Four-Year Treatment of Patients with Parkinsonism Using Amantadine Alone or with Levodopa

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Half of 94 parkinsonian patients improved on amantadine therapy during acute double-blind trials. In a four-year follow-up, amantadine given alone or added to a stable dose of levodopa had its greatest effect in the first month and helped few patients after six months. Levodopa either alone or added to a stable dose of amantadine had a beneficial effect lasting three years or more.

The side-effects of edema and livido reticularis occurred twice as often in women. Confusion and hallucinations appeared sooner on a regimen of 300 mg of amantadine a day, but the ultimate incidence was the same on 200 mg a day. Withdrawal effects from amantadine are no less frequent or serious than from other antiparkinson medications and are not evidence that amantadine is still helping the patient. Considering the years of exposure, the morbidity and mortality do not indicate any risks peculiar to amantadine. Our mortality in all groups combined was 2.4 times that of the age- and sex-matched United States population.

Timberlake WH, Vance MA: Four-year treatment of patients with parkinsonism using amantadine alone or with levodopa. Ann Neurol 3:119–128, 1978

In 1968 a 58-year-old patient reported to Dr R. S. Schwab that her parkinsonian symptoms had decreased while she had been taking amantadine to prevent the flu [17]. In an open trial he confirmed her improvement and that of other patients on anticholinergic drugs or levodopa [18]. To determine the benefits and risks of amantadine, in 1970 we initiated three acute, double-blind, placebo-controlled trials of amantadine at 200 or 300 mg a day administered alone or in combination with levodopa. Quantitative as well as qualitative assessments were continued at monthly and then at three-month intervals. Some patients had a double-blind challenge at six months or at longer intervals. We compared the effects, particularly using a hand ergometer, the side-effects, and the complications resulting from the use of amantadine, levodopa, or both in our patients after the first four years of treatment.

Material

The 94 patients participating in this treatment program had been referred to the Lemuel Shattuck Hospital by their family doctor or neurologist for treatment of parkinsonism. Each patient received an explanation of the study, including the nature of a double-blind trial which would involve periods of placebo treatment. They were assured that they could leave the program at any time for any reason without prejudice to their continued treatment at the hospital. All consented.

As indicated in Table 1, one-third of the patients were women. The age of the patients and the duration, cause, and prior treatment of the disorder were not remarkable compared with the general parkinsonian population. Most patients had impaired balance but were not confined to a wheelchair (Stage III or IV according to the Hoehn-Yahr scale [7]) at the time they entered the study.

Methods

Medication

During the initial trials, because of the great variability in the disease, each patient served as his or her own control. Amantadine, 100 mg, and its placebo were supplied (courtesy of Dr M Paulshock of E I du Pont Company) in identical capsules and administered as scheduled in Table 2. Levodopa, 500 mg, and its placebo were likewise supplied in identical capsules and increased by one capsule a day during treatment periods (reduced if side-effects occurred).

Patients already on antiparkinson medications were tested for one week on that medication. Then they were weaned as completely as was tolerable from anticholinergics and, in the first study, levodopa (3 patients). They were tested for one week on this "baseline" medication, which was continued unchanged throughout the acute trial periods. Tranquilizers and sedatives were proscribed. On careful comparison, anticholinergic medication did not appear to alter the response to amantadine, and those patients remaining on anticholinergics are not separated in the analysis of the response presented here.

In the "1970 inpatient" nine-week study, each of 33 patients was randomly assigned to one of four treatment

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Accepted for publication July 20, 1977.

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Table 1. Patient Data in the Amantadine Study

Factor	1970 Inpatient[a]	1971 Outpatient	1972 Study	Total
Male	21 (16)	17	24	62
Female	12 (11)	3	17	32
Total	33 (27)	20	41	94
Age range	51–81 (52–77)	43–74	35–79	35–81
Mean	63.2 (62.5)	64.5	63.8	63.8
Mean duration	8.3 (7.7)	11.0	9.4	9.1
Stage I	1 (0)	0	0	1
Stage II	2 (1)	1	5	8
Stage III	8 (8)	11	14	33
Stage IV	18 (14)	7	20	45
Stage V	4 (4)	1	2	7
Probable or definite postencephalitic disease	3 (2)	2	2	7
Progressive supranuclear palsy	1 (1)	1	1	3
Stereotaxic operations				
Unilateral	1 (1)	5	3	9
Bilateral	0 (0)	2	2	4

[a]Numbers in parentheses refer to those patients subsequently put on levodopa.

