[22,23] Participants wore the accelerometer on an elastic belt that was positioned at the waist. To ensure that the accelerometer was worn correctly, participants were shown how to wear the accelerometer and were given detailed written instructions. All participants wore the activity monitor during waking hours for seven days, except while showering or swimming. The measurements were performed in the daily environment of the participants; participants were instructed to behave naturally. Accelerometer signals were sampled with 30Hz and analyzed with Actilife version 6.6.2 software.[a] For all 3 axes, activity counts were calculated for 10-second epochs. From this, the vector magnitude was calculated. In the Actilife software, the low-frequency extension option was enabled. A 180-minute (or longer) period of continuous zero counts was defined as a nonwear period and was excluded from further analyses. Days with at least 660 minutes of wear time were considered valid. For data to be included in the analysis, at least 5 valid measurement days were required. Additional calculations were performed using Microsoft Excel and MATLAB.

Outcome measures

PB outcomes were analyzed per individual. They were calculated as group means for valid days of the total measurement period and were averaged for the number of days. To describe day patterns, we only included weekdays because including weekend days may confound the day pattern data.[24]

For the dimensions of PB, the first dimension included length of the day: the wear time per day (min). The second dimensions was the amount of physical activity, including total counts per day (CPD) and counts per minute (CPM). Additionally, for weekdays, CPM were calculated for each hour and summarized for 3 periods of the day[14,24]: morning (5:00 $_{AM}$ to 12:00 $_{M}$), afternoon (12:00 $_{M}$ to 6:00 $_{PM}$) and evening (6:00 $_{PM}$ to 12:00 $_{AM}$). For data to be included in these analyses, the minimal wear time per hour was set at 30 minutes. Finally, the time spent in intensity categories was included as a dimension. Based on counts and valid default vector magnitude cutpoints,[25-27] each minute was categorized as sedentary (0 – 150 counts), light (151 – 2690 counts), and moderate-to-vigorous activity (MVPA) (>2691 counts). The time spent in each category was expressed as a percentage of the wear time per day.

Distribution of the duration of periods

The distribution of the duration of periods (bout length) of sedentary and MVPA behavior was assessed according to the method described by Chastin et al.[17,18,28] A sedentary bout was defined as at least 1 minute of CPM ≤150, and an MVPA bout was defined as at least 1 minute of CPM ≥2691. Bout detection was performed with Actilife[a], and bout time series were exported to MATLAB for further analysis. The following bout parameters were calculated per day. First, the number of bouts was calculated. Second, the mean bout length (min) was calculated: because the length of bouts was lognormally distributed, the natural log of the data was taken. The mean of the log data was calculated and backtransformed to the original scale. The third parameter was the variation of bout length (coefficient of variation, CoV). This outcome was obtained after dividing the SD by the mean bout length (min) from the lognormal transformed data. It indicates whether the bout length shows much (high value) or little (lower value) within-subject variability. The fourth parameter was the

fragmentation of bouts (F).[16,29] This variable was calculated as the number of bouts divided by the summed duration (min) of all bouts. A higher fragmentation index indicates that time spent sedentary or active is more fragmented with shorter bouts. The final parameter was the gini index. The Gini index reflects the pattern of accumulation of bouts and was calculated separately for sedentary and MVPA behavior. The Gini-index varies from 0 to 1; where a Gini index score near 1 indicates that the summed bout time is composed of longer bouts rather than short bouts. A lower Gini index score indicates that there are a larger number of periods of different lengths, with a dominance of short bouts.[17,18,28]

Statistical analysis

SPSS version 21 was used for data analysis. Descriptive data are presented as mean ± SD or as otherwise indicated. The significance level was set at P<.05 for all analyses. Differences between groups were examined using independent t tests. Effect size estimates based on Cohen's *d* (i.e., difference between mean scores for 2 groups divided by the pooled SD) were calculated for all outcomes.

RESULTS

Of the 29 persons with MS, 4 had invalid data and 2 could not be matched with control subjects. The persons with MS recruited 57 control subjects, of which 2 were excluded because of mobility limitations, 4 were excluded because of fatigue or depression, 2 could not be contacted, and 26 were redundant or could not be matched to a person with MS. Finally, data were obtained from 23 persons with MS and 23 matched control subjects. The characteristics of both groups are shown in Table 3.1. Persons with MS were severely fatigued and had low EDSS scores, showing minimal neurological impairments; 87% had Relapsing Remitting MS. The matched controls had a more favorable work status (i.e., more were employed) (*P*=.04*)*.

The results for PB of persons with MS and controls are shown in Table 3.2. Persons with MS had significantly lower amounts of physical activity levels per day and

for all day periods, except for the afternoon. The CPM results per day period for weekdays are shown in Figure 3.1. Day pattern outcomes were based on weekdays, because as we previously stated weekend days may confound the day patterns. Therefore, we did an additional analysis to compare the groups on weekend days: no differences between the groups on CPM day patterns (morning, afternoon and evening) were found, indicating that day patterns indeed differ for weekdays and weekend days. For the other PB outcomes, the results were not different for weekdays or weekend days, except for length of day: both persons with MS (mean difference, 57min; *P*<.001) and controls (mean difference, 35min; *P*=.006) had shorter days on weekends.

Table 3.1 Participant characteristics

	MS (N=23)	Controls (N=23)
Sex (M/F)	5/18	5/18
Age (y)	45.7 ± 10.2 (24-66)	45.7 ± 10.2 (27-67)
Type MS (RR/SP)	20/3	
EDSS*	2.0 (3.0)	-
MS duration (years)	9.3 ± 7.1 (0-21)	-
Work status†		
Employed	13	21
Part time/full time	10/3	15/6
Unemployed/ searching Invalidity	2	0
benefits/sick leave	3	0
Other: housekeeping, retired	5	2
BMI (kg/m^2)	24.8 ± 4.3 (18.7-34.2)	23.4 ± 2.6 (19.3-29.4)
FSS	5.4 ± 1.0 (2-6.6)	
CIS fatigue domain	43.2 ± 6.6 (32-54)	16.0 ± 7.6 (8-31)

NOTE. Values are mean ± SD (range), n, or as otherwise indicated.
Abbreviations: BMI, body mass index; CIS, Checklist Individual Strength; EDSS, Expanded Disability Status Scale; F, female; FSS, Fatigue Severity Scale; M, male; NA, not applicable; RR, relapsing remitting; SP, secondary progressive.* values is median(interquartile range) † Groups differed significantly.

Figure 3.2 shows the relative time spent in each PB intensity category. Persons with MS spent more time in sedentary behavior (*P*=.045) and less time in moderate-to-vigorous activity, i.e. MVPA (*P*=.042) than controls.

The distribution analyses of sedentary periods showed a significantly different accumulation of sedentary periods between groups. Persons with MS had a higher sedentary Gini index, meaning that they had longer sedentary bouts and fewer short bouts than controls; other measures of sedentary behavior did not differ. Additionally, there was a tendency for persons with MS to have a less fragmented pattern of sedentary behavior (F_{Sed}) and more variability in bout length (CoV_{Sed}). The MVPA period distribution analysis showed that persons with MS had a significantly lower number of MVPA bouts than controls. Also, the accumulation of MVPA bouts (Gini-index) differed between the 2 groups, indicating that persons with MS build up their MPVA time with more short bouts and fewer long bouts.

Table 3.2. Physical behavior outcomes

Outcomes PB	MS Group (N=23)	Controls (N=23)	*P*	Mean difference (95 % CI)	Cohen's *d* Effect Size
Length of day (min)	907 ± 84	943 ± 51	.085	-36 (-77 to 5)	0.52
Amount of physical activity					
CPD ($\times 10^3$)	520 ± 173	676 ± 218	.010*	-156 (-273 to -39)	0.78
Day CPM	577 ± 198	712 ± 209	.030*	-135 (-256 to -14)	0.66
Morning CPM	661 ± 304	861 ± 332	.039*	-200 (-389 to -11)	0.63
Afternoon CPM	610 ± 239	699 ± 248	.223	-89 (-234 to 56)	0.36
Evening CPM	467 ± 203	642 ± 324	.034*	-175 (-336 to -14)	0.65
Intensity category (%)					
Sedentary	63.2 ± 9.0	57.5 ± 9.4	.045*	5.6 (0.1 to 11.1)	0.61
Light	29.0 ± 5.9	32.2 ± 6.6	.091	-3.2 (-6.9 to .5)	0.51
MVPA	7.8 ± 4.0	10.2 ± 3.8	.042*	-2.4 (-4.7 to -0.09)	0.62
Distribution Sedentary					
No. of bouts	799 ± 200	823 ± 168	.657	-24 (-134 to 85)	0.13
Mean length (min)	2.62 ± 0.55	2.40 ± 0.33	.108	0.22 (-0.05 to 0.49)	0.48
F_{Sed}	.26 ± .07	.30 ± .06	.064	-0.03 (-0.07 to 0.002)	0.56
CoV_{Sed}	16.1 ± 1.6	15.2 ± 1.4	.067	0.8 (-0.06 to 1.75)	0.55
Gini index: sedentary	.50 ± .05	.47 ± .05	.039*	0.033 (0.002 to 0.064)	0.63
Distribution MVPA					
No. of bouts	63 ± 43	92 ± 47	.032*	-29 (-56.2to -2.6)	0.65
Mean length (min)	1.78 ± 0.77	1.70 ± 0.25	.612	0.09 (-0.25to 0.43)	0.15
F_{MVPA}	.53 ± .19	.46 ± .12	.148	0.07 (-0.03to 0.16)	0.43
CoV_{MVPA}	11.1 ± 3.7	13.0 ± 3.0	.070	-1.8 (-3.8to 0.2)	0.55
Gini index: MVPA	.31 ± .12	.39 ± .11	.023*	-0.08 (-0.15to -0.01)	0.70

NOTE. Values are in mean ± SD or as otherwise indicated.

Abbreviations: PB, physical behavior; CPD, counts per day; MVPA, moderate-to-vigorous intensity activities; F_{Sed} or $F_{MVPA,}$ fragmentation of sedentary or MVPA bouts; CoV_{Sed} CoV_{MVPA}, coefficient of variation of sedentary or MVPA bout length. *Groups differed significantly.

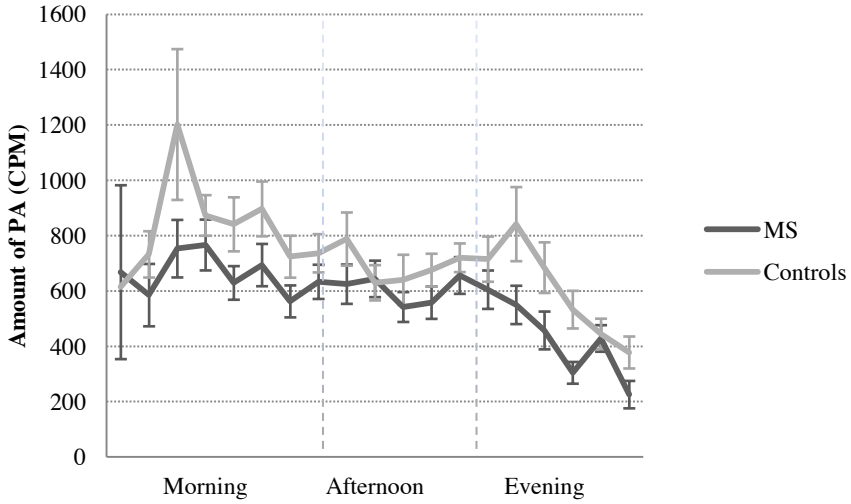

Figure 3.1. Amount of physical activity per period of the weekday.
Expressed in mean CPM per hour with the standard error of the mean (SEM).

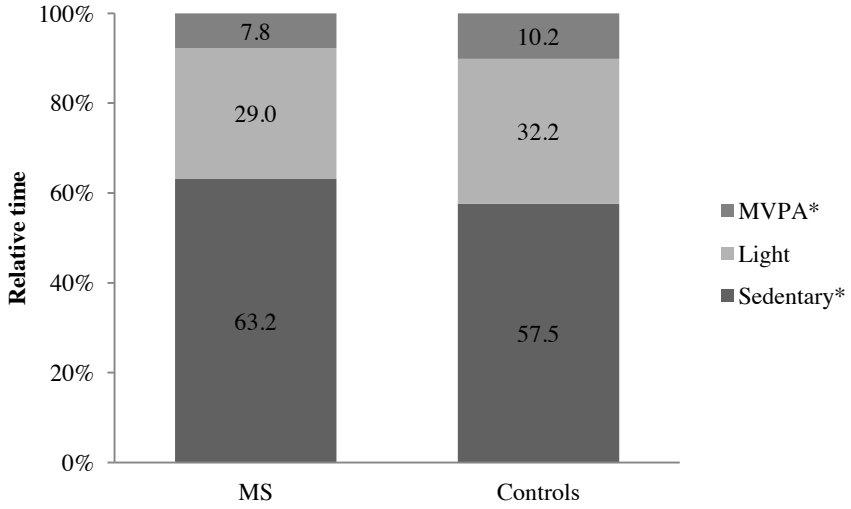

Figure 3.2. Relative time spent in intensity categories.
Categories expressed in mean percentages with the SEM. * Significant differences between persons with MS and matched control subjects.

DISCUSSION

The aim of the present study was to elucidate which dimensions (e.g., day patterns, intensity of activities, distribution of activities) of PB are affected in fatigued persons with MS compared with age- and sex-matched control subjects. In general, fatigued persons with MS had lower physical activity levels. The effects on other aspects of PB were variable, but every dimension analyzed (i.e., day patterns, intensity categories, distribution of the duration of different aspects of PB) revealed ≥1 significant difference between groups.

The finding that persons with MS had lower amounts of daily physical activity levels is consistent with other studies,[9,10,30-32] despite the differences in devices and settings used. Lower amounts of daily physical activity may result from a shorter day or less activity per minute or hour. Our results indicate that the latter explanation is more likely: we found a nonsignificant mean difference of -36 minutes (95% CI,-77 to 5) in length of day between groups, whereas CPM differed significantly (mean difference,-135; 95% CI,-256 to -14).

We also studied other dimensions of PB, including day patterns, intensity of activities and distribution of duration of periods of sedentary and MVPA behavior. It was shown that persons with MS were less active during the morning and evening, but not during the afternoon (although there was a trend toward less activity). We cannot explain the lack of difference between groups during the afternoon. Rietberg[19] recently studied day patterns in persons with MS compared with controls based on a 24-hour measurement period; lower amounts of physical activity levels were observed throughout the day and during all 3 day periods compared with healthy controls. The difference in findings with respect to afternoon data between studies may reflect patient population differences: fatigue was not an inclusion or exclusion criterion for the Rietberg study. Another difference between the studies is that Rietberg focused on specific postures or activities (walking) and expressed these as durations, whereas we included all activities and expressed them as amounts of activity per minute (CPM).

PB intensity was another detailed outcome examined in our study. Categories of sedentary behavior, light activity and higher activity (MVPA) were defined by preset

cut-points of counts. The results indicate that persons with MS spent more time in the sedentary category and less in the higher intensity (MVPA) category. Klaren[20] also showed that persons with MS spent less time in MVPA than matched controls. To our knowledge, time spent sedentary in persons with MS has not been studied previously. However, the literature shows that amount of sedentary behavior is an independent determinant of health.[33,34] Although significant, the differences we detected in time spent in the sedentary category between groups were small (5.6%; 95% CI, 0.1 to 11.1; *P=.045*).

Distribution outcomes (e.g., fragmentation, Gini-index) are related to the duration and pattern of periods of sedentary and higher activity (MVPA) behavior. The most comprehensive outcome, the Gini-index, gives information about how sedentary and MVPA periods are distributed over time. Results of the Gini index suggest that persons with MS accumulate sedentary time in longer sedentary periods, with a trend toward less fragmented sedentary patterns and more variable lengths of sedentary periods. Furthermore, persons with MS had fewer higher activity (MVPA) periods, and these were of shorter duration. For fatigued persons with MS, the distribution of different PB over the day may depend on adaptation strategies used to reduce perceived fatigue. It may be more efficient to have more fragmented activity and rest periods; longer periods of sedentary behavior may indicate overload or deconditioning behavior. Chastin[17,18] found similar results for accumulation of sedentary periods in patients with Parkinson disease[17] and chronic fatigue syndrome.[18] However, their Gini index values were higher, meaning that their total measured sedentary behavior consisted of more long sedentary periods. This difference may be because of their inclusion of night as sedentary time, which results in overall longer sedentary period measurements.

The focus of our study was to conduct a detailed analysis of several dimensions of PB of fatigued persons with MS. It was assumed that MS affects not only total amount of physical activity, but other dimensions of PB as well. Our results support this assumption: effects on total amount of physical activity and most detailed outcomes were noted. This study showed how detailed measures provide more insight into how MS affects PB. These outcomes can be used by clinicians and

therapists for the development and evaluation of rehabilitation treatments, such as Energy Conservation Management,[13] which emphasizes balancing rest and active behavior to decrease fatigue levels and increase participation.

Limitations

Employment may be a determinant of several PB outcomes. In our study, persons in the control group were more often employed. However, it can be assumed that differences in employment result from the disease and therefore should not be considered as a confounder. To examine the potential effect of employment, we compared weekdays and weekend days to show that persons with MS and controls had comparable PB dimensions; therefore, employment seemed to be a nonsignificant influence.

Another limitation is the small sample size. The small sample size affected our power to detect statistically significant differences. Therefore, it might be that some outcomes that were nonsignificant in our study would have been significant in a larger sample. An additional limitation is that this study evaluates only ambulatory persons with MS and fatigue; therefore, results may not be generalizable to all persons with MS. Furthermore, small group sizes prevented us from performing subgroup analysis by fatigue level.

Conclusions

Our study shows that ambulatory fatigued persons with MS are less physically active per day, especially in the morning and evening, and more time is spent sedentary and less time is spent at higher-intensity (MVPA) activity compared with age- and sex-matched controls. The results suggest that physical behavior of fatigued persons with MS consists of relatively longer sedentary periods and fewer and relatively shorter higher-intensity periods. Overall, it can be concluded that detailed analysis provides more insight into how physical behavior is affected in fatigued persons with MS. The results of this exploratory study should be confirmed in prospective studies.

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Chapter 4

Physical behavior is associated with physical fatigue in persons with multiple sclerosis-related fatigue

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ABSTRACT

Background: Fatigue affects 80% of persons with Multiple Sclerosis and is associated with daily physical functioning or, more precisely, with an individual's physical behavior. Both fatigue and physical behavior are multidimensional concepts.
Objective: To study the association between the dimensions of physical behavior with multiple sclerosis-related (MS) fatigue.
Methods: Cross-sectional analysis of two-hundred-twelve persons with MS. Participants were severely fatigued with a Fatigue Severity Scale median (IQR): 5.4 (4.8-5.9) and were minimally to moderately neurologically impaired based on the Expanded Disability Status Scale: 2.5 (2.0-3.5). Seventy-three percent had relapsing-remitting MS.
Fatigue was measured by questionnaires (i.e., Checklist Individual Strength, Modified Fatigue Impact Scale), and the dimensions subjective, physical, cognitive and psychological fatigue were distinguished. Physical behavior was measured using an Actigraph GT3X+, and outcomes were categorized into the dimensions activity amount, activity intensity, the day pattern, and distribution of activities.
Results: The physical behavior dimensions were significantly associated with only the physical fatigue dimension (omnibus F-test: 3.96; df1 = 4, df2 = 207; *P=.004*). Additional analysis showed that the activity amount (Unstandardized beta coefficient [ß] = -0.16; 95% CI,-0.27 to -0.04; *P=.007*), the activity intensity (ß = -0.18; 95% CI, -0.31 to -0.06; *P=.004*) and the day pattern of activity (ß = -0.17; 95% CI,-0.28 to -0.06; *P=.002*) were the physical behavior dimensions that were significantly associated with physical fatigue.
Conclusions: Physical behavior is weakly associated with physical fatigue and is not associated with other fatigue dimensions.

INTRODUCTION

Fatigue affects 80% of persons with Multiple Sclerosis (MS)[1-3] and occurs among all MS subtypes and disability levels.[4] MS-related fatigue is defined by the Multiple Sclerosis Council for Clinical Practice Guidelines[5] 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'. From this definition, it seems plausible that MS-related fatigue is associated with daily physical functioning[1,4,6] or, more precisely, with an individual's physical behavior[7-9] (i.e., the body postures, movements and activities performed in daily life[10]). However, the definition of MS-related fatigue is rather general, and lacks specificity regarding different dimensions of fatigue and its consequences. Fatigue questionnaires also have this lack of specificity, as exemplified by questions such as 'fatigue interferes with my daily functioning' (Fatigue Severity Scale[11]).

The complexity of the relationship between fatigue and physical behavior is also evident from the literature. Several studies[12-21] have focused on the relationship between fatigue and different aspects of physical behavior to disentangle their mutual relationship. However, overall, the evidence for the relationship between fatigue and physical behavior — with fatigue affecting physical behavior and/or vice versa — is weak. Furthermore, the results are conflicting, as some studies support an association, i.e. when there is more fatigue the person is less physical active,[12-14] while other studies report either a weak association or none at all.[15-21] As a result, there is currently no consensus about associations between fatigue and physical behavior.

This lack of consensus can maybe explained by the limited attention paid to the multi-dimensionality of fatigue[1,22] and that of physical behavior.[10] Both fatigue and physical behavior can be regarded as umbrella constructs that consist of several dimensions. For example, perceived fatigue consists of subjective, physical, cognitive and psychological dimensions.[23] Relying on a sum score of all of these dimensions or considering one dimension alone may mask the existence of any association with physical behavior. Similarly, physical behavior is composed of different dimensions. Most literature has primarily focused on the 'amount of physical activity' as the most

important component of physical behavior.[24-28] However, it is questionable whether this outcome is the most valid. In the literature, also involving other populations, there has been growing interest in evaluating other dimensions of physical behavior, such as day patterns (morning, afternoon, evening), intensity of activity, as well as the distribution of activity and sedentary behavior.[7,9,29,30] Denial of the multi-dimensionality of physical behavior can mask any potential effects or associations.

So far, only one study investigated the relationship between fatigue and physical behavior considering the multi-dimensional components of fatigue.[20] In that study of Rietberg et al, there were no associations detected when considering the total fatigue scores; however, the physical dimension of fatigue was significantly associated with the total amount of physical activity. A ß of -.044 indicated that a one-point increase in physical fatigue was associated with an average decline of 5.5 minutes in physical activity over 24 hours. However, the study did not consider the multi-dimensionality of physical behavior.

More detailed knowledge about the relationship between MS-related fatigue and physical behavior will provide better understanding of consequences of MS on daily functioning, which can be useful in designing treatment modalities. This could conceivably lead to the development of more effective treatments that are tailored to individual needs and therefore to improved rehabilitation. The aim of the present study was to explore associations between different dimensions of fatigue and physical behavior in ambulatory persons with MS-related fatigue.

METHODS

Participants

The present study population consisted of people with MS who were included (until March 2014) as participants in the TREFAMS-ACE research program: Treating Fatigue in MS with Aerobic Training, Cognitive Behavioral Therapy and Energy Conservation Management (TREFAMS-ACE).[31] This research program consisted of three multi-center RCTs that evaluated the effectiveness of rehabilitation treatments on fatigue and

participation in MS patients. The inclusion criteria in this research program were as follows: definite diagnosis of MS; severe fatigue, as indicated by a score of ≥ 35 on the fatigue domain of the Checklist Individual Strength (CIS20r); ambulatory status (i.e., Expanded Disability Status Scale (EDSS)[32] ≤ 6.0; no diagnosis of depression (i.e., Hospital Anxiety and Depression Scale (HADS) < 11); no initiation or change to pharmacological treatment for fatigue during the previous three months; and age 18 to 70 years. The protocol for this study was approved (NL number 33451.029.10; METc VUmc.nr 2010/289) by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands. Details of the TREFAMS-ACE study have been described elsewhere.[31] All participants provided written informed consent. An additional inclusion criterion for the present study was the availability of baseline accelerometer data.

Measurements

Fatigue. Fatigue was measured with two self-reported fatigue questionnaires that cover different dimensions of fatigue.[33,34] The Checklist Individual Strength (CIS20r)[35] is a multi-dimensional questionnaire that consists of 20 items, rated on a 7-point scale. The CIS20r is divided into four dimensions of fatigue and related behavioral aspects: the subjective experience of fatigue (8 items); reduction in motivation (4 items); reduction of physical activity (3 items); and reduction in concentration (5 items). The CIS20r focuses on fatigue experienced in the previous two weeks. The CIS20r has several reliable psychometric properties, such as good internal consistency and test-retest reliability for total scores and dimensions scores, as well as good construct and concurrent validity. Furthermore, the multi-dimensional construct is supported by factor analysis.[23,33,36,37] The Modified Fatigue Impact Scale (MFIS)[38] is a multi-dimensional questionnaire that consists of 21 items, rated on a 5-point Likert scale. MFIS assesses the perceived impact of fatigue on for dimensions: physical (9 items), cognitive (10 items) and psychosocial (2 items) functioning during the previous four weeks. The MFIS is frequently used in MS research and has been shown to have good test retest reliability on the total and domain scores, as well as good construct

and concurrent validity. The multi-dimensional structure has also been confirmed.[23,38-40] For both questionnaires, higher scores reflect more fatigue.

Physical behavior. The assessment of physical behavior was conducted in the daily environment of the participants using 3-dimensional accelerometry (ActiGraph GT3X+ model[a]; 4.6 x 3.3 x 1.5 cm; 19 g). This device is valid and reliable in measuring physical behavior in persons with MS.[2,41] Participants wore the accelerometer on an elastic belt around their waist during waking hours for seven days and were requested to remove it only during water-based activities, such as showering or swimming. Accelerometer signals were sampled with 30 Hz and downloaded using an epoch length of 10 sec and the low filter extension (LFE) option in Actilife software (v. 6.6.2). Activity counts from all three axes, i.e. the vector summed value known as 'vector magnitude' (VM), were calculated. For every AG, a compliance and control quality check was performed once data were downloaded. Non-wear periods were defined as a 180-min (or longer) period of continuous zero counts without allowing for interruption and were filtered from the raw data using a semi-automated algorithm and excluded from further analyses. Days with at least 660 minutes of wear time were considered to be valid. For data to be included in the analysis, at least 5 valid measurement days were required.[42] From Actilife the data were imported into Microsoft Excel for each person separately, additional calculations on bouts and cut points were performed using Microsoft Excel and MATLAB.

Outcomes

Four dimensions of fatigue were derived from seven subscales of the two fatigue questionnaires (CIS20r and MFIS). We categorized the dimensions by maintaining the original subscales and combining the subscales of the two fatigue questionnaires of items that were conceptually similar. We tested this by examining the relationships such that the subscales were moderately ($r > 0.3$) (physical and psychological) or highly ($r \geq 0.8$) (cognitive) correlated. The four dimensions were: 1) Subjective fatigue: CIS subjective fatigue score; 2) Physical fatigue: CIS physical activity scores and MFIS physical scores; 3) Cognitive fatigue: CIS concentration scores and MFIS cognitive scores; 4) Psychological fatigue: CIS motivation scores and MFIS psychosocial scores.

Physical behavior variables were selected based on the results provided in a previous study by Blikman et al.[7] In the present study, ten physical behavior variables were categorized into four physical behavior dimensions:

1) Amount of activity: the amount of daily activity of a person based on the activity expressed in total counts per day and counts per minute. Higher amounts of activity are assumed to be beneficial.

2) Intensity categories: the time spent in different intensity categories as a percentage of the total wear time per day. Percentages were calculated for the time spent in sedentary activities (0-150 counts), light physical activity (151-2690) and moderate-to-vigorous physical activity (MVPA) (>2691).[43-45] More time spent in higher intensity categories is assumed to be beneficial from the perspective of functioning and health (i.e., less sedentary, more light and more MVPA).

3) Day patterns: how the amount of activity is spread over the day (morning, afternoon and evening period). Based on previous research[7], we reported the outcome as a 'day pattern ratio', which was calculated by counts per minute in the evening (6:00 $_{PM}$ - 12:00 $_{AM}$) divided by counts per minute in the morning (5:00 $_{AM}$ - 12:00 $_{M}$). A higher (or equal) ratio is assumed to express a higher amount of remaining capacity to be active during the evening, which can be considered to be beneficial.

4) Distribution: how specific periods of behavior (such as sedentary activity or MVPA) are distributed over the day based on the Fragmentation index[46] of periods of sedentary behavior and MVPA behavior. Fragmentation is calculated as the number of periods divided by the summed duration of all periods. A higher fragmentation index indicates more fragmented behavior with shorter periods. Second, the Gini index[47] was calculated again both for periods of sedentary behavior and MVPA behavior. The Gini index ranges from 0 to 1. A lower Gini index reflects a situation in which short periods dominate. A higher sedentary Fragmentation index and a lower sedentary Gini index is assumed to reflect better functioning, while the opposite applies to MVPA behavior.

