

Amantadine for fatigue in multiple sclerosis (Review)

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ABSTRACT

Background

Fatigue is one of the most common and disabling symptoms of people with Multiple Sclerosis (MS). The effective management of fatigue has an important impact on the patient's functioning, abilities, and quality of life. Although a number of strategies have been devised for reducing fatigue, treatment recommendations are based on a limited amount of scientific evidence. Many textbooks report amantadine as a first-choice drug for MS-related fatigue because of published randomised controlled trials (RCTs) showing some benefit.

Objectives

To determine the effectiveness and safety of amantadine in treating fatigue in people with MS.

Search strategy

We searched The Cochrane MS Group Trials Register (July 2006), The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 1, 2006), MEDLINE (January 1966 to July 2006), EMBASE (January 1974 to July 2006), bibliographies of relevant articles and handsearched relevant journals. We also contacted drug companies and researchers in the field.

Selection criteria

Randomised, placebo or other drugs-controlled, double-blind trials of amantadine in MS people with fatigue.

Data collection and analysis

Three reviewers selected studies for inclusion in the review and they extracted the data reported in the original articles. We requested missing and unclear data by correspondence with the trial's principal investigator. A meta-analysis was not performed due to the inadequacy of available data and heterogeneity of outcome measures.

Main results

Out of 13 pertinent publications, 5 trials met the criteria for inclusion in this review: one study was a parallel arms study, and 4 were crossover trials. The number of randomised participants ranged between 10 and 115, and a total of 272 MS patients were studied. Overall the quality of the studies considered was poor and all trials were open to bias. All studies reported small and inconsistent improvements in fatigue, whereas the clinical relevance of these findings and the impact on patient's functioning and health related quality of life remained undetermined. The number of participants reporting side effects during amantadine therapy ranged from 10% to 57%.

Authors' conclusions

The efficacy of amantadine in reducing fatigue in people with MS is poorly documented, as well as its tolerability. It is advisable to: (1) improve knowledge on the underlying mechanisms of MS-related fatigue; (2) achieve an agreement on accurate, reliable and responsive outcome measures of fatigue; (3) perform good quality RCTs.

PLAIN LANGUAGE SUMMARY

More research is needed into the effect of Amantadine for fatigue for people with multiple sclerosis

Amantadine for fatigue in multiple sclerosis (Review)

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Multiple sclerosis (MS) is a chronic disease affecting young and middle-aged adults. One of the most common and disabling symptoms of MS is fatigue. Different approaches have been used to try and improve this, including energy conservation, specialised fitness training and drug treatments. Amantadine has been used to try to relieve fatigue in MS. This review found that Amantadine efficacy in reducing MS-related fatigue and its tolerability are poorly documented and more research is needed.

BACKGROUND

Fatigue is one of the most common and disabling symptoms of Multiple Sclerosis (MS). Between 76% and 92% of people with MS report fatigue and between 55% and 75% of them consider fatigue one of the most debilitating symptoms (Krupp 1997). Fatigue can be defined as a sense of tiredness or lack of energy greater than expected for the daily effort and degree of disability. Difficulty exists in the clinical assessment of fatigue. Patient's self report is considered the most appropriate evaluation modality since it takes into account the fatigue-related changes in functioning according to patient's direct experience (Krupp 1997). Although many tools have been devised, up to now no validated scale has been used with unanimous consent.

Different pathophysiological mechanisms, either peripheral or central, have been suggested for fatigue associated with MS. Some of these mechanisms or other mechanisms can be responsible for fatigue linked to the use of drugs (e.g. interferons, steroids, immunosuppressive agents, benzodiazepines, and anti-spasticity agents), or concomitant diseases (e.g. chronic infections).

Amantadine is an anti-influenza agent as it inhibits replication of influenza A viruses (Hayden 1996). However, the use of amantadine has been discouraged in seasonal and pandemic influenza in a recent systematic review (Jefferson 2006a; Jefferson 2006b). Amantadine may be effective as an adjunct to interferon-based combination therapy in patients with chronic hepatitis C (Lim 2005). Its dopaminergic effect was discovered after serendipitous evidence of improvement in symptoms of Parkinson's disease (Schwab 1972). Similarly, the first evidence of improved fatigue in MS was from a patient treated with amantadine for influenza prophylaxis (Murray 1985). Activity on glutamate receptors has also been shown (Stoof 1992).

