A Randomized Controlled Trial of Amantadine in Fatigue Associated With Multiple Sclerosis

The Canadian MS Research Group

ABSTRACT: One hundred and fifteen patients with definite multiple sclerosis (M.S.) and chronic persistent fatigue were studied. This ten-week cross-over study consisted of a 2-week baseline period and two 3-week treatment periods separated by a 2-week washout. Patients received either amantadine 100 mg bid or matching placebo capsules. Fatigue, the effect of fatigue on an individually pre-selected activity and its effect on activities of daily living, were evaluated. Amantadine produced a small but statistically significant decrease in fatigue. An important placebo effect was noted. Mean fatigue during the washout period was lower than during the placebo run-in period, independently of which treatment had been given first. Side effects were numerous both on amantadine and on placebo. Only insomnia was significantly more common with amantadine.

RÉSUMÉ: Une éprouve controlée au hasard de l'amantadine à propos de la fatigue associée à la sclérose en plaques. Cent quinze patients avec la sclérose en plaques se plaignant d'une fatigue chronique et persistente, ont été étudiés. L'étude en croisé a duré 10 semaines et comprenait deux périodes de traitement de 3 semaines (amantadine 100 mg bid ou placebo) chacune précédée de deux semaines de placebo. Nous avons évalué la fatigue, son effet sur une activité choisie par le patient, et son effet sur les activités quotidiennes. L'effet de l'amantadine a été bénéfique, réduisant le niveau de fatigue par une marge minuscule, mais statistiquement significative. L'effet placebo était important. Indépendamment du traitement initial, la moyenne de fatigue était plus faible lors de la deuxième période de placebo que lors de la première. Les effets secondaires ont été nombreux durant le traitement à l'amantadine et au placebo. Seule l'insomnie était significativement plus fréquente avec l'amantadine.

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Fatigue is one of the more distressing and common symptoms of multiple sclerosis (M.S.)[1] It is an unusual and abnormal form of fatigue, different from that experienced by normal individuals after excessive exercise, lack of rest or lack of sleep. It can be defined as a sense of tiredness or lack of energy, greater than expected for the daily effort and the degree of disability. Its origin is unknown and it significantly interferes with the desire or ability to perform basic, daily, functions.

Freal reported that 78% of M.S. patients complained of fatigue.[1] In 56% of all patients it interfered with activities of daily living. In 1985, Murray reported that 76% of his M.S. patients had fatigue, which was felt to be different in type and degree from that which they had prior to the disease.[2] In many instances, it was their major complaint and often prevented them from carrying out normal activities and work even when their other neurological symptoms were not disabling. The unusual fatigue did not necessarily follow the course of disease activity and it did not always worsen when the patient's neurological status worsened.

Schapira reported two M.S. patients who responded to amantadine.[3] Over the course of a three-month treatment period, one patient had improved bladder and bowel control, improved speech, less unsteadiness, and loss of diplopia, dizziness, and tremor. Symptoms worsened when amantadine was discontinued, and improved when amantadine was resumed. The second patient had improved speech and gait within ten days of initiating treatment. However, a subsequent double-blind study of amantadine did not demonstrate a significant improvement in the neurological deficit.[4] In a cross-over study, Murray[2] found that 66% of the patients noted mild to marked improvement in fatigue while on amantadine compared to only 22% on placebo.

The present study was designed to determine if the beneficial results reported by Murray could be demonstrated in a larger patient population and to answer the following additional questions: Does reduction of fatigue improve the patients ability to carry out activities of daily living? Do changes in fatigue correlate with changes in the disability status as measured by the Expanded Disability Status Scale (EDSS)? Is this fatigue a

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reflection of the degree of depression which is not unusual in this patient population?

METHODS

Eleven multiple sclerosis research clinics in Canada entered patients who met the following criteria: at least a 6-month history of definite M.S. according to the Schumacher criteria;[5] and at least a 3-month history of chronic, persistent, moderate to severe, daily fatigue. Exclusion criteria included: pregnancy; hypersensitivity to amantadine; congestive heart failure or peripheral edema; hepatic or renal impairment; epilepsy; history of depression or other psychiatric disorders; acute anemia; thyroid disorders; diabetes; gastric or duodenal ulcers; and alcohol or drug abuse. The only concomitant medications permitted were small doses of muscle relaxants (baclofen, dantrolene) to control spasticity; anticholinergics (oxybutynin) for bladder control; and short-acting benzodiazepines at bedtime.

