Treatment of Fatigue in Multiple Sclerosis: Aerobic Training, Cognitive Behavioural Therapy, Energy Conservation Management

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To determine whether rehabilitation treatment strategies effectively reduce fatigue and improve participation in MS patients with fatigue, and how they exert their effects.Research questionsQ1) Does AT result in reduced fatigue and improved...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39391

Source
ToetsingOnline

Brief title
TREFAMS-ACE

Condition

- Other condition
- Demyelinating disorders

Synonym
fatigue, multiple sclerosis

Health condition

20 gezonde proefpersonen tbv extra onderzoek beweegedrag

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMw;programma Revalidatie-Onderzoek II (Fonds NutsOhra)

Intervention

Keyword: Fatigue, Multiple Sclerosis, Randomized Clinical Trials, Rehabilitation Medicine

Outcome measures

Primary outcome

Fatigue: Checklist Individual Strength (CIS) subscale fatigue

Participation: Impact on Participation and Autonomy (IPA)

Disease Activity: Number of exacerbations < 1 yr

Secondary outcome

Secundary outcome parameters:

QoL: Medical Outcome study Short Form 36 (SF36)

Rehabilitation Activities Profile (RAP)

Fatigue Severity Scale (FSS)

Patient-related variables:

Socio-demographic (age, gender, ethnicity, living arrangement, employment, SES,

etc)

Diagnosis MS

Severity of MS: Expanded Disability Status Scale

Severity of fatigue: Checklist Individual Strength (CIS) subscale fatigue

Comorbidities: Cumulative Illness Rating Scale (CIRS)

Diagnosis of treatable causes fatigue

Fatigue Medication < 3 months

Other determinants:

Aerobic capacity: VO2max/peak; Ventilatory Threshold

Daytime Sleepiness: Epworth Sleepiness Scale

Depresssion: CES-D

Activity pattern: Activity Monitor en PASIPD

Coping: Coping Inventory for Stressful Situations (CISS-21)

Cognitions: Fear of disease progression, Illness Cognitions Questionnaire

General Self Efficacy Scale

Efficiency of Energy Management: Energy Conservation Strategies Survey

Perceived Social Support: Social Support List, discrepancy

Social Interactions: Social Support List, interactions

Blood samples

HPA axis parameters

Pro-inflammatory cytokines

Anti-inflammatory cytokines

Process-related variables

Therapy adherence: Attended therapy sessions

Therapy adherence: Completed home assignments/logbook

Co-interventions

Success of blinding the observers

RCT-specific

1. Aerobic Training (n=90)

Physical Work Capacity Test PWC170 (Predicted VO2max at HR 170 bpm) (PWC-170)

Training Intensity: Borg Scale

2. Cognitive Behavioral Therapy (n=90)

Impact of Event Scale

Pictorial Representation of Self and Illness Measure (PRISM)

Fatigue Catastrophizing Scale

SF36 pain subscale

Pain Catastrophizing Scale

SIP subscales sleep and rest, social interactions

Psychological Distress: Symptom Check List 90 (SCL90)

Study description

Background summary

In early multiple sclerosis (MS) fatigue seriously affects social participation. Aerobic Training (AT), the use of Energy Conservation Management (ECM), and Cognitive Behavioural Therapy (CBT) may positively influence fatigue, but evidence is not conclusive. A comprehensive pathophysiological mechanism explaining fatigue is lacking.

Study objective

To determine whether rehabilitation treatment strategies effectively reduce fatigue and improve participation in MS patients with fatigue, and how they exert their effects.

Research questions
Q1) Does AT result in reduced fatigue and improved participation?
Q2) Does ECM result in reduced fatigue and improved participation?
Q3) Does CBT improve participation and reduce fatigue?
Q4) Which treatment strategy most effectively improves participation?
Q5) Is a reduction in fatigue accompanied by a normalisation in Hypothalamus-Pituitary-Adrenal (HPA) axis function, a reduction in pro-inflammatory serum cytokines or an increase in anti-inflammatory serum cytokines?

Study design

270 ambulatory MS patients suffering from fatigue will be recruited for three Randomized Clinical Trials (RCT). Each treatment protocol will consist of 12 individual therapist-supervised sessions and home assignments during 4 months. The control treatment consists of written patient information that is discussed in three 45 minute sessions with an MS nurse. All RCTs use the same design, with an intervention and a control group, and use the same outcome measures. Measurements will take place at -1 week, baseline, 8 and 16 weeks, and 6 and 12 months. The primary outcome measures are fatigue (Fatigue subscale of the Checklist Individual Strength) and participation (Impact on Participation and Autonomy Questionnaire). The variables age, gender, ethnicity, cytokines in serum, activation of the HPA-axis, aerobic capacity, Ventilatory Threshold, vitality, daytime sleepiness, coping, self-efficacy, illness cognitions, efficiency of energy management, and comorbidity will be used to study the working mechanisms of the interventions. In order to assure a good data-quality, a web-based, centrally
managed database will be used. For each RCT the primary analysis will be based on an intention to treat protocol using longitudinal data-analysis techniques, including Generalized Estimating Equations and Hierarchical Linear Models, that will be constructed to detect differences between within-group changes, and that are corrected for number of exacerbations and ethnicity. Mediation analyses will be used to examine the working mechanisms, namely changes in HPA-axis functioning and changes in proand anti-inflammatory cytokine levels, of the interventions.

