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A QUALITATIVE AND QUANTITATIVE EVALUATION OF AMANTADINE IN THE TREATMENT OF PARKINSON'S DISEASE*

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AMANTADINE hydrochloride (adamantanamine, Symmetrel) has been used for several years as an antiviral agent effective in prophylaxis against Asian influenza (A_2) [1, 2]. Schwab *et al* [3] first used amantadine in Parkinson's disease after one patient reported remission of her symptoms while taking the drug to prevent influenza. Schwab and his associates treated 163 Parkinsonian patients with 100–300 mg of amantadine daily. Sixty-six per cent of the group exhibited subjective or objective improvement of akinesia, rigidity, and/or tremor, and sustained benefit was noted in over half of the patients for a period of 3–8 months. Weeth *et al* [4] treated 39 patients in a similar open trial and found mild to moderate improvement in 23 patients (59 per cent). Parkes *et al* [5] conducted a double-blind crossover trial of amantadine (200 mg/day) vs. placebo, each given for a fortnight, involving 37 patients. Thirty-five patients completed the trial, and 26 of them expressed a preference for amantadine, five preferred placebo and four had no preference. The symptoms improved in order of greatest frequency were mobility, tremor, facial expression, speech, general well-being and balance. They also evaluated general history, functional disability, walking history, appearance, tremor, rigidity, limb dexterity, mood, time to walk 25 yd, and time to write a set phrase. All scores except walking history and rigidity improved significantly ($p < 0.05$) when amantadine was compared to placebo. The mean time required to walk 25 yd was reduced from 29 to 25 sec, and the time to write a set phrase decreased from 40 to 37 sec. The only significant difference found between the group giving a clear preference for amantadine and the group that did not was age,

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with the group preferring amantadine having a mean age of 56 yr and the group preferring placebo or giving no preference having a mean age of 64 yr. Factors that did not influence response to amantadine included severity of disease, stereotactic surgery and concomitant medication.

Fieschi *et al* [6] conducted a similar double-blind study involving 18 patients. A 22-item rating scale and three timed performance tests were used to evaluate the effects of placebo and amantadine. They found a more marked placebo effect and also a greater effect on rigidity than had been reported by Parkes and his associates. Hunter *et al* [7] evaluated 17 patients in a double-blind trial. Four of the patients received placebo throughout the 8 weeks of the trial, four received only amantadine (200 mg daily), four received placebo the first 4 weeks and amantadine the final 4 weeks, and four received amantadine the first 4 weeks and placebo the final 4 weeks. Weekly assessment of physical signs and functional disabilities revealed small but significant differences in some physical signs and no significant differences in disability scores. All but one of the measures of individual signs were improved, but no individual measure was significantly changed.

Every trial of amantadine to date has found evidence of at least some improvement in patients with Parkinson's disease. Patient acceptance has been excellent and the incidence of significant toxic effects has been low in the 200–300 mg/day range [5]. However, estimates of its efficacy have been inconsistent and there is a paucity of information on the quantitative effect of amantadine on various parameters of neurological function.

Our laboratory has been engaged for several years in the development of a battery of tests for the quantitative evaluation of neurological function. We feel that such tests are well suited for use in evaluating therapy in Parkinson's disease. Not only are these measures recorded on interval or ratio scales and sensitive to relatively slight changes, they also offer the advantage of assessing a wide range of neurological function, including measures of the many components of motor, sensory and psychological performance. It is therefore possible to determine the magnitude of effectiveness of the treatment program and the specific nature of improvement that can be expected. The battery of tests is administered by trained paramedical personnel. They are specifically instructed not to discuss the effect of any medication which the patient might be taking, and do not have access to previous scores. Consequently the data are as objective as can be obtained with this type of testing.

A feature complicating the interpretation of most amantadine trials to date involves the concurrent use of standard anti-Parkinsonian medications. Consequently, we have attempted to establish the efficacy of amantadine alone, since it may have a similar mechanism of action to standard medications. Finally, we felt it important to determine in a comprehensive fashion the effects of amantadine on mental state and activities of daily living, functions upon which the patient primarily determines the preference for a treatment when it is non-toxic.

PATIENTS AND METHODS

Patients

Consecutive patients applying for anti-Parkinsonian therapy at The University of Michigan Medical Center were asked to participate in the proposed drug trial. The trial design was described and they were told that they would be asked to reduce their

present medication to the lowest tolerable level, preferably terminating all other medications for the 12 weeks of the study. Patients were screened to eliminate those having concurrent medical problems, questionable diagnoses, or physical disabilities making it impossible for them to stand or transfer to and from a wheel-chair or to commute to the regular re-evaluation examinations. Patients who had undergone stereotactic surgery also were eliminated. Otherwise, patients were accepted irrespective of sex, age, or duration of illness. In total, three patients were eliminated because of questionable diagnosis, three because of previous stereotactic surgery, four because they were satisfied with their current therapy, and one because he later insisted that he would be unable to tolerate the subsequent evaluation examination. Of the final 42 patients accepted in the study, there were 26 males and 16 females, their ages ranging from 48 to 85 yr (mean 65 yr). The average duration of their disease was 8 yr. Thirty-six of the patients were able to discontinue all other traditional anti-Parkinsonian medications prior to and throughout the study. Of the six patients remaining on anti-Parkinsonian therapy, four remained on a trivial dosage (two patients on Pagitane^{R}, 1.25 mg q.d.; one, on Artane^{R}, 2 mg q.d.; and one, on Parsidol^{R}, 50 mg once per week); whereas, two patients required a larger dosage (one patient, Artane^{R}, 6 mg q.d., and the other Cogentin^{R}, 6 mg q.d.). Because no significant differences were found when the data were analyzed with and without these patients, they have been included in all the analyses.

Trial design

Patients were instructed to taper their present medications, discontinuing antihistamines immediately and tapering anticholinergics over a 1 week period. Patients who could not tolerate this change were instructed to choose from their medication one tablet twice daily, establishing a routine for at least 1 week prior to their second visit. On the average, patients called the neurologists (Drs. Walker and Tourtellotte) three times during the 'tapering period' and each time the patient was asked: 'Can you tolerate being just like you are, with no additional medication, for 6–12 weeks; that is, can you tolerate being placed on placebo medication?' Prior to removal of their pretrial medication, the battery of qualitative and quantitative neurological examinations were administered to each patient. Various laboratory tests (serology, hematocrit, white blood cell count and differential, BUN, SGOT, alkaline phosphatase and urinalysis) were obtained.

Four weeks after their initial visit each patient returned, having been successfully off all medication or on a stable regimen. An interval history was obtained and their neurological function re-evaluated. Patients were then randomly divided into two groups with one group given 100 mg amantadine twice daily and the other group given placebo capsules of similar taste and appearance. Three weeks later, patients returned for re-evaluation. An interval history was obtained and neurological function evaluated. Unused capsules were returned and later counted and identified. The amantadine and placebo groups were then reversed. Three weeks later, patients returned for the final trial evaluation. An interval history was obtained, neurological function evaluated, and unused capsules returned. A summary of the experimental paradigm is shown in Table 1. It is emphasized that the same 42 patients received both treatments.

TABLE 1. EXPERIMENTAL PARADIGM

Group	No. of patients	Medication taken during week 1	2–5	6–8	9–11
1	21	S	O	A	P
2	21	S	O	P	A

S = Standard anti-Parkinsonian medication being used upon entry to trial.
O = Off all medications.
P = Placebo.
A = Amantadine.

Assessment

Both qualitative and quantitative measures of the patients' functional capacity were obtained throughout the trial. The clinical evaluations were obtained and the quantitative neurological examination was administered on four separate occasions; while the patients were on their standard medications, while they were off all medications or tapered to their lowest tolerable level, and while they were on placebo and amantadine. The Simulated Activities of Daily Living Examination (SADLE) and the Neuro-Psychological Examination (NPE) described below were not administered during the patients' initial visit while they were on their conventional medications but were administered on all subsequent visits. A brief summary of the assessment measures follows:

(A) *Qualitative measures*

(1) *Patients' impression*

Patients were asked to subjectively evaluate any change in condition after both placebo and amantadine treatment. Each patient determined (1) whether the drug had been useful, and (2) whether he was worse, no different, 25 per cent improved, 50 per cent improved, 75 per cent improved, or completely well after treatment compared to his pretreatment condition. Patients were also asked to specify in what ways, if any, their condition had changed.

(2) *Neurologists' overall subjective impression*

The 'blinded' neurologists were asked to subjectively evaluate their preference for the two treatments. Such a subjective evaluation included their clinical observations as well as their interpretation of reported side effects, of the patients' subjective impressions, and of qualitative evaluation forms described below.

(3) *Qualitative evaluation*

Two subjective evaluation forms were filled out by the same 'blinded' neurologists throughout the trial. The first evaluation required the neurologists to categorize the individual patient's functional disabilities with respect to walking, dressing, hygiene, eating and feeding, and speech using the disability scales shown in Appendix A [8]. A total functional disability score was obtained by adding the scores for the specific areas. The second evaluation required the neurologists to evaluate relevant physical signs (i.e., tremor, rigidity, cogwheeling, weakness, finger dexterity, succession movements, bradykinesia, foot tapping, associated movements, rising, posture,

stability and gait) using the traditional classifications of normal, minimal, mild, moderate and severe.

(4) Motion pictures of patients performing a routine series of tasks were recorded at each examination period as a permanent visual record of the patients' motor capabilities. The movie sequence included a record of the patient sitting at rest in a chair; performing a series of rapid succession movements (right and left); performing a series of coordinated movements, including picking up a glass and bringing it to his mouth (right and left); tapping his feet; repeatedly rising and sitting in a chair; standing without support; walking; and turning.

(B) *Quantitative measures*

(1) An Activities of Daily Living (ADL) test battery was administered to assess the patients' performance on standardized tests which simulate acts of daily living (SADLE). The time necessary to complete individual tests such as putting on a shirt, tying a bow, using buttons, dialing a telephone, manipulating a safety pin, opening an envelope, opening a door, vocalizing, etc., was recorded. The test names along with their abbreviations and a brief description of each test are shown in Appendix B. These tests were administered by a trained 'blind' occupational therapist (J. A. Sagath) whose only responsibility was to obtain data. She was instructed not to discuss the effect of medication and she had no access to previous scores.

(2) A Clinical Quantitative Neurological Examination (CQNE) was administered to each patient. This battery of motor and sensory tests assesses basic abilities including strength, steadiness, simple reaction time, hand and foot speed, hand and foot coordination, psychomotor coordination, manual and finger dexterity, gait and station, and fatigue. The sensory tests include evaluation of visual acuity, touch sensation, vibration sensation, 2-point discrimination, and position sense. These tests are more completely described in previous articles [9–11], and more recently in Potvin's Ph.D. Thesis (see footnotes in Appendix B and C). A brief description of each test appears in Appendix C, including the measures, the units, and the instrumentation. These tests were administered by a trained 'blind' physical therapist (Kazmierczak or Shimp) whose only responsibility was to obtain data. (She was instructed not to discuss the effect of medication and she had no access to previous scores.)

