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Efficacy of targeted versus non-targeted exercise and behavioural interventions on fatigue in multiple sclerosis: systematic review and meta-analysis

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Citation

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Review question(s)

The specific objectives are to:

(1) Provide a narrative synthesis of all the interventions, including a summary of the nature of the intervention using the Template for intervention Description and Replication (TiDieR), and assessment of study quality (risk of bias), alongside the standardised intervention effect sizes. As a detailed synthesis already includes studies evaluating interventions specifically targeting MS fatigue (ref: CRD42016033763), the narrative synthesis will focus on studies evaluating interventions that (a) do not specifically target fatigue, or (b) measured fatigue as a secondary outcome.

(2) Conduct (pair-wise) meta-analyses to pool effect sizes across intervention types (exercise, behavioural, mixed) and estimate statistical heterogeneity.

(3) Directly compare specific types of targeted versus non-targeted exercise, behavioural and combined interventions on fatigue in multiple sclerosis, using network meta-analyses.

(4) Conduct exploratory moderator and sensitivity analyses to explore how treatment effects vary according to health care professional (HCP) contact, type of MS, and study quality (i.e. risk of bias).

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 as their most troubling symptom (Giovannoni, 2006). Kingwell, E., J. J. Marriott, et al. (2013). "Incidence and prevalence of multiple sclerosis in Europe: a systematic review." BMC Neurology 13(1): 128.

Giovannoni, G. (2006). "Multiple sclerosis related fatigue." Journal of Neurology, Neurosurgery & Psychiatry 77(1): 2-3.

Participants/ population

Adults (aged 18 and over) with a confirmed diagnosis of multiple sclerosis (McDonald 2001; Polman 2005;Polman, 2011) and all disease subgroups (relapsing remitting, secondary progressive and primary progressive multiple sclerosis). Studies that include people with MS together with people with other medical conditions will be included if data 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)

For the narrative synthesis, study interventions must be defined as any behavioural or exercise intervention that does not specifically target fatigue, but rather aims to improve other primary outcomes, such as mood, fitness, strength, walking ability, quality of life etc., and examines fatigue severity/impact as a secondary outcome. Studies specifically targeting fatigue from the previous review (Ref. CRD42016033763) will also be included alongside these studies in the multiple treatment meta-analysis. 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 CBT for depression, relaxation, mindfulness training, 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. For the multiple treatment meta-analysis treatment effects of intervention subtypes will be estimated using treatment as usual as the reference comparator.

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 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

The primary outcome of this review will be fatigue severity and/or impact of fatigue measured using a validated uni- or multi-dimensional 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, I992).

Fatigue severity and/or impact of fatigue at the first post-intervention assessment point, including post-intervention

means and pre-post change scores between groups.

Secondary outcomes

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). In addition, self-reported fatigue severity and/or impact of fatigue (as measured above) at follow-up. Kluger, B. M., L. B. Krupp, et al. (2013). "Fatigue and fatigability in neurologic illnesses proposal for a unified taxonomy." Neurology 80(4): 409-416.

Cognitive or physical fatigability measured at post-treatment. Fatigue severity and/or impact of fatigue measured at 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. All discrepancies related to eligibility will be discussed between the two reviewers and other team members will be consulted if a consensus cannot be reached.

To ensure accuracy of data extraction across reviewers, an initial random sample of 20% of studies will be extracted by four independent reviewers using a data extraction tool developed a priori based on the Cochrane Handbook recommendations and a truncated version of the TIDieR Guidance (Hoffmann et al 2014).

As part of this process, inter-rater agreement for risk of bias (RoB) (see section 27) will be checked using Cohen's kappa coefficient statistic (Cohen, 1960). Specifically, a first round of 10% of double-extracted RoB information will be checked for consistency. This will be followed by training to resolve any discrepancies and then a second round of double extraction of the same studies. A third round of double extraction will be conducted on the next 10% of studies. If there is 'good' consistency across the second and third rounds (i.e. 20%) (Altman, 1991), all remaining studies will be single-extracted, with meta-analytic data cross-checked by another reviewer.