The mechanism of the potential action of amantadine for fatigue remains unclear. An antiviral activity, an immunologically mediated action (Bertolone 1993), or an amphetamine-like action have been suggested (Rosenberg 1988; Cohen 1989).

Since 1987, some benefits of amantadine have also been reported by randomised, double-blind, placebo controlled trials (CMSRG 1987; Rosenberg 1988; Cohen 1989; Krupp 1995). As a consequence, many textbooks report amantadine as a first-choice drug for MS-related fatigue.

A non systematic narrative overview on amantadine in MS-related fatigue was published in 1993 by Kemp and Gora (Kemp 1993). Another overview based on a literature review including several

databases (MEDLINE, CINAHL, Nursing and Allied Health literature Index, ClinPSYC) has been published by a panel of experts (Anonymous 1998). The latter concluded that approximately 20 to 40% of mildly to moderately disabled people with MS showed significant short-term reduction in fatigue with amantadine therapy, which was well tolerated. A "rapid review" on treatment for fatigue in MS (Branas 2000), with a wide section for amantadine treatment, showed inconclusive results.

OBJECTIVES

The objectives of this review were to assess the efficacy and safety of amantadine in reducing fatigue in people with MS.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Double-blind, randomised, controlled trials (RCTs) and crossover trials were included.

Types of participants

Patients diagnosed as having clinically definite or probable MS according to Schumacher (Schumacher 1965), Poser (Poser 1983) or McDonald criteria (McDonald 2001), and also reporting fatigue. No strict definition of fatigue was required.

Types of intervention

Amantadine hydrochloride versus placebo or other drugs.

Types of outcome measures

(1) FATIGUE SPECIFIC

(a) Patient's subjective response (dichotomous outcome: better versus worse or not changed)

(b) Changes in validated scales for fatigue assessment (continuous outcomes)

(2) GLOBAL OUTCOMES - DISEASE SPECIFIC

Changes in Expanded Disability Status Scale (EDSS) (Kurtzke 1983), Ambulation Index (AI) (Hauser 1983), Multiple Sclerosis Functional Composite (MSFC) (Fischer 1999) and MS-specific health related quality of life questionnaires were considered as continuous outcomes

(3) GLOBAL OUTCOMES - NON DISEASE SPECIFIC

(a) Changes in non MS-specific disability or health related quality of life scales (continuous outcomes)

(b) Willingness to continue treatment

(4) SAFETY - ADVERSE EFFECTS

Safety and tolerability were assessed from the number of dropouts and adverse events (dichotomous outcomes). Adverse events were categorised into (i) mild-moderate and (ii) major events (death, or any event requiring hospitalisation or medical intervention).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Multiple Sclerosis Group methods used in reviews.

We searched The Cochrane MS Group trials register (July 2006), The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2, 2006), MEDLINE (PUBMED) (January 1966 to July 2006) EMBASE (EMBASE.COM) (January 1974 to July 2006).

In addition, we used the following methods:

(1) screening of reference lists of all available review articles and primary studies found;

(2) handsearch of the abstract book of recent symposia of European Committed Therapies and Rehabilitation in MS (from 1993 to 2002), Italian Neurological Society (from 1990 to 2002), European Federation of Neurological Sciences (from 1996 to 2002), and American Academy of Neurology (from 1997 to 2002);

(3) personal contact with corresponding authors of relevant trials or reviews, and other MS experts;

(4) contact and inquiry of drug manufactures of amantadine.

The MEDLINE and EMBASE search strategies are given in Table 03.

METHODS OF THE REVIEW

Two reviewers (CT and EP) independently decided whether the identified papers were pertinent for the review by reading their abstracts. Once the studies were judged pertinent, three reviewers (CT, AS, EP) independently read the full texts, and decided which studies to include.

Only the RCTs scoring A (adequate allocation concealment) or B (unclear allocation concealment) according to the Cochrane Collaboration quality assessment criteria (Higgins 2005) were considered eligible for this review. Quality of RCTs was assessed through Jadad's scale (Jadad 1996). The scale consists of 3 items: description of randomisation, blinding and attrition. The possible range of this scale score is between 0 (worst) and 5 (best).