(3) A neuro-psychological test battery was administered to evaluate specific higher and lower level cerebral functions (NPE).

The tests included the Peabody Picture Vocabulary test, a color naming and recognition subtest from the Eisenson test for Aphasia, a double simultaneous (face-hand) stimulation test, a discrimination test of right-left and body parts, the Raven Coloured Progressive Matrices test, the Hooper Visual Organization test, a written and oral digit substitution test, and the Wechsler Adult Intelligence Scale subtests (digit span, digit-symbol, picture completion, picture arrangement, and object assembly). These tests were administered by a trained 'blind' psychologist (A. Smith or R. Champoux) whose only responsibility was to obtain data. He was instructed not to discuss the

effect of medication and he had no access to previous scores. The results of this portion of the trial will be reported more completely elsewhere.

Control subjects

Normative data previously were established for all of the quantitative tests except the activities of daily living (SADLE) items using 80 young asymptomatic subjects, mean age 21.5 yr, S.D.=2.2 yr. Normative data for the (SADLE) were obtained using 23 spouses of patients participating in the amantadine trial. The mean age of the control group was 61.5 yr, S.D.=3.8 yr. Normal scores are included in Tables 4 and 7.

RESULTS

Patients' impressions

Patients were asked to evaluate their condition at the end of placebo and amantadine treatment. Responses to the question: 'Was the drug useful to you?' are summarized in Table 2 for both placebo and amantadine treatment. There was a significant tendency for amantadine treatment to be subjectively classified as useful by the patients as compared to placebo treatment ($p<0.01$ using the McNemar test for correlated proportions), with 64 per cent of the patients responding favorably to amantadine treatment as compared to 21 per cent of the patients responding favorably to placebo treatment.

TABLE 2. RESULTS OF ADMINISTRATION OF PLACEBO AND AMANTADINE TO 42 PARKINSONIAN PATIENTS. PATIENTS' OVERALL SUBJECTIVE IMPRESSIONS. PATIENTS' RESPONSE TO: 'WAS THE DRUG USEFUL TO YOU?'

Patients' response after placebo treatment	Patients' response after amantadine treatment		
	Useful	Not useful	Row total
Useful	7% (3)*	14% (6)	21% (9)
Not useful	57% (24)	21% (9)	78% (33)
Column total	64% (27)	35% (15)	

*Indicates 7% (3 patients) found the drug useful while on placebo treatment *and* useful while on amantadine treatment.

The patients' subjective overall evaluations of change in condition are summarized in Fig. 1, demonstrating that a greater number of patients responded 'worse' or 'no change' following placebo treatment than following amantadine treatment while fewer patients responded they were improved following placebo treatment than following amantadine treatment.

Patient impressions of specific improvements are summarized in Table 3. Examination of this table suggests that administration of amantadine did not result in improvement in any one specific area, although the most frequent patient responses included improved walking, faster movements, less tremor, increased ability to get out of a chair and bed, and clearer speech. Patient impressions after receiving placebo treatment most frequently involved decreased tremor.

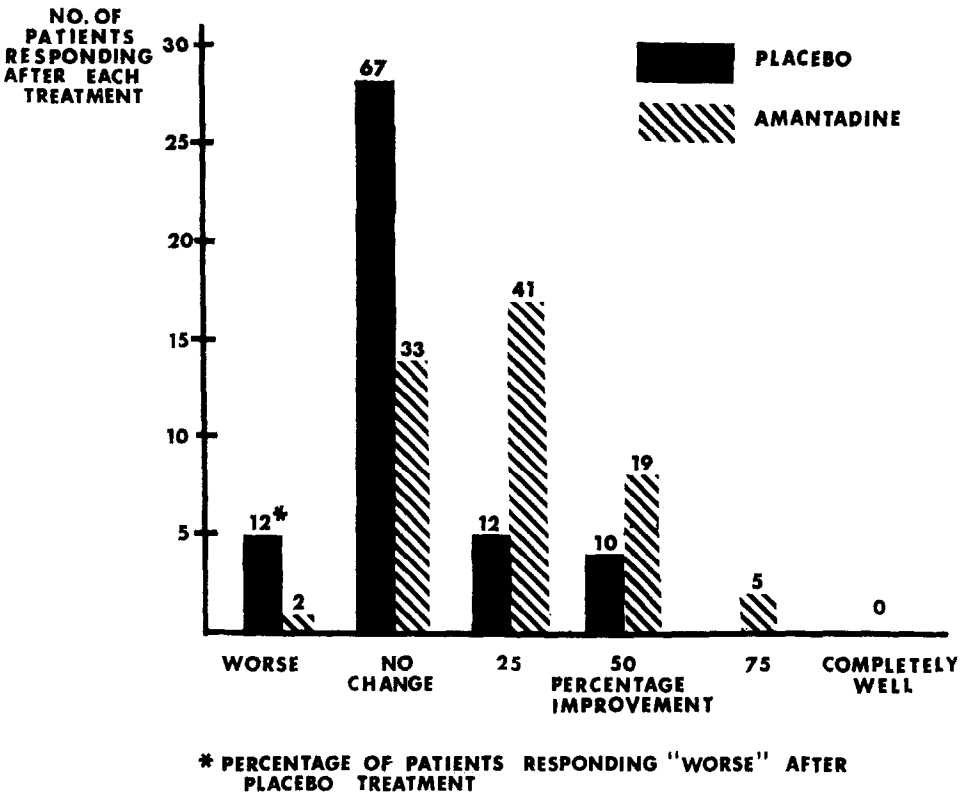

FIG. 1. Patients' overall subjective evaluations. Patients' responses to the question: 'Are you worse, no different, 25 per cent improved, 50 per cent improved, 75 per cent improved, or completely well after treatment as compared to your pretreatment condition?'

Neurologists' overall subjective impressions

The subjective clinical impression was that amantadine had a moderate but positive effect upon the majority of patients as compared to placebo treatment. Using information recorded during the interval histories, the neurologists were asked to distinguish between placebo and amantadine, responding to the question 'Which is the better drug in the treatment of the individual patient?' Amantadine was preferred over placebo for 74 per cent of the patients (31 patients). Utilizing the sign test, this is a significant impression ($p < 0.01$).

Qualitative evaluation sheets

General Functional Disability Scores are shown in Fig. 2, comparing average scores obtained while the patients were on their previous medication, pretreatment, placebo and amantadine. These qualitative measures of activities of daily living indicate by inspection that amantadine treatment has a modest but positive effect, being better than placebo treatment, pretreatment, or the previous medication in each of the categories evaluated. Utilizing the sign test a significant difference ($p < 0.05$) between amantadine and placebo treatment existed for walking, hygiene, eating and

TABLE 3. PATIENTS' SUBJECTIVE EVALUATION. PATIENTS' RESPONSES TO: 'HOW ARE YOU SPECIFICALLY IMPROVED?'

A. Patient Impressions of Improvement after Receiving Amantadine*

How are you improved (if at all?):	No. of patients
Walking improved	13
Walking farther and faster	6
Moving faster	9
Tremor less	9
Getting out of a chair and bed easier	9
Speech clearer	7
Talk faster	2
Able to feed self better	4
Less tired	4
Dress easier	3
Misc: more strength, turnover in bed better, more confident, more enthusiasm, better balance, more alert, better writing, less stiffness, posture better, read better	19

B. Patient Impressions of Improvement after Receiving Placebo

How are you improved (if at all?):	No. of patients
Tremor less	6
Walking improved	3
Mood better	2
Misc: more strength, less tired, speech clearer, able to do more, balance better, more alert, able to put hand in back pocket, more mobile, feel better generally, less constipated, sleep better	10

*Patients asked, 'In what specific ways are you better, if any?' The categories listed are paraphrased reductions of the patients' own comments. Some patients are entered into several specific categories of improvement.

feeding, speech and total disability score, but not for dressing. Additional subjective evaluations using the more detailed qualitative evaluation forms are summarized in Fig. 3. Mean scores by inspection indicate that amantadine treatment was preferable over placebo treatment for 17 of the 18 items evaluated. The greatest improvement again was recorded for the evaluation of gait. Significant improvement of amantadine over placebo (sign test, $p < 0.05$) was found for tremor of the head, succession movements of the upper extremities, weakness of the lower extremities, rising from a chair, posture and gait. Only foot tapping showed more patients worsened on amantadine, but this was not significant.

Quantitative measures

Simulated activities of daily living examination (SADLE). Results of the tests of the SADLE are summarized in Table 4. Scores are shown for 23 asymptomatic spouse controls and 42 parkinsonian patients prior to treatment (after the patients had been tapered to minimal or no medication). In addition, scores obtained following administration of placebo and amantadine are shown for both treatment groups separately as well as the combined group. The results of the paired *t*-tests comparing placebo to amantadine treatment for each of the test items also are shown. Fourteen of the 19 items indicate significantly better patient performance after amantadine treatment when compared to placebo treatment for the combined groups. Inspection of the

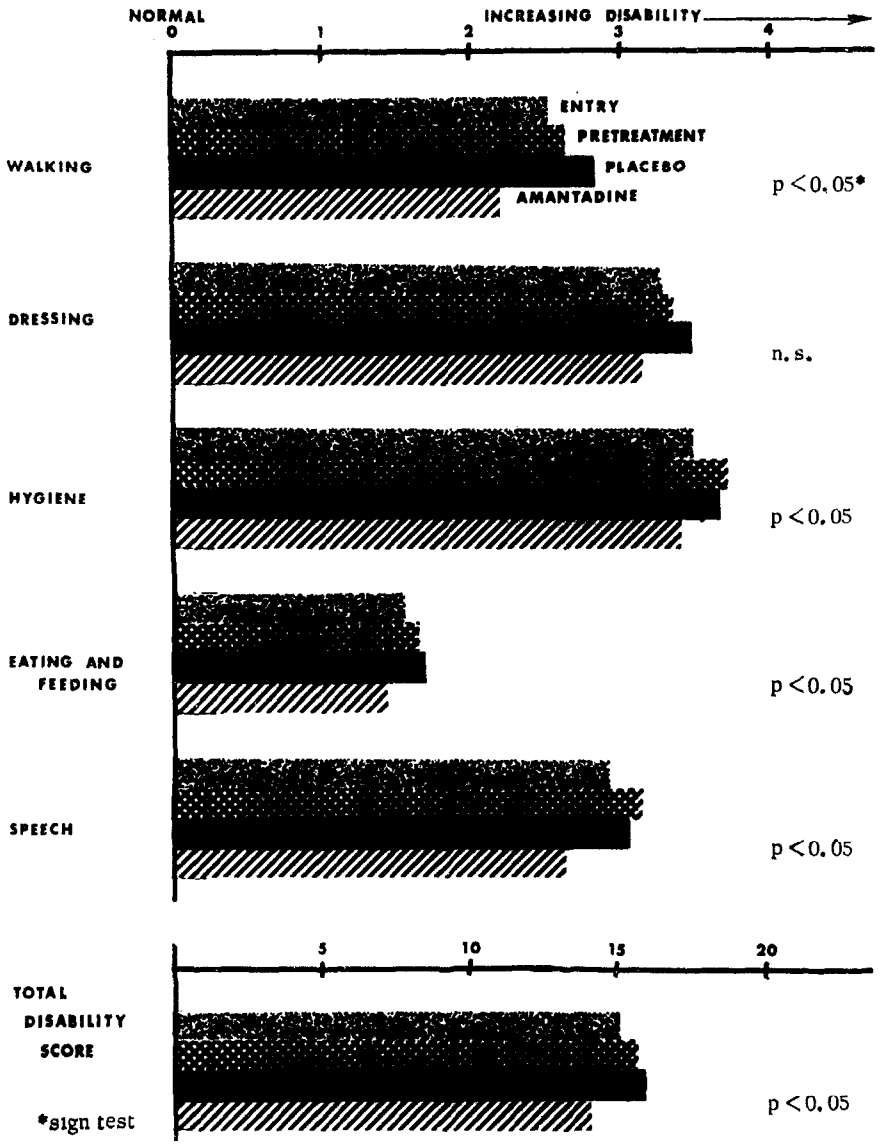

FIG. 2. General functional disability scores comparison of previous medication (entry), pretreatment placebo and amantadine. Neurologists' evaluations by inquiry of activities of daily living, mean scores for all 42 patients. (See Appendix A for data sheet used.)