Eligible patients were enrolled into a 10-week, randomized, double-blind, crossover, placebo-controlled trial. There were two 3-week treatment periods (weeks 3, 4, 5 and weeks 8, 9, 10) during which patients received either amantadine 100 mg b.i.d. or an identical placebo. Each treatment period was preceded by a single-blind, two-week placebo period (weeks 1, 2 and weeks 6, 7).

At the initial visit the patients were instructed as to how to use visual analogue scales. They were then given 2 seven-day supplies of unnumbered medication (placebo) and told to take 1 capsule twice daily. The medication was blister-packed, and attached to a patient diary. Patients recorded their fatigue daily on a 50 mm visual analogue scale (VAS) with 'no fatigue' on the left of the scale and 'as bad as could be' on the right. At the end of each week, patients summarized the daily fatigue evaluations on a single VAS. Patients were asked to select one activity which was most affected by fatigue, and the M.S. symptom other than fatigue which was most bothersome. These variables were also evaluated weekly on a 50 mm VAS. Similarly, 13 activities of daily living were evaluated weekly. The left end of the scale was labeled 'able to do freely', the right was labeled 'unable to do'.

At the end of the first 2 weeks, patients returned to the clinic. We calculated the mean of the 2 weekly fatigue evaluations and the mean of the 2 weekly evaluations of the effect of fatigue on the selected activity. If both mean scores were less than 25 mm on the 50 mm scale, the patients were excluded from the study. If either mean score was 25 or greater, the patients were randomized to receive either amantadine 100 mg b.i.d. or placebo for the first 3-week treatment period. The computer-generated randomization was done in blocks of 4 patients. Separate randomizations were done for each clinic.

At this first follow-up visit, and at each of the 3 remaining visits (end of weeks 5, 7 and 10), functional systems were assessed using the Kurtzke Expanded Disability Status Scale[6] (EDSS). Patients also completed the Beck Depression inventory[7] at each follow-up visit. This self-rating scale is commonly used in research to measure behavioural manifestations of depression in both clinically depressed and non-clinically depressed patients.[8] This was felt to be important for two reasons. Firstly, depression is not uncommon in this group of patients, and fatigue can be one of the signs of depression. Secondly, there have been isolated reports of amantadine affecting depression.[9,10]

Table 1: Reasons for exclusions

Initial enrollment	165
Insufficient fatigue during run-in period	50
Randomized	115
Drop-outs	6
Reason	
peptic ulcer (week 5 (placebo))	1
increased fatigue (week 7 (placebo))	1
depression (week 7, 8 (placebo))	2
acute confusional state (week 8 (amantadine))	1
non-compliant (week 8, 9, 10 (amantadine))	1
Completions	109
Protocol violations	23
insufficient baseline fatigue, should not have been randomized	21
relapse requiring steroids (weeks 8, 9, 10 (placebo))	2
Efficacy Analyzable	86

At each visit, patients were asked if they had noted any unusual or unpleasant effects since their last visit. Side effects were then elicited by use of a checklist. In addition, both the patient and the investigator were asked for an overall evaluation of the previous 2 or 3-week period on a 5-point scale (1 = poor; 2 = fair; 3 = good; 4 = very good; 5 = excellent). At the end of the trial, both were asked to select a preferred period (weeks 1, 2; weeks 3, 4, 5; weeks 6, 7; or weeks 8, 9, 10).

Demographic differences between sequence groups (amantadine first or placebo first) were tested by the two-sample t-test. Categorical data such as sex, M.S. type and classification, were tested using appropriate Chi-square tests. Scores from the visual analogue scales were measured in mm from the left side and were analyzed using a cross-over analysis of variance model. McNemar's test for matched-pair data was used to compare treatment preference responses.

The pre-treatment ratings of the 13 activities of daily living were analyzed by a factor analysis model. Correlations among the 13 items were investigated. Two main factors were detected by this analysis. The first, which we named physical function, included work, going out, shopping, housework, and travel. The second, intellectual function, was made up of concentration, reading, memory, mood, and decisiveness. Three items were not loaded in either factor. They were self-care, energy level and muscles soreness. These items were accounted for in a total score of the activities of daily living which was the sum of all 13 activity scores. The physical and intellectual factor scores were each calculated by adding the score for all five activities included in each factor.