Statistical analysis

Prior to statistical analysis, the standardized values (z-scores) of the fatigue and physical behavior variables were calculated by SPSS, resulting in a distribution with a mean of zero and a variance of one. After standardization, a lower z- value related to fatigue implied less fatigue, and a higher z-score for physical behavior indicated a more beneficial type of physical behavior. The standardized values of the variables within one dimension were averaged for each individual. Standard linear regression analysis was used to assess the association between the standardized dimensions of physical behavior as the independent variables in the model and the standardized dimensions of fatigue as the dependent variables. A negative ß regression coefficient indicated that per unit increase of the standardized physical behavior dimension, the standardized fatigue dimension was reduced by the amount of ß, and vice versa for a positive ß. Assumptions of normality, heteroscedasticity and multicollinearity were graphically checked using residual plots. First, four regression models were used, each focusing on one of the fatigue dimensions, while including the whole set of physical behavior dimensions simultaneously. When evaluating the results of the linear regression analyses, we used the omnibus F-tests to investigate if at least one of the four physical behavior dimensions was significantly associated with a specific fatigue dimension. If this test was significant, additional analyses were conducted to determine which of the specific physical behavior dimensions were significantly associated with the fatigue dimension under study. Subsequently, we also performed the same analyses after adjusting for age and gender. In addition to the fatigue dimensions, we studied the association between the physical behavior dimensions and fatigue total scores (i.e., CIS total, MFIS total) to compare the findings resulting from the fatigue total scores and fatigue dimensions. SPSS version 21 was used for data analysis. Descriptive data are presented as the median (IQR) or as otherwise indicated. The significance level was set at $p < 0.05$. Additional analysis adjustments were made for multiple comparisons.

RESULTS

Initially, 222 baseline accelerometer data files of participants were available. Ten data files were excluded because they did not meet the inclusion criteria for valid measurements (i.e., over 5 valid measurement days). Ultimately, baseline accelerometer data from 212 persons with MS were available for analysis. The mean number of valid days was 6.7, and the mean wear time per day was 904 minutes. The participant characteristics are shown in Table 4.1. The participants with MS were severely fatigued as defined by the Fatigue Severity Scale[48], and their EDSS scores showed minimal to moderate neurological impairments. In addition, 73.1% had relapsing remitting MS.

Table 4.1 Participant characteristics

		Participants (N=212)
Gender (M/F)		56/156
Age (years)		47.9 (39.8-53.7)
Type MS:	Relapsing - Remitting	155 (73.1%)
	Primary Progressive	22 (10.4%)
	Secondary Progressive	21 (9.9%)
	Else/ unknown	14 (6.6%)
EDSS		2.5 (2.0-3.5)
MS duration (years)		6.3 (2.4-13.9)
Employed (Part-time/full-time)		106 (81/25)
FSS		5.4 (4.8-5.9)

Values are given as medians (with IQR 1st quartile – 3rd quartile) or in numbers of participants for gender, type of MS (with percentages) and employment. Abbreviations: EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale.

The mean and range of the original non-standardized physical behavior variables and fatigue variables are shown in Table 4.2.

Table 4.2 Characteristics of the physical behavior and fatigue variables

Physical Behavior	Mean (range)	Fatigue	Mean (range)
Amount of activity:		*Subjective:*	
Counts per day	498569 (148679-1157422)	CIS20r subjective	44 (14-56)
Counts per minute	550 (165-1237)	*Physical:*	
Intensity categories:		CIS20r physical activity	13 (3-21)
Sedentary activity(%)	64 (40-85)	MFIS physical	21 (6-33)
Light activity (%)	28 (13-43)	*Cognitive:*	
MVPA (%)	7 (0.4-21)	CIS20r concentration	21 (5-35)
Day Patterns:		MFIS cognitive	19 (1-37)
Day pattern ratio	0.75 (0.14-2.53)	*Psychological:*	
Distribution:		CIS20r motivation	15 (4-28)
F-index sedentary	0.25 (0.12-0.46)	MFIS psychosocial	4 (0-8)
Gini index sedentary	0.53 (0.36-0.69)	*Total scores:*	
F-index MVPA	0.53 (0.11-1.00)	CIS20r total	91 (34-134)
Gini index MVPA	0.31 (0.00-0.71)	MFIS total	44 (9-75)

Variables were categorized per physical behavior dimension or fatigue dimension. Abbreviations: CIS20r, Checklist Individual Strength; MFIS, Modified Fatigue Impact Scale; MVPA, moderate-to-vigorous activity; F-index, Fragmentation index.

The omnibus F-test of the standard linear regression analysis showed that one or more physical behavior dimensions were significantly associated with the physical fatigue dimension (omnibus F-test: 3.96; df1=4, df2=207; *P=.004*), and not with subjective (omnibus F-test: 1.48; df1=4, df2=207; *P=.210*), cognitive (omnibus F-test: 1.06; df1=4, df2=207; *P=.379*) or psychological fatigue (omnibus F-test: 1.00; df1=4, df2=207; *P=.409*). The physical behavior dimensions were not significantly associated with the total scores of fatigue (CIS20r total *P=.165*; MFIS total *P=.398*).

Additional analyses of the significant association between physical behavior and physical fatigue revealed that the physical behavior dimensions of the amount of activity, categories of intensity and day pattern were all significant and negatively associated with physical fatigue (Table 4.3). The distribution dimension was not associated with physical fatigue. Comparable associations were found following adjustments for age and gender (Table 4.3).

Table 4.3 Four unadjusted and adjusted linear regression models with physical fatigue as the dependent variable and with each physical behavior dimension separately as the independent variable.

Models including the	Unadjusted			Adjusted for Age and Gender		
PB dimension:	ß	95% CI for ß	*p*	ß	95% CI for ß	*p*
Activity amount*	-0.16	-0.27 to -0.04	***.007***	-0.14	-0.25 to -0.03	***.017***
Intensity Categories*	-0.18	-0.31 to -0.06	***.004***	-0.17	-0.29 to -0.04	***.008***
Day pattern*	-0.17	-0.28 to -0.06	***.002***	-0.16	-0.27 to -0.05	***.004***
Distribution	-0.11	-0.27 to 0.05	*.168*	-0.07	-0.23 to 0.09	*.402*

*Significant association, activity amount R^2 = .035, intensity categories R^2 = .038, day pattern R^2 = .043.
Abbreviations: PB, physical behavior; ß, Unstandardized beta coefficients; CI, confidence interval.

DISCUSSION

The present study examined associations between dimensions of fatigue and dimensions of physical behavior in a sample of 212 persons with severe MS-related fatigue. To our knowledge, no study has examined this relationship while taking into account the multi-dimensionality of both constructs. Three out of four dimensions of physical behavior (the total amount, the intensity, and the day pattern of activities) were associated with the physical fatigue dimension, while there were no significant associations between the other fatigue dimensions and physical behavior dimensions.

In a previous study we compared physical behavior outcomes and dimensions between fatigued MS patients and healthy comparison subjects.[7] Although there were some differences between outcomes, the overall conclusion of that study was that these groups differed in physical activity level, and in other physical behavior dimensions, such as day patterns, intensity, and distribution. The results of the current study are different with respect to the absence of a relationship between the distribution dimension of physical behavior and the physical dimension of fatigue. This indicates that distribution - as expressed by e.g. the Gini Index - is affected in fatigued MS patients but is not related to fatigue, and that it is the most divergent physical behavior dimension.

None of the physical behavior dimensions was associated with the total scores

of the fatigue questionnaires. Similar results were reported by Rietberg et al[20], who showed that an analysis of the total scores of fatigue measures yielded no associations, whereas the physical dimension of fatigue was associated with the total amount of physical activity, one of our components of physical behavior. Both our study and the study of Rietberg[20] suggest that the fatigue dimensions are distinct from each other and different from the total fatigue scores, which has also been concluded by other studies investigating measurements of fatigue.[23,49] This finding suggests that fatigue dimensions should be used separately in both research and clinical practice and that the sum scores should not solely be relied on. Additionally, our results also support the importance of studying physical behavior in more detail[7], e.g. when treating patients with MS or studying the effectiveness of rehabilitation, because else important effects may be missed.

Although there was a significant negative association between the dimensions of physical fatigue and physical behavior (i.e. more fatigued persons have a less active physical behavior), these associations were nonetheless weak. A possible explanation may be that most of the participants included in this study were severely fatigued, with a relatively small range in fatigue scores. In studies that focus on relationships between outcomes, a large between-subject range in outcomes will more easily result in significant results. The weak relationships must therefore be considered in this perspective, and we propose future studies with a more heterogeneous population with respect to fatigue. Such studies may provide further insights into relationships between fatigue and physical behavior.

Rietberg et al[20] showed that stronger associations between fatigue and physical behavior became evident after adjusting for patient characteristics, such as age, MS type, anxiety and depression. In our population, fatigue was present in all types of MS and independent of MS duration. We therefore not selected these as possible confounders. Furthermore, adjusting for depression was unnecessary because a diagnosis of depression was an exclusion criterion in the present study. In our study, age and gender did not bias the association between physical behavior dimensions and physical fatigue, and minimally altered the adjusted ß values.

The association between fatigue and physical behavior found in our study

may lead to new perspectives on the treatment of fatigue in people with MS. The results of our study do not allow any causal statements, but do support the further exploration of treating physical fatigue by changing physical behavior, e.g. by making changes in the time spent in intensity categories (i.e. less sedentary and more light or MVPA intensity activities) or by balancing the day pattern of activities (i.e. equally spreading activities over morning and evening or increasing the level of activity in the evening). The clinical impact of changing physical behavior to decrease physical fatigue may be small.

Limitations

The present study has some limitations. Firstly, we already discussed the relatively small range in fatigue scores of the subjects, which is the result of the inclusion criteria of the RCT's from which the data of the current study were used. Secondly, causal relationship cannot be determined using a cross-sectional study design. Specifically, while changes in physical behavior may influence fatigue, the converse may also be true. For example, Rietberg et al[20] studied the association between physical behavior and fatigue and defined fatigue as the independent variable. Thirdly, our sample consisted of fatigued and ambulatory persons that were enrolled in a RCT study, most of whom had relapsing-remitting MS with minimal to moderate neurologic impairment and no evidence of depression. These criteria limit the generalizability of our findings to all persons with MS. Fourthly, accelerometers have limitations, for example difficulty with measuring low activity patterns, which in our GT3X model was improved with the low-frequency extension filter. Also different processing techniques (e.g. wear-time, cut-points) for accelerometers can influence the outcomes.[50] We therefore clearly described our data processing settings which were appropriate at the time of our analysis. However, as activity monitor technology and protocols are rapidly changing, other data processing settings could become more suitable. Finally, the fatigue and physical behavior measurements were not assessed across exactly the same period of time. Fatigue questionnaires were most often completed one week before the activity monitor measurement. However, the fatigue questionnaires measured fatigue over the previous two (CIS20r) or four weeks

(MFIS) and gave a good indication of the level of chronic fatigue generally experienced by persons with MS. Although fatigue fluctuates between days, participant scores on these questionnaires are likely to remain stable. Therefore, we would not expect associations to be different if the measurements had been conducted in the same week.

Conclusion

In ambulatory persons with MS-related fatigue, a weak association was found between physical fatigue and several physical behavior dimensions (i.e., the amount, the intensity and the day pattern of activities). By increasing physical behavior, persons with MS-related fatigue may benefit from reduced levels of physical fatigue. No associations between dimensions of physical behavior and subjective, cognitive and psychological fatigue were noted. Fatigue and physical behavior are multi-dimensional, which may imply that different treatment modalities should be considered in the treatment of fatigue. The results subscribe the importance of considering specific fatigue and physical behavior dimensions in addition to the total scores when treating patients with MS or studying the effectiveness of rehabilitation treatments.

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Chapter 5

Effectiveness of Energy Conservation treatment in reducing fatigue in Multiple Sclerosis: a systematic review and meta-analysis

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ABSTRACT

Objectives: To systematically review the effects of Energy Conservation Management (ECM) treatment for fatigue in Multiple Sclerosis (MS), and to study the effect of ECM treatment on restrictions in participation and quality of life (QoL).
Data Sources: PubMed, CINAHL, Embase and Web Of Knowledge were searched to identify relevant randomized controlled trials (RCTs) and controlled clinical trials.
Study Selection: To select potential studies, 2 reviewers independently applied the inclusion criteria.
Data Extraction: Two reviewers independently extracted data and assessed the methodological quality of the studies included. If meta-analysis was not possible, qualitative best-evidence synthesis was used to summarize the results.
Data Synthesis: The searches identified 532 studies, 6 of which were included. The studies compared the short-term effects of ECM treatment and control treatment on fatigue and QoL; 1 study reported short-term and midterm effects on participation, but found no evidence for effectiveness. Meta-analyses (2 RCTs, N=350) showed that ECM treatment was more effective than no treatment in improving subscale scores of the (1) Fatigue Impact Scale: cognitive (mean difference [MD] = -2.91; 95% confidence interval [CI], -4.32 to -1.50), physical (MD = -2.99; 95% CI, -4.47 to -1.52) and psychosocial (MD = -6.05; 95% CI, -8.72 to -3.37); and (2) QoL: role physical (MD = 17.26; 95% CI, 9.69-24.84), social function (MD = 6.91; 95% CI, 1.32-12.49) and mental health (MD = 5.55; 95% CI, 2.27-8.83). Limited or no evidence was found for the effectiveness of ECM treatment on the other outcomes in the short-term or midterm. None of the studies reported long-term results.
Conclusions: The systematic review results provide evidence that, in the short-term, ECM treatment can be more effective than no treatment (waiting controls) in reducing the impact of fatigue and in improving 3 QoL scales – role physical, social function and mental health – in fatigued patients with MS. More RCTs that also study long-term results are needed.

INTRODUCTION

Fatigue is a frequent, frustrating, overwhelming and often disabling symptom that affects patients with Multiple Sclerosis (MS). The Multiple Sclerosis Council for Clinical Practice Guidelines defines fatigue 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(p2)] Fatigue affects approximately 80% of patients with MS[2], up to two-thirds of whom indicate it as their main complaint[3], with fatigue severely limiting their daily activities and restricting participation, i.e. their performance of social roles.[4,5] It also has a major impact on quality of life (QoL).[6]

Rehabilitation treatments for relieving this disabling fatigue in patients with MS include energy conservation course, exercise therapy, cognitive behavioral therapy and multidisciplinary treatments.[1] In clinical practice, a well-known treatment used in occupational treatment for fatigued patients with MS focuses on teaching energy conservation strategies. Although many treatments for energy conservation strategies have been described[1,7-9], few programs have been standardized and published. The treatment program used most frequently in occupational treatment and described in the literature is Managing Fatigue[10], which is referred to as Energy Conservation Management (ECM). It has been tested in several studies and many countries.[11-15] To fit the unique needs of each individual, ECM promotes a positive attitude focused on decision-making and the optimum use of available energy. It is also intended to reduce the impact and severity of fatigue, to increase patients' use of energy-conserving strategies, and improve their confidence in their ability to manage fatigue.[10] Energy conservation strategies have been defined as 'the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home and leisure activities in all relevant environments'.[1(p17)] The strategies include balancing work and rest, communicating personal needs to others, analyzing and modifying activities to reduce energy expenditures, delegating activities, examining and modifying standards and priorities, using the body efficiently, organizing work spaces, and using assistive technologies to conserve energy.

Although there have been several systematic reviews of the effectiveness of

rehabilitation treatments in MS, including multidisciplinary treatment[16], exercise therapy[17], psychosocial intervention[18], and occupational therapy-related treatments[19,20], they were focused on outcomes other than fatigue. While 2 reviews on non-pharmalogical treatments did evaluate fatigue, they included other diagnoses beside MS.[21,22] To date, no extensive systematic review is available reporting on the evidence-based effectiveness of ECM treatments and how they affect fatigue in patients with MS. Given the high incidence of fatigue in patients with MS and the frequent use of ECM treatment, the effect of ECM treatment to reduce fatigue may be important in MS rehabilitation treatments. Additionally, the current ECM literature might identify gaps that could indicate new points of focus for studying the effects of ECM strategies as a treatment for fatigue.

We therefore systematically reviewed the effects of ECM treatment for fatigue in MS. We also studied whether ECM treatment affected restrictions in participation and QoL.

METHODS

Search Strategy

The PubMed, CINAHL, Embase and Web Of Knowledge databases were searched systematically to identify relevant randomized controlled trials (RCTs) and controlled clinical trials (CCTs) up to May 8, 2012. Keywords for identifying MS patients, ECM treatment and fatigue were included in the search string. The complete search strategy is shown in Supplement 5.1. Reference lists from the studies included were screened.

Inclusion Criteria

References were included if they met the following selection criteria:

- *Type of studies:* RCTs and CCTs
- *Participants:* Patients diagnosed with MS irrespective of age, gender, subtype of MS or onset of the disease. We also included studies that include another diagnosis as

well as MS, but only if results were provided for a MS subgroup.
- *Interventions:* all studies evaluating the effectiveness of an energy management course/training (ECM) or of fatigue management aimed at reducing fatigue, irrespective of the frequency, duration or mode of delivery. The program had to include energy conservation techniques or strategies. Multidisciplinary fatigue management studies were also included if the program contained clearly defined energy management techniques.
- Comparisons with placebo, controlled or another intervention group
- Outcome measurements had to be reported on perceived (subjective) fatigue. If perceived restrictions in social participation or on QoL outcomes were measured, these were described as well.
We used no language restrictions.

Study Selection

On the basis of the inclusion criteria, two reviewers (L.B., H.K.) independently screened the title and abstract of the studies identified for inclusion. Studies were included if they met the inclusion criteria. Any disagreements were resolved by discussion and, if no agreement was achieved, a third reviewer (B.H.) was consulted.

Data Extraction

Using a customized data-extraction table, 2 reviewers (L.B., H.K.) independently extracted the data from each study included. Any disagreements were resolved by discussion; if no agreement was achieved, a third reviewer (B.H.) was consulted. The following data were extracted from each study: descriptions of the participants; characteristics of the intervention and the control treatment (contents, duration, frequency, mode of delivery etc.); and outcome measures and *P* values. For the review, we used data only based on the comparison between the intervention and the control group. The follow-up time was categorized as short-term (closest to 3mo), midterm (closest to 6mo), and long-term (closest to 1y). If a compliers' analysis was also available, we gave preference to data extraction from the intention-to-treat analysis.

Methodological Quality Assessment

Methodological quality was assessed by 2 reviewers (L.B., H.K.) separately. A consensus method was used to resolve disagreements and a third reviewer (B.H.) was consulted if disagreements persisted. To assess the potential risk of bias per study, the quality criteria list of Furlan et al[23] was used. Each criterion had to be scored as yes (+), unclear (?), or no (-), where yes indicated that the criterion had been met and thus suggested a low risk of bias. High quality was defined as a score of 50% or more (ie, a 'yes' score on ≥50% of the criteria) on the methodological quality assessment.[23]

Data Synthesis

Under the following conditions, we conducted a meta-analysis: if a sufficient number of studies were identified, and if they were found to be sufficiently similar with regard to intervention and the control treatment, participants' characteristics (age, type of MS), and methodology (length of follow-up). By calculating the mean difference (MD) and 95% confidence interval (CI) with both random-effects and fixed-effects models, the results were then pooled for outcomes on the same scale. Statistical heterogeneity was assessed by visual inspection of the forest plots and by considering the I^2 measures. The threshold for I^2 was set at 25%: I^2 values <25% indicate homogeneity, allowing a fixed-effects model, and I^2 values ≥25% indicate heterogeneity, requiring a random-effects model. Review Manager 5.1 software (Cochrane Information Management System-IMS) and the inverse variance method with generic inverse data type was used to combine the study data extracted, to calculate the MDs and CIs, and to use forest plots to visualize the results. For each study effect sizes were calculated (i.e., MD and 95% CI) if these were not given in the article. If meta-analysis was not possible, a best-evidence synthesis was used as a second-best method to summarize the results of the studies included. A rating system was used that consisted of 5 levels of scientific evidence, and took account of the design, methodological quality and outcome of the original studies.[24]

The following levels were defined:

- *Strong evidence for effectiveness*: consistent (when ≥75% of the studies report the

same findings) positive (significant) findings among multiple high-quality RCTs
- *Moderate evidence for effectiveness*: consistent positive (significant) findings among multiple low quality RCTs and/or multiple high-quality CCTs and/or 1 high-quality RCT
- *Limited evidence for effectiveness*: positive (significant) findings in 1 low-quality RCT and/or 1 high/low-quality CCT
- *Conflicting evidence for effectiveness*: provided by conflicting (significant) findings in the RCTs and/or CCTs (<75% of the studies reported consistent findings)
- *No evidence found for effectiveness*: RCTs and/or CCTs available, but no (significant) differences between intervention and control groups were reported
No RCTs or CCTs found

RESULTS

Characteristics of the studies included

The initial literature search identified 754 studies, 170 from PubMed, 370 from Embase, 62 from CINAHL and 152 from the Web Of Knowledge. After duplicates had been removed, 532 studies remained. If the full text of an abstract was not available, we requested the authors to send it. We eventually assessed 29 full-text articles for eligibility. Six of these, with in total 494 patients with MS, met the inclusion criteria and were included in this review. The process of inclusion and exclusion was modeled on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow-diagram[25] (Figure 5.1). Four studies were RCTs[11,13,26,27], 2 were CCTs[14,15], and all had been published between 2003 and 2011. All studies had used crossover designs; until the point of crossover, all were RCTs or CCTs.

We contacted the authors of each study, requesting additional information or data on the study outcomes. All authors sent these data, some of which were previously unpublished, and gave their permission to use them. Four studies based their ECM intervention programs on the 6-week Packer course 'Managing Fatigue'[10], and 2 studies based their ECM-related intervention programs on the MS fatigue guidelines.[1]

Data Extraction

Supplement 5.2 summarizes the details of participants, treatments, control interventions, and outcomes measured in the 6 studies included in the review. For the calculations in this review we used either the original data[13,15], additionally data sent by personal communication[14,26,27] or a combination[11] of these.

Methodological quality assessment

Table 5.1 shows the methodological quality of the 6 studies. The 4 RCTs[11,13,26,27] and 1 of the CCTs[15] were classified as high quality, indicating low risk of bias. The other CCT[14] was of low quality, indicating high risk of bias. In all studies descriptions of the co-interventions undergone by participants during the intervention or follow-up were either described poorly or not at all.

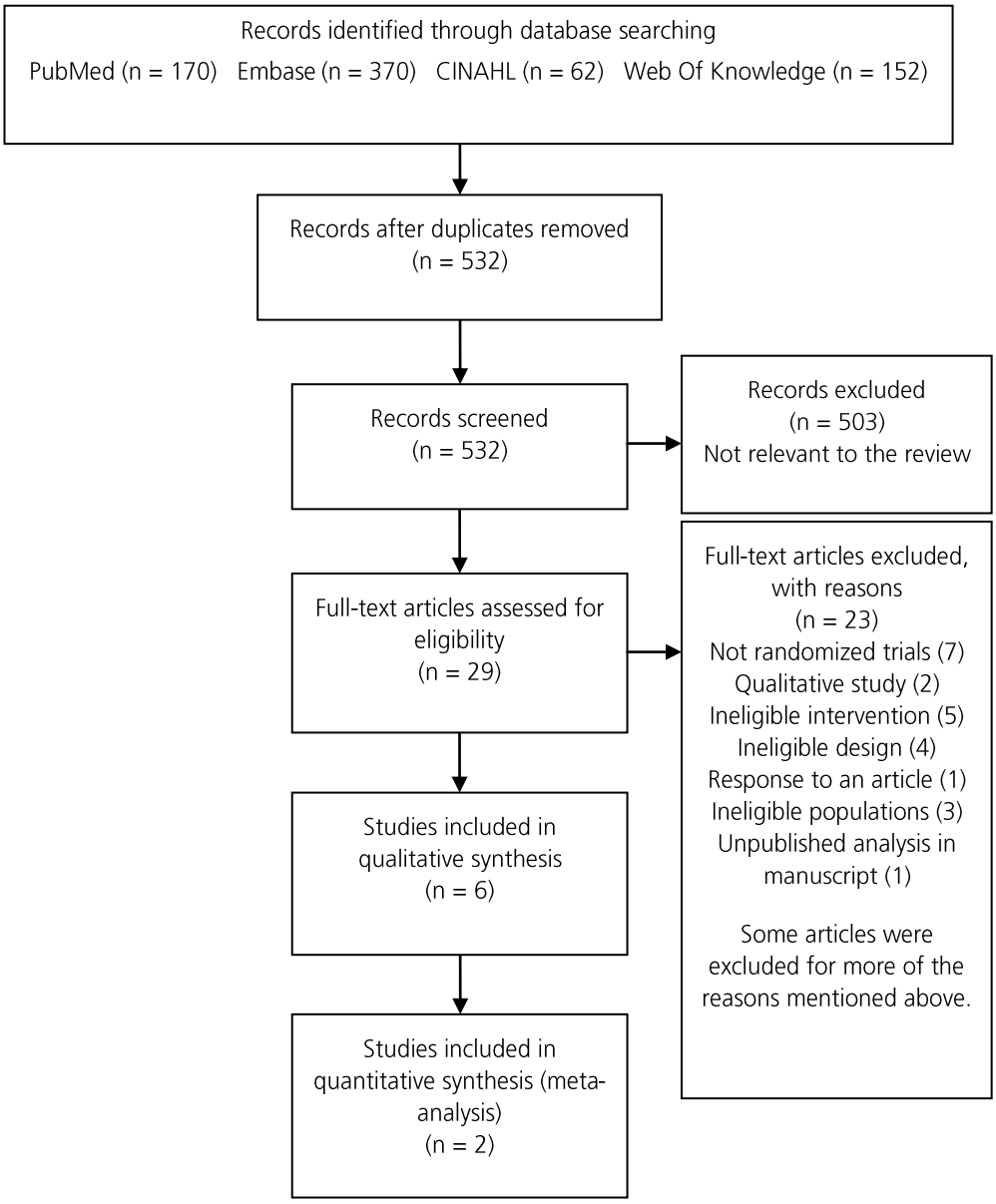

Figure 5.1. Flow diagram of the literature search

Table 5.1. Risk of bias table and methodological quality scores of the studies included.

Study	1.Adequate Random-ization?	2.Alloca-tion Conceal-ment?	3.Blinding Patients?	4.Blinding care provider?	5.Blinding Outcome Assessors ?	6.Incom-plete Outcomes Addressed? Drop-outs?	7.Partici-pants Analyzed in their Allocated Group?	8.Free of Suggestio n of Selective Outcome Reporting ?	9.Similar-ity of Baseline Charac-teristics?	10.Co-interven-tions Avoided or Similar?	11.Com-pliance Accep-table in All Groups?	12.Timing of the Outcome Assess-ment Similar?	Maxi-mum Score	Score Study	%
Mathiowetz[13] (2005)	+	+	-	-	?	+	+	+	+	+	+	+	12	9	75
Kos[27] (2007)	+	+	-	-	?	+	+	-	+	+	+	+	12	8	67
Finlayson[11] (2011)	+	+	-	-	-	+	+	+	+	-	+	+	12	8	67
Hugos[26] (2010)	+	+	-	-	-	-	+	+	+	+	+	+	12	8	67
Vanage[15] (2003)	-	-	-	-	-	+	+	+	+	?	+	+	12	6	50
Sauter[14] (2008)	-	-	-	?	-	+	+	+	+	?	+	-	12	5	42

Scores yes (+), unclear (?), or no (-), where yes indicated that the criterion had been met and thus suggested a low risk of bias. High quality was defined as a score of 50% or more (ie, a 'yes' score on ≥50% of the criteria) on the methodological quality assessment.

EFFECTIVENESS OF ECM TREATMENT

Data from the studies that could not be pooled were described using a best-evidence synthesis. The calculated effect sizes are presented in Table 5.2. Because of the heterogeneity between the studies with regard to type of MS, the different outcomes measured, and the content of the intervention and the control treatments, pooling was impossible in most cases. However, 2 studies[11,13] made it possible to pool data from the subscale outcomes of the Fatigue Impact Scale (FIS) and health-related QoL scale–the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). Since there were 2 studies, a sensitivity analysis was unnecessary. Table 5.3 presents a complete overview of the evidence provided by the 2 meta-analyses and by the best-evidence synthesis for the different comparisons and their outcomes.