For randomisation, two points were given for randomised studies in which randomisation method was described and adequate; one

point was given for randomised studies in which randomisation method was not described.

For blinding, two points were given to double blind studies in which concealment method was described and adequate, one point for double blind studies not describing concealment method. One point was given if information on attrition was reported. A quality scale for crossover trials was also devised, consisting of Jadad's scale items and one adjunctive item regarding the washout period: one point was deducted from the Jadad's score if the washout period was not described, there was no washout period, or the washout was described and judged inappropriate by the rater.

The scoring for allocation concealment and the Jadad's scale were rated by three reviewers (CT, AS, EP). Disagreement among reviewers was discussed and resolved, where possible, by consensus. Otherwise a decision was achieved by the vote of the majority.

The principal investigator of each trial was contacted to obtain information about the results of each (or at least the first) study period and in particular if there was missing or unclear data.

DESCRIPTION OF STUDIES

See table of included studies for details.

We identified 13 publications pertinent to the review through electronic and manual searches. After reading the full published text, we excluded eight articles: one was a narrative overview (Kemp 1993); four were non randomised studies (Murray 1985; Plaut 1987; Maciejek 1989; Chiba 1992) one study (two publications) considered only para-clinical endpoints (Sailer 1996; Sailer 2000), and one study was a duplicate publication of a study included in the present review (Geisler 1996). No unpublished trials were identified by our search procedures. Thus 5 trials met the criteria for inclusion in this review (CMSRG 1987; Rosenberg 1988; Cohen 1989; Krupp 1995; Tomassini 2004). These trials were published between 1987 and 2004.

Methods and interventions

Two studies compared Amantadine versus other drugs: (i) a three-arm parallel trial comparing six-week treatment with amantadine (100 mg b.d.i), pemoline, or placebo (Krupp 1995); (ii) a 3 months crossover trial of amantadine versus acetyl L-carnitine (Tomassini 2004). The other three studies were crossover RCTs (CMSRG 1987; Rosenberg 1988; Cohen 1989) designed to compare amantadine (100 mg b.i.d) with placebo. The length of each treatment phase ranged between 1 week and 3 months, and the length of the washout phase ranged between 1 and 2 weeks.

Two studies had a 2 week run-in period in which participants were monitored to determine fatigue severity (CMSRG 1987; Krupp 1995).

Participants

All but one study (Rosenberg 1988) included participants with probable or definite MS according to pre-specified criteria, and complaining of moderate to severe fatigue. The study from Rosen-

berg et al. did not specify the diagnostic criteria considered, and included patients with anamnestic fatigability (Rosenberg 1988). Regarding severity of fatigue at enrolment, the Canadian trial included participants who, in the run-in period, scored 25 mm or above on a 50 mm visual analogue scale (VAS) ranging between “no fatigue” (0) and “as bad as could be” (50) (CMSRG 1987). Cohen 1989 considered eligible MS people scoring 80 or over in the Fatigue Assessment Inventory-based (FAI) scale. The FAI score is a patient’s self assessed fatigue inventory developed by the authors, made of 42 items, each scoring from 1 (not at all) to 4 (very representative). The maximum possible score is 168 (Cohen 1989). The parallel trial comparing 6-week treatment with amantadine, pemoline, or placebo (Krupp 1995) included patients with a baseline Fatigue Severity Scale (FSS) (Krupp1989) score of 4.0 or more.

All studies but one (Rosenberg 1988) excluded people with severe depression and with significant other medical comorbidities, and people taking fatigue inducing drugs. In particular, as far as the Tomassini 2004 study is concerned, patients should have been under Interferon beta treatment for at least 1 year in order to avoid occurrence of fatigue which was considered to occur more frequently in the early phase of such a treatment.

Overall, the number of randomized patients ranged between 10 and 115 (Table 01).