Table 2. Protocols for Initial Amantadine, Placebo, and Levodopa Treatments

Week:	1	2	3	4	5	6	7	8
1970 INPATIENT STUDY OF 33 PATIENTS[a]								
	2 Plac Amant	2 Amant	2 Amant & L-dopa			2 Plac Amant & Plac L-dopa		
	2 Plac Amant	2 Amant	2 Amant & Plac L-dopa			2 Plac Amant & L-dopa		
	2 Amant	2 Plac Amant	2 Plac Amant & L-dopa			2 Amant & Plac L-dopa		
	2 Amant	2 Plac Amant	2 Plac Amant & Plac L-dopa			2 Amant & L-dopa		
1971 OUTPATIENT STUDY OF 20 PATIENTS[b]								
	2 Plac Amant		2 Amant		3 Plac Amant		3 Amant	
	2 Amant		2 Plac Amant		3 Amant		3 Plac Amant	
	3 Plac Amant		3 Amant		2 Plac Amant		2 Amant	
	3 Amant		3 Plac Amant		2 Amant		2 Plac Amant	
1972 OUTPATIENT STUDY OF 41 PATIENTS[c]								
	3 Plac Amant		Amant & Plac Amant & Amant		3 Amant		. . .	

[a]Baseline medication: 7 patients on anticholinergics.
[b]Baseline medication: all on levodopa, 2 on anticholinergics.
[c]Baseline medication: 15 on levodopa, 3 on anticholinergics, 16 on levodopa and anticholinergics.

Amant = amantadine; Plac = placebo; L-dopa = levodopa.

schedules (see Table 2). We compared double-blind with placebo control for the following regimens: (1) the effect of amantadine alone for one, three, or four weeks; (2) the effect of levodopa alone for three weeks; and (3) the effect of amantadine and levodopa for three weeks.

All 20 patients in our "1971 outpatient" trial were on an optimum dose of levodopa. Their amantadine assignments are shown in Table 2.

In our "1972 outpatient" study with 41 patients, a week's supply of "amantadine" capsules was loaded into a disc that dispensed one capsule at a time in order, for three doses a day. The order of treatment (200 or 300 mg per day or placebo) was randomized.

After these initial trials had been completed and the responses evaluated, the code for that patient, which had been sealed in a separate envelope, was broken. If the patient had done well or the response was equivocal, the optimum dose of new medication was continued. If the

response to amantadine was poor and the patient was not already using levodopa, levodopa was added.

Testing

During the initial trials and the challenge periods, inpatients were tested daily and outpatients, twice a week. During the open periods of the study, patients were tested at their monthly or three-month clinic visit. All results were referred to the mean baseline score of each individual. The following categories were considered.

1. Akinesia was measured using a Schwab ergograph to which a work-adder was attached to give a total score in units for one minute of effort for each hand. The results for the weaker hand are reported here. To illustrate control values, the results for the normal spouse of the patient on this and other tests are included in Table 4.
2. Rigidity was estimated during passive flexion and extension of the right and left wrists. Each motion was scored on a scale of 0 to 4. The maximum score for complete rigidity would be 16.
3. Tremor was estimated on a 0 to 4 scale for each extremity. Maximum tremor for the four extremities would be 16. Quantitation using an accelerometer and integration of the half cycles was unsuccessful because of difficulties in maintaining the equipment.
4. The size of the patient's handwriting was assessed by measuring the length of the handwritten sentence "This is the way I write today" from the vertical of the T to that of the y. Improvement increased the length of the sentence.
5. Time to walk 3 m, turn, and return was measured in seconds. If a patient walked only with assistance, that was recorded. When a patient walked sometimes alone and other times with assistance, the duration of time after the change, being incommensurable, was not used in this report.

Various activities of daily living were also timed, but the results varied too widely for meaningful correlation with treatment.

Because the disabilities of the patients were so different, comparisons of unit scores or of "percentage improvement" tend to be distorted. For the ergometer tests, reported in most detail here, we divided patients into three groups according to their baseline scores. We then determined the standard deviation from the mean to obtain ergometer scores for individual patients in each group. The 26 patients of Group 1 had ergometer scores of 0 to 10 and an average SD of 2.9. The 46 patients of Group 2 had ergometer scores of 11 to 100 and an SD of 15.9. The 22 patients of Group 3 had ergometer scores from 101 to 238 and an SD of 17.4. In this way, we were able to consider the number of patients in a particular circumstance who changed by 1 or 2 SD from their baseline scores.

A checklist of side-effects, including "other," was completed at each testing.

Results

Short-Term Effects

AMANTADINE AT 200 MG VERSUS PLACEBO AND WITH LEVODOPA (1970 INPATIENT STUDY). Some of the 33 patients noticed improvement the first day they were given amantadine. During the first week, the ergometer scores for half the patients improved by one or two SD. This ratio continued in the smaller groups for the four weeks of double-blind treatment (Table 3).

During the placebo period, although the change varied as much as 2 SD, the number of patients who improved was counterbalanced by the number who became worse. When placebo followed amantadine, improvement was not maintained.

When levodopa was gradually added to the placebo, there was no change in mean ergometer score the first week. During the second week the mean score improved 8 units and during the third week, 11 units.

When levodopa was gradually added to amantadine, the scores were already 10 units better than baseline, and they showed no further change until the third week, when they too improved an average of 11 units.