Below, the effectiveness of ECM treatment on the 3 outcomes–fatigue, participation and QoL–are presented separately.

EFFECTIVENESS OF ECM TREATMENT ON FATIGUE

ECM treatment versus support group

The CCT of Vanage et al.(2003)[15] (N=37, high-quality) compared an ECM treatment group with a support group. From baseline to 8 weeks' follow-up in a 100% progressive MS patient group, the FIS total score improved significantly (*P*=.008) in favor of the ECM treatment group. The 3 FIS subscale scores–cognitive functioning (*P*=.042), physical functioning (*P*=.026) and psychosocial functioning (*P*=.007)–also improved significantly in favor of this group. The effect sizes calculated for the 2 groups at 8 weeks showed that the FIS total score (MD= -23.80; 95% CI, -45.65 to -1.95) and the psychosocial subscale (MD= -13.80; -25.17 to -2.43) were significantly better in favor of the ECM treatment group.

The best-evidence synthesis shows that there is limited evidence for the short-term effectiveness of ECM treatment over a support treatment on the impact of fatigue.

Table 5.2. Calculated effect sizes of data from studies that could not be pooled.

			Follow-up term Short		Mid		Long	
			Effect size		Effect size		Effect size	
Study	Outcome		MD (95% CI)	*P*	MD (95% CI)	*P*	MD (95% CI)	*P*
Vanage et al,[15] 2003	Fatigue		Groups compared at 8 weeks					
	FIS	Total	-23.80 (-45.65 to -1.95)	.03*	NR		NR	
		Cognitive	-6.10 (-12.33 to 0.13)	.06	NR		NR	
		Physical	-3.90 (-9.58 to 1.78)	.18	NR		NR	
		Psychosocial	-13.80 (-25.17 to -2.43)	.02*	NR		NR	
Finlayson et al,[11] 2011	Fatigue		Groups compared at 7 weeks					
	FIS	Total	-17.00 (-25.60 to -8.40)	.0001*	NR		NR	
Sauter et al,[14] 2008	Fatigue		Groups compared at 7 weeks					
	MFIS	Total	-10.71 (-20.03 to -1.39)	.02*	NR		NR	
		physical	-3.02 (-7.21 to 1.17)	.16	NR		NR	
		cognitive	-7.92 (-13.77 to -2.07)	.008*	NR		NR	
		psychosocial	0.23 (-1.36 to 1.82)	.78	NR		NR	
	FSS scale score		-0.10 (-0.77 to 0.57)	.77	NR		NR	
	MS Fatigue Scale		0.21 (-0.64 to 1.06)	.63	NR		NR	
Kos et al,[27] 2007	Fatigue		Groups compared at 7 weeks		Groups compared at 28 weeks			
	MFIS Total		1.00 (-5.44 to 7.44)	.76	-4.28 (-11.77 to 3.21)	.26	NR	
	FSS		1.50 (-3.49 to 6.49)	.56	0.42 (-4.23 to 5.07)	.86	NR	
	Participation-IPA		-0.05 (-0.33 to 0.23)	.72	-0.09 (-0.42 to 0.24)	.59	NR	
Hugos et al,[26] 2010	Fatigue		Groups compared at 8 weeks					
	MFIS Total		-4.61 (-13.73 to 4.51)	.32	NR		NR	
	FSS		1.73 (-6.11 to 9.57)	.67	NR		NR	

Abbreviations: FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; IPA, Impact on Participation and Autonomy; MFIS, Modified Fatigue Impact Scale. NR, no results. *Significantly more effective in favor of the ECM treatment group

Table 5.3 Overview of evidence for effectiveness of ECM or ECM-related treatments (meta-analysis and best-evidence syntheses).

Outcome	Follow-up Short	Mid	Long
ECM treatment vs. support groups			
Studies included: Vanage et al,[15] 2003	*Best-evidence synthesis*		
Fatigue	+ (FIS total and all subscales)	NR	NR
Participation	NR	NR	NR
QoL	NR	NR	NR
ECM treatment vs. waiting controls			
Studies included: Mathiowetz et al,[13] 2005; Finlayson et al, [11] 2011; and Sauter et al,[14] 2008			
	Meta-analysis		
Fatigue (FIS)	FIS subscales results[11,13] comparing the difference		
Subscales:	between the groups, Pooled Effect size (MD(95% CI),*P*)		
Cognitive	-2.91 (-4,32 to -1.50), .0001*	NR	NR
Physical	-2.99 (-4.47 to -1.52), .0001*	NR	NR
Psychosocial	-6.05 (-8.72 to -3.37), < .00001*	NR	NR
Participation	NR	NR	NR
QoL (SF-36)	SF-36 subscale results[11,13] comparing the difference		
Subscales:	between the groups, Pooled Effect size (MD(95% CI),*P*)		
Physical function	1.35 (-1.80, 4.50), .40	NR	NR
Role physical	17.26 (9.69, 24.84), < .00001*	NR	NR
Body pain	4.35 (-0.49, 9.19), .08	NR	NR
General Health	2.52 (-1.05, 6.10), .17	NR	NR
Vitality	7.39 (-0.40, 15.17), .06	NR	NR
Social function	6.91 (1.32, 12.49), .02*	NR	NR
Role emotional	9.85 (-0.26, 19.96), .06	NR	NR
Mental health	5.55 (2.27, 8.83), .0009*	NR	NR
	Best-evidence synthesis		
Fatigue	+[14](MFIS total & subscale cognitive)	NR	NR
Participation	NR	NR	NR
QoL	NR	NR	NR
ECM-related treatments (FTC[26] or MFMP[27]) vs. waiting controls[26] or placebo intervention[27]			
Studies included: Hugos et al,[26] 2010; and Kos et al,[27] 2007			
	Best-evidence synthesis		
Fatigue	ND	ND	NR
Participation	ND	ND	NR
QoL	NR	NR	NR

Abbreviations: FIS, Fatigue Impact Scale; QoL, Quality of Life; MFIS, Modified Fatigue Impact Scale; FTC, Fatigue: Take Control;; MFMP, Multidisciplinary Fatigue Management Program; ND, no differences found: randomized or controlled clinical trials available, but no differences found for effectiveness of the treatment between intervention and control groups; NR, no results; +, limited evidence found.
* Significantly more effective in favor of the ECM treatment group.

ECM treatment versus waiting controls

Two high-quality RCT studies by Mathiowetz et al[13] (N=169) and Finlayson et al[11] (N=181) studied the effectiveness of the ECM treatment versus no treatment (waiting controls) and reported on the FIS subscale outcomes at short-term follow-up. The data of the FIS subscales were pooled in a meta-analysis using a fixed-effect model. This showed that ECM treatment was more effective than no treatment (waiting controls) in reducing fatigue impact. ECM treatment improved FIS subscale scores significantly on the cognitive scale (MD= -2.91; 95% CI, -4.32 to -1.50; I^2=0%), the physical scale (MD= -2.99; 95% CI, -4.47 to -1.52, I^2=0%) and the psychosocial scale (MD= -6.05, 95% CI, -8.72 to -3.37, I^2=0%); see Figure 5.2 for the FIS subscale forest plots.

Further, the effect size calculated for the FIS total score at 7 weeks' follow-up reported by Finlayson et al[11] showed better fatigue scores in the ECM treatment group (MD= -17.00; 95% CI, -25.60 to -8.40) than in the waiting control group. The effect size calculated for the Modified Fatigue Impact scale (MFIS) at 7 weeks' follow-up reported by the CCT of Sauter et al[14] (N=32, low quality) showed better fatigue scores in the ECM treatment group for the total score (MD= -10.71; 95% CI, -20.03, -1.39) and for the cognitive subscale (MD= -7.92; 95% CI, -13.77 to -2.07) than in the waiting control group.

Between the groups from baseline to 7 weeks, Finlayson et al[11] and Sauter et al[14] found no significant differences for Fatigue Severity Scale (FSS) scores; and Sauter et al[14] found no significant differences either on the mean weekly scores for daily level of fatigue or on the MS-specific Fatigue Scale (MSFS).

The meta-analysis shows that, in the short-term, ECM treatment was more effective than no treatment (waiting controls) for all subscales of the FIS. The best-evidence synthesis shows that, on the modified scale of the total fatigue impact and its cognitive subscale, there is limited evidence that ECM treatment is more effective in the short term than no treatment (waiting controls). No evidence for effectiveness was found for the severity of fatigue, the daily fatigue scores, and the exogenous and endogenous effects on fatigue (MSFS).

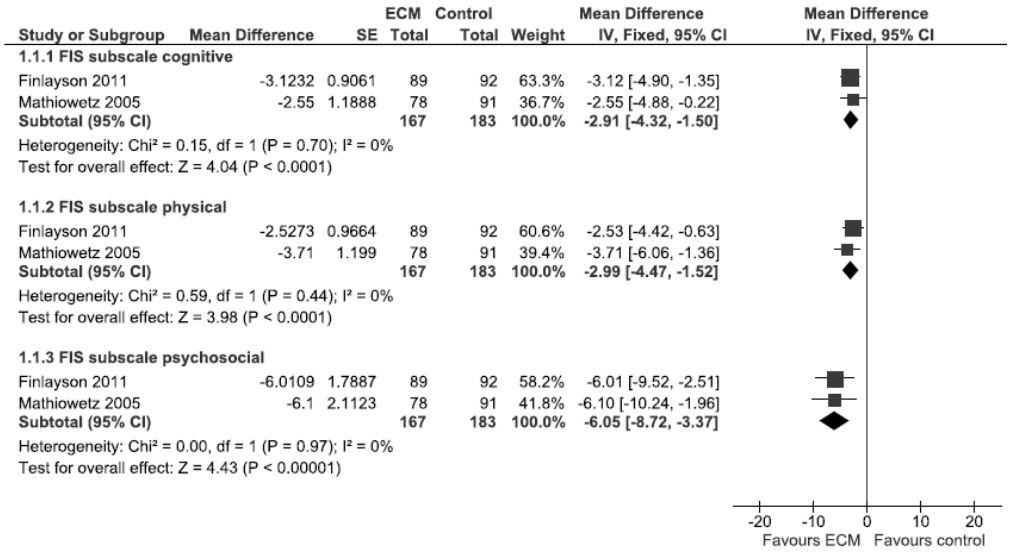

Figure 5.2. Forest plots for the effect of ECM treatment versus control treatment on fatigue assessed with the FIS subscales.

Abbreviations: df, degrees of freedom; IV, inverse variance.

Other ECM-related fatigue treatments versus a waiting list or placebo intervention group

The authors of the pilot RCT by Hugos et al[26] (N=30, high-quality) sent additional data on the comparison at 8 weeks, before the waiting control group crossed over to the intervention. There were no significant differences between the 'fatigue take control' treatment group and the waiting control group for the MFIS total or the FSS at 8 weeks' follow-up, as reported in Table 5.2. Neither did Kos et al[27] (N=51, high-quality RCT) find any significant differences between the multidisciplinary fatigue management program (MFMP) intervention and the placebo intervention for the MFIS total and FSS from baseline to 7 weeks and to 28 weeks' follow-up.

The best-evidence synthesis shows that there is no evidence that, in the short-term and midterm, the effectiveness of the ECM-related treatments on fatigue impact and severity is any greater than that of no treatment (waiting controls) or placebo intervention.

EFFECTIVENESS OF THE ECM TREATMENT OR OTHER ECM-RELATED FATIGUE TREATMENTS ON PARTICPATION AND QOL

Participation

Of the 6 studies, 1 reported on participation. This was an ECM-related treatment study[27] that compared the MFMP intervention with a placebo intervention and assessed the Impact on Participation and Autonomy scale (IPA). It found no significant differences in the short-term or midterm.

We found no RCTs or CCTs that studied the effects of the Packer-based ECM treatment on restrictions in participation. Neither, on the basis of the best-evidence synthesis, was any evidence found for the effectiveness of the ECM-related fatigue treatment MFMP on restrictions in participation.

Quality of Life: ECM treatment versus waiting controls

Two of the 6 studies reported an outcome on Quality of Life (QoL); the other 4 studies did not. In the short-term, 2 studies[11,13] reported on the QoL outcome SF-36. The data of the SF-36 subscales were pooled in a meta-analysis using a fixed-effect model, the substantial heterogeneity in the vitality subscale required a random-effects model. This showed that ECM treatment was more effective than no treatment (waiting controls) in improving the QoL subscales role physical (MD= 17.26; 95% CI, 9.69 to 24.84, I^2=0%), social function (MD= 6.91; 95% CI, 1.32 to 12.49, I^2=0%), and mental health (MD= 5.55; 95% CI, 2.27 to 8.83, I^2=0%), for the forest plot see Supplement 5.3. There was no difference between the treatment groups for 5 QoL domains: physical function, body pain, general health, vitality and role emotional.

The meta-analysis shows that, in the short-term, ECM treatment was more effective than no treatment (waiting controls) for 3 QoL subscales: role physical, social function and mental health.

DISCUSSION

The aim of the present study was to systematically review the effects of ECM treatment for fatigue in patients with MS. We also studied the effects of ECM treatment on restrictions in participation and on QoL. Six studies were included in this review. They compared the effects in MS patients of ECM or ECM-related treatment with those of no treatment (waiting controls), a placebo, or support. All studies included outcomes on fatigue, 1 also studied participation and 2 also studied QoL. All 6 reported short-term effects; 1 also reported midterm effects.

Fatigue

Our meta-analysis of 2 high-quality studies[11,13] with a large sample showed that ECM treatment based on Packer reduced fatigue impact in the short-term. This is supported by the qualitative best evidence synthesis of the ECM treatment studies[11,14,15]; namely, strong and moderate evidence was found. No evidence was found, based on a small sample, that fatigue was reduced by the ECM-related treatment programs based on the MS Fatigue Guidelines.[26,27] However, supported by the results of an analysis on the total group, Hugos et al[26] suggested that the treatment may reduce fatigue; therefore, a larger study is planned to test the efficacy of this program. None of the studies found evidence that ECM treatment was effective with regard to the other fatigue outcomes.

Participation

Only 1 study[27] reported on the effects of ECM-related treatment on participation in the short-term and midterm, but found no evidence that it was effective.

Quality of Life

Our meta-analysis for the QoL outcome SF-36 of the same 2 high-quality studies[11,13] showed that ECM treatment improved 3 QoL domains in the short-term: role physical, social function and mental health. Here, meta-analysis demonstrates its value: it was only by pooling 2 studies that ECM treatment was shown to improve the QoL

domains mental health and social function.

The crossover designs of all 6 studies produced no results on long-term effects of the ECM treatment on fatigue, restrictions in participation, or QoL outcomes.

The evidence for the effectiveness of the ECM treatment on fatigue was based mainly on the meta-analysis in which subscales of the FIS were pooled. In the scientific literature we found that (1) FIS total and subscales are sufficient to measure fatigue impact as an overall or subscore[28], (2) it is not advised to use the MFIS total score as an overall score because its multidimensionality makes it invalid[29]; and (3) a study by Mathiowetz et al[30] recommended that FIS should be used to evaluate the effectiveness of fatigue management interventions such as energy conservation education for people with MS. These findings reinforce our conclusion on the effectiveness of ECM treatment on fatigue, which was measured with the FIS. The inadvisability of using MFIS may explain the apparent lack of improvement when MFIS was used to measure fatigue after ECM-related treatment.

The studies included in our review identified 3 gaps in the literature on ECM treatment that might indicate points of focus for researching the effects of ECM strategies as a treatment for fatigue.

The first gap is that the 6 studies made their follow-up measurements after the control group had crossed over, and therefore described a group whose members had all received the ECM treatment. Although, 2 studies reported beneficial effects of the ECM treatment up to 6 months[11] and to 1-year follow-up[31], no comparison was made between the intervention and control group. Consequently, at present, the scientific literature contains no RCTs that compare intervention and control groups on long-term follow-up. Besides, ECM treatment with its focus on energy management strategies intends to bring about behavioral changes. Behavioral change implies that it takes time for a patient to implement the strategies they learned during the treatment. Further, Finlayson et al[32] noted that program benefits begin to weaken 3 months post intervention. Altogether, it would be valuable to study the midterm and long-term effects of ECM-treatment on fatigue, participation and QoL in a controlled design.

The second gap is that, fatigue seriously affects societal participation of patients with MS patients.[4,5] The social consequences of MS may in fact be of more concern to patients than impairments or specific activity limitations. The energy conservation strategies learned during ECM treatment are also intended to improve societal participation. Except for one, the studies included in this review did not measure outcomes on restrictions in participation. Future studies on the effects of ECM treatment should therefore add participation outcomes.

The final gap is that, while most clinical practices use a one-to-one format, the current scientific literature has studied the ECM treatment only in group format[10-15,26,27,33,34]. Group processes in themselves may influence patients' behavior changes in ways the ECM program does not intend. We recommend that the effectiveness of ECM treatment is also investigated in other formats, such as an individual one-to-one format. Nowadays, many occupational therapists use one-to-one formats for outpatient rehabilitation treatment. Valuable additional evidence would be provided if the results of the ECM treatment group-format were extended to a one-to-one format.

Study Limitations

We believe this review provides an up-to-date evidence-based overview of the effectiveness of ECM treatment in reducing fatigue in fatigued MS patients. However, some limitations have to be addressed. First, although 2 high-quality studies with a total of 350 participants provided evidence for the effectiveness of ECM-treatment on the impact of fatigue and QoL, our results are based on only 6 studies and should thus be interpreted cautiously. Second, because all 6 studies failed to meet some of the risk-of-bias domains, their results may be biased; in all 6, the nature of the intervention made it impossible to blind participants, care providers and outcome assessors. Even though the advised threshold[23] for methodological quality was chosen arbitrarily, a threshold of 40% or 60% would not have altered the conclusions of this review. Third, although we conducted a complete search, we could not exclude the possibility of publication bias, as we might have missed unpublished studies with for example nonsignificant or negative results. We did, however, personally contact the

authors of the 6 included studies to gain additional unpublished data of their results.

Conclusion

To the best of our knowledge, this study was the first systematic review and meta-analysis to study the effects of ECM treatment for fatigue and whether it affects restrictions in participation and QoL in patients with MS. The results provide evidence that ECM treatment can be more effective than no treatment (waiting controls) in reducing the impact of fatigue and improving 3 QoL scales–role physical, social function and mental health–in fatigued MS patients in the short-term. Only 1 study presented results on participation: no evidence was found that ECM treatment was effective on this outcome. Although ECM treatment intends behavioral changes that take time to implement, none of the included studies reported long-term results. More high-quality RCTs, that also study long-term effects, are needed to confirm our findings and before firm conclusions can be made.

Acknowledgements

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SUPPLEMENT 5.1 SEARCH STRATEGY

PubMed

(energy manag*[tw] OR energy conserv*[tw] OR energy sav*[tw] OR work simpl*[tw] OR adaptive pac*[tw] OR fatigue manag* [tw] OR managing fatigue[tw]) AND (Multiple scleros*[tw] OR Nervous System Diseases[mesh] OR stroke[tw] OR chronic fatigue[tw] OR Parkinson[tw] OR Spinocerebellar Atax*[tw]) NOT (animals[mesh] NOT humans[mesh])

Embase

(((energy* OR fatigue) NEAR/3 (manag* OR conserv* OR sav*)):ti,ab,de OR (work NEXT/1 simpl*):ti,ab,de OR (adaptive NEXT/1 pac*):ti,ab,de) AND ('neurologic disease'/exp OR ((Multiple NEXT/1 scleros*) OR stroke OR 'chronic fatigue' OR Parkinson OR (Spinocerebellar NEXT/1 Atax*)):ti,ab,de) NOT ([animals]/lim NOT [humans]/lim)

CINAHL

("energy manag*" OR "energy conserv*" OR "energy sav*" OR "work simpl*" OR "adaptive pac*" OR "fatigue manag*" OR "managing fatigue" OR "work simpl*" OR "adaptive pac*") AND ("neurologic disease" OR "Multiple scleros*" OR stroke OR "chronic fatigue" OR Parkinson OR "Spinocerebellar Atax*")

Web Of Knowledge

("energy manag*" OR "energy conserv*" OR "energy sav*" OR "work simpl*" OR "adaptive pac*" OR "fatigue manag*" OR "managing fatigue" OR "work simpl*" OR "adaptive pac*") AND ("neurologic disease" OR "Multiple scleros*" OR stroke OR "chronic fatigue" OR Parkinson OR "Spinocerebellar Atax*")

SUPPLEMENT 5.2 CHARACTERISTICS OF THE STUDIES

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
Vanage et al. (2003)[15]	Type of MS: 100% Progressive MS	N= 21 (ECM-group)	N= 16 (Control-group)	FIS (8 wk) Total and Sub-scale fatigue scores		*Article results:* Results from baseline to 8 weeks for ECM vs. control group
Crossover design	Age: Group A: 56.3(10.5)y Group B: 54.7(10.5)y	Energy conservation course by Packer†, treatment by an Occupational Therapist Modifications from the original Packer program: 2 more course sessions, 1 hour/week less and smaller groups	Traditional support group Content: Occupational Treatment (crafts and art-work), Physical Treatment (stretch & strength) and the chaplain-lead support group (discuss MS illness and its daily challenges). Support period is followed by the ECM course (cross-over design)	*Total*	$p = 0.008$	ECM from 72.5(25.7) to 53.0(25.8) vs. Controls from 77.1(34.8) to 76.8(38.5)
CCT	EDSS: ≥ 5.5 FSS: 5.3(0.9) for both groups	Group-format: face-to-face		*Cognitive*	$p = 0.042$	ECM from 15.7(8.9) to 10.8(7.7) vs. Controls from 18.2(9.5) to 16.9(10.8)
				Physical	$p = 0.026$	ECM from 23.6(5.9) to 17.9(7.1) vs. Controls from 21.9(9.4) to 21.8(9.8)
		Group size: 3-8 patients Duration: 8 weeks with 8 sessions (1h each)	Group size: 3-8 patients Duration: 8 weeks with 8 Sessions (1h each)	*Psychosocial*	$p = 0.007$	ECM from 33.2(14.1) to 24.3(13.5) vs. Controls from 37.0(18.5) to 38.1(20.0)
						Results from personal correspondence: The p-values of FIS total and subscales as reported above. The control-group crossed over after 8 weeks from baseline and from then FU-results were reported for the total group (ECM+control).

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
Sauter et al. (2008)[14] Crossover design CCT	Type of MS: 53% RR; 13.3% PP; 33.3% SP Age: Not reported EDSS: 4.0(1.9) FSS: 5.5(0.87) total group	N= 13 (ECM-group) Energy conservation course by Packer†, treatment by an Occupational Therapist Group-format: face-to-face Group size: 6-8 patients Duration: 6 weeks with 6 sessions (2h each)	N= 13 (WL-group) Waitlist control group Control period is followed by the ECM course (cross-over design) Group size: 6-8 patients Duration: 6 weeks	Daily level of fatigue (7 wk)	The differences in mean scores of group A vs. B were NS No p-value reported	*Article results:* Fatigue scores from baseline to 7 weeks in mean week scores. Rated on a VAS scale from '10-extremely fatigued' to '0-not fatigued at all'. ECM from 6 to 5.5 WL from 6 to 6.8 (remark: Scores are not exact but estimated from figure 1 of the article) *Results from personal correspondence:*
				MFIS (7 wk)		Results of ECM vs. WL group at 7 weeks
				Total	$p = 0.036$	45.46(9.49) for ECM vs. 56.17(14.29) for WL
				Physical	$p = 0.180$ NS	22.15(5.23) for ECM vs. 25.17(5.67) for WL
				Cognitive	$p = 0.016$	19.08(7.08) for ECM vs. 27.00(8.10) for WL
				Psychosocial	$p = 0.781$ NS	4.23(1.48) for ECM vs. 4.00(2.52) for WL
				MS fatigue scale (7 wk)		Results of ECM vs. WL group at 7 weeks
					$p = 0.654$ NS	4.92(1.12) for ECM vs. 4.71(1.09) for WL

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
				FSS (7 wk)		Results of ECM vs. WL group at 7 weeks
					p = 0.707 NS	5.4(0.78) for ECM vs. 5.5 (0.95) for WL
						The WL-group crossed over after 6 weeks from baseline and from then FU-results were reported for the total group (ECM+WL)
Mathiowetz et al. (2005)[13]	Type of MS: 61,5% RR; 18.9% SP 5.9% PP; 1.8% PR; 11.8% unknown	N= 78 (ECM-group)	N= 91 (WL-group)			*Article results: ITT Likelihood*
	Age: 48.34(8.44)y in the total group in the *ITT* analysis	Energy conservation course by Packer†, treatment by 12 Occupational Therapists	Waitlist control group Control period is followed by the ECM course (cross-over design)	FIS (7 wk) Subscales		Difference in means (with 95% CI) between ECM-group vs. WL-group from baseline to 7 week FU*.
Crossover design RCT		Group-format: face-to-face		*Cognitive*	p = 0.0092	-2.55 (-4.88, -0.21)
		Group size: 7-10 patients	Group size: 7-10 patients	*Physical*	p = 0.0002	-3.71 (-6.06, -1.37)
	EDSS: Not reported	Duration: 6 weeks with 6 sessions, 2h/week	Duration : 6 weeks	*Psychosocial*	p = 0.0005	-6.10 (-10.24, -1.95)
	FSS: 5.93(0.65)			SF36 (7 wk) Subscales		Difference in means (with 95% CI) between ECM-group vs. WL-group from baseline to 7 week FU*.
				Physical function	p = 0.4290 NS	1.75 (-4.36, 7.87)
				Role Physical	p = 0.0040	15.18 (0.78, 29.57)
				Body Pain	p = 0.4100 NS	2.69 (-6.33, 11.71)
				General Health	p = 0.7179 NS	0.81 (-5.40, 7.02)
				Vitality	p < 0.0001	11.64 (5.48, 17.79)

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
				Social Function	$p = 0.0515$ NS	6.06 (-2.49, 14.60)
				Role Emotional	$p = 0.0687$ NS	13.23 (-6.77, 33.24)
				Mental Health	$p = 0.0062$	6.12 (0.01, 12.24)
						Results from personal correspondence: not applicable
						The WL-group crossed over after 7 weeks from baseline and from then FU-results were reported for the total group (ECM+WL)
Finlayson et al. (2011)[11]	Type of MS: 52% RR; 22% SP; 9% PP; 6% PR; 9% unknown; 2% no data	N = 89 (ECM-group)	N = 92 (WL-group)			*Article results: ITT Likelihood*
Crossover design RCT	Age: 56(9)y in the total group in the ITT analysis	Energy conservation course by Packer†, treatment by an Occupational Therapist	Waitlist control group Control period is followed by the ECM course (cross-over design)	FIS (7 wk) Subscales		Mean difference of week 7 minus baseline scores between the groups *
		Group-format: Teleconference-delivered		*Cognitive*	$p = 0.0013$	-3.12 (6.10)
				Physical	$p = 0.0144$	-2.53 (6.47)
				Psychosocial	$p = 0.0021$	-6.01 (12.06)
	EDSS: Not reported PDDS: 4(2) FSS: 5(1)	Group size: 5-7 patients Duration: 6 weeks with 6 sessions of 70-min teleconference calls	Group size: 5-7 patients Duration: 6 weeks	FSS (7 wk)		Mean differences of week 7 minus baseline scores between the groups
					$p = 0.2403$ NS	-0.18 (0.96)

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
				SF36 (7 wk) Subscales		Mean difference of week 7 minus baseline scores between the groups *
				Physical function	$p = 0.5384$ NS	1.20 (12.40)
				Role Physical	$p = 0.0002$	18.06 (30.49)
				Body Pain	$p = 0.1044$ NS	5.02 (19.64)
				General Health	$p = 0.1522$ NS	3.37 (14.96)
				Vitality	$p = 0.1367$ NS	6.68**(15.70)
				Social Function	$p = 0.0594$ NS	7.54 (25.35)
				Role Emotional	$p = 0.1699$ NS	8.69 (40.26)
				Mental Health	$p = 0.0123$ NS	5.32 (13.38)
						** result deviated from the mean difference that we have calculated with the means of the groups separately
						Results from personal correspondence:
				FIS (7 wk) Total score	No p-values of the difference between groups were given	Results of the total FIS score for baseline vs. week 7 ECM group: 120(31) vs. 103(29) WL group: 125(28) vs. 120(30)
				FIS (7 wk) Subscales		Mean difference of week 7 minus baseline scores for ECM group vs. WL group*
				Cognitive		-4.23(6.01) for ECM vs.-