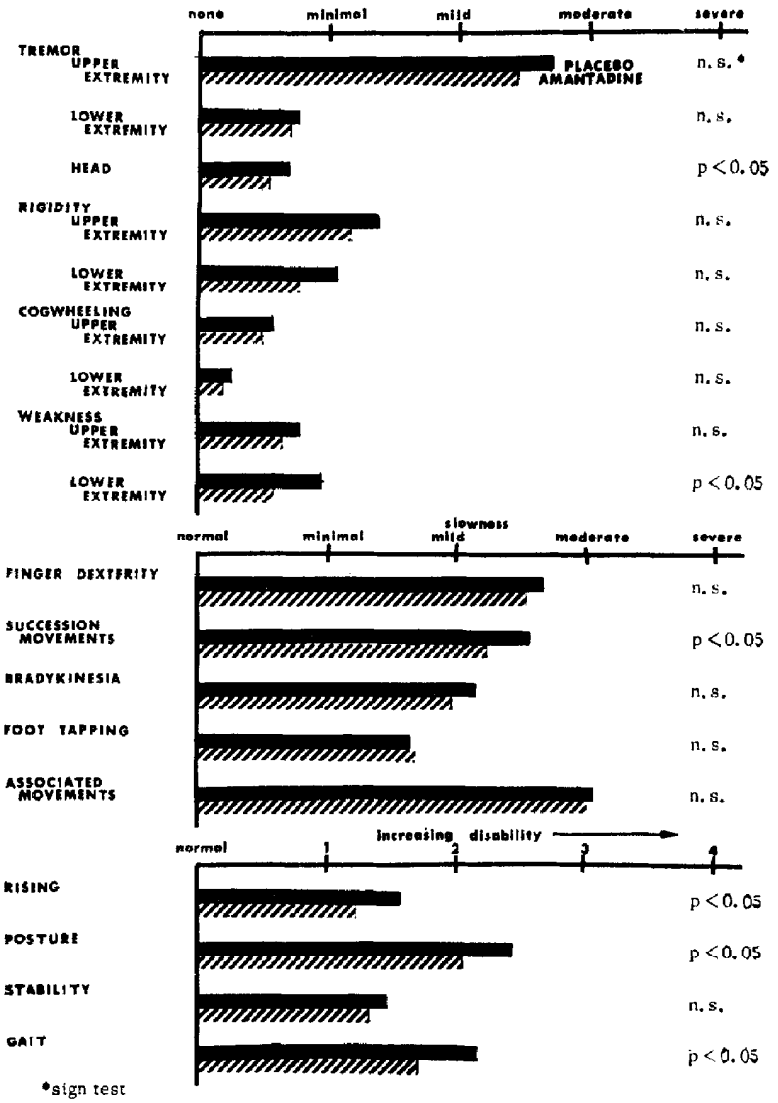

FIG. 3. Evaluation of relevant physical signs of Parkinsonism after placebo and amantadine treatment. Neurologists' subjective evaluation. Mean scores for all 42 patients.

TABLE 4. RESULTS OF TESTS OF SIMULATED ACTIVITIES OF DAILY LIVING EXAMINATION (SADLE) COMPARISON OF PATIENT SCORES PRETREATMENT AND AFTER ADMINISTRATION OF AMANTADINE AND PLACEBO WITH CONTROL VALUES

Task[1]	Control° (Mean±S.D.) n=23	Pretreatment (no or minimal medication) n=42	Group 1 (Amantadine before placebo)			Group 2 (Placebo before amantadine)			Combined treatment groups		
			Amant. n=21	Placebo n=21	Paired t-test	Placebo n=21	Amant. n=21	Paired t-test	Amant. n=42	Placebo n=42	Paired t-test
Shirt	9.4 (±2.4)	147.0	119.9	149.8	2.19†	133.8	100.8	2.42†	110.4	141.8	3.30‡
Button (large)	4.9 (±0.7)	27.5	16.3	29.2	1.63	29.9	25.5	0.62	20.9	29.6	1.63
Button (small)	4.9 (±1.0)	39.2	22.4	41.7	2.50†	36.3	31.3	0.81	26.9	39.0	2.42†
Zipper	4.3 (±1.1)	12.5	10.1	14.5	1.77*	13.0	8.0	2.02*	9.1	13.8	2.71‡
Bow	7.4 (±1.6)	43.9	32.6	40.3	1.25	37.5	30.4	1.63	31.5	38.9	1.99*
Cutting	8.8 (±1.6)	38.0	26.6	37.0	2.00*	42.6	37.5	1.74*	32.1	39.8	2.60†
Fork	2.5 (±0.6)	5.9	4.5	7.7	1.21	7.8	4.8	1.17	4.7	7.8	1.71*
Pouring	6.3 (±1.0)	21.3	16.6	18.5	1.36	18.8	11.6	1.44	14.1	18.7	1.75*
Toothpaste	5.9 (±1.7)	15.8	15.1	18.4	1.25	21.1	16.1	2.89‡	15.6	19.8	2.66†
Dialing	12.2 (±1.4)	21.9	18.1	22.2	2.09†	21.3	19.1	1.12	18.6	21.8	2.28†
Safety pin	4.4 (±1.0)	19.3	10.3	19.7	1.38	22.2	21.1	0.19	15.7	21.0	1.18
Envelope	7.1 (±3.1)	29.0	30.3	26.9	−1.00	29.3	27.8	0.43	29.1	28.6	−0.40
Door	3.3 (±0.6)	7.7	8.1	12.4	1.27	13.8	6.0	2.17†	7.1	13.1	2.46†
Drinking	12.1 (±3.7)	30.3	20.3	22.6	0.92	27.3	23.9	1.70	22.1	25.0	1.80*
Vocalizing	17.8 (±9.0)[2]	14.9	16.8	16.1	0.65	14.3	14.6	0.31	15.7	15.2	0.69
Scrub-D	8.1 (±2.0)	22.3	16.1	17.5	0.91	22.3	13.8	1.71	15.0	19.9	1.89*
Scrub-N	7.3 (±1.6)	22.0	15.7	15.7	0.02	23.0	19.3	3.34‡	17.5	19.4	2.15†
Glove-D	2.3 (±0.7)	9.4	8.9	14.5	1.69	9.8	4.3	1.62	6.6	12.2	2.37†
Glove-N	2.3 (±0.6)	10.3	7.5	11.4	1.44	8.4	8.0	0.95	7.8	9.9	1.57

° Values based on scores of 23 asymptomatic spouse controls.

[1] All test scores are measured in seconds; see Appendix B for abbreviations.

[2] Increased time indicates improved performance for this test.

*Indicates significance at the 0.10 level.

†Indicates significance at the 0.05 level.

‡Indicates significance at the 0.01 level.

Table 5. Simulated activities of daily living examination (SADLE) comparison between amantadine and placebo utilizing the sign test

Task°	Treatment group 1				Treatment group 2				Combined groups			
	Worse on amant.	Same on amant.	Better on amant.	*p*	Worse on amant.	Same on amant.	Better on amant.	*p*	Worse on amant.	Same on amant.	Better on amant.	*p*
Shirt	6	4	11	0.332	4	4	13	0.059†	10	8	24	0.024*
Button (large)	10	0	11	1.00	6	0	15	0.078*	16	0	26	0.164
Button (small)	8	1	12	0.504	6	2	13	0.168	14	3	25	0.108
Zipper	5	1	15	0.042†	4	0	17	0.008‡	9	1	32	<0.001‡
Bow	10	1	10	1.000	4	1	16	0.012	14	2	26	0.080*
Cutting	9	0	12	0.664	5	1	15	0.042†	14	1	27	0.060*
Fork	9	0	12	0.664	8	1	12	0.504	17	1	24	0.348
Pouring	8	1	12	0.504	5	0	16	0.026†	13	1	28	0.028†
Toothpaste	12	0	9	0.664	3	1	17	0.002‡	15	1	26	0.118
Dialing	9	0	12	0.664	5	0	16	0.026†	14	0	28	0.044†
Safety pin	11	0	10	1.000	8	1	12	0.504	19	1	22	0.878
Envelope	11	4	6	0.332	5	5	11	0.210	16	9	17	1.000
Door	10	1	10	1.000	4	0	17	0.008‡	14	1	27	0.060*
Drinking	7	0	14	0.190	7	3	11	0.480	14	3	25	0.108
Vocalizing	8	1	12	0.504	11	0	10	1.000	19	1	22	0.756
Scrub-D	7	0	14	0.190	2	0	19	<0.001‡	9	0	33	<0.001‡
Scrub-N	7	0	14	0.190	3	1	17	0.002‡	10	1	31	0.002‡
Glove-D	5	3	13	0.096*	6	0	15	0.078*	11	3	28	0.010‡
Glove-N	10	1	10	1.000	8	1	12	0.504	18	2	22	0.626

° See appendix B for abbreviations.

*Indicates significance at the 0.10 level.

†Indicates significance at the 0.05 level.

‡Indicates significance at the 0.01 level.

remaining five test items reveals that all but one (envelope) favor amantadine treatment. Examination of the scores for treatment Groups 1 and 2 indicates no striking differences between the two groups.

