Which exercise or behavioural fatigue interventions are effective for people with multiple sclerosis (MS)? A systematic review with detailed intervention breakdown and meta-analysis

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Citation
Rona Moss-Morris, Tom Mercer, Claire White, Sarah Thomas, Marietta Van de Linden, Anthony Harrison, Reza Safari, Sam Norton. Which exercise or behavioural fatigue interventions are effective for people with multiple sclerosis (MS)? A systematic review with detailed intervention breakdown and meta-analysis. PROSPERO 2016:CRD42016033763 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42016033763

Review question(s)
The overall aim of this review is to provide guidance as to which of the existing exercise and behavioural interventions appear most promising for the treatment of MS fatigue. The specific objectives are to:

(1) Provide a narrative synthesis of all the interventions including a breakdown of the key contextual and treatment components of each of the interventions, the acceptability of the interventions (uptake and adherence), and the study quality (risk of bias) alongside the standardized intervention effect sizes.

(2) Conduct meta-analyses of effect sizes across interventions with similar key intervention components.

(3) Compare the overall effect sizes of the exercise and behavior interventions followed by subgroup analysis within each of these groups (e.g. behavioral interventions: energy conservation, CBT, combined; exercise interventions: aerobic endurance, strength, balance and combined).

(4) Conduct exploratory moderator and sensitivity analyses to explore how treatment effects vary according to whether interventions were guided by theory or not, different levels of health care professional contact (e.g. email support, telephone, face-to-face), types of MS, comparators used, and study quality.

Searches
The following data sources will be searched:

Cumulative Index to Nursing and Allied Health Literature (CINAHL),
Excerpta Medica DataBase (EMBASE),
PsycINFO,
MEDLINE,
Allied and Complementary Medicine Database (AMED),
Latin-American and Caribbean Centre on Health Sciences Information (LiLACS),
Physiotherapy Evidence Database (PeDRo),
SPORTDiscus,
Web of Science, and
The Cochrane Central Register of Controlled Trials (CENTRAL).

Reference lists and citations of included studies and previous MS fatigue reviews.

Trial registers: Cochrane Library, WHO ICTRP, NIHR, ClinicalTrials.gov, Controlled-trials, Dissertation Abstracts International World Cat, Greylit.org, and Open Grey.

In addition, there will be contact with experts in the field.

There will be no language restrictions or date restrictions imposed.

Additional information about the search strategy can be found in the attached PDF document.

**Types of study to be included**

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) of any behavioural and/or exercise intervention for multiple sclerosis (MS) including parallel group, crossover and cluster trials. A study will be labelled CCT where the allocation mechanism is not truly random (i.e. quasi-randomisation) or is unclear in the manuscript.

**Condition or domain being studied**

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) (Kingwell et al., 2013). Fatigue affects around 90% of people with MS (pwMS), with over two-thirds reporting it is their most troubling symptom (Giovannoni, 2006).


**Participants/ population**

Adults (aged 18 and over) with a confirmed diagnosis of multiple sclerosis (McDonald 2001; Polman 2005; Polman, 2011) including all disease subgroups (relapsing remitting, secondary progressive and primary progressive multiple sclerosis). Studies which include people with MS together with people with other medical conditions will be included if data for the MS group are reported separately. Where data for participants with MS are not reported but studies contain a heterogeneous sample with at least 50% of participants with MS we will contact the authors to try to obtain the results for the MS subgroup.

**Intervention(s), exposure(s)**

The intervention should be clearly defined as a behavioural or exercise fatigue intervention. For the purposes of this review a behavioural intervention is one that aims to result in behavioural, lifestyle, or attitudinal changes and may include changes in physical activity. Behavioural interventions are broad ranging, typically incorporating self-management aspects and may include energy conservation, relaxation, mindfulness training, CBT, educational strategies, and multimodal approaches. An exercise intervention is one that primarily aims to increase lifestyle physical activity or introduce structured exercise but may also include components of behavioural interventions. Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure and includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities (WHO, http://www.who.int/topics/physical_activity/en/). Exercise is defined as a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of one or more components of physical fitness is the objective (WHO, http://www.who.int/mediacentre/factsheets/fs385/en/). Exercise interventions are also varied and include structured exercise (such as aerobic, strength and conditioning training), balance interventions, active gaming interventions (such as Xbox Kinect, Nintendo Wii), mind-body (such as yoga, Tai Chi/Qi Gong), dance, water-based (such as aquatic exercise), other lifestyle physical activity, combinations of exercise as well as components of behavioural interventions.

**Comparator(s)/ control**
The comparator could include no intervention, usual care, standard medical care, placebo treatment or another active intervention.