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
						1.11(6.18) for WL
				Physical		-3.74(6.74) for ECM vs. -1.21(6.23) for WL
				Psychosocial		-8.39(11.66) for ECM vs. -2.38(12.39) for WL
				SF36 (7 wk) Subscales		Mean difference of week 7 minus baseline scores for ECM group vs. WL group*
				Physical function		3.73(14.66) for ECM vs. 2.53(10.05) for WL
				Role Physical		15.79(31.31) for ECM vs. -2.27(29.76) for WL
				Body Pain		4.17(20.28) for ECM vs. -0.85(19.07) for WL
				General Health		3.13(15.50) for ECM vs. -0.24(14.48) for WL
				Vitality		6.97(17.11) for ECM vs. 3.30(14.38) for WL
				Social Function		8.38(24.95) for ECM vs. 0.85(25.69) for WL
				Role Emotional		10.96(39.40) for ECM vs. 2.27(40.99) for WL
				Mental Health		6.78(13.29) for ECM vs. 1.47(13.44) for WL
						The WL-group crossed over after 7 weeks from baseline and from then FU-results were reported for the total group (ECM+WL)

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
Hugos et al. (2010)[27]	Type of MS: Mild/moderately disabled MS; exact type of MS not reported	N = 15 (FTC-group)	N = 15 (WL-group)			*Article results:*
		Fatigue: Take Control program (FTC) based on the MS fatigue Guidelines‡	Waitlist control group Control period is followed by the FTC program (crossover design)	MFIS (baseline) Total score	p = 0.636 NS	Baseline results for FTC vs. WL group 44.00(10.66) for FTC vs. 45.87(10.33) for WL
Crossover design Pilot RCT	Age: 55.41(9.10)y in FTC; 58.44(7.68)y in WL	Group-format: face-to-face				The mean score (with SE) of MFIS total for FTC and WL group were described in a figure in the article for every measurement in the study, no p-values were reported
	EDSS: 4.90(1.18) in FTC 5.50(0.78) in WL FSS: 52.47(6.77) in FTC 51.53(8.44) in WL (a total summary score was used instead of the average response score with a maximum of 9)	Group size: 6-9 patients Duration: 6 weeks with 6 sessions of 2h/week	Group size: 6-9 patients Duration: 8 weeks and group met biweekly to complete 5 assessments			
				MFIS (baseline) Subscales		Baseline results for FTC vs. WL group
				Physical	p = 0.617 NS	21.36(5.31) for FTC vs. 22.33(5.07) for WL
				Cognitive	p = 0.959 NS	19.27(7.89) for FTC vs. 19.13(6.13) for WL
				Psychosocial	p = 0.774 NS	4.20(2.04) for FTC vs. 4.40(1.72) for WL
				FSS (baseline)		Baseline results for FTC vs. WL group
					p = 0.741 NS	52.47(6.77) for FTC vs. 51.53(8.44) for WL
				MFIS (8 wk) Total score		*Results from personal correspondence:* Results at 8 weeks for FTC vs. WL group

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
					p = 0.337 NS	39.79(13.95) for FTC vs. 44.40(11.41) for WL
				FSS (8 wk)		Results at 8 weeks for FTC vs. WL group
					p = 0.668 NS	49.13(9.00) for FTC vs. 47.40(12.60) for WL
						The WL-group crossed over after 8 weeks from baseline and from then FU-results were reported for the total group (ECM+WL)
Kos et al. (2007)[28]	Type of MS: Group A: 72% RR; 7% PP; 7% CP; 14% no data	N = 28 (Group A)	N = 23 (Group B)	MFIS (baseline)		*Article results:* Baseline results for group A vs. B in median(IQR)
Crossover design RCT	Group B: 61% RR; 13% PP; 17% CP; 9% no data	Multidisciplinary fatigue Management program (MFMP) based on the MS fatigue Guidelines‡	Placebo intervention program Content: topics not directly related to fatigue and	Total score	p = 0.719 NS	46 (38-54) for A vs. 46 (42-54) for B
	Age: 42.9(9.1)y for group A; 44.5(9.9)y for group B	Group-format: face-to-face	general MS information Control period (26 weeks) is followed by the MFMP (crossover design)	Subscales *Physical*	p = 0.468 NS	22 (17-26) for A vs. 22.5 (19-26) for B
				Cognitive	p = 0.792 NS	21 (16-26) for A vs. 20.5 (16-25) for B
				Psychosocial	p = 0.302 NS	4 (3-6) for A vs. 5 (4-6) for B
	EDSS: Not reported FSS: Not an inclusion criteria	Group size: 28 Duration: 4 weeks with 4 sessions of 2h/week	Group size: 23 Duration: 4 weeks with 4 sessions of 2h/week			

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
						Results from personal correspondence:
				MFIS (28 wk) Total score		Results group A vs. B at baseline, at 7 weeks, and at 28weeks
					p = 0.793 NS	Baseline: 46.32(10.92) for A vs. 47.13(10.89) for B
					p = 0.763 NS	week 7: 44.67(12.02) for A vs. 43.67(11.38) for B
					p = 0.267 NS	week 28: 42.56(13.26) for A vs. 46.84(13.83) for B
				FSS (28 wk)		Results group A vs. B at baseline, at 7 weeks, and at 28weeks
					p = 0.485 NS	Baseline: 51.14(10.81) for A vs. 52.69(6.62) for B
					p = 0.557 NS	Week 7: 50.58(8.81) for A vs. 49.08(9.23) for B
					p = 0.860 NS	Week 28: 51.77(8.52) for A vs. 51.35(8.35) for B
				IPA (28wk)		Results group A vs. B at baseline, at 7 weeks, and at 28weeks
					p = 0.393 NS	Baseline: 1.44(0.64) for A vs. 1.59(0.52) for B
					p = 0.713 NS	Week 7: 1.38(0.54) for A vs. 1.43(0.47) for B
					p = 0.591 NS	Week 28: 1.49(0.68) for A vs. 1.58(0.52) for B

Study	Participants (Values are mean(SD) or as otherwise stated)	Intervention	Control treatment	Outcomes (total time of follow-up)	P-value	Results (Values are mean(SD) or as otherwise stated)
						Group B crossed over after 28 weeks from baseline and from then FU-results were reported for the total group (A+B)

Abbreviations: RR, Relapsing-Remitting; SP, Secondary Progressive; PP, Primary Progressive; RP, Relapsing Progressive; CP, Chronic Progressive; EDSS, Expanded Disability Status Scale; h, hours; wk, weeks; y, year; ITT, Intention-to-treat; FU, Follow-up; NS, not significant; vs., versus; FIS, Fatigue Impact Scale; MFIS, Modified FIS; FSS, Fatigue Severity Scale; IPA, Impact on Participation and Autonomy; SF-36, Medical Outcomes Study Short-Form General Health Survey. In all fatigue scales, higher scores indicated that the patient is more fatigued. Higher scores for the IPA meant that the disease had a higher impact on participation and autonomy, higher scores for QoL meant a higher QoL.

* In this study the level of significance was adjusted for multiple testing a *p* smaller than 0.05/3 for the FIS and 0.05/8 for the SF-36 was significant.

† ECM course based on Packer six-week program 'Managing Fatigue': a six-week program based on the theory of psycho-educational group development and used a range of pedagogical techniques including lectures, discussions, long-term and short-term goal setting, practice activities and homework activities to assist participants' integration of EC principles into their performance of everyday tasks. The six sessions addressed the importance of rest throughout the day, positive and effective communication, proper body mechanics, ergonomic principles, modification of the environment, changing standards, setting priorities, activity analysis and modification, and living a balanced lifestyle.

‡ ECM-related course based on the MS fatigue Guidelines: FTC is a six-week program that present many ideas for behavioral, environmental and lifestyle changes that may enhance energy effectiveness and quality of life, the course is very similar to that of Packer but more attention is given to exercise and it is specifically designed for people living with MS-related fatigue; MFMP is a four-week program support and stimulate self-care strategies to cope with MS-related fatigue and highlights multidisciplinary aspects, besides energy saving methods and strategies by an occupational therapist.

SUPPLEMENT 5.3 FOREST PLOTS SF-36 SUBSCALES

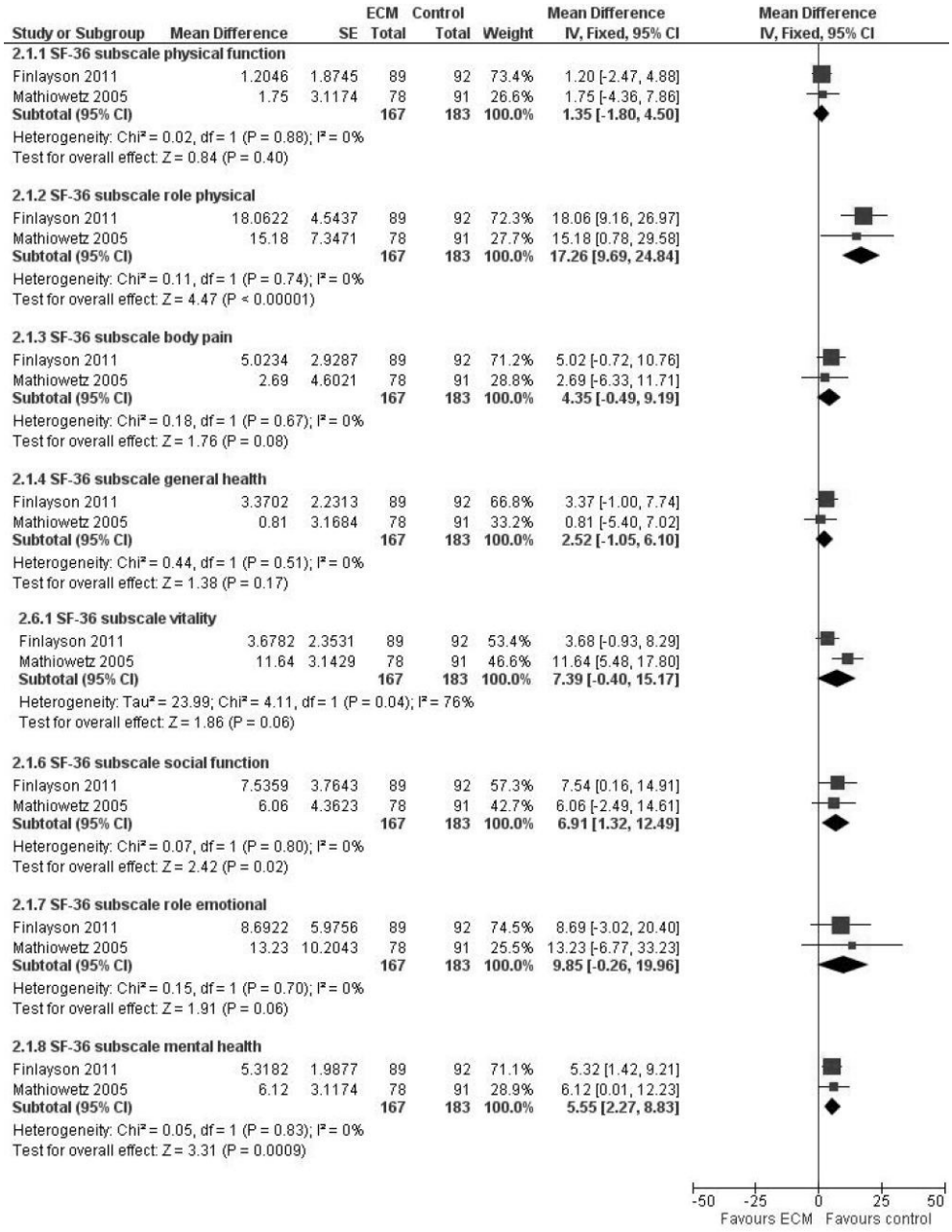

Figure 5.3. Forest plots for the effect of ECM treatment versus control treatment on SF-36 subscales. Abbreviations: df, degrees of freedom; IV, inverse variance.

Chapter 6

Effectiveness of Energy Conservation Management on fatigue and participation in Multiple Sclerosis: A Randomized Controlled Trial

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ABSTRACT

Background: Fatigue is a frequently reported and disabling symptoms in multiple sclerosis (MS).
Objective: To investigate the effectiveness of an individual Energy Conservation Management (ECM) intervention on fatigue and participation in persons with primary MS-related fatigue.
Methods: A total of 86 severely fatigued and ambulatory adults with a definite diagnosis of MS were randomized in a single-blind, two-parallel-arm randomized clinical trial to the ECM group or the information-only control group in outpatient rehabilitation departments. Blinded assessments were carried out at baseline and at 8, 16, 26 and 52 weeks after randomization. Primary outcomes were fatigue (fatigue subscale of Checklist Individual Strength-CIS20r) and participation (Impact on Participation and Autonomy scale-IPA).
Results: Modified intention-to-treat analysis was based on 76 randomized patients (ECM, n=36; MS-nurse, n=40). No significant ECM effects were found for fatigue (overall difference CIS20r between the groups = -0.81; 95% confidence interval (CI), -3.71 to 2.11) or for four out of five IPA domains. An overall unfavorable effect was found in the ECM group for the IPA domain social relations (difference between the groups = 0.19, 95% CI, 0.03 to 0.35).
Conclusion: The individual ECM format used in this study did not reduce MS-related fatigue and restrictions in participation more than an information-only control condition.

INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive neurological disease, with onset generally occurring in relatively young adults. MS causes a variety of clinical symptoms: neurological impairments, fatigue and depression.[1] Fatigue is the most frequently reported and disabling symptom of MS. However, the exact pathophysiological mechanism is still not completely understood.[2] MS-related fatigue has been defined by the Multiple Sclerosis Council for Clinical Practice Guidelines 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'.[3] Fatigue severely limits a person's daily activities and restricts societal participation.[4]

Reducing limitations of activities in daily life is an important rehabilitation treatment goal. Fatigue is multidimensional and can be managed using multiple approaches, including pharmacological therapies (such as Amantadine, Modafinil) and non-pharmacological therapies such as aerobic training, cognitive behavioral therapy, energy management, mindfulness or multidisciplinary treatment. At this time, there is no consensus about treatment for fatigue in MS. The non-pharmacological (or rehabilitation) therapies appear to have more significant effects on fatigue reduction than pharmacological treatments, but evidence is not conclusive.[5] However, multidisciplinary treatment, which often combines multiple different rehabilitation treatments, has not been shown to be effective.[6,7]

Energy conservation management (ECM) is a well-known strategy for fatigue rehabilitation by occupational therapists.[8] ECM involves teaching people to identify and modify their activities, through systematic analysis of daily work, home and leisure activities, in order to reduce the impact of fatigue on daily life.[3] The ECM group program, with several formats such as face-to-face, teleconference, self-study modules and online education, is based on the work of Packer et al[9] and originally addressed the management of fatigue secondary to chronic illness. The group program is effective in MS-related fatigue and quality of life issues at short-term compared to waitlist controls.[10-13] Although some studies have shown that beneficial effects were maintained up to six months after treatment,[12,14] a systematic review of

the available evidence shows that (randomized) controlled studies have produced little long-term data.[15] Also, participation outcomes are lacking in the performed studies. Furthermore, individual treatment formats are regularly applied in clinical practice, despite the lack of evidence for effectiveness of these approaches.[15]

This study was designed to investigate the effectiveness of an individual ECM intervention on fatigue and participation in persons with primary MS-related fatigue.

PATIENTS & METHODS

Study design

This study, a single-blind, two-parallel-arms randomized clinical trial (RCT) was performed in two outpatient rehabilitation departments in the Netherlands. The study was part of the multi-trial program Treating Fatigue in MS with Aerobic Training, Cognitive Behavioral Therapy and Energy Conservation Management (TREFAMS-ACE),[16] in which the effectiveness of three rehabilitation treatments on fatigue and participation is being evaluated. The protocol used in this study was described in the study design paper by Beckerman et al.[16] The protocol for this study was approved (NL number 33451.029.10; METc VUmc.nr 2010/289) by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands, and local feasibility statements were obtained from each participating center.

Study groups

Experimental intervention: Individual Energy Conservation Management. The protocol was based on the group program developed by Packer et al.[9], and consisted of 12 sessions by an occupational therapist over 4 months (Appendix 2 of this thesis). *Information-only control condition* consisted of three MS nurse consultations of 45 minutes each by experienced MS nurses over 4 months (Appendix 2 of this thesis). The nurses were trained to refrain from providing treatment or treatment advise. Instead, standardized information about MS-related fatigue was provided. The control group intended to control for attention and information about fatigue.

The therapists/nurses completed a program checklist to assess whether each participant and therapist/nurse adhered to the program.

Power analysis

The standard sample size calculation was based on the Checklist Individual Strength (CIS20r) fatigue subscale. This subscale has been previously used in studies of MS patients. In all, 45 patients per study arm were needed to detect a clinically relevant difference of 8 points at the end of treatment on the CIS20r fatigue subscale, with an standard deviation (SD) of 12.7, with a power of 80%, an alpha of 0.05 and a maximum attrition rate of 20%.[16]

Participants

Potential eligible persons with MS were initially recruited and informed by MS teams (rehabilitation physicians, MS nurses and neurologists) at the two participating outpatient clinics (Rijndam Rehabilitation department of Erasmus MC, Rotterdam, and Libra Rehabilitation Medicine & Audiology, location Leijpark at Tilburg). A rehabilitation physician checked the inclusion and exclusion criteria (Table 6.1). Before enrolment in the study, all participants provided written informed consent.

Table 6.1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Definitive diagnosis of MS - Severely fatigued (Checklist Individual Strength [CIS20r] subscale fatigue ≥ 35) - Aged between 18 and 70 years - Ambulant (Expanded Disability Status Scale [EDSS] score ≤ 6.0) - No evident signs of an MS exacerbation or a corticosteroid treatment < 3 months - No infections, anaemia, thyroid dysfunction	- Depression (Hospital Anxiety and Depression Scale [HADS] subscale depression >11) - Severe co-morbidity (Cumulative Illness Rating Scale [CIRS] item scores ≥ 3) - Primary sleep disorders - Current pregnancy or having given birth < 3 months - Newly initiated pharmacological (e.g. Amantadine) or non-pharmacological treatment for fatigue (e.g. ECM, AT, CBT or other) < 3 months

MS: multiple sclerosis; ECM: energy conservation management; AT: aerobic training; CBT: cognitive behavioral therapy. See Beckerman et al. 2013 (17) for a complete list of all inclusion and exclusion criteria

Randomization and masking

Following baseline measurements, the participants were randomly assigned to ECM or the control group. The randomization was concealed and computer-generated with a block size of 8, and stratified by treatment center. An independent investigator carried out the randomization, and informed the patient and the planning bureau of the allocated treatment. Patients were explicitly instructed and reminded not to disclose which treatment they were receiving to the single-blinded assessor. Furthermore, before analyses study identification numbers were re-coded (by the independent researcher) in order to facilitate blind analyses.

Outcomes

All measurements were carried out 1 week prior to randomization and at 8, 16 (i.e. post intervention), 26 and 52 weeks after starting the treatment. Outcome measures consisted of validated self-reported questionnaires and assessor-based interviews. The self-reported questionnaires were offered to participants via internet or on paper, and were completed at home. The sequence of the questionnaires was randomized between measurement occasions. The assessor-based interviews were conducted during the measurement visit to the participating outpatient rehabilitation departments.

Primary outcome measures. Fatigue was measured with the CIS20r, using the domain subjective experience of fatigue, focusing on the past two weeks.[17] This fatigue domain consists of eight items, scored on a 7-point scale, with a total score ranging from 8 to 56. Higher scores reflecting more fatigue. A difference of 8 points on the CIS20r subscale fatigue between the groups was considered clinically relevant.[16,18]

Societal participation was assessed with the Impact on Participation and Autonomy questionnaire (IPA),[19] developed to assess the severity of restrictions in participation and autonomy. The IPA addresses perceived participation, reflected in 32 items in five domains, including autonomy indoors, autonomy outdoors, family role, social relations, and work and education. Responses to items range from 0 to 4, and for each domain a mean item score is calculated; higher scores indicate greater

restrictions in participation and autonomy. A study in a heterogeneous outpatient rehabilitation population, including patients with neuromuscular disorders, showed that the IPA was moderately able to detect within-patient improvement over time [20]; another study showed similar small to moderate standardized response means of 0.0 up to 0.3.[21] However, no studies have been conducted on the clinimetric properties of the IPA in individuals with MS.

Secondary outcome measures. Because MS-related fatigue is a multidimensional phenomenon, several other fatigue measures were included as secondary outcomes:

1. The remaining three domains of the CIS20r: motivation (4 items), physical activity (3 items), and concentration (5 items); higher scores indicate lower motivation, lower physical activity, and more concentration problems due to fatigue.
2. The Modified Fatigue Impact Scale (MFIS): total sum score and subscale scores for the physical, cognitive and psychosocial domain, higher scores reflect a greater impact of fatigue.[22]
3. The Fatigue Severity Scale (FSS) estimates the severity, frequency and impact of fatigue on daily life, a higher score indicating more perceived fatigue.[23]

In addition, the Medical Outcomes Study Short Form 36 (SF-36)[24] and the Rehabilitation Activities Profile (RAP)[25] were used to measure daily functioning and participation on several life domains.

Other parameters. In the ECM group only, the Energy Conservation Strategies Survey (ECSS)[26] was administered once, directly after the intervention. It assesses participants' use of 14 suggested energy conservation strategies that were emphasized in the ECM course. It rates strategy use as a direct result of the course and the perceived effectiveness (scale of 1=not effective to 10=very effective).

Exacerbations during the study were registered if confirmed by a neurologist and treated with medication. Serious adverse events (SAEs) were registered by the principal investigator and were reported to the Medical Ethical Committee. The definition of an SAE is included in the design paper.[16]

Statistical analysis

Statistical analysis was performed by a researcher blinded to the group allocation. Effectiveness of the ECM intervention was analyzed on a modified intention-to-treat (ITT) principle, using data on each randomized subject with at least one post-randomization measurement. We used Linear Mixed Models with a three-level structure (repeated measures, patients and therapists). First, we evaluated the between-group differences on average during the 1-year study with group allocation and baseline values of the particular outcome variable as covariates (overall intervention effect). Then we assessed the between-group differences at the separate four follow-up measurements (T8, T16 and T26 and T52) by adding time (treated as a categorical variable and represented by dummy variables), and an interaction between group allocation and time to evaluate the effect of ECM at the specific time-points (time-specific intervention effects). With the time×group interaction analyses, the differences between the groups in changes within all time-intervals were evaluated. As we used mixed model analyses, no imputation of missing data was performed.[27] Additionally, we used linear mixed models to analyze the within group changes of the two primary outcomes (CIS20r and IPA) between baseline and T16 and between baseline and T52 for both the ECM group and the control group.

We present the difference between groups (*B*), *P*-values and 95% confidence intervals (CIs) for the crude models and for models adjusted for center, gender, exacerbations during the study (yes or no) and time since diagnosis (in years). IBM SPSS Statistics version 22 (Chicago, IL) was used for statistical analysis. A *P*-value of ≤0.05 was considered significant.

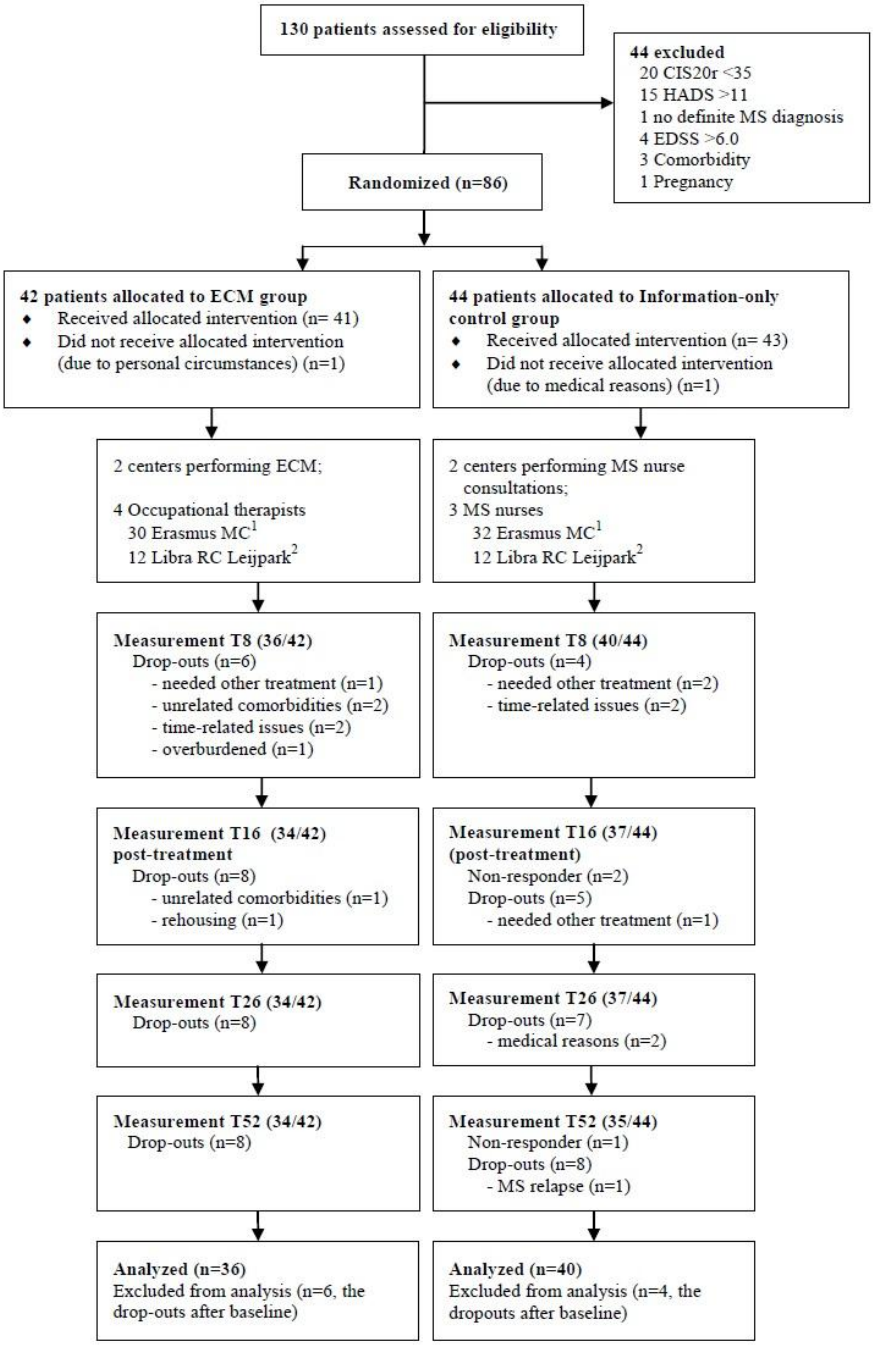


Figure 6.1 Trial profile
Centers [1]Rijndam Rehabilitation at Erasmus MC Rotterdam, [2]Libra Rehabilitation Medicine & Audiology, location Leijpark at Tilburg. The number of drop-outs is cumulative.

RESULTS

Eligible participants were recruited between November 2011 and March 2014, and 86 fatigued persons with MS were randomized. Figure 6.1 shows the flow diagram. Baseline personal and clinical characteristics of all participants are presented in Table 6.2. In all, 10 persons, 6 in the intervention group and 4 in the control group dropped out before the second measurement (T8). As these individuals missed all follow-up measurements we excluded them from further analysis, thus data from 76 patients were available for the so-called modified ITT analysis.[28] Except for fewer years with MS (mean difference 5 years, p=.04), the drop-outs did not differ significantly (see Table 3). The use and perceived effectiveness of energy conservation strategies was administered in 34 participants, 85% of the participants had implemented ≥ 6 strategies, with a mean of 10 strategies and they perceived the strategies as effective (mean rate of 7). During the treatment period one serious adverse event (relapse) was reported in the ECM group, and one (ischemic bone disease) in the control group. During the follow-up period three SAEs were reported in both groups. The events were reported to and judged by the Medical Ethics Committee to be not directly associated with the intervention.

Table 6.2 Participant characteristics of people with MS allocated to ECM or control group

	ECM (N=42)	Control group (N=44)
No. of males/females	8/34	14/30
Age (years), mean (SD)	47.7 (11.0)	46.6 (11.5)
No. type MS; RR/PP/SP/unknown	32/2/7/1	32/4/7/1
Years since diagnosis	6.5 (3.7-17.3)	7.5 (3-14)
EDSS	2.5 (2-4)	1.8 (1-4)
Treatment adherence	83%	86%

MS: multiple sclerosis; ECM: energy conservation management; SD: standard deviation; EDSS: Expanded Disability Status Scale; RR: Relapsing-Remitting; PP: Primary Progressive; SP: Secondary Progressive
Values in Median (Q1-Q3) or as otherwise stated.

