Treatment of fatigue in multiple sclerosis: a systematic review of the literature
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CRD summary
The review concluded there was limited evidence of the effectiveness of pharmacological or psychosocial/psychological approaches in the management of fatigue for people with Multiple Sclerosis. The authors’ cautious conclusion appeared reasonable, but it should be borne in mind that it was based on a number of small and quite variable poor-quality studies.

Authors' objectives
To evaluate pharmacological and psychosocial or psychological interventions for fatigue in multiple sclerosis (MS).

Searching
MEDLINE, LILACS, PsycINFO, Web of Knowledge, Cochrane Database of Systematic Reviews, DARE, Ingenta, Zetoc, ADOLEC, National Research Register, HMIC, NeLH and GALE databases were searched for studies in English in November 2006. Search terms were reported. Relevant reference lists were scanned for additional studies.

Study selection
Randomised controlled trials (RCTs), either parallel group or crossover trials, that evaluated treatment for fatigue in MS were eligible for inclusion. Both blinded and open label trials were eligible.

Interventions assessed in the included studies were amantadine, pemoline, Prokarin, Modafinil or aspirin (ASA) compared with placebo, interferon Beta-1B alone, pulsed electromagnetic therapy compared with placebo, yoga or aerobic exercise compared with waiting list control, cooling therapy compared with sham control, energy conservation or delayed intervention control, or energy conservation training. Outcomes were measured by a variety of published instruments (details reported in the review).

Two reviewers independently selected studies for inclusion. Disagreements were resolved through consensus.

Assessment of study quality
Validity was assessed using the following criteria: blinding; attrition rates; validated outcome measures; intention-to-treat analysis; power calculations or sample size estimations; interventions and assessments; screening of participants; length of assessment period; conclusions and recommendations. Studies were given a rating of low, low to moderate, moderate, moderate to high or high.

The authors did not state how many reviewers conducted the assessment.

Data extraction
The authors reported neither how data extraction was conducted nor how many reviewers performed the data extraction.

Methods of synthesis
Included studies were grouped into pharmacological or psychosocial/psychological categories and combined in a narrative synthesis.

Results of the review
Fifteen studies (n=1,182) were included in the review: eight randomised controlled trials (RCTs); four non-randomised controlled studies; and three single-group studies.

Two studies were rated as moderate to high quality, four studies as moderate to low quality, six studies as moderate quality and three studies were rated as low quality. Eight studies lacked an adequate control group, four studies reported
insufficiently precise measures of fatigue, four studies had short assessment periods or follow-up and four studies had small sample sizes.

**Pharmacological studies (10 studies):**

Results reported mixed evidence of effectiveness for pharmacological interventions for fatigue in participants with MS: three studies reported a significant decrease in fatigue for amantadine (p<0.01), pemoline (p=0.06) and 200mg per day doses of modafinil (p<0.01) and Prokarin (p value not reported) compared to placebo; three studies reported mixed effects for outcomes and three studies reported no statistically significant differences between groups. Five studies reported adverse events occurring during the study period (data reported in the review).

**Psychosocial/psychological studies (five studies):**

Five studies reported a significant decrease in fatigue for participants with MS who underwent either electromagnetic therapy, yoga, exercise, energy conservation courses or cooling therapy.

**Authors' conclusions**

There was limited evidence-based advice for people with MS to help management of fatigue using pharmacological or psychosocial approaches. More methodologically rigorous research was recommended.

**CRD commentary**

The review addressed a broad research question that encompassed a wide range of intervention types. Inclusion criteria were not clearly defined with respect to outcomes. Several relevant sources were searched, but there may have been potential language bias as included studies were restricted to those published in English. Methods were used to minimise reviewer errors and bias in the selection of studies, but it was unclear whether similar steps were taken in the assessment of validity and extraction of data. Validity was assessed using specified criteria and results of the assessment were reported. A narrative synthesis was appropriate due to differences between studies in terms of interventions, measurement of outcomes and study design. However, it appeared that the authors included observational studies, despite these being explicitly stated as part of their exclusion criteria. The authors appropriately discussed limitations of the evidence, including the bias of using waiting-list controls and crossover trials that may have introduced an artificial intervention effect. The authors’ cautious conclusion appeared reasonable, but it should be borne in mind that it was based on a number of small and quite variable poor-quality studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further robust research across the broad range of interventions represented in this review was needed to evaluate the effectiveness of pharmacological treatment and psychosocial/psychological therapies (particularly energy conservation) for fatigue in patients with MS.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.