RESULTS

From May to October 1985, 165 patients entered the initial 2-week placebo run-in period. Of these, 115 had sufficient fatigue and were randomized at the second visit and 50 were excluded since they had insufficient fatigue as measured on the visual analogue scales (both mean scores <25 mm). Six did not complete the study for reasons outlined in Table 1. Two additional patients were excluded from analysis as they had been started on treatment with steroids during the trial. Of the remain-

ing 107, an additional 21 patients, who completed the study, should not have been randomized at week two since they had insufficient baseline fatigue. Since the objective was to study patients with moderate to severe fatigue, emphasis was placed on the efficacy analysis of the remaining 86 patients. For the main efficacy variables, the results of the analysis of all 107 patients are also presented. All 107, as well as the dropouts were included in the safety analysis.

Table 2 presents the demographic data for both the efficacy-analyzable patients and for all randomized patients. The characteristics of the patient population did not change significantly by excluding the protocol violators and drop-outs. There were no significant differences between the group that received amantadine during weeks 3, 4, and 5 (sequence 1) and the group that received the active treatment during weeks 8, 9 and 10 (sequence 2). Although not statistically significant, Sequence 2 had 21 males compared with 14 males in Sequence 1. Relapsing/remitting and relapsing/progressing classifications made up 81% of the efficacy-analyzable population. Spinal cord involvement was very common (93%); cerebral involvement was rare (6%). The mean duration of M.S. was 7.9 years; duration of fatigue was 4.2 years. The mean Kurtzke disability score was 4.3 with a range of 0 to 8.

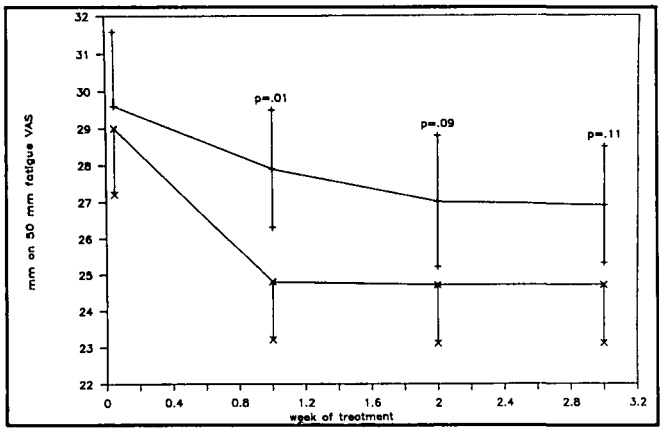

Figure 1 — Mean weekly fatigue scores (95% confidence intervals). Overall comparison of treatment periods: p<.01. x amantadine; + placebo.

A cross-over analysis of variance comparing the run-up and washout periods, detected a significant period effect: the mean fatigue severity during the washout period (27.0) was significantly lower than that during the run-up (31.6), independent of which treatment was received during weeks 3, 4 and 5 (period 1). Therefore, an analysis of covariance model was fitted for each treatment week using a mean of the two baseline fatigue severity scores as a covariate.

The mean decrease in fatigue severity was greater with amantadine than with placebo for each of the three weeks (Figure 1). It was significantly ($p<.01$) greater at week one only. In addition to the comparison at each week, an analysis of variance with repeated measures was used for an overall treatment comparison. Treatment effect was significant in favour of amantadine ($p<.01$). Furthermore, mean changes from baseline were tested within each treatment. The amantadine treatment mean change from baseline was significant ($p<0.01$) at all three weeks. The placebo treatment change from baseline was significant ($p<0.05$) for weeks 2 and 3 only.

The majority (55%) of the efficacy-analyzable patients identified walking or standing as the activity most affected by the level of fatigue (Table 3). With amantadine, the mean decrease in the effect of fatigue on the activity was significantly greater ($p<.05$) than with placebo for each of the three weeks (Figure 2). The overall treatment effect was also significant in favor of amantadine ($p<0.01$). The mean change from baseline was highly significant ($p<0.005$) for each of the three weeks of amantadine treatment, but only for the third week of placebo treatment ($p<0.05$).