The observed data over time are presented in Table 6.3 and the primary outcomes are graphically presented in Figure 6.2. The results of the corresponding linear mixed

model analyses are presented in Table 6.4. No significant overall or time-specific intervention effects were found for the CIS20r fatigue subscale. The interval-specific time effects were also non-significant, with the exception of the interval T8-T26 which showed a larger decrease in the ECM group (B=-6.2; 95% CI,-10.5 to -1.8; see also Figure 6.2).

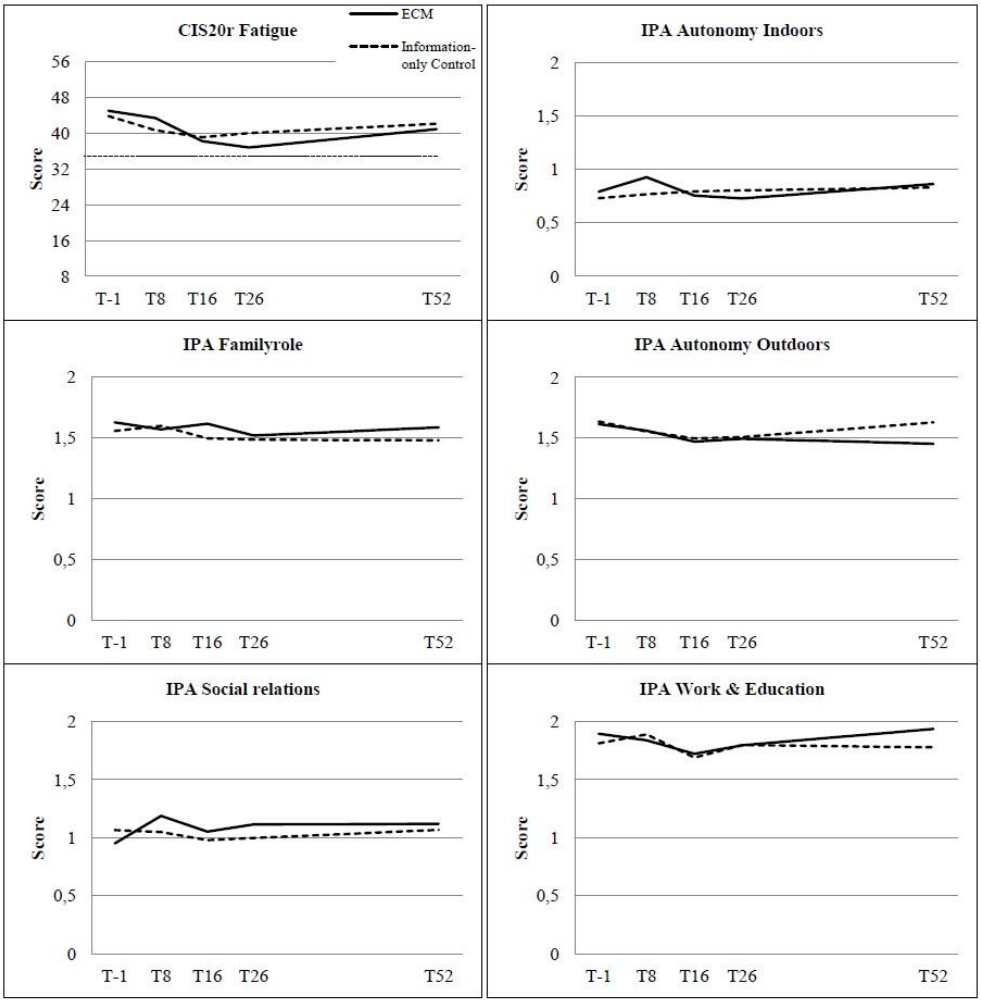
The IPA (all domains) showed no overall or time-specific intervention effects. The only positive overall effect was for the IPA domain social relations, in favor of the control group (B=0.19; 95% CI, 0.03 to 0.35), an outcome also reflected in time-specific effects at T8 and T26. No interval-specific effects were found for the IPA outcomes.

Table 6.3 Observed data over time, specified per allocated study group.

	ECM study group						Control group					
	T-1* (n=42)	T-1 (n =36)	T8 (n=36)	T16 (n=34)	T26 (n=34)	T52 (n=34)	T-1* (n=44)	T-1 (n=40)	T8 (n=40)	T16 (n=37)	T26 (n=37)	T52 (n=35)
Primary outcomes												
CIS20r Fatigue	44.3±7.9	44.6±7.1	43.4±6.5	38.2±8.2	36.8±10.1	40.9±9.6	43.6±7.1	43.9±6.9	40.7±9.8	39.1±8.5	40.1±9.4	42.1±8.9
IPA												
Autonomy indoors	0.80±0.66	0.79±0.65	0.92±0.55	0.75±0.60	0.73±0.58	0.86±0.74	0.76±0.69	0.73±0.64	0.77±0.64	0.79±0.74	0.80±0.81	0.83±0.70
Family role	1.68±0.64	1.63±0.63	1.57±0.60	1.62±0.70	1.52±0.68	1.59±0.68	1.54±0.80	1.56±0.73	1.60±0.69	1.50±0.74	1.49±0.81	1.48±0.81
Autonomy outdoors	1.61±0.69	1.58±0.63	1.56±0.59	1.47±0.52	1.49±0.63	1.45±0.70	1.64±0.63	1.64±0.53	1.55±0.57	1.50±0.63	1.51±0.79	1.63±0.79
Social life relations	0.95±0.44	0.93±0.41	1.19±0.56	1.05±0.52	1.11±0.51	1.12±0.57	1.06±0.57	1.05±0.53	1.05±0.49	0.98±0.54	1.00±0.57	1.06±0.55
Work & education	1.89±0.66	1.87±0.66	1.84±0.80	1.72±0.65	1.79±0.67	1.94±0.83	1.81±0.88	1.83±0.86	1.89±0.99	1.69±0.72	1.80±0.87	1.78±0.90
Secondary outcomes												
CIS20r Total	93.5±17.7	94.4±16.3	90.3±13.3	82.9±15.6	79.2±20.3	87.3±20.4	91.2±15.7	92.5±15.5	86.9±22.5	83.2±19.0	86.0±22.7	90.8±21.6
Motivation	15.5±5.6	15.5±5.5	14.4±4.9	13.5±4.0	12.5±4.6	13.9±5.8	15.0±4.8	15.1±4.6	14.6±5.4	14.3±5.2	14.8±6.1	14.9±5.5
Physical activity	12.8±4.9	12.7±4.9	12.2±3.9	11.7±3.9	10.5±3.9	12.1±4.1	12.6±4.9	12.8±4.8	12.3±5.1	12.0±4.4	12.0±4.5	13.0±4.4
Concentration	20.9±7.4	21.6±6.9	20.2±7.6	19.5±7.1	19.4±7.3	20.4±7.4	20.0±7.8	20.8±7.7	19.3±8.7	17.8±7.7	19.1±8.6	20.7±7.8
MFIS Total	45.1±11.7	46.5±10.6	42.9±10.2	41.2±11.4	40.4±13.0	41.4±13.9	42.7±14.4	43.8±13.3	40.9±14.1	40.0±14.5	38.4±15.9	40.6±16.7
Physical	21.2±4.8	21.5±4.8	20.3±4.2	20.0±5.2	19.6±5.6	20.2±6.3	20.5±5.7	20.8±4.9	20.1±5.9	19.8±5.6	18.6±6.9	20.0±7.3
Cognitive	19.9±7.6	20.9±6.5	18.6±7.3	17.4±6.6	17.2±7.1	17.5±7.0	18.2±8.8	18.9±8.7	16.9±8.6	16.3±8.9	16.3±9.1	16.9±9.5
Psychosocial	4.0±1.8	4.2±1.7	4.0±1.2	3.7±1.3	3.6±1.5	3.7±1.8	4.0±1.9	4.1±1.7	3.9±1.7	3.9±1.7	3.5±1.8	3.6±1.7

		ECM study group						Control group					
		T-1* (n=42)	T-1 (n =36)	T8 (n=36)	T16 (n=34)	T26 (n=34)	T52 (n=34)	T-1* (n=44)	T-1 (n=40)	T8 (n=40)	T16 (n=37)	T26 (n=37)	T52 (n=35)
FSS		5.3±0.8	5.3±0.7	5.2.±0.7	5.3.±0.8	5.3±1.0	5.3±0.9	5.1±0.9	5.2±0.8	5.2±0.9	5.1.±0.7	5.1.±0.9	5.3±0.9
SF-36	Phys funct	53.9±24.8	54.3±24.9	55.3±25.5	53.7±25.3	55.7±22.9	55.4±25.7	59.2±26.4	59.1±25.4	59.1±26.8	59.3±26.8	59.2±24.6	54.0±28.5
	Role physical	24.4±33.8	22.9±32.4	35.4±41.1	33.1±35.2	38.2±43.2	37.5±37.6	34.1±37.4	33.1±38.6	35.3±37.9	42.6±37.7	51.4±41.6	37.1±36.6
	Body pain	65.3±21.3	64.9±21.9	63.9±22.9	67.9±23.4	63.7±21.4	61.3±22.9	67.3±21.9	67.5±21.6	66.9±23.1	70.2±20.9	65.1±23.7	68.2±23.5
	General health	49.4±14.0	49.4±14.6	52.4±13.8	50.7±14.0	50.7±12.7	51.0±15.4	50.7±13.1	50.7±13.3	48.7±14.5	48.9±13.2	47.9±14.0	49.6±13.4
	Vitality	41.1±15.3	40.4±13.4	39.7±10.8	45.3±13.4	43.5±18.2	44.0±18.5	40.5±15.0	39.4±14.2	41.7±14.3	43.7±14.7	43.3±17.8	42.2±17.6
	Social function	62.2±16.9	61.8±17.1	61.8±14.3	66.5±20.8	68.7±17.2	66.5±21.3	60.5±22.5	60.3±21.3	65.4±20.4	67.2±18.9	67.6±20.5	65.7±19.0
	Role emotional	68.3±41.0	65.7±41.0	70.4±38.0	65.7±36.2	73.5±36.5	76.5±39.8	62.1±39.7	60.0±40.8	66.7±41.2	65.8±36.4	81.1±35.6	68.6±41.9
	Mental health	67.7±15.5	67.9±14.6	67.4±18.6	73.1±14.1	73.9±16.3	70.6±18.7	68.8±14.7	68.7±14.9	68.5±15.1	72.6±15.5	71.6±15.7	69.5±17.1
RAP	Communication	0.4±0.7	0.4±0.7	0.5±0.7	0.3±0.6	0.3±0.7	0.6±0.9	0.4±0.7	0.4±0.7	0.5±0.8	0.4±0.7	0.4±0.8	0.5±0.7
	Mobility	2.9±2.2	2.9±2.1	3.0±1.8	2.6±2.1	2.9±2.1	3.8±2.9	2.5±2.0	2.4±1.9	2.2±1.9	2.4±2.2	2.6±2.0	3.8±3.3
	Self-care	3.1±2.0	3.1±1.9	2.6±2.2	3.0±2.2	2.9±2.3	3.7±2.8	2.2±2.2	2.1±2.0	2.2±2.0	1.8±1.8	2.1±2.0	2.3±2.3
	Occupation	3.7±1.7	3.7±1.7	4.1±1.7	3.6±1.6	3.7±1.9	3.9±1.6	3.4±2.2	3.4±2.2	3.1±2.0	3.5±2.0	3.3±2.1	3.3±1.8
	Relationships	1.7±1.6	1.6±1.5	1.0±1.0	0.7±1.1	0.4±0.7	1.0±1.6	1.9±1.4	1.9±1.5	0.7±1.0	0.5±0.8	0.6±1.0	0.9±1.3

T-1: baseline; T8, T16, T26 and T52: 8, 16, 26 and 52 weeks after randomization; ECM, Energy Conservation Management; CIS20r, Checklist Individual Strength (fatigue domain max range 8-56); IPA, Impact on Participation and Autonomy (max range 0-3); MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; SF-36, Health-related quality of life; RAP, Rehabilitation Activities Profile; SD, standard deviation. Reported as mean ± SD * All randomized participants at baseline.



Solid line: Energy Conservation Management (ECM) intervention group; dashed line: Information-only control group; small dotted line: value of severe fatigue CIS20r≥35. CIS20r – Checklist Individual strength subscale subjective fatigue: higher scores reflect more fatigue; IPA – Impact on Participation and Autonomy: higher scores reflect more barriers in participation and autonomy.

Figure 6.2 Graphs of the observed data on the primary outcomes CIS20r fatigue and five IPA domains

Table 6.4 Results of the linear mixed models analyses for the primary outcomes fatigue (CIS20r fatigue) and participation (IPA).

Primary Outcomes		Crude Model				Adjusted Model[a]				Effect size
		B	*P*	95% CI		*B*	*P*	95% CI		
CIS20r fatigue	Overall	-0.81	0.58	-3.72	2.11	-0.80	0.59	-3.73	2.12	0.09
	T8	2.64	0.18	-1.23	6.50	2.65	0.18	-1.22	6.52	0.31
	T16	-1.42	0.48	-5.38	2.53	-1.49	0.46	-5.46	2.48	0.18
	T26	-3.54	0.08	-7.49	0.42	-3.55	0.08	-7.52	0.42	0.36
	T52	-1.46	0.47	-5.46	2.54	-1.45	0.48	-5.46	2.56	0.16
IPA Autonomy Indoors	Overall	0.00	0.97	-0.17	0.17	0.03	0.72	-0.15	0.21	0.04
	T8	0.13	0.22	-0.08	0.35	0.16	0.16	-0.06	0.37	0.27
	T16	-0.07	0.52	-0.29	0.15	-0.04	0.70	-0.26	0.18	0.06
	T26	-0.10	0.38	-0.32	0.12	-0.07	0.53	-0.29	0.15	0.10
	T52	0.03	0.78	-0.19	0.25	0.06	0.59	-0.16	0.28	0.08
IPA Family role	Overall	-0.00	1.00	-0.22	0.22	0.02	0.83	-0.20	0.25	0.03
	T8	-0.05	0.72	-0.31	0.22	-0.03	0.85	-0.29	0.24	0.05
	T16	0.04	0.78	-0.23	0.31	0.06	0.65	-0.21	0.34	0.08
	T26	-0.03	0.81	-0.30	0.24	-0.01	0.96	-0.28	0.27	0.01
	T52	0.05	0.72	-0.22	0.32	0.07	0.59	-0.20	0.35	0.09
IPA Autonomy Outdoors	Overall	0.00	0.97	-0.20	0.21	0.02	0.85	-0.19	0.23	0.03
	T8	0.05	0.66	-0.19	0.30	0.07	0.58	-0.18	0.31	0.12
	T16	-0.00	1.00	-0.25	0.25	0.01	0.91	-0.24	0.26	0.02
	T26	0.04	0.77	-0.21	0.29	0.05	0.67	-0.20	0.30	0.07
	T52	-0.09	0.49	-0.34	0.16	-0.07	0.58	-0.32	0.18	0.09
IPA Social Relations	Overall	0.19	0.02	0.03	0.35	0.20	0.02	0.03	0.36	0.38
	T8	0.22	0.03	0.03	0.42	0.23	0.02	0.03	0.43	0.44
	T16	0.15	0.15	-0.05	0.34	0.15	0.14	-0.05	0.35	0.29
	T26	0.22	0.03	0.02	0.42	0.23	0.03	0.02	0.43	0.43
	T52	0.17	0.10	-0.03	0.37	0.18	0.09	-0.03	0.38	0.33
IPA Work and Education	Overall	-0.01	0.92	-0.23	0.21	0.00	0.97	-0.22	0.23	<0.01
	T8	-0.06	0.70	-0.36	0.24	-0.05	0.77	-0.35	0.26	0.06
	T16	-0.01	0.93	-0.33	0.30	0.00	0.99	-0.32	0.32	<0.01
	T26	-0.06	0.69	-0.38	0.25	-0.05	0.77	-0.36	0.27	0.06
	T52	0.10	0.52	-0.21	0.42	0.12	0.46	-0.20	0.44	0.14

CI: confidence interval; CIS20r: Checklist Individual Strength, domain fatigue: higher scores indicate more fatigued; IPA: Impact on Participation and Autonomy: higher scores reflect greater restrictions in participation and autonomy.
Crude analyses are adjusted for the baseline value of the particular outcome.
[a]Adjusted for center, gender, exacerbations, time since diagnosis. The effect size is calculated by the regression coefficient (of the adjusted model) divided by the pooled standard deviation.

The results on the secondary fatigue outcomes were identical to CIS20r fatigue. For the other secondary outcome measures, no overall or time-specific (see Table 6.5 and 6.6) intervention effects were noted. In general, the adjusted analyses did not affect results (see Table 6.4, 6.5, 6.6).

Table 6.5 Results of the linear mixed models analyses for secondary outcomes.

		Crude Model				Adjusted Model[a]			
		B	*p*	95% CI		*B*	*p*	95% CI	
CIS20r Concentration	Overall	0.36	0.77	-2.03	2.74	0.44	0.72	-2.00	2.88
CIS20r Motivation	Overall	-1.00	0.18	-2.47	0.47	-1.03	0.16	-2.49	0.42
CIS20r Phys Activity	Overall	-0.57	0.38	-1.86	0.72	-0.60	0.37	-1.93	0.72
CIS20r Total	Overall	-2.03	0.52	-8.33	4.28	-1.92	0.55	-8.33	4.49
MFIS Physical	Overall	-0.01	0.99	-2.03	2.00	0.08	0.93	-1.89	2.06
MFIS Cognitive	Overall	-0.22	0.85	-2.49	2.06	-0.02	0.98	-2.31	2.27
MFIS Psychosocial	Overall	0.08	0.76	-0.44	0.61	0.13	0.62	-0.39	0.66
MFIS Total	Overall	-0.13	0.95	-4.55	4.30	0.20	0.93	-4.17	4.58
FSS	Overall	0.04	0.76	-0.22	0.30	0.03	0.82	-0.23	0.28
SF-36 Physical function	Overall	2.37	0.37	-2.81	7.55	2.22	0.40	-3.06	7.50
SF-36 Role physical	Overall	-1.00	0.87	-12.94	10.95	-1.33	0.83	-13.46	10.80
SF-36 Body pain	Overall	-1.43	0.64	-7.40	4.56	-1.25	0.69	-7.41	4.91
SF-36 General health	Overall	3.01	0.14	-1.05	7.07	2.85	0.18	-1.31	7.00
SF-36 Vitality	Overall	-0.22	0.93	-4.94	4.49	-0.17	0.94	-4.99	4.64
SF-36 Social function	Overall	-1.63	0.56	-7.22	3.96	-2.15	0.44	-7.72	3.42
SF-36 Role emotional	Overall	-0.05	0.99	-11.84	11.74	0.69	0.91	-11.55	12.94
SF-36 Mental health	Overall	0.61	0.79	-3.97	5.19	0.67	0.78	-4.06	5.40
RAP Communication	Overall	0.01	0.92	-0.17	0.19	0.01	0.89	-0.17	0.20
RAP Mobility	Overall	0.21	0.52	-0.44	0.86	0.24	0.47	-0.43	0.91
RAP Self-care	Overall	-0.10	0.73	-0.69	0.48	-0.08	0.78	-0.66	0.50
RAP Occupation	Overall	-0.26	0.27	-0.73	0.21	-0.24	0.31	-0.70	0.22
RAP Relationships	Overall	-0.11	0.55	-0.48	0.26	-0.11	0.56	-0.48	0.26

CI: confidence interval; CIS20r: Checklist Individual Strength; MFIS: Modified Fatigue Impact Scale; FSS: Fatigue Severity Scale; SF-36: health-related quality of life; RAP: Rehabilitation Activities Profile.
Crude analyses are adjusted for the baseline value of the particular outcome.
[a]Adjusted for center, gender, exacerbations, time since diagnosis.

Table 6.6 Results of linear mixed models analysis for time-specific intervention effects of the secondary outcomes.

		Crude Model				Adjusted Model[a]			
		B	*p*	95% CI		*B*	*p*	95% CI	
CIS20r Concentration	T8	0.42	0.77	-2.43	3.27	0.49	0.74	-2.40	3.38
	T16	0.96	0.52	-1.94	3.86	1.03	0.49	-1.92	3.98
	T26	0.30	0.84	-2.60	3.20	0.40	0.79	-2.54	3.35
	T52	-0.37	0.80	-3.29	2.55	-0.26	0.86	-3.23	2.71
CIS20r Motivation	T8	-0.24	0.82	-2.27	1.79	-0.25	0.81	-2.27	1.77
	T16	-0.64	0.55	-2.71	1.44	-0.68	0.52	-2.76	1.39
	T26	-2.26	0.03	-4.34	-0.19	-2.32	0.03	-4.40	-0.25
	T52	-0.97	0.36	-3.07	1.13	-1.01	0.34	-3.11	1.08
CIS20r Phys Activity	T8	0.09	0.92	-1.61	1.79	0.05	0.95	-1.67	1.78
	T16	-0.18	0.84	-1.91	1.56	-0.21	0.81	-1.98	1.55
	T26	-1.42	0.11	-3.16	0.31	-1.46	0.10	-3.23	0.31
	T52	-0.92	0.31	-2.67	0.84	-0.94	0.30	-2.73	0.84
CIS20r Total	T8	2.93	0.48	-5.17	11.03	3.03	0.47	-5.14	11.19
	T16	-1.26	0.76	-9.54	7.01	-1.27	0.77	-9.63	7.09
	T26	-6.97	0.10	-15.24	1.31	-6.88	0.11	-15.24	1.48
	T52	-3.75	0.38	-12.11	4.60	-3.62	0.40	-12.05	4.82
MFIS Physical	T8	0.02	0.99	-2.55	2.60	0.11	0.93	-2.43	2.65
	T16	-0.65	0.63	-3.29	1.99	-0.60	0.65	-3.20	2.01
	T26	0.63	0.64	-2.01	3.26	0.74	0.58	-1.87	3.34
	T52	-0.07	0.96	-2.73	2.59	0.07	0.96	-2.56	2.70
MFIS Cognitive	T8	0.41	0.77	-2.36	3.18	0.58	0.68	-2.20	3.36
	T16	-0.81	0.57	-3.63	2.02	-0.64	0.66	-3.48	2.20
	T26	-0.15	0.91	-2.98	2.67	0.05	0.97	-2.79	2.89
	T52	-0.42	0.77	-3.27	2.43	0.20	0.89	-3.07	2.66
MFIS Psychosocial	T8	0.15	0.67	-0.54	0.83	0.19	0.59	-0.49	0.87
	T16	-0.18	0.61	-0.88	0.52	-0.14	0.70	-0.84	0.56
	T26	0.20	0.58	-0.50	0.89	0.25	0.48	-0.45	0.95
	T52	0.16	0.65	-0.54	0.87	0.22	0.53	-0.48	0.93
MFIS Total	T8	0.63	0.82	-4.81	6.07	0.92	0.74	-4.47	6.31
	T16	-1.66	0.57	-7.22	3.89	-1.40	0.62	-6.92	4.11
	T26	0.68	0.81	-4.87	6.23	1.03	0.71	-4.48	6.54
	T52	-0.30	0.92	-5.89	5.30	0.10	0.97	-5.46	5.65
FSS	T8	0.03	0.85	-0.30	0.37	0.03	0.88	-0.31	0.36
	T16	0.06	0.71	-0.28	0.41	0.05	0.77	-0.29	0.39
	T26	0.07	0.68	-0.27	0.42	0.06	0.72	-0.28	0.40
	T52	-0.02	0.93	-0.37	0.33	-0.02	0.89	-0.37	0.32
SF-36 Physical function	T8	-0.47	0.88	-6.62	5.68	-0.53	0.87	-6.76	5.70
	T16	0.86	0.79	-5.40	7.12	0.72	0.82	-5.64	7.07
	T26	3.07	0.33	-3.19	9.34	2.91	0.37	-3.45	9.27
	T52	6.68	0.04	0.37	12.98	6.50	0.05	0.10	12.90
SF-36 Role physical	T8	3.71	0.66	-12.96	20.38	3.44	0.69	-13.32	20.20
	T16	-4.06	0.64	-21.16	13.04	-4.19	0.63	-21.43	13.05
	T26	-8.40	0.33	-25.50	8.70	-8.83	0.31	-26.06	8.41
	T52	4.46	0.61	-12.81	21.74	3.88	0.66	-13.53	21.29
SF-36 Body pain	T8	-1.94	0.63	-9.79	5.91	-1.78	0.66	-9.75	6.19
	T16	1.09	0.79	-6.94	9.12	1.35	0.75	-6.82	9.52

		Crude Model				Adjusted Model†			
		B	*p*	95% CI		*B*	*p*	95% CI	
	T26	0.65	0.87	-7.38	8.68	0.80	0.85	-7.37	8.97
	T52	-5.49	0.18	-13.60	2.62	-5.37	0.20	-13.62	2.87
SF-36 General health	T8	4.73	0.07	-0.44	9.90	4.63	0.08	-0.61	9.86
	T16	1.57	0.56	-3.70	6.85	1.34	0.62	-4.01	6.69
	T26	3.41	0.20	-1.87	8.70	3.22	0.24	-2.14	8.57
	T52	2.07	0.45	-3.26	7.40	1.88	0.49	-3.52	7.28
SF-36 Vitality	T8	-4.82	0.15	-11.37	1.72	-4.81	0.15	-11.41	1.79
	T16	2.20	0.52	-4.50	8.91	2.38	0.49	-4.40	9.16
	T26	-0.45	0.89	-7.16	6.25	-0.38	0.91	-7.16	6.40
	T52	2.83	0.41	-3.95	9.61	2.87	0.41	-3.98	9.73
SF-36 Social function	T8	-4.38	0.29	-12.42	3.66	-4.74	0.25	-12.75	3.27
	T16	-1.30	0.76	-9.54	6.94	-1.77	0.67	-10.01	6.48
	T26	0.05	0.99	-8.20	8.29	-0.56	0.89	-8.79	7.68
	T52	-0.52	0.90	-8.87	7.82	-1.14	0.79	-9.48	7.20
SF-36 Role emotional	T8	1.64	0.84	-14.73	18.02	2.29	0.79	-14.38	18.96
	T16	0.24	0.98	-16.52	17.00	1.08	0.90	-16.02	18.18
	T26	-8.82	0.30	-25.59	7.95	-8.05	0.36	-25.15	9.05
	T52	6.55	0.45	-10.41	23.50	7.30	0.41	-9.98	24.58
SF-36 Mental health	T8	-0.59	0.85	-6.75	5.57	-0.58	0.86	-6.84	5.68
	T16	1.06	0.74	-5.25	7.36	1.19	0.71	-5.23	7.62
	T26	1.73	0.59	-4.58	8.03	1.81	0.58	-4.61	8.23
	T52	0.49	0.88	-5.88	6.86	0.56	0.86	-5.92	7.05
RAP Communication	T8	-0.03	0.83	-0.26	0.21	-0.02	0.85	-0.26	0.22
	T16	0.04	0.72	-0.20	0.29	0.05	0.69	-0.20	0.30
	T26	0.15	0.24	-0.10	0.39	0.15	0.24	-0.10	0.40
	T52	-0.12	0.32	-0.37	0.12	-0.12	0.34	-0.37	0.13
RAP Mobility	T8	-0.31	0.43	-1.10	0.47	-0.28	0.49	-1.08	0.52
	T16	0.20	0.63	-0.60	1.00	0.24	0.57	-0.58	1.06
	T26	0.37	0.37	-0.44	1.17	0.40	0.34	-0.42	1.21
	T52	0.59	0.15	-0.21	1.39	0.62	0.13	-0.19	1.44
RAP Self-care	T8	0.20	0.44	-0.44	1.01	0.31	0.49	-0.41	1.02
	T16	-0.45	0.23	-1.19	0.28	-0.43	0.25	-1.17	0.30
	T26	0.14	0.70	-0.59	0.88	0.15	0.68	-0.58	0.89
	T52	-0.48	0.21	-1.22	0.26	-0.45	0.23	-1.19	0.28
RAP Occupation	T8	-0.82	0.01	-1.43	-0.20	-0.78	0.01	-1.39	-0.17
	T16	0.15	0.63	-0.48	0.79	0.17	0.60	-0.46	0.79
	T26	-0.01	0.99	-0.64	0.63	0.01	0.97	-0.61	0.64
	T52	-0.29	0.37	-0.93	0.34	-0.27	0.40	-0.90	0.36
RAP Relationships	T8	-0.32	0.20	-0.82	0.17	-0.32	0.20	-0.82	0.18
	T16	-0.20	0.45	-0.71	0.32	-0.19	0.47	-0.71	0.33
	T26	0.24	0.36	-0.28	0.75	0.24	0.37	-0.28	0.75
	T52	-0.12	0.63	-0.64	0.39	-0.13	0.63	-0.65	0.39

CI: confidence interval; CIS20r: Checklist Individual Strength: higher scores indicate greater impact of fatigue on concentration, motivation or activity; MFIS: Modified Fatigue Impact Scale: higher scores indicate greater impact of fatigue; FSS: Fatigue Severity Scale: higher scores reflect more severe fatigue; SF-36: health-related quality of life: higher scores reflect a more favorable health status or a higher vitality; RAP: Rehabilitation Activities Profile.
[a]Adjusted for center, gender, exacerbations, time since diagnosis.