Outcome measures

The studies used different methods to measure fatigue. The most frequently reported outcome was participant’s preference, or his subjective impression of benefit. The CMSRG 1987 considered as efficacy end-points the preferred treatment period by the patient and the physician. Furthermore, participants recorded their daily fatigue experience on a 50 mm VAS ranging between “no fatigue” and “as bad as could be”. Rosenberg 1988 considered as a unique end point patient’s drug preference. Cohen 1989 reported both patient’s preference and changes in a fatigue scale developed by the authors which consisted of the following seven indices for fatigue: energy, muscle strength, concentration/memory, motivation, ability to finish a task, problem solving, and well being. Each item was scored on a five point scale, ranging from one (poor) to five (excellent). The parallel trial considered three efficacy end-points: the MS-Specific Fatigue Scale (MS-FS) (Schwartz 1993), the FSS (Krupp1989), and the patient’s verbal reports (Krupp 1995). Both fatigue scales were clinically validated. The MS-FS is a disease-specific six-item inventory, and the FSS a non MS-specific nine-item global measure of the effect of fatigue on daily living.

In the Tomassini 2004 study the primary efficacy measure was the FSS (Krupp1989); a secondary efficacy measure was the Fatigue Impact Scale - FIS - (Fisk 1994). The FIS is a non MS-specific 40-item tool (score ranging 0-4 for each item) which allows a multidimensional evaluation (cognitive, physical, social role and psychological). It was not validated at the time of the Tomassini 2004 study. Nowadays, studies which validate versions of the FIS (or modified-versions) have been published (Mathiowetz 2003;

Hauser 2003; Flensner 2005; Kos 2005; Pittion-Vouyovitch06). All the trials reported the number of side effects and drop outs, except for the Tomassini 2004 study in which the prevalence of side-effects was not separately reported.

None of the crossover trials gave data on each study period. We contacted the principal investigators of all the included RCTs for further information, and an extraction form was also enclosed to facilitate data provision. We have so far received apologetic answers of inability to give information from the authors of two studies (Cohen 1989; Tomassini 2004). Thus this review was carried out on the basis of data available in the original published papers.

METHODOLOGICAL QUALITY

See table of included studies for details.

All trials were reported as randomised. All but one included study met category B of the criteria of randomisation. Only one study described the method of randomization as computer-generated (CMSRG 1987). The Tomassini 2004 study was ranked B notwithstanding the Authors’ personal communication about the fact that randomization was computer-generated.

All trials were reported as conducted in a “double-blind” fashion. Two studies partially described the method of blinding (CMSRG 1987; Krupp 1995). Allocation concealment following randomization and masking of outcome assessment were not specified in any included RCTs. All trials obtained a score of 3 on Jadad’s scale (or modified Jadad’s scale for crossover trial).

The number of drop outs was reported by all the included trials. In Rosenberg’s trial all 10 randomised participants completed both study periods (Rosenberg 1988). The percentage of drop outs reported by the Canadian trial was 8.5%, though 21 out of 115 randomised participants were excluded from the analysis since their level of fatigue did not fulfil the eligible criteria. The resulting percentage of randomised participants which were not analysed was 25% (CMSRG 1987). The percentage lost to follow up reported by the parallel study was 22% (Krupp 1995). Cohen 1989 reported a similar percentage (24%). Six patients withdrew from the Tomassini 2004 study because of adverse reactions.

Information on intention to treat analysis for the main outcomes was not available in the original papers, and most continuous outcomes figures were discussed but not reported in detail in the tables or in the text.

A washout period was present in all crossover trials, and its duration (from 1 week to 3 months) seems sufficient to avoid a carry over effect of amantadine. However, it was not possible to verify this hypothesis since separate data from each study period were universally lacking in the original publications, nor were they provided on our request by the authors. In one study only, the authors attempted to verify the potential occurrence of a period effect (CMSRG 1987). In one study only, the carry over effect was taken into consideration, through evaluating washout differences

against the null hypotheses of no change during washout periods (Tomassini 2004).

RESULTS

A total of 190 patients were randomized (and 148 analysed in the original papers) in crossover studies, with figures ranging from 10 to 115. Out of 109 patients randomized in the parallel-arm trial, 39 received amantadine, 27 pemoline, and 43 placebo. The effect of amantadine on overall subjective improvement was reported by all the included trials except for the Tomassini 2004 study, but we could not summarize results since data for each study period were not available for the crossover studies.

