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Rapid review

Treatments for fatigue in multiple sclerosis: a rapid and systematic review

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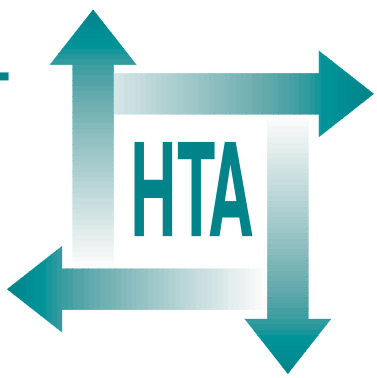
Health Technology Assessment
NHS R&D HTA Programme



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Treatments for fatigue in multiple sclerosis: a rapid and systematic review

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List of abbreviations and glossary

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

List of abbreviations

ARIF	Aggressive Research Intelligence Facility
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CCT	controlled clinical trial
CES–D	(a self-report depression scale)
d.f.	degrees of freedom
EDSS	Expanded Disability Status Scale
EMF	electromagnetic field
FAMS	Functional Assessment of Multiple Sclerosis*
FSQ	Functional Status Questionnaire*
FSS	Fatigue Severity Scale
GSS	General Social Survey*
ITT	intention to treat
MS	multiple sclerosis
MS-FS	Multiple Sclerosis-specific Fatigue Scale
N/A	not applicable*
NICE	National Institute for Clinical Excellence
NS	not significant*
PT	placebo/treatment
QoL	quality of life*
RCT	randomised controlled trial
RIV	Rand Index of Vitality*
RR	relative risk*
SBU	Swedish Council on Technology Assessment in Health Care
SD	standard deviation*
SE	standard error*
SF-36	Short Form Health Survey
TP	treatment/placebo
VAS	visual analogue scale

*Used only in tables

Glossary

Parallel RCT A type of study in which individuals are randomised into groups to receive different interventions or a placebo. Each individual receives only one type of intervention or the control. The effects in different groups are then compared.

Crossover RCT A type of study in which individuals receive two or more interventions or a placebo, one after the other. The order of treatments should be decided randomly. Each person receives all the interventions and the control. The effects on individuals when on the interventions are then compared with the effects in the same individual when on the control.

Period effect in a crossover RCT This refers to any systematic tendency for the effect of the intervention to vary according to whether it was received in the first period or the second period of the trial. Period effects can have several causes: individuals may improve or worsen during the study; extreme values tend to revert towards the mean; measures (particularly subjective ones) may vary systematically depending how often they are repeated; carryover effects may be present (see below).

Carryover effect in a crossover RCT This occurs when the effect of the intervention during the first period affects or interacts with the effect of the intervention during the second period. In other words, the effect of the intervention in the first period is sufficiently long-lived that it 'carries over' to the second period. This may affect either intervention or just one of them.

Meta-analysis A statistical procedure to generate a summary measure of the effect of an intervention, pooling the results from the included studies in a review.

Sensitivity analysis in a meta-analysis This involves testing whether the summary measure obtained is greatly altered if different assumptions are used when incorporating data about which there is uncertainty over their true value.

Executive summary

Background

Multiple sclerosis (MS) is an important problem both for people with the disease and for society. There is no cure, and alleviation of symptoms forms the cornerstone of care. Excessive fatigue that severely limits activity is experienced by at least two-thirds of the estimated 60,000 people with MS in the UK.

Objectives

- To identify current treatments for fatigue in MS and their evidence-base.
- To systematically review the evidence for those treatments that have been investigated in more than one rigorous study, in order to determine their effectiveness and cost-effectiveness.

Methods

The review was carried out in two stages: a formal scoping review (to assess the range of interventions used by people with MS), and a systematic review for treatments that had been identified as promising and that had been investigated in clinical trials (as identified in the scoping review). A systematic review of research on costs and cost-effectiveness of those interventions identified as promising was also performed.

Electronic databases, including MEDLINE and EMBASE, were searched for the period 1991–June 1999 (scoping review) and 1966–December 1999 (systematic review). Reference lists from publications were also searched, and experts were contacted for any additional information not already identified.

Results

Interventions identified for the treatment of fatigue in MS

- Behavioural advice. This is the main element of initial clinical management and no rigorous research of its effectiveness was identified.
- Drugs (amantadine, pemoline, potassium-channel blockers and antidepressants).
- Training, rehabilitation and devices (cooling vests and electromagnetic fields).
- Alternative therapies (bee venom, cannabis, acupuncture/acupressure and yoga).

Only two drugs, amantadine and pemoline, met the criteria for full systematic review.

Effectiveness of amantadine

One parallel and three crossover trials were found, involving a total of 236 people with MS. All studies were open to bias. All studies showed a pattern in favour of amantadine compared with placebo, but there is considerable uncertainty about the validity and clinical significance of this finding. This pattern of benefit was considerably undermined when different assumptions were used in the sensitivity analysis.

Effectiveness of pemoline

One parallel and one crossover trial were found involving a total of 126 people with MS. 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.

Health economic analysis

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

Conclusions

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.

Recommendations for research

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 required 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 (see above) should be considered, as should basic scientific research into the underlying mechanism of fatigue in MS.

Chapter 1

Aim and background

Aim of the review

The aim of the review was to assess the effectiveness and cost-effectiveness of the treatments for reducing fatigue in people with multiple sclerosis (MS).

Background

The treatment of MS has been recently identified by the National Institute for Clinical Excellence (NICE) as an important target for evaluation. There is no cure and any treatments currently available are directed towards slowing the progression of disease, reducing relapses or alleviating the wide spectrum of symptoms.

Recent attention has focused on new drugs for slowing disease progression and reducing relapses. However, it is clear that these are not panaceas, so the identification of effective drugs for the alleviation of the symptoms remains very important. One of the major symptoms experienced by the vast majority of people with MS is an overwhelming fatigue that interferes with all aspects of daily living.

This review is part of a series evaluating the effectiveness and cost-effectiveness of treatments for MS and focuses on the treatments that prevent or reduce the debilitating fatigue of MS.

Description of health problem

Pathogenesis, aetiology and natural history of MS

MS is a disease of the CNS that causes the destruction of the myelin sheath of nerve fibres.[1] Sclerotic plaques (scar-like lesions) with perivascular inflammation form in the de-myelinated parts of the nerve, blocking or distorting normal transmission of nerve impulses.[1,2] They may occur anywhere within the CNS and frequently in the periventricular areas of the cerebral hemispheres, the optic nerves, the brainstem, the cerebellum and the spinal cord.[2]

The aetiology of MS is not known,[1] but there are several theories including the possibility that MS is caused by a slow-acting virus, a delayed reaction to a common virus, or an autoimmune reaction.[1] There are no consistent observations of viral isolates in people with MS,[2] and the inflammation in the CNS supports the autoimmune theory,[2] where the body attacks its own myelin.

As a result of the large number of potential sites for sclerotic lesions to develop, there is wide variation in the symptoms and combinations of symptoms in different people.[1] Common early symptoms include weakness in limbs, incontinence, retrobulbar or optic neuritis (causing temporary or partial loss of vision), and bladder dysfunction.[1] Initial episodes are frequently not investigated due to their spontaneous remission.[1] Other symptoms include fatigue, spasticity, pain, tremor, vertigo, ataxia, alteration of sensations, depression and cognitive changes.[1] Following the initial symptoms, there may be a latent period of up to 10 years before further symptoms occur. As the disease progresses, periods of remission become shorter and exacerbations more disabling.[1]

Several surveys of the symptoms and their frequency have been carried out in people with MS. The 1997 MS Society Survey[3] in the UK of 233 people with MS showed that the three most common symptoms were fatigue, balance problems and muscle weakness (*Table 1*). Of these respondents, 65% rated fatigue, 50% rated bladder or bowel problems and 44% rated balance problems as one of the three worst symptoms.

TABLE 1 *Most common symptoms in people with MS. UK MS Society Survey 1997*[3]

Symptom	Respondents currently experiencing symptom
Fatigue	86%
Balance problems	73%
Muscle weakness	69%
Bladder or bowel problems	66%
Numbness/tingling	64%
Muscle stiffness	64%
Pain	54%
Muscle spasms	51%

MS is usually classified by its clinical course, though there is some variation in the classifications used.[1] Frequently, MS is divided into four categories.[2]

- **Benign** Mild intermittent relapses with nearly complete resolution (about 10–20% of people with MS)
- **Relapsing-remitting** Episodes of acute or subacute neurological dysfunction followed by periods of improvement and stabilisation; this is the most common form of the disease (30–40% of people with MS)
- **Primary progressive** Never has a relapsing-remitting course but begins with slow progression of signs and symptoms (10–20% of people with MS)
- **Secondary progressive** Begins with a relapsing-remitting course but the disease gradually worsens (20–30% of people with MS).

There is no explanation about what causes the cycles of relapses or remissions[1] or what determines the progression of the disease, though it may be due to initial re-myelination by local oligodendrocytes, a mechanism that eventually fails.[4]

Diagnosis of MS requires the occurrence of two attacks of neurological symptoms, each lasting a minimum of 24 hours and separated by at least a month.[5] Lesions in two distinct areas of the CNS (e.g. blurred vision and a numb limb) must be involved. People with MS can be classified as having clinically definite or clinically probable MS according to the number of attacks and number of lesions.[5]

- **Clinically definite** Two attacks and clinical evidence of two lesions (or paraclinical evidence of the second)
- **Clinically probable** Two attacks and either clinical or paraclinical evidence of one lesion; or one attack and clinical evidence of two lesions (or paraclinical evidence of the second).

These classifications can also be supported by laboratory evidence of immunoglobulin G in the cerebrospinal fluid or increased immunoglobulin G in the CNS relative to serum.

Magnetic resonance imaging is the most sensitive technique available to detect the brain lesions in MS,[1] but clinical and cerebro-spinal fluid data should be used to supplement the imaging to avoid misinterpretation. Diseases such as AIDS, Lyme disease and sarcoidosis of the CNS produce similar imaging patterns.[1]

Epidemiology of MS

The epidemiology of MS is not well known.

Prevalence in UK

The estimates for the prevalence of MS in England and Wales are between 89–108 cases per 100,000 (RG Richards & F Sampson, School of Health and Related Research: unpublished, draft report submitted to NICE, 2000). This suggests that there are approximately 60,000 people with MS in the UK. Higher prevalences of MS in Scotland and Northern Ireland suggest the actual total may be considerably higher; 85,000 has been suggested (MS Society). MS is more common in relatives of people with MS than in the general population.

Age

Typical age of onset is between 20 and 45 years and it rarely appears before 15 or after 50.[2]

Sex

MS is more common in women than in men. Women are approximately twice as likely to develop the disease as men are.[1]

Race

MS is primarily a disease of Caucasians. Northern Europeans and their descendants are the most susceptible.[6]

Geographical patterns

There is a clear gradient with latitude, the prevalence increases with distance from the equator in both hemispheres, though the highest prevalence rates are significantly higher in the northern hemisphere. Migration may alter the risk of occurrence.[6]

Fatigue in the general population

Every individual experiences fatigue during day-to-day living activities. Fatigue can be separated into four types.[7]

- **Physical exertion** This type of fatigue occurs after hard physical activity and is the predominant fatigue experienced by normal people.
- **Depression** Fatigue can be associated with clinical signs of depression, for example appetite change, sleep disturbance, poor self-esteem, loss of interest and loss of energy.

- **Nerve-impulse fatigue** Fatigue can occur when the nerve impulses to particular muscles are worked beyond their capacity.
- **Lassitude** Lassitude can be described as an abnormal sense of tiredness or lack of energy that is disproportional to the amount of energy expended and to the level of disability.[8]

Nature and aetiology of fatigue in MS

The nature of fatigue in MS is clearly distinct from normal fatigue.

Fatigue is frequently reported by people with MS as one of the most common and most disabling symptoms,[9–19] often occurring on a daily basis.[13] In MS, people experience two main types of fatigue: fatigability is the increased weakness with exercise or as the day progresses;[2] and lassitude is an abnormal constant and persistent sense of tiredness.

Fatigue in MS can be differentiated from fatigue in normal people because:

- it worsens with heat
- it prevents sustained physical activity
- it interferes with physical functioning
- it comes on easily
- it interferes with role performance
- it causes frequent problems.[14]

However, as in healthy adults, fatigue is aggravated by exercise, stress and depression and tends to become worse later in the afternoon.[14]

The mechanism for fatigue in MS is not known, which is reflected in the limited range of treatments available and the difficulty in identifying new treatments. It is likely that several different factors contribute.[20] Fatigue might arise as a result of poor sleep patterns due to other symptoms such as nocturia, pain and spasticity, as well as the effects of increased effort due to weakness and spasticity.[20] Fatigue might be due to impaired motor function or impaired drive to the motor cortex, or as a result of depression.[20] When assessing people with fatigue, it is important to acknowledge the possible contribution of other symptoms, and eliminate the possibility of side-effects from drugs used to treat other symptoms.

Epidemiology of fatigue in MS

Up to 86% of people with MS experience fatigue at any one time, 65% class it as one of their three worst symptoms and 30% as their worst.[3] Assuming a total of 60,000 people with MS in the UK, this suggests that approximately 40,000 individuals are significantly affected by the condition of interest. If the total number of people with MS in the UK is as high as 85,000, this figure rises to approximately 57,000.

Table 2 shows the prevalence of fatigue in several surveys of people with MS.

There is no difference in the level of fatigue between men and women[10,11,15] but fatigue may be greater in older people with MS and those with the progressive type of disease.[11,15] The correlation between fatigue and functional impairment shown on neurological examination or disease progression is not clear.[21]

Impact and prognosis of fatigue in MS

Fatigue in MS can be very disabling. It often requires people to sit, lie down or sleep.[21] This has a major impact on all aspects of life, particularly employment. People with MS are often unable to keep their jobs and report that fatigue is one of the major reasons.[16] Fatigue also limits social relationships and self-care activities[10] and generally limits a person's ability to perform tasks requiring physical effort.[22] Fatigue also affects cognitive functioning, such as impairing thought processes and the ability to cope and concentrate.[19,23] It may precipitate affective and behavioural responses, such as irritability, anxiety and depression. In some people it can occur daily or most days, though not often permanently.[10] Fatigue may also worsen the other symptoms of MS.[13]

We could not identify any specific information on prognosis of fatigue in people with MS. It appears that fatigue is a chronic ongoing problem in people with MS. Fatigue is closely related to activity, therefore its impact may paradoxically diminish as the disability of the person with MS progresses.