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) and, if appropriate, description of the duration, frequency, how delivered, who delivered, format of delivery, training of person delivering, whether adapted for MS, and whether concomitant interventions were given: 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 dropout 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. Intervention descriptions will be based on relevant elements within TIDieR Guidance (Hoffmann et al., 2014). Altman DG (1991) Practical statistics for medical research. London: Chapman and Hall. Cohen, Jacob (1960). A coefficient of agreement for nominal scales. Educational and Psychological Measurement. 20 (1): 37–46. Hoffmann, T. C. and M. F. Walker (2015). "TIDieR-ing up' the reporting of interventions in stroke research: the importance of knowing what is in the 'black box." International Journal of Stroke 10(5): 657-658.

Risk of bias (quality) assessment

RoB assessment will be conducted 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. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The Cochrane Collaboration's tool for assessing

risk of bias in randomised trials. BMJ. 2011, 343: d5928-10.1136/bmj.d5928.

Strategy for data synthesis

Planned quantitative analyses. Where data are available from more than one study of a particular intervention type we will pool treatment effects estimates. Specifically, in three pair-wise random effects meta-analyses separately for behavioural, exercise and combined interventions respectively, versus any comparator, to determine overall effects. The decision to pool data will be based on the number of studies and the detailed intervention descriptions indicating sufficient methodological homogeneity within intervention types. 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).

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 intra 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. Elbourne, D. R., Altman, D. G., Higgins, J. P., Curtin, F., Worthington, H. V., & Vail, A. (2002). Meta-analyses involving cross-over trials: methodological issues. International journal of epidemiology, 31(1), 140-149. Popay, J., H. Roberts, et al. (2006). Guidance on the conduct of narrative synthesis in systematic reviews a product from the ESRC methods programme version 1. ESRC methods programme [Online] Available Updated 2006

Analysis of subgroups or subsets

The main analysis will be based on three pairwise meta-analyses of the total treatment effect for all the behavioural, exercise, and mixed studies. Planned sub-group analyses based on grouping sub-types within these main types (e.g. Mindfulness, CBT for depression, combined; aerobic endurance, resistance, balance, flexibility and combination) with any type of comparator group (i.e. active or inactive controls). Due to known methodological heterogeneity in control comparators from a previous review of fatigue targeted interventions, a multiple treatment meta-analysis will estimate the treatment effect of intervention subtypes against a common comparator (treatment as usual) incorporating both non-targeted and targeted fatigue interventions. This analysis will incorporate data from targeted fatigue interventions extracted in a separate review (CRD42016033763). The method for computing the pooled treatment effect estimates will use a multivariate meta-analysis framework implemented in Stata using maximum likelihood methods. Variables potentially explaining between-study heterogeneity will be included as covariates (e.g. MS type, risk of bias, publication year, targeted vs non-targeted). In addition to pooled treatment effects, the estimates from the multivariate meta-analysis will be used to estimate the rank ordering treatment subtypes by efficacy using estimates of their ranking probabilities (i.e. surface under the cumulative ranking curve SUCRA). Consistency in the direct and indirect effects will be considered and the models results presented only where this is there is no indication of biased estimates.

Where possible 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.

Dissemination plans

The findings will initially be presented to the MS Society UK Clinical Trial Network (CTN) Fatigue working group (which includes service users). This will be followed by a stakeholder event. The purpose of this event is to present the findings from the review to people with MS (pwMS) and health care providers. 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.

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http://www.kcl.ac.uk/ioppn/depts/psychology/research/ResearchGroupings/healthpsych/index.aspx and
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01 December 2015

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01 October 2016

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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.

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English

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England, Northern Ireland, Scotland, Wales

Subject index terms status
Subject indexing assigned by CRD

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Behavior Therapy; Exercise; Fatigue; Humans; Multiple Sclerosis

Stage of review
Ongoing

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22 August 2016

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22 August 2016

Stage of review at time of this submission	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No