Following the same schedules, rigidity and walking time were improved to a degree similar to the changes measured by ergometer. Sentence length was less responsive, and tremor was not altered (Table 4).

ACUTE EFFECT OF AMANTADINE AT 200 MG VERSUS 300 MG (1971 AND 1972 OUTPATIENT STUDIES). Among the 61 patients in the two cross-over comparisons of 200 and 300 mg of amantadine versus placebo, 5 were taking no other medication, 5 were on anticholinergic drugs, 33 were on levodopa, and 18 were on levodopa plus an anticholinergic medication.

One-third of the patients (21 of 61) improved while on 300 mg of amantadine, one-fourth (14 of 61) while on 200 mg of amantadine, and one-tenth (6 of 60) while on the placebo (Table 5). The severity of the initial disability did not affect the response. Chi-square distribution analysis showed a significant difference ($p < 0.05$) only when a dosage of 300 or 200 mg of amantadine is compared with the placebo.

Ten patients in the "1971 Outpatient" group received the placebo twice, once before and once after amantadine. The mean ergometer scores in these periods were 103 units and 87 units, respectively. This suggests a withdrawal effect after amantadine was stopped.

Long-Term Effects

During the open, long-term follow-up, the responses of 87 patients were evaluated only up to the next change in type of medication, if any. We considered the patients in four categories, irrespective of anticholinergic medication: (1) patients on amantadine alone; (2) patients on a stable dose of levodopa to which amantadine was added; (3) patients newly started on levodopa without amantadine; and (4) patients who had levodopa added to amantadine at the end of the acute trials.

Table 3. Number of Patients Changing Ergometer Scores during Early Weeks on Amantadine Alone or on Placebo[a]

	Worse			Better	
Week	−2 SD	−1 SD	No Change	1 SD	2 SD
33 PATIENTS ON ONE-WEEK TRIAL[b]					
1	0 (2)	1 (2)	19 (25)	7 (4)	6 (2)
7 PATIENTS ON THREE-WEEK TRIAL					
1	0 (0)	0 (1)	4 (4)	3 (0)	0 (1)
2	0 (0)	0 (1)	5 (5)	0 (0)	2 (1)
3	0 (0)	1 (1)	4 (5)	0 (0)	2 (1)
7 PATIENTS ON FOUR-WEEK TRIAL					
1	0 (1)	0 (0)	3 (4)	0 (0)	4 (2)
2	0 (1)	2 (0)	3 (5)	1 (1)	1 (0)
3	0 (1)	1 (0)	4 (5)	1 (1)	1 (0)
4	1 (1)	1 (1)	2 (5)	1 (0)	2 (0)

[a]Numbers in parentheses are the responses during the corresponding placebo periods.
[b]By chi-square analysis, the difference between amantadine and placebo is significant ($p < 0.05$) for these 33 patients.

Table 4. Differences between Double-Blind Treatments during the Acute Trials

	Ergometer[a]			Rigidity[b]			Sentence Length[c]			Walk Time[d]			Tremor[e]		
Therapies 1 and 2	No.	Mean on 1	Change on 2	No.	Mean on 1	Change on 2	No.	Mean on 1	Change on 2	No.	Mean on 1	Change on 2	No.	Mean on 1	Change on 2
Plac, Amant 2															
1970	33	31.5	9.6[f]	33	4.7	1.1[g]	31	7.3	0.4[h]	31	15.8	2.5[g]	15	3.1	0.1
1971	20	92.1	11.8[g]	20	4.2	1.1[f]	20	8.8	0.5	19	9.0	0.3	17	1.8	0.3
1972	40	52.5	11.2[f]	41	5.8	1.7[f]	39	8.5	0.5	37	12.1	1.7[f]	22	2.2	0.3
Total	93	54.2	10.8[f]	94	5.0	1.4[f]	90	8.2	0.5[g]	87	12.7	1.7[f]	54	2.3	0.2
Plac, Amant 3															
1971	20	92.1	15.5[h]	20	4.1	0.7[h]	20	8.8	0.3	19	9.0	0.8[h]	17	1.8	0.5
1972	40	52.5	14.4[f]	41	5.8	2.1[f]	39	8.5	0.3	37	12.1	2.0[f]	21	2.1	0.4
Total	60	65.7	14.8[f]	61	5.2	1.6[f]	59	8.6	0.3	56	11.0	1.6[f]	38	2.0	0.5[h]
Amant 2, Amant 3															
1971	20	103.9	3.8	20	3.0	−0.5[i]	20	9.3	−0.1[i]	20	9.4	0.5	17	1.4	0.2
1972	41	62.3	3.3	41	4.1	0.4	41	8.9	−0.1	39	10.8	0.6	22	1.8	0.1
Total	61	75.9	3.5	61	3.8	0.2	61	9.0	−0.1	59	10.3	0.6[h]	39	1.7	0.2

[a]Normal: men, 120 ergometer units; women, 63 ergometer units.
[b]Scale of 0 to 4 for four movements.
[c]Normal: men, 13.7 cm; women, 14.6 cm.
[d]Normal: men, 7 seconds; female, 6.8 seconds.
[e]Scale of 0 to 4 for four limbs.
[f]Significance: $p < 0.001$ (Student t test).
[g]Significance: $p < 0.01$ (Student t test).
[h]Significance: $p < 0.05$ (Student t test).
[i]Negative change means deterioration on therapy 2.