Measurement of fatigue

There are several self-report instruments for measuring fatigue. These include the FSS,[24] the Fatigue Impact Scale,[22] the Fatigue Assessment Instrument,[25] the Fatigue Rating Scale[18] and the Fatigue Descriptive Scale.[10] The FSS and the Fatigue Impact Scale measure the effect of fatigue on functioning, whereas the Fatigue Assessment Instrument measures fatigue

TABLE 2 *Prevalence of fatigue in people with MS*

Study	Population (*n*)	Fatigue scale	Definition for fatigue	Experiencing fatigue *n* (%)	Fatigue is one of worst symptoms *n* (%)	Fatigue is worst symptom *n* (%)
UK MS Society Symptom Management Survey, 1997[3]	MS Society members Mailed questionnaire (*n* = 223)	Not stated	Not stated	192 (86)	145 (65)	67 (30)
Iriarte *et al.*, 1996[9]	Clinically definite MS (*n* = 50)	Not stated – an original scale Score 0–17	Person mentioning fatigue	31 (62)		3 (6)
Iriarte *et al.*, 1999[10]	Clinically definite MS Consecutive patients with MS at outpatients clinic (*n* = 155)	Fatigue Descriptive Scale (0–17) FSS (average of nine questions with seven levels)	Complaint of fatigue	118 (76)		
Colosimo *et al.*, 1995[11]	Clinically definite MS Consecutive patients with MS referred to outpatients clinic (*n* = 507)	Modified from FSS: A: I am easily fatigued B: exercise brings on my fatigue C: fatigue interferes with my work, family or social life	Two or more of these statements	269 (53)		
Freal *et al.*, 1984[13]	Clinically definite MS Mailshot to variety of sources (*n* = 656)	No specified scale	Presence of fatigue	514 (78)		
Krupp *et al.*, 1988[14]	Clinically definite MS (*n* = 32)	Structured interview	Question: Are you bothered by fatigue? Fatigue defined as "sense of physical tiredness and lack of energy, distinct from sadness or weakness"	28 (88)		9 (28)
Tola *et al.*, 1998[15]	Clinically definite MS (*n* = 48)	FSS (nine domains; seven levels)	Score ≥ 3 points in each domain	31 (65)	28 (58)	
Jackson *et al.*, 1991[16]	Employed people with MS registered with the Vancouver Island MS Society Mailshot (*n* = 31)	No definition	Symptom affecting employment	25 (81)		

FSS, Fatigue Severity Scale

continued

TABLE 2 contd *Prevalence of fatigue in people with MS*

Study	Population (*n*)	Fatigue scale	Definition for fatigue	Experiencing fatigue *n* (%)	Fatigue is one of worst symptoms *n* (%)	Fatigue is worst symptom *n* (%)
Ford *et al.*, 1998[18]	56.3% clinically definite MS Consecutive patients with MS attending neurology clinic (*n* = 68)	Fatigue Rating Scale (14-item self-report questionnaire; four levels)	Cut off: > 3–4 (total fatigue score)	58 (85)		
Fisk *et al.*, 1994[19]	Clinically probable or clinically definite MS (*n* = 85)	Fatigue Impact Scale (40 items; four levels)	People asked whether they have any problems due to fatigue	78 (92)	59 (69)	12 (14)

severity, situation, consequences and response to rest or sleep.[18] The Fatigue Rating Scale separates mental and physical aspects of fatigue and the Fatigue Descriptive Scale measures severity and defines the characteristics of fatigue. Further details on these scales and comments on their validity are provided in appendix 1.

Current service provision

Interventions for fatigue in people with MS are not prescribed in a systematic way. It is largely up to people with MS to seek therapies and try them out. Most of the drugs prescribed (amantadine, antidepressants and other stimulants) are funded by the NHS but are licensed for other indications (Note: pemoline is not available in the UK at present). Clinicians would be able to offer occupational and physical therapy under the NHS, but not usually alternative medications such as acupuncture and cooling vests, or cannabis.

Much of the advice given to people with MS in order to deal with and prevent fatigue is based on lifestyle management techniques and ways of minimising the energy required to do necessary daily tasks.[7,26]

In addition, the nature of the fatigue should be thoroughly investigated to rule out other causes of fatigue, fatigue as a result of other MS symptoms or as a result of side-effects of MS drugs.[27]

Beyond this there are several drugs that have been tried as a second line of treatment and several non-drug interventions that are thought to help. Lack of knowledge regarding the mechanisms of fatigue means that effective treatments are difficult to find and people with MS are often left to try anything that might work, however tenuous the underlying rationale.

Future alternatives

This report is not prompted by new interventions for the treatment of fatigue. In this sense there is no new technology under consideration. There are, however, a wide variety of treatments claimed to alleviate fatigue in MS, which do not appear to be being made available in a systematic way. If this report identifies a range of interventions of proven effectiveness and cost-effectiveness then such treatments should be provided in a coordinated manner. The implications of this would clearly depend on the number and nature of the interventions in question. If the potential treatments are identified as unproven, then further research would be required. If treatments are definitely ineffective, then clear advice for people with MS, carers, clinicians and commissioners should result, indicating the inappropriateness of such treatments being offered for fatigue in MS.

Chapter 2
Methods

The review was carried out in two stages: a scoping review and a systematic review of both effectiveness and cost-effectiveness (economic analysis) of treatments. The rationale behind this is that there are no firmly recommended interventions for treating fatigue in MS, but instead many different therapies that people have tried and reported anecdotally as possibilities. It was decided that giving a clear indication of the range of interventions on which there was evidence, or not, was as important as detailed reviews of those for which there was evidence available. The first stage of the review, therefore, was a formal scoping review, which was intended to identify all the possible therapies.

Formal scoping review

Objective
The purpose of the scoping review was to assess the range of interventions that had been applied and the likely availability of evidence on each of these.

Search strategy
Reviews regarding treatments for fatigue in MS were systematically identified using the following sources.

- **Electronic bibliographic databases** Cochrane Library 1999 Issue 2; MEDLINE (Ovid) 1991–June 1999; EMBASE (Ovid) 1991–June 1999 (the index terms multiple sclerosis, fatigue, cognition, and textwords tired/tiredness, lethargy/lethargic, lassitude were used)
- **Other databases** ARIF database of systematic reviews, GEARS, National Research Register, InterDEC database
- **Publications** *Bandolier*
- **Internet sites** of the following international health technology assessment organisations: Canadian Coordinating Office for Health Technology Assessments (CCOHTA), US National Institutes of Health, Swedish Council on Technology Assessment in Health Care (SBU)
- **Contacting experts**.

Further detail is provided in appendix 2.

Although the search focused on identifying existing reviews, the output of the scoping review also drew on appropriate information from primary studies, for example as identified from lists of included studies in reviews.

Data analysis
The extent of research information available on **all possible** interventions was identified and recorded. This was performed by a single reviewer initially, and subsequently re-assessed for accuracy by a second.

From the list of potential interventions identified, the criteria for choosing those to be systematically reviewed were:

- evidence available – at least two rigorous evaluations
- low cost
- acceptable side-effect profile
- potentially beneficial
- widely cited as useful
- potential license indication
- support for value from experience of use in other similar conditions.

The first criterion, in combination with two others was the threshold set for further in-depth systematic reviews.

Systematic review of effectiveness

Objective
The purpose of this systematic review was to comprehensively search and systematically review evidence of the effects and overall effectiveness of those interventions identified as promising (amantadine and pemoline).

Search strategy
Controlled trials were comprehensively identified by:

- **electronic bibliographic databases** MEDLINE (Ovid) 1966–Dec 1999; EMBASE (DataStar) 1974–79; EMBASE (Ovid) 1980–Dec 1999;

Cochrane Library 1999, Issue 4 (Cochrane Controlled Trials Register). Search terms included the index terms: amantadine, multiple sclerosis, pemoline; and the text-words: amantadine, symmetrel, multiple sclerosis, pemoline, cylert and volital. A search strategy to filter trials was also employed where necessary.

- **checking citation lists from obtained references**
- **contacting experts**.

Further detail is provided in appendix 2.

Inclusion criteria

Study design

Controlled trials, with either a placebo or an alternative intervention arm were included in the review.

Population

People with clinically definite MS were included in the review, without restriction by age, sex or category of MS. Presence of fatigue at baseline was not a necessary criterion.

Intervention

Studies were reviewed if they used arms that included interventions identified from the scoping review as promising (amantadine and pemoline).

Outcome measures

Studies that measured fatigue as an outcome, ideally using an accepted and validated fatigue scale were reviewed. Other important effects were recorded.

Data extraction

Key data concerning study characteristics, study quality and results were extracted independently by two reviewers using a series of proforma. The contact reviewer resolved any differences or general areas of difficulty.

Quality assessment strategy

Assessment of validity was based on the Jadad scale.[28] Handling of randomisation, blinding and withdrawals/drop-outs were recorded separately and converted into an overall quality score according to the method suggested by Jadad. A proforma was used independently by two reviewers and differences resolved with reference to the contact reviewer.

The basic approach outlined in the protocol was amplified in order to take into account difficulties in quality assessment arising from the need to include crossover trials in addition to trials with parallel control groups. This study design offers the same advantage as randomised controlled trials (RCTs) in avoiding confounding arising from differences in the characteristics of the subjects exposed to treatment and control. However, it achieves this differently. All trial subjects included in the analysis are exposed to both treatment and placebo in different time periods.

Unfortunately, crossover trials also suffer from the possibility of a period effect, where any impact attributable to the treatment differs depending on whether the treatment is given during the first or second period. This might arise because of a carryover effect of the new treatment from one period to the next, particularly if a washout period is not included or is impossible. However, carryover is not the only contributor to a period effect; the natural history of the condition or the necessity for repeated measures of an outcome may also be important.

Although this problem of analysing crossover trials is clearly defined, the means of dealing with it is less certain.[29,30] This, together with incomplete reporting, makes it particularly difficult to assess whether a crossover trial has dealt with the issue adequately. Further complication in assessing the quality of crossover trials, is that the implications of shortcomings in randomisation and loss to follow-up seem to be different.

These are widely acknowledged problems for those attempting to systematically review such studies. In dealing with this we generally followed the approach suggested in the *Cochrane Collaboration Handbook*[31] supplemented with advice from D Altman (Institute of Health Sciences, Oxford). On this basis, to assess the study quality of crossover studies included, we used the Jadad scale, but posed four additional questions to capture predicted sources of bias that seemed particularly relevant to the topic in question:

- 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?
- Were people who did not complete any of the periods excluded from the analysis?

Answers to these questions were independently assessed by two reviewers and recorded.

Methods of analysis and synthesis

The data gathered for each outcome were mainly summarised in a tabular format and conclusions based on the pattern of results revealed. Direction of effects, size of effects and overall effectiveness were specifically considered. Particular attention focused on gauging the clinical importance of the effect as well as its presence. Meta-analysis using RevMan 4.0.4 software was employed for one outcome, taking clear account of clinical and statistical heterogeneity. For this outcome a sensitivity analysis was undertaken to take into account uncertainty about the most appropriate denominator to use for the subject preference outcome.

With respect to the need to include data from crossover trials, we again followed the approach suggested by the *Cochrane Collaboration Handbook*.[31] The least problematic way of incorporating crossover trials into a systematic review is to include data from period 1 alone, as though it were from a randomised trial. This was not open to us as the results were only available for treatments and placebos in periods 1 and 2 combined. In keeping with uncertainty about the problems of interpreting crossover trials, we clearly differentiated the results derived from any data provided by randomised trials with parallel control groups.

Economic analysis

Objective

The purpose of the economic analysis was to systematically review research on the costs and cost-effectiveness of those interventions identified as promising (amantadine and pemoline).

In the light of a virtual complete absence of any data contributing to this objective, we amplified the original method to identify indirect data that might allow tentative modelling of cost-effectiveness or cost–utility. In addition to systematically reviewing the effects and effectiveness of amantadine and pemoline, including impact on quality of life, this was addressed by seeking answers to the following four questions.

1. **What is the generic estimate of quality of life of people with MS?** Ideally data would come from a random sample survey of representative people with MS, using an accepted and validated generic measure of quality of life.
2. **What proportion of the reduction in quality of life is due to symptomatic fatigue?** Ideally this should be an analysis comparing quality of life in fatigued and non-fatigued people with MS.
3. **What are the costs of MS?** Ideally this should be a cost analysis from the perspective of society, the NHS and the person with MS.
4. **What proportion of these costs are due to fatigue?**

Search strategy

Published studies were identified by:

- **electronic bibliographic database** MEDLINE (Ovid) 1980–Feb 2000 using the following MeSH and textwords: economics, costs, cost analysis, fees and charges, pharmacoeconomics, economic value of life, multiple sclerosis, fatigue, lethargy, quality of life, health status, amantadine, pemoline.
- **other databases** NHS centre for Reviews and Dissemination Database of Health Technology Assessments, NHS Economic Evaluation Database
- **Internet sites** of the following health technology assessment/health economics units: Wessex Development and Evaluation Committee, Trent Institute for Health Services Research, University of York Centre for Health Economics, Oxford University, CCOHTA, SBU, McMaster University, World of MS
- **checking citation lists** from obtained references.

Inclusion criteria

Studies of all types relevant to the objectives above were accepted, despite the stated preference for specific types of study.

Analysis

The data identified were summarised and presented with reference to the following headings: costs; existing health economic analyses; and information to facilitate modelling. Modelling of health economic impact, although initially planned, was not conducted.

Handling of industry submission

No industry data were submitted for this report.

Chapter 3
Results

Formal scoping review

Quantity of research available

The scoping review revealed in excess of 100 hits. Of these the majority were reviews or papers giving background information. These in turn yielded 15 evaluations providing some evidence on effectiveness for eight potential interventions: four drugs, three types of training or rehabilitation, and one device. Four potential interventions or groups of them were identified where the only evidence for effectiveness was anecdote or best practice.

Table 3 shows the interventions for fatigue in MS that were identified from the scoping review. The quantity and quality of research supporting their use are also presented.

Drugs for fatigue in MS

Amantadine (Symmetrel®)

Amantadine is an antiviral agent with dopaminergic properties, sometimes used in Parkinson's disease. It appears to have some benefit in fatigue, though its mechanism of action is unknown.[47] It is usually taken at a dosage of 200 mg/day[4] and is quite well tolerated, though possible adverse effects include ankle oedema with livedo reticularis, diminished concentration, nervousness and sleeping disturbances.[4] Several RCTs investigating its effect were initially found.

Pemoline (Cylert® and Volital®)

Pemoline is a CNS stimulant that also acts by an unknown mechanism.[4] It is started at a dose of 18.75 mg/day and increased by similar doses.[27] It is less favoured than amantadine for treatment of fatigue, and side-effects, such as anorexia, irritability, nausea and insomnia have been noted.[48] Pemoline is not currently available in the UK. Three possible RCTs were initially found.

Potassium-channel blocking drugs

Potassium-channel blockers such as 4-aminopyridine and 3,4-diaminopyridine may also prove effective for fatigue, weakness and ambulation.[27,49] One RCT was found, which compared 4-aminopyridine with 3,4-diaminopyridine.

Antidepressants

New antidepressants, such as fluoxetine, sertraline and bupropion have been tried in MS-related fatigue, and anecdotal reports suggest some benefit,[27] though no clinical studies were unearthed. Side-effects of these drugs may include anorexia, anxiety, insomnia, gastrointestinal complaints and increased spasticity.

Non-drug interventions for fatigue in MS

Behavioural advice

Although reported to be the mainstay of management of fatigue in MS, no research was discovered indicating the effectiveness of general advice on activity pacing and lifestyle advice to help people with MS cope with fatigue. This should be distinguished from targeted advice taking into account the individual's circumstances, incorporated into a fatigue management programme, often delivered by occupational therapists and clinical nurse specialists. However, even in this case research on effectiveness is at a very early stage.

Aerobic exercise

Although vigorous exercise might exacerbate the fatigue of MS, it is thought that moderate exercise to improve aerobic capacity might be beneficial for fatigue as well as other symptoms.[43] One RCT of a 15-week aerobic training programme was found in the search.

Extended outpatient rehabilitation

One non-randomised placebo-controlled trial has investigated the effect of an extended form of outpatient rehabilitation that includes support for the person with MS and the family.[45] It seemed to show benefit in a number of domains, including fatigue.