Table 5 summarizes the results of a sign test analysis, comparing the number of patients better on amantadine treatment to the number better after placebo treatment for the individual and combined treatment groups. Any measurable improvement or deterioration in performance was regarded as a change for the purposes of this analysis. Ten of the 19 test items demonstrate that a significantly greater number of patients performed better after amantadine treatment than after placebo treatment for the combined groups. Inspection of the remaining nine tests demonstrates a similar trend but not at a significant level. Separate comparison of treatment Groups 1 and 2 indicates that Group 2 (treated with placebo before amantadine) demonstrated a more significant preference for amantadine than did Group 1 (treated with amantadine before placebo). This finding may be interpreted as an indication that learning effects in these tests, although slight, are significant. However, the nature of the crossover trial minimizes this effect when the two treatment groups are combined for analysis.

In order to determine the magnitude of response to placebo and amantadine, the SADLE test scores are better expressed as a percentage of age matched normal

TABLE 6. SUMMARY OF SIMULATED ACTIVITIES OF DAILY LIVING EXAMINATION (SADLE) TEST-SCORES FOR THE COMBINED GROUPS SHOWN IN TABLE 4 EXPRESSED AS PERCENTAGE OF NORMAL FUNCTION. PRETREATMENT, PLACEBO AND AMANTADINE

Test	Percentage of normal		
	Pretreatment	Placebo	Amantadine
Shirt	6.4	6.6	8.5‡
Button (large)	17.8	16.6	23.4
Button (small)	12.5	12.6	18.2†
Zipper	34.4	31.2	47.3‡
Bow	16.9	19.0	23.5*
Cutting	23.2	22.1	27.4†
Fork	42.4	32.1	53.2*
Pouring	29.6	33.7	44.7*
Toothpaste	37.3	29.8	37.8†
Dialing	55.7	56.0	65.6†
Safety pin	22.8	21.0	28.0
Envelope	24.5	24.8	24.4
Door	42.9	25.2	46.5†
Drinking	39.9	48.4	54.8*
Vocalizing	83.7	85.4	88.2
Scrub-D	36.3	40.7	54.0*
Scrub-N	33.2	37.6	41.7†
Glove-D	24.5	18.9	34.8†
Glove-N	22.3	23.2	29.5
Total	31.9	30.8	39.6

*Indicates significance at the 0.10 level, placebo vs. amantadine (paired *t*-test).

†Indicates significance at the 0.05 level, placebo vs. amantadine (paired *t*-test).

‡Indicates significance at the 0.01 level, placebo vs. amantadine (paired *t*-test).

TABLE 7. THE CLINICAL QUANTITATIVE NEUROLOGICAL EXAMINATION (CQNE) COMPARISON OF PATIENT SCORES UPON ENTRY, PRETREATMENT AND AFTER ADMINISTRATION OF AMANTADINE AND PLACEBO WITH CONTROL VALUES°

Task		Control (Mean ± 2 S.D.) Scores and units	Entry (previous medication)	Pre-trial (no or minimal medication)	Treatment Group 1 (Amant. before placebo)			Treatment Group 2 (Placebo before amant.)			Combined treatment groups		
					Amant.	Placebo	Paired *t*-test	Placebo	Amant.	Paired *t*-test	Amant.	Placebo	Paired *t*-test
Vision													
Visual acuity, right		100%	91.1	92.5	90.1	88.5	1.09	91.2	91.5	0.31	90.8	89.9	1.02
Visual acuity, left		100%	84.7	89.3	85.1	83.5	0.39	86.2	85.6	−0.22	85.4	84.9	0.31
Upper extremities													
Strength of movements													
Grip	D	75.7 (31.7–119.7) lb	39.9	39.9	41.7	40.0	1.35	42.8	47.3	3.32‡	44.5	41.4	3.34‡
	N	71.9 (30.5–103.3) lb	35.3	37.4	34.4	34.0	0.26	38.8	41.3	2.17†	37.9	36.4	1.76*
Wrist dorsiflexion	D	39.1 (16.7–61.5) lb	31.6	29.3	30.0	29.1	1.06	31.1	31.1	0.29	30.6	30.1	0.86
	N	35.8 (15.2–56.4) lb	28.7	27.2	27.1	27.5	−0.32	29.5	30.7	1.30	28.9	28.5	0.66
Shoulder abduction	D	20.3 (6.3–34.3) lb	12.5	11.8	13.9	13.6	0.45	12.5	14.5	2.69†	14.2	13.1	2.01*
	N	19.8 (6.2–32.2) lb	12.8	11.7	12.5	12.7	−0.32	12.6	13.2	0.35	12.9	12.7	0.14
Control of movements													
Steadiness, supported	D	1 (hole size)	5.1	5.1	4.3	5.0	2.22†	5.4	5.7	−0.78	5.0	5.2	0.75
	N	1 (hole size)	4.1	3.9	3.5	3.7	1.10	3.4	3.6	0.55	3.6	3.6	0.0
Steadiness, unsupported	D	3 (hole size)	6.4	5.9	4.9	5.3	1.69	6.3	7.1	−1.72*	6.0	5.8	−0.68
	N	3 (hole size)	5.5	5.2	4.6	4.6	0.24	4.8	5.0	−0.83	4.8	4.7	−0.60
Reaction time	D	8.7 (7–11) counts (1 count =	14.5	15.6	13.3	14.0	0.91	14.0	13.4	0.89	13.4	14.0	1.29
	N	,, 20 msec)	15.5	15.4	12.8	14.0	1.85*	14.4	13.8	0.68	13.3	14.2	1.44
Speed of hand	D	7.2 (5.6–8.7) taps/sec	5.0	4.7	4.7	4.5	1.16	4.8	4.9	0.70	4.8	4.7	1.18
	N	6.6 (4.9–8.2) taps/sec	4.3	3.7	4.2	4.2	0.00	3.9	3.8	−0.46	4.0	4.1	−0.28
Speed-coordination, hand	D	2.0 (1.5–2.6) hits/sec	1.2	1.1	1.3	1.1	2.03*	1.1	1.2	2.15†	1.3	1.1	2.98‡
	N	2.0 (1.5–2.5) hits/sec	1.2	1.1	1.2	1.0	3.07‡	1.0	1.2	2.18†	1.2	1.0	3.86‡
Index of performance, hand	D	12.9 (10.2–15.5) bits/sec	6.9	6.3	7.4	6.6	3.30‡	6.5	7.2	2.75†	7.3	6.6	4.32‡
	N	12.3 (9.7–14.9) bits/sec	6.5	6.2	7.1	6.1	4.62‡	6.4	6.8	1.88*	7.0	6.3	4.43‡
Rotary pursuit	D	64 (44–84) % time on target	13.4	22.1	26.5	24.2	0.35	20.3	26.9	2.35†	26.7	22.3	1.83*
	N	55 (25–85) % time on target	12.5	18.9	26.0	21.6	1.73*	21.4	26.2	2.36†	26.1	21.5	2.94‡
Purdue pegboard	D	29 (26–32) No. of pegs	10.3	10.0	12.1	10.4	2.52†	10.3	11.7	2.04*	11.9	10.4	3.27‡
	N	,,	11.7	11.1	12.3	11.3	2.14†	10.7	11.8	2.59†	12.1	11.0	3.34‡
Pencil rotation	D	15 (12–18) No. of rotations	9.3	8.5	8.5	8.0	1.73*	9.1	9.4	1.26	9.1	8.6	2.13*
	N	13 (10–16) No. of rotations	9.8	8.5	9.0	7.7	4.01‡	8.8	8.8	0.0	8.9	8.3	2.46†

TABLE 7. *Continued*

Fatigue of movements												
Grip strength	D	70.0 (58–94) %	72.7	72.8	74.2	76.1	−0.44	72.7	76.6	0.55	75.4	74.4	0.05
fatigue	N	,,	79.8	78.2	76.2	77.0	−0.13	72.5	74.4	0.37	75.3	74.8	0.09
Speed of hand	D	83.1 (72–94) %	86.0	76.4	91.7	88.5	0.38	79.9	90.6	1.94*	91.2	84.2	1.40
fatigue	N	,,	75.3	84.6	78.8	84.1	−1.10	85.9	91.7	0.52	85.3	84.8	0.04
Speed-coordination,	D	88.9 (66–112) %	86.1	83.0	87.5	82.8	1.00	84.5	96.5	1.09	92.0	83.7	1.37
hand, fatigue	N	,,	81.4	81.4	91.5	89.3	0.39	93.6	80.1	−2.23†	85.8	91.5	−1.09
Sensation													
Touch, hand	D	6.0 (6–6) cm	5.9	5.8	5.7	6.0	−1.93*	5.4	6.0	1.98*	5.9	5.7	0.66
	N	,,	5.9	5.8	5.9	6.0	−1.00	5.7	6.0	1.19	6.0	5.9	0.96
Vibration, finger	D	0.2 (0.1–0.5) μ	0.5	0.5	0.7	0.7	0.11	2.9	0.7	0.92	0.7	1.8	0.89
	N	,,	1.6	1.6	0.5	0.5	0.25	2.9	0.6	0.94	0.6	1.7	0.95
Position	D	1 (1–1)"	1.1	1.1	1.2	1.0	−1.71	1.2	1.0	1.23	1.1	1.1	0.21
	N	,,	1.1	1.2	1.1	1.0	−1.45	1.2	1.0	1.00	1.0	1.1	0.47
Two-point	D	3.8 (2–5) mm	5.0	4.9	5.2	5.2	0.0	5.4	5.0	1.28	5.1	5.3	1.16
discrimination	N	,,	5.0	5.0	5.2	5.2	0.0	5.0	5.5	−1.00	5.4	5.1	−0.94
Lower extremities													
Strength													
Foot dorsiflexion	D	63.0 (35.0–91.0) lb	50.6	46.2	47.2	45.4	1.87*	46.8	47.0	−0.59	47.1	46.1	1.62
	N	61.9 (37.7–87.1) lb	49.4	46.9	50.9	49.4	1.43	46.5	45.8	−0.46	48.4	48.0	0.54
Hip flexion	D	43.3 (20.5–66.1) lb	20.9	20.1	20.9	21.9	−1.52	20.8	21.9	1.84*	21.4	21.4	0.37
	N	41.6 (18.4–64.8) lb	20.5	19.2	21.3	20.7	0.85	21.4	22.1	1.12	21.7	21.1	1.42
Control of movements													
Speed of foot	D	5.0 (3.4–6.6) taps/sec	2.9	2.8	3.2	3.0	1.30	3.1	3.3	0.90	3.3	3.1	1.57
	N	4.9 (3.3–6.5) taps/sec	2.9	2.9	3.0	3.0	0.13	2.6	2.8	0.63	2.9	2.8	0.62
Speed-coordination of foot													
Forward step	D	2.0 (1.3–2.6) hits/sec	0.9	0.9	1.1	0.8	2.53†	0.9	1.0	0.44	1.1	0.9	2.28†
	N	2.0 (1.4–2.6) hits/sec	0.9	0.9	1.1	0.9	3.12‡	0.9	1.0	0.94	1.1	0.9	2.91‡
Index of performance, foot													
Forward step	D	7.3 (5.4–9.1) bits/sec	3.1	3.1	3.8	3.0	1.97*	3.2	3.4	0.46	3.6	3.1	1.89*
	N	,,	3.2	3.2	3.7	3.3	1.77*	3.3	3.4	0.63	3.6	3.3	1.82*