Plac = placebo; Amant 2 = amantidine, 200 mg per day; Amant 3 = amantidine, 300 mg per day.

Table 5. Number of Patients Changing Ergometer Scores among 61 on an Initial Trial of Amantadine or Placebo

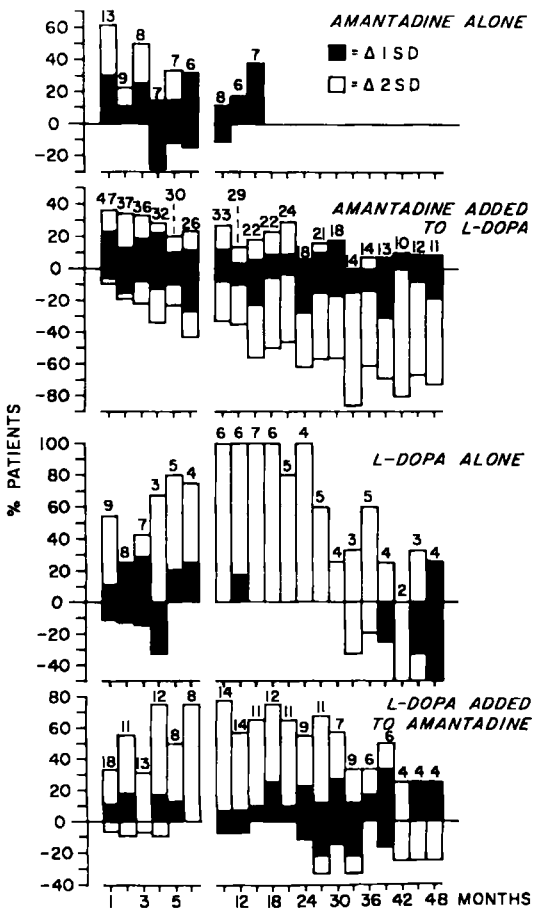
	Worse			Better	
Treatment	−2 SD	−1 SD	No Change	1 SD	2 SD
Amantadine, 300 mg/day	2	1	37	14	7
Amantadine, 200 mg/day	4	1	42	9	5
Placebo	5	10	39	5	1

Patients in the second category—i.e., those who were already on levodopa—had baseline ergometer scores that were about twice as high as those in the other groups (category 1, 29 units; category 2, 80 units; category 3, 44 units; and category 4, 31 units). This was not unexpected. The Hoehn-Yahr classifications of the category 2 patients were also better.

CATEGORY 1: AMANTADINE ALONE. Thirteen patients did well enough during the initial trial to continue without levodopa: 7 on 200 mg and 6 on 300 mg a day. Five were also on anticholinergics. From the second to the twenty-first month there was an evenly distributed attrition of 12 patients: 5 due to side-effects, 4 requiring the addition of levodopa, and 3 failing to return.

At one month, 9 of the 13 patients had ergometer scores that improved by 1 SD or more (Fig 1). At three months only half of those remaining on amantadine scored better. At six months only 2 patients were improved. One patient maintained his improvement until his death at sixteen months. The last patient who came for testing at twenty-one months was unimproved. She could not tolerate levodopa before and remained on amantadine plus procyclidine; at the time of writing she was only able to feed herself.

Fig 1. Percentage of patients on the four treatments whose ergometer performance changed by 1 or 2 SD during forty-eight months. The number above the bar is the number of patients tested at that time. The scale is monthly for the first six months.



CATEGORY 2: LEVODOPA PLUS AMANTADINE. Forty-seven patients on a stable dose of levodopa (1971 and 1972 studies) were continued on amantadine, 18 on 200 mg and 29 on 300 mg a day.

At one month, ergometer scores in one-third of the patients were improved by 1 SD or more. This was still true at three months, but at that time one-fifth were worse. Thereafter, more patients were worse than were better. From thirty-six months on, only 1 patient, on 300 mg, maintained improvement.

Again, side-effects caused an even attrition; by the end of four years, half of the patients had had to be taken off amantadine.

CATEGORY 3: LEVODOPA ALONE. Of the 9 patients started on levodopa without amantadine after the acute trials, 4 of 8 tested were better at one month. At three months, 2 patients had not improved and did not return. From the sixth to the twenty-fourth month, all of the 7 remaining patients were better (2 SD). At forty-eight months, 1 of the remaining 4 patients remained improved and 2 were worse.