In the Canadian trial 35 out of 115 randomised participants (30%) preferred the amantadine phase while 51 of them (44%) preferred other trial phases: 18 patients (16%) preferred the placebo phase, 5 (4%) the washout phase, and 28 (24%) did not express any preference (CMSRG 1987). In Rosenberg 1988 at the end of the study there were six responder patients (60%), i.e. participants who preferred amantadine, versus 4 (40%) non responders (one participant preferred placebo and three had no preference). In Cohen 1989, 8 out of 29 randomized patients (28%) preferred amantadine, 4 (14%) preferred placebo, and 10 (34%) did not express any preference. Krupp et al. assessed the benefit perceived by the participant at the end of treatment and two weeks later (post-treatment follow up) (Krupp 1995). Thirteen out of 39 participants assigned to amantadine (33%) perceived benefit while on the drug, while 15 (38%) perceived benefit at post-treatment follow up. Fourteen out of 43 of those assigned to placebo (32%) had benefit while on placebo, and 13 (30%) at post-treatment follow up. The results of continuous outcomes for each trial correspond to those available in the original papers, and are reported in Table 02.

The number of participants reporting side effects during amantadine treatment was overall 40% (ranging from 10% to 57%) versus 35.5% during placebo treatment.

Overall no major events were reported, side effects were generally mild, and included hallucinations, nausea, dizziness, hyperactivity, anxiety, and insomnia. However, in one study the drop-out rate because of side effects was about 28% (5/18) (Tomassini 2004). No synthesized results are given due to large heterogeneity in outcome measures between trials, and incomplete data, such as information on each separated study phase for crossover studies (Curtin 2002 A; Curtin 2002 B).

DISCUSSION

Overall the methodological quality of the studies considered was poor. Data and methods reported in the original papers were not described by the authors with sufficient detail. All the crossover studies did not report data from each (or at least the first) treat-

ment period separately. The results for many continuous outcome measures considered were reported incompletely (for some outcomes only p-values were given) or in different ways so that it was not possible to estimate the treatment effect. Despite attempts to contact principal investigators, we were unable to obtain the data necessary to perform a combined analysis. Overall the percentage of patients who preferred amantadine was low in all but one study (Rosenberg 1988) performed on a small sample of patients. In one study, authors concluded that amantadine was less tolerated and less effective than acetyl L-carnitine for the treatment of MS-related fatigue (Tomassini 2004).

A high percentage of patients lost to follow-up was observed. The studies reported inconsistent results and the clinical relevance of them and the impact on patient's functioning and health related quality of life remains undetermined.

As far as the tolerability is concerned, it must be reported that some reviews about the use of amantadine in different diseases provide some doubts about its tolerability. In particular, the authors of two Cochrane reviews on Parkinson disease (Crosby 2003a; Crosby 2003b), claim about the tolerability of amantadine saying that rigorous analysis of selected RCTs reveals insufficient evidence of its safety (and of its efficacy in Parkinson disease). The authors of a Cochrane review on influenza A therapy state that amantadine induces significant gastrointestinal adverse effects and that some study withdrawals have to be related to adverse effects of the central nervous system (CNS) (Jefferson 2006a; Jefferson 2006b). Finally, in a recent review about influenza (Kamps 2006), CNS side effects (dizziness, nervousness, agitation, difficulty concentrating, insomnia, and lowered seizure threshold) are reported to occur in a substantial number of patients treated with amantadine, in particular: in a four-week prophylaxis trial, these symptoms occurred in up to 33 % of young individuals (Bryson 1980); in another trial, 13% patients receiving amantadine withdrew from the study because of CNS side effects (Dolin 1982).

AUTHORS' CONCLUSIONS

Implications for practice

Due to the poor methodological quality and limited clinical relevance of findings, straightforward recommendations for practice cannot be made. Overall there is no evidence supporting the use of amantadine.

Implications for research

The insufficient quality of the available studies warrants further research. Trials on amantadine or other intervention for MS-related fatigue definitely need adequate sample sizes, parallel arms randomized controlled designs, as well as clinically relevant, reliable and responsive outcome measures. The definition of MS-related fatigue should be better specified. Furthermore future trials should follow specific guidelines concerning the inclusion criteria,

control of co-interventions and co-morbidities, and should follow internationally published guidelines for reporting trials.

POTENTIAL CONFLICT OF INTEREST

None.