Cooling systems

Warm environments often exacerbate fatigue in people with MS. Cooling vests have become commercially available but there is little evidence so far of any effectiveness; further studies need to be carried out.[27]

Alternative therapies

There are many anecdotal reports of people with MS benefiting from alternative medications such as bee venom,[50] cannabis/cannabinoids,[51]

TABLE 3 *Potential interventions for fatigue in MS identified from a formal scoping review. The quantity and quality of research underpinning their use*

Potential intervention	Evidence		
	Study	**Arms**	**Fatigue outcome?**
Drug[a]			
Amantadine	Canadian MS Research Group, 1987[32] RCT (crossover)	Amantadine vs placebo	Yes
	Rosenberg & Appenzeller, 1988[33] RCT (crossover)	Amantadine vs placebo	Yes
	Cohen & Fisher, 1989[34] RCT (crossover)	Amantadine vs placebo	Yes
	Krupp *et al*., 1995[35] RCT (parallel)	Amantadine vs pemoline vs placebo	Yes
	Geisler *et al*., 1996[36] RCT (parallel)	Amantadine vs pemoline vs placebo	Yes
	Murray, 1985[37] CCT (crossover)	Amantadine vs placebo	Yes
	Chiba *et al*., 1992[38] Case series	Amantadine	Yes
Pemoline	Weinshenker *et al*., 1992[39] RCT (crossover)	Pemoline vs placebo	Yes
	Krupp *et al*., 1995[35] RCT (parallel)	Amantadine vs pemoline vs placebo	Yes
	Geisler *et al*., 1996[36] RCT (parallel)	Amantadine vs pemoline vs placebo	Yes
4-Aminopyridine	Polman *et al*., 1994[40] RCT (crossover)	4-Aminopyridine vs 3,4,diaminopyridine	Yes
	Polman *et al*., 1994[41] Case series	4-Aminopyridine	Yes
3,4,Diaminopyridine	Polman *et al*., 1994[40] RCT (crossover)	4-Aminopyridine vs 3,4,diaminopyridine	Yes
	Sheean *et al*., 1998[42] Case series	3,4,Diaminopyridine	Yes
Antidepressants		Anecdote	
Non-drug			
Behavioural advice		Established clinical practice	
Aerobic training	Petajan *et al*., 1996[43] RCT (parallel)	Exercise for 15 weeks vs no exercise	Yes
Endurance training	Svensson *et al*., 1994[44] Case series	Endurance training	Yes

[a]*Since completion of this report a further potentially valuable drug intervention, modafinil, has been identified*

CCT, controlled clinical trial

continued

TABLE 3 contd *Potential interventions for fatigue in MS identified from a formal scoping review. The quantity and quality of research underpinning their use*

Potential intervention	Evidence		
	Study	**Arms**	**Fatigue outcome?**
Outpatient rehabilitation	Di Fabio, 1998[45] CCT (parallel)	Extended outpatient rehabilitation; control group those on waiting list	Yes
Cooling systems		Anecdote	
Pulsing magnetic field	Richards *et al.*, 1997[46] RCT (parallel)	Enermed device vs placebo	Yes
Alternative medications (bee venom; cannabis/ cannabinoids; acupuncture/ acupressure; yoga)		Anecdote	
CCT, controlled clinical trial			

acupuncture/acupressure, yoga and treatment with weak electromagnetic fields (EMFs). There is at least one trial investigating EMF with fatigue as an outcome,[46] though the search did not reveal any clinical studies on any of the other possible alternative medications. Large-scale trials in cannabinoids have recently been commenced, which include people with MS.[52] However their primary outcome is spasticity, not fatigue.

Interventions systematically reviewed

Amantadine and pemoline were taken forward to the systematic review stage on the basis that they are cheap, potentially beneficial and widely cited as useful. More importantly, however, they were the only two interventions where there had been rigorous evaluation repeated at least twice. It was considered that only in these situations were systematic reviews likely to amplify conclusions available from the original studies identified in *Table 3*. This should not however imply that these are necessarily those interventions most likely to alleviate fatigue in MS. The choice made was essentially pragmatic.

The addition of potassium-channel blockers to amantadine and pemoline was debated. However, it was finally not taken forward because of the four trials identified,[40,53–55] only one[40] included fatigue as an outcome.

Summary of formal scoping review

- There is a wide range of interventions claimed to be of value for fatigue in MS.
- These interventions include drugs, training and rehabilitation, devices (cooling vests and EMFs) and alternative medications (bee venom, cannabis/ cannabinoids, acupuncture/ acupressure and yoga).
- Relative to the apparent significance of the symptom, there appears to be remarkably little rigorous research on the effectiveness of these interventions.
- A remarkable omission is the almost total absence of any research on the effectiveness of the most usual initial clinical management, behavioural advice.
- Evidence on the effects, effectiveness and cost-effectiveness of two drugs, amantadine and pemoline were subsequently systematically reviewed as part of this report. This was mainly done for pragmatic reasons and should not imply that these two agents are necessarily those likely to have the greatest potential to alleviate fatigue.

Systematic review of amantadine

Quantity of research available

Seven potential evaluations had already been identified from the scoping review. Three of these were subsequently excluded: two because they were not randomised and one because it duplicated an existing trial. The additional searches revealed 57 hits, but no new trials. Further details on the excluded studies are provided in appendix 3.

Thus, four studies met the inclusion criteria for the review.[32–35]

Characteristics of included studies

Details of the characteristics of the included studies are shown in *Table 4*.

Study designs

One study was a parallel RCT[35] and three studies were crossover RCTs.[32–34] Pictorial representations of the studies are shown in *Figure 1*.

The parallel trial was a three-arm study comparing both amantadine and pemoline against placebo and is also included in the systematic review of pemoline. All except one of the included studies were therefore crossover trials. The specific implications of this fact will be discussed in the next section on study validity.

The periods of treatment ranged from 1 to 4 weeks for the crossover studies. The treatment period in the parallel trial was 6 weeks. Two studies[32,35] included a run-in period of 2 weeks during which patients were monitored and assessed.

The crossover trials included washout periods of 1–2 weeks.

Populations examined

All included studies used similar inclusion criteria: people with definite MS clinically ascertained according to reasonably well-established criteria and complaining from moderate-to-severe fatigue usually for more than 3 months.

Those studies reporting exclusion criteria (three out of four) used similar ones. These were: medical conditions that cause fatigue; psychiatric disorders, particularly depression; the use of medication that could influence fatigue; and disease relapses requiring treatment.

The population studied can therefore be regarded as fairly similar in all studies.

Three studies[32,34,35] accounting for 95% of patients studies, used some form of baseline assessment and cut-off points for fatigue level. In fact the Canadian MS Research Group study[32] excluded 71 out of 165 (43%) patients who were enrolled initially because of their low level of fatigue. The level of fatigue of the studied patients is therefore likely to be higher than the average level of fatigue of people with MS as a whole.

The total number of patients studied is relatively small (n = 236).

Intervention and comparison

The intervention was amantadine, 100 mg twice daily compared with placebo in all four studies. The duration of the intervention was not long (1–6 weeks), and consequently this makes it impossible to estimate long-term effectiveness.

Outcomes

A number of outcomes were considered in different studies. In keeping with inclusion criteria all studies assessed fatigue.

Fatigue, being essentially a subjective assessment, is difficult to measure. Studies used a variety of methods to measure fatigue (e.g. diaries, visual analogue scales (VAS), questionnaires). Two general measures were recognised: patient-assessed and researcher-assessed measures. All studies used some form of patient self-assessment.

Patient-assessed fatigue

Two of the studies[32,34] required patients to do some sort of daily monitoring of their fatigue, the results of which were then summarised. One study[32] used VAS. Such results are difficult to interpret. As the authors of this study point out, patients require training and understanding of their use. This is also seen in the use of VAS in one of the studies of pemoline. The study on amantadine asked patients to use the VAS to record the level of fatigue, while the study on pemoline used VAS to record changes (improvement or deterioration) in fatigue against baseline. Other outcomes on fatigue used several types of point scales.

Researcher-assessed fatigue

All studies complemented self-assessment by using some sort of assessment by researchers. Two studies[33,34] only used this at baseline and the other two at several points in time. Only one study[35] used validated instruments, FSS, MS-FS scales (see appendix 1) for such assessment. It is not clear in the other studies what the assessment consisted of.

Clinical significance of fatigue

Only one study[32] included some measure of treatment impact by looking at activities of daily living. Even this study did not use any of the standard validated instruments (e.g. Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)) and therefore it is difficult to

TABLE 4 *Systematic review of effectiveness of amantadine on fatigue in MS. Characteristics of included studies*

	Krupp *et al.*, 1995[35]	**Canadian MS Research Group, 1987[32]**	**Rosenberg Appenzeller, 1988[33]**	**Cohen & Fisher, 1989[34]**
Design	RCT parallel	RCT crossover	RCT crossover	RCT crossover
Inclusion criteria	Definite MS Baseline fatigue ≥ 4 on FSS after 2-week monitoring phase	Definite MS Chronic, persistent, moderate-to-severe daily fatigue for ≥ 3 months and mean score ≥ 25 mm on VAS after 2-week monitoring phase	Definite MS Fatigability (not further defined)	Definite or probable MS Symptomatic fatigue (fatigue assessment inventory 42 items) for ≥ 3 months daily
Exclusion criteria	Psychiatric disorders; listed medical conditions; listed medications that might influence fatigue or disease course	Psychiatric disorders; listed medical conditions; listed medications that might influence fatigue or disease course	Not stated	Psychiatric disorders; listed medical conditions; listed medications that might influence fatigue or disease course
No. of patients randomised	82 39 amantadine 43 placebo	115	10	29
Intervention	Amantadine, 100 mg twice daily for 6 weeks	Amantadine, 100 mg twice daily for 3 weeks	Amantadine, 100 mg twice daily for 1 week	Amantadine, 100 mg twice daily for 4 weeks
Comparator	Placebo	Placebo	Placebo	Placebo
Outcomes assessed: Fatigue-specific; patient-assessed	At end of week 8: 1. Verbal self-report of fatigue: same, better or worse (preferred treatment while still taking medication) At end of week 10: 2. Verbal self-report of fatigue: same, better or worse (preferred treatment 2 weeks after discontinuing medication)	Daily: 1. Recording of level of fatigue on a 50 mm VAS, weekly summarised on single VAS Weekly: 2. Activity most affected by fatigue on VAS 3. Activities of daily living (13 items) by VAS At end of weeks 2, 5, 7, 10: 4a. Overall evaluation of treatment/placebo period on a five-point scale: poor, fair, good, very good, excellent At end of study: 5a. Preferred treatment	At end of weeks 1, 3: 1. Patients asked to select drug of preference (preferred treatment)	Daily: 1. Diary of experience of fatigue across seven dimensions three times a day on a five-point scale At end of study: 2. Period resulted in less fatigue (preferred treatment)

Note: The relevant outcome measures for each study have been numbered. For ease of reference, the same numbers are used in subsequent tables of results for the same outcomes

continued

TABLE 4 contd *Systematic review of effectiveness of amantadine on fatigue in MS. Characteristics of included studies*

	Krupp *et al.*, 1995[35]	**Canadian MS Research Group, 1987[32]**	**Rosenberg Appenzeller, 1988[33]**	**Cohen & Fisher, 1989[34]**
Outcomes assessed: Fatigue-specific; researcher-assessed	At end of weeks 8, 10: 3. MS-FS 4. FSS 5. RIV (measures energy)	At end of weeks 2, 5, 7, 10: 4b. Overall evaluation of treatment/placebo period on a five-point scale: poor, fair, good, very good, excellent At end of study: 5b. Preferred treatment	Baseline only At week 0: 2. Fatigability on a four-point scale	Baseline only At week 0: 3. Fatigue inventory of effects on daily living
Side-effects	Recorded	Recorded	Recorded	Recorded
Other outcomes assessed	At weeks 0, 2, 5, 8, 10: CES–D (depression); St Mary's Hospital Sleep Questionnaire; Neurologic examination and EDSS	Other most bothersome MS symptom VAS; EDSS; Beck depression scale	EDSS; strength and endurance testing; biochemical tests (cortisol, endorphin, vasopressin, lactate, pyruvate)	Neurobehavioural evaluation to detect fatigue during performance of various tasks (eight measures)

Note: The relevant outcome measures for each study have been numbered. For ease of reference, the same numbers are used in subsequent tables of results for the same outcomes

MS-FS, MS-specific Fatigue Scale; RIV, Rand Index of Vitality; CES–D, a self-reported depression scale; EDSS, Expanded Disability Status Scale

ascertain the impact of the treatment on quality of life. This is a major limitation in drawing conclusions on overall effectiveness.

Patient preference
All studies included some information on the preferred treatment during the crossover trial, or the equivalent of this in the parallel trial. The reported preference of treatment, although of easier comparability and more clinical significance, does not allow any assessment of the size of the effects.

Side-effects
Side-effects were recorded in all four studies.

Other outcomes
A variety of other outcomes (strength, biochemical test results, cognitive measures and psychological tests) were also measured, often as secondary outcomes or for the purpose of baseline assessment. The results of these were considered to contribute little beyond the outcomes listed above, and are not presented further in this report.

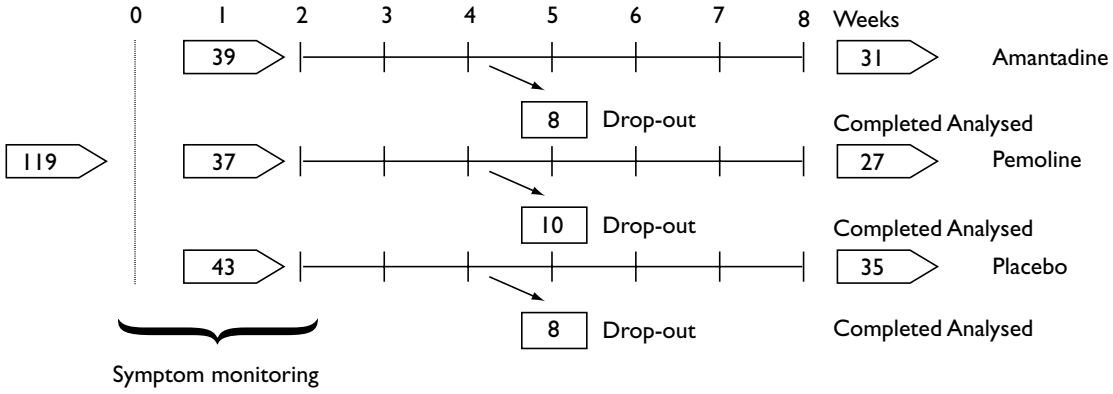
Validity of included studies

Details of validity are presented in *Table 5*, with additional information on loss to follow-up in *Table 6* (reference to *Figure 1*, may also be helpful in understanding the threats to validity discussed).

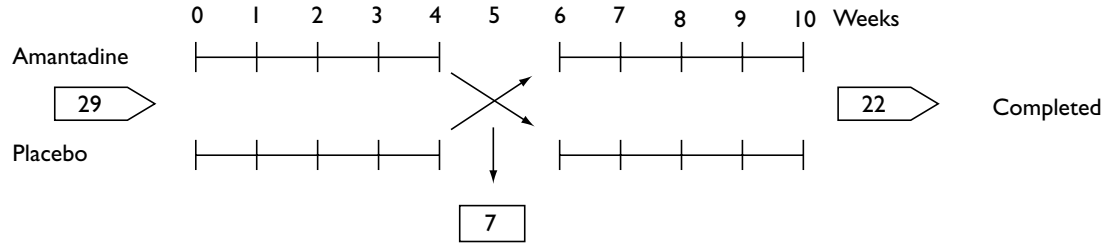
One trial with a parallel control arm[35] was included and appraised according to standard criteria. Although of small size, the study was moderately well conducted with a Jadad score of 3 (maximum 5). The relative shortcomings concerned allocation concealment following randomisation and uncertainty about whether allocation was masked during the assessment of outcome. Furthermore, the loss to follow-up (20%) was close to a level where the benefits of randomisation are undermined to a point where validity is impaired.