CATEGORY 4: AMANTADINE PLUS LEVODOPA. Eighteen patients on amantadine, 200 mg per day, had levodopa added. From the twelfth month on, side-effects necessitated withdrawing amantadine from 3 patients.

The ergometer scores of 6 patients were better (more than 1 SD) at one and three months. From six to twenty-four months, 7 of the 9 tested were improved. At thirty months, 3 patients were still better and 1 was worse. At forty-eight months, only 1 of the 4 patients tested was better and 1 was worse.

The maximum ergometer response to amantadine alone or to levodopa plus amantadine occurred within the first month and lessened substantially from then on. These two categories are combined in Figure 2 as the "amantadine" lines. On the other hand, patients started on levodopa alone reached a peak improvement at eighteen months and began to worsen at thirty-six months. When levodopa was added to amantadine, the levodopa pattern predominated. These two groups are combined in the "L-dopa" lines of Figure 2. The distinction is less clear-cut in the assessment of handwriting and is obscure in the test for walking time (Fig 2).

We saw no beneficial effects from amantadine on

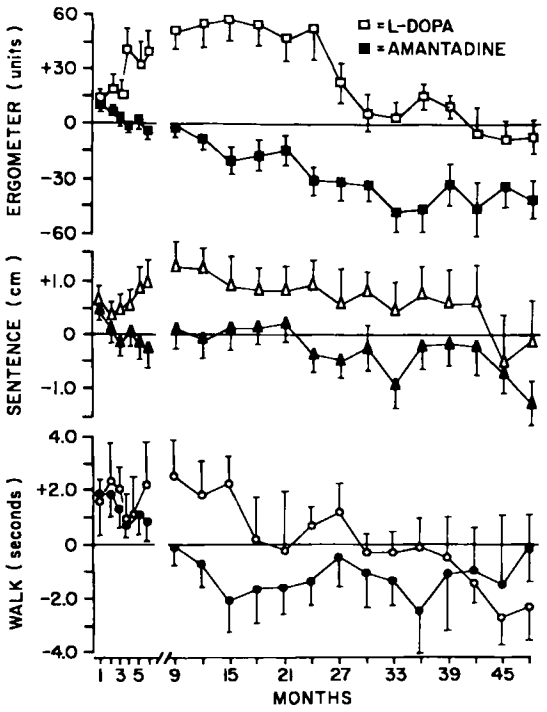


Fig 2. Comparison of the response curves for levodopa and amantadine (see text) for ergometer, sentence length, and walking time. The bars represent 1 SE about the mean. The scale is monthly for the first six months.

the oculogyric crises of 5 patients. Of the 3 patients with progressive supranuclear bulbar palsy, 1 improved with amantadine but improved further when it was combined with levodopa, and 2 were unchanged when amantadine was added to levodopa.

Side-Effects

Side-effects that either appeared for the first time or increased while the patient was on a treatment were considered to be related to that treatment. The incidence of such apparently drug-related side-effects is shown in Table 6, in which the incidence of side-effects from levodopa is also given for each treatment group. Dyskinesia, nausea, and hypotension did not appear to be affected by the use of amantadine.

The *peripheral side-effects* of amantadine—edema of the lower legs and livedo reticularis—occurred in one-third of our patients. They appeared twice as often among the women ($p < 0.05$ by chi-square test). This is a sex relationship noticed for livedo reticularis by Shealy and co-workers [19]. A 25% greater frequency at a dosage level of 300 mg than at 200 mg was not statistically significant.

As described by others [20], livedo reticularis first appeared on the anteromedial thighs, spread over the lower legs, and was seen last on the anteromedial forearms. From a faint, lavender network it sometimes intensified to an almost black-purple color over a few minutes, a symptom perhaps related to emotional stress. It appeared any time from two weeks to twenty months after amantadine was initiated, but most frequently during the third to sixth month. At times its occurrence seemed to be dose related, but other times it fluctuated counter to the dose of amantadine. In 2 patients it continued two and three years, respec-

Table 6. Side-Effects[a,b]

	Initial Period				Long-Term Follow-up			
Side-Effects	Amant N = 42)	Amant Added to L-dopa (N = 52)	L-dopa (N = 16)	L-dopa Added to Amant (N = 17)	Amant (N = 13)	Amant Added to L-dopa (N = 47)	L-dopa (N = 9)	L-dopa Added to Amant (N = 18)
Confusion and/or hallucinations	3 (1)	6 (3)	2 (2)	2 (1)	5	19	2	7
Edema	2 (0)	3 (0)	0 (0)	0 (0)	8	25	2	11
Livido reticularis	1 (0)	2 (0)	0 (0)	0 (0)	5	23	0	6
Involuntary movements	0 (0)	26 (27)	6 (0)	11 (0)	0	27	6	9
Nausea and/or vomiting	1 (1)	2 (1)	7 (0)	10 (4)	0	2	3	4
Anorexia	1 (0)	1 (0)	2 (0)	1 (0)	0	1	1	2
Symptomatic hypotension	1 (0)	0 (0)	2 (0)	2 (0)	0	0	2	0

[a]Numbers in parentheses refer to number of patients experiencing side-effects in corresponding placebo periods.
[b]With the exception of involuntary movements, long-term side effects are recorded only if the effect first appeared or increased while the patient was taking the drug during the follow-up period.