Intervention

1) Aerobic Training consists of 12 individual therapist-supervised 45-minute physical exercise sessions with an intensity of at least 60%VO2max in a period of 4 months;[10] in the first 8 weeks one therapist-supervised session will be given per week, in the subsequent 8 weeks one therapist-supervised session will

be given every other week. The sessions include a warming-up and cooling down. In addition, patients will perform 2 aerobic training sessions per week at home of the same duration and at the same intensity as measured by heart rate.[10] The available treatment protocol has been adapted for this study.

2) Individualized Cognitive Behavioural Therapy (CBT). CBT will focus on the fatigue maintaining behaviour and cognitions of the patient, which are based on existing literature and experience in clinical practice. They may involve insufficient coping with the disease, fear of disease progression, dysfunctional illness cognitions, dysregulation of sleep, dysregulation of activity, and low social support and negative social interactions. Because of the existence of differences between individuals, therapy will be adapted to each individual. The general aim
of the CBT is to improve daily functioning and to lessen the fatigue by changing fatigue maintaining cognitions and behavior within the limits of the disease (MS). We hypothesize that the changedcognitions and changed behaviour reduce the amount of perceived environmental stressors. This may lead to less stress and may thus lead to normalization of HPA axis functioning, a reduction of pro-inflammatory cytokines or an increase in anti-inflammatory cytokines, which may lead to reduced central fatigue. CBT consists of 12 individual therapist-supervised 45-minute therapy sessions in a period of 4 months, and an individualized schedule to gradually expand participation. The time interval between therapy session will be gradually increased as therapy progresses.

3) The use of Energy Conservation Management (ECM). We hypothesize that ergonomic advice and coaching towards more efficient use of available energy leads to a reduction in environmental stressors. This reduction may lead to less stress and may thus lead to normalization of HPA-axis functioning, a reduction of pro-inflammatory cytokines or an increase in anti-inflammatory cytokines, which may lead to reduced central fatigue. A reduction in central fatigue is expected to improve participation. Individualized ECM consists of 12 individual therapist-supervised 45-minute sessions, in which energy-management and ergonomic advices are given, in a period of 4 months; in the first 8 weeks one therapist-supervised session will be given per week, in the subsequent 8 weeks one therapist-supervised session will be given every other week. In addition, individualized home-assignments are given. The treatment protocol that has been described by Mathiowetz et
al. has been adapted for this study.

4) Control treatment
The control treatment for each RCT consists of currently available standardized written patient information and will be provided in a standardized manner by an MS nurse. Patients receive this information package personally in the first week. In week 6 and 12, 45-minute appointments with the MS nurse will be scheduled in order to ask questions about the information package. This control treatment covers two important aspects that we want to control for: 1) good information about MS related fatigue, and 2) attention of a professional who

has experience in MS in order to reassure the patient that his concerns or questions will be taken seriously. The nurses will receive instructions on how to provide the information without additional therapeutic interventions or specific personal advises.

Study burden and risks

Participants in the intervention groups receive 12 treatments over a period of 16 weeks. Participants in the control group receive usual care and information about MS-related fatigue by an MS nurse (one or more contacts). It also gives each participant five times to test untill one year after the start of the study (randomization). These measurements take approximately 2 hours each time. Questionnaires can be completed by the participants at home. This will cost an estimated five times for 1 hour. Risks are assessed as low.

Each participant is individually supervised by an experienced therapist or psychologist. Nevertheless, there may be adverse effects.For each intervention group these adverse effects may be duifferent. 1) aerobic training: warm-up and cool down to prevent the participant from sudden excessive physical exercise, muscle soreness or injuries. 2) cognitive behavioral therapy: possible confrontational 3) energy management: possible confrontational 4) usual care: no risks expected.
Cardio-respiratory exercise testing: Risks as described by cycling test (ergometry): muscle pain, shortness of breath, faint or shaky feeling after exercise;
Questionnaires: possibly confrontational.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Diagnosis of MS according to the criteria of McDonald
- an Expanded Disability Status Scale score of 6 or lower, i.e. able to walk without walking aid,
- suffering from fatigue, defined as a score higher than 35 on the subscale fatigue of the Checklist Individual Strength (CIS)
- In the last three months prior to inclusion the patients should not have used Amantadine, Modafinil, Ritalin or Pemoline for their fatigue.
- Age between 18-70 years

Exclusion criteria

Treatable causes of fatigue. other than central MS-related fatigue

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-10-2011
Enrollment:	290
Type:	Actual

Ethics review

Approved WMO Date:	05-04-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL33451.029.10