Authors' objectives
To review evidence of the effects and overall effectiveness of promising interventions in the treatment of fatigue in multiple sclerosis (MS).

Searching

Study selection
Study designs of evaluations included in the review
Controlled trials with either a placebo or an alternative intervention were included in the review.

Specific interventions included in the review
Amantadine and pemoline.

Participants included in the review
Patients diagnosed with clinically definite multiple sclerosis (MS) without restriction by age, sex, or category of MS. Presence of fatigue at baseline was not a necessary criterion. Clinically definite MS was defined as: two attacks and clinical evidence of two lesions (or paraclinical evidence of the second).

Outcomes assessed in the review
Outcomes assessed were: patient-assessed fatigue, researcher-assessed fatigue, clinical significance of fatigue, patient preferences, and side effects. Other important outcomes (strength, biochemical test results, cognitive measures and psychological tests) were also recorded but not reported in the review.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors used the Jadad scale (see Other Publications of Related Interest no.1) to assess the quality of included studies. To further assess the crossover studies included in the review, the authors used four additional questions to capture predicted sources of bias: were systematic period effects or carryover discussed and/or identified; was there a washout period and what was its duration; were the number of people in sequences treatment then placebo (TP) or placebo then treatment (PT) clearly stated; and were people who did not complete any of the periods excluded from the analysis. Two authors independently performed the quality scoring. Differences were resolved with reference to the contact reviewer.

Data extraction
Two authors independently performed the data extraction using a series of proforma. The contact reviewer resolved any differences or general areas of difficulty.

Data were extracted for the categories of: study identification and year of publication, patient characteristics, study design, measure of quality of life, comparator population, EDSS scores, mean quality of life scores, and difference
Methods of synthesis
How were the studies combined?
The outcome of patient-preferred treatment in the amantadine studies was assessed by pooling relative risks (RRs), with 95% confidence intervals (CIs) using a fixed-effect model. The remaining outcomes were combined in a narrative synthesis.

How were differences between studies investigated?
Heterogeneity was assessed in the amantadine studies was assessed by pooling relative risks (RRs), with 95% confidence intervals (CIs) using a fixed-effect model.

Results of the review
Four studies were included for the review of amantadine (one parallel RCT and three crossover RCTs) with 236 participants. Two studies were included for the review of pemoline (one parallel RCT and one crossover RCT) with 126 participants.

In the review of amantadine all studies were open to bias. All studies showed a pattern in favour of amantadine compared with placebo, but there was considerable uncertainty about the validity and clinical significance of the findings. The pattern of benefit was considerably undermined when different assumptions were used in the sensitivity analysis. The effect on patient preference favoured amantadine using optimistic assumptions (RR 1.9, 95% CI: 1.4, 2.7) but favoured placebo using pessimistic, but realistic, assumptions (RR 0.80, 95% CI: 0.62, 1.01). The number of patients reporting side effects ranged from 20 to 60%, with no great difference between treatment and placebo.

In the review of pemoline, both studies were open to bias. There was no overall tendency in favour of pemoline over placebo and an excess of reports of adverse effects with pemoline.

Cost information
The drug costs of amantadine and pemoline are modest (£200 and £80 per annum). No economic evaluations were identified in the systematic review and available data were insufficient to allow modelling of cost-effectiveness in this review.

Authors' conclusions
The authors state that there is insufficient evidence to allow people with MS, clinicians or policy makers to make informed decisions on the appropriate use of the many treatments on offer. Only amantadine appears to have some proven ability to alleviate the fatigue in MS, though only a proportion of users will obtain benefit and then only some of these patients will benefit sufficiently to take the drug in the long term.

CRD commentary
This was a good review. The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be thorough. The authors also include searches for unpublished and grey literature. The quality of the included studies was formally assessed and discussed in the review. The authors have reported how the articles were selected, and who performed the selection, and the validity assessment and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined where possible in a statistical meta-analysis using a fixed-effect model and narratively otherwise. The authors did assess possible heterogeneity. The conclusions appear to follow from the results of the review.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.
Research: The authors state that the frequency, severity and impact of fatigue, the poverty of available research, and the absence of any ongoing research suggest that new research is an urgent priority. People with MS, clinicians and policy makers should work together to ensure that the evidence is collected as quickly as possible by encouraging involvement in rigorous research.

Research should not be restricted to the two drugs reviewed in depth in this report. All interventions identified in the scoping review should be considered, as should basic scientific research into the underlying mechanism of fatigue in MS.

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