DISCUSSION

The aim of this study was to evaluate the effectiveness of an individual ECM intervention on fatigue and participation in fatigued persons with MS. An individual ECM intervention provided by an occupational therapist was compared to a control condition that consisted of MS-nurse consultations. No between group differences were found for fatigue (measured with the subjective fatigue domain of the CIS20r) and participation (measured with the IPA). Similar results were found for secondary outcomes, that is, non-significant and non-clinically relevant effects. Based on these findings, our study does not support the implementation of our individual ECM format as a treatment for MS-related fatigue.

The results of our study are not completely in agreement with the known literature. A previous review[15] of ECM studies[10-12,29] showed that MS-related fatigue was effectively improved by the ECM group program on short-term follow-up, while long-term evaluation suggested that these effects sustained. However, in contrast to our study, these studies compared the ECM group with a no-treatment waitlist control group.[10-12,14] Moreover, in the studies with a large sample size[10,11,14] the between-group differences were statistically significant but very small from a clinical perspective. Studies that used comparable control groups (e.g. peer support, attention)[30,31] reported outcomes in line with our results: no additional effect of the ECM. In another category of studies, studies including energy management as part of a multidisciplinary rehabilitation treatment[6,7], again no significant difference on fatigue was found in comparison to a control group. However, it should be noted that direct comparison between our study and other studies is difficult, due to differences in control group content, the format of ECM (e.g. individual vs group), patient enrolment criteria, and differences in the used outcome measures.

Explanations for the lack of significant differences between the ECM and the control group on the primary outcomes might include earlier experience with ECM longer than 3 months ago. In all, 20% of the included participants (10 in the intervention and 8 in the control group) had earlier experiences with ECM strategies, and this may have resulted in less improvement during the treatment period as these

strategies may have already been applied to relieve fatigue. However, 85% of the patients in the ECM group implemented over six ECM strategies and perceived the applied strategies as effective. This level is comparable to levels reported in other studies.[32,33] Therefore, we consider it unlikely that earlier experience of ECM was an important effect modifier.

Although the instruments in our study were carefully selected, and measurements were precise and standardized, self-reported questionnaires may show insufficient responsiveness. For example, Rietberg et al[34] reported low responsiveness for the CIS20r, with a smallest detectable change of 11.8 for CIS20r fatigue in MS. The IPA also showed small to moderate response means; however, the clinimetric properties for persons with MS are still unknown. Nevertheless, the results of secondary outcomes in our study show similar patterns and therefore do not support a possible lack of responsiveness of CIS20r fatigue and IPA.

Although our results clearly showed no differences between the study groups on fatigue outcomes, within-group analyses (Supplement 6.1) showed statistically significant differences on fatigue between baseline and post-intervention (T16), and between baseline and long-term follow-up for the ECM group. Nevertheless, these effects were below the predefined 'clinical relevance' threshold of 8 points on the CIS20r fatigue subscale[16] and therefore considered as clinically not relevant. However, the 8-point threshold is rather arbitrary than evidence-based. On the other hand, the 8-point threshold has been cited in several studies[18,35] as a clinically relevant decrease in fatigue. Another approach to detecting clinically relevant effects of an intervention is to use the CIS20r fatigue subscale threshold of 35 as an indicator of severe fatigue. In our study, the mean fatigue score was never below 35, confirming the ineffectiveness of ECM both between groups and within the group.

With the exception of a small negative effect of ECM on the IPA domain social relations, the other IPA domains showed no intervention effects, in agreement with results reported by Rietberg et al.[7] who compared a multidisciplinary intervention, including energy management, with MS nurse consultations. One explanation might be that our study population already experienced few restrictions to participation and autonomy. The negative impact of ECM on the social relations

may be related to a greater awareness, due to the treatment, amongst ECM participants, which may have resulted in a more critical frame of mind. In contrast to our study, other studies have shown improvements of ECM on several domains of the SF-36,[10,11] compared to a waitlist control group.

One of the limitations of the present study could be the sample size, as we were unable to enroll all 90 participants and the percentages of drop-outs (19% in the ECM group, 11.4% in the control group) was near the estimated 20% attrition rate.[16] Nonetheless, because the 95% CIs of the primary outcomes were generally small, we suspect that a larger sample size would not have resulted in different outcomes, and that our study was adequately powered. Furthermore, although control conditions are an essential method of managing threats to internal validity, they may also have unintended effects on the primary outcomes. The small positive effects in our control group can be the result of the provided information, but can also be attributed to a heightened awareness because of the attention, or to the possibility that the MS-nurses have inadvertently provided advise. Another limitation is the generalizability to all persons with MS, because all our participants were ambulant. Finally, selection bias can be caused by factors such as time-constraints, distance constraints or the severity of fatigue.

The findings of our RCT have clinical implications, because ECM was not more effective for reducing fatigue compared to the information-only control condition. Although the decline within the ECM group approached a clinically relevant change, on average, participants still remained severely fatigued. However, some patients improved more than others, and future analyses will focus on factors that mediated the effects of ECM. An important result of the present study is that the participants appreciate the given strategies and perceived those as useful, so ECM seems to have a subjective good effect for fatigued persons with MS. Furthermore, it is known that TREFAMS-CBT protocol (submitted) has significant effect on fatigue on the short term. Therefore, a combination of ECM and CBT to get an even more powerful intervention to reduce fatigue in persons with MS may be useful.

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SUPPLEMENT 6.1

Table. Within-group effects of the primary outcomes.

Primary Outcomes			ECM group				Control group			
			B	*P*	95% CI		*B*	*P*	95% CI	
CIS20r fatigue		T-1 to T16	-6.29	**0.00**	-9.38	-3.21	-4.56	**0.00**	-7.53	-1.59
		T-1 to T52	-3.62	**0.02**	-6.71	-0.53	-1.76	0.25	-4.78	1.27
IPA	Autonomy	T-1 to T16	-0.04	0.58	-0.20	0.11	0.04	0.60	-0.11	0.19
	Indoors	T-1 to T52	0.06	0.42	-0.09	0.22	0.05	0.56	-0.11	0.19
	Family role	T-1 to T16	-0.06	0.53	-0.25	0.13	-0.05	0.58	-0.24	0.13
		T-1 to T52	-0.09	0.36	-0.28	0.10	-0.09	0.36	-0.27	0.10
	Autonomy	T-1 to T16	-0.12	0.18	-0.30	0.05	-0.14	0.11	-0.30	0.03
	Outdoors	T-1 to T52	-0.14	0.12	-0.31	0.04	-0.06	0.48	-0.23	0.11
	Social	T-1 to T16	0.12	0.10	-0.02	0.26	-0.07	0.32	-0.20	0.07
	Relations	T-1 to T52	0.18	**0.01**	0.04	0.32	-0.03	0.71	-0.16	0.11
	Work and	T-1 to T16	-0.15	0.25	-0.40	0.10	-0.10	0.43	-0.34	0.14
	Education	T-1 to T52	0.06	0.65	-0.19	0.31	-0.01	0.95	-0.25	0.24

Results of the Linear Mixed Models analyses, no adjustments for baseline values. CIS20r – Checklist Individual Strength, domain fatigue: higher scores indicate more fatigued; IPA – Impact on Participation and Autonomy: higher scores reflect greater restrictions in participation and autonomy

Chapter 7

Energy Conservation Management for fatigued people with MS: who benefits?

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ABSTRACT

Background: An Energy Conservation Management (ECM) intervention was compared with an information-only control condition in the setting of a randomized controlled trial (RCT). While the ECM intervention itself was not superior, positive within-group effects were found. However, it was not clear which patients derive the greatest benefit from ECM treatment.
Objective: To investigate whether demographic, disease-related, or personal determinants can predict a response to ECM. A secondary objective was to compare these determinants to those in the control condition.
Design: Secondary analysis of a single-blind, two-parallel-arms RCT.
Setting: Outpatient rehabilitation departments.
Subjects: Ambulatory adults with severe MS-related fatigue.
Interventions: ECM or control condition.
Main Measures: Treatment responders and non-responders were categorized by their CIS20r fatigue change scores between baseline and end of treatment. Determinants were confirmed at baseline. Logistic regression analyses were used to assess the determinants of response and to assess differences in determinants between groups.
Results: In total, 69 participants were included (ECM N=34; MS nurse N=35). In the ECM group, fatigue severity (OR=1.18, 95% CI [0.97-1.43]), perception of fatigue (0.67, [0.47-0.95]), ICQ disease benefits (0.77, [0.58-1.03]), and social support discrepancies (1.12, [0.98-1.27]) were related to the probability to being a responder. The influence of 'perception of fatigue' and 'disease benefits' differed significantly between ECM and the control group.
Conclusion: These results suggest that fatigued people with MS who are more severely fatigued, have a less negative perception of fatigue, perceive fewer disease benefits, and who perceive a higher discrepancy in social support show the best response to ECM treatment.

INTRODUCTION

A randomized controlled trial (RCT) is the gold standard for evaluating the efficacy and effectiveness of an intervention. However, primary trial analyses and conclusions generally consider the entire study sample, often disregarding differences between subgroups and individuals who did or did not benefit from the intervention. Understanding which patients may benefit from treatment can be helpful for clinicians when selecting patients who are more likely to be responsive to an intervention.

Energy Conservation Management (ECM) is a commonly used treatment in Multiple Sclerosis (MS). ECM involves teaching people to identify and develop modifications to their activities in order to reduce the impact of fatigue on daily life. This is achieved by a systematic analysis of daily work, home and leisure activities, with the ultimate goal of greater activity and better participation.[1] We recently conducted a randomized clinical trial that compared the effectiveness of ECM in severely fatigued people with MS to an information-only control condition (MS nurse consultations).[2] This study found no significant difference between ECM and MS nurse consultations in terms of effects on fatigue and participation, i.e. we found no added value of ECM compared to MS nurse consultations. However, within-group analyses showed a significant decrease of fatigue in the ECM group (at 16, 26 and 52 weeks). This suggests that a considerable proportion of participants in this group responded positively to ECM. Similar results were found in the control condition.

Before recommending the ECM intervention to fatigued people with MS, it is important to distinguish which factors contribute to the effect of treatment. From previous research[3,4] it is known that demographic, disease-related, cognitive and behavioral factors moderate the effects of fatigue interventions. For example, the effects of ECM on fatigue as measured with the Fatigue Impact Scale (FIS) are moderated by age and gender but not by physical impairment or employment status. The greatest benefit was experienced by younger participants and women.[3] A more qualitative study[4] elucidated factors that influence the use of energy conservation strategies, with the results indicating that themes such as experience with the disease (i.e., progression, level of disability, and fatigue experience), sense of self, and

environmental factors (i.e., physical surrounding and social support) influence the use of energy conservation strategies. In particular, the progressiveness of the disease, the effect of fatigue on everyday life, and strong social support enhanced the use of many strategies, while variability of the disease, struggles with the sense of self, and rigid environments with limited social support all hindered strategy use.[4]

The aim of the present study was to investigate whether demographic, disease-related, and/or personal determinants influence the effect of the ECM intervention on fatigue in people with MS. A secondary aim was to investigate whether these determinants differ from the determinants in the control condition.

METHODS

Participants

This study was a secondary analysis of data from the ECM RCT which investigated the effect of ECM compared with a control condition (MS nurse consultations).[2] The RCT was part of a multicenter research program: Treating Fatigue in MS with Aerobic Training, Cognitive Behavioral Therapy and Energy Conservation Management (TREFAMS-ACE).[5] The protocol for this study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands. Details of the TREFAMS-ACE study have been described in the design paper of Beckerman et al.[5]. The main enrollment criteria for this research program were: definite diagnosis of MS; severe fatigue as indicated by a score of ≥ 35 on the fatigue domain of the Checklist Individual Strength (CIS20r); ambulatory status (i.e., Expanded Disability Status Scale (EDSS)[6] ≤ 6.0; no diagnosis of depression (i.e., Hospital Anxiety and Depression Scale (HADS) < 11); no initiation or change of pharmacological or non-pharmacological treatment for fatigue during the previous three months; and aged 18 to 70 years. The participants were randomly assigned to ECM or the control condition.[2] All participants provided written informed consent.

Study groups

Energy Conservation Management: The individual ECM intervention protocol was based on the group program developed by Packer et al.[7]. For the purposes of this study, the original content of the ECM group program was adapted to fit 12 one-on-one 45-min sessions by an occupational therapist over the 4-month intervention period. Measurements took place at baseline, at eight (T8) and at sixteen weeks (T16) after the start of treatment, thus during and directly after treatment. For the long-term follow-up, measurements were performed at 26 (T26) and 52 weeks (T52).

Information-only control condition: This consisted of three MS nurse consultations of 45 minutes each, given by experienced MS nurses over a period of four months. The nurses were trained to refrain from providing treatment or treatment advice. Instead, standardized information about MS-related fatigue was provided. The control group intervention was intended as a control for the effects of attention and information about fatigue.

For an extensive overview of the content of the ECM and control group interventions, we refer to the study design paper[5] and the RCT paper.[2]

Outcomes & determinants

The primary outcomes of the original RCT study were fatigue, measured by the Checklist Individual Strength (CIS20r domain fatigue)[8], and participation, measured by the Impact Participation and Autonomy questionnaire (IPA).[9] For the purposes of the present study, we focused on the change in fatigue as measured with the CIS20r.

Responders and non-responders were categorized by their CIS20r fatigue change score between baseline and T16. The measurement at T16 was chosen because it directly follows the end of the intervention. A responder was defined as a participant with a clinically relevant fatigue change score during the intervention (CIS20r fatigue baseline minus CIS20r fatigue at T16), defined as a change of ≥ 8 points on the CIS20r subscale fatigue.[5]

Baseline scores (i.e. before intervention) were used for the determinants. Based on literature[3,4] and clinical experience, and taking into account the sample size, the following determinants were selected:

Demographic factors: age (years) and gender (male/female).
Disease-related factors: years with definite MS, and earlier experience with ECM intervention (yes/no).
Personal factors:
- Fatigue severity as measured by the CIS20r, using the domain 'subjective experience of fatigue' (8 items). The CIS20r has been validated for MS patients[10] and higher scores reflect greater fatigue.
- Perception of Fatigue, measured by an adaptation of the Brief Illness Perception Questionnaire (B-IPQ)[11]. The adaptation involves replacing the word 'illness' with 'fatigue' to allow measurement of beliefs about MS-related fatigue instead of beliefs about the illness MS. Two items were excluded because they were not relevant to fatigue perceptions.[11] The remaining 7 questions of the modified B-IPQ (mBIPQ) are rated on a 0 (not at all) to 10 (extremely) scale and measure a patient's cognitive and emotional representation of their fatigue, including consequences, timeline (how long will the fatigue last), personal control, treatment control, illness coherence, concern, and emotional responses. Higher scores represent a more negative perception of fatigue and lower scores a more positive view.
- Self-efficacy, assessed with the General Self-Efficacy Scale (GSES).[12] Higher scores reflect higher perceived self-efficacy.
- Illness Cognitions about MS, as measured by the Illness Cognitions Questionnaire (ICQ).[13] This questionnaire has 3 subscales: 1) helplessness (focusing on the negative consequences of the disease and generalizing them to functioning in daily life), 2) acceptance (acknowledging being chronically ill and perceiving the ability to manage the negative consequences of the disease), and 3) disease benefits (experiencing positive, long-term consequences of the disease). The subscales focus on the experience people attribute to their disease. Higher scores represent more helplessness, acceptance and disease benefits.
- Social Support is measured by the sum scores of social Interactions (SSLI) and Discrepancies (SSLD) of the Social Support List.[14] For interactions, i.e. the extent to which people are supported, a high score means receiving much support; for discrepancies, i.e. the extent to which the received support fulfills the specific needs of

the participant, a high score indicates that the participant perceives a serious shortage in social support.
- Possible mood disorders with respect to anxiety were measured as a part of the Hospital Anxiety and Depression Scale (HADS).[15] Higher scores indicate more anxiety.
- Coping styles: task-oriented, emotion-oriented, and avoidance were measured with the Coping Inventory for Stressful Situations (CISS-21).[16] Higher scores reflect more use of a coping style.

Statistical analyses

Using univariable and multivariable logistic regression analyses, we investigated the baseline determinants in both groups associated with the probability of being a responder. Initially, each determinant was investigated in separate univariable models. For the multivariable analyses a backward selection procedure was used, starting with the variables with a p-value < 0.20 in the univariable analysis. For the final model, due to the relatively low sample size, $p < 0.10$ was used to keep variables in the model. The results are expressed in odds ratios (OR).

We also investigated whether the influence of determinants was different between the groups by comparing point estimates and 95% confidence intervals for the particular determinants between the groups. IBM SPSS Statistics version 22 (Chicago, IL) was used for statistical analysis.

RESULTS

Eligible participants in the RCT study were recruited from November 2011 to March 2014. In total, 86 participants were included in the RCT. Seventeen persons were excluded from analysis: 10 dropped out after baseline measurement, 3 dropped out after the second measurement (T8), 2 missed the third measurement (T16), and 2 persons did not comply with treatment. Of the 69 remaining subjects, 34 were assigned to the ECM group and 35 to the control condition, of whom 14 were classified as responders to ECM and 14 to the control condition. Table 7.1 shows the

baseline personal and clinical characteristics of the ECM and control groups.

Table 7.1 Participants characteristics

		ECM group		Control group	
		Resp. N=14	Non-resp. N=20	Resp. N=14	Non-resp. N=21
Male/Female (number)		1/13	5/15	5/9	6/15
Age (years)		49.8 ± 11.5	48.8 ± 11.0	42.7 ± 12.3	49.7 ± 11.1
Type MS: RR/PP/SP/unknown (number)		10/2/2	16/0/4	13/1/0	13/2/6
EDSS score (median (IQR))*		2.8 (2-4)	2.5 (1.4-4)	1.5 (1-2)	3.0 (1-4.5)
Years since diagnosis (median (IQR))		6.5 (4.8-19.3)	8.5 (4-18.5)	7.5 (3.8-13.5)	8.0 (3.5-17.5)
ECM experience (number yes/no)*		5/9	5/15	0/14	5/16
CIS20r fatigue (CIS20r)		48.4 ± 4.9	42.1 ± 7.8	46.0 ± 6.6	42.5 ± 7.4
fatigue change score		15.7 ± 4.1	-0.1 ± 5.2	12.9 ± 3.4	-1.1 ± 6.0
Perception of fatigue (mBIPQ)		43.4 ± 4.2	47.2 ± 5.9	44.7 ± 3.7	44.3 ± 6.8
Self-efficacy (GSES)		31.0 ± 3.4	31.4 ± 4.6	31.4 ± 3.9	29.2 ± 4.4
Illness Cognitions (ICQ)	Helplessness	13.1 ± 4.9	12.4 ± 3.8	11.4 ± 3.7	12.4 ± 4.0
	Acceptance	15.9 ± 4.5	14.7 ± 3.6	16.4 ± 2.4	14.0 ± 3.8
	Disease benefits*	14.2 ± 4.8	16.7 ± 4.1	18.4 ± 3.0	15.0 ± 4.6
Social Support	Interactions (SSLI)	82.4 ± 15.8	84.0 ± 14.3	78.6 ± 12.6	78.4 ± 13.4
	Discrepancies(SSLD)	51.2 ± 14.0	43.2 ± 7.9	45.6 ± 10.7	46.7 ± 10.7
Anxiety (HADS)		6.9 ± 4.4	6.1 ± 3.4	5.6 ± 2.4	6.9 ± 2.6
Coping styles (CISS-21)	Task-oriented	25.9 ± 4.5	24.8 ± 4.5	24.9 ± 4.8	23.0 ± 4.4
	Emotion-oriented	19.1 ± 5.5	20.4 ± 5.9	20.0 ± 7.5	21.0 ± 4.7
	Avoidance	18.6 ± 4.8	19.3 ± 5.8	17.9 ± 4.3	15.7 ± 4.0

ECM: energy conservation management; RR: Relapsing Remitting; PP: Primary Progressive; SP: Secondary Progressive; EDSS: Expanded Disability Status Scale; IQR: interquartile range; CIS20r: checklist individual strength; mBIPQ: modified brief illness perception questionnaire; GSES: general self-efficacy scale; ICQ: illness cognitions questionnaire; SSLI/D: social support list interactions/discrepancies; HADS: hospital anxiety and depression scale; CISS-21: coping inventory for stressful situations. Values in Mean (SD) or as otherwise stated, baseline scores of the variables except for the fatigue change score.* The responders in the two study groups differed.

Multivariable logistic regression analysis of the ECM group revealed that fatigue severity, perception of fatigue, ICQ disease benefits, and social support discrepancies were related to the probability of being a responder to ECM (Table 7.2). These results indicate that fatigued people with MS are more likely to show a response when at baseline they are more severely fatigued, have a less negative perception of fatigue, experience fewer disease benefits, and when they perceive a higher discrepancy in social support. However, only the influence of 'perception of fatigue' and 'disease benefits' differed significantly between ECM and the control group (Table 7.2).

Table 7.2 Determinants explaining the probability of a fatigue response to the ECM or control conditions

	ECM group						Control group					
	Univariable			Multivariable			Univariable			Multivariable		
Variables	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.01	0.95-1.07	0.78				0.95	0.89-1.01	0.09[a]			
Gender	4.33	0.45-42.02	0.21				0.72	0.17-3.06	0.65			
Years since diagnosis	1.01	0.94-1.09	0.78				0.97	0.88-1.07	0.52			
ECM experience	1.67	0.38-7.39	0.50				na	na	na			
CIS20r fatigue at baseline	1.18	1.02-1.37	0.02[a]	1.18	0.97-1.43	0.09	1.08	0.97-1.20	0.16[a]			
Perception of Fatigue(mBIPQ)	0.86	0.73-1.01	0.06[a]	0.67	0.47-0.95	0.02	1.01	0.90-1.14	0.84			
Self-efficacy (GSES)	0.98	0.82-1.16	0.78				1.14	0.95-1.37	0.14[a]			
Illness Cognitions												
Helplessness	1.04	0.88-1.23	0.64				0.93	0.77-1.12	0.47			
Acceptance	1.08	0.91-1.29	0.375				1.26	1.00-1.59	0.05[a]			
Disease benefits	0.87	0.74-1.04	0.12[a]	0.77	0.58-1.03	0.08	1.25	1.02-1.54	0.03[a]	1.25	1.02-1.54	0.03
Social Interactions (SSLI)	0.99	0.95-1.04	0.75				1.00	0.95-1.06	0.95			
Social Discrepancies (SSLD)	1.07	1.00-1.15	0.06[a]	1.12	0.98-1.27	0.09	1.00	0.93-1.06	0.76			
Anxiety (HADS)	1.06	0.89-1.28	0.51				0.81	0.60-1.08	0.14[a]			
Coping (CISS21)												
Task-oriented	1.06	0.90-1.24	0.49				1.10	0.96-1.29	0.25			
Emotion-oriented	0.96	0.85-1.09	0.52				0.97	0.87-1.09	0.64			
Avoidance	0.98	0.86-1.11	0.74				1.14	0.95-1.36	0.16[a]			

ECM: energy conservation management; OR: odds ratio; CI: confidence interval; na: not applicable; CIS20r: checklist individual strength; mBIPQ: modified brief illness perception questionnaire; GSES: general self-efficacy scale; ICQ: illness cognitions questionnaire; SSLI/D: social support list interactions/discrepancies; HADS: hospital anxiety and depression scale; CISS-21: coping inventory for stressful situations. Outcome variable: responder or non-responder. [a]Variables with a p-value < 0.20 in the univariable analysis that were selected for multivariable analysis and a backward selection procedure was performed to obtain the final model.

DISCUSSION

Investigation of the efficacy of Energy Conservation Management (ECM) in severely fatigued people with MS in a randomized controlled trial setting found no significant differences in effects on fatigue between the intervention (ECM) and information-only control condition (MS nurse consultations). However, in the course of that study we noticed that some participants showed a meaningful response to ECM that corresponded to a clinically relevant decrease in fatigue. This indicates that certain individuals respond to ECM, whereas others show little or no response. For occupational therapists and in rehabilitation practice it is important to know who will or will not benefit from ECM. Therefore, the aim of this study was to identify the demographic, disease-related, and personal determinants that define a response to the ECM intervention.

Being more severely fatigued, having a less negative perception of fatigue, experiencing fewer disease benefits, and perceiving a discrepancy in social support are the four baseline determinants of a response to ECM in fatigued people with MS. When we compared the ECM group with the control condition, two determinants distinguished the ECM group: perception of fatigue and disease benefits.

Our results indeed showed that people who were more fatigued at baseline improved more than those who were less fatigued. Possible explanations for this finding are that people who are more severely fatigued have a larger potential range of improvement, that they might be more open to fatigue management advice and/or that they more urgently feel the necessity of implementing energy management strategies to relieve fatigue.

Similar results were found for a perceived social support discrepancy and disease benefits: people with poorer baseline scores – i.e. perceiving less social support and fewer disease benefits – responded better to ECM. Topics concerning social support and disease benefits are part of the strategies that are advised and practiced within ECM treatment. For example, disease benefit components are reflected in strategies on life priorities and personal goals, positive personality changes, and strengthened personal relationships. Similarly, ECM strategies

concerning social support are reflected in delegating activities, communicating a need for help, and planning. Therefore, the effect of ECM on fatigue might be mediated by changes in perceptions of social support and disease benefits during ECM treatment. Consequently, poorer scores on disease benefits and a social support discrepancy at baseline might have increased the implementation of energy management strategies during ECM, had larger effects on the discrepancy in social support and disease benefits, and thus reduced the levels of fatigue. Our results on social support discrepancy contrast with those of Holberg et al.(4). In a qualitative study Holberg et al. examined the determinants ('themes') influencing the implementation and continued use of energy conservation strategies. They found that higher levels of social support were related to enhanced use of ECM strategies. However, it should be noted that a one-to-one comparison is difficult as these authors focused not on fatigue but on the implementation of energy management strategies, and they made no use of questionnaires such as the Social Support List.

In our study the results for the 'perception of fatigue' determinant differed from other determinants in that better scores from a clinical perspective (i.e. a less negative perception of fatigue) resulted in a greater probability of being an ECM responder. This finding agrees with results from numerous studies of cognitive behavioral treatment (CBT). For example, Knoop et al.[11] studied variables mediating the effect of CBT on MS fatigue, and concluded that a change in the negative perception of fatigue plays a crucial role in the reduction of fatigue in MS after CBT. More positive views on fatigue (i.e. perceiving it as more controllable, as something one can understand, as time limited and as having less serious concrete and emotional consequences) were closely related to a reduction in the severity of fatigue. Similar findings were reported by the CBT trial (in submission) of the TREFAMS study.

Not all determinants were important. For example, no effects were found for the component of the Social Support List that focuses on social interactions. We also found no effects of determinants that can be related to the 'sense of self' theme of Holberg et al.[4], such as illness cognitions, self-efficacy and coping. Besides the qualitative study by Holberg, the only other study to focus on the determinants of the effects of ECM on fatigue was reported by Finlayson et al.[3]. These investigators found

a moderating effect of age and gender, i.e., younger participants and women experienced greater benefits. By contrast, in our study these factors were not significant, which might be due to a lower mean age and a smaller age range in our study, thus reducing the power to find a moderating effect. A power issue might also be the explanation for gender not being a determinant in our study: only one male was included in the responder group.

One of the main limitations of our study was the sample size. Power calculations in the original RCT[5] were based on detection of the overall effect of ECM and not on subgroup analysis.[17] Moreover, a clinically important interaction effect is difficult to determine. Therefore, the focus was on differential effects rather than statistical significance.[18] Due to the specific (individualized) format of our ECM intervention and the specific (ambulant) participants included, another limitation is the generalizability of our results. Finally, due to sample size and in order to minimize the chance of unintended findings, we focused on only a selection of all possible determinants. Although the determinants in this study were carefully selected based on literature and clinical experience, there is no consensus on which determinants are the most important. For all these reasons the results of this study should be interpreted cautiously and ostensible effects should be explored in future studies.