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* Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	CMSRG 1987
Methods	
Participants	

Characteristics of included studies (Continued)

Interventions

Outcomes

Notes

Allocation concealment D – Not used

Study	Cohen 1989
Methods	Single centre Design: RCT crossover Duration 10 weeks: - 4 + 4 weeks treatment periods - 2 weeks washout period
Participants	Departments of Neurology, University of Massachusetts (Worcester) Patients with probable or definite MS** with daily symptomatic fatigue for at least 3 months, FAI > 80 and EDSS < 6 - 29 randomized - 22 analysed
Interventions	amantadine 100 mg b.i.d. vs placebo
Outcomes	(1) preferred treatment period (at the end of study) (2) Daily rating for 7 indices of fatigue on 5 point scale (1-5) (3) Neurobehavioral performances (8 neuropsychological tests) (4) EDSS (5) Side effects
Notes	- 7 drop outs (24%, 4 patients during placebo and 3 during amantadine period) - Jadad score: 3
Allocation concealment	B – Unclear

Study	Krupp 1995
Methods	Multicentre Design: RCT parallel Duration 10 weeks: - 2 weeks run in period(fatigue monitoring) - 6 weeks treatment period - 2 weeks final washout period
Participants	3 Medical Centres in the New York area Patients with probable or definite MS** and FSS score > 4 - 109 randomized - 39 amantadine - 27 pemoline - 43 placebo - 83 analysed (31, 17, 35), - 70 analysed (23, 23, 24) for self assessment!
Interventions	amantadine 100 mg b.i.d. vs pemoline up to 56.25 mg daily vs placebo

Characteristics of included studies (Continued)

Outcomes	(1) Benefit perceived (2) MS-FS (3) FSS (4) RIV (5) CES-D (6) St Mary Hospital Sleep Questionnaire (modified form) (7) EDSS (8) Side effects (at the end of treatment and 2 weeks later)
Notes	- 26 drop outs reported (22%, 8 patients during amantadine, 10 during pemoline and 8 during placebo) - not reported self assessment of 49 patients during study and of 53 after washout period - not available for analysis comprehensive numerical data for all continuous outcomes - Jadad score: 3

Allocation concealment B – Unclear

Study Rosenberg 1988

Methods	Single centre Design: RCT crossover Duration 3 weeks - 1+ 1 week treatment periods - 1 week washout period
Participants	Departement of Neurology, University of New Mexico (Albuquerque) Patients with definite MS and fatigability (anamnestic) - 10 randomized - 10 analysed
Interventions	amantadine 100 mg b.i.d. vs placebo
Outcomes	(1) Preferred treatment period (1-3 weeks) (2) faticability scale score (0 to 4) (3) EDSS (4) Side effects
Notes	- not available for analysis numerical data for continuous outcomes - Jadad score: 3
Allocation concealment	B – Unclear

Study Tomassini 2004

Methods	Single centre Design: RCT crossover. Duration: 3+ 3 week treatment periods - 3 week washout period
Participants	Department of Neurological Sciences, University of Rome “La Sapienza” - Italy. Patients with definite MS** (both relapsing-remitting MS and secondary-progressive MS) with clinical evidence of fatigue as documented by a score >4 on the Fatigue Severity Scale (FSS). - 36 randomized - 30 analysed
Interventions	amantadine 100 mg b.i.d.

Amantadine for fatigue in multiple sclerosis (Review)

vs acetyl L-carnitine 1g b.i.d.

Outcomes	(1) FSS (2) FIS (3) BDI (4) SEC
Notes	- not available for analysis numerical data for continuous outcomes - Jadad score: 3
Allocation concealment	D – Not used
<p>BDI: Beck Depression Inventory (Beck 1961) CES-D: Centre for Epidemiologic Studies Depression Scale - the scores range from 0 to 60 (Radloff 1977) EDSS: Expanded Disability Status Scale - the scores range from 1.0 to 10.0 (Kurtzke 1983) FAI: fatigue assessment inventory - 42 items evaluating fatigue impact on daily living, the final score range from 42 to 168 (for each item score ranges from 1 = not at all to 4 = very representative fatigue) (Cohen 1989) FSS: Fatigue Severity Scale - the scores ranges from 1 (no fatigue) to 7 (most disabling fatigue) (Krupp 1989) MS-FS: Multiple Sclerosis-specific Fatigue Scale - the scores range from 1 to 7 (Schwartz 1993) RIV : Rand Index of Vitality - the scale measures energy and the scores range from 4 to 24 (Brooks 1979) VAS:50mm Visual Analogue Scale, “no fatigue” in the left of the scale and “as bad as could be” on the right (CMSG 1987) FIS: Fatigue Impact Scale (Fisk 1994) SEC: Social Experience Checklist (SEC) (Tempelaar 1989) * Schumacher criteria (Schumacher 65) ** Poser criteria (Poser 83)</p>	