**Context**

Included interventions may vary in duration and take place in the hospital, in the community, at home or some combination and could be self-directed or supervised or a combination. Interventions may be delivered face-to-face, or via the internet, SMART device, tele- or video-conference, in groups or one-to-one or in some combination. Interventions will be excluded if they do not clearly define the intervention as a fatigue intervention and/or do not measure fatigue severity and/or impact of fatigue as an outcome. Pharmacological and dietary studies will be excluded except where diet is included as part of a broader behavioural approach.

**Outcome(s)**

**Primary outcomes**

Fatigue severity and/or impact of fatigue measured using a validated uni- or multidimensional self-report fatigue scale (such as the Fatigue Severity Scale (Krupp et al., 1989), the Modified Fatigue Impact Scale (PVA, 1998), The Chalder Fatigue Scale (Chalder et al., 1993), the Neurological Fatigue Index (Mills et al., 2010), The PROMIS short form (Cook et al., 2012), the Checklist Individual Strength (Vercoulen et al., 1996), visual or numerical rating scales or an appropriate validated subscale of broader instruments (such as the Vitality subscale of the SF36 (Ware and Sherbourne, 1992)).

Fatigue severity and/or impact of fatigue at post-intervention. Post-intervention is defined as within two months following the stated duration of the intervention.

**Secondary outcomes**

Self-reported fatigue severity and/or impact of fatigue (as measured above) at follow-up. In addition, any broadly relevant physical or cognitive/mental fatigability measures will be extracted. Fatigability has been defined as “the magnitude or rate of change in a performance criterion relative to a reference value or given time of task performance or measure of mechanical output” (Kluger, Krupp, & Enoka, 2013, p.411). Measures of performance fatigue may be defined as decrements in performance in voluntary activation, strength, power and endurance during sustained tasks. The cognitive domain of fatigability has been measured as “declines in either reaction time of accuracy over time on continuous performance tasks, or a probe task given before and immediately after a fatiguing cognitive task” (Kluger, Krupp, & Enoka, 2013, p.414).


Fatigue severity and/or impact of fatigue measured at 3-6 and >6 months follow-up. Cognitive or physical fatigability measured at post-treatment, 3-6 and >6 months follow-up.

**Data extraction, (selection and coding)**

All titles and abstracts will be reviewed by two independent reviewers. The full paper review will be conducted by two independent reviewers. Coding and data extraction will be performed by two independent reviewers using a data extraction tool developed a priori based on the Cochrane Handbook recommendations. The additional data extraction for the process analysis based on the TIDieR Guidance (Hoffmann et al 2014) will be single-extracted. All discrepancies will be discussed between the two reviewers and the team will be consulted if a consensus cannot be met.

Data to be extracted will include: Study ID, date, country and clinical setting, study design, rationale of study, eligibility criteria, participant characteristics (e.g. age, gender, years since diagnosis, type of MS, degree of disability), flowchart of participants through all stages of study, description of intervention, basic intervention costs if available, description of comparison group(s) Comparability of baseline characteristics between treatment and control arms (number enrolled in trial and each group, presence of sample size calculation, numbers included at each follow-up and reasons for drop and withdrawal, attempts at masking, description of randomisation, allocation concealment and description of follow-up). Outcome measures, timing of outcome administration/measurement, whether intention-to-treat (ITT) analysis was undertaken, secondary outcomes included such as quality of life and mood and whether positive effects were reported for the secondary outcomes, for nominal outcomes (denominator and numerator in each
category for each group), for interval and ordinal data (N, mean, SD for each group) or (N, median, IQR or range) as appropriate.

The intervention component analysis will be based in part on TIDieR Guidance (Hoffmann et al., 2014). This will include:

1. Brief name and description of intervention.

2. Why? Describing any rationale, theory [model of MS fatigue] or goal of the elements essential to the MS intervention.

3. What? Materials: Describing any physical or standardised informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. If materials are available, provide information on where the materials can be accessed, such as website for participants, author’s website, online appendix).

4. What? Procedures: Describing each of the component procedures, activities, and/or processes used in the intervention, including any enabling or support activities. This includes categorising the type of intervention, and listing the intervention components or treatment processes.

5. Who provided? For each category of intervention provider (such as psychologist, nursing assistant), describing their qualification/expertise, background, and any specific training given.

6. How? Describing the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.

7. Where? Describing the type(s) of location(s) where the intervention occurred (e.g. hospital, community, home-based setting), including any necessary infrastructure or relevant features.