The three other included studies were randomised double-blind crossover trials.[32–34] Judged by the criteria used in the Jadad scale, the validity is similar with uncertainty about allocation concealment following treatment allocation and uncertainty about whether allocation was still masked at assessment of outcome. Furthermore, as for the parallel trial there are high losses to follow-up in two crossover trials.[32,34] However, it should be acknowledged that the implications of loss to follow-up are less clear in crossover trials provided the analysis is restricted to individuals who have received

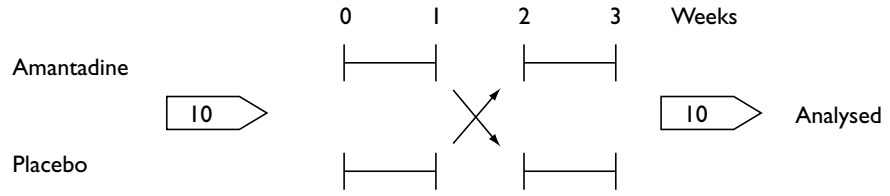
Krupp *et al.*, 1995[35]



Cohen & Fisher, 1989[34]



Rosenberg & Appenzeller, 1988[33]



Canadian MS Research Group, 1987[32]

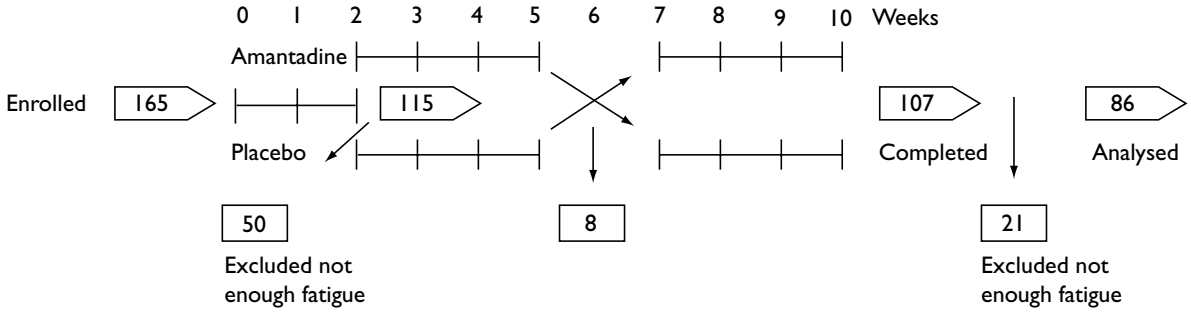


FIGURE 1 *Trial designs for amantadine*

both treatment and control, and it is clear to what larger population the results of the paired analyses relate.

Superficially it appears that the three crossover trials[32–34] are possibly less open to bias than the parallel trial. This is incorrect for reasons introduced in the methods section. Interpretation of crossover trials presents considerable challenges where results are not available for the first period of treatment/control alone; this was the case in these three studies. Instead we had to consider the results for the first and second periods of treatment/control combined. This introduces the possibility that a period effect (i.e. any effect associated with treatment is different if the drug is received in the first period or the second) may lead to an overestimate or underestimate of any differences observed between amantadine and placebo. Although the means to take any period effect into account are a subject of some debate, one thing is clear and that is that some attempt should be made in the analysis to identify whether such a period effect is present. As *Table 5* shows, only one of the three included crossover trials does so.[32] They identified that fatigue in the first period of the crossover trial was greater than fatigue in later periods. This introduces the possibility in both this trial and the others that if more patients receive their treatment in the first period than the second, this in itself could alter the estimate of effect on fatigue. Some reassurance would be provided by knowledge about the numbers receiving amantadine first

TABLE 5 *Systematic review of effectiveness of amantadine on fatigue in MS. Quality of included studies*

	Krupp et *al.*, 1995[35]	**Canadian MS Research Group, 1987[32]**	**Rosenberg & Appenzeller, 1988[33]**	**Cohen & Fisher, 1989[34]**
Design	Parallel	Crossover	Crossover	Crossover
No. of people randomised	39 amantadine 43 placebo	115	10	29
Randomisation				
Was the trial described as 'randomised'?	Yes	Yes	Yes	Yes
Was the method of randomisation not stated or unclear	Unclear	Stated	Unclear	Unclear
Was there concealment of treatment allocation?	Unclear	Unclear	Unclear	Unclear
Double blinding				
Was the trial described as 'double-blind'?	Yes	Yes	Yes	Yes
Was the treatment allocation masked from the participants?	Yes	Yes	Unclear	Unclear
Was the treatment allocation masked from the investigators?	Yes	Unclear	Unclear	Unclear
Was the treatment allocation masked at the outcome assessments?	Unclear	Unclear	Unclear	Unclear
Withdrawals and drop-outs[a]				
Was the number of withdrawals in each group stated?	Yes	Yes	Yes	Yes
Jadad score[b]	3	3	3	3
Aspects specific to crossover trials				
Were systematic period effects or carryover discussed and/or identified?	N/A	Yes	No	No
Washout period?		2 weeks	1 week	2 weeks
Was the number of people in sequences PT and TP clearly stated?		No	No	No
Were people who did not complete any of the periods excluded from the analysis?		Unclear	All completed	Yes

[a] *More detailed information in* Table 6
[b] *The Jadad score was not designed to assess quality of crossover trials and so may not accurately represent their quality*
N/A, not applicable

or second, but this is not available in any of the trials. Knowing that the subjects were allocated randomly should provide reassurance that similar numbers received treatment first, but this assumes knowledge about loss to follow-up during the course of the crossover trial, which again, is not available.

The unfortunate consequence of this is that a period effect is likely but that it is not adequately accounted for, so throwing doubt on all conclusions reached in these studies.

Summary of direction of effects on all fatigue-related outcomes

Based on the results as reported in the studies themselves there is an overall tendency to positive results with amantadine in all trials (*Table 7*). The results of the parallel trial, which does not have the problems of interpretation indicated for crossover

TABLE 6 *Systematic review of effectiveness of amantadine on fatigue in MS. Exclusions and drop-outs*

	No. enrolled	No. randomised	No. completing trial	No. analysed	No. of drop-outs	No. drop-outs/ no. randomised
Parallel study						
Krupp *et al.*, 1995[35]	82	39 amantadine	31	31	8	
		43 placebo	35	35	8	
		82 both arms	66	66	16	20%
Crossover studies						
Canadian MS Research Group, 1987[32]	165	115[a]	107	86[c]	29	25%
		94[b]	86[b]	86[b]	8[b]	9%[b]
Rosenberg & Appenzeller, 1988[33]	10	10	10	10	0	0
Cohen & Fisher, 1989[34]	Unknown	29	22	22	7	24%

[a] *50 excluded before randomisation (not enough fatigue)*
[b] *Numbers if the 21 excluded at the end are considered in the same way as the 50 excluded before randomisation*
[c] *21 excluded at end of trial (not enough fatigue at beginning of trial)*

TABLE 7 *Systematic review of effectiveness of amantadine on fatigue in MS. Direction of effects on all fatigue-related outcomes*

Study	Outcome measured	Direction of effect	Statistical significance ($p < 0.05$)
Parallel study			
Krupp *et al.*, 1995[35]	1. Preferred treatment at the end of trial	Favours placebo	No
	2. Preferred treatment 2 weeks after end of trial	Favours amantadine	Yes
	3. Fatigue MS-FS	Favours amantadine	Yes
	4. Fatigue FSS	Favours amantadine	No
	5. RIV vitality	Raw data not provided	No
Crossover studies			
Canadian MS Research Group, 1987[32]	1. Effects on fatigue VAS	Favours amantadine	No
	2. Effects on most affected activity VAS	Favours amantadine	Yes
	3. Effects on activities of daily living; total score	Favours amantadine	Yes
	4. Response over previous period	Favours amantadine	Yes
	5. Preferred treatment	Favours amantadine	Yes
Rosenberg & Appenzeller, 1988[33]	1. Preferred treatment	Favours amantadine	Yes
Cohen & Fisher, 1989[34]	1. Fatigue; daily ratings; point scale 1–5	Favours amantadine	No
	2. Preferred treatment	Favours amantadine	Yes

trials, shows the same direction and therefore provide some reassurance of the validity of the pattern of findings.

Preferred treatments

This is the only outcome on which all studies provide some information (*Table 8*). Even so, the meaning of patient preference in crossover and parallel trials is not completely equivalent. Problems also arise because the parallel trial[35] reports two different results: at the end of the trial (still taking treatment) and at 2 weeks after the trial. Furthermore, the results appear to be incomplete, with the denominators used differing from the numbers randomised.

For the crossover trials, the percentage of patients who prefer amantadine ranges from 37% to 60%. In the parallel study the percentage who would continue with amantadine, if this is the arm they had been allocated to, ranged from 33% to 79% depending on when and how the preference rate was calculated. In either case, it is important to note that preference for placebo was substantial, and in the Krupp study[35] the number preferring amantadine became greater than placebo only when the results from 2 weeks after the end of the trial, following the second washout period, were considered.

We calculated and used relative risks in order to explore the pattern of results and perform statistical and sensitivity analyses. For the parallel trial the results at 2 weeks after the end of the trial were used.

In *Figure 2*, the results of this analysis under 'optimistic' assumptions are presented. In this we accepted the results 'as reported' in the parallel study, and calculated the relative risk of preferring amantadine versus placebo, excluding no preference and preference for washout, in the crossover trials. The analysis favours amantadine and shows reasonable statistical homogeneity. The summary relative risk of 1.9 (95% CI, 1.4 to 2.7) suggests that approximately twice as many people prefer amantadine to placebo.

In *Figure 3*, the results of a second analysis under 'pessimistic', but realistic assumptions

TABLE 8 *Systematic review of effectiveness of amantadine on fatigue in MS. Preferred treatments*

Study	Treatment	Preference (%)	RR (95% CI) (amantadine vs placebo)	RR (95% CI): (amantadine vs any other preference)	Notes
Parallel study					
Krupp *et al.*, 1995[35]	Amantadine[b] Placebo	13/23 (57) 14/24 (58)	1.0 (0.6 to 1.6)	Same	At end of trial
(as reported[a])	Amantadine[b] Placebo	15/19 (79) 13/25 (52)	1.5 (1.0 to 2.4)	Same	2 weeks after end of trial
Krupp *et al.*, 1995[35]	Amantadine[b] Placebo	13/39 (33) 14/43 (33)	1.0 (0.6 to 1.9)	Same	At end of trial
(ITT analysis)	Amantadine[b] Placebo	15/39 (38) 13/43 (30)	1.3 (0.7 to 2.3)	Same	2 weeks after end of trial
Crossover studies					
Canadian MS Research Group, 1987[32]	Amantadine Placebo No preference Washout	35/86 (41) 18/86 (21) 28/86 (33) 5/86 (6)	1.9 (1.2 to 3.2)	0.7 (0.5 to 0.9)	
Rosenberg & Appenzeller, 1988[33]	Amantadine Placebo No preference	6/10 (60) 1/10 (10) 3/10 (30)	6.0 (0.9 to 41)	1.5 (0.6 to 3.7)	
Cohen & Fisher, 1989[34]	Amantadine Placebo No preference	8/22 (37) 4/22 (18) 10/22 (46)	2.0 (0.7 to 5.7)	0.6 (0.3 to 1.1)	

[a] *Although not stated in study, we assumed that people expressing no preference were excluded from numerator and denominator*
[b] *Numbers wanting to carry on with amantadine or placebo*

ITT, intention to treat; RR, relative risk; CI, confidence interval

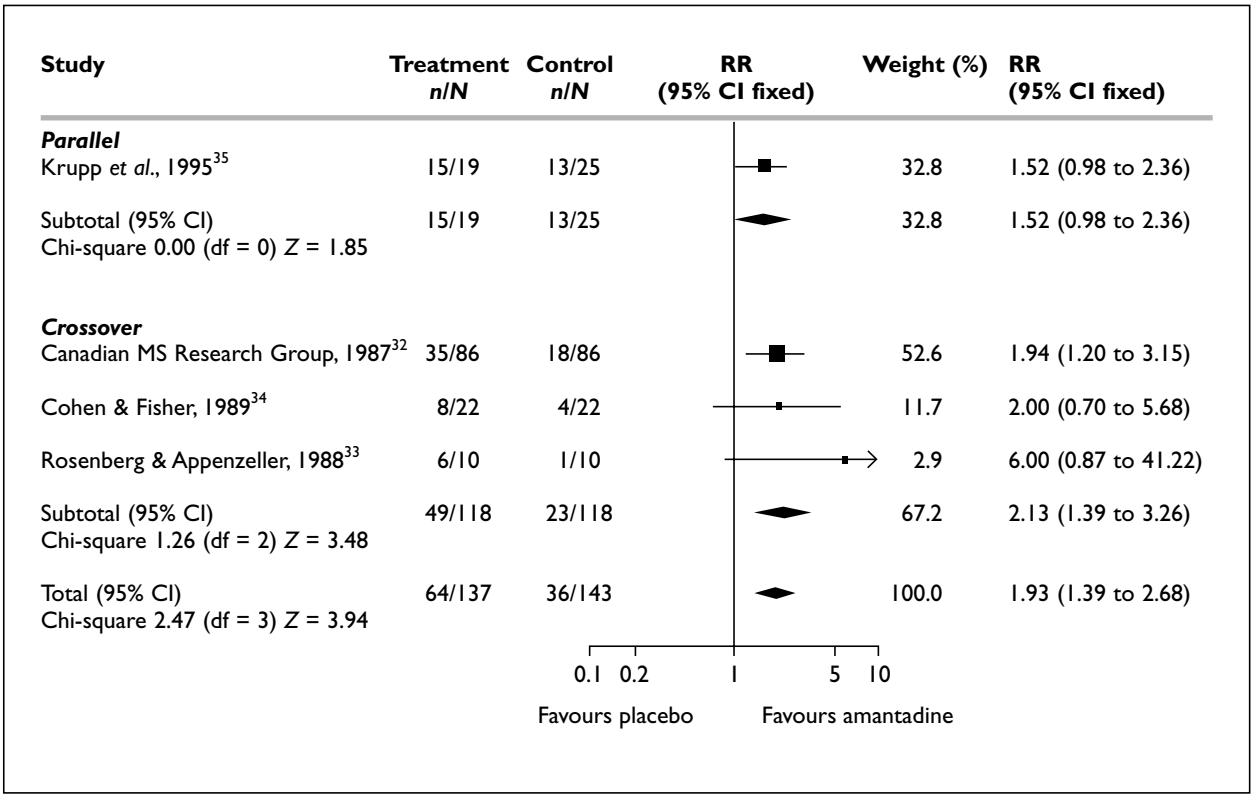


FIGURE 2 *Systematic review of effectiveness of amantadine on fatigue in MS. Effect of amantadine versus placebo on patient preference (optimistic assumptions)*