Clinical message

Four determinants could potentially identify responders to ECM: fatigue severity, fatigue perception, disease benefits and social discrepancies. Our results suggest that being more severely fatigued, having a less negative perception of fatigue, perceiving fewer disease benefits, and perceiving a higher discrepancy in social support increases the probability of being a responder to ECM. Two determinants for ECM responders were distinctive from responders in a control condition: fatigue perception and disease benefits.

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Chapter 8

General Discussion

The studies included in this thesis were designed with two objectives in mind: 1) to assess the effectiveness of Energy Conservation Management in reducing fatigue and improving societal participation in fatigued people with Multiple Sclerosis (MS), i.e., the TREFAMS-E study, and 2) to study physical behavior in fatigued people with MS in greater detail. The TREFAMS-E study was a component of the TREFAMS-ACE program, which consisted of three randomized controlled trials (RCT) designed to study the effects of Aerobic Training (AT), Cognitive Behavioral Therapy (CBT), and Energy Conservation Management (ECM) on MS-related fatigue and societal participation in 270 fatigued people with MS.[1] In the following paragraphs, the main findings and central themes, the strengths and limitations, and the clinical implications of this thesis will be discussed.

MAIN FINDINGS

Our systematic review concerning the effectiveness of ECM in relieving fatigue in people with MS showed that in terms of a short-term reduction of the impact of fatigue and improved Quality of Life (QoL), ECM treatment is more effective than no treatment. However, most of the included studies lacked sufficient control conditions, long-term results, and variety in treatment formats and participation outcomes.

Furthermore, we found that fatigued people with MS differed from controls not only in the amount of physical activity undertaken but also in the day patterns, intensity and distribution of activities. A subsequent cross-sectional analysis of 212 fatigued persons with MS showed that the physical behavior dimensions 'activity amount', 'activity intensity' and the 'day pattern' of activity were weakly but significantly associated with physical fatigue only.

The results of the RCT led us to conclude that an individual ECM program was not more effective in reducing fatigue and improving societal participation than an information-only control condition. Further analysis of this data suggested that a higher fatigue severity, a less negative perception of fatigue, perceiving fewer disease benefits, and perceiving a higher discrepancy in social support may be important determinants on whether a fatigued person with MS becomes a responder to ECM.

THE TREFAMS-ACE STUDY

In addition to determining the effectiveness of three different rehabilitation treatments, the TREFAMS-ACE study was designed to provide important insights into the mechanisms that underlie treatment responses. The main strength of the TREFAMS-ACE program was the concurrent study in three RCTs, with the same design and outcome measures, of the effectiveness of three different rehabilitation treatments aimed at reducing fatigue and improving participation in people with MS. The primary outcome measures in all three RCTs were fatigue and participation. Fatigue is a common symptom in MS[2] and results in restrictions both in activities and in participation.[3] Decreasing fatigue is therefore an important treatment goal in MS.[4] However, there is currently no consensus on how to treat fatigue in MS. Non-pharmacological (or rehabilitation) treatments appear to be more effective in fatigue reduction than the existing pharmacological treatments, but available evidence is still inconclusive.[5] However, multidisciplinary treatments that often combine different rehabilitation treatments have not yet been shown to be effective in relieving fatigue.[6,7] One of the underlying motivations for the TREFAMS-ACE study was to allow rehabilitation treatments to be assessed for individual effectiveness. Based on evidence available in literature, the PhD candidates of the RCTs carried out reviews of the individual treatments and concluded that all studied interventions (AT, CBT or ECM) have proven effectiveness in fatigue reduction.[8-10] However, these literature reviews also revealed the limitations of the available evidence. For ECM, the review showed that the literature lacked evidence supporting the long-term effectiveness of ECM, lacked RCTs with adequate control conditions, and that the effects of participation were not considered. Furthermore, the currently available evidence is based only on the ECM group format, whereas individual treatment is more common in clinical practice. Therefore, our ECM study is the first RCT to assess the long-term effects of individual ECM treatment and to account for participation outcomes.

MULTIPLE SCLEROSIS AND FATIGUE

For a very subjective symptom such as fatigue it is perhaps unsurprising that a wide range of definitions have developed. For our purposes, we chose a definition of MS-

related fatigue as defined by the Multiple Sclerosis Council for Clinical Practice Guidelines: 'a subjective lack of physical and/or mental energy that is perceived by the individual (or caregiver) to interfere with usual and desired activities'.[11] This definition corresponds with our view that MS-related fatigue is a multidimensional phenomenon that interferes with daily activities. However, even this definition of MS-related fatigue is relatively general and lacks the specificity to define the various dimensions of fatigue and their consequences.

Due to the many and varied definitions of fatigue, most studies rely on subjective evaluation, i.e., patient self-reported questionnaires. The multidimensional nature of fatigue and the heterogeneity in the definition of fatigue is reflected in the many questionnaires that are used to assess fatigue.[12,13] For example, perceived fatigue consists of subjective, physical, cognitive and psychological dimensions.[14] To avoid conclusions that are based on just one fatigue outcome and on restricted dimensions of fatigue, we used several fatigue questionnaires including the Checklist Individual Strength (CIS20R), Fatigue Severity Scale (FSS), and Modified Fatigue Impact Scale (MFIS). However, the RCT results do not support an influence for a particular fatigue dimension and measurement instrument: neither ECM nor the control condition resulted in different effects as measured by these fatigue questionnaires. However, study of the association between physical behavior and fatigue dimensions, with the finding that only the physical fatigue dimension was associated with physical behavior dimensions, did suggest that the fatigue dimensions are distinct from each other and differ from the total fatigue scores.

One of the main problems confronting all clinical studies of MS fatigue is that the origin and pathophysiology of MS-related fatigue is still poorly understood. Modifying fatigue by rehabilitation treatment is therefore particularly challenging, and determining the optimal treatment involves a considerable degree of uncertainty. However, as long as fatigue symptoms hinder people in their daily activities, we should continue our search for effective fatigue treatments that help to relieve this symptom, in addition to our quest to unravel the pathophysiology of fatigue. A recent review of the pathophysiology of fatigue has been published by Ayache and Chalah.[15] Studies of the pathophysiology of fatigue are also a component of the TREFAMS-ACE

research program. Although analyses are still ongoing, the aim of these studies is to provide insight into the general neurobiological mechanisms (e.g., cortisol and cytokines) of MS-related fatigue.

ENERGY CONSERVATION MANAGEMENT (ECM)

The RCT described in this thesis was not the first study to focus on the effectiveness of ECM. We included six studies in a systematic review (Chapter 5), two of which[16,17] were used in a meta-analysis. Both studies showed an effect of the ECM group treatment 'Managing Fatigue, a six-week Course for Energy Conservation' on impact of fatigue and quality of life.[18] However, weaknesses in these studies included a focus on short-term effects only, the absence of a control condition (the control group were persons on a waiting list), and not including participation as an outcome measure. In the other four studies included in the review (for which data could not be pooled) ECM was shown to have either a limited[19,20] or no effect.[6,21] In two studies[6,20] the control group was not a waiting list group, but received some type of control intervention. Furthermore, fatigue outcomes (MFIS or FSS vs. Fatigue Impact Scale (FIS) in the meta-analysis) and the content of the interventions differed slightly, as two studies[6,21] based their ECM-related intervention programs on the MS fatigue guidelines.[11] These differences might explain the dissimilar results of studies in the systematic review.

All studies in the review were designed to measure only the short-term effects of ECM treatment. Only Mathiowetz et al. reported, in a subsequent paper[22], that the effects of ECM were sustained at one year. However, it should be noted that in this particular study a cross-over design was used, which means that both study groups eventually received ECM treatment. The one-year follow-up only included subjects that received the ECM intervention, and therefore comparison with a control group was not possible.

Another point that should be mentioned concerns the reported effect sizes of the studies included in the meta-analysis. A between-group difference of 2.5 (on a 40-point subscale range) to 6 points (on an 80-point subscale range) improvement was found on the Fatigue Impact Scale (FIS) subscales. Although ECM showed

statistically significant benefits, the effects are small from a clinical perspective. From the review it could be concluded that the ECM literature lacks evidence on long-term effectiveness, clinically relevant changes in fatigue, well-designed control groups, participation outcomes, and that existing results are restricted to a group format.

ECM IN THE TREFAMS-ACE STUDY

The results of our RCT do not support the effectiveness of ECM, compared to MS nurse consultations (control condition), in relieving MS-related fatigue or improving participation. These results therefore contrast with the results of our meta-analysis, but are in agreement with two[6,21] of the four studies included in the systematic review for which data could not be pooled.[10] An explanation for the contrast with the meta-analysis studies might be that in these studies[16,17] the control condition included waiting-list patients, while in our study the MS nurse consultation control condition was attention-controlled and thus the contrast between conditions might be smaller. Simply put, the content and quality of the MS nurse consultations in our RCT might have contributed to producing minimal differences between the two conditions.

It should also be noted that we used an individual treatment format, adapting the group program to fit 12 one-to-one 45 min sessions over the 4 month intervention period. TREFAMS-ACE aimed to keep the three rehabilitation treatments in each RCT as similar as possible, and all were thus designed in an individual treatment format. This individual format is different from the regular Packer treatment. A group approach can potentially lead to additional effects due to group dynamics and the sharing of peer experience. However, in individual treatment greater attention is focused on personalizing the treatment and on homework designed to develop effective personal solutions for relieving fatigue and improving social participation.

Adaptations were also made to some other aspects of the original six-week ECM group program by Packer et al.[18]: firstly, we enriched the original content of the ECM group program by adding occupational treatment instruments and techniques, such as the Canadian Occupational Performance Measure (COPM), goal setting following SMART-principles, scaling of activities with the 'Activiteitenweger', learning

styles, and motivational interviewing. However, we found no significant differences between the groups.

Overall, the findings of the ECM RCT do not support the prescription of ECM to improve MS-related fatigue and societal participation. Patients benefit equally from MS nurse consultations, although neither produces clinically relevant effects. Furthermore, as the ECM intervention comprises many more sessions than the control condition, we can safely conclude (regardless of cost effectiveness calculations) that this treatment is more expensive than the MS nurse consultations. Nevertheless, although the RCT results did not support the use of ECM, some individuals in the ECM group did perceive the treatment as useful. For example, our ECM within-group findings showed statistically significant improvements in fatigue directly after ECM treatment, although we duly noted that this improvement was not clinically relevant when a "clinical relevance" threshold of 8 points on the CIS20r fatigue subscale was applied.[1] In addition, the mean fatigue score never dipped below the CIS20r threshold of 35, which was the indicator of severe fatigue in this study. It is perhaps worth mentioning that ECM is effective from the perspective of transferring information and learning strategies: in the strategies survey (ECSS) people with MS in the ECM group reported that they appreciated the strategies provided and perceived these as useful and effective for relieving their fatigue.

An intriguing aspect of the RCT results was the within-group effects of ECM on fatigue, thus the identification of fatigued people with MS who show a better response than others to ECM could be important. Understanding which patient might benefit is important in clinical decision making. To this end, we studied whether baseline demographic, disease-related, and personal determinants could identify ECM responders, and how these determinants are distinct from those in the control condition (Chapter 7). The participants in the ECM group that had lowered their levels of fatigue by clinically relevant values were labeled as ECM responders. The results of this analysis showed that four determinants could potentially be important identifiers of ECM responders: fatigue severity, fatigue perception, disease benefits and social discrepancies. Moreover, two ECM responder determinants were distinctive from responders in the control condition: fatigue perception and disease benefits. These

results suggest that being more severely fatigued, having a less negative perception of fatigue, perceiving less disease benefits, and perceiving a higher discrepancy in social support may be important determinants of a response to ECM. These findings also complement literature evidence on moderators of ECM[23]; see discussion in chapter 7. However, the results of our study should be interpreted cautiously (mainly because of the small sample size) and need to be further explored in larger studies.

PHYSICAL BEHAVIOR

Physical behavior (PB) has received special attention in this thesis. PB is defined as the changes to a patient's posture, movement and activity in the conditions of daily life.[24] PB is an umbrella term consisting of several dimensions, including amount of activity, day patterns, frequency and intensity of activities, and distribution of activities and rest. PB is an important domain of functioning, it is known to be affected in MS, and PB is assumed to have a relationship to fatigue. In addition, in ECM PB is of additional interest because many of the energy management strategies rely on changes in everyday activities, including PB. In the studies described in this thesis (chapters 3 & 4), we studied PB in greater detail than has been previously done by others. The background to this approach was that PB is a multi-dimensional construct, that MS might affect several dimensions of PB, and that detailed measures might provide better insight into the PB of fatigued people with MS and the effects of treatment.[25,26]

In chapter 3, we compared fatigued people with MS with healthy age and gender matched controls. We know from literature that people with MS are generally less active than healthy controls.[27-31] Several outcomes were derived from an accelerometer, such as amount of physical activity (i.e., counts per day and per minute), day patterns (i.e., counts per day period: morning, afternoon, evening), intensity categories (i.e., sedentary, light physical activity, moderate-to-vigorous physical activity (MVPA)), and the distribution of MVPA and sedentary activities. We found that fatigued persons with MS indeed showed lower amounts of physical activity (per day as well as per minute) than controls. The effects on other aspects of PB were variable, but within every dimension one or more PB outcomes were significantly different between the fatigued people with MS and controls. For

instance, fatigued people with MS were less physically active in the morning and evening, and also spent a higher percentage of their time sedentary and less time at higher MVPA intensities. Furthermore, with respect to the distribution of activities, fatigued people with MS had fewer MVPA periods, and a different distribution of sedentary and MVPA periods compared to controls. Consequently, several PB dimensions such as physical activity level, day patterns, intensity, and distribution can potentially distinguish fatigued people with MS and healthy controls. Our findings resulted from comparisons at a group level. It is possible, however, that this approach might have been too general. Although our analyses assumed a homogeneous population, if our study sample had been larger it might have been possible to distinguish subgroups within our study cohort.

The detailed PB outcomes provided us with greater insight into PB than possible with general activity outcomes such as total amount of activity. The selection of detailed PB outcomes may be dependent on the PB you wish to study. In the future, PB profiles may allow the categorization of patients according to their PB characteristics.

PHYSICAL BEHAVIOR AND MS-RELATED FATIGUE

Physical behavior (PB) is assumed to be related to fatigue. However, the evidence for a relationship between fatigue and PB — with fatigue affecting PB and/or vice versa — is weak, and due to conflicting results there is currently no consensus on the association of fatigue and PB. As both concepts are known to be multidimensional, fatigue and PB might well have a complex relationship. In chapter 4, we studied the association between fatigue and PB while accounting for the multi-dimensionality of both constructs. To study a possible association, we used the dimensions of fatigue (subjective, physical, cognitive and psychological fatigue) and the more detailed PB outcomes of chapter 3. We concluded that the 'physical fatigue' dimension was significantly and negatively associated with the PB dimensions 'amount of activity', 'intensity categories' and 'day pattern', although the relationships were admittedly weak. The results indicated that more fatigued persons have a less optimal PB. However, none of the other fatigue dimensions were associated with PB. An

explanation for the weak associations may be that most of the participants included in the study were severely fatigued, resulting in a sample with a small fatigue severity range and an attendant lowering of the strength of the examined relationships between fatigue and PB. The implications of these findings therefore require careful consideration. Additionally, and as discussed in the previous paragraph, our findings were based on total group data and it is therefore possible that subgroups with specific profiles might be distinguished. Our results also underlined that, in addition to the total scores, it is important to consider specific fatigue and PB dimensions when studying the effectiveness of rehabilitation treatments or when treating patients with MS. Otherwise important effects may be missed. Overall, we conclude that the clinical impact of changing PB to decrease physical fatigue may be small.

PHYSICAL BEHAVIOR AND ECM

From a clinical perspective, beyond the level of physical activity (e.g., total number of activity counts or number of steps), MS rehabilitation treatments may indirectly influence multiple dimensions of physical behavior (PB). It may be expected that ECM participants, as a result of the treatment, will show changes in their rest and activity balance (e.g., distribution of activities and rest). However, we did not assess the activity distribution outcomes in the RCT, as chapter 4 showed that fatigue and the distribution dimension of PB are not associated. Another goal of ECM is balancing the day pattern of activities, i.e., spreading activities equally over the morning and evening. The day pattern outcome showed an association with a lower physical fatigue level (chapter 4). Hence, in the RCT we did not use subdivision of day patterns. In addition, by means of well-balanced activity planning, more intensive activities may become possible, whereas weighing norms and priorities may also result in different physical activity patterns. In the ECM RCT study we assessed certain PB outcomes: the performance measures 'physical activity scale for individuals with physical disabilities' (PASIPD), and activity monitoring (Actigraph GT3X+) outcomes (counts per day and per minute, intensity of activities (sedentary, light, moderate to vigorous physical activity). None of the outcomes showed significant differences between the ECM group and the control group during the study. Activity monitor data was measured

longitudinally, so considerable data are available for future analyses and it may be useful to complement these data with measurements of a more heterogeneous (e.g., for fatigue) MS group.

GENERALIZABILITY OF RESULTS

All our results were based on ambulatory fatigued people with MS. It was difficult to include sufficient participants, as many potential participants declined the invitation to participate due to distance issues or because their perceived high levels of fatigue made them unwilling to engage in a study involving intensive treatments and a long follow-up. Of those willing to participate, one third was excluded because they did not meet the inclusion criteria. The main reasons for exclusion were depression (HADS > 11) or the absence of severe fatigue (CIS20r < 35). With the exclusion of participants and those declining to participate, some sample bias may have occurred. On the other hand, 86 participants could be included and drop-outs were within permissible attrition rates, so the necessary power to study group differences was maintained. Multiple MS types and fatigue severities were represented in the RCT, and as the ECM intervention is suitable for all types and degrees of MS severity, we do not expect different results for the effects on fatigue in another MS group.

CLINICAL IMPLICATIONS

While the RCT did not directly support the use of ECM in the treatment of fatigue in people with MS, the absence of added value with respect to MS nurse consultations does not mean that ECM cannot be a useful treatment for other daily life restrictions faced by people with MS. ECM has two defined aims: firstly, it involves guiding people to identify and modify their activities through the systematic analysis of daily work, home and leisure activities, with the aim of reducing the impact of fatigue on daily life. One way to assess this impact is by applying the COPM, which assesses patients' perceived ability to perform daily activities and their satisfaction with relevant daily activities. Other studies[32,33] have shown that the COPM is a good outcome measure for effects of occupational treatment. Unfortunately, in our study COPM was not chosen as an outcome measure in advance, and therefore it was not registered by the

therapist in such a way that it could be later used as an outcome. Secondly, ECM is designed to increase a patient's use of energy-conserving strategies and improve confidence in their ability to manage fatigue. We did measure the use and perceived effectiveness of the strategies, and the results showed that 85% of the participants had implemented ≥ 6 strategies, with a mean of 10 strategies, and that these strategies were rated as 'effective', with a mean value of 7 on a scale of 10 (very effective). Problems with the distribution of activities, balancing day-schedule and reconsidering priorities and standards without the need for relieving fatigue are still reasons to advise people with MS (and also other diseases) to follow an ECM intervention.

FUTURE RESEARCH

Comparison with the other RCTs in the TREFAMS-ACE program indicated that the interventions in those RCTs showed statistically significant positive results on fatigue in the short term, hence positive effects cease almost consecutively with the cessation of treatment. However, the changes in MS-related fatigue following aerobic training were not clinically relevant and it appeared to be difficult for patients to adhere to the required training regime. CBT can effectively reduce severe MS-related fatigue in the short term, however, more research is needed on how to maintain this effect over the longer term. Additional effects on societal participation could not be shown for any of the interventions. At the present moment, CBT seems to be the best treatment option for MS-related fatigue. However, study findings suggest that it may be useful to combine aspects of the ECM and CBT to create a more powerful intervention aimed at reducing fatigue in persons with MS. As energy management strategies in our ECM group[34] were used frequently and rated as effective in relieving fatigue, they may represent a useful addition to the CBT program. Furthermore, the three identically designed RCTs in the TREFAMS-ACE program may allow data pooling and an optimal comparison between the three trials. Future analyses will focus in more detail on the differences between interventions.

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Summary

Fatigue is a frequent, frustrating, overwhelming and often disabling symptom that affects the majority of people with Multiple Sclerosis (MS), resulting in severely limited daily activities and restricted participation (i.e. performance of social roles). Fatigue is also related to changes in the physical behavior of people with MS, in which both motor and sensory disorders play a role. Relieving the effects of severe fatigue on daily life is an important treatment goal in MS. The broader objective of the studies included in this thesis was to assess the effectiveness of Energy Conservation Management (ECM) in reducing fatigue and improving societal participation in fatigued people with MS. ECM is a type of occupational treatment applied in the context of rehabilitation, and is based on the Packer group course 'Managing fatigue'. ECM aims to create a positive attitude towards active decision-making, to stimulate the optimum use of available energy, to increase a patient's use of energy-conserving strategies, and to improve their confidence in their ability to manage fatigue. Another important objective was to study in greater detail the physical behavior in fatigued people with MS and the association between fatigue and physical behavior.

This thesis is a part of the 'Treating Fatigue in Multiple sclerosis: Aerobic Training, Cognitive Behavioral Therapy and Energy Conservation Management' (TREFAMS-ACE) multicenter program. The two main objectives of the TREFAMS-ACE study were (1) to assess the effectiveness of three different rehabilitation treatment strategies in reducing fatigue and improving societal participation in fatigued people with MS, and (2) to study the neurobiological mechanisms of action that underlie treatment effects and MS-related fatigue in general. The extended study protocol is described in Chapter 2. The program included three single-blinded RCTs, all with the same two-parallel-arms design. In all RCTs the control arm consisted of an information-only condition. The only differences between the RCTs were the experimental treatment, some specific treatment-related outcomes, and the locations where the studies took place. Patients were randomized to either the trial-specific treatment consisting of 12 therapist sessions over 4 months, or an information-only control condition provided by an experienced MS nurse and consisting of three consultations within 4 months. All measurements were carried out 1 week prior to randomization and at 8, 16 (i.e. post-intervention), 26 and 52 weeks after starting the

treatment, and included self-reported questionnaires, visits to the rehabilitation center, and saliva tests and activity monitoring at home.

The studies included in this thesis primarily focus on the ECM component of the research program (Chapter 5, 6 & 7); furthermore, two studies used baseline data of physical behavior and fatigue from the RCT (Chapter 3 & 4).

Fatigue limits activities in daily life and also affects physical behavior. Conversely, physical behavior can also affect fatigue. Previous studies have shown that the relationship between fatigue and physical behavior is complex, and the results of studies have often conflicted. Thus far, the effects of MS and MS-related fatigue on physical behavior have been studied primarily from the perspective of physical activity levels (e.g., total number of activity counts), which is just one of the dimensions of physical behavior and perhaps not the most clinically relevant or most responsive physical behavior parameter in MS. Possible other dimensions of physical behavior that can be considered are day patterns, the frequency and intensity of activities, and the distribution of activity and rest.

To study the effects of MS and MS-related fatigue on physical behavior in greater detail, in **Chapter 3** we compared various aspects of physical behavior in fatigued people with MS and healthy controls. The results showed that besides physical activity level (i.e. fewer activity counts per day and per minute), fatigued people with MS also differed from matched healthy controls in other PB dimensions: those in the MS group spread their activities differently over the day (less physically active in the morning and evening, but not in the afternoon), they spent a higher percentage of their time sedentary, and they spent less time in the moderate-to-vigorous physical activity (MVPA) category. Furthermore, people with MS showed fewer MVPA periods and a different distribution of sedentary and MVPA periods, respectively longer and shorter periods over the day. The study showed that fatigued people with MS not only differ from healthy controls in general activity outcomes such as total amount of activity, but also in several other physical behavior outcomes.

In **Chapter 4**, we studied the association between physical behavior and fatigue accounting for the multi-dimensionality of both constructs. To study the association, we used four dimensions of fatigue (subjective, physical, cognitive and

psychological fatigue) and the more detailed physical behavior outcomes of Chapter 3. We concluded that the physical fatigue dimension was significantly and negatively associated with the physical behavior dimensions 'amount of activity', 'intensity categories', and 'day pattern', although the relationships were weak. These relationships indicate that persons who are more physically fatigued have a physical behavior pattern that diverges considerably from that of healthy people. None of the other fatigue dimensions were associated with one of the physical behavior outcomes. These results underlined the importance of considering specific fatigue and PB dimensions in addition to the total scores.

Prior to the ECM RCT, we systematically reviewed the evidence for the effectiveness of ECM in people with MS (Chapter 5). Based on six studies and a meta-analysis, we concluded that the ECM group program by Packer et al. is effective in treating MS-related fatigue and improving quality of life over the short-term (at eight weeks) in comparison to a waiting-list control condition. However, although the differences were statistically significant, they were small from a clinical perspective. Furthermore, the review concluded that there was a lack of literature evidence related to long-term effectiveness, clinically relevant changes in fatigue, well-designed control groups, and participation outcomes, and that evidence supporting ECM was restricted to a group format.

In Chapter 6, we describe the results of our RCT concerning the effects of ECM. As primary outcomes, the short and long-term effects of ECM on fatigue (Checklist Individual Strength, CIS20r) and participation (Impact on Participation and Autonomy questionnaire, IPA) in fatigued persons with MS were assessed. Several other fatigue measures (CIS20r remaining subscales, Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS)), as well as daily functioning measures (Health survey Short-Form (SF-36), Rehabilitation Activities Profile (RAP)) were included as secondary outcomes and a treatment-specific Energy Conservation Strategies Survey (ECSS) was included. Analysis was based on 76 randomized ambulatory fatigued people with MS. The results showed that ECM was no more effective in reducing MS-related fatigue and improving societal participation than an information-only control condition: no statistically significant or clinically relevant differences were found.

However, additional analyses showed that persons with MS did implement the provided ECM strategies in daily life and that they experienced these strategies as useful.

Although there was no significant difference between the intervention group and the control group, the RCT showed within-group effects of ECM on fatigue. Identification of fatigued people with MS who show a better response to ECM is important. Therefore, in Chapter 7 we studied whether baseline demographic, disease-related and personal determinants can identify responders to the ECM intervention and how these determinants are distinct from those in the controls. In total, 69 participants were included (ECM 34; MS nurse 35). The participants who had clinically-relevant reductions in fatigue, a difference of ≥ 8 on the CIS20r, were labeled as responders. In the ECM group, four determinants (baseline fatigue, fatigue perception, illness cognitions questionnaire (ICQ) subscale disease benefits, and social discrepancies) were related to the probability of being a responder. Two determinants (fatigue perception, ICQ disease benefits) were distinctive for the ECM group. The results suggest that fatigued people with MS who show the greatest response to ECM treatment are more severely fatigued at the start, have a less negative perception of fatigue, perceive fewer disease benefits and perceive serious discrepancies in social support.

Finally, Chapter 8 provides a general discussion of the results of this thesis. The main conclusion of our RCT is that ECM does not have significant added value for fatigued people with MS. Our results also underline the multidimensionality of fatigue and physical behavior. The general discussion examines possible explanations for the negative findings of the RCT, for the differences with the systematic review, and the complex relation between physical behavior and fatigue. Finally, the clinical implications and possible directions for future research are considered.

Nederlandse samenvatting

Vermoeidheid is een veel voorkomend symptoom bij mensen met Multiple Sclerose (MS) en komt vaak in de beginfase van de ziekte voor. Het wordt ervaren als een frustrerend, overweldigend en vaak invaliderend symptoom. De vermoeidheid brengt ernstige beperkingen met zich mee in dagelijkse activiteiten en participatie, bijvoorbeeld het persoonlijk functioneren in de sociale omgeving. Vermoeidheid is ook gerelateerd aan veranderingen in het beweeggedrag van mensen met MS, waarbij motorische functiestoornissen en gevoelsstoornissen ook een rol spelen. Behandeling van de vermoeidheid en het verminderen van de beperkingen in het dagelijks leven is een doel dat voor de patiënt en binnen de revalidatiegeneeskunde belangrijk is. Er is echter nog geen effectieve behandeling van vermoeidheid bekend. Toch krijgen vermoeide mensen met MS een revalidatiebehandeling, waarbij veelal sprake is van multidisciplinaire behandeling met aspecten van training, educatie en gedragstherapie.