The most bothersome symptoms of M.S. other than fatigue were stiffness, weakness or pain in the legs (Table 3). The most bothersome symptom did not demonstrate significant between-treatment differences ($p>.05$). Both treatments had significant decreases from baseline for two of the three weeks, with a significant between-treatment difference ($p=.02$) at week 2

Table 2: Demographic data

	All patients n = 115		Efficacy-analyzable n = 86	
	mean	s.e.m.	mean	s.e.m.
Age (years)	40.8	1.0	40.1	1.0
Weight (Kg)	65.5	1.3	*66.9	1.5
Disability Status (EDSS)	4.2	0.2	4.3	0.2
Duration of M.S. (years)	7.8	0.6	7.9	0.7
Duration of fatigue (years)	4.2	0.4	4.2	0.4
	n	%	n	%
Females	76	66	51	59
Classification				
relapsing/remitting	57	50	41	48
relapsing/progressing	33	29	28	33
chronic progressing	22	19	15	17
benign	3	3	2	2
Type of M.S.				
cord	105	91	80	93
brain stem	54	47	45	52
cerebellar	54	47	41	48
cerebral	7	6	5	6
ocular	69	60	51	59

* significant difference ($p<0.05$) between sequences.

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only. There was no significant change in disability status in either group. Disability scores were unchanged in 76% of patients. Eight patients had a lower score on amantadine than on placebo; 13 patients had lower scores on placebo.

Fatigue scores, scores of the activity most affected by fatigue, and the scores of the most bothersome symptom, were also analyzed for all patients (n = 107). This analysis included the 23 protocol violators. The overall between-treatment significance levels were all at least one order of magnitude smaller. The most noticeable difference was that the treatment effect on the most bothersome MS symptom, was now significant (p = .0002). The apparent improvement while on amantadine in the single M.S. symptom chosen by the patient was not reflected in the mean expanded disability status scores (for all patients): amantadine 4.26 (s.e.m. = 0.40), placebo 4.32 (s.e.m. = 0.41).

At the end of weeks 2, 5, 7 and 10, both the patient and investigator evaluated the preceeding two or three-week period. Twenty-one patients rated their response higher during the amantadine treatment period than during placebo; 8 patients rated it higher during the placebo treatment period (p = 0.016). The investigator's evaluation had 21 respond better with amantadine and 9 respond better with placebo (p = 0.028).

The selection of a preferred treatment period, by the patient and the physician, was also considered as an efficacy measurement. Twenty-eight patients and investigators for 28 patients did not note a preference. Five patients preferred the washout period: four following amantadine and one following placebo. Thirty-five patients (41%) preferred amantadine; 18 (21%) preferred placebo (p<0.02). Thirty-six physicians (42%) rated the amantadine period as the better period, compared to 17 (20%) who preferred the placebo period (p<0.01).

In addition to assessing fatigue severity, the patients evaluated its effect on 13 activities of daily living. Table 4 presents mean total scores and factor scores for each week and the results of the two treatment comparisons. The mean decreases in the total and factor scores with amantadine at week 2 and week 3, were statistically significant. Mean decreases with placebo were slight, and none were significant. Comparisons between the two treatments showed that the mean decreases in the physical function factor score with amantadine were significantly greater than those with placebo (p<.05) over the 3 weeks of treatment.

At weeks 2, 5, 7 and 10, the patients were also assessed with a Beck Depression Inventory evaluation (21 item version) and the total score was recorded. There was no significant difference in mean Beck Inventory Score between amantadine (mean = 7.34, s.e.m. = 0.81) and placebo (mean = 7.59, s.e.m. = 0.84) treatment periods.

At each visit, the patients reported any adverse experiences. All 115 patients who received coded medication were included in the tabulation regardless of their status in the efficacy analysis. After an open-ended probe, patients were specifically questioned about 13 adverse experiences. There was no significant difference between the percentage of patients reporting adverse experiences in the two treatments: amantadine (57%) and placebo (54%) (Table 5). In comparing each adverse experience between the two treatments, the only one with a significant difference was insomnia. Thirteen patients had insomnia only with amantadine, while four patients had insomnia only with placebo (p = .029).