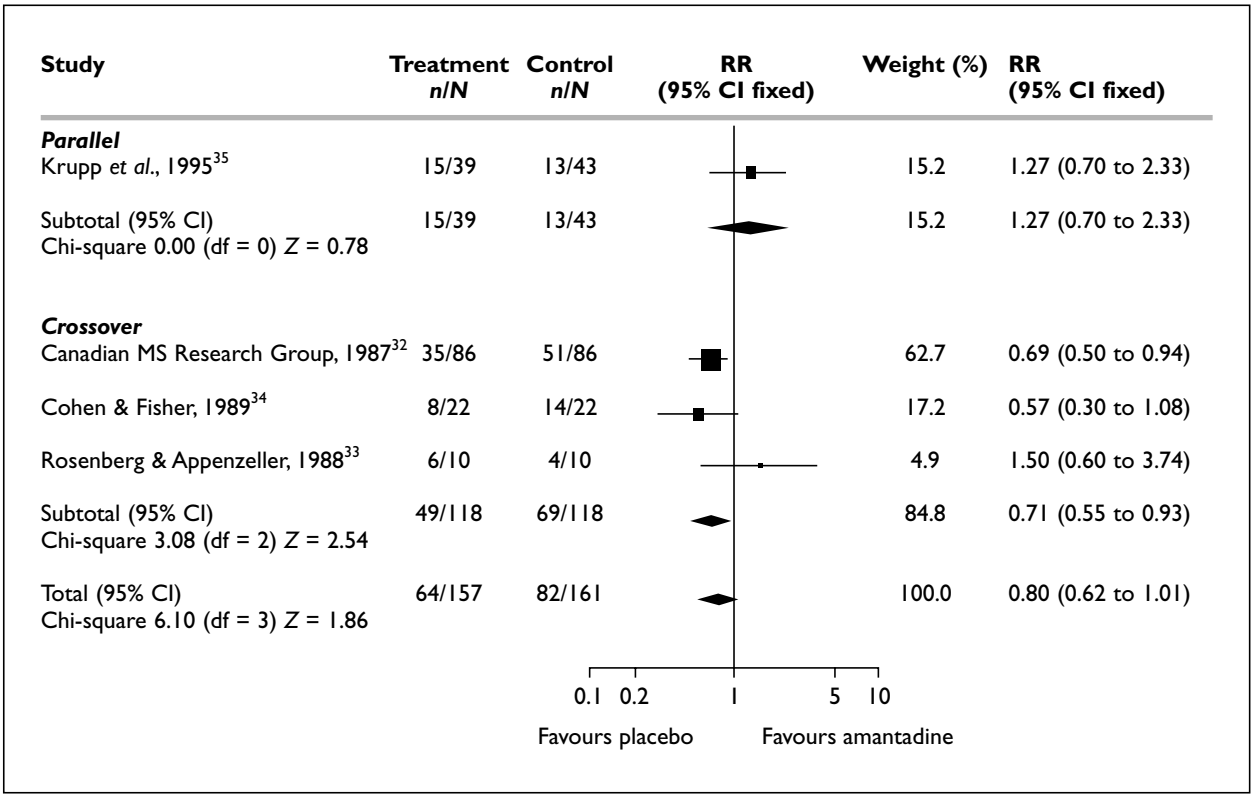


FIGURE 3 *Systematic review of effectiveness of amantadine on fatigue in MS. Effect of amantadine versus placebo on patient preference (pessimistic assumptions)*

concerning the most informative way to present the results are presented. This time we used results data from the intention-to-treat (ITT) analysis for the parallel trial, and for the crossover trials counted no preference and preference for washout together with the preferences for placebo.

This second analysis shows that the results are highly sensitive to changes in the assumptions. In particular, the direction of effects changes for two of the studies. This clearly suggests the need for caution in interpreting the results of the included studies on an as-reported basis.

Fatigue-specific outcomes

Patient preference provides little information regarding the size of effects. Such information might have been provided by more quantitative measures of fatigue.

One trial, the Canadian MS Research Group Trial[32] asked people with MS to record the level of fatigue experienced on a VAS. The results show an improvement in fatigue as shown in *Table 9,* but this is quite small. The difference between amantadine and placebo did not reach statistical significance and, in any case, it is extremely difficult to interpret what the clinical meaning of an additional 1.7 mm change on a 50 mm scale actually is.

Fatigue was also measured quantitatively using assessment tools based on point scales and questionnaires (*Table 10*). All these measures

TABLE 9 *Systematic review of effectiveness of amantadine on fatigue in MS. Level of fatigue as measured with VAS*

	Fatigue measure	Group	Baseline mean VAS score (mm)	End mean VAS score (mm) (95% CI)	Change (mm)	Notes
Crossover study						
Canadian MS Research Group, 1987[32]	1. Record of level of fatigue	Amantadine	29	25 (23 to 26)	–4.3	Test for difference NS ($p > 0.05$)
		Placebo	30	27 (25 to 29)	–2.6	

Note: Data in this table were read from graphs in the published paper. On the scale used, 0 mm represents "no fatigue" and 50 mm represents fatigue "as bad as can be"; decreases in scores hence represent improved fatigue

NS, not significant

TABLE 10 *Systematic review of effectiveness of amantadine on fatigue in MS. Level of fatigue as measured with point scales and questionnaires*

	Fatigue measure	Group	Scores		Change	Difference
Parallel study						
Krupp *et al.*, 1995[35]	3. MS-FS[a]		Baseline mean score	End mean score	Change	At week 6
		Amantadine	4.9 (SE 0.24)	4.4 (SE 0.29)	–0.5	$F = 3.40$ $p = 0.04$
		Placebo	4.7 (SE 0.14)	4.7 (SE 0.20)	+0.1	
			Baseline mean score	End mean score	Change	At week 6
	4. FSS[a]	Amantadine	5.6 (SE 0.17)	5.2 (SE 0.22)	–0.45	$F = 1.13$ $p = 0.33$
		Placebo	5.6 (SE 0.15)	5.4 (SE 0.20)	–0.22	NS
Crossover study						
Cohen & Fisher, 1989[34]	1. Daily Ratings Point Scale (1 poor to 5 excellent)[b]		Mean score during period			
		Amantadine	3.2 (SE 0.04)			0.22 $p = 0.58$
		Placebo	3.0 (SE 0.03)			NS

[a]*Lower values in the MS-FS and FSS measures indicate less fatigue*
[b]*Higher values in the Daily Ratings Point Scale indicate less fatigue*

SE, standard error

show small improvements favouring amantadine. One of these is statistically significant.

Impact on function

None of the measures considered so far give an estimate of the significance of the improvements either in clinical or quality-of-life terms. The Canadian MS Research Group Trial is the only study that offers any hint on this important aspect. They asked patients to rate the effect of the treatment on 13 activities of daily life, including walking, standing and housework. The results in *Table 11* show small improvements in favour of amantadine, particularly for physical functions. However, this falls far short of the information necessary to estimate, even crudely, the potential impact of amantadine on quality of life.

Side-effects

The number of patients reporting side-effects ranges from 20% to 60%. There are no great differences between rates in active treatment or placebo groups (*Table 12*). The Canadian MS Research Society trial[32] reports the only statistically significant increase, for an increase in insomnia with amantadine.

TABLE 11 *Systematic review of effectiveness of amantadine on fatigue in MS. Effects on 13 activities of daily living*

	Treatment	Baseline mean score	End mean score	Mean change	Test for differences in means
Crossover study					
Canadian MS Research Group, 1987[32]	Amantadine	27 (SE 1.13)	24 (SE 1.06)	–2.5	$p = 0.09$
	Placebo	26 (SE 0.74)	26 (SE 0.74)	–0.3	
Note: for physical component $p = 0.04$*; scores range from 0 "ability to do freely" to 50 "unable to do"; decreases in score represent improvement in function*					

TABLE 12 *Systematic review of effectiveness of amantadine on fatigue in MS. Side-effects*

Study	Measures	Amantadine	Placebo	Study period (weeks)	Nature of side-effects
Parallel study					
Krupp *et al.*, 1995[35]	No. of patients reporting side-effects	Unknown	Unknown	6	Sleep disturbance; palpitations
	No. of side-effects reported	5	3		
	No. of drop-outs or cessation of drug due to side-effects	2 (rash, anxiety)	1 (sleep disturbance)		
Crossover studies					
Canadian MS Research Group, 1987[32]	No. of patients reporting side-effects	66/115 (57%)	62/115 (54%)	3	Insomnia[a]; anxiety; headaches; nausea
	No. of side-effects reported	159	136		
	No. of drop-outs or cessation of drug due to side-effects	1? (acute confusional state)	0		
Rosenberg & Appenzeller, 1988[33]	No. of patients reporting side-effects	Unknown (at least 1)	Unknown	1	Nightmares; hyperactivity
	No. of side-effects reported	Unknown	Unknown		
	No. of drop-outs or cessation of drug due to side-effects	0	0		
Cohen & Fisher, 1989[34]	No. of patients reporting side-effects	4	4	4	Constipation
	No. of side-effects reported	Unknown	Unknown		
	No. of drop-outs or cessation of drug due to side-effects	At least 1 (nausea, anxiety)	Possibly 1 (constipation)		
[a]*Statistically significant difference* ($p < 0.05$)					

Summary of systematic review of amantadine

- Four studies were included. One was a parallel trial and three were crossover trials. We are confident that most of the relevant research has been identified.
- The volume of research identified is small.
- All studies are open to bias. There are uncertainties about randomisation and blinding of researchers when assessing outcomes.
- Particular problems were encountered assessing the validity of crossover trials, particularly in relation to the possible impact of period effects in the results.
- There are limitations in the fatigue-related outcomes employed. The clinical significance of small changes in many scales used is uncertain.
- There is lack of information on the impact of the interventions on the quality of life of people with MS. This is a fundamental drawback considering the subjective nature of fatigue.
- Based on reported results there is a consistent pattern in favour of amantadine compared with placebo. However, there is uncertainty. For the outcome of patient preference, where information is available from all included studies, re-calculating the results using less-optimistic assumptions considerably undermines the impression of benefit.
- There is little information to assess the size of the effects of amantadine, but these seem likely to be small.
- There is minimal information to allow any conclusions on the impact of the treatment on the quality of life of people with MS or their ability to function. Furthermore, for those individuals who seem to benefit from the treatment, there is no information on long-term benefits or side-effects.

Systematic review of pemoline

Quantity of research available

Three potentially rigorous evaluations had already been identified from the scoping review. One was excluded because it was duplicative. Details of this are provided in appendix 3. The additional searches revealed 43 hits, but no new trials.

Thus, two studies met the inclusion criteria for the systematic review on pemoline.[35,39]

Characteristics of included studies

Details of the included studies are shown in *Table 13.*

Study designs

One study[35] was a parallel RCT with a placebo control arm. This study, by virtue of having two treatment arms, was also included in the systematic review of amantadine. The other was a crossover trial.[39] A pictorial representation of the studies is shown *Figure 4.*

The periods of treatment were 6 weeks (parallel trial) and 4 weeks (crossover trial). One study[35] included a run-in period of 2 weeks, during which patients were monitored and assessed. The crossover trial included a washout period of 2 weeks.

Populations examined

All included studies used similar inclusion criteria: people with definite MS clinically ascertained according to reasonably well-established criteria, and complaining from moderate-to-severe fatigue usually for more than 3 months.

Exclusion criteria were practically identical. These were: medical conditions that cause fatigue, psychiatric disorders particularly depression, the use of medication that could influence fatigue, and disease relapses requiring treatment.

As in the case of amantadine, the population studied can therefore be regarded as fairly similar in all studies and representative of people with MS with a considerable degree of fatigue, likely to be greater than the average experienced by people with MS.

The total number of patients studied is small (n = 126).

Intervention and comparison

The intervention was pemoline administered in titrated (gradually increasing) doses to achieve a tolerable drug dose. This was compared with placebo. The minimum dose of pemoline was 18.75 mg/day; the maximum of 56.25 mg/day in one study and 75 mg/day in the other. The duration of the intervention was 6 weeks in the parallel trial and 4 weeks in the crossover trial.

Outcomes

As in the case of amantadine, a number of outcomes were considered in the two studies. The two studies both assessed fatigue. Many of the same issues discussed for amantadine arise for pemoline, see *Results of systematic review of amantadine (Outcomes),* above.

TABLE 13 *Systematic review of effectiveness of pemoline on fatigue in MS. Characteristics of included studies*

	Krupp et *al.*, 1995[35]	**Weinshenker et *al.*, 1992[39]**
Design	RCT parallel	RCT crossover
Inclusion criteria	Definite MS Baseline fatigue ≥ 4 on FSS after 2-week monitoring phase	Definite MS Fatigue for ≥ 3 months
Exclusion criteria	Psychiatric disorders; listed medical conditions; listed medications that might influence fatigue or disease course	Psychiatric disorders; listed medical conditions; listed medications that might influence fatigue or disease course
No. of patients randomised	80 37 pemoline 43 placebo	46
Intervention	Pemoline 18.75–56.25 mg/day for 6 weeks	Pemoline 18.75–75 mg/day for 4 weeks
Comparator	Placebo	Placebo
Outcomes assessed: Fatigue-specific; patient-assessed	At end of week 8: 1. Verbal self-report of fatigue: same, better or worse (preferred treatment while still taking medication) At end of week 10: 2. Verbal self-report of fatigue: same, better or worse (preferred treatment 2 weeks after discontinuing medication)	Daily: 1. Recording of fatigue change in a 50 mm VAS at a specified time of day compared with baseline Weekly: 2. Recording of improvement compared with previous week (preferred treatment) At end of week 4, 10: 3. Overall rating of fatigue relief: poor, fair, good, excellent
Outcomes asessed: Fatigue-specific; researcher-assessed	At end of week 8, 10: 3. MS-FS 4. FSS 5. RIV (measures energy)	
Side-effects	Recorded	Recorded
Other outcomes assessed:	At weeks 0, 2, 5, 8, 10: CES-D (depression); St Mary's Hospital Sleep Questionnaire; Neurologic examination and EDSS	Modified Beck self-rating depression scales

Fatigue
The parallel study[35] used validated instruments, FSS and MS-FS to measure fatigue (see appendix 1). The crossover study[39] used VAS, asking patients to record changes (improvement or deterioration) in fatigue against baseline.

Clinical significance of fatigue
None of the studies included any measure of impact on ability to function or quality of life. They provide no information that might allow the review to draw conclusions on overall effectiveness in pemoline.

Patient preference
Both studies included some information on the treatment most preferred.

Side-effects
Side-effects were recorded in both studies.