[*Table 7 continued on next page*]

Table 7. *Continued*

Task		Control (Mean±2 S.D.) Scores and units	Entry (previous medication)	Pre-trial (no or minimal medication)	Treatment Group 1 (Amant. before placebo)			Treatment Group 2 (Placebo before amant.)			Combined treatment groups		
					Amant.	Placebo	Paired *t*-test	Placebo	Amant.	Paired *t*-test	Amant.	Placebo	Paired *t*-test
Speed-coordination of foot													
Side step	D	2.0 (1.3–2.6) hits/sec	1.0	0.9	1.1	0.9	1.95*	1.0	1.1	2.15†	1.1	1.0	2.86‡
	N	2.0 (1.4–2.7) hits/sec	1.0	0.9	1.1	0.9	3.33‡	1.0	1.1	1.39	1.1	1.0	3.33‡
Index of performance, foot													
Side step	D	7.4 (5.6–9.1) bits/sec	3.4	3.2	3.9	3.3	1.87*	3.2	3.9	2.76†	3.9	3.3	3.26‡
	N	,,	3.4	3.0	3.8	3.2	2.28†	3.3	3.7	2.18†	3.8	3.3	3.14‡
Standing													
Eyes open: two legs		30.0 (30–30) sec	25.2	27.7	29.2	25.8	1.77*	27.7	29.4	1.07	29.3	26.8	2.07†
one leg	D	,,	9.3	8.5	8.5	7.3	0.93	15.0	14.2	−0.15	11.4	11.2	0.09
	N	,,	10.4	9.5	10.2	10.0	0.10	13.2	10.3	−0.59	10.3	11.6	−0.52
Eyes closed: two legs		,,	23.3	25.3	23.9	22.1	1.23	27.0	29.7	1.28	26.8	24.6	1.78*
one leg	D	29.3 (24–30) sec	3.4	2.8	3.0	3.1	−2.19†	8.3	6.3	−0.40	4.7	5.7	−0.81
	N	,,	3.7	4.7	3.2	5.1	−1.98*	8.5	5.0	−0.71	4.1	6.8	−1.08
Tandem gait, supported		2.6 (1.6–3.5) steps/sec	1.1	1.2	1.1	1.0	2.27†	1.1	1.2	1.23	1.2	1.1	2.32†
Tandem gait, unsupported		2.3 (1.7–3.0) steps/sec	1.0	1.0	1.0	0.8	2.98‡	0.9	1.0	0.72	1.0	0.9	2.12†
Fatigue of movements													
Hip strength fatigue	D	104.4 (77–132) %	116.8	112.4	110.7	94.5	2.97‡	115.7	105.4	−1.47	108.1	105.1	0.72
	N	,,	105.8	118.5	104.0	93.2	1.89*	111.3	103.4	−1.75*	103.7	102.3	0.63
Foot speed fatigue	D	79.9 (64–96) %	96.9	78.1	64.8	78.1	−1.68	76.4	82.9	1.29	73.9	77.3	−0.35
	N	,,	78.2	72.9	81.6	74.1	0.89	76.7	74.8	−0.42	78.2	75.4	0.54
Speed-coordination, foot, fatigue													
Forward step	D	94.0 (73–115) %	79.1	70.0	70.5	77.6	−0.33	73.0	69.0	−0.60	69.8	75.3	−0.65
	N	,,	69.8	77.2	60.3	78.9	−1.64	79.0	74.2	−0.78	67.3	79.0	−1.75*
Side step	D	94.8 (72–118) %	66.8	69.9	75.6	85.1	−0.51	72.7	83.5	1.13	80.0	78.9	0.54
	N	,,	70.8	66.2	66.3	74.9	−0.90	70.5	73.6	0.09	70.0	72.7	−0.66

TABLE 7. *Continued*

Sensation												
Touch, toe	D	5.6 (4–6) cm	3.9	3.6	3.9	4.8	−2.00*	3.4	4.8	3.50‡	4.4	4.1	0.95
	N	,,	4.1	3.6	3.8	4.8	−1.93*	3.6	4.7	3.61‡	4.3	4.2	0.80
Vibration, toe	D	0.5 (0.1–1.0) μ	7.0	6.4	7.0	7.3	0.37	8.3	5.4	1.18	6.2	7.8	1.24
	N	,,	6.6	5.9	5.7	5.5	−0.26	8.7	5.9	1.18	5.8	7.1	1.00
Position	D	1 (1–1)	1.0	1.3	1.2	1.2	0.0	1.2	1.0	0.94	1.1	1.2	0.78
	N	,,	1.1	1.2	1.0	1.0	0.0	1.3	1.1	1.10	1.1	1.2	1.04

° Indicates values based on scores of 80 asymptomatic young adults.

*Indicates significance at the 0.10 level.

†Indicates significance at the 0.05 level.

‡Indicates significance at the 0.01 level.

D=Dominant.

N=Nondominant.

TABLE 8. CLINICAL QUANTITATIVE NEUROLOGICAL EXAMINATION (CQNE) COMPARISON BETWEEN PLACEBO AND AMANTADINE UTILIZING THE SIGN TEST

Task		Treatment group 1 (Amant. before placebo)				Treatment group 2 (Placebo before amant.)				Combined groups			
		Worse on amant.	Same on amant.	Better on amant.	*p*	Worse on amant.	Same on amant.	Better on amant.	*p*	Worse on amant.	Same on amant.	Better on amant.	*p*
Vision													
Visual acuity, right		5	7	9	0.424	4	8	7	0.548	9	15	16	0.230
Visual acuity, left		6	6	9	0.608	6	9	4	0.754	12	15	13	1.000
Upper extremities													
Strength of movements													
Grip	D	7	2	12	0.360	4	0	17	0.008‡	11	2	29	0.006‡
	N	10	0	11	1.000	6	1	13	0.168	16	1	24	0.268
Wrist dorsiflexion	D	7	2	12	0.360	9	1	10	1.000	16	3	22	0.418
	N	11	3	7	0.480	7	0	13	0.264	18	3	20	0.472
Shoulder abduction	D	7	2	12	0.360	4	2	14	0.030†	11	4	26	0.020†
	N	8	3	10	0.814	7	3	10	0.630	15	6	20	0.500
Control of movements													
Steadiness, supported	D	4	7	10	0.180	10	4	7	0.630	14	10	17	0.720
	N	4	10	6	0.754	8	10	3	0.226	12	20	9	0.664
Steadiness, unsupported	D	4	8	8	0.388	8	9	4	0.388	12	17	12	1.000
	N	5	8	6	1.000	8	11	2	0.110	13	19	8	0.384
Reaction time	D	10	0	11	1.000	10	2	8	0.814	20	2	19	1.000
	N	7	0	13	0.264	9	0	11	0.824	16	0	24	0.268
Speed of hand	D	7	3	11	0.480	12	0	9	0.664	19	3	20	1.000
	N	11	1	9	0.824	8	3	10	0.814	19	4	19	1.000
Speed-coordination, hand	D	4	2	13	0.050†	5	5	11	0.210	9	7	14	0.404
	N	3	2	14	0.012†	6	2	13	0.168	9	4	27	0.004‡
Index of performance, hand	D	4	0	17	0.008‡	5	1	15	0.042†	9	1	32	<0.001‡
	N	2	1	18	<0.001‡	8	0	13	0.384	10	1	31	0.002‡
Rotary pursuit	D	12	2	7	0.360	6	0	15	0.078*	18	2	22	0.636
	N	4	3	13	0.050†	5	2	14	0.064*	9	5	27	0.004‡
Purdue pegboard	D	4	4	13	0.050†	4	5	12	0.076*	8	9	25	0.004‡
	N	4	3	14	0.030†	5	3	13	0.096*	9	6	27	0.004‡

TABLE 8. *Continued*

Pencil rotation	D	5	4	12	0.144	7	3	11	0.480	12	7	23	0.090*
	N	1	4	16	<0.001‡	11	1	9	0.824	12	5	25	0.048†
Fatigue of movements													
Grip strength fatigue	D	9	1	11	0.824	10	1	9	1.000	19	2	20	1.000
	N	11	0	10	1.000	10	1	8	0.814	21	1	18	0.750
Speed of hand fatigue	D	9	0	12	0.664	5	0	16	0.026†	14	0	28	0.044†
	N	14	0	7	0.190	8	0	13	0.384	22	0	20	0.878
Speed-coordination, hand, fatigue	D	6	1	12	0.238	8	2	10	0.814	14	3	22	0.242
	N	9	0	10	1.000	12	0	8	0.504	21	0	18	0.750
Sensation													
Touch, hand	D	4	15	0	<0.001‡	0	16	4	<0.001‡	4	31	4	1.000
	N	1	18	0	<0.001‡	0	18	2	<0.001‡	1	36	2	1.000
Vibration, finger	D	7	4	10	0.630	9	2	10	1.000	16	6	20	0.618
	N	5	5	11	0.210	10	6	5	0.302	15	11	16	1.000
Position	D	3	18	0	<0.001‡	0	19	2	<0.001‡	3	37	2	1.000
	N	2	19	0	<0.001‡	0	20	1	<0.001‡	2	39	1	1.000
Two-point discrimination	D	4	13	4	1.000	5	8	8	0.582	9	21	12	0.664
	N	5	11	5	1.000	5	14	2	0.454	10	25	10	1.000
Lower extremities													
Strength													
Foot dorsiflexion	D	6	2	13	0.168	9	0	11	0.824	15	2	24	0.200
	N	7	0	14	0.190	10	0	10	1.000	17	0	24	0.348
Hip flexion	D	14	0	7	0.190	4	1	15	0.020†	18	1	22	0.636
	N	7	1	13	0.264	6	0	14	0.116	13	1	27	0.038†
Control of movements													
Speed of foot	D	9	1	11	0.824	8	0	13	0.384	17	1	24	0.348
	N	10	0	11	1.000	8	0	13	0.384	18	0	24	0.440
Speed-coordination of foot, Forward step	D	2	6	13	0.008‡	9	3	9	1.000	11	9	22	0.080*
	N	3	4	14	0.012†	9	4	8	1.000	12	8	22	0.122

[*Table 8 continued on next page*]