Characteristics of excluded studies

Study	Reason for exclusion
Chiba 1992	
Geisler 1996	Dual publication (patients considered in Krupp 95)
Kemp 1993	Review article
Maciejek 1989	Not RCT
Murray 1985	Not RCT
Plaut 1987	Not RCT
Sailer 1996	Only paraclinical measures (abstract)
Sailer 2000	Only paraclinical measures

ADDITIONAL TABLES

Table 01. Participants included in trials

Study ID	Treatment	N randomised	N analyzed	N excluded	N drop out (DO)	% DO/randomised
CMSRG 1987		115	86	21	8	9.3*
Rosenberg 1988		10	10	0	0	0
Cohen 1989		29	22	0	7	24.1
Krupp 1995		119	93	\	26	21.8

Table 01. Participants included in trials (Continued)

Study ID	Treatment	N randomised	N analyzed	N excluded	N drop out (DO)	% DO/randomised
Tomassini 2004	Amantadine	39	31	\	8	20.5
	Pemoline	37	27	\	10	27.0
	Placebo	43	35	\	8	18.6
		36	30	\	6	16.7
	Amantadine	18	13	\	5	27.8
	Acetyl L-carnitine	18	17	\	1	5.6

Footnote:

*calculated not including 21 patients excluded

Table 02. Results of continuous outcomes from studies

Study ID	Outcomes	Time	Treatment no.	Treatment mean	95% CI - SE* -SD**	Control no.	Control mean	95% CI - SE* -SD**
CMSRG 1987	Weekly fatigue on VAS (fig. 1)§	Baseline	86	28.9	23.3-26.3	86	29.6	31.6-27.6
		Week 1	86	24.8	23.2-26.4	86	27.9	26.3-29.5
		Week 2	86	24.7	23.1-26.3	86	27.0	25.2-28.8
		Week 3	86	24.7	23.1-26.3	86	26.9	25.3-28.6
CMSRG 1987	Effect on VAS for a selected activity (fig. 2)§	Baseline	86	29.3	27.4-31.2	86	29.6	31.8-27.4
		Week 1	86	25.3	23.5-27.1	86	27.8	26.0-29.6
		Week 2	86	24.1	22.2-26.0	86	26.8	25.6-29.2
	Effects on VAS for 13 ADL (tab 4)§	Week 3	86	24.1	22.2-26.0	86	26.8	25.0-28.5
		Baseline	86	26.6	1.13*	86	26.2	1.06*
		Week 1	86	25.1	0.74*	86	25.1	0.74*
		Week 2	86	23.6	0.74*	86	25.1	0.74*
	Week 3	86	24.1	0.74	86	25.9	0.74*	

Cohen 1989	Diary rating for 7 indices of fatigue on 5 points scale		22	3.18	0.04*	22	2.96	0.03*
Krupp 1995	MS-FS (fig.1)§	baseline	31	5.0	1.3**	35	4.7	1.9**
		pre-treat.	31	4.89	0.23**	35	4.68	0.15**
		end-treat.	31	4.4	0.3**	35	4.72	0.2**
	FSS (fig.2)§	baseline	31	5.7	0.8**	35	5.7	0.8**
		pre-treat.	31	5.62	0.2**	35	5.63	0.15**
		end-treat.	31	5.18	0.25**	35	5.4	0.2**
Tomassini 2004	FSS change vs baseline (fig.2)§	amantadine	30	0.15	-0.1-0.4			
		acetyl L- carnitine	30	-0.2	-0.5-0.05			
		washout after amantadine	30	-0.15	-0.4-0.05			
		washout after acetyl L-carnitine	30	-0.1	-0.35-0.2			
	§ from original articles							