Other outcomes
Again a variety of other outcomes (neurobiological measures, cognitive tests and psychological tests) were also measured, often as secondary outcomes or for the purpose of baseline assessment. The results of these were considered to contribute

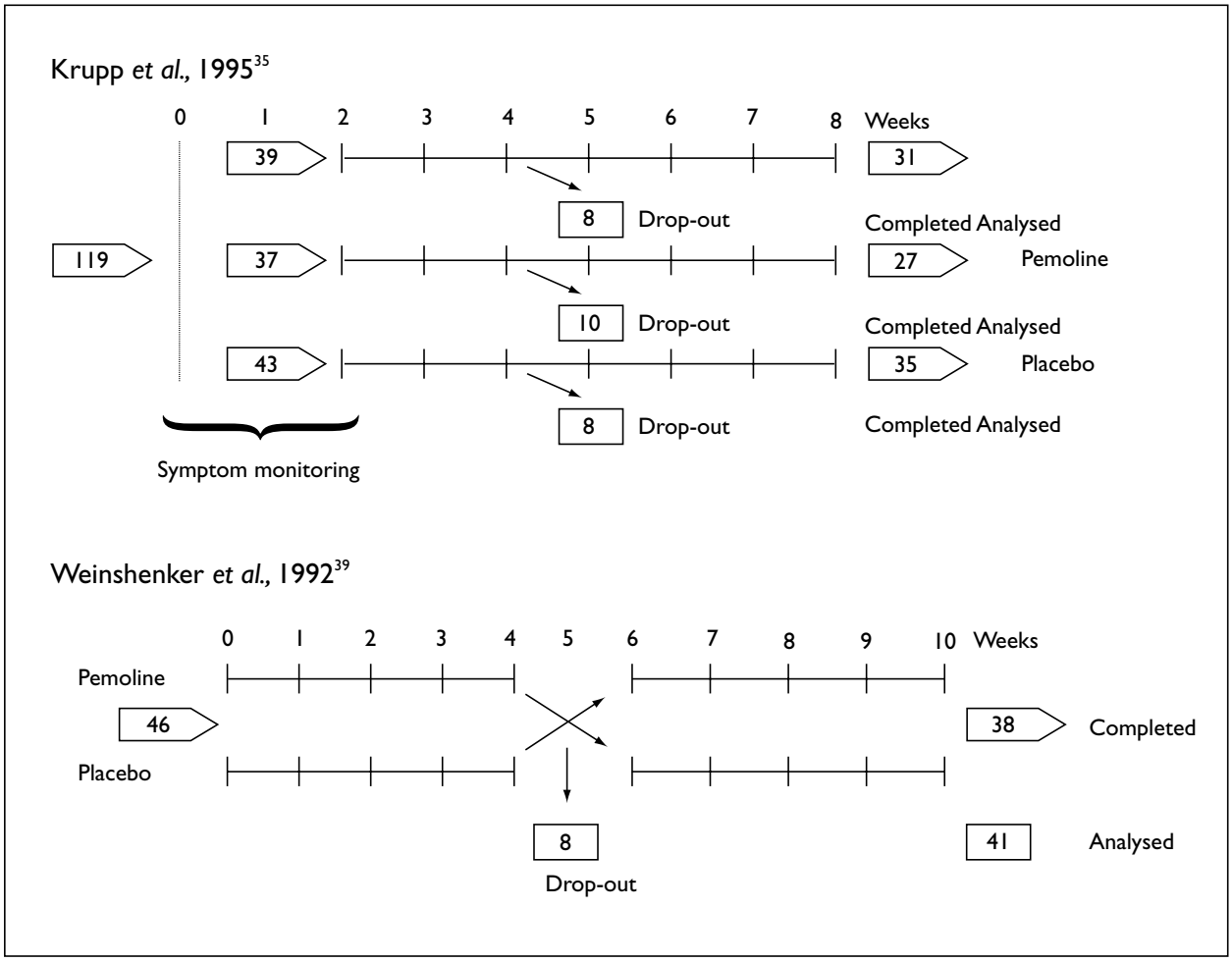


FIGURE 4 *Trial designs for pemoline*

little beyond the outcomes listed above, and are not presented further in this report.

Validity of included studies

Details of validity are presented in *Table 14* with additional information on loss to follow-up in *Table 15* (reference to *Figure 4,* may also be helpful in understanding the threats to validity discussed).

Similar issues regarding study validity apply as for amantadine (see *Results of systematic review of amantadine,* (*Validity of included studies*) above).

The parallel trial[35] included was already discussed in the section on amantadine and the same threats to validity apply, namely lack of clarity concerning randomisation method, uncertainty about whether the assessment of outcome was blind, and loss to follow-up.

As regards difficulty of interpretation of the single crossover trial of pemoline[39] this study does make a specific statement indicating that there was no sequence effect and no interaction between treatment and sequence. Unfortunately, this improvement in validity is offset by the analysis not being restricted to pairs who had completed both periods. This, together with uncertainty about method of randomisation, blindness of assessment of outcome and loss to follow-up, suggest that as with the crossover trials identified in the amantadine review, great caution is also required in interpreting this crossover trial.

Summary of direction of effect of all fatigue-related outcomes

The overall picture, shown in *Table 16,* is not clear for pemoline. Three out of seven reported outcomes have results favouring placebo, and these three negative results come from the study[35] with the design that produced less uncertainty concerning interpretation. None of the results is statistically significant.

TABLE 14 *Systematic review of effectiveness of pemoline on fatigue in MS. Study quality*

	Krupp *et al.*, 1995[35]	**Weinshenker *et al.*, 1992[39]**
Design	Parallel	Crossover
No. of people randomised	37 pemoline 43 placebo	46
Randomisation		
Was the trial described as 'randomised'?	Yes	Yes
Was the method of randomisation not stated or unclear?	Unclear	Unclear
Was there concealment of treatment allocation?	Unclear	Unclear
Double blinding		
Was the trial described as 'double-blind'?	Yes	Yes
Was the treatment allocation masked from the participants?	Yes	Yes
Was the treatment allocation masked from the investigators?	Yes	Unclear
Was the treatment allocation masked at the outcome assessments?	Unclear	Unclear
Withdrawals and drop-outs[a]		
Was the number of withdrawals in each group stated?	Yes	Yes
Jadad score[b]	3	3
Aspects specific to crossover trials		
Were systematic period effects or carryover discussed and/or identified?	N/A	Yes
Washout period?		2 weeks
Was the number of patients in sequences PT and TP clearly stated?		No
Were people who did not complete any of the periods excluded from the analysis?		No

[a] *More detailed information in* Table 15
[b] *The Jadad score was not designed to assess quality of crossover trials and so may not accurately represent their quality*

TABLE 15 *Systematic review of effectiveness of pemoline on fatigue in MS. Exclusion and drop-outs*

	No. enrolled	**No. randomised**	**No. completing trial**	**No. analysed**	**No. of drop-outs**	**No. drop-outs/ no. randomised**
Parallel study						
Krupp *et al.*, 1995[35]	80	37 treatment	27	27	10	
		43 placebo	35	35	8	
		80 both arms	62	62	18	23%
Crossover study						
Weinshenker *et al.*, 1992[39]		46	38	41	8	17%

Preferred treatment

When responses as to which is the preferred treatment are considered (*Table 17*) the parallel trial[35] gives a negative result. Consistently more participants favoured placebo than pemoline. The result of the other trial is positive, though the difference with placebo is very small and it does not achieve statistical significance.

Fatigue-specific outcomes

The study by Weinshenker and co-workers[39] uses VAS for patients to record changes in their level of fatigue compared with baseline. It shows a small

TABLE 16 *Systematic review of effectiveness of pemoline on fatigue in MS. Direction of effects on all fatigue-related outcomes*

Study	Outcome measured	Direction of effect	Statistical significance ($p < 0.05$)
Parallel study			
Krupp *et al.*, 1995[35]	1. Preferred treatment at the end of trial	Favours placebo	No
	2. Preferred treatment 2 weeks after end of trial	Favours placebo	No
	3. MS-FS	Favours placebo	No
	4. FSS	Favours pemoline	No
	5. RIV	Raw data not provided	No
Crossover study			
Weinshenker *et al.*, 1992[39]	1. Effects on fatigue VAS	Favours pemoline	No
	2. Preferred treatment	Favours pemoline	No
	3. Overall rating of fatigue relief	Favours pemoline	No

TABLE 17 *Systematic review of effectiveness of pemoline on fatigue in MS. Preferred treatment*

Study	Treatment	Preference (%)	RR (95% CI) (pemoline vs placebo)	RR (95% CI) (pemoline vs any other preference)	Notes
Parallel study					
Krupp *et al.*, 1995[35]	Pemoline[b]	7/22 (32)	0.6 (0.3 to 1.3)	Same	At end of trial
	Placebo	13/25 (52)			
(as reported[a])	Pemoline[b]	10/23 (43)	0.7 (0.4 to 1.3)	Same	2 weeks after end of trial
	Placebo	14/24 (58)			
Krupp *et al.*, 1995[35]	Pemoline[b]	7/37 (19)	0.6 (0.3 to 1.4)	Same	At end of trial
	Placebo	13/43 (30)			
(ITT analysis)	Pemoline[b]	10/37 (27)	0.8 (0.4 to 1.6)	Same	2 weeks after end of trial
	Placebo	14/43 (33)			
Crossover study					
Weinshenker *et al.*, 1992[39]	Pemoline	21/41 (51)	1.1 (0.7 to 1.7)	1.0 (0.7 to 1.6)	
	Placebo	19/41 (46)			
	None	1/41 (2)			

[a] *Although not stated in study, we assumed that people expressing no preference were excluded from numerator and denominator*
[b] *Numbers wanting to carry on with pemoline or placebo*

TABLE 18 *Systematic review of effectiveness of pemoline on fatigue in MS. Level of fatigue as measured with VAS*

	Fatigue measure[a]	Group	Baseline mean VAS score (mm)	End mean VAS score (mm)	Change (mm)	Notes
Crossover						
Weinshenker *et al.*, 1992[39]	1. Record of change in fatigue	Pemoline	N/A	N/A	+6.7	NS ($p > 0.05$)
		Placebo	N/A	N/A	–0.1	

[a] *On the scale used 0 mm represents "fatigue worsened as much as possible" and 50 mm represents "fatigue was completely relieved"; increases in scores hence represent improved fatigue*

improvement for patients on pemoline compared with both baseline and placebo (*Table 18*). The difference between pemoline and placebo is not statistically significant.

The study by Krupp and co-workers,[35] which uses FSS and MS-FS, shows either a negative effect for the latter and a tiny positive effect for the former. Both are statistically non-significant (*Table 19*).

TABLE 19 *Systematic review of effectiveness of pemoline on fatigue in MS. Level of fatigue as measured with point scales and questionnaires*

	Fatigue measure	Group	Scores		Change	Difference
Parallel study						
Krupp *et al.*, 1995[35]	3. MS-FS[a]		Baseline mean VAS score:	End mean VAS score:	Change	Difference in treatment vs placebo at week 6
		Pemoline	4.7 (SE 0.20)	4.7 (SE 0.18)	–0.03	$F < 1.0$ $p = 0.394$
		Placebo	4.7 (SE 0.14)	4.7 (SE 0.20)	–0.06	
Krupp *et al.*, 1995[35]	4. FSS[a]		Baseline mean VAS score:	End mean VAS score:	Change	Difference in treatment vs placebo at week 6
		Pemoline	5.7 (SE 0.18)	5.4 (SE 0.27)	+0.3	$F < 1.0$ $p = 0.845$
		Placebo	5.6 (SE 0.15)	5.4 (SE 0.20)	+0.2	
Crossover study						
Weinshenker *et al.*, 1992[39]	3. Overall rating of relief		Excellent or good:			
		Pemoline	19/41 (46%)			
		Placebo	8/41 (20%)			
		Both	0/41 (0%)			
		None	14/41 (34%)			

[a]*Lower values in the MS-FS and FSS indicate less fatigue*

When compared in terms of overall rating of relief, the study by Weinshenker and co-workers reports an advantage for pemoline compared with placebo (*Table 19*).

Impact on function

None of the studies on pemoline provide any information to assess the possible impact of the treatment on patient quality of life.

Side-effects

The two studies report a considerable number of side-effects with pemoline, which despite incomplete recording, are clearly greater than placebo (*Table 20*).

The study by Weinshenker and co-workers[39] reports that 13 out of the 46 randomised patients elected to continue with pemoline after the trial. Of these, three discontinued within 3 months, another three after 1 year. Of the remaining seven who continued using the drug, three used it intermittently and four regularly. This is the only piece of information on longer-term use, but it indicates that only a very small proportion of people with MS are likely to benefit from the drug in the long term.

Summary of systematic review of pemoline

- Two studies were included. One was a parallel trial and the other a crossover trial. We are confident that most of the relevant research has been identified.
- The volume of research identified is small.
- Both studies are open to bias. There are uncertainties about randomisation and blinding of researchers when assessing outcomes.
- Particular problems were encountered assessing the validity of the crossover trial, particularly inclusion in the analysis of people who did not complete both treatment periods.
- There is an absolute lack of information on the impact of the intervention on the quality of life of patients. This is a fundamental drawback considering the subjective nature of fatigue.
- Even for the reported results there is no clear overall tendency in favour of pemoline or placebo.
- If there is any effect, the size of it is probably small.
- There is no information to allow any conclusions on the impact of the treatment on the quality of life of people with MS or on their ability to function.

Economic analysis of amantadine and pemoline for fatigue in MS

Costs

The drug costs for amantadine were obtained from the *British National Formulary*[56] as £15.35 for 56 × 100 mg tablets. Thus, for a dose of 100 mg twice

TABLE 20 *Systematic review of effectiveness of pemoline on fatigue in MS. Side-effects*

Study	Measures	Pemoline	Placebo	Study period (weeks)	Nature of side-effects
Parallel					
Krupp *et al.*, 1995[35]	No. of patients reporting side-effects	Unknown	Unknown	6	Sleep disturbance; nausea; mood change; palpitations
	No. of side-effects reported	6	3		
	No of drop-outs or cessation of drug due to side-effects	2 (irritability, anxiety)	Unknown		
Crossover					
Weinshenker *et al.*, 1992[39]	No. of patients reporting side-effects	> 25%	Unknown	4	Irritability; insomnia; nausea; anorexia
	No. of side-effects reported	Unknown (at least 57)	Unknown		
	No of drop-outs or cessation of drug due to side-effects	3	Unknown		

daily, this is equivalent to £3.84 per week, or approximately £200 per year.

Pemoline is no longer available in the UK. However, in 1995, the cost was £1.38 for 25 × 20 mg tablets,[57] which amounted to £1.55 per week, or approximately £80 per year, if taken at the maximum dose of four per day.

No further information on costs was identified either in the primary studies assessing the effects and effectiveness of amantadine and pemoline or the literature identified in the course of the additional search for prior health economic assessments. In particular, there was an absence of information on the following:

- costs associated with administration
- costs potentially averted through increased ability of people with MS with fatigue to carry out daily activities themselves.

Prior health economic assessments

Despite an extremely broad search no health economic assessments of interventions affecting fatigue, particularly cost-effectiveness and cost–utility analyses, were identified. The absence of information on the impact of interventions to relieve fatigue on quality of life was also confirmed.

Information for modelling of cost–utility

The search did identify a limited amount of information. This is presented in relation to each of the four specific questions posed.

What is the generic estimate of quality of life of people with MS?

Table 21 presents details of seven studies that measured quality of life in people with MS.[58–64] All were cross-sectional surveys in people with MS in the USA, Canada or Europe. Five studies[58–62] had a comparator population (either general population or other chronic diseases). Two studies used the SF-36,[58,60] and the remainder used a variety of scales.

The most comprehensive study was the Canadian Burden of Illness Study, reported in 1998,[58] which consecutively recruited 208 adult people with clinically or laboratory-supported definite MS from 14 MS clinics in Canada. Ten were excluded because they were taking beta-interferon. Recruitment was stratified by disease severity as measured by the EDSS score. Each person with MS was requested to complete the SF-36 to describe their health over the previous 4 weeks. The SF-36 scores were compared with scores for a normal American population of similar age. As EDSS score increased, physical function, role-physical and social function showed a statistically significant decrease in quality of life. The vitality score (indicative of energy and fatigue) also showed a decreasing trend, though this was not statistically significant ($p = 0.07$). Compared with the general population, all of the eight domain scores were significantly lower in each group of people with MS. This was more marked in the most severely disabled group but was still on average 30% lower in the mild MS group than the general population.