Table 8. *Continued*

Task		Treatment group 1 (Amant. before placebo)				Treatment group 2 (Placebo before amant.)				Combined groups			
		Worse on amant.	Same on amant.	Better on amant.	*p*	Worse on amant.	Same on amant.	Better on amant.	*p*	Worse on amant.	Same on amant.	Better on amant.	*p*
Index of performance, foot, Forward step	D	7	3	11	0.480	9	2	10	1.000	16	5	21	0.512
	N	7	2	12	0.360	9	2	10	1.000	16	4	22	0.418
Speed-coordination of foot, Side step	D	4	6	11	0.118	4	6	11	0.118	8	12	22	0.016†
	N	4	4	13	0.050†	7	3	11	0.480	11	7	24	0.040†
Index of performance, foot, Side step	D	5	4	12	0.144	5	2	14	0.064*	10	6	26	0.012†
	N	6	3	12	0.238	6	3	12	0.238	12	6	24	0.066*
Standing													
Eyes open: two legs		1	15	5	0.218	0	18	2	<0.001‡	1	33	7	0.070*
: one leg	D	7	6	8	1.000	5	5	11	0.210	22	21	19	0.756
	N	6	6	9	0.608	6	7	8	0.790	12	13	17	0.458
Eyes closed: two legs		2	15	4	0.688	1	17	2	1.000	3	32	6	0.508
: one leg	D	11	7	3	0.058*	4	6	11	0.118	15	13	14	1.000
	N	10	6	5	0.302	7	9	5	0.774	17	15	10	0.248
Tandem gait, supported		4	4	13	0.050†	7	4	10	0.630	11	8	23	0.058*
Tandem gait, unsupported		3	6	12	0.036†	9	2	10	1.000	12	8	22	0.122
Fatigue of movements													
Hip strength fatigue	D	6	0	15	0.078*	13	2	5	0.096*	19	2	20	1.000
	N	6	0	15	0.078*	14	0	6	0.118	20	0	21	1.000
Foot speed fatigue	D	14	0	5	0.020†	7	0	14	0.190	21	0	19	0.874
	N	9	0	11	0.824	11	1	9	0.824	20	1	20	1.000
Speed-coordination, foot, fatigue													
Forward step	D	9	0	6	0.608	9	1	8	1.000	18	1	14	0.596
	N	12	1	5	0.238	12	0	6	0.238	24	1	11	0.040†
Side step	D	9	2	6	0.608	6	0	12	0.238	15	2	18	0.728
	N	10	0	7	0.630	7	0	11	0.480	17	0	18	1.000

TABLE 8. *Continued*

Sensation												
Touch, toe	D	7	9	3	0.344	2	7	11	0.022†	9	16	14	0.404
	N	8	8	3	0.226	1	7	12	0.004‡	9	15	15	0.308
Vibration, toe	D	7	5	9	0.804	9	1	11	0.824	16	6	20	0.618
	N	8	1	12	0.504	5	0	16	0.026†	13	1	28	0.028†
Position	D	3	16	2	1.000	1	18	2	1.000	4	34	4	1.000
	N	1	19	1	1.000	1	18	2	1.000	2	37	3	1.000

*Indicates significance at the 0.10 level.

†Indicates significance at the 0.05 level.

‡Indicates significance at the 0.01 level.

D=Dominant.

N=Nondominant.

function ($\frac{\text{patient score}}{\text{normative score}} \times 100$, with scores expressed in terms of tasks accomplished per second except for vocalization and drinking when the inverse ratio was used). See Table 6. It is then possible to determine how effective amantadine is in bringing the patient back to normal function. The average percentage of normal function for all 19 of the SADLE tests was 31.9 per cent pretreatment, 30.8 per cent after placebo treatment and 39.6 per cent after amantadine treatment.

Clinical quantitative neurological examination (CQNE)

A summary of the CQNE results is shown in Table 7. Control scores obtained from 80 asymptomatic young adults (mean age=22.4 yr) are compared to patient scores upon entry (previous medication), pretreatment (no or minimal medication), and after placebo and amantadine treatment. Examination of the paired *t*-test analyses indicates a significant preference for amantadine in the following test areas:

Strength of movements

1. Grip strength, dominant and nondominant.
2. Shoulder abduction, dominant.

Coordination of movements

1. Speed-coordination of hand, dominant and nondominant.
2. Index of performance, dominant and nondominant hand.
3. Rotary pursuit tracking, dominant and nondominant hand.
4. Finger dexterity, Purdue pegboard and pencil rotation, dominant and nondominant.
5. Speed-coordination of foot, forward and side step, dominant and nondominant.
6. Index of performance, dominant and nondominant foot, forward and side step.

Station and gait

1. Standing, eyes open, two legs together.
2. Standing, eyes closed, two legs together.
3. Tandem gait, walking without and with support.

Results indicate specific improvement in all of the coordination tests, with improvement in some of the strength, station and gait tests. Significant changes were not observed for those tests measuring sensation (vision, touch, vibration, position or 2-point discrimination), steadiness, simple reaction time, speed of hand, strength of the lower extremities, or fatigue with the exception of increased fatigue as measured by one of the foot coordination fatigue tests. Comparison to the remainder of the fatigue tests suggests that this isolated finding is of little significance.

The results of a sign test analysis upon the CQNE scores after placebo and amantadine treatment are summarized in Table 8. As before, any measurable improvement or deterioration was regarded as a change for the purposes of this analysis. Findings are similar to those using the *t*-test, indicating improved performance following amantadine treatment in some of the strength tests, the coordination tests, and unsupported tandem gait test, and two of the fatigue measures. A statistically significant difference also was found for amantadine treated patients for one of the vibration tests. This was the only significant sensory finding.

These results obtained from the SADLE and CQNE test batteries confirm the findings obtained with the subjective and qualitative methods (patients' impressions,

neurologists' overall impression, functional disability scores, and evaluation of relevant physical signs). There is no question that amantadine is a better treatment than placebo for Parkinson's disease.

In order to simplify the analysis of the CQNE data and to express it in more clinical terms, functionally related tests were grouped into the following categories:

1. Vision (visual acuity).
2. Strength (grip, wrist dorsiflexion, shoulder abduction, foot dorsiflexion, hip flexion).
3. Steadiness (hole steadiness, supported and unsupported).
4. Reaction time (simple reaction time).
5. Speed (speed of hand, speed of foot).
6. Coordination (speed coordination of hand and foot; index of performance, hand and foot; rotary pursuit; Purdue pegboard; pencil rotation).
7. Fatigue (grip strength fatigue, hip strength fatigue, speed of hand and foot fatigue, speed-coordination of hand and foot fatigue).
8. Station (standing: eyes open, two legs and one leg; eyes closed, two legs and one leg).
9. Gait (tandem gait, supported and unsupported).
10. Sensation (touch, hand and toe; vibration, finger and toe; position, upper and lower extremities; 2-point discrimination).

The overall CQNE findings can be summarized by first expressing all of the test scores as a percentage of normal function ($\frac{\text{patient score}}{\text{normative score}} \times 100$ or $\frac{\text{normative score}}{\text{patient score}} \times 100$ when better performance reflects a lower score, e.g., vibration sense), and then averaging all of the test scores representative of a functional category. For example, after expressing all of the strength test scores for a given patient in terms of 'percentage of normal function', the measure of grip strength, wrist dorsiflexion, shoulder abduction, etc., can be averaged to obtain a single measure of STRENGTH. The actual measures, expressed as percentage of normal function, are shown in Table 9. A summary of the change in percentage of normal function, comparing placebo and amantadine scores to pretreatment scores for the functional categories is shown in Fig. 4. The functional category demonstrating the most significant improvement is coordination, with strength and gait also demonstrating improvement, significant at $p < 0.05$. None of the other functional categories show significant change.

Neuro-psychological test battery (NPE)

Of the 14 NPE tests administered, only one, the digit-symbol substitution test, demonstrated a significant difference between placebo and amantadine treatment. The digit-symbol test requires the subject to substitute a symbol for a digit, writing the symbol on a piece of paper. As such, the test does have significant motor output and is more than a measure of purely cognitive function. Moreover, of all the subtests in the Wechsler Adult Intelligence Scale, digit-symbol is most sensitive to changes in fine manual dexterity and visual-motor coordination. Performance following amantadine treatment was significantly better than after placebo treatment at the $p < 0.05$ level. A comparison after placebo and amantadine treatment of those tests having quantitative measures is shown in Fig. 5.

TABLE 9. SUMMARY OF CLINICAL QUANTITATIVE NEUROLOGICAL EXAMINATION (CQNE) TEST SCORES FOR THE COMBINED GROUPS SHOWN IN TABLE 7 EXPRESSED AS PERCENTAGE OF NORMAL FUNCTION[1]. PRETREATMENT, PLACEBO AND AMANTADINE SCORES

Functional categories	Percentage of normal			Paired *t*-test Difference between amantadine and placebo
	Pretreatment	Placebo	Amantadine	
Vision	91.0	87.4	88.1	0.70
Strength	60.0	62.6	64.4	2.69†
Steadiness	51.1	54.9	53.6	−0.55
Reaction time	62.2	66.4	67.3	0.89
Speed	58.3	60.6	62.4	1.20
Coordination	40.9	42.0	47.9	5.09‡
Fatigue	91.7	93.7	94.3	0.40
Station	44.2	48.3	49.2	0.48
Gait	41.1	40.1	44.6	2.22†
Sensation	75.8	75.3	76.6	0.66
Total upper extremity	65.1	66.9	68.5	2.24†
Total lower extremity	59.1	61.4	63.3	1.44
Combined upper and lower extremity	62.1	64.2	65.9	2.02†

†Indicates significance at the 0.05 level.

‡Indicates significance at the 0.01 level.

[1]As established by test scores obtained from 80 young adults.

Factors influencing response to amantadine

The 27 patients who responded favorably to amantadine treatment were compared to the 15 patients who did not. The age (66 yr vs. 64 yr), sex (63 per cent males in group responding vs. 62 per cent males in group not responding), and treatment group assignment (54 per cent of patients responding to amantadine in Group 1) were similar for both groups. The duration of disease was greater for those patients responding to amantadine than those who did not (10 yr vs. 5 yr; $p < 0.05$). In addition, the degree of disability as determined by the neurologists was greater in those patients responding to amantadine than those who did not, although this difference was not significant. The average stage of the group responding to amantadine was 3.1 while the average stage of the group that did not respond was 2.5. (See Hoehn *et al* [12] for the stages of Parkinsonism based on the level of clinical disability.) Subjective comparison of the six patients using concurrent anti-Parkinsonian medications suggests greater improvement for this group of subjects as compared to those patients using no concurrent medication. The small sample size (six patients) makes statistical analysis inappropriate. Evaluation of the General Disability Scale for these six patients indicates an improvement of 24 per cent after amantadine treatment when compared to pretreatment scores contrasted to a 9 per cent improvement for the remaining patients. However, analyses of quantitative data indicate no significant changes in the results when these six patients are not included in the evaluation.