Table 3: Activities and symptoms

	n	%
Activity most affected		
walking/standing	47	55
housework	16	19
grooming	6	7
working	4	5
going out	3	3
reading/concentrating	3	3
other	7	8
Most bothersome symptom		
legs (stiff, weak or sore)	22	26
balance	13	15
bladder and bowel control	3	3
visual disturbances	9	10
walking	4	5
backache	2	2
numbness	7	8
weakness in hands or arms	5	6
spasms	4	4
general weakness	5	6
pain	3	3
incoordination	2	2
other	7	8

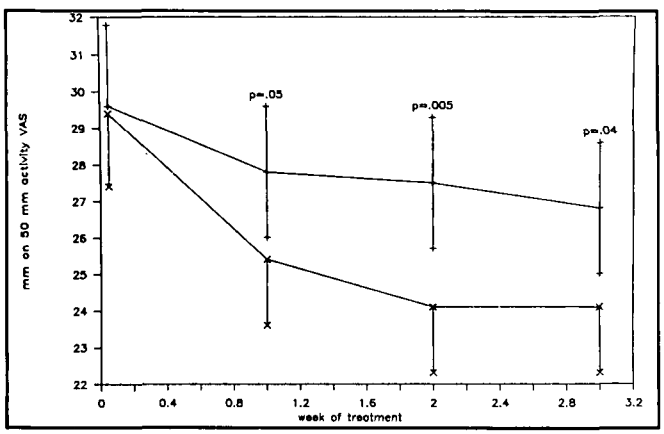

Figure 2 — Mean weekly scores of the effect of fatigue on a selected activity (95% confidence intervals). Overall comparison of treatment periods: p < .01. x amantadine; + placebo.

Discussion

The major problems in this study were the definition and measurement of fatigue. Fatigue in multiple sclerosis appears to be different from 'normal' fatigue. During the initial stages of the protocol development, we arrived at the following definition of fatigue: a sense of tiredness or lack of energy, of unknown origin, greater than expected for the daily effort and the degree of disability, and which significantly interferes with the desire or ability to perform basic, daily, physical and intellectual functions. The results of the study suggest that patients with a greater degree of disability do not necessarily have a greater degree of fatigue. Improvements in fatigue were not accompanied by changes in the disability scores. Furthermore, there was no correlation between improvement in fatigue and improvement in the M.S. symptom most bothersome to the patient.

At the end of the initial 2-week run-up period, 30% of the patients were eliminated from the study due to low baseline fatigue scores. Prior to the study, these patients had all com-

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plained of moderate to severe persistent daily fatigue. It is unlikely that they had all over-emphasized the extent of their fatigue. It is more likely that either they did not understand the use of the visual analogue scale or that the scale was not the most appropriate tool to measure fatigue. Another plausible explanation is that there was a high placebo response during this initial 2-week period. In separate editorial reviews, both McFarlin[11] and Noseworthy[12] have remarked that the placebo effect is common in therapeutic trials in M.S.

It was interesting to note that the major influence of fatigue in these patients appeared to be on physical rather than intellectual functions. This was shown both by the patient's choice of the most affected activity, as well as by the analysis of the activities of daily living. It also appears that measuring the

Table 4: Mean total score, physical function factor and intellectual function factor weekly between treatment comparisons and change from baseline

Response	Amantadine n	Amantadine Mean	Amantadine s.e.m.	Placebo n	Placebo Mean	Placebo s.e.m.	Between Treatment Diff.
Total Score (13 Items)							
Baseline	86	26.56	1.13	86	26.16	1.06	
Week 1	86	25.06	0.74	85	25.10	0.74	.89
Week 2	85	23.55*	0.74	86	25.08	0.74	.16
Week 3	86	24.09*	0.74	86	25.85	0.74	.09
Physical Function Factor (F1)							
Baseline	86	11.78	0.49	86	11.54	0.51	
Week 1	86	10.96	0.31	85	11.41	0.31	.25
Week 2	85	10.73*	0.31	86	11.27	0.31	.195
Week 3	86	10.76*	0.31	86	11.64	0.31	.04
Intellectual Function Factor (F2)							
Baseline	86	8.50	0.60	86	8.26	0.55	
Week 1	86	8.23	0.35	85	7.71	0.34	.37
Week 2	85	7.47*	0.35	86	7.77	0.35	.57
Week 3	86	7.67*	0.35	86	8.25	0.34	.19

* significant change from baseline, $p<0.05$

F1 includes work, going out, shopping, housework and travel.
F2 includes concentration, reading, memory, mood and decisiveness.