TABLE 21 Economic analysis of treatments for fatigue in MS: MS quality-of-life studies

Study	Population	Design	Measure of QoL	Description of measure	Comparator population	EDSS scores	Mean QoL scores	Difference from comparator
Canadian Burden of Illness Study Group, 1998[58]	People with MS Canada *n* = 198	Cross-sectional	SF-36	Eight domains: physical function; role-physical; bodily pain; general health; vitality; social function; role-emotional; mental health Scores transformed to a 0–100 scale; also a summary component score in two clusters: physical and mental component summaries	General population	Mild ≤ 2.5 (*n* = 62) Moderate 3.0–6.0 (*n* = 68) Severe ≥ 6.5 (*n* = 68)	Physical / Mental 39.6 / 44.1 32.6 / 45.8 26.5 / 47.3	People with mild MS on average 30% lower than general population QoL decreases with severity
Murphy *et al.*, 1998[62]	People with MS (clinically defined or laboratory-supported) France, Germany, UK *n* = 270	Cross-sectional	FSQ	Self-completed questionnaire; 34 items describing physical (e.g. acitivities of daily living), psychological and social function (e.g. work, interaction, social activity)	People consulting with general practitioner for other reasons; matched by age and sex to people with MS	For UK only: Stage I: 1.0–3.5 (*n* = 30) Stage II: 4.0–6.0 (*n* = 29) Stage III: 6.5–8.0 (*n* = 29)	Physical function significantly decreased with increased severity Social and psychological function did not vary significantly	MS / Control Physical 44.3 / 82.3 Psychological 60.9 / 74.5 Social 65.4 / 78.0 General well-being item (medians) Stage I: 50 Stage II: 25 Stage III: 25 } *p* = 0.01 MS: 25 *p* = 0.0001 Control: 50

QoL, quality of life; FSQ, Functional Status Questionnaire

continued

TABLE 21 contd Economic analysis of treatments for fatigue in MS: MS quality-of-life studies

Study	Population	Design	Measure of QoL	Description of measure	Comparator population	EDSS scores	Mean QoL scores	Difference from comparator
Aronsen, 1997[59]	People with MS and caregivers Canada *n* = 697	Cross-sectional	QoL questions from GSS	Individuals to rate on a five-point scale from very satisfied to very dissatisfied (1–4) plus no opinion (5) for six components of health, job or major activity, housing, finances, family and friendships, QoL as a whole These were generally dichotomised into "very satisfied" vs all other categories; also several other items	Canadian general population able-bodied and disabled in 1985	NS	% very satisfied with: MS / Able-bodied Health 13 / 49 Job 24 / 43 Finances 23 / 34 Housing 57 / 51 Family relations 66 / 68 Friendships 61 / 67 Life as a whole 28 / 51 Also compared with the general disabled population, significantly fewer ($p < 0.05$) people with MS were "very satisfied" with health, job or major activity, or life as a whole	
Granger *et al.*, 1990[63]	People with MS USA *n* = 24	Cross-sectional	General life satisfaction	1. I am very well satisfied 2. I am fairly well satisfied 3. I am more satisfied than not 4. I am not satisfied	None	NS	Very satisfied: *n* = 5 Fairly well satisfied: *n* = 8 More satisfied than not: *n* = 5 Not satisfied: *n* = 6	N/A
Provinciali *et al.*, 1999[64]	People with MS (definite) Italy *n* = 83	Cross-sectional	FAMS	No details	None	< 3.5: *n* = 43 3.5–6.0: *n* = 19 > 6.0: *n* = 21	72.1 (SD 36.9) 110 (SD 37.7) 111 (SD 28.7) QoL significantly decreased after EDSS = 3.5, but no further decline	N/A

QoL, quality of life; GSS, General Social Survey; FAMS, Functional Assessment of MS; SD, standard deviation

continued

TABLE 21 contd Economic analysis of treatments for fatigue in MS: MS quality-of-life studies

Study	Population	Design	Measure of QoL	Description of measure	Comparator population	EDSS scores	Mean QoL scores	Difference from comparator
Rudick *et al.*, 1992[61]	People with MS USA *n* = 68	Cross-sectional	Farmer QoL index	41 questions grouped into four clusters: 1. Functional and economic 2. Social and recreational 3. Affect and life in general 4. Medical problems Response rated on five-point scale (1 = worst, 5 = best) and summed by subscale and overall	People with inflammatory bowel disease (IBD, *n* = 164) and rheumatoid arthritis (RA, *n* = 75)	NS	Median scores: MS / IBD / RA Functional & economic: 29 / 52 / 35 Social & recreational: 45 / 61 / 51 Affect & life in general: 37.5 / 46 / 39 Medical problems: 7 / 10 / 7 QoL total score: 119.5 / 168 / 130 MS is significantly worse than IBD for all subscales ($p < 0.0001$); MS is only significantly different from RA for functional & economic score ($p = 0.03$) The correlation between EDSS and QoL total score was significant (–0.28; $p = 0.02$)	
Komaroff *et al.*, 1996[60]	People with relapsing remitting MS USA (Brigham & Women's Hospital) *n* = 25	Cross-sectional	SF-36	Eight scales; outcome presented as a pattern of the eight different scales	People with chronic fatigue (*n* = 223), general population (*n* = 2474), hypertension (*n* = 2089), acute myocardial infarction (*n* = 107), depression (*n* = 502)	NS	MS / General population Physical: 53.2 / 84.2 Role-physical: 33.0 / 81.0 Pain: 70.9 / 75.2 General health: 44.8 / 72.0 Vitality: 27.0 / 60.9 Social: 60.5 / 83.3 Role-emotional: 66.6 / 81.3 Mental health: 66.9 / 74.7	

QoL, quality of life

This general result of marked reduction in quality of life in MS is confirmed by other studies.[60,62]

What proportion of the reduction in quality of life is due to symptomatic fatigue?

Two potentially useful studies were found.[59,65]

A large cross-sectional survey (n = 697)[59] involved sending questionnaires about quality of life, taken from the General Social Survey, to people with MS. Individuals were asked to rate (on a five-point scale: very satisfied to very dissatisfied or no opinion) six components of health, job or major activity, housing, finances, family and friendships, and quality of life overall (*Table 21*). Fatigue and walking problems were the most prevalent and distressing symptoms. Experiencing fatigue (88% of sample) was associated with decreased overall quality of life, with the relative risk of being "less than very satisfied with quality of life" for fatigued people with MS of 1.82 (95% CI, 1.18 to 2.83) relative to non-fatigued people.

Another survey of 168 people with MS in northern California[65] reported that of the 58% who were totally or partially disabled, 65% attributed their disability in part or in whole to fatigue.

From these results, it is clear that quality of life in MS with any given degree of severity is worse in those who suffer fatigue. The degree to which reduced quality of life is attributable to fatigue as opposed to other symptoms is not, however, quantified.

What are the costs of MS?

Ten studies were located that gave potentially useful information about the costs of MS. Four were based on the situation in the USA[66–69] two in Canada[70,71] two in the UK[72,73] and two in other parts of Europe.[74,75] All were cost-of-illness studies and the majority took the societal perspective, though costs to individuals and to the medical services were also given in the breakdown of the analyses. The general points were that:

- costs increased with increasing disability[66–68,71,72,74]
- in all severity groups, the majority of the financial burden is borne by people with MS[66,69,71,72]
- the major societal costs were indirect (such as lost daily activity/leisure time/productivity)[69,71]
- less than 5% of the costs to the NHS were from general practitioners' prescriptions.[73]

Two studies provide information on costs of MS in the UK setting.[72,73]

The first study[72] is a prevalence-based cost-of-illness study, which used a sample survey of 672 members of the MS society, combined with literature research into unit costs. The study covered the UK and sampled people with MS by:

- the branch officer passing a questionnaire to an equal number of people with MS with each of three severities of MS (A = walking unaided for an unlimited distance; B = walking unaided for a limited distance; C = needing a wheelchair most of the time) (total n = 192)
- random allocation of the remaining 807 within each regional health authority.

The questionnaire supplied information on private costs and units of care (e.g. number of hospital inpatient and outpatient visits). Both direct costs (actual expenditure) and indirect costs (opportunity costs) were calculated and presented under three broad headings:

- the burden on the State
- the burden on the individual, and
- the burden on industry.

The total burden was calculated by assuming an MS population of 87,873 in the UK. The burden on the State included NHS costs, Department of Social Security benefits and lost tax revenue. The burden on the individual included private expenses and lost earnings. The burden on industry included absenteeism, health insurers' costs, charities and research.

The costs to carers included time off from their employment, but not time spent caring out of work hours. The cost to individuals did not include wider quality-of-life issues or lost leisure time.

Average annual costs to the State ranged from £2106 per person with MS for the mildest MS group to £11,901 for the most severely affected (1994 prices). For the individual, this was £2643 to £10,756 per year. Assuming the three mobility levels are equally distributed in the UK population, this amounted to:

- state benefits of £287 million per annum
- NHS costs of £153 million per annum
- lost tax revenue of £148 million per annum
- a total burden to the State of £588 million.

The annual burden on the individual was almost as large as the State at £395 million, and the burden on industry was lower at £76 million.

The second study,[73] attempted to produce a general model with which to estimate the overall costs of MS in the UK in the late 1990s. This model included social security provision, social services/health authority provision, private expenditure, lost earnings and medical costs. The published literature was used to estimate the number of people with MS, the proportion unemployed, the average wage in the UK and age and sex ratios of people with MS. Medical costs were estimated using data from a commercial medical statistics organisation, Hospital In-patient Enquiry, and other published literature on hospital use by people with MS. Private care costs were estimated from general information about the costs of disablement from the Disablement Income Group. The loss of earnings by voluntary carers was not estimated.

The annual costs for England and Wales were estimated at £48 million (1993/94 prices) to the NHS, to the individual at £263 million, social security at £118 million and social services/health authority provision at £124 million. These costs were substantially lower than the first study reported above. The two studies differed in that Blumhardt's study was based on estimated figures from the literature, rather than an actual survey. Lost revenue due to taxes, burden on industry and loss of earnings by carers were also not included.

What proportion of these costs are due to fatigue?

Unfortunately no information on this key question was identified.

Conclusions from information for modelling of cost–utility

It is possible to estimate the reduced quality of life in people with MS, with indications that they have at least a 30% lower quality of life than the normal population. Information was also available on the costs of MS. The best study estimates this at £153 million to the NHS and £395 million per annum to the individual.[72] There is some uncertainty about the accuracy of these estimates, but it is clear that the burden is substantial and that a large proportion of the costs of MS falls on the individual.

Unfortunately for the purposes of this report, information on the proportion of the costs or quality-of-life reduction that is attributable to the fatigue component of MS is wholly absent. It would thus seem highly speculative to attempt to estimate it without further primary research, which is outside the remit of this report. This, in turn, dictated that even the most crude modelling of health economic impact of treating fatigue in MS would be inappropriate, further reinforced by the uncertainty revealed in the preceding sections about the likely effectiveness of amantadine and pemoline.

It does seem that any treatment that could reduce or eliminate the fatigue of MS would have substantial impact on quality of life, given that 80–90% of people with MS suffer from fatigue.[3] Further, if the interventions were of similar cost to amantadine (and pemoline, if licensed,) and costs of administration were minimal, it seems likely that such interventions would be cost-neutral. Although the NHS bears only a small proportion of the total burden of cost for MS, such is the size of this burden, that any savings in hospital and other treatment services may well outweigh the extra drug costs. Undoubtedly however, the bulk of the benefit arising from an effective treatment for fatigue in MS would be to the individuals themselves, who might be able to remain in full-time paid employment for longer.

Summary of health economic impact

- Drug costs for amantadine and pemoline are approximately £200 and £80 per year, respectively.
- Direct information on the costs associated with administration and costs averted are wholly absent.
- There are no previous assessments of health economic impact.
- Cost analyses for MS, including two in the UK setting, show that the burden of MS is very high.
- A large proportion of the cost is borne by the individual.
- Quality of life in people with MS with mild disability is on average 30% worse than the normal population. More severe disease is associated with worse quality of life.

- It is not possible to indicate what proportion of lost quality of life is attributable to fatigue, though it is clear that fatigued people with MS have a worse quality of life than non-fatigued people with MS.
- There is no information on the proportion of costs attributable to fatigue.
- Modelling of the potential health economic impact of treating fatigue was not possible.
- However, simple logic suggests there is potential for even a partially effective treatment for fatigue in MS, of cost similar to amantadine or pemoline, to be cost-neutral.

Chapter 4

Discussion

Importance of fatigue in MS

- MS has a prevalence of approximately 100 per 100,000. This suggests that the total number of people with MS in the UK is approximately 60,000. Estimates as high as 85,000 have been produced.
- The total burden of costs associated with the condition is high. In the UK NHS costs may be as high as £153 million per annum. The burden to individuals is higher, estimated at £395 million per annum.
- There is no cure for MS.
- Most of the management of the condition consists of minimising the disability arising from the disease and helping people deal with the consequences of residual disability.
- The quality of life of people with MS is substantially reduced relative to the normal population.
- Fatigue in MS is consistently reported as a symptom that gives rise to impairment of function. Approximately two-thirds of people with MS indicate that it is one of the worst symptoms. Thus, 40,000 or possibly even 57,000 people with MS may have the condition of interest.
- Furthermore, it is clear that fatigue, independently of severity of disease, contributes to reduction in quality of life. Unfortunately the amount cannot be quantified.
- The fatigue in MS is quantitatively and qualitatively different from that which the normal population might experience day-to-day.

Effects and effectiveness of treatments to alleviate fatigue in MS

General

- Many treatments have been suggested to be of value for the alleviation of fatigue in MS, for example behavioural advice, drugs, training and rehabilitation, devices (cooling vests and EMFs) and alternative medications (bee venom, cannabis/cannabinoids, acupuncture/acupressure and yoga).
- Given the importance of the condition, the number of rigorous evaluations of effects and effectiveness identified covering all these interventions is very small – 13 studies.
- A major gap is an almost total absence of evidence on the effectiveness of behavioural advice, the mainstay of initial clinical management.
- Only two drugs, amantadine and pemoline, have been subject to repeated rigorous evaluation. The research findings on these two agents were systematically reviewed in this report. This should not imply that these two agents are necessarily those likely to have the greatest potential to alleviate fatigue.

Amantadine

- For amantadine four studies were identified. One was a parallel trial and three were crossover trials.
- Based on the reported results from these, there is consistent evidence of a beneficial effect of amantadine on fatigue, but with the following important provisos.
- The validity of all studies is eroded by uncertainties about randomisation and blinding of researchers when assessing outcomes.
- The validity of the three crossover trials is difficult to determine given the inherent problems of interpretation with this trial design, and is probably compromised based on our assessment of how the possibility of a period effect had been accounted for or not.
- For patient preference, the only outcome on which data were available for all the included studies, the pattern favouring amantadine is highly dependent on whether ITT analysis was used in the parallel trial and whether no preference or preference for washout periods was counted as an indication against the use of amantadine in the crossover trials.
- Even if the direction of effect in favour of amantadine is accepted, the size of this effect is difficult to quantify and is probably small.
- Furthermore, the clinical significance of any effect and the likely impact on a person's ability to function and their quality of life is highly uncertain.

Pemoline

- For pemoline, two studies were identified. One was a parallel trial and the other a crossover trial.
- Even for the reported results the direction of effects did not consistently favour either pemoline or placebo.
- Most of the provisos mentioned as far as interpretation of the results of the studies on amantadine are concerned, also applied to the two studies on pemoline.