Het eerste doel van de in dit proefschrift beschreven studies was het bepalen van de effectiviteit van een Energiemanagement (ECM) behandeling op het verminderen van vermoeidheid en verbeteren van de sociale participatie. ECM is een ergotherapeutische behandeling, gebaseerd op de Packer groepsbehandeling 'Managen van vermoeidheid'. ECM heeft als doel een positieve houding gericht op actieve besluitvorming te stimuleren en de mensen zo optimaal mogelijk om te laten gaan met de beschikbare energie door het optimaliseren van de balans tussen de eisen van het dagelijks leven en de beschikbare energie. Door het toepassen van energiemanagementstrategieën probeert men het vertrouwen in het vermogen de vermoeidheid te kunnen managen te vergroten. Het tweede doel van de uitgevoerde studies was het meer in detail in kaart brengen van de gevolgen van MS op beweeggedrag en de relatie tussen vermoeidheid en beweeggedrag van vermoeide mensen met MS meer gedetailleerd te onderzoeken.

De studies die in dit proefschrift zijn beschreven zijn onderdeel van een multicenter onderzoeksprogramma met de naam 'Behandeling van vermoeidheid bij MS: Aerobe training, Cognitieve gedragstherapie en Energiemanagement' (TREFAMS-ACE). De twee hoofddoelen van het TREFAMS-ACE programma zijn (1) het bepalen van de effectiviteit van drie verschillende revalidatiebehandelingen op het verminderen

van vermoeidheid en verbeteren van sociale participatie; en (2) het onderzoeken van de (neuro)biologische werkingsmechanismen die ten grondslag liggen aan het behandeleffect en MS-gerelateerde vermoeidheid in het algemeen. Dit tweede doel wordt niet behandeld in dit proefschrift. Het uitgebreide protocol van het TREFAMS-ACE onderzoek staat beschreven in **Hoofdstuk 2**. Het onderzoeksprogramma bestaat uit drie multicenter RCT's die gekenmerkt worden door hetzelfde design, verschillen in de aangeboden interventie, dezelfde controleconditie, en de overeenkomst in uitkomstmaten (naast enkele interventie-specifieke uitkomstmaten). De interventies bestaan uit 12 therapiesessies in 4 maanden, de controleconditie (het geven van informatie) bestaat uit 3 consulten met een gespecialiseerde MS verpleegkundige in 4 maanden. Er zijn 5 meetmomenten: 1 week voor de randomisatie (baseline), 8 en 16 weken (tijdens en net na de behandeling) en de lange termijn follow-up metingen op 26 en 52 weken na de start van de behandeling. De metingen bestaan uit zelfgerapporteerde vragenlijsten, fysiek afgenomen testen in het revalidatiecentrum, en het afnemen van speekseltesten en het dragen van een activiteitenmonitor wat in de thuissituatie plaats vond.

De studies van dit proefschrift richten zich primair op het ECM-deel van het onderzoeksprogramma (Hoofdstuk 5, 6 en 7); daarnaast is in twee studies gebruik gemaakt van het baseline beweeggedrag- en vermoeidheidsdata van alle RCT's (Hoofdstuk 3 en 4).

Vermoeidheid heeft invloed op het uitvoeren van functionele activiteiten in het dagelijkse leven en ook het beweeggedrag zal beïnvloed worden door vermoeidheid. Anderzijds is het ook mogelijk dat beweeggedrag een effect heeft op vermoeidheid. Eerdere studies hebben laten zien dat de relatie tussen vermoeidheid en beweeggedrag complex is, met elkaar tegensprekende resultaten. Tot nu toe is de relatie tussen MS en MS-gerelateerde vermoeidheid en het beweeggedrag voornamelijk onderzocht vanuit de beweeggedragdimensie hoeveelheid fysieke activiteit. Maar de mate van fysieke activiteit is slechts één van de dimensies van beweeggedrag, en is mogelijk ook niet de meest klinisch relevante en responsieve uitkomstmaat van beweeggedrag in MS. Andere mogelijke dimensies van beweeggedrag zijn bijvoorbeeld dagpatronen, de frequentie en intensiteit van

activiteiten, en de verdeling van activiteiten en sedentair gedrag. We wilden de gevolgen van MS op beweeggedrag en de relatie tussen MS-gerelateerde vermoeidheid en beweeggedrag in meer detail onderzoeken.

In Hoofdstuk 3 vergeleken we daarom de verschillende dimensies van beweeggedrag tussen vermoeide mensen met MS en gezonde controles met eenzelfde leeftijd en geslacht. De resultaten lieten zien dat - naast de totale hoeveelheid fysieke activiteit (d.w.z. minder activiteiten per dag en per minuut) - de vermoeide mensen met MS ook verschilden van de controles in andere beweeggedragdimensies: een andere verdeling van hun activiteiten over de dag (minder actief in de ochtend en de avond), een hoger percentage van hun beweegtijd spenderen ze zittend (sedentair) en ze spenderen minder tijd aan gemiddeld-tot-intensieve activiteiten. Ook verdelen ze de perioden van sedentaire en gemiddeld-tot-intensieve activiteit anders over de dag dan gezonde mensen.

In Hoofdstuk 4 onderzochten we de associatie tussen beweeggedrag en vermoeidheid, rekening houdend met de multidimensionaliteit van beide constructen. Om de relatie te kunnen onderzoeken gebruikten we vier dimensies voor vermoeidheid (subjectief, fysiek, cognitief en psychologisch) en de meer gedetailleerde beweeggedragdimensies die we in hoofdstuk 3 ook gebruikten. We concludeerden dat de dimensie fysieke vermoeidheid significant en negatief geassocieerd was met de beweeggedragdimensies totale hoeveelheid activiteit, intensiteit van activiteiten, en het dagpatroon. Daarbij moet wel worden opgemerkt dat het zwakke associaties betrof. Deze associaties geven aan dat personen die meer fysiek vermoeid zijn een sterker afwijkend beweeggedrag hebben. Geen van de andere vermoeidheiddimensies waren geassocieerd met een van de beweeggedraguitkomsten. De resultaten onderschrijven het belang van het onderscheiden van specifieke vermoeidheid- en beweeggedragdimensies, in aanvulling op totale vermoeidheid- en beweeggedraguitkomsten.

Voorafgaand aan de ECM-RCT is op een systematische manier onderzocht of er bewijs is voor de effectiviteit van de ECM-behandeling (Hoofdstuk 5). Gebaseerd op zes studies en een meta-analyse concludeerden we dat het ECM-groepsprogramma van Packer e.a. op de korte termijn (8 weken) en in vergelijking

met een wachtlijst-controle conditie effectief is in het behandelen van MS-gerelateerde vermoeidheid en verbetering geeft in de kwaliteit van leven. De verschillen waren weliswaar statistisch significant, maar vanuit klinisch oogpunt klein en mogelijk niet relevant. Bovendien ontbrak het in de beschikbare literatuur aan bewijs voor effectiviteit op de lange termijn, een goed opgezette controleconditie en uitkomsten op participatie. Daarnaast geldt het bewijs voor effectiviteit alleen voor een groepsbehandeling.

In Hoofdstuk 6 worden de resultaten van de RCT beschreven. Primaire uitkomstmaten zijn vermoeidheid (gemeten met de Checklist Individuele Spankracht – CIS20r) en participatie (gemeten met de Impact op Participatie en Autonomie vragenlijst -IPA). Als secundaire uitkomstmaten zijn nog enkele vermoeidheidsmaten (CIS20r subschalen, Impact van Vermoeidheid schaal – MFIS), Ernst van de Vermoeidheid schaal – FSS), maten over het dagelijks functioneren (Gezondheid vragenlijst – SF-36, Revalidatie Activiteiten Profiel – RAP) afgenomen, en als interventiespecifieke uitkomst is de energiemanagementstrategieën vragenlijst (ECSS) afgenomen. Analyses zijn verricht op 76 ambulante vermoeide mensen met MS. De resultaten lieten zien dat de ECM-behandeling niet effectiever was dan de controleconditie. Er werden geen statistisch significante verschillen of klinisch relevante verschillen aangetoond. De analyses op de aangereikte energiemanagement strategieën lieten zien dat de mensen met MS de strategieën gebruikten in hun dagelijkse leven en ze ook nuttig vonden.

Ondanks dat we geen significante verschillen vonden tussen de interventie- en de controlegroep, liet de RCT wel effecten binnen de groep zien op vermoeidheid. Voor behandelaars is het van belang te weten of er subgroepen van vermoeide mensen met MS zijn, die beter reageren op de behandeling. Daarom is onderzocht of er op baseline gemeten demografische, ziekte-gerelateerde en persoonlijke determinanten geïdentificeerd konden worden die een hogere kans geven op het baat hebben bij de ECM interventie (beschreven in Hoofdstuk 7). Bij 69 mensen (ECM 34, controle 35) is er een responder – nonresponder analyse verricht. Een responder is daarbij gedefinieerd als een persoon die een klinisch relevante vermindering van 8 punten op de CIS20r vragenlijst laat zien. De resultaten lieten zien dat de

determinanten ernst van vermoeidheid, beleving van de vermoeidheid, ervaren voordelen van de ziekte en ervaren sociale ondersteuning significant gerelateerd waren aan de kans om ECM-responder te zijn. Dit suggereert dat vermoeide mensen met MS die op baseline ernstiger vermoeid zijn, een minder negatieve beleving van vermoeidheid hebben, minder ziekte voordelen ervaren en een tekort ervaren aan sociale ondersteuning een hogere kans hebben om goed te reageren op de ECM-behandeling. Twee determinanten (beleving van de vermoeidheid en ervaren voordelen van de ziekte) hadden een ander effect op het responder zijn in de ECM groep dan in de controlegroep en waren daardoor onderscheidend voor de ECM groep.

In Hoofdstuk 8 bediscussiëren we de bevindingen. De belangrijkste bevindingen zijn dat in onze RCT ECM niet van toegevoegde waarde was. Daarnaast onderstrepen de resultaten (activiteitenmonitoring) de multidimensionaliteit van vermoeidheid en beweeggedrag. De discussie besteedt specifieke aandacht aan de mogelijke redenen van de negatieve RCT-bevindingen, de discrepantie met de systematische review, de complexe relatie tussen beweeggedrag en vermoeidheid, de klinische implicaties en suggesties voor toekomstig onderzoek.

Appendix 1

TREFAMS-ACE Study Group

TREFAMS-ACE Study Group

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Appendix 2

Overview TREFAMS-Energy Conservation Management treatment and Control condition

Overview TREFAMS-Energy Conservation Management treatment and Control condition

Overview of the TREFAMS-ECM treatment and control condition according to the TIDieR checklist, Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.

ENERGY CONSERVATION MANAGEMENT

Background

The Energy Conservation Management (ECM) treatment protocol is based on the group course 'Managing Fatigue' developed by Packer et al. (1995). The aim of ECM is not so much to correct the underlying mechanisms of fatigue, nor to accept that the solution is to decrease activity levels or reduce the breadth and extent of activities. Instead, the aim is to promote a positive attitude aimed at active decision-making and the optimum use of the available energy to fit the unique needs of each individual. ECM is also intended to reduce the impact and severity of fatigue, to increase patients' use of energy-conserving strategies and to improve their confidence in their ability to manage fatigue. For the present study, the original content of the ECM program was adapted to fit 12 one-on-one 45 minutes sessions over the 4 month intervention period. In the TREFAMS-ACE study with three equally designed RCTs, the experimental fatigue interventions consisted of 12 supervised treatment sessions in 16 weeks. Dose and duration of the sessions were based on clinical practice, knowledge about time needed for a behavioral change and previous trials.

What

The content of ECM was bundled in an ECM workbook (available in Dutch only) that was given to the participant during the first session. For an extensive overview of the content of the ECM, see Table 1. Attention was paid to individual learning and approaching styles to assimilate the program contents. Motivational interviewing was used as a communication technique to assist patients in exploring and resolving

ambivalence to change. Energy conservation strategies were an important part of every treatment session. These strategies are based on the Energy Conservation Strategies Survey (ECSS, by Mallik et al., 2005) that was administered once, directly after the ECM is completed. A variety of teaching methods was used, including providing information, discussions, long-term and short-term goal setting, practice activities and homework activities, all aimed at assisting the participant's integration of energy conservation principles into the performance of everyday tasks.

Who provided

ECM was given by trained occupational therapists who were already familiar with MS, energy conservation strategies, and the Packer group course 'Managing Fatigue'. They received a program guideline and a one-day refresher course on treatment principles and strategies, and they were required to be qualified in Motivational Interviewing techniques. A patient received treatment from one and the same occupational therapist.

Where

Outpatient rehabilitation departments that participated in the study.

How, When and How much

ECM was delivered by 12 individual face-to-face sessions of 45 minutes over the 4 month intervention period.

Tailoring

All treatment topics are discussed but the order of the worksheets 'b' to 'g' are allowed to be changed. Also the content of the homework activities are individualized, based on the treatment goals of the patient.

Modifications

N/A

Adherence

Both the occupational therapists and the MS nurses completed a program checklist to assess whether each participant and therapist/nurse adhered to the program. The participants in the ECM group had a treatment compliance of 83%, with a mean of 11 sessions.

Table 1. Individual Energy Conservation Management.

Sessions	Content of the sessions
Introduction session	•Getting to know the patient, identification of problems in daily life with help of the COPM, impact of fatigue on daily life • Hand out workbook IECM, activity list per day/week to give insight in load and loadability of the patient, and learning style assessment
Analysis of the problems	• Discuss activity/participation problems, outcomes of load and loadability from the activity lists • Analysis of problems, determine questions of help, and the learning and approaching style • Formulate the problems and treatment goals
Treatment sessions	*a. Information about fatigue* • types, causes and factors influencing fatigue • banking (saving) and budgeting (deciding how to spend) energy *b. Importance of rest* • how fatigue can influence your daily life • rest as a way of relieving fatigue *c. Balancing your schedule* • components of a balanced lifestyle • how to balance (light and heavy) activities • planning a weekly schedule *d. Communication* • expressing needs to others • breaking down negative attitudes about fatigue and rest *e. Priorities and standards* • breaking down activities in order to simplify them as much as possible • budgeting energy, making decisions about priorities and standards *f. How to do activities* *g. Ergonomics, body positions and assistive devices* • Organization of needed environments (work, home) to promote good body mechanics • Organization of needed environments to save energy • technology and equipment that can save energy • structure of body/biomechanics • how to use body properly/ergonomics
Evaluation session	

CONTROL CONDITION

Background

The information-only control condition consisting of MS-nurse consultations for MS-related fatigue covered two important study aspects to control for: (1) reliable information on MS-related fatigue; and (2) attention from an experienced MS professional in order to reassure the patient that his/her concerns or questions about fatigue will be taken seriously.

What

All MS-nurses involved in one of the TREFAMS-ACE trials participated in a 1-day training course. In this course the MS-nurses shared their approach to taking a fatigue-related nursing history, they were instructed as to how to provide relevant information on MS-related fatigue without giving concrete therapeutic advice that affects the contrast with the experimental interventions, and they were informed of the restrictions concerning the referral of patients to other first or second line healthcare professionals within the hospital. These newly-learned skills were practiced using role-playing.

Equipment

A study-specific (Dutch) brochure was developed with the aim to provide standardized information about MS-related fatigue. Any advices to first or second line health care professionals was removed.

Who

Experienced and trained MS-nurses. A patient receives treatment from one and the same MS-nurse.

How, when and how much

Control group consisting of three individual face-tot-face consultations of 45 minutes each, over a 4-month period. The content of the consults were quite strictly

protocolized. A consult was guided by the questions that patients asked about the fatigue information provided.
Session 1 (baseline): Acquaintance, MS-related fatigue history, and providing standardized brochure.
Session 2 (1.5 months): Evaluating brochure and goal-setting.
Session 3 (4 months): Goal and treatment evaluation.

Where

MS-specialized outpatient clinic

Modifications

In some cases the face-to-face sessions were replaced with phone sessions.

Adherence

The number of sessions completed, the topics that were discussed, as well as the amount of allied healthcare during the study period was recorded.
In the control group 86% of the participants took part in all three MS nurse consultations.

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About the author

Curriculum Vitae

List of publications

PhD portfolio

CURRICULUM VITAE

Lyan Juliana Maria Blikman was born in Nijverdal on the 31st of January 1987. In 2005 she completed secondary school (Atheneum) at Pius X College in Almelo, with a specialization in Nature and Health. Between 2005 and 2010 she studied Human Movement Sciences at the University of Groningen (Rijksuniversiteit Groningen - RUG), which resulted in a Bachelors (2008) and then a Masters (2010) degree. During that time she also was active in rowing at the competitive level in the 'ladies eight 06-07' of Gyas Groningen. For her Masters of Human Movement Sciences, she specialized in Aging, which included an internship at the Neurology department of University Medical Center Groningen, under the supportive supervision of Prof. Natasha Maurits and Dr. Yvo Kamsma, where she studied the physical activity of patients with Parkinson's disease. Before starting this internship she was not attracted by a career in science, but due to a better understanding of research and the inspiring supervision and support of Natasha and Yvo, her interest in science was sparked.

Following her Masters, she found a PhD position at the Erasmus MC Rotterdam in the Department of Rehabilitation Medicine, starting in November 2010. The research project was the TREFAMS-E trial, and involved study of the effectiveness of Energy Conservation Management as a treatment for MS-related fatigue. This trial forms part of the multicenter TREFAMS-ACE program, in which the effect of Aerobic Training and Cognitive Behavioral Therapy were also studied. From 2015 she was only able to work part-time on the research project, due to personal circumstances, finally completing the PhD research as presented in this thesis in 2017.

Lyan now works at the University of Twente, initially as a program manager research support at the Library, ICT-Services & Archive, and currently as coordinator research support at the Faculty of Behavioral, Management and Social Sciences.

LIST OF PUBLICATIONS

Blikman LJ, van Meeteren J, Twisk JW, de Laat FA, de Groot V, Beckerman H, Stam HJ, Bussmann JB, TREFAMS-ACE study group. Energy Conservation Management for fatigued people with MS: who benefits? [submitted]

Blikman LJ, van Meeteren J, Rizopoulos D, de Groot V, Beckerman H, Stam HJ, Bussmann JB, TREFAMS-ACE study group. Physical behavior is associated with physical fatigue in persons with multiple sclerosis-related fatigue. [submitted]

Blikman LJ, van Meeteren J, Twisk JW, de Laat FA, de Groot V, Beckerman H, Stam HJ, Bussmann JB, the TREFAMS-ACE study group. Effectiveness of energy conservation management on fatigue and participation in multiple sclerosis: A randomized controlled trial. *Mult Scler.* 2017:1352458517702751

Heine M, van den Akker LE, **Blikman LJ**, Hoekstra T, van Munster E, Verschuren O, Visser-Meily A, Kwakkel G, TREFAMS-ACE study group. Real-time assessment of fatigue in patients with multiple sclerosis: How does it relate to commonly used self-report fatigue questionnaires? *Arch Phys Med Rehabil.* 2016 Nov;97(11):1887-1894.

Blikman LJ, van Meeteren J, Horemans HL, Kortenhorst IC, Beckerman H, Stam HJ, Bussmann JB. Is physical behavior affected in fatigued persons with multiple sclerosis? *Arch Phys Med Rehabil.* 2015 Jan;96(1):24-29.

Malekzadeh A, Van de Geer-Peeters W, De Groot V, Teunissen CE, Beckerman H, and **TREFAMS-ACE study group**. Fatigue in Patients with Multiple Sclerosis: Is It Related to Pro- and Anti-Inflammatory Cytokines? *Dis Markers.* 2015; 2015:758314.

Blikman LJ, Huisstede BM, Kooijmans H, Stam HJ, Bussmann JB, van Meeteren J. Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review and meta-analysis. *Arch Phys Med Rehabil.* 2013; 94(7):1360-1376.

Beckerman H, **Blikman LJ,** Heine M, Malekzadeh A, Teunissen CE, Bussmann JB, Kwakkel G, van Meeteren J, de Groot V, the TREFAMS-ACE study group. The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE program. *Trials*. 2013;14(1):250.

van Meeteren J, Bussmann JB, **Blikman LJ**, Heine M, Malekzadeh A, Teunissen CE, Kwakkel G, de Groot V, Beckerman H, the TREFAMS-ACE study group. Effectiviteit van aerobe training, cognitieve gedragstherapie en energiemanagement bij MS-gerelateerde vermoeidheid TREFAMS-ACE studie. *Nederlands Tijdschrift voor Revalidatiegeneeskunde*. 2012(6).

Abstracts:

Blikman LJ, van Meeteren J, Twisk J, de Laat F, de Groot V, Beckerman H, Stam HJ, Bussmann JB, TREFAMS-ACE study group. Effectiveness of energy conservation management on fatigue and participation in multiple sclerosis: a randomized clinical trial. *ECTRIMS Online Library*. Sep 15, 2016; 146628

van Meeteren J, **Blikman LJ**, Rizopoulos D, de Groot V, Beckerman H, Stam HJ, Bussmann JB, TREFAMS-ACE study group. Physical behavior is associated with physical fatigue in persons with multiple sclerosis related fatigue. *ECTRIMS Online Library*. Sep 15, 2016; 146629.

Blikman LJ, van Meeteren J, Horemans HL, Beckerman H, Stam HJ, Bussmann JB. How does MS affect physical behaviour: a comparison with healthy controls. 19th annual conference RIMS 2014 Brighton, Abstracts in *Multiple Sclerosis Journal* June 2014 20(7): 970 O-9.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student:	Lyan J.M. Blikman	PhD period:	2010 – 2017
Erasmus MC Department:	Rehabilitation Medicine	Promotor:	Prof. dr. H.J. Stam
Research School:	-	Supervisor:	Dr. J. van Meeteren & Dr. J.B.J. Bussmann

1. PhD training

	Year	Workload
General courses		
- Biomedical English Writing and Communication	2011-2012	4 ECTS
- Research Integrity	2011	2 ECTS
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1 ECTS
- CPO-mini-course: methodology of patient orientated research and preparation for subsidy application	2011	8 hours
Specific courses		
- Workshop Advanced Medical Writing and Editing (Nihes ESP71)	2014	0.7 ECTS
- Biostatistics for clinicians (Nihes-EWP22)	2012	1 ECTS
- Regression analysis for clinicians (Nihes-EWP23)	2013	1.9 ECTS
- Repeated measurements (Nihes-CE08)	2013	1.4 ECTS
- Longitudinale data-analyse (Emgo/EpidM)	2013	3 ECTS
- Training 'Omgaan met groepen' (Tutoraat 2012)	2012	4.5 hours
- RAP assessment instruction by Dr. V. de Groot, VUmc	2011	2 hours
- Motivational Interviewing	2011	1 ECTS
- Training 'personal effectiveness'	2013	24 hours
Seminars and workshops		
- Prezi workshop: how to make presentations in Prezi	2011	2 hours
- Medical Library: workshop in EndNote	2011	2 hours
- Consulted library for review search strategies	2011	2 hours
- 'Publishing and Acceptance Criteria for Scientific Journals' by Ian Cressie	2012	3 hours
- CPO/CQM Joint Symposium Study Design: Beyond Simple Randomization	2012	3 hours
- Erasmus MC PhD-day 2012	2012	5 hours
- Postdoc Network meeting 'Effective Time Management: why is it so hard?' by Gilbert Bookelman	2013	3 hours
- Postdoc Network meeting 'Stepping Stones for Grant Writing and Interviews'	2013	3 hours
- Erasmus MC Postdoc Network meeting 'Presenting yourself and your work'	2014	3 hours
- PhD Postdoc Network meeting 'Where your PhD can take you: career opportunities'	2014	3 hours

Oral presentations			
-	'TREatment of disabling FAtigue in MS: Aerobic training, Cognitive behavioral therapy and Energy conservation management' & 'Resultaten van de TREFAMS-ACE studie: De effecten van energie management op vermoeidheid, participatie en activiteit' at monthly regional meeting for rehabilitation physicians at Rijndam Rehabilitation Center, Rotterdam	2011, 2015	0.7 ECTS
-	'TREatment of disabling FAtigue in MS: Aerobic training, Cognitive behavioral therapy and Energy conservation management' & 'Effectiveness of Energy Conservation Management (ECM) treatment for reducing fatigue in Multiple Sclerosis (MS); a systematic review (and meta-analysis)' & 'Resultaten van de TREFAMS-ACE studie: De effecten van energie management op vermoeidheid, participatie en activiteit in MS patiënten', all at Research meeting, dept. Rehabilitation Medicine Erasmus MC Rotterdam	2011, 2012 & 2015	1 ECTS
-	'TREatment of disabling FAtigue in Multiple Sclerosis', MSMS 2012, Ede	2012	1 ECTS
-	'TREFAMS-ACE: TREatment of disabling FAtigue in MS: Aerobic training, Cognitive behavioral therapy and Energy conservation management', Rehabilitation Center Leijpark, Tilburg	2014	1 ECTS
-	'Physical behaviour in MS'(oral) & 'Physical behaviour of ambulatory fatigued MS patients'(poster), 19th RIMS congress, Brighton (UK) Best Oral Presentations (2nd place) awarded at RIMS 2014 Brighton UK	2014	1 ECTS
-	'Mini-symposium Treating Fatigue in Multiple Sclerosis: 'Physical behaviour and its association to MS-related fatigue', DCRM 2014, Rotterdam	2014	1 ECTS
-	Workshop 'Behandeling bij vermoeidheid: energiemanagement': 'Ergotherapeutische energiemanagement interventies en de effecten op vermoeidheid', MSMS 2014, Ede	2014	1 ECTS
-	'MS en vermoeidheid: Energiemanagement: Resultaten van een systematisch review, behandelprogramma Trefams-E en de resultaten van een RCT', Scholingsdag MS voor ergotherapeuten, Arnhem	2016	1 ECTS
-	'Treating fatigue in Multiple Sclerosis: Energy Conservation Management (ECM)', TREFAMS-ACE group at VUmc, Amsterdam	2016	1 ECTS
-	'Treating fatigue in Multiple Sclerosis – Energy Management', Wetenschapcafe Tilburg at RC Leijpark.	2016	1 ECTS

-	'Resultaten van de TREFAMS-ACE studie: De effecten van energie management op vermoeidheid & participatie in vermoeide MS patiënten', TREFAMS-ACE resultaten patiëntendag, Amsterdam	2016	1 ECTS
-	'Mini-symposium Treating Fatigue in MS: what's the evidence?: Managing of energy or something else? Effectiveness of Energy Conservation Management on fatigue and participation in Multiple Sclerosis: Results of a RCT', DCRM 2016, Maastricht	2016	1 ECTS

Poster presentations

-	'Treating Fatigue in Multiple Sclerosis: Aerobic Training, Cognitive Behavioural Therapy, Energy Conservation Management. The TREFAMS-ACE study design' together with PhD-researchers TREFAMS, MS-Onderzoeksdagen in Oegstgeest, Stichting MS Research	2011	1 ECTS
-	'Effectiveness of Energy-Conservation Management treatment in reducing fatigue in Multiple Sclerosis: a systematic review and meta-analysis', MS research days, Doorwerth	2012	1 ECTS
-	'Physical behavior is associated with physical fatigue in persons with multiple sclerosis related fatigue' & 'Effectiveness of Energy Conservation Management on fatigue and participation in multiple sclerosis: a Randomized Clinical Trial', ECTRIMS Londen (UK)	2016	10 hours

(Inter)national conferences

-	2e Jaarcongres DSNR 'vermoeidheid in de neurorevalidatie', Utrecht	2012	1 ECTS
-	Multidisciplinair MS (MSMS) symposium, Ede	2012	1 ETCS
-	MS Goes Live Rotterdam informatiestand voor Trefams	2013	1 ECTS
-	Multidisciplinair MS (MSMS) symposium, Ede	2013	1 ECTS
-	Ergotherapie & Zelfmanagement congres, Nijmegen	2014	1 ECTS
-	RIMS 2014 - Rehabilitation in MS: Linking science to clinical practice, Brighton (UK).	2014	1 ECTS
-	Dutch Congress of Rehabilitation Medicine (DCRM) 2014, Rotterdam	2014	1 ECTS
-	MSMS symposium, Ede	2014	1 ECTS
-	Scholingsdag MS voor ergotherapeuten, Arnhem	2015	1 ECTS
-	Dutch Congress of Rehabilitation Medicine (DCRM) 2016, Maastricht	2016	1 ECTS

Other		
- Research meetings dept. Rehabilitation Medicine Erasmus MC. Rotterdam	2010-2015	5 ECTS
- Research report committee 2010, 2011, 2012	2011-2014	16 hours
- Reanimatie cursus	2011, 2012	4 hours

2. Teaching

	Year	Workload
Lecturing		
- Training IECM MS Occupational therapists Erasmus MC Rotterdam & RC Leijpark Tilburg	2011,2012	8 hours
- Training MSvp treatment in Utrecht, and Rotterdam	2011,2012	6 hours
Supervising practicals and excursions, Tutoring		
- Supervising literature review medical students	2011	6 hours
- Tutoraat Geneeskunde	2012,2013	1.5 ECTS
- Supervising 'Keuzeonderzoek Geneeskunde' of medical student	2013	1 ECTS