Side effects

Treatment was not associated with important adverse side effects in any of the cases. As noted by other investigators [13], more side effects were reported with

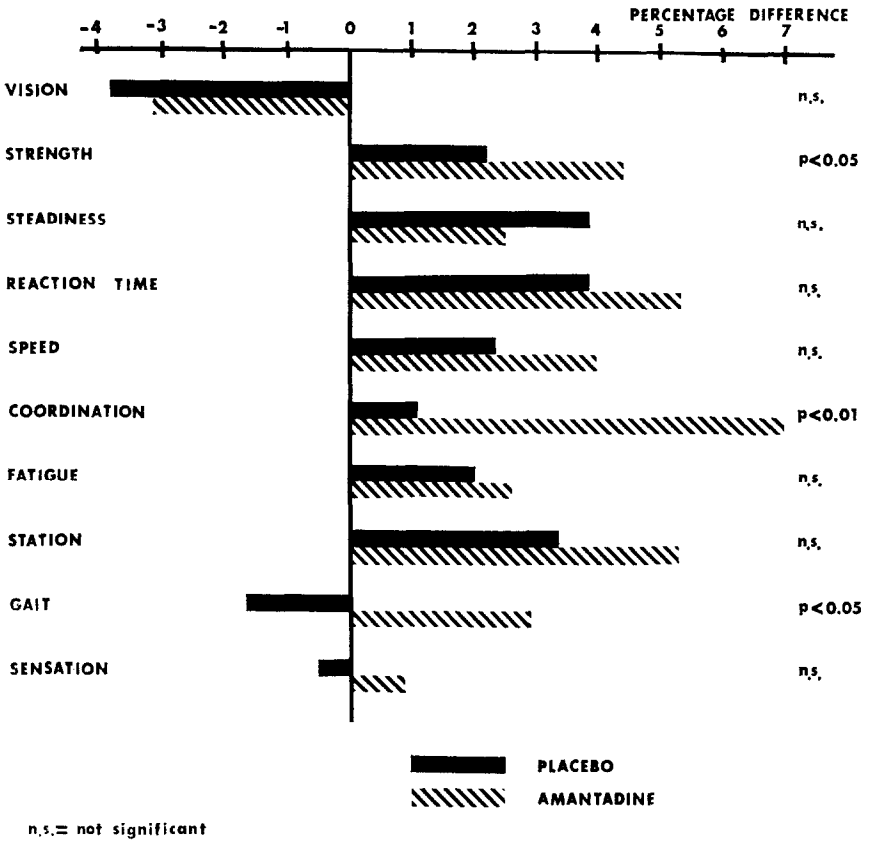

FIG. 4. Clinical quantitative neurological examination (CQNE) (functional categories). Comparison of percentage of normal function of placebo and amantadine treated patients when compared to pretreatment scores.

placebo treatment than with amantadine treatment. Results are shown in Table 10. Eight patients had a transient increase of leukocytes in their urine while on amantadine, although no patient had more than 15 cells per high power field. There were no symptoms of urinary tract infection.

DISCUSSION

The qualitative and quantitative measures employed in this trial demonstrate that amantadine is superior to placebo in the treatment of Parkinson's disease. Moreover, the benefit appears to be greater than that afforded by the patients' standard medications used upon entry to this study.

Walking, as evaluated by both patients and neurologists, improved more than the other subjective measures, but hygiene, eating, feeding and speech also improved. Clinical neurological evaluation demonstrated improvement in tremor, weakness, succession movements, rising, posture and gait. This broad improvement contrasts with the findings of Hunter *et al* [7] who reported only a small beneficial effect on physical signs and no significant effect upon functional abilities. The larger size of our series (42 vs. 12) may account for this disagreement.

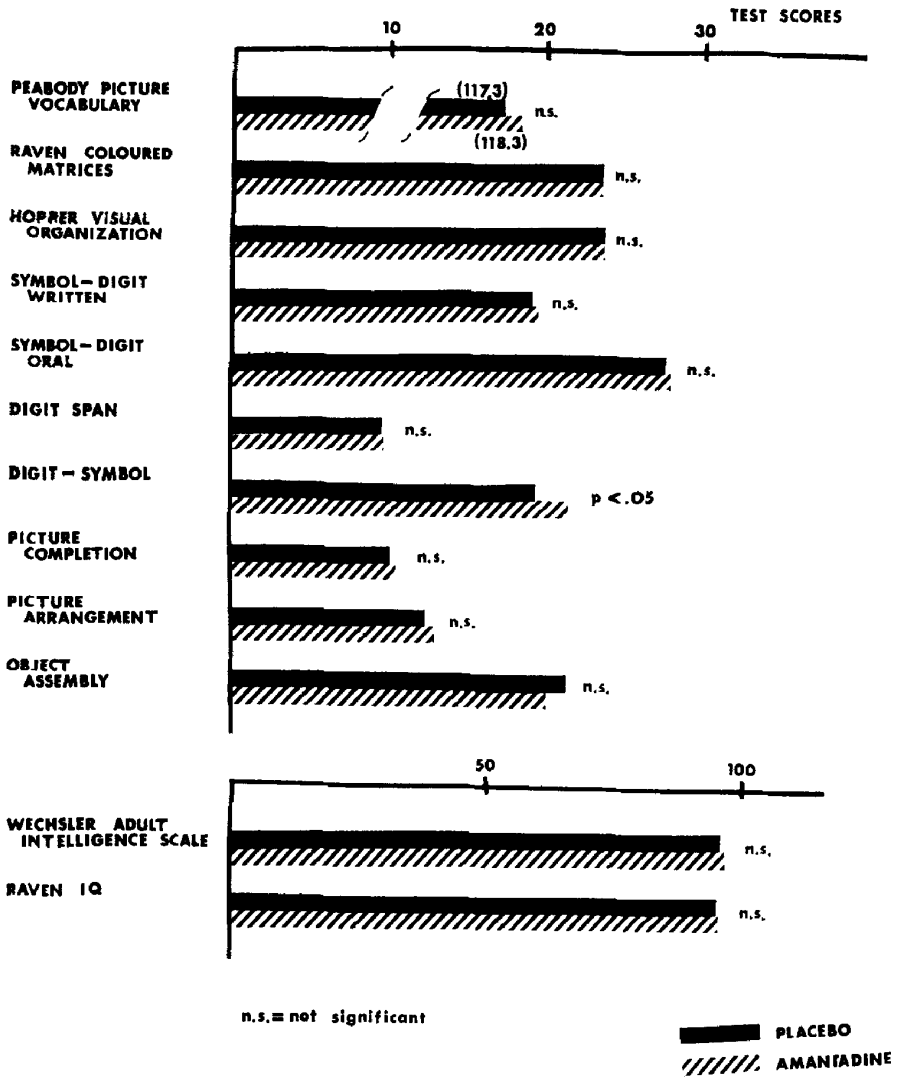

FIG. 5. Neuro-psychological examination (NPE). Effect of placebo and amantadine treatment on Parkinsonism.

Quantitative analysis of a broad range of motor, sensory, and cognitive tests revealed significant improvement only in the motor sphere. The most marked improvement was noted in tasks associated with fine finger manipulations, gross arm and leg movements, station, and gait. Overall strength also improved slightly, but significantly. The improvement in these basic abilities corresponded with improvement in the tests of simulated activities of daily living, a battery of tests designed to mimic tasks which patients must carry out in order to care for themselves. The agreement with subjective assessment establishes the consensual validity of the quantitative measures. Note that the specific areas of improvement could not have been determined without a comprehensive battery of motor, sensory, and psychological tests.

TABLE 10. NUMBER OF PATIENTS REPORTING SIDE EFFECTS DURING AMANTADINE AND PLACEBO TREATMENT

	Placebo	Amantadine
Nervousness	2	0
Anorexia	0	1
Weight loss	2	4
Insomnia	4	0
Easy fatigability	3	1
Dizziness	4	1
Headache	1	0
Loss of consciousness	0	0
Nausea, vomiting	0	0
Indigestion	0	0
Diarrhea	0	0
Constipation	1	3
Unsteadiness	3	2
Confusion	1	1
Depression	1	1
Early waking	0	0
Difficulty concentrating	0	0
Psychosis, hallucinations	0	0
Abnormal movements	1	0
Rash	0	0
Dry mouth	2	0
Blurred vision	2	2
Urinary straining	2	2
Edema	1	0
No side effects	18	26

Another important finding resulting from the use of a battery of tests is the security of knowing that the drug does not produce a decrement in performance in those areas not specifically affected. Talland [14], for example, found a diminution in certain cognitive functions (verbal rate, learning, Necker cube oscillation) in Parkinsonian patients using Artane^{R} or Parsidol^{R} compared with patients not using these drugs. We think a battery such as ours would be useful in evaluating any drug for the detection of deleterious nervous system side effects.

We emphasize that all mention of improvement has been expressed in terms of statistical significance. As is often the problem in any study involving a relatively large number of patients, statistically significant findings may result from small changes, so small as to be of little biological significance. Alternatively, in studying basic abilities such as strength, reaction time, or hand coordination, it is difficult to determine what effect small changes in these items will have upon the overall functional capacity of the patient. One major advantage of the quantitative measures expressed in interval or ratio units when contrasted with the subjective scales expressed in ordinal units involves the capability of expressing the patients' performance as a percentage of normal function. This permits the physician to establish more meaningful estimates involving the actual degree of improvement that can be expected following a specific drug trial. In this study, many of the measures evaluated in this fashion improved only slightly. However, the average increase (from 31.9 to 39.6 per cent of normal function) following amantadine treatment for the tests of simulated activities of daily living (Table 6) is probably of considerable biological significance to the individual patient.

Another way of establishing drug efficacy is to compare a new drug with standard medications. In every category tested, amantadine performed as well as or better than the patients' standard, optimal drug therapy, though few of the comparisons reached statistical significance.

SUMMARY

A double-blind crossover trial of amantadine vs. placebo was carried out involving 42 patients with Parkinson's disease: 64 per cent of the patients on amantadine experienced subjective improvement compared to 21 per cent on placebo. A comprehensive battery of qualitative and quantitative tests was carried out on each patient on entry to the study, after previous standard treatment was discontinued or reduced to a minimal tolerable dose, while on placebo, and while on amantadine, at 3 week intervals. Almost all relevant symptoms and physical signs improved, and the neurologists judged amantadine superior to placebo in 74 per cent of the patients. Quantitative measurement revealed significant improvement in 10 of 19 tests of simulated activities of daily living, in several tests of strength and station, and in all tests of coordination and gait. When the amantadine scores were compared to the placebo scores, an average improvement of 29 per cent occurred in the simulated activities of daily living, 14 per cent in tests of coordination, 11 per cent for gait and 3 per cent for strength. Sensation and neuropsychologic performance were unaffected and side effects were minimal. Comparison of amantadine scores with entry scores obtained when the patients were on standard anti-Parkinsonian medications suggested that amantadine may also be superior to classical medications. The response to amantadine was not related to age, sex, or severity of disease, but those who responded were found to have a significantly longer duration of illness. Amantadine is a non-toxic, easily administered drug useful in the treatment of Parkinson's disease.

It should be emphasized that the quantitative tests used in this study yielded interval data. This resulted in more valid comparisons with normal, particularly when expressed in terms of the percent of the age-matched normal function.

Finally, this is the first report which describes a battery of quantitative tests designed to measure in part the effect of a drug on activities of daily living. It could be that these results were the most indicative of a significant effect in this experiment, since it is an improvement in the accomplishment of activities of daily living, not neurological tests, by which a patient with Parkinsonism bases his judgement of the effectiveness of a non-toxic treatment.