Amant = amantadine; L-dopa = levodopa.

tively, after amantadine was stopped. The daughter of 1 of these patients also had livedo reticularis, but it was not due to amantadine.

Many parkinsonian patients have stasis edema. We have reported only the instances in which edema appeared for the first time or increased while the patient was on amantadine and was otherwise unexplained. Its occurrence did not seem to be related to prior edema. Edema and livedo may develop independently, though both occurred in 27 of our patients. One woman had massive, painful edema reaching to the groin. It cleared only after amantadine treatment was stopped, bedrest was initiated with legs elevated, and diuretics were given. Venograms disclosed no occlusive disease.

The *central side-effects* of amantadine—confusion and hallucinations—occurred more often in elderly patients, as expected. Forty-seven percent of those over 65 years old experienced these effects as opposed to 23% of younger patients ($p < 0.05$). Hallucinations appeared earlier in patients who were on 300 mg of amantadine, but the ultimate incidence was the same on 200 mg. The incidence of confusion was greater on 300 mg of amantadine but did not reach statistical significance. The proportion of confused patients in our small series was not significantly greater when amantadine was given in combination with anticholinergic medication or levodopa. However, in 2 patients who underwent repeated trials, hallucinations cleared when either 100 mg of amantadine or 500 mg of levodopa was removed, which suggests an additive effect.

The peak incidence of confusion ranges from the third to the ninth month. Only once did hallucinations begin after more than a year of amantadine. The latest appearance of confusion was in the third year. The peripheral and central side-effects seem to be independent; either may precede the other by up to twelve months.

Probably because we had reduced the anticholinergic medications as much as possible, none of our patients had atropine poisoning as reported by Schwab and associates [18]. During the initial trials, 2 patients on anticholinergics had an increase of dry mouth and blurred vision when they were given amantadine but not when they received a placebo. These symptoms did not occur with amantadine alone, although a recent study suggests that the action of amantadine may have an anticholinergic component [14].

Laboratory Tests

As previously observed with levodopa, elevation of blood urea nitrogen occurred in 6 patients, once to 50 mg per deciliter, during the acute trials while these patients were receiving amantadine (3 not on levodopa); none of the patients receiving placebo had an elevation in BUN. Transient elevations of alkaline phosphatase occurred during the initial periods in 3 patients. During the follow-up period, alkaline phosphatase rises persisted for more than two years in 5 other patients on levodopa. In 1 of these patients, this was possibly related to carcinoma of the bile duct. In another the elevation persisted after amantadine was discontinued.

Three patients had persistently positive Coombs' tests while they were taking levodopa, 2 before and 1 two months after starting amantadine.

Serial electroencephalograms were not affected except in a 36-year-old woman with preexisting adrenal insufficiency. She had previously had mild, generalized, low-voltage slowing on levodopa, 3.7 gm, and procyclidine, 15 mg a day. The slowing decreased when she received 1 gm of levodopa. After she had taken 300 mg of amantadine a day for two weeks, the EEG showed 25-second paroxysms of generalized high-voltage, 6 Hz slow waves occasionally preceded by spikes. There was no abnormal movement or impairment of consciousness. The paroxysms stopped when she was asked to close her eyes. During the subsequent period when she was taking 200 mg of amantadine a day, there were 1-second paroxysms of generalized sharp activity in the theta range but no spikes. Both times the activation had only physiological effects. She was discharged to a nursing home and no further EEGs were done. She was taken off amantadine twenty months later. After a year and a half, while on Sinemet (combination of carbidopa and levodopa), she began to have generalized jerking seizures. This patient died a few months later. At autopsy the brain abnormalities were only those of mild parkinsonism.

Withdrawal

When antiparkinson medication is reduced quickly, some patients have an increase in symptoms. Sixteen of 31 patients entering our studies on anticholinergic medications could not tolerate complete reduction of their medication in preparation for the baseline period.

During the initial trials, a sixth of the placebo periods had to be cut short when they followed amantadine. This intolerance of amantadine withdrawal was greater among patients who had not tolerated withdrawal from anticholinergic drugs (5 of 11) than among those who had (1 of 12). Patients who had difficulty when amantadine was withdrawn after one or two weeks during the initial trial were twice as apt to have difficulty when it was withdrawn again after months or years of amantadine treatment.

Reversal of the withdrawal effects by introducing amantadine treatment again is not an indication of a continued beneficial effect of that medicine. The

withdrawal and its effect often occurred long after the ergometer scores had fallen below baseline in the follow-up period. As with most withdrawal effects, it was self limited (Fig 3). In 17 patients who had amantadine stopped permanently because of side-effects, the ergometer score fell by 24 units ($p < 0.01$) during the first week, but then improved gradually (Fig 4).