Health economic impact (for amantadine and pemoline)

- The drug costs for an individual taking amantadine or pemoline are small, £200 and £80 per year, respectively.
- Direct information on the costs associated with administration and costs averted are wholly absent.
- There are no prior assessments of health economic impact.
- Although there is information on the reduction in quality of life associated with MS, there is no information on what proportion of this might be avoided if a completely effective treatment for fatigue were available.
- Although there is information on the costs associated with MS, there is no information on what proportion of these costs might be attributable to fatigue.
- The two points above, coupled with the high degree of uncertainty about the effectiveness of amantadine and pemoline, meant that it was not plausible to attempt any economic modelling.
- In consequence any assertions about cost-effectiveness or cost–utility are highly speculative.
- However, simple logic suggests there is potential for even a partially effective treatment for fatigue in MS, of a cost similar to amantadine and pemoline, to be cost-neutral.

Methodological strengths and weaknesses of the review

The overwhelming limitation of this report is the small volume and imperfect quality of the research identified.

Beyond this, the review methods used will have minimised any bias in the reviewing process. In particular, we are confident that most of the relevant rigorous research has been identified. The limited number of studies identified precludes an investigation of the potential for publication bias. We would also highlight the technical difficulties encountered in assessing the validity of crossover trials and the difficulties encountered in quantitatively synthesising the results of the trials identified. Time to contact authors of the included studies may have resolved some of the uncertainties.

Implications

People with MS and their carers

In contrast to the plethora of treatments that have been suggested to be of value, only amantadine appears to have some proven ability to alleviate the fatigue in MS. Even for this drug, however, there is considerable room for doubt. Certainly only a proportion of those taking amantadine will obtain benefit, and in only a proportion of these will the benefit be sufficient to take the drug in the long term. This review has highlighted the difficulties of measuring the impact of any new treatment on fatigue, which suggests that it is important for new treatments in this area to be rigorously evaluated. Claims for the effectiveness of treatment based on isolated case reports should be treated with extreme caution.

NHS

It is clear that fatigue is a serious symptom with the **potential** to be alleviated in a cost-neutral manner.

Amantadine may be beneficial in some people. However, there is insufficient evidence to conclude that the benefits of offering amantadine routinely to all people with MS with fatigue would be efficient. Consequently the NHS has a responsibility to ensure that appropriate research is undertaken in this area. Clinicians should be encouraged to treat people in the context of a trial. An alternative that might still generate useful research information outside formal trials would be use of *n*-of-1 studies.[76,77]

Implications for future research

For such an important symptom, which is responsible for a substantial burden of morbidity associated with MS, the deficiencies in the evidence-base available are staggering.

- Many treatments offered have no rigorous research evidence underpinning them. Rigorous research is required on these interventions.

- The research designs predominantly used to assess the effectiveness of amantadine and pemoline are highly difficult to interpret. Some of the observed difficulties of crossover trials can be overcome, but there seems to be an increasing consensus that crossover designs have little methodological advantage over parallel trials. We would suggest the preferred designs for any future research are RCTs with parallel control groups.
- The outcome measures used in the existing research are also problematic. A major difficulty is interpreting whether the fatigue measures used adequately represent the impact on a person's ability to function and the global impact on quality of life. New trials should incorporate measures to assess the wider impact on the individual, as well as specific measures of fatigue. Trials should have the statistical power to detect change in the measures of wider impact, as this is the key outcome.
- The poverty of information on costs and hence health economic impact is also important. If trials are to be conducted, the costs should be collected in parallel. From these, cost-effectiveness or cost–utility can then be measured directly, or modelled.
- Ideally, in order to help prioritise the research, we would like to be able to suggest which of the available treatments is most likely to prove beneficial. Such is the poverty of the available rigorous research evidence that it has not been possible. As an alternative, the only practical approach may be to rely on anecdote systematically collected from people with MS and clinicians. Research on effectiveness should not be restricted to the two drugs, amantadine and pemoline, 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. Arguably there may be sufficient evidence of ineffectiveness to exclude pemoline from further investigation. A key outcome from reviewing the research on these agents has been to highlight general problems to be avoided in assessing the impact of any treatment on fatigue in MS.

Conclusions

- Fatigue in MS is an important symptom for people with MS, carers, the NHS and society as a whole.
- Unfortunately, there is insufficient available evidence to allow people with MS, clinicians or policy makers to make informed decisions on the appropriate use of the many treatments on offer.
- 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. In the interim, people with MS, clinicians and policy makers should work together to ensure that the new evidence required is collected as quickly as possible by encouraging involvement in rigorous research.
- This 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.
- Because the conclusions reached will only be amplified when further research is conducted and we can identify no ongoing research directly addressing the relief of fatigue in MS, we suggest an expiry date for this report as 1 January 2005.

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Appendix 1

Outcome measures and rating scales

Rating scales for fatigue

A number of instruments have being designed to measure fatigue. There are several ways of addressing the problem of giving numerical values to such measures.

One method is to use VAS. Basically VAS consists of a line that represents the spectrum of possible values. Subjects are asked to mark a point in the line that best represents their position in that range of values. The numerical value is then calculated by measuring the distance of the point from the beginning of the scale.

Alternatively ordinal-numerical scales use a range of numbers (e.g. 1 to 10) and ask subjects to give scores based on that range.

A third method is the use of Likert scales. In this case the possible spectrum of values is divided into categories (e.g. poor, fair, good, very good, excellent). Numerical values can then be expressed in terms of the percentage of subjects choosing each category or by giving numerical values to each category.

The use of all of these methods is subject to specific methodological problems and requirements.

FSS

The FFS[78] is a list of nine statements designed to assess perceived fatigue. Each statement is rated on a scale of 1 (strong disagreement) to 7 (strong agreement). The individual score is the mean of the numerical responses to the nine statements.

MS-FS

This was developed by Schwartz and co-workers.[25] It is a 29-item fatigue severity instrument, which includes four different fatigue subscales. Each statement is rated on a scale of 1 (completely disagree) to 7 (completely agree).

Fatigue Assessment Instrument

This appears to be identical to the MS-FS (see above).

Fatigue Impact Scale

This was developed by Fisk and co-workers[22] to evaluate the effects of fatigue on quality of life. It asks subjects to rate perceived influence of fatigue on cognitive, physical, and social dimensions using a five-point scale from 0 (no problem) to 4 (extreme problem).

Fatigue Rating Scale

This was developed by Chalder.[79] It is a 14-item self-report questionnaire. It contains two subscales, one measuring physical fatigue and the other mental fatigue.

Fatigue Descriptive Scale

This was proposed by Iriarte and co-workers.[10] It is specific for MS and assesses people with MS on five aspects of fatigue. It has a range of values from 0 to 17.

Rating scales for disability

EDSS

The EDSS was proposed in 1983 by Kurtzke[80] based on previous work by the same author in 1955 and 1961. It has been widely used as a tool to measure disability and overall function in MS.

Appendix 2

Search strategies

Scoping review

This strategy was designed specifically to target published or ongoing systematic reviews and was based on the ARIF search protocol. The high sensitivity of the strategies used for MEDLINE and EMBASE resulted in the identification of all types of reviews, along with some primary studies.

- **Cochrane Library (1999, Issue 2)**
  01 (Multiple sclerosis) or multiple-sclerosis:ME
  02 (Fatigue) or fatigue:ME
  03 1 AND 2

- **ARIF Database; Bandolier; GEARS; InterDEC database; National Research Register; National Institutes of Health (website); SBU (website).**
  The databases were searched using the term 'multiple sclerosis' and the contents of other sources were browsed.

- **MEDLINE (Ovid) 1991–June 1999**
  01 multiple sclerosis/
  02 exp fatigue/
  03 exp cognition/
  04 (fatigue$ or tired$ or letharg$).tw.
  05 lassitude$.tw.
  06 or/2-5
  07 1 and 6
  08 (meta-analysis or review literature).sh.
  09 meta-analy$.tw.
  10 metaanal$.tw.
  11 meta-analysis.pt.
  12 (systematic$ adj4 (review$ or overview$)).tw.
  13 review,academic.pt.
  14 case report.sh.
  15 letter.pt.
  16 historical article.pt.
  17 review of reported cases.pt.
  18 review,multicase.pt.
  19 review literature.pt.
  20 8 or 9 or 10 or 11 or 12 or 13 or 19
  21 14 or 15 or 16 or 17 or 18
  22 20 not 21
  23 7 and 22

- **EMBASE (Ovid) 1991–June 1999**
  01 exp multiple sclerosis/
  02 exp fatigue/
  03 exp cognition/
  04 (fatigue$ or tired$ or letharg$ or lassitude$).tw.
  05 (2 or 3 or 4) and 1

Systematic reviews

Search strategies to identify clinical trials on amantadine

- **MEDLINE (Ovid) 1966–Dec 1999**
  01 randomized controlled trial.pt.
  02 controlled clinical trial.pt.
  03 randomized controlled trials.sh.
  04 random allocation.sh.
  05 double blind method.sh.
  06 single blind method.sh.
  07 or/1-6
  08 (animal not human).sh.
  09 7 not 8
  10 clinical trial.pt.
  11 exp clinical trials/
  12 (clini$ adj25 trial$).ti,ab.
  13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind or mask$)).ti,ab.
  14 placebos.sh.
  15 placebo$.ti,ab.
  16 random$.ti,ab.
  17 research design.sh.
  18 or/10-17
  19 18 not 8
  20 19 not 9
  21 9 or 20
  22 (amantadine$ or symmetrel$).tw.
  23 amantadine/
  24 or/22-23
  25 multiple sclerosis/
  26 (multiple$ adj sclerosis$).tw.
  27 or/25-26
  28 24 and 27
  29 21 and 28

- **EMBASE (DataStar) 1974–1979**
  01 controlled-trial
  02 randomized-controlled-trial
  03 clinical-trial
  04 controlled-study
  05 clinical-study

06 prospective-study
07 double-blind-procedure
08 randomization.de.
09 major-clinical-study
10 or/1-9
11 amantadine.de.
12 (amantadine$ or symmetrel$)
13 or/11-12
14 multiple-sclerosis
15 multiple$ adj sclerosis$
16 or/14-15
17 13 and 16
18 17 and 10

- **EMBASE (Ovid) 1980–Dec 1999**
  01 controlled trial/
  02 randomized controlled trial/
  03 clinical trial/
  04 controlled study/
  05 clinical study/
  06 prospective study/
  07 double blind procedure/
  08 randomization/
  09 major clinical study/
  10 or/1-9
  11 amantadine/
  12 (amantadine$ or symmetrel$).tw.
  13 or/11-12
  14 multiple sclerosis/
  15 (multiple$ adj sclerosis$).tw.
  16 or/14-15
  17 13 and 16
  18 10 and 17

Search strategies to identify clinical trials on pemoline

- **MEDLINE (Ovid) 1966–Dec 1999**
  01 randomized controlled trial.pt.
  02 controlled clinical trial.pt.
  03 randomized controlled trials.sh.
  04 random allocation.sh.
  05 double blind method.sh.
  06 single blind method.sh.
  07 or/1-6
  08 (animal not human).sh.
  09 7 not 8
  10 clinical trial.pt.
  11 exp clinical trials/
  12 (clini$ adj25 trial$).ti,ab.
  13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind or mask$)).ti,ab.
  14 placebos.sh.
  15 placebo$.ti,ab.
  16 random$.ti,ab.
  17 research design.sh.
  18 or/10-17
  19 18 not 8
  20 19 not 9
  21 9 or 20
  22 pemoline/
  23 (pemoline$ or cylert$ or volital$).tw.
  24 or/22-23
  25 multiple sclerosis/
  26 multiple$ adj sclerosis.tw.
  27 or/25-26
  28 24 and 27
  29 21 and 28

- **EMBASE (DataStar) 1974–1979**
  01 controlled-trial
  02 randomized-controlled-trial
  03 clinical-trial
  04 controlled-study
  05 clinical-study
  06 prospective-study
  07 double-blind-procedure
  08 randomization.de.
  09 major-clinical-study
  10 or/1-9
  11 pemoline.de.
  12 (pemoline$ or cylert$ or volital$)
  13 or/11-12
  14 multiple-sclerosis
  15 multiple$ adj sclerosis$
  16 or/14-15
  17 13 and 16
  18 17 and 10

- **EMBASE (Ovid) 1980–Dec 1999**
  19 controlled trial/
  20 randomized controlled trial/
  21 clinical trial/
  22 controlled study/
  23 clinical study/
  24 prospective study/
  25 double blind procedure/
  26 randomization/
  27 major clinical study/
  28 or/1-9
  29 pemoline/
  30 (pemoline$ or cylert$ or volital).tw.
  31 or/11-12
  32 multiple sclerosis/
  33 (multiple$ adj sclerosis$).tw.
  34 or/14-15
  35 13 and 16
  36 10 and 17

Appendix 3

Studies excluded from systematic reviews

Amantadine

Three studies were excluded. The first one[38] was excluded because it was a case series. The second one[36] was a parallel trial with three arms primarily looking at the effects of amantadine and pemoline on cognitive functioning, but also including fatigue as a secondary outcome. It was excluded because participants in the study were a subset of people with MS from another included study.[35] The third study[47] was a non-randomised controlled trial. Data from this study are presented in *Table 22*.

Pemoline

One study was excluded. This was a parallel trial[36] with three arms primarily looking at the effects of amantadine and pemoline on cognitive functioning, but also including fatigue as a secondary outcome. It was excluded because the particicpants in the study were a subset of people with MS from another included study.[35]

TABLE 22

Study characteristics	
Design	CCT crossover
Inclusion criteria	Definite MS; persistent fatigue > 3 months
Exclusion criteria	Not mentioned
No. of patients randomised	32
Intervention	Amantadine 100 mg twice daily
Comparison	Placebo
Outcome:	Fatigue assessment
	Patient: daily recording in diary 3/day four-point scale: none, mild, moderate, severe *Researcher*: evaluation of improvement in fatigue?

Study quality	
Was the trial described as 'randomised'?	No
Was the method of randomisation not stated or unclear?	Unclear
Was there concealment of treatment allocation?	Unclear
Was the trial described as 'double-blind'?	Yes
Was the treatment allocation masked from the participants?	Unclear
Was the treatment allocation masked from the investigators?	Unclear
Was the treatment allocation masked at the outcome assessments?	Unclear
Were the number of withdrawals in each group stated?	Yes?
Jadad score	1
Were systematic period effects or carryover discussed and/or identified?	No
Washout period?	1 week
Was the number of people in sequences PT/TP clearly stated?	No
Were people who did not complete any of the periods excluded from the analysis?	N/A

continued

TABLE 22 contd

Results	**Amantadine** ***n* (%)**	**Placebo** ***n* (%)**
Fatigue improvement		
Marked	10 (31)	0 (0)
Moderate	5 (16)	1 (3)
Mild	5 (16)	6 (19)
No change	12 (38)	25 (78)
+ change	20 (63)	7 (22)
No change	12 (38)	25 (78)
Statistics	$p < 0.0005$	
Direction of effect	Favours amantadine	
Willingness to continue treatment (preferred treatment)		
Amantadine	19/32 (59)	
Placebo	0/32 (0)	
None	13/32 (41)	
Direction of effect	Favours amantadine	
Side-effects		
No. of patients reporting side-effects	7/32 (22)	6/32 (19)
No. of side-effect events reported	Unknown	Unknown
Side-effects drop-outs or cessation of drug	1 (hallucination)	2
Treatment duration	3 weeks	
Nature of main side-effects	Hyperactivity, nausea	

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We look forward to hearing from you.

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