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APPENDIX A

GENERAL DISABILITY SCALES

Neurologists' Evaluation by Inquiry of Activities of Daily Living [8].

Scale A. WALKING

Always walks alone	
Normal	0
Gait only slightly deviant from normal in quality and speed; turning is the most difficult task, posture essentially normal	1
Quality of gait is poor and rate is slow; posture moderately affected; there may be a tendency toward mild propulsion; turning is difficult	2
Gait is extremely abnormal; very slow and posture grossly affected; there may be propulsion	3
Sometimes walks alone	
Walks short distances with ease; walking outdoors is difficult but often accomplished without help; rarely walks longer distances alone	4
Walks from room to room with only moderate difficulty; may occasionally walk outdoors without assistance	5
Walks from room to room without assistance, but moves slowly and uses external support; never walks alone outdoors	6
Never walks alone	
Requires potential help indoors and active help outdoors	7
Requires moderate help indoors; walks outdoors with considerable help	8
Needs considerable help even for short distances; cannot walk outdoors with help	9
Cannot walk at all, even with maximum assistance	10

Scale B. DRESSING

Complete self help	
Normal	0
Dress self completely with only slightly more time and effort than normal	1
Dress self completely with slowness and great effort	2
Requires partial assistance	
Handles all dressing alone with the exception of fine activities (tie, buttons)	3
Performs more than half of dressing activities alone, with considerable effort and slowness	4
Performs about half of dressing activities independently	5
Performs only gross dressing activities alone (hat, coat)	6
Requires complete assistance	
Gives considerable help through bodily movements	7
Can give some help through bodily movements	8
Movements of patient neither help nor hinder assistant	9
Patient is a hindrance rather than a help to assistant	10

Scale C. HYGIENE

Complete self help	
Normal	0
Hygiene maintained normally, with exception of slight slowness	1
Hygiene activities are moderately time-consuming; no substitute methods; few accidents	2
Hygiene maintained independently, but with effort and slowness; accidents are not infrequent, may employ substitute methods	3
Requires partial assistance	
Manages most of personal needs alone; has substituted methods for accomplishing difficult tasks (electric razor)	4
Requires assistance for some tasks not difficult in terms of coordination	5
Requires assistance for half of toilet needs	6
Performs a few tasks alone with assistant nearby	7
Requires complete assistance	
Hygiene maintained well; gives aid to assistant	8
Reasonably good hygiene with assistance, but does not provide assistant with significant help	9
Unable to maintain proper hygiene with even maximum help	10

Scale D. EATING AND FEEDING

Eating	
Normal	0
Follows a normal diet, but chewing and swallowing are labored	1
Eats some hard foods routinely, but these require time and effort	2
Liquids and soft foods handled with ease, hard foods occasionally eaten, but require great effort and much time	3
Eats only liquids and soft foods; these are consumed very slowly	4
Eating so impaired that a hospital setting is required to get adequate nutrition	5
Feeding	
Normal	0
Fully feed self with rare accidents, slower than normal	1
Handles all feeding alone with moderate slowness; still may get assistance in specific situation (cutting meat in restaurant); accidents are not infrequent	2
Performs most feeding activities alone, slowly and with effort; requires help with specific tasks (cutting meat, filling cup)	3
Performs only a few tasks independently	4
Requires complete assistance	5

Scale E. SPEECH

Speech	
Normal	0
Speech entirely adequate; minor voice disturbances present	1
Speech easily understood, but voice or speech rhythm may be disturbed	2
Communication accomplished with ease, although speech impairment detracts from content	3
Speech can always be understood if listener pays close attention; both articulation and voice may be defective	4
Speech always employed for communication, but articulation is still very poor; usually uses complete sentences	5
Uses speech for most communication, but articulation is highly unintelligible; may have occasional difficulty in initiating speech; usually speaks in single words or short phrases	6
Attempts to use speech for communication, but has difficulty in initiating vocalization; may stop speaking in middle of phrase and be unable to continue	7
Vocalizes to call attention to self	8
Vocalizes but rarely for communicative purposes	9
Does not vocalize at all	10

APPENDIX B

SIMULATED ACTIVITIES OF DAILY LIVING EXAMINATION (SADLE)* AND ABBREVIATIONS†

	Test	Abbreviation	Time limit (sec)
1.	Putting on a shirt	Shirt	300
2.	Managing visible buttons; 1 in button	Button (large)	120
3.	Managing visible buttons; $\frac{1}{2}$ in button	Button (small)	120
4.	Opening and closing a zipper	Zipper	60
5.	Tying a bow	Bow	120
6.	Cutting with a knife	Cutting	120
7.	Using a fork	Fork	60
8.	Pouring water into a glass	Pouring	120
9.	Squeezing toothpaste from a tube	Toothpaste	60
10.	Dialing a telephone	Dialing	60
11.	Opening and closing a safety pin	Safety pin	120
12.	Opening and closing a door	Door	60
13.	Opening an envelope	Envelope	60
14.	Drinking from a glass with a straw	Drinking	60
15.	Prolonged vocalization	Vocalizing	—
16.	Washing hands; using dominant hand using nondominant hand	Scrub-D Scrub-N	120
17.	Putting on gloves; using dominant hand using nondominant hand	Gloving-D Gloving-N	60

*Scores are obtained by averaging two timed trials for all tests with the exception of the toothpaste and drinking tests where one timed trial is used.

†For a complete description of SADLE tests see: POTVIN, A. R.: The Effects of Age, Motivation and Learning on Performance in the Quantitative Examination of Neurological Function. Ph.D. Thesis, University of Michigan, 1971.

APPENDIX C

THE CLINICAL QUANTITATIVE NEUROLOGICAL EXAMINATION (CQNE)

TEST ITEMS, MEASURE, UNITS AND INSTRUMENTATION*

Test	Measure	Units	Instrumentation
I. Vision	Central visual efficiency	per cent	Snellen chart (multi-hole glasses)
II. Upper extremities			
A. Strength of movements			
1. Grip	Ave. of maximums of first 2 trials	lb of force	Jamar hand dynamometer
2. Wrist dorsiflexion	Ave. of 2 trials	lb of force	Modified Newman myometer
3. Shoulder abduction	Ave. of 2 trials	lb of force	Modified Newman myometer
B. Control of movements			
1. Steadiness, hole steadiness			14 hole steadiness apparatus
a. Supported	Smallest hole no. for no contacts in 10 sec	—	
b. Unsupported	Smallest hole no. for no contacts in 10 sec	—	
2. Simple reaction time	Ave. of last 10 trials	counts (1 count = 20 msec)	Simple reaction time indicator with finger release button
3. Speed of hand	10 sec trial/10	taps/sec	Hand tapping board with interval counters
4. Speed-coordination of hand 2, alternate tapping			Hand tapping board with interval counters
a. Correct taps	Correct taps from 10 sec trial/10	correct taps/sec	
b. Index of performance	Corrected index of difficulty/movement time	bits/sec	
5. Rotary pursuit	Ave. of last 2 trials	per cent time on target	Lafayette rotary pursuit apparatus
6. Finger dexterity, Purdue pegboard	60 sec trial	pegs/60 sec	Purdue pegboard
7. Finger dexterity, pencil rotation	Ave. of 2 trials	rotation/20 sec	8 inch pencil

APPENDIX C. *Continued*

C. Fatigue of movements			
1. Strength, grip	$\frac{\text{5th trial}}{\text{1st trial}} \times 100$	per cent	Jamar hand dynamometer
2. Speed of hand	$\frac{\text{Taps in last 10 sec}}{\text{Taps in first 10 sec}} \times 100$	per cent	Hand tapping board with interval counters
3. Speed-coordination of hand 2, alternate tapping	$\frac{\text{Correct taps in last 10 sec}}{\text{Correct taps in first 10 sec}} \times 100$	per cent	Hand tapping board with interval counters
D. Sensation			
1. Touch, hand	Length of filament at which all 3 strokes felt	cm	Cochet and Bonnet aesthesiometer
2. Vibration sense, index finger	Ave. of 3 trials	microns	Biothesiometer (120 Hz)
3. Position sense	Joint at which position sensed correctly all 4 times	—	None
4. Two-point discrimination	Smallest separation identified as 2 points	mm	Sweet two-point compass
III. Lower extremities			
A. Strength of movements			
1. Foot dorsiflexion	Ave. of 2 trials	lb of force	Modified Newman myometer
2. Hip flexion	Ave. of first 2 trials	lb of force	Modified Newman myometer
B. Control of movements			
1. Speed of foot	10 sec trial/10	taps/sec	Foot tapping board with interval counters
2. Speed-coordination of foot, alternate tapping forward step			Foot tapping board with interval counters
a. Correct taps	Correct taps from 10 sec trial/10	correct taps/sec	
b. Index of performance	Corrected index of difficulty/movement time	bits/sec	

[*Appendix C continued on next page*]

APPENDIX C. *Continued*

Test	Measure	Units	Instrumentation
3. Speed-coordination of foot, alternate tapping, side step			Foot tapping board with interval counters
a. Correct taps	Correct taps from 10 sec trial/10	correct taps/sec	
b. Index of performance	Corrected index of difficulty/movement time	bits/sec	
4. Standing			Stopwatch
Eyes open; two legs together	Max. of 3 trials	sec	
one leg	Max. of 3 trials	sec	
Eyes closed; two legs together	Max. of 3 trials	sec	
one leg	Max. of 3 trials	sec	
5. Tandem gait			Stopwatch and parallel bars
Without support, one length	No. steps/no. sec	steps/sec	
With support, two lengths	No. steps/no. sec	steps/sec	
C. Fatigue of movements			
1. Strength, hip	$\frac{\text{5th trial}}{\text{1st trial}} \times 100$	per cent	Modified Newman myometer
2. Speed of foot	$\frac{\text{Taps in last 10 sec}}{\text{Taps in first 10 sec}} \times 100$	per cent	Foot tapping board with interval counters
3. Speed-coordination of foot, alternate tapping, forward step	$\frac{\text{Correct taps in last 10 sec}}{\text{Correct taps in first 10 sec}} \times 100$	per cent	Foot tapping board with interval counters
4. Speed-coordination of foot, alternate tapping, side step	$\frac{\text{Correct taps in last 10 sec}}{\text{Correct taps in first 10 sec}} \times 100$	per cent	Foot tapping board with interval counters
D. Sensation			
1. Touch, great toe	Length of filament at which all 3 strokes felt	cm	Cochet and Bonnet aesthesiometer
2. Vibration sense, great toe	Ave. of 3 trials	microns	Biothesiometer (120 Hz)
3. Position	Joint at which position sensed correctly all 4 times		None

*For a complete description of CQNE tests see: POTVIN, A.R.: The Effects of Age, Motivation and Learning on Performance in the Quantitative Examination of Neurological Function. Ph.D. Thesis, University of Michigan, 1971.