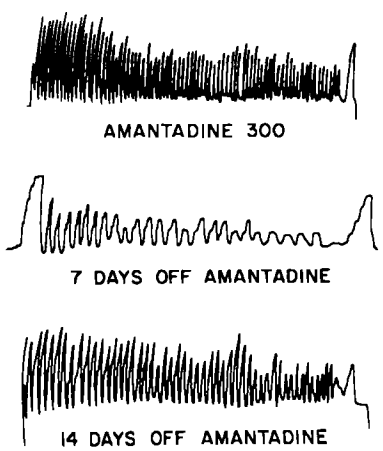
Withdrawal from amantadine, as from anticholinergic drugs or levodopa, may not only be distressing but also may lead to life-threatening complications, particularly pneumonia. Two of our patients had difficulty breathing and swallowing. This necessitated transfer to the intensive care unit where their aspiration pneumonia was successfully treated.

This withdrawal effect is not just a psychological reaction to a decrease in the number of capsules being taken. When a placebo was substituted for amantadine (double-blind) during twenty-five challenge periods, the condition of 10 patients worsened by more than 1 SD on the ergometer; only 1 patient was better. Thereafter, we dropped the placebo from the challenge protocol. We were not able to prevent the withdrawal effect by increasing anticholinergic medication or levodopa, nor could it be avoided by lowering the amantadine 100 mg on alternate days at one-week intervals.

Retreatment

Schwab [18] reported that 5 patients who did not respond at first to treatment did so when retried months later. Two of our patients who did not respond initially and who were retried more than a year later still failed to respond. Two of 3 patients who responded initially but who were taken off the treatment because of side-effects responded when retried later, but edema again developed in 1.

Fig 3. Spontaneous recovery of the ergograph in a patient after withdrawal from amantadine, 300 mg per day, while on levodopa, 5.5 gm per day.



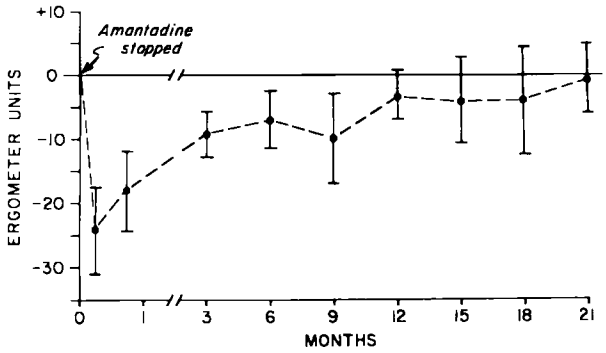


Fig 4. Recovery of ergometer scores in 19 patients following withdrawal of amantadine. Not all of the patients were tested at each interval. The bars indicate the standard error about the mean. Note the change of scale at one month.

Morbidity and Mortality

There were no deaths during the initial trials. In the follow-up period, when years of exposure to the particular treatment were taken into account, there appeared to be no mortality or morbidity peculiar to amantadine (Table 7).

Because of the peripheral vascular effects of amantadine, we were concerned about possible coronary vascular effects. We saw no relevant changes in electrocardiograms. Angina developed in 2 patients who were taking amantadine, but there were no EKG changes and the angina resolved without any decrease in amantadine. Three patients who had been on amantadine, 300 mg, for more than a year had cerebral infarcts.

Schwab and associates [18] mentioned a patient who had seizures at an amantadine dosage of 800 mg daily. Critchley [5] reported 1 patient who had convulsions on 300 mg a day. In our series, a 72-year-old man whose EEGs were normal during the initial trials had several grand mal seizures and stupor without focal neurological changes after three months of amantadine at 300 mg. The seizures were controlled by anticonvulsant medication. His EEGs showed only diffuse, mild slowing. At autopsy, including the brain, no cause for the seizures or the stupor was found.

From the onset of our study to the cutoff date of August, 1976, the mortality rate in our 94 patients on all treatment regimens was 2.4 times that of the age- and sex-matched normal United States population [22]. There were fewer women in the study; their adjusted mortality rate was 3.1, compared with 2.2 for the men.

The three most frequent causes of death among our patients were pneumonia, cardiac disease, and neoplasm (Table 8). This is in agreement with the finding of others [7, 10]. In our small sample, the deaths from amantadine were not excessive. The 3 cases of cancer

Table 7. Morbidity Experienced by Patients from Entry into Study through August, 1976

Complication	Amant Alone	Amant, aCh	Amant, L-dopa	Amant, aCh, L-dopa	L-dopa Alone	L-dopa, aCh	aCh Alone	Off	Unknown	Total
Patient-years (exposure)	9	6	88	80	57	61	2	12	8	303
Myocardial infarction	1	0	0	2	0	0	0	0	0	3
Stroke	0	0	1	2	0	0	0	0	0	3
Thrombophlebitis	0	0	0	1	0	2	0	0	0	3
Increased angina	1	0	1	0	0	1	0	0	0	3
Seizures	0	0	2	0	0	1	0	0	0	3
Hip fracture	0	0	3	0	0	1	0	0	0	4
Total	2	0	7	5	0	5	0	0	0	19

Amant = amantadine; aCh = anticholinergics.