Table 03. MEDLINE (PUBMED) and EMBASE /(EMBASE.COM) Search strategies

PUBMED

1. Multiple Sclerosis[MESH]
2. Myelitis, Transverse[MESH:noexp]
3. Demyelinating Diseases[MESH:noexp]
4. Encephalomyelitis, Acute Disseminated[MESH]
5. "multiple sclerosis" OR "transverse myelitis" OR "optic neuritis" OR devic OR adem OR "neuromyelitis optica" Field: Title/Abstract
6. #1 OR #2 OR #3 OR #4 OR #5
7. "Clinical Trial"[Publication Type]
8. randomized Field: Title/Abstract
9. placebo Field: Title/Abstract
10. "drug therapy"[Subheading]
11. randomly Field: Title/Abstract
12. trial Field: Title/Abstract
13. groups Field: Title/Abstract

EMBASE

- 1 'encephalomyelitis'/exp
- 2 'demyelinating disease'/exp
- 3 'multiple sclerosis'/exp
- 4 'myelo optic neuropathy'/exp
- 5 'multiple sclerosis':ti,ab
- 6: neuromyelitis optica:ti,ab
7. encephalomyelitis:ti,ab
8. adem:ti,ab
- 9 .devic:ti,ab
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. 'crossover procedure'/exp
12. 'double blind procedure'/exp
13. 'single blind procedure'/exp
14. 'randomized controlled trial'/exp
- 15.random*:ti,ab

Table 03. MEDLINE (PUBMED) and EMBASE /(EMBASE.COM) Search strategies (Continued)

PUBMED	EMBASE
14.#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	16.factorial*:ti,ab
15.#6 AND #14	17.crossover:ti,ab
16.“Fatigue”[MeSH]	18.cross AND over:ti,ab
17.“Muscle Fatigue”[MeSH]	19. placebo*:ti,ab
18.“Fatigue Syndrome, Chronic”[MeSH]	20. 'double blind':ti,ab
19.“chronic fatigue syndrome*” Field: Title/Abstract	21. 'single blind':ti,ab
20.fatigue Field: Title/Abstract	22. assign*:ti,ab
21.muscle AND fatigue Field: Title/Abstract	23.allocat*:ti,ab
22.“Chronic Fatigue” Field: Title/Abstract	24. volunteer*:ti,ab
23.#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	25.11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
24.#15 AND #23	26.10 and 25
25.“Amantadine”[MeSH]	27. 'fatigue'/exp
26.amantadine[Title/Abstract] OR symmetrel[Title/Abstract] OR midantan[Title/Abstract] OR viregyt[Title/Abstract]	28.'chronic fatigue syndrome'/exp
27.#25 OR #26	29.'muscle fatigue'/exp
28.#24 AND #27	30.fatigue:ti,ab
	31.'muscle fatigue':ti,ab
	32.'chronic fatigue syndrome':ti,ab
	33.'chronic fatigue':ti,ab
	34.27 or 28 or 29 or 30 or 31 or 32 or 33
	35.26 and 34
	36.'amantadine'/exp
	37.(amantadine:ti,ab OR symmetrel:ti,ab OR midantan:ti,ab OR viregyt:ti,ab)
	38.(mantadan:ti,ab OR symadine:ti,ab OR endantadiner:ti,ab
	39.36 or 37 or 39
	40. 35 and 39

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [adverse effects; *therapeutic use]; Antiviral Agents [adverse effects; *therapeutic use]; Cross-Over Studies; Dopamine Agents [adverse effects; *therapeutic use]; Fatigue [*drug therapy; etiology]; Multiple Sclerosis [*complications]; Randomized Controlled Trials as Topic

MeSH check words

Humans

COVER SHEET

Title Amantadine for fatigue in multiple sclerosis
Authors Pucci E, Branás P, D'Amico R, Giuliani G, Solari A, Taus C

Contribution of author(s)	<p>GG and AS first had the idea of systematically reviewing data on amantadine therapy in MS-related fatigue. They designed the protocol for the first time, with the help of CT and EP.</p> <p>CT and EP independently decided whether the identified papers were pertinent for the review by reading their abstracts. CT, AS and EP independently read the full texts, and decided which studies to include; BP participated in that process in the previous version of the review.</p> <p>RD gave methodological and statistical advice.</p> <p>All the authors gave some contributions in writing the present and the previous versions; the latter was mainly prepared by CT and EP. The principal responsible for preparing the present version was EP.</p> <p>Dr C. Hyde contributed to preparing the previous version of this review. He was not able to participate in the present update.</p>
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