8. When and how much? Describing the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose. In addition, describing how much homework or between sessions activity has been prescribed, relative to in-session activity completed with the health care professional or researcher.

9. Tailoring: If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.

10. Modifications: If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).

11. How well? Planned: If therapist fidelity/adherence was assessed, describing how and by whom, and if any strategies were used to maintain or improve fidelity, describe them. Actual: If therapist fidelity/adherence was assessed, describing the extent to which the intervention was delivered as planned.

12. How well? Participant Adherence: If participant adherence was assessed, describing how and by whom, and if any strategies were used to maintain or improve participant adherence.


Risk of bias (quality) assessment
Risk of bias (ROB) will be assessed by two independent reviewers according to the Cochrane Handbook for Systematic Reviews of Risk of Bias tool (Higgins 2011), including: random sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other potential sources of bias.

Strategy for data synthesis

Planned quantitative analyses. Where data are available from more than one study of a particular intervention we will pool results from these in a meta-analysis for each outcome with comparisons between relevant intervention and comparator groups for behavioural, exercise and combined interventions to determine overall effect using a random effects estimate. The decision to pool data will be based on the detailed intervention component analysis. Where insufficient data are available or where clinical and methodological heterogeneity means that it is not possible to pool results in meta-analysis we will present individual study estimates of effect and conduct a narrative synthesis (Popay et al., 2006). Measures of treatment effect. Where studies use the same type of intervention, comparator and type of outcome, we will pool the results using random effects meta-analysis with mean differences or standardised mean differences for continuous measures or risk ratios for dichotomous outcomes. Where there are multiple intervention groups within a trial, we will combine all relevant data from multiple intervention or multiple control groups into a single intervention or control group to avoid multiple counting of participant data. In studies where the effects of clustering have not been taken into account, and where inter cluster correlation (ICC) coefficients have been reported, we will adjust the standard deviations for the design effect to avoid unit of analysis errors. In the case of crossover trials we will assess the risk of bias associated with the suitability of the design and the potential for a carryover effect following behavioural or exercise interventions. Where bias is judged to be minimal analysis of data will be conducted using a paired analysis (Elbourne, 2002) where possible or where this information is not available, only data up to the point of first crossover will be used for analysis. Heterogeneity will be classified using the thresholds given in the Cochrane handbook http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm. Analyses will examine sources of heterogeneity. We will conduct sensitivity analyses based on study quality. We will use stratified meta-analyses to explore heterogeneity in effect estimates according to: study quality; study populations; the logistics of intervention provision; and intervention content. We will also assess evidence of publication bias.

Analysis of subgroups or subsets

The main analysis will be based on total effect for all the behavioural studies and one for the exercise studies, and planned sub-group analyses based on grouping sub-types within these categories (e.g. Energy conservation, CBT, combined; aerobic endurance, resistance, balance, flexibility and combination) with any type of comparator group (i.e. active or inactive controls). Exploratory moderator and sensitivity analyses will include health care professional contact (HCP) compared to no or limited HCP contact (e.g. session dosage), type of MS (relapsing- remitting versus more progressive forms of MS), studies comparing interventions to active placebo comparators and treatment as usual (e.g. exercise vs no-exercise control), and low or high study quality based on the RoB assessment, non randomised trials and randomised trials.

Dissemination plans

The findings will be initially presented to the MS Society UK Clinical Trial Network (CTN) Fatigue working group (which includes service users) for feedback. This will be followed by a stakeholder event. The purpose of the event is to present the findings from the review to people with MS (pwMS), health care providers including neurologists, MS specialist nurses, occupational therapists, physiotherapists, psychologists and if possible commissioners. Finally, a condensed version of the final report will be submitted for publication in a peer-reviewed scientific journal. The data will also be presented at relevant conferences.

Contact details for further information

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Anticipated or actual start date
01 December 2015

Anticipated completion date
01 October 2016

Funding sources/sponsors
Multiple Sclerosis Society UK (Award Reference: 26).

Conflicts of interest
Two members of the review team, Professor Rona Moss-Morris and Dr Sarah Thomas have published randomised controlled trials of behavioural interventions for fatigue in multiple sclerosis which meet the inclusion criteria of the current review. Preliminary searches, formal screening of search results against eligibility criteria, data extraction, risk of bias assessment and data analysis will be conducted independently of these individuals.

Language
English

Country
England, Northern Ireland, Scotland, Wales

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Exercise; Exercise Therapy; Fatigue; Humans; Multiple Sclerosis; Physical Therapy Modalities; Treatment Outcome
**Stage of review**
Ongoing

**Date of registration in PROSPERO**
16 May 2016

**Date of publication of this revision**
06 June 2016

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