Table 5: Summary of adverse experiences: number of patients tabulated by study period

	STUDY PERIOD			
	Pre-Amantadine Placebo 2 Weeks	Amantadine Treatment 3 Weeks	Pre-Placebo Placebo 2 Weeks	Placebo Treatment 3 Weeks
Number of patients treated	115	115	115	115
Number of patients reporting adverse experiences	51	66	57	62
Number of occurrences	116	159	117	136
Percentage of patients reporting adverse experiences	44%	57%	50%	54%
Adverse Experience				
Hallucinations	0	1	0	0
Nightmares	0	6	1	2
Anorexia	2	6	4	7
Ataxia	8	12	11	10
Insomnia*	12	34	13	19
Dizziness	8	14	8	8
Headache	20	16	22	19
Convulsions	0	0	0	0
Anxiety	8	10	6	4
Nausea	12	7	8	9
Vomiting	1	4	1	2
Edema	4	2	5	9
Congestive Heart Failure	0	0	0	0
Other	41	49	38	47

* significant difference in number of episodes between amantadine and placebo treatment periods, $p<0.05$.

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effect of fatigue on activities, especially one pre-selected by the patient, is more sensitive than simply asking patients to rate fatigue. It has been shown in rheumatoid arthritis, that the evaluation of a function chosen by the patient, shows the greatest change with treatment (as compared to rating pain).[13]

Even after being defined, fatigue remains difficult to measure. Fatigue, its effect on a pre-selected activity, and on activities of daily living, were all measured on visual analogue scales. These scales have been widely used to measure feelings, functional capacity and pain. They are more sensitive to small changes than categorical scales, and more powerful statistical tests can often be applied to the data. However, a greater understanding on the part of the patient, and some training, are required.

As is the case with pain, fatigue is usually accompanied by other sensations. The patient's interpretation of a constant level of fatigue may vary according to the intensity of other sensations. The Beck Depression Inventory scores suggest that in this study, depression did not play a detectable role in the patient's interpretation of fatigue. Other unknown and unmeasured factors may have confounded the measurement of fatigue.

Fatigue scores, patient and physician ratings, physical activities of daily living, and patient preferences, all point to the same conclusion: amantadine decreases fatigue. Although statistically significant, the reduction in fatigue as measured by visual analogue scales, was small and the clinical significance is unclear. Perhaps more meaningful is the finding that a significant proportion of patients found amantadine preferable to the placebo. This suggests that amantadine may have a role in the control of fatigue in M.S.

The results of a recent study by Plaut[14] also suggest that amantadine may have a beneficial effect in M.S. As in our study, the neurological state and disability status were unchanged by treatment with amantadine. However, Plaut reported a significant reduction in the rate of relapse in the amantadine-treated group. Although no significant alteration in mood was detected, mild relapses may have gone unnoticed in patients who felt mildly stimulated by amantadine.[14]

Although the mechanism of this moderate reduction of fatigue by amantadine is unknown, it could possibly be a non-specific, general CNS stimulation. At therapeutic doses, amantadine increases the release of noradrenaline (NA) as well as dopamine, from terminal nerve fibers in the CNS.[15] This increase in dopamine, and probably amantadine's anticholinergic effects, contribute to its beneficial effect in Parkinson's disease and in drug-induced extra-pyramidal disorders. An increase in the CNS release of NA is the mechanism of action of amphetamines. The insomnia reported by patients in this study, is consistent with a non-specific CNS stimulation. Insomnia is also a complaint of Parkinson's patients taking amantadine. Amantadine has, however, been reported to be ineffective in the treatment of narcolepsy.[16,17]

Based on these results, trials of amantadine may be warranted on individual patients with M.S., whose activities of daily living are restricted by fatigue. However, the routine use of amantadine does not appear to be justified before further studies better define the risk/benefit ratio of this therapy. These studies should include scales measuring the effect of amantadine treatment on the quality of life of patients with multiple sclerosis.

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