Table 8. Mortality of Patients from Entry into Study through August, 1976

Cause of Death	Amant Alone	Amant, aCh	Amant, L-dopa	Amant, aCh, L-dopa	L-dopa Alone	L-dopa, aCh	aCh Alone	Off	Unknown	Total
Pneumonia	0	0	5	0	3	4	0	2	0	14
Coronary artery disease	1	0	3	4	2	1	0	0	0	11
Cancer	0	0	0	2	2	0	1	0	1	6
Septicemia	0	0	0	0	1	0	0	0	0	1
Stroke	0	0	0	1	0	0	0	0	0	1
Unknown	0	0	1	0	0	0	0	0	3	4
Total	1	0	9	7	8	5	1	2	4	37

Amant = amantadine; aCh = anticholinergics.

of the pancreas are perhaps worth noting. However, the 3 patients involved were each on different medication.

Discussion

The peak effect of amantadine occurs in the first week, when half of the patients show improvement. By three months, however, the mean ergometer score returns to baseline. Only 1 of our original 13 patients who continued on amantadine alone was improved at eighteen months. This experience corroborates the six- to eight-week falloff originally noted by Schwab and co-workers [18] in half of their patients.

Similarly, Mawdsley and associates [13], who reexamined their 83 patients every two weeks, found maximum improvement at the first reexamination. After a month they allowed their patients, if dissatisfied, to shift to levodopa; by four months only 2 patients remained on amantadine. A smaller, double-blind study by Hunter and co-workers [9] likewise reported slight and transient benefit from amantadine.

Other follow-up studies showed different results. Campbell and Williams [4] and Butzer and co-workers [2] reported that approximately one-third of their patients maintained improvement for nine to twelve months. Callaghan and associates [3] in a very small number of patients also found the benefit of amantadine to be sustained for twelve months. Forty of the 66 patients studied by Parkes and co-workers [15] required additional levodopa; but qualitative tests of the other 26 patients remained improved for one year. Zeldowicz and Huberman [23] stated that there was "no loss of therapeutic effect" in a mean twenty-one-month follow-up of patients on amantadine alone.

In contrast, when our patients who failed to respond to amantadine were started on levodopa alone, the subsequent improvement was greater and lasted for two years before beginning to decline. This is consistent with the experience of others who have used levodopa in the past [1, 8, 11, 12, 21].

When levodopa was added to a dose of amantadine, the resulting improvement in our patients had the magnitude and duration of levodopa alone, not the transient effect of amantadine alone or of amantadine added to levodopa. Three patients who were on amantadine when levodopa was begun again did not require less levodopa than before. Patients on amantadine and levodopa were not spared from dyskinesia or the "on-off" effect of levodopa.

Zeldowicz and Huberman [23] thought that aman-

tadine improved the beneficial effects of levodopa for six months in 37 patients because when amantadine was replaced by a placebo, the patients' conditions worsened. Only by reinstating amantadine was the situation corrected. This technique was used also by Fahn and Isgreen [6] to show prolonged benefit.

That symptoms of parkinsonism worsen when amantadine is reduced is a "withdrawal effect." It is not an indication of therapeutic effect, for it may occur either when there has been little benefit or after all benefit is lost, and because it slowly but spontaneously clears. It is a distressing and sometimes life-threatening problem [16]. It may occur when the dose is reduced by a single capsule. The reintroduction of a syrup form of amantadine (5 ml = 50 mg) will make possible more gradual reduction of dose.

Our overall mortality rate of 2.4 times the age- and sex-matched population of the United States is close to the 2.5 of Barbeau's patients on levodopa [1]. Sweet and McDowell [21] and Markham and associates [11] reported lower mortality rates (1.9 and 0.8, respectively) among patients on levodopa. However, in the era before levodopa, Hoehn and Yahr [7] reported a mortality of 2.9 and Kurland [10], of 1.4. The wide range of values implies that our samples were too small and that although medication improves the performance of many patients for several years, researchers should be cautious about assuming a beneficial effect of medical treatment on mortality until they are able to affect the underlying disease process.

We have found that the beneficial effects of amantadine are definite but usually brief. The central side-effects are sometimes distressing, and the problems of withdrawal may be serious. These factors deserve careful consideration when amantadine is to be used either alone or in combination with other antiparkinson drugs.

Trade Names

Amantadine: Symmetrel
Levodopa: Bendopa, Dopar, Larodopa
Procyclidine: Kemadrin

We acknowledge the help of Dr Irving Zieper and Dr Cwira Rickter in